Some Quaternary 2,2'-Disubstituted Biphenyls

A Thesis submitted to the

University of London for the Degree of

Doctor of Philosophy

by

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February 1963

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ABSTRACT

In only a few cases can a reasonably valid comparison be made between the optical stabilities of unbridged biphenyls and those bridged with a 7-membered bridging ring. An attempt was made in this work to prepare bridged and unbridged biphenyl compounds with similar interfering groups and to compare their optical stabilities. Quaternary salts derived from various 2,2'-bisbromomethylbiphenyls were chosen since by condensation of the latter with suitable amines analogous bridged and unbridged biphenyls can be produced, with the further advantage that the resolving groups are not directly attached to the biphenyl nucleus.

2-Bromomethyl-1-(o-bromomethylphenyl)naphthalene was synthesised and 2,7-dihydronaphtho(2',1':3,4)-5,6-benzazepinium-1-spiro-1'''-piperidinium iodide and 2,2'-bis(N-pyridinium-methyl)-5,6-benzbiphenyl dibromide were obtained. Attempts to prepare more of the dipyridyl salt or to obtain salts with other tertiary bases were not successful.

2,2'-Dimethyl-4,4'-dinitrobiphenyl was synthesised. However on side-chain bromination it gave a mixture of mono- and dibromo-compunds of very similar solubilities.

2,2'-Bisbromomethylbiphenyl was condensed with N-methylephedrine, pyridine, trimethylamine and dimethylamine.

No unstable optical activity was detected in the resulting quaternary salts. The salts were subjected to Hofmann degradation conditions. The bis-ephedrinium hydroxide gave the expected 2,2'-bis(dimethylaminomethyl)biphenyl in appreciable yields only when carbon dioxide was excluded ; the diamine was accompanied by: (-)-N-methylephedrine, 9-dimethylamino-9,10-dihydrophenanthrene and the 2,7-dihydro-1,1-dimethyl-3,4:5,6-dibenzazepinium cation. 9-Dimethylamino-9,10-dihydrophenanthrene was also isolated from the products of Hofmann degradation of 2,2'-bis(trimethylammoniomethyl)biphenyl and of 2,7-dihydro-1,1-dimethyl-3,4:5,6-dibenzazepinium hydroxides. This seems to indicate incursion of a Stevens type of rearrangement into the normal Hofmann degradation of these salts.

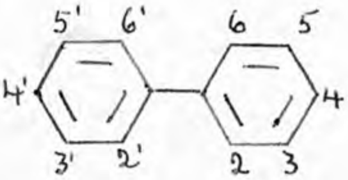
2,2'-Bisbromomethyl-4- and -6-nitrobiphenyls have been synthesised and condensed with (-)-ephedrine, dimethylamine and trimethylamine. The 2,7-dihydro-1-methyl-1-(β -hydroxy-α -methyl-β -phenylethyl)-4'-nitro-3,4:5,6-dibenzazepinium salt was separated into at least two diastereoisomers both of which showed unstable optical activity at room temperature. (-)2,7-Dihydro-1,1-dimethyl-4'-nitro-3,4:5,6-dibenzazepinium picrate was obtained and its racemisation in acetone was studied. 2,2'-Bis-(trimethylammoniomethyl)-6-nitrobiphenyl (+)Camphorsulphonate was prepared.

CONTENTS :

INTRODUCTION

The biphenyl molecule (1) is collinear and the two benzene rings can rotate almost freely about the 1-1'-bond, the calculated energy barrier for the passage through the flat coplanar state being only 3.9 kcal.mole^{-1}(Howlett,J.,1960,1055).

(1)



X-ray crystal analysis (Dhar,Indian.J.Physics,1932,7,43) shows the molecule to be coplanar in the crystal, with the 1-1' bond of length 1.48 Å. Trotter (Acta Cryst.,1961,14,1135) has recently confirmed the above basic coplanar structure of biphenyl in the crystalline state, though according to him the 1-1' bond length is 1.505 Å; ~~and~~ the 2,2',6,6'- hydrogen bond angles are slightly deformed, the hydrogen atoms remaining in the plane of the rings (G.B. Robertson, Nature, 1961, 191, 593). X-ray crystal analysis however gives information about grouped molecules and the intermolecular cohesive forces have to be considered in the results obtained. Thus coplanarity of the two rings need not necessarily be the favoured conformation of an isolated molecule.

Electron diffraction study of biphenyl vapour (Karle and Brockway, J.Amer.Chem.Soc., 1944,66,1974; Bastiansen, Acta Chem.

Scand.,1949,3,408) which gives data for isolated molecules, shows that in the gaseous phase the biphenyl molecule deviates from coplanarity of the two rings by about 45° ($\pm 10^{\circ}$), while dipole moment measurements (Littlejohn and Smith,J.,1953, 2456) of 2-monosubstituted biphenyls in solution give observed moments which agree with values calculated for near-orthogonal configurations. Dipole moment measurements on 2,2'-disubstituted biphenyls (Littlejohn and Smith, ibid., 1954, 2552) indicate angles between the planes of the 2 rings of the order of 75° (halogens,NO_2) with a slight cis disposition, the angles increasing with the size of the halogen substituents. 3,3'-Dinitro biphenyl (Littlejohn and Smith,loc.cit.) with an angle between the benzene ring planes of 105° was found to have a slight trans disposition.

The ultra-violet absorption spectra provide another means of studying the conformation of biphenyl and its derivatives. This method gives direct information only about conjugation between the two phenyl rings but analysis of spectra and in particular of the changes observed on introduction of substituents into the biphenyl molecule have lead to conclusions relating resonance and the conformation of the phenyl rings. Biphenyl shows a high intensity band (called the conjugation band) at 2490 Å with an intensity ϵ (molecular extinction coefficient) of 17,300 (in ethanol) which has been assumed to arise as a result of resonance between the two aromatic nuclei, the 1-1'-bond acquiring some double bond character. Since conjugation operates by overlapping of the π-orbitals of the two benzene rings, the presence of this band was accepted as demonstrating the planarity of the biphenyl molecule in solution. The overlap of the π-orbitals is obviously maximal in the coplanar conformation but it still exists, becoming increasingly smaller, when the angle between the rings increases, and becomes zero only at 90°. At small interplanar angles there should be only a relatively slight loss of resonance and it seems that near-planarity should also produce effective conjugation.

Introduction of substituents into the biphenyl nucleus affects the spectrum in a way which depends on their position in the parent phenyl ring, as well as upon their own nature. *Ortho*-substituents have a very large steric effect. If they are large enough the two benzene rings cannot become coplanar or rotate freely about the 1-1'-bond. Electronic spectra are very sensitive to the steric effects and introduction of one fluorine atom into the *ortho*-position of the biphenyl results in a considerable short-wave shift to λ max. 2415 Å and reduction in intensity to 16,500 of the conjugation band (Beaven and Hall, *J.*, 1956,4637). With two chlorine atoms in the *ortho*-positions the conjugation band is left only as an inflection at λ inf.2300 Å with a further reduction in intensity to 6600. In 2-methylbiphenyl there is a shift of 120 Å to shorter wave-length, (Friedel, Orchin &

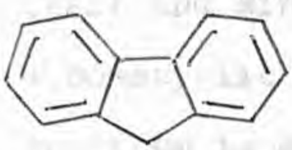
Reggel, J.Amer.Chem.Soc.,1948,70,199), while in 2,2'-dimethylbiphenyl the conjugation band has almost completely vanished and the absorption resembles that of toluene (Beaven,Hall,Lesslie and Turner,J.,1954,131).

Replacement of o-methyl substituent in monosubstituted biphenyl by ethyl, n -propyl or n -butyl has only a small effect since a longer alkyl chain can take up a position in which it contributes little additional overlap (Braude and Evans, J.,1954, 607; Braude, Fawcett and Webb, ibid, 1049).

In addition to the steric effect which is always in opposition to the fundamental biphenyl resonance the ortho-substituents affect the spectrum owing to their electronic interaction with the parent phenyl ring. This factor may either support or oppose the fundamental biphenyl resonance.

By joining the 2,2'-positions of biphenyl with a two or more atom bridge, molecules can be produced in which the collinear benzene rings are held in a non-coplanar conformation and in which the strainless multiplanar bridge is the main factor determining the conformation of the molecule.

The simplest 2,2'-bridged biphenyl, fluorene (2), does not satisfy the above requirements since it is a strained planar structure in which the rings are no longer coaxial (Brown and Bortner, Acta Cryst.,1954,7,139; Burns and Iball,Nature,1954,173, 635).



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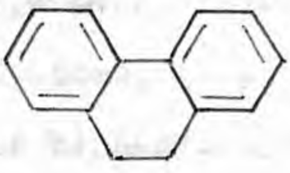

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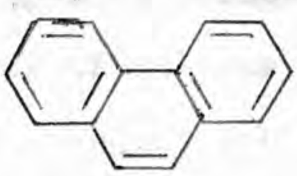
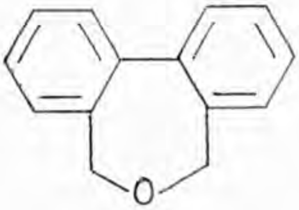


(4)

Bridging the 2,2'-positions with two methylene groups (3) involves apparently no strain, the biphenyl skeleton remaining collinear. Models suggest that the two benzene rings are at an angle of 15.0° - 16.0° (Hall and Minhaj, J., 1957, 4584) and one would expect therefore the conjugation in (3) to be greater than in biphenyl itself. The ultra-violet spectrum of (3) seems to support this view - a typical high intensity band is present at $\lambda_{max.}$ 2635 Å, a longer wave-length than in biphenyl itself and with a slightly higher intensity ($\varepsilon_{max.}$ 18.000). Contributions from separate phenyl chromophores give rise to a broad, well resolved band at $\lambda_{max.}$ 2995 Å with $\lambda_{max.}$ 4750 (Beaven, Hall, Lesslie and Turner, J., 1952, 854). The spectrum of phenanthrene (4) shows high conjugation consistent with a flat structure (Newman and Hussey, J. Amer. Chem. Soc., 1947, 69, 3023).

Bridging the 2,2'-positions with 3 atoms to produce a 7-membered ring is particularly easy (Kenner et al., J., 1911, 99 2101; Beaven et al., loc. cit.), the calculated value for the angle θ between the planes of the two benzene rings for a strainless conformation being 43° for (5), 47° for (6) and 49° for (7; R=H)

(Hall and Minhaj, J., 1957, 4584). In biphenyl compounds bridged by a homocyclic bridge of 3 atoms, (7 ; R = CO_2Me or CH_2OH) the spectrum is of the simple biphenyl type with the conjugation band at 2490 Å, but slightly reduced in intensity to ca. 15,000 (Beaven, Bird, Hall, Johnson, Lesslie and Turner, J., 1955, 2708). The spectrum of (5) is very similar. There are no long wave features. Thus both (5) and (7), which cannot be coplanar show by their biphenyl-type spectrum that the two rings are no less conjugated than in (1).



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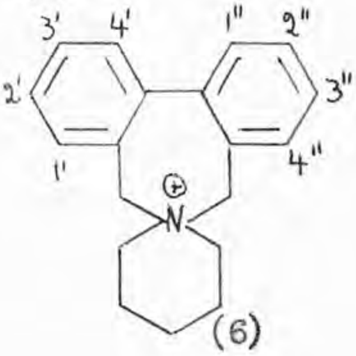

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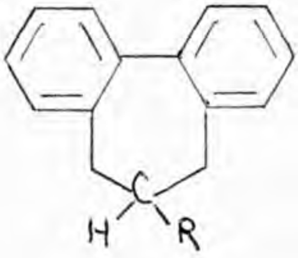


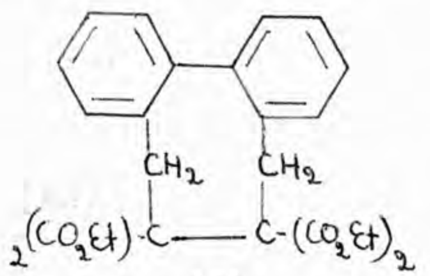
(7)

The spectra of (6) with 4' and 1''- positions disubstituted by F, Cl, Br and I form a series showing increasing steric hindrance with increase in the size of the halogen atom (Ahmed and Hall, J., 1960, 4165). The bridged dichloro compound shows a fairly well resolved conjugation band, in the dibromo compound there is a suggestion of it as an inflection, and even in the di-iodo compound θ does not become large enough for all conjugation to be obliterated. This is in marked contrast to the observations on o-substituted non-bridged biphenyls, where the spectrum of 2,2'-dichlorobiphenyl shows only an inflection and that of 2,2'-dibromobiphenyl not even that. In non-bridged compounds the interaction between *o*-substituents is the main factor determining the conformation of the molecule and steric strain caused by large *o*-substituents can most easily be reduced by increase in θ. In bridged compounds the bridge determines the conformation and relief of strain can be distributed among several factors :(a) compression of substituents,(b) their out-of-plane bending,(c) increase in angle between the benzene rings, causing distortion of the bridging ring.

In biphenyl compounds bridged with 4 atoms across the 2,2'-positions to form an 8 membered ring a greater twist of the two benzene rings about the common axis, with a consequent further reduction in conjugation, is required to accommodate the bridge.

Models show that there are two possible conformations in this case, (a) $\theta = 60\text{-}65^\circ$ and (b) $\theta = 75\text{-}80^\circ$. For steric reasons, supported also by spectral evidence, the second is not likely to be the preferred conformation.

In the 8-ring compounds (8) and (9) (Beaven,Bird,Hall, Johnson, Ladburg, Lesslie and Turner, *J.*, 1955, 2708),



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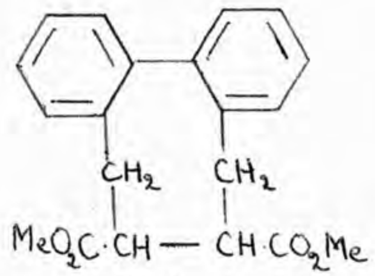
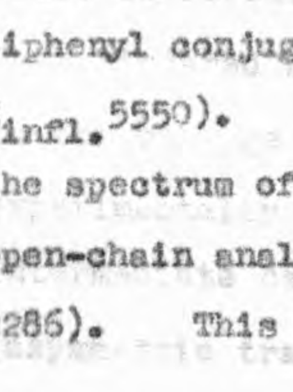


(9)

the conjugation ([illegible]) is considerably reduced as compared with (7). The conjugation band is reduced in intensity and has shifted to 2365 Å, and there are long-wave inflections.

Biphenyl compounds with a 5-membered bridge at the 2,2'-positions are difficult to synthesize. The value of θ in these compounds cannot be accurately estimated since they do not possess single conformations corresponding to minimum angle strain. Mislow, Hyden and Shaefer (J.Amer.Chem.Soc., 1962, 84, 1449) have recently synthesized 1,2,3,4-dibenz~~y~~cyclonona-1,3-diene-7-carboxylic acid (10) and have calculated from spectral data θ to a first approximation as 68°. Comparison of its absorption spectrum with that of lower ring homologues shows a pronounced blue shift and drop in intensity of the biphenyl conjugation band (inflection at $\lambda_{\text{infl.}}$ 2310Å, $E_{\text{infl.}}$ 5550). The long wave features are clearly resolved and the spectrum of (10) is nearly superimposable on that of the open-chain analogue (11) (Everitt, Hall and Turner, J., 1956, 2286). This indicates severe reduction in conjugation.



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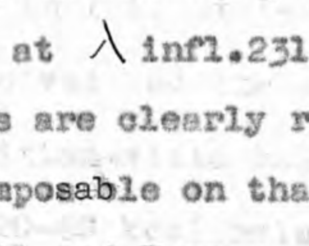


(11)

The configuration of the biphenyl skeleton in compounds containing substituents in one or more of the 2,2',6,6'-positions can be investigated by study of the optical activity of such systems and the results can be compared with conclusions about conformation of o-substituted biphenyls drawn from the analysis of their ultra-violet absorption spectra. Ortho-substituents introduced into the biphenyl molecule hinder rotation about the 1,1'-bond and increase the energy barrier to passage through a symmetrical state. With suitable ortho-substiuents the substituted biphenyls are dissymmetric in any non-planar conformation and might be shown to be optically active provided their half-times of racemisation are observable, that is at least 1-2 minutes Many hindered biphenyls have been resolved and the energy-barrier to the passage through the flat transition-state has been found experimentally to be of the order of 20-30 kcal.mole^{-1}. In some intermediate cases the compounds have been optically activated (asymmetric transformation) but not resolved, while in compounds without ortho-substituents or with only small ortho-substituents the passage through the co-planar state is so facile that they cannot even be optically activated.

The rate constants for racemisation depend on the energy of activation for configurational changes and on the entropy of activation ($\Delta S^{\ddagger}$), which is reflected in the non-exponential term (A), (often called the frequency factor) of the Arrhenius equation : $k_{rac} = A \exp.(-E/RT)$. Racemisation follows first-order kinetics and values of (A) of 10^{11} to 10^{13} sec.$^{-1}$ (de la Mare, *Progress in Stereochemistry*.Klyne,1954,p.120), are regarded as typical of unimolecular reactions (see also Hall and Harris, *J.*,1960,490). Values of ($\Delta S^{\ddagger}$) can be derived from experimentally determined values of (A) by using Glasstone, Laidler and Eyring's absolute reaction rate equation :

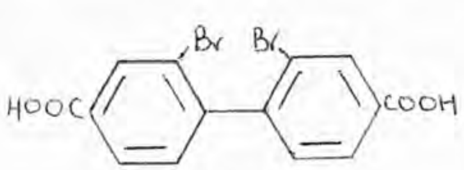
$$k_{rac} = \kappa (kT/h) \exp.(-\Delta H^{\ddagger}/RT) \exp.(\Delta S^{\ddagger}/R)$$

where κ = transmission coefficient ; $\Delta H^{\ddagger}$ = change in enthalpy on formation of transition state in racemisation ; k = Boltzmann constant. Values of (A) above 10^{13} give positive entropy factors, encountered, with one exception (22), in bridged biphenyls only. With (A) $10^{11.5}$ to 10^{11} the calculated energy of activation for racemisation is 17 kcal.mole^{-1} for observable optical activity. (Howlett, *J.*, 1960, 1055).

On steric grounds, the *ortho*-substituents can be arranged in the following sequence of decreasing effectiveness in preventing racemisation in unbridged biphenyls

$Br > Me > Cl > NO_2 > CO_2H > OMe > F$ (Adams and Yuan, *Chem. Rev.* 1933,*12*,261).

With the smallest substituents possible, the energy of activation E is too small for experimental determination, for 2,2'-difluorobiphenyl it is calculated at 6 kcal.mole^{-1}, but that for 2,2'-dichlorobiphenyl should be just within experimental reach at 18 kcal.mole^{-1}, (Howlett, loc. cit). In fact the biphenyl with smallest *ortho*-substituents which was optically activated by second order asymmetric transformation of the acid with brucine from ethyl acetate solution is 2,2'-dibromo-4,4'-diphenic acid (14) with E 19kcal.mole^{-1}(ethanol), t½ 13.4 min. at 1.0°, (Harris, *J.*, 1960, 1905; Harris, *Proc.Chem.Soc.*, 1959, 367). Attempts to activate the corresponding benzidine compound (15) have so far failed, (K.L. Cheung, Bedford College, 1962, Ph.D. Thesis).



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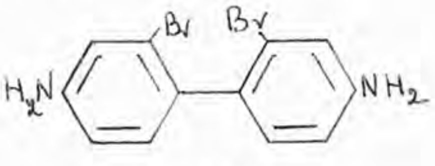
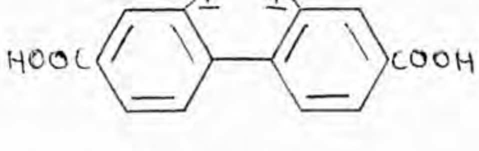


(15)

In the di-iodo series (K.L. Cheung, Bedford College, 1962, Ph.D. Thesis) the acid (16) is much more stable, with t½ 104 min. at 25°, E 21.6 kcal.mole^{-1}, than the corresponding benzidine (17) with t½ 5.3 min. at 25°, E 19.9 kcal.mole^{-1} (both in dimethylformamide).



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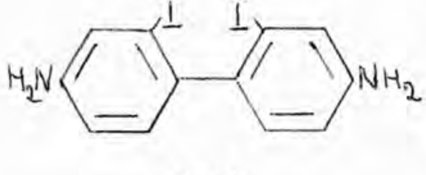

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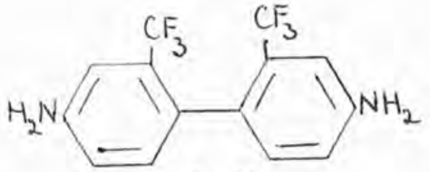
Compound (18) has been obtained optically active by second-order asymmetric transformation of its hydrogen tartrate and subsequent decomposition of the salt with aqueous ammonia below 10°, (Hall and Harris, Proc.Chem.Soc., 1959, 396). It has a half-life of 58.4 min. at 39° in ethanol.



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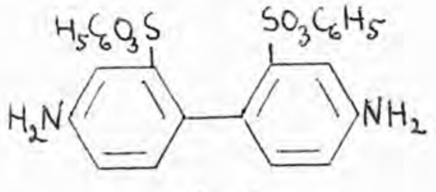
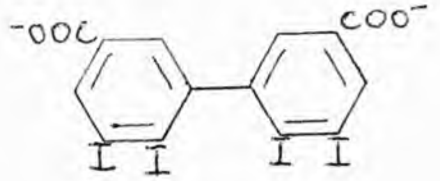


(19)

The corresponding dimethyl compound has not so far been optically activated. The $-CF_3$ falls in effective size probably between $-CH_3$ and $-SO_3Ph$. Lesslie and Turner's (J.,1932,2021) biphenyl benzidine 2,2'-disulphonate (19) was stable at room temperature, retaining full optical activity for 3 days, but racemised rapidly at 100°.

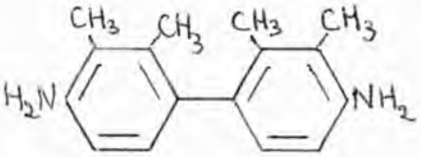


(20)

Compound (20) (Rieger and Westheimer, J.Amer.Chem.Soc., 1950,72,19) has E 28.02 kcal.mole^{-1}, (A) 11.7 sec.$^{-1}$ in aqueous sodium hydroxide. The added 3,3'-substituents have a marked effect on optical stability. On purely steric grounds the 3,3'-groups would be expected to have a "buttressing"effect, preventing the groups in 2,2'-positions bending away from the ortho hydrogens in the other ring, thus increasing the strain in the planar configuration required for racemisation. The sequence of decreasing effectiveness for this 3,3' buttressing effect has been found to be:-

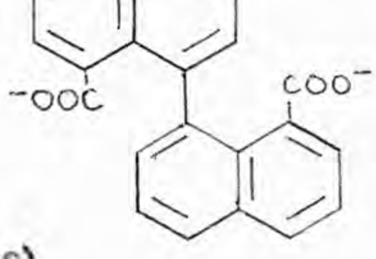
$NO_2 > Br > Cl > Me > MeO$ (de la Mare, Progress in Stereochemistry, Klyne, 1954, p.90).

Another optically active compound in which the blocking methyl groups are buttressed is (21), (Theilacker and Hopp, Chem.Ber., 1959, 92, 2293).



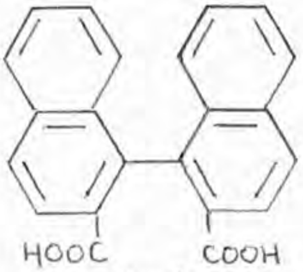
(21)

Fused rings in the 5,6- 5',6' positions act as ortho substituents. Thus several 1,1'-binapthyls are known which are optically active owing to restricted rotation about the 1,1'- bond. Compound (22) has been resolved (Messenheimer and Beisswenger, Chem. Ber. ~~Ber.dtsch.chem.~~ ~~Ges~~,1932,65,32) and the racemisation data gave values of E 26.01 kcal.mole^{-1}; (A) 10$^{15.2}$ sec.$^{-1}$; entropy factor + 9.2 e.u. (in 0.1 N NaOH), (Harris and Mellor, Chem.and Ind. 1959, 949).



(22)

This appears to be the only non-bridged biphenyl type compound with a positive entropy factor for racemisation.



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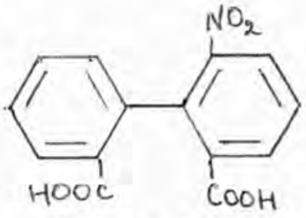

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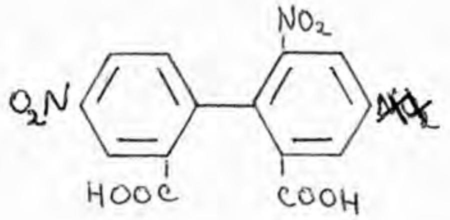
Earlier, Kuhn and Albrecht, (*Annalen*,1928, 465,282) obtained (23) optically active and it was found that rotation of its solution in N-methyl-formamide remained unchanged after heating at *ca.*175° for 8 hr~~s~~. (Hall and Turner, *J.*, 1955, 1242).

In the sequence of decreasing effectiveness in preventing racemisation in hindered biphenyls the *o*-nitro group falls between chlorine and the carboxyl group. No compounds containing only 1 or 2 NO_2 groups in the *o* positions, without substituents in the 6,6'- positions, have been obtained optically active. However, 6-nitro (24), 4,6'-dinitro (25) and 4,6,4'-trinitro (26)diphenic acids have been obtained optically active.



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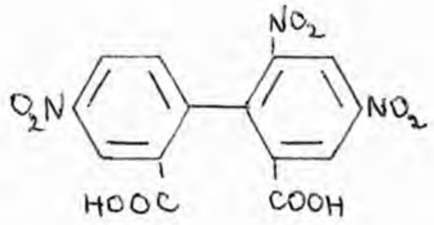


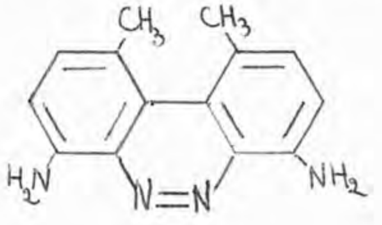
(26)

Their racemisation velocities have been redetermined recently as the mode of operation of the nitro-group in influencing optical stability is at present uncertain (Brooks, Harris and Howlett, J., 1957, 1934). The activation energy for racemisation was found to be 22.6 kcal.mole^{-1} (in 2N Na_2CO_3) in all three compounds, and the marked increase in optical stability on addition of the NO_2 group in the para position is shown to depend on the entropy of activation factors :- (24) $\Delta S^{\ddagger}$; -12.3 e.u.; (A), $10^{10.6}$ sec.$^{-1}$; (25) $\Delta S^{\ddagger}$, -14.7 e.u. ; (A), $10^{10.1}$ sec.$^{-1}$; (26) $\Delta S^{\ddagger}$, -16.3 e.u. ; (A) $10^{9.7}$ sec.$^{-1}$.

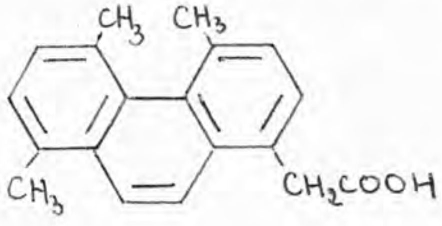
Suitable bridging of the 2,2'-positions of biphenyl produces molecules which retain the basic collinear biphenyl structure but which are twisted and disymmetric so as to accommodate the strainless multiplanar bridge. Such molecules should exist in optically stable enantimorphic forms, whether or not further substituents are present in the 6,6'-positions. The energy barrier to passage through the symmetrical transition state for racemisation will depend on distortion of bond angles, on stretching and bending of bonds and on the non-bonded interaction introduced in this conformation.

(a) Compounds with a 2-atom bridge. In these compounds the nature of the bridge leads to two types of effect.

(i) In compounds like (27) (Theilacker and Baxmann, Naturwiss., 1951, 38, 156) and (28) Newman and Hussey, J.Amer.Chem.Soc., 1947, 69, 976, 3023) the phenanthrene (28) and the benzo(c)cinnoline (27) skeletons are flat as shown by their ultra-violet spectra.



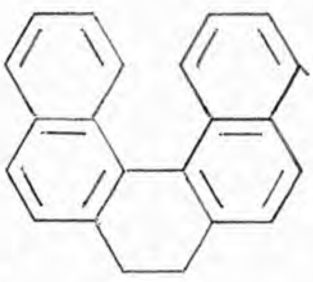
(27)



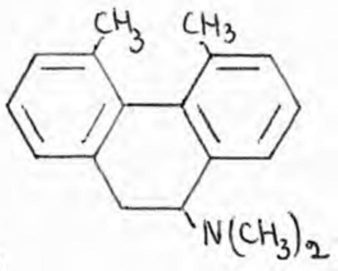
(28)

The optical activity results here from the methyl groups being forced out of the plane of the benzene rings: this has been described as intramolecular overcrowding (Bell and Waring, J., 1949, 2689).

(ii) In compounds like (29) (Hall and Turner, J., 1955, 1242) and (30) (Wittig and Zimmermann, Chem.Ber., 1953, 629), the calculated angle between the benzene rings is 15-16°.

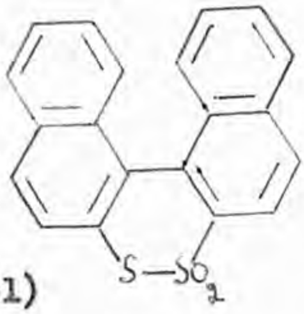


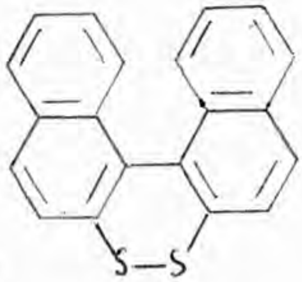
(29)



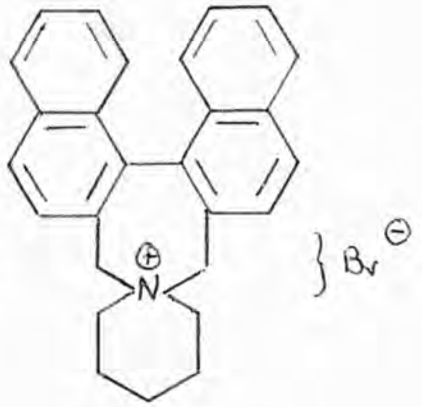
(30)

and in (31) and (32) (Armarego and Turner, J., 1956, 3668) models indicate this angle to be ca. 35° when there are no substituents in the 5,6,5',6' - positions of the biphenyl skeleton. Some distortion from this conformation has still to take place to accommodate the fused benzene rings in the 5,6-5',6'-positions or the methyl groups in the 6,6'-positions. The necessary distortion is larger in case of (29) and (30) than in compounds (31) and (32).

(31) 

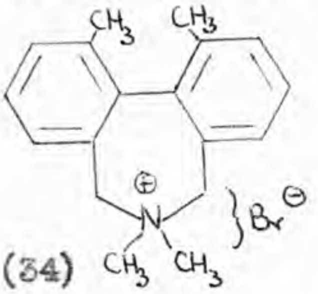
(32) 

(b) Compounds with a 3-atom bridge. Increase of the bridge from six to seven atoms leads to a considerable increase in optical stability (Hall and Turner, J., 1955, 1242). For example compound (33) has a half-life time of racemisation of the order of 26 hours at 172° (ethylene glycol) while that for (29) is only 158 minutes at 110.5° (toluene) (Hall, J., 1956, 3674) and 13 minutes at ca. 136° (ethylbenzene). Compound (33) has $[\alpha]^{20}_{5461}$ + 306.5°.

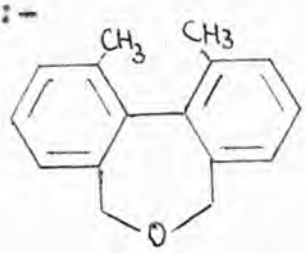
(33) 

The steric effect of substituents is the same, so that increased optical stability must be due to the greater configurational stability of the 7-membered ring compound (greater distortion is necessary in order that the molecule may pass through the planar configuration necessary for optical inversion). Both (29) and (33) are less stable optically than the corresponding unbridged compound (23).

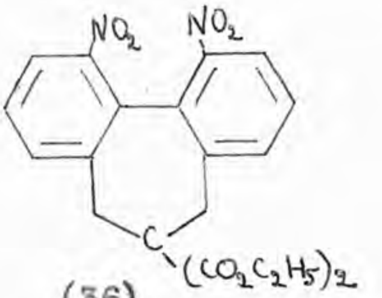
A considerable number of bridged compounds with a 3-atom homo- or heterocyclic bridge containing other substituents in the biphenyl skeleton have been obtained optically active; some are given below:-



(34)

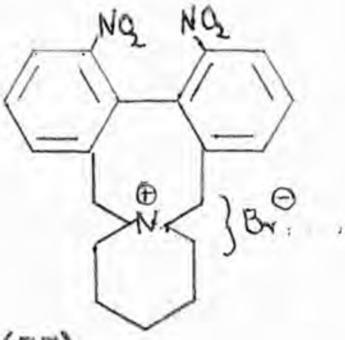


(35)



(36)

(34) and (35), Wittig and Zimmermann, Chem.Ber., 1953, 86, 629 ;
(36) Iffland and Siegel, J.Amer.Chem.Soc., 1958, 80, 1947 ;



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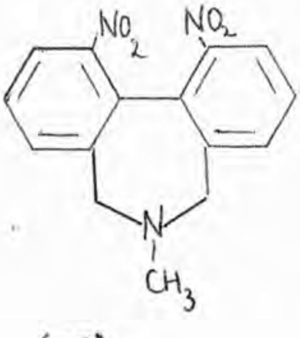
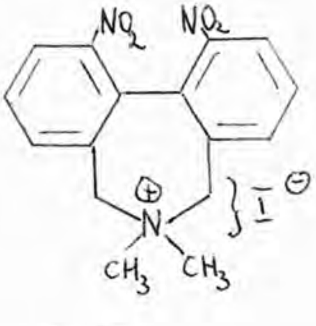
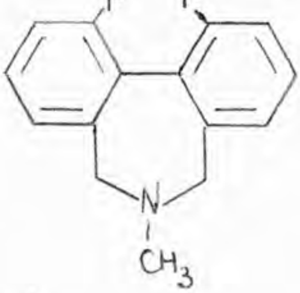


(38)

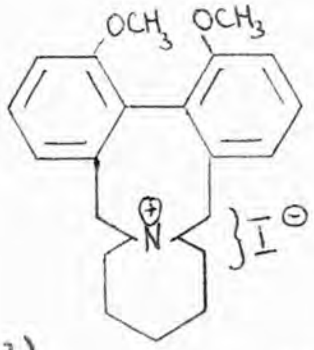


(39)

(37), Fitts, Siegel and Mislow, ibid. 1958, 80, 480 ;
(38) and (39), Ahmed and Hall, J., 1958, 3043.



(40)

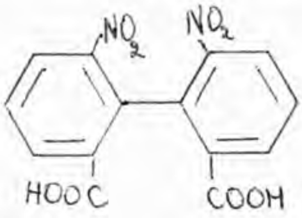


(41)

The dinitro cyclic amine (38) had $[\alpha]^{19}_{5461}$ − 1343° and + 1333° respectively. It was stable in benzene solution up to *ca.* 100° and racemised slowly at 125°, with half-life for racemisation of 16 hours at this temperature. The amine (38) was markedly less stable than (41) (Beaven, Hall, Lesslie, Turner, *J.*, 1952, 854) which was only partly racemised when its cyclohexanol solution was boiled for 8 hours (160°). The difference in stability may be partly accounted for by the difference in the valency of nitrogen in (38) and (41), as (39) with half-life for racemisation of 4.75 hours at 145° (acetone) is twice as stable as (38), but still not as stable as (41).

Compound (38) is also less stable than the corresponding unbridged compound (42) (Kuhn and Albrecht, *Annalen*, 1927, *455* 272). However the unbridged acids (42) do not correspond precisely to the bridged compound (38) ; in (42) resolving carboxylic groups are directly attached to the biphenyl nucleus in the 2,2'-positions while in the bridged compound the 2,2'-

positions are occupied by methylene groups and the amine group which serves as handle for resolution is well removed from the biphenyl rings. Furthermore the unbridged compound may racemise by either of the two paths : 1) like groups pass each other, 2) unlike groups pass each other, while only the first route is possible in the case of the bridged compound.

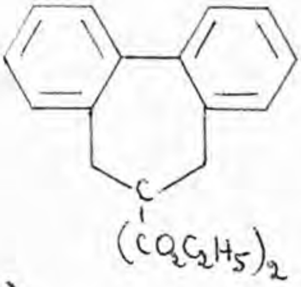


(42)

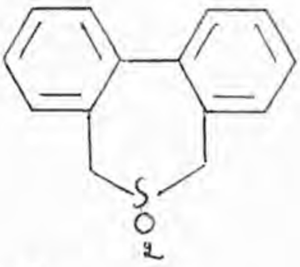
The difluoro amine (40) was obtained optically active, but probably not optically pure, its hydrochloride racemised in aqueous acid at 80° with half-life of 6.5 hours.

Thus in compounds with a 3-atom bridge the order of stability is $OCH_3 > NO_2 > F$. This is in contrast to the observations on unbridged systems where the order is $NO_2 > OCH_3 > F$. (Adams and Yuan, <u>Chem. Rev.</u>, 1933, <u>12</u>, 261).

Only two compounds with a 3-atom bridge and without ortho-substituents have been obtained optically active :



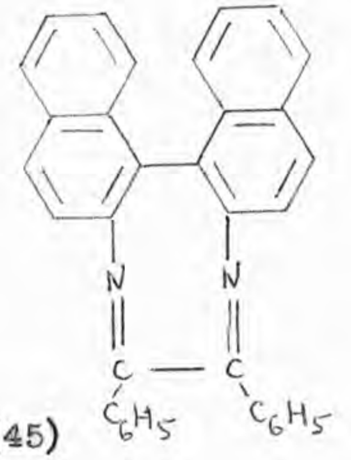
(43)



(44)

(43), Iffland and Siegel, *J.Amer.Chem.Soc.*, 1958, *80*, 1947. (44), Truce and Emrick, *ibid*, 1956, *78*, 6130. These compounds are of low optical stability and have low optical rotations. In (43) it was found that activity is lost in about 5 hours at 31.5°. Compound (43) had $[\alpha]_D^{32.5}$ + 2.25° and (44), with a heterocyclic bridge, had $[\alpha]_D^{25}$ + 3.1°.

(c) *Compounds with a 4-atom bridge.* Only a few compounds with an 8-membered bridging ring have been obtained optically active. In (45) (Kuhn and Goldfinger, *Annalen*, 1929, *470*, 183) and (46) (Bell, *J.*, 1952, 1527), the double bonds in the unsaturated bridging ring make the whole molecule rigid, and the compounds are optically very stable. Recently, Dvorken, Smyth and Mislow, (*J.Amer.Chem.Soc.*, 1958, *80*, 486) obtained the two acids (47) in optically active forms and found that both compounds were optically highly labile, the cis-acid racemising and the trans-acid mutarotating with half-lives of 85 min. and 12 min. respectively (ethanol at 31.5°). They are thus of the same order of optical stability as the 7-membered ring homocyclic compound (42).



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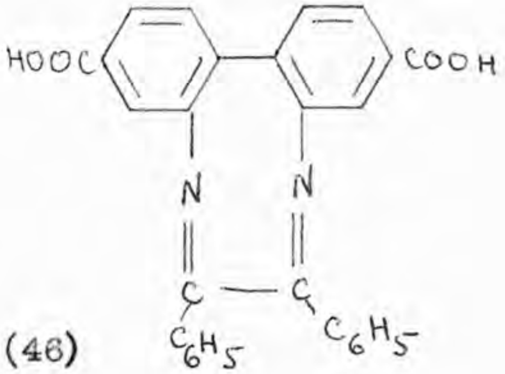
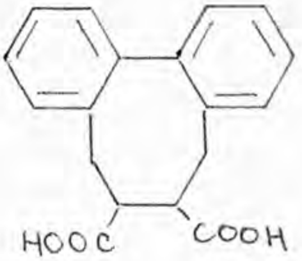


(46)

The dibenzazocine picrate (48) (Ahmed and Hall, J., 1959 3383) was found to be much less optically stable than Mislow's acids. The replacement of the carbon atom by the smaller nitrogen may be partly responsible for the lower optical stability of (48). The picrate racemised in acetone at 2° with half-live of 24.5 min. and at 23° with half-life 1.4 min. It had an activation energy, E, of 22.1 kcal.mole^{-1} and the frequency factor (A) was $10^{14.2}$ sec.$^{-1}$, (positive entropy factor). Mislow's cis-acid in 2.32 N sodium hydroxide had E 25.4 kcal.mole^{-1} and (A) $10^{14.6}$ sec.$^{-1}$, (positive entropy factor), but in ethanol E was 22.8 kcal.mole^{-1} and (A) $10^{12.5}$sec.$^{-1}$(negative entropy factor).



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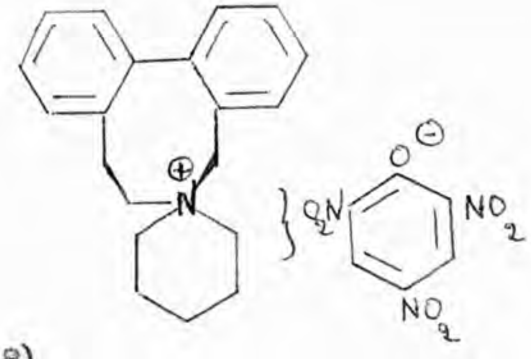
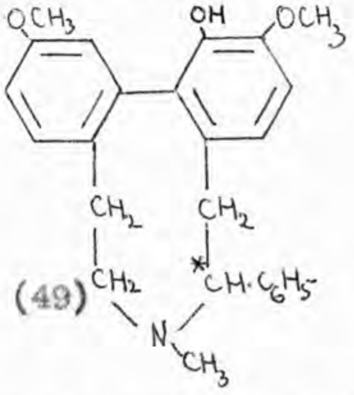


(48)

(d) Compounds with a 5-atom bridge. 2,2'-Bridged biphenyls with a nine-membered bridging ring are rather difficult to synthesize. Compound (49) (Robinson, Proc.Roy.Soc.A.1947, 192, 14) was obtained optically active, starting from the natural product thebaine and degraded by exhaustive methylation into optically active (50), in which the asymmetric carbon atom has been removed.

Quite recently Mislow, Hyden and Shaefer (J.Amer.Chem.Soc., 1962, 84, 1449) obtained a bridged biphenyl with a 9-membered homocyclic bridging ring (51) which was optically active. The (-)acid ($[\alpha]_D$ -48.4° in benzene) was obtained by second-order asymmetric transformation during crystallization of its quinidine salt from acetone and subsequent decomposition of the latter.



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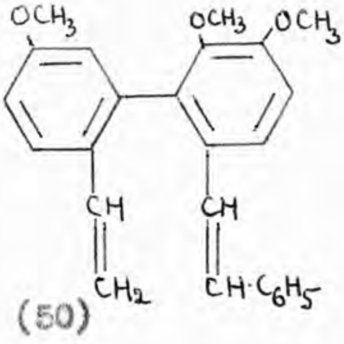
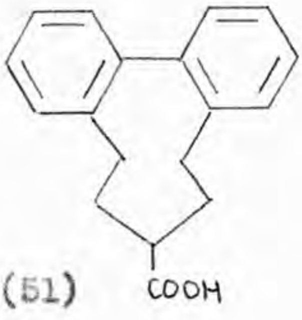


(50)



(51)

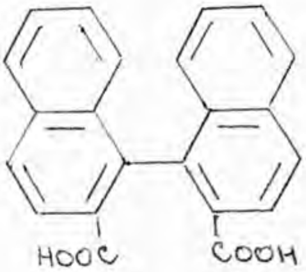
It was optically stable at room temperature ($t_{0.5}^{25°}$ ca. 24hrs.) and racemised in boiling benzene ($t_{0.5}^{80°}$ ca. 2 min.) in less than one hour. Its energy of activation was found to be 24.0 kcal.mole^{-1} and (A) $10^{12.5}$ sec.$^{-1}$. The acid is more stable optically than the corresponding 8-ring compound (47).

If the assumption is made that the activation energy for racemisation, E, is roughly independent of the solvent and of the substituents on the bridge, then it appears that E remains approximately constant in the homologous series of bridged biphenyls (43,47,51) with 7,8, and 9-atom bridging rings. (Calculated E for (43) lies between 20.8 and 26.2 kcal.mole^{-1}, the value of (A) being assumed to be between 10^{11} and 10^{15}). As the bridge length increases, the angle of twist between the two benzene rings increases to accommodate the strainless bridge. Mislow et _al._ , (_loc.cit._), suggest that the angle strain in the transition state can be relieved by buckling of the bridge, and is associated with an increase in non-bonded interaction of opposed α -hydrogens, the two factors roughly compensating each other, the energy-barrier consequently remaining roughly constant. In the 9-ring compound the barrier arises largely from interaction of the non-bonded hydrogens orientated in direct opposition.

(e) Not much work has been done on _higher ring homologues_ but it seems that after a certain stage the size of the ring would give enough freedom of movement to enable the biphenyl rings to become coplanar (in a _trans_ position) and thus they would again be optically unstable.

The present work had in view farther study of configurational effects in some 1,2:3,4-dibenzocyclic compounds with a seven-membered bridging ring. In only a few known cases can a reasonably valid comparison be made between unbridged biphenyls and those with a seven-membered bridging ring and in these cases the bridged compounds are optically <u>less</u> stable, presumably because the molecules are here held in a position which is already part of the way towards the transition state for racemisation.

Thus (23) is more stable than (33) ; (52) more than (53) and (54) more than (38).



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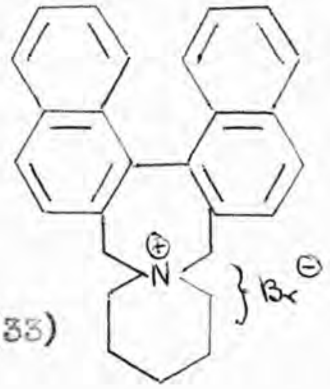

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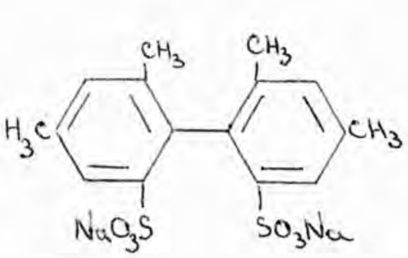

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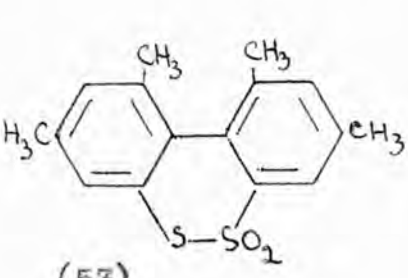

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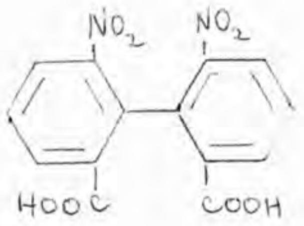

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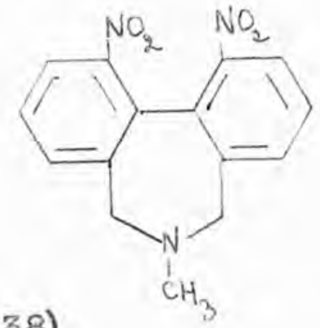
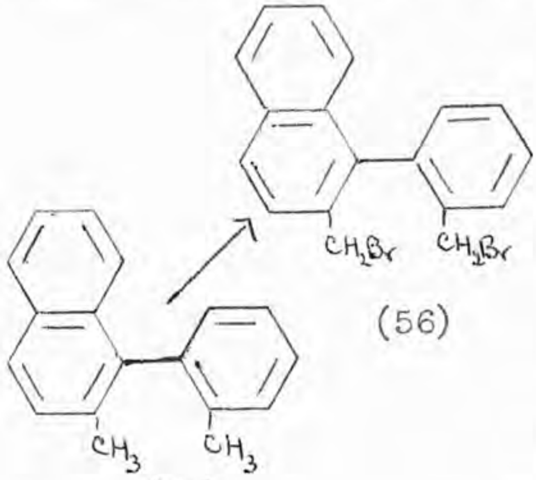


(38)

2-Methyl-1-*o*-tolynaphthalene (55) was chosen as a suitable parent biphenyl in order to prepare salts (57) and (58) from the corresponding dibromo compound (56) obtained on side-chain bromination of the hydrocarbon. In these quaternary



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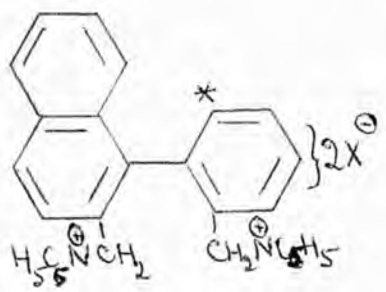
(55)



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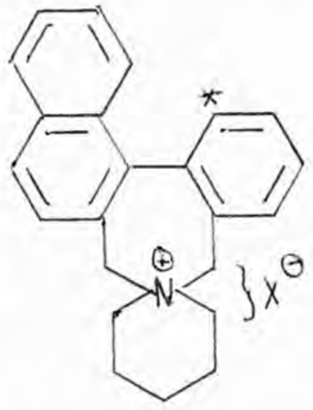
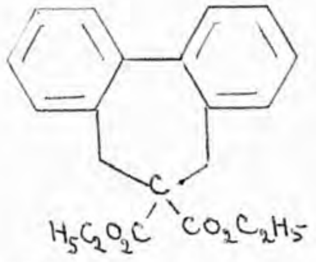


(58)

compounds the blocking groups are chemically very similar, and the resolving groups are not directly attached to the biphenyl nucleus, so that the effects of electronic interactions between substituents in the 2,2'-positions and the nucleus would be expected to be minimal. Also it seems that both (57) and (58) would racemise in the same way. In (58) the biphenyl skeleton is already at an angle of *ca.*50° and would racemise by the naphthyl part passing Hydrogen*; in (57) the same path seems the easier one on inspection of the model of the molecule.

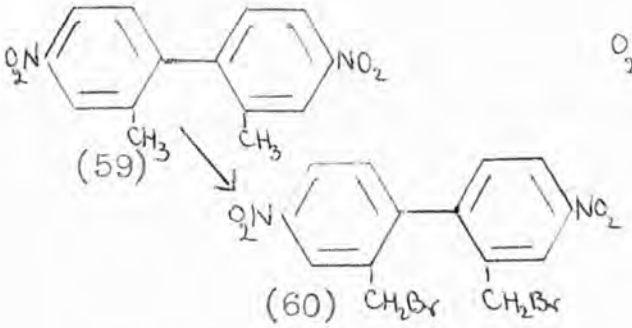
In addition the optical stability of (57) and (58) could be compared with binaphthyl compounds (23) and (33). Recent work on bridged biphenyls suggest that in the absence of other ortho-substituents, compounds with a bridge of three atoms possess low optical stability. Thus the stability of (58) could be compared with that of (43). The fused benzene ring would be expected to increase both the optical stability and the specific rotation of (58) as compared with (43). Compound (43) has $[\alpha]_{D}^{32.5}$ + 2.25 while (33) has $[\alpha]_{5461}^{20}$ + 306.5°.



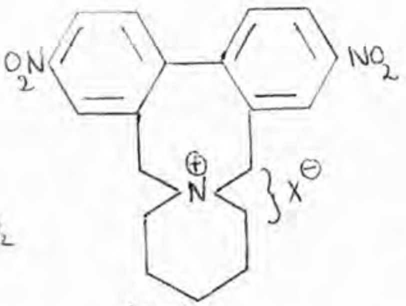
(43)

Side-chain bromination of 2-methyl-1-o-tolylnaphthalene proved to be erratic, and though sufficient of the dibromo-compound was prepared to obtain the dipyridinium salt (57 ; X = Br) and the cyclic compound (58; X=I) as well as the camphorsulphonate of (57), there was not enough to obtain that of (58) chemically pure and to proceed to optical resolution or activation.

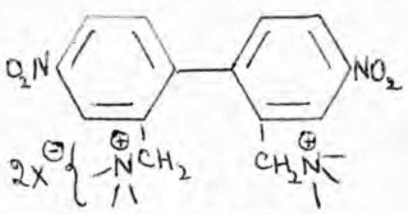
It was thought that another approach to the problem could be made via the quaternary salts derived from 2,2'-dibromo-4,4'-dinitroditolyl (60) obtained by side-chain bromination of (59)



(59) (60)



(61)

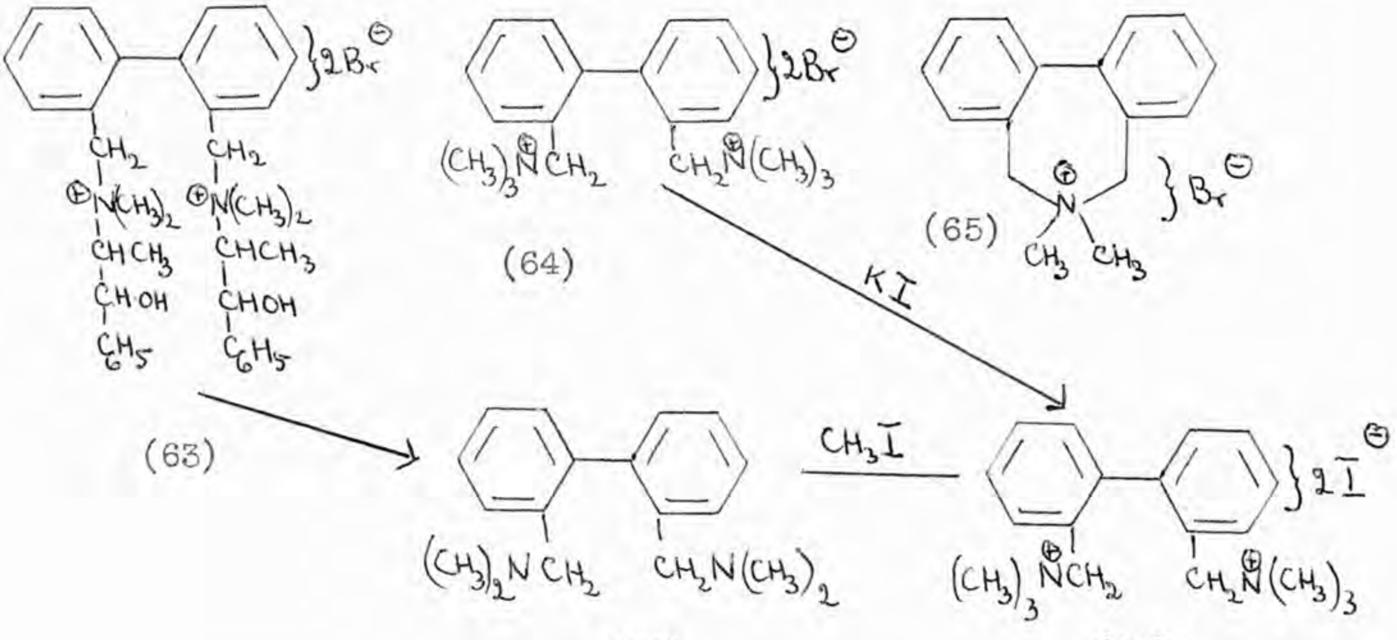


(62)

Again the blocking groups are similar and the resolving groups are not directly attached to the nucleus. However, (61) and (62) would not be expected to racemise by the same path, the open-bridge compound racemising by the <u>o</u>-substituents passing 6- and 6'-hydrogens respectively. The nitro-groups in the 4,4'-position were introduced to obtain higher specific rotations as their bathochromic effect on the electronic absorption bands might be expected to increase the optical rotary power in the visible region. Also a certain amount is already known about their effect on the increase of optical stability of <u>unbridged</u> biphenyls. (Brooks, Harris and Howlett, <u>J</u>, 1957, 1934). Compound (59) has been synthesized but on side-chain bromination it gave a mixture of mono- and di-bromides and their separation by fractional crystallization led to extremely small yields.

The difficulties encountered in the bromination of the ditolyl derivatives (55) and (59), and the subsequent difficulty in obtaining quaternary salts by condensation of the impure product with tertiary and secondary amines, led to an attempt to prepare such salts from 2,2'-dibromoditolyl itself, which can be obtained in excellent yield by the action of hot hydrobromic acid on the corresponding diol (Hall, Lesslie and Turner, J., 1950 711) . The 2,2'-dibromoditolyl was condensed with (-) N-methylephedrine to give (63). It was hoped that the *ortho*-substituents would be large enough to produce unstable optical activity at low temperatures; this was not, however, detected.

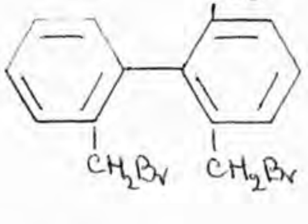
The ditolyl was also condensed with trimethylamine to give (64) and with dimethylamine to give (65). A Hofmann degradation of (63), followed by condensation of the resulting diamine (66) with methyl iodide, would be expected to lead to a compound identical with (67).



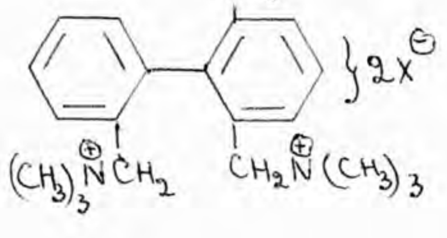
(63) (64) (65) (66) (67)

Accordingly (63) was converted into the hydroxide and degraded. Very little of the expected amine (66) was obtained. Ring closure and Stevens-type rearrangement led to the isolation of salts of (65) and derivatives of 9,10-dihydrophenanthrene. In view of the products isolated in the degradation of the bis-ephedrinium compound (63), the action of heat on the hydroxides of (64) and (65) was also studied.

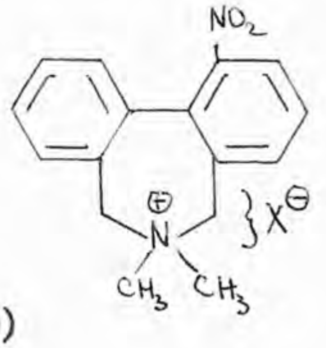
Another approach to the configurational studies of bridged and unbridged biphenyls was made via compound (68). Its condensation with trimethylamine would give the unbridged compound (69) while that with dimethylamine should give compound (70). The blocking groups are again similar and the resolving groups not directly attached to the nucleus. Again it is probable that (69) would find it easier to racemise by the 6-nitro group passing the quaternary 2'-group. The optical stability of (70) could be compared with Ahmed and Hall's (J.,1958,3043) dinitro-compounds (38) and (39) and with the unsubstituted diester (43).



(68)



(69)



(70)

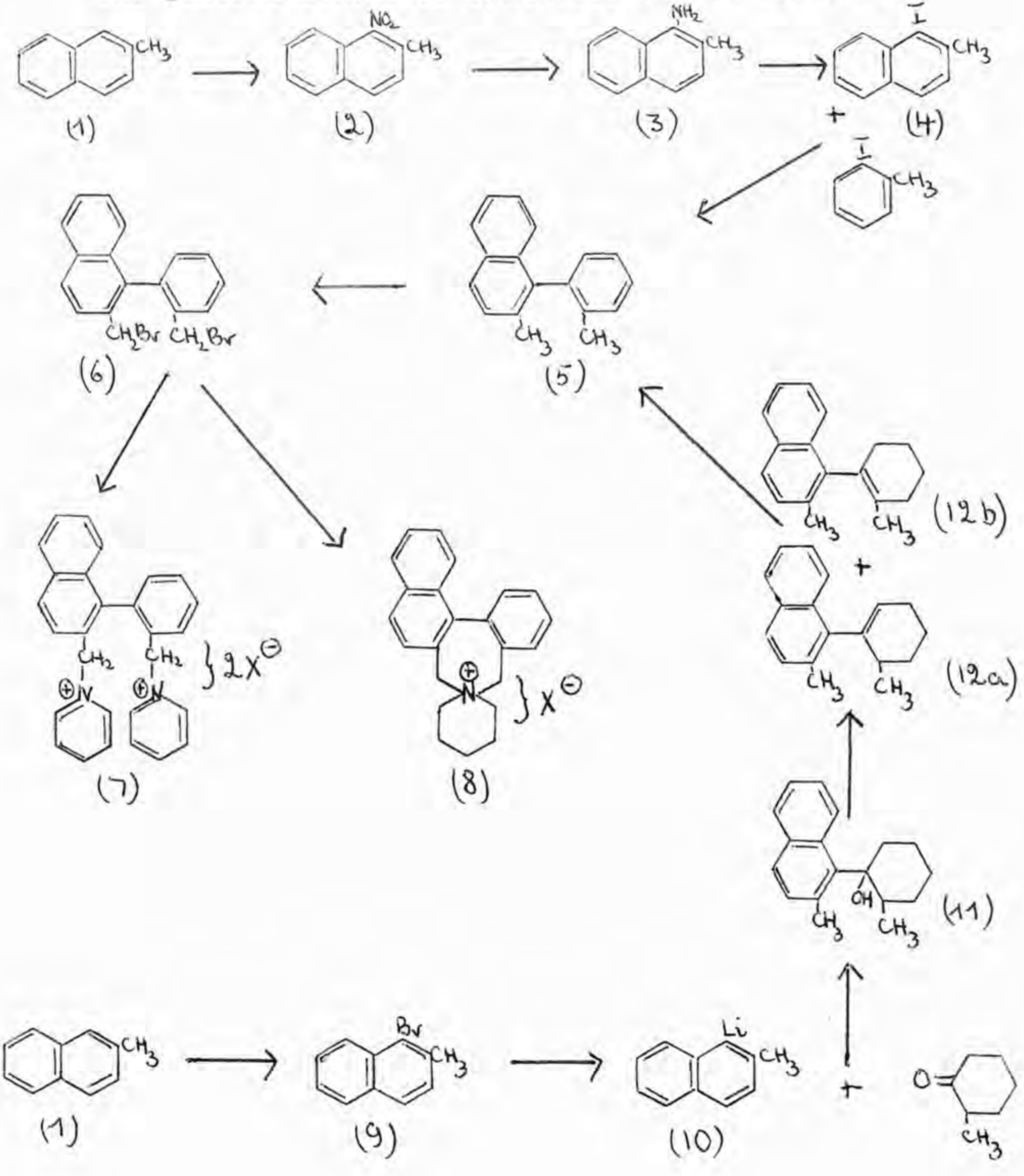
The (-)picrate of compound (70) was obtained optically active by second-order asymmetric transformation of the corresponding (+) α-bromocamphor-π-sulphonate and subsequent decomposition of the salt with alcoholic picric acid at <u>ca</u>.-10°. Its racemisation in acetone was studied and the values of activation energy (E) and of the Arrhenius parameter (A) were determined.

The condensation of 2,2'-bisbromomethyl-6-nitrobiphenyl with trimethylamine gave a mixture of mono- and di-quaternary salts. The solvated di-quaternary dibromide (69; X=Br) was purified via the dipicrate and the dicamphorsulphonate of (69) was eventually isolated. Work on resolution or activation of (69) is at present in progress.

DISCUSSION

(a) Quaternary Salts formed from 2-Bromomethyl-1-(o-bromomethylphenyl)-naphthalene.

The general scheme of synthesis was as follows:



2-Methyl-1-nitronaphthalene (2) was prepared by the method of Fiertz-David and Manhart (Helv.Chim.Acta, 1937,20,1024). The yields (37-43%) were much lower than those reported by the authors (60%) although their conditions were strictly followed.

Reduction of the nitro compound to the amine (3) presented some difficulty at first. The method of Roger and Adams (J.Amer.Chem.Soc.,1942,64,1475), in which hydrogen under pressure and in presence of Raney nickel catalyst is used proved unsuccessful and the unchanged nitro compound was recovered. The wet iron method, using a few c.c. of glacial acetic acid, was successful but yields (30%) were small (Wertheim,Org.Synth.,1943, 2,471, edited Blatt). Lesser and Aczél's method (Annalen,1913, 402,30), in which reduction is carried out by coarse iron filings in 50% acetic acid, proved most successful. By using quantities given by the authors an 88% yield was obtained, the authors quoting 60-70%. It was found that doubling the scale of the reduction reduced the yield to 73%, while a fourfold increase in scale reduced it still further to 66%.

The amine was diazotised in sulphuric acid at about 5° and converted into the iodo compound (4) by reaction with potassium iodide solution. Yields of 50-66% were obtained. Most of the 1-iodo-2-methylnaphthalene was prepared in this way.

A new method of direct iodination of hydrocarbons with iodine and iodic acid was reported by Wirth, Königstein and Kern, (*Annalen*, 1960,634,84), after most of the 1-iodo-2-methylnaphthalene had been synthesized. These authors used it on naphthalene and it was therefore applied to 2-methylnaphthalene and gave a 66% yield. This convenient and direct route to 1-iodo-2-methylnaphthalene gives an almost sixfold increase in yield as compared with the standard diazo route, where yield based on 2-methylnaphthalene was 11.5% (the average overall).

An attempt was made to synthesize 2-methyl-1-o-tolylnaphthalene by heating together a mixture of o-iodotoluene and 1-iodo-2-methylnaphthalene in the presence of copper bronze. o-Iodotoluene itself gives good yields of 2,2'-ditolyl. The behaviour of 1-iodo-2-methylnaphthalene alone under Ullman conditions was first investigated since, if 2,2'-dimethyl-1,1'-binaphthyl would thus be obtained, its performance on a vapour phase chromatographic column could be studied and the distribution of products in the mixed Ullman reaction could then be followed.

Two Ullman reactions on 1-iodo-2-methylnaphthalene were carried out. In the first activated copper bronze (Kleiderer and Adams, *J.Amer.Chem.Soc.*,1933,55,4219) was used at 240-250° and after 2 hours the reactant started to decompose rapidly and on working up just over a third of the 1-iodo-2-methylnaphthalene used was isolated as its decomposition product 2-methylnaphthalene; some unchanged iodo compound was also recovered. The reaction was repeated under milder conditions, using un-activated copper-bronze at 180-190°. No evolution of iodine was observed during the reaction, but no dinaphthyl compound was isolated. It seems conclusive that the dinaphthyl compound is not formed easily under the Ullman conditions and is therefore unlikely to be an important by-product in the mixed Ullman reaction.

The mixed Ullman synthesis of 2-methyl-1-*o*-tolylnaphthalene was first attempted at 160-170° in dimethylformamide as solvent (Kornblum and Kendal, *J.Amer.Chem.Soc.*,1952 *74*, 5782). The product was examined by vapour phase chromatography on Apiezon M on Celite columns. Only peaks corresponding to the reactants and to 2-methylnaphthalene were observed. The synthesis was repeated without solvent and at a higher temperature, the reactants being kept at 190-200° for 6 hr. A 23% yield of pure 2-methyl-1-*o*-tolylnaphthalene was obtained. The unchanged reactants and 2-methylnaphthalene were also isolated. The composition of the product and yields remained the same when the reaction was carried out at 210-225° for 3 hr.

The products of the Ullman reaction were examined using a Griffin V.P.C.-Gas-Liquid Partition Chromatography Apparatus Mark II. It was found that high boiling hydrocarbons and iodo compounds such as 2-methyl-1-*o*-tolylnaphthalene and ✓2-methyl-1-iodonaphthalene, tend to give very broad ill-defined peaks unless highly specific conditions, which have to be found by trial and error, are used.

In general, increase of temperature had a most marked effect on shortening of retention times and steepening of peaks. Decrease in nitrogen flow rate also improved definition of these peaks. These points may be illustrated by the experimental results obtained with 1-iodo-2-methylnaphthalene using a 3 foot column of Apiezon M on celite 545 with nitrogen as carrier gas:

Temp.	183°	197°	203°
Flow-Rate L/hr	1.9	1.7	1.9
Ret.Time in cms.	32.4	20.3	16.9
Height of peaks cms.	3.5	5.8	6.6
Width of peaks at base cms.	7.6	5.3	5.2

Similar results were obtained with 2-methyl-1-*o*-tolylnaphthalene and further improvement was achieved by using a longer column and by changing the stationary phase to 30% silicone on celite 545:

	Apiezon 3'		Silicone 6'
Temp.	182°	198°	228°
Flow-Rate L/hr.	3.3	2.0	1.6
Ret.Time cms.	52.5	20.85	16.3
Height of peak cms.	0.9	1.9	4.85
Width of peak at base cms.	14.0	11.0	1.6

In all cases two drops of the freshly distilled substance were injected onto the colum using the same syringe -

the results can therefore be said to be comparable in a general though not in an absolute way.

Since yields in the Ullmann reaction on a mixture of 1-iodo-2-methylnaphthalene and *o*-iodotoluene were poor, an alternative route to 2-methyl-1-*o*-tolylnaphthalene, by the reaction between 1-lithio-2-methylnaphthalene and 2-methylcyclohexanone followed by dehydration and dehydrogenation was used. This was essentially the method used by Bergman and Pelchowicz (*J.Org.Chem.*,1954,*19*,1383) but the authors synthesized 2-methyl-1-*o*-tolylnaphthalene from o-tolyllithium and 2-methyl-1-tetralone whereas in the present work 1-lithium-2-methylnaphthalene and 2-methylcyclohexanone were used.

1-Bromo-2-methylnaphthalene was prepared by the method of Hall and Mitchell (*J.*,1951,1375 ; modification of Adams and Binder, *J.Amer.Chem.Soc.*,1941,*63*,2773). The 1-lithio compound was obtained from the bromo compound by adding the latter to finely divided lithium placed in dry ether and kept under nitrogen. Addition of 2-methylcyclohexanone to the lithio compound yielded the carbinol (11).

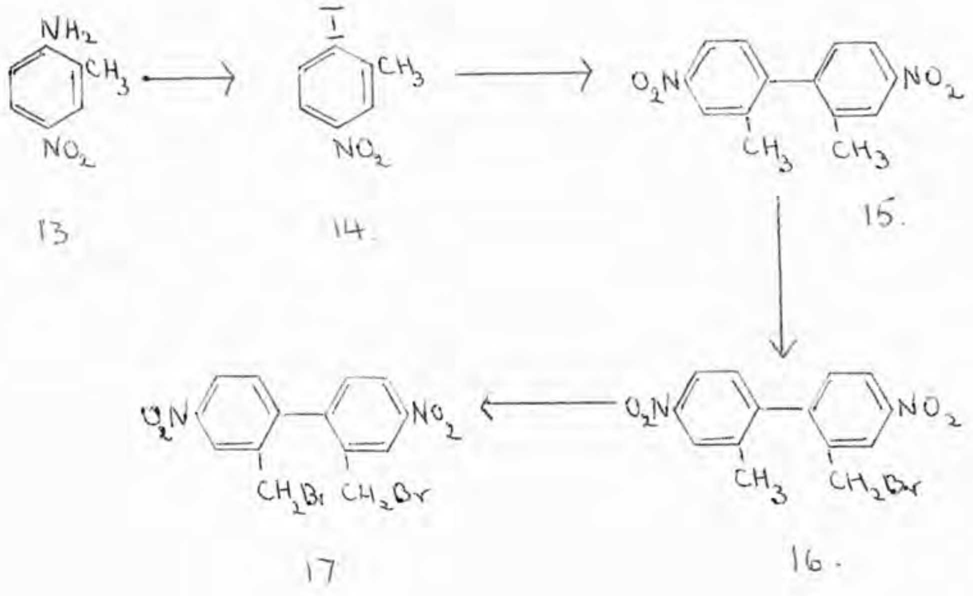
Dehydration of the carbinol was carried out with naphthalene-β-sulphonic acid. Just over half of the 2-methylcyclohexanone used was recovered at this stage, together with 2-methylnaphthalene in amounts corresponding to a third of the 1-bromo-2-methylnaphthalene used. The highest boiling fraction consisted mainly of a mixture of the two isomeric olefins (12a and 12b). The purity of this fraction was controlled by V.P.C. the product being redistilled till pure. Columns 6 foot long of 30% silicone E 301 on celite were found most satisfactory for these compounds, they gave reasonable retention times and one well defined peak for the two olefins. Yields calculated on the basis of the ketone actually used varied from 48% to 81% with an average over six preparations of 62%. The wide fluctuation in yields was due to the difficulty of purification by repeated distillation under reduced pressure.

The olefins were dehydrogenated with 5% palladium-charcoal, the process being repeated till the product gave a single peak on a silicone on celite column. In an attempt to complete the reaction in one step, sulphur was used as dehydrogenating agent together with palladium-charcoal (Johnson,J.,1957, 4155). Owing to the difficulty of removing sulphur from the product, (by prolonged treatment with sodium), which resulted in considerable lowering of yield, this method was not used in further dehydrogenations. In general two dehydrogenations with palladium-charcoal followed by distillation under reduced pressure gave very pure 2-methyl-1-o-tolylnaphthalene in 46-47% yields (calculated on the basis of olefins used).

The bromination of 2-methyl-1-o-tolylnaphthalene was carried out with N-bromosuccinimide in the presence of benzoyl peroxide, a method used by Werner (J.Org.Chem.,1952, 17, 523) for ditolyls. The product was a dark brown oil which was used as such for condensation with bases to obtain quaternary salts. Since the results were in general very poor, the brominating agent was checked on 1-bromo-2-methylnaphthalene (Newman and Kosak, J.Org.Chem., 1949,14,375). N-Bromo-succinimide was used (i) crude from the bottle, (ii) recrystallised from glacial acetic acid and dried in a vacuum desiccator over potassium hydroxide (Organic Syntheses,1953,33,97), (iii) recrystallised from water and dried in air (Ucciani and Naudet, Bull.Soc.chim. France,1960,1153). The results were almost identical and the yields of 1-bromo-2-bromo-methylnaphthalene were good (67-70%).

The crude 2-bromomethyl-1-(o-bromomethylphenyl)-naphthalene was condensed with the extremely active base piperidine to give the bridged compound (8;X = Br) in only 14% yield. Condensation with pyridine in dry benzene gave the dipyridyl salt (7 ; X = Br) as a monohydrate in a 20% yield. However, subsequent attempts to prepare more of the same salt failed. The (+)-camphorsulphonate prepared from the dibromide failed to crystallise during 2½ years. Condensation with other tertiary bases was tried. Iso-quinoline gave a mixture of the di- and mono- quaternary salts. In experiments with N-methyl-ephedrine and trimethylamine only base hydrobromides were isolated, while triethylamine and dimethylaniline yielded gums which could not be crystalised. Other solvents besides benzene were tried- nitro-benzene, 96% ethanol, ethanol and acetone were used but with no success.

(b) Synthesis of 2,2'-Bisbromomethyl-4,4'-dinitro-biphenyl:



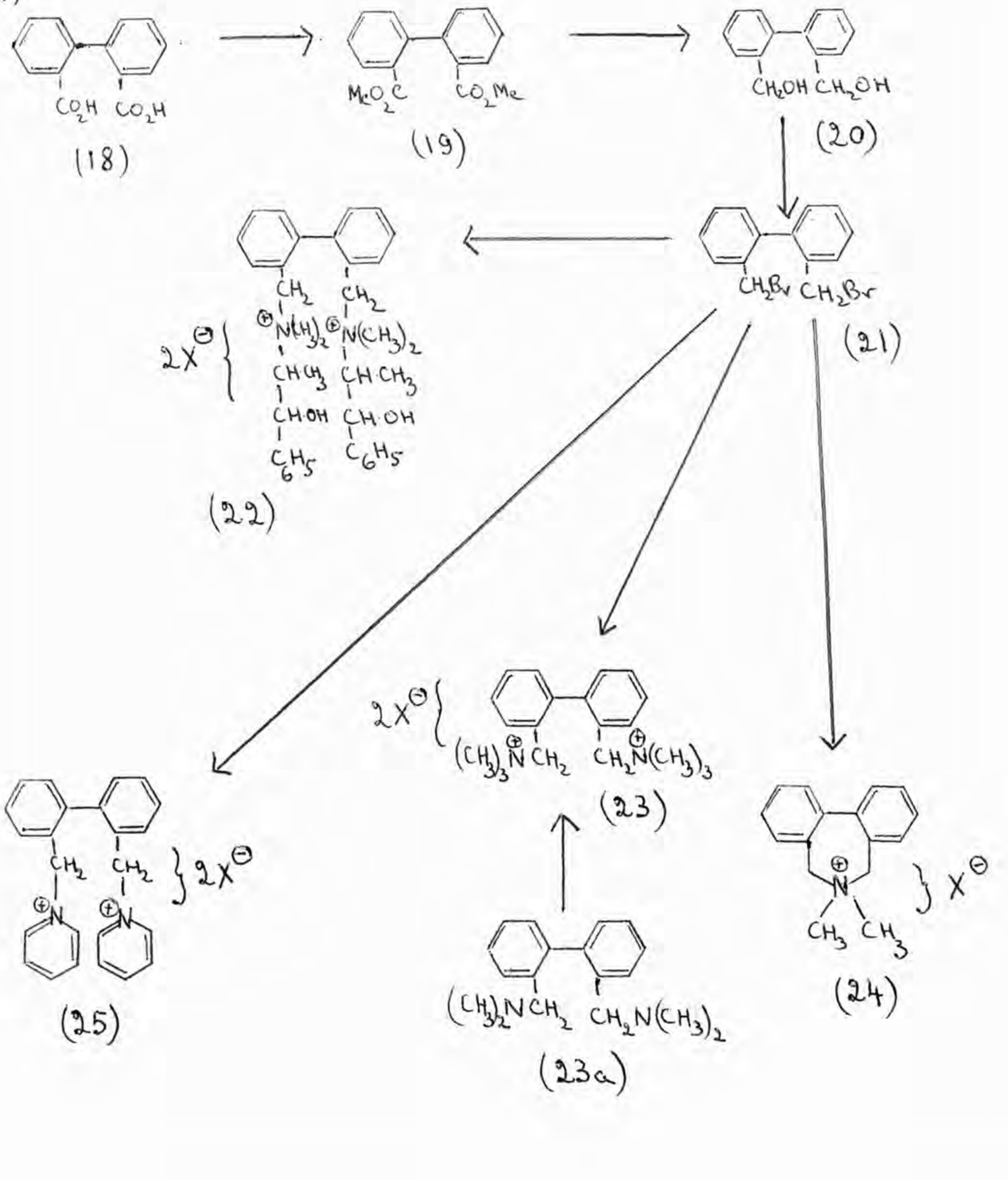
An attempt was made to prepare the 2,2'-dimethyl-4,4'-dinitrobiphenyl from 2-amino-5-nitrotoluene in one step by diazo coupling - a method used by Ullmann and Frentzel (Chem. *Ber.*, 1905, *38* 729.) By diazotising at 0° in concentrated sulphuric acid and adding to the cold solution freshly prepared cuprous chloride in concentrated hydrochloric acid, the authors obtained a 54% yield of the 2,2'-dimethyl-4,4'-dinitro compound and 15% of dinitroazo compound. The preparation was carried out twice but the main product in each case was the dinitroazo compound.

The dinitro compound (15) was prepared via the corresponding iodo compound from 2-amino-5-nitrotoluene by the method of Carlin and Foltz (*J.Amer.Chem.Soc.*, 1956,*78*,1997). The diazotisation of the amine and conversion into the iodo compound presented no problems. The reaction of 2-iodo-5-nitrotoluene with copper bronze was carried out not at 280° and without solvent as described by Carlin and Foltz but in dimethylformamide at *ca.* 160°. It was found that at 280° a good deal of charring with considerable formation of tar occurred. The resulting yields were low. By carrying out the reaction in solvent and at lower temperature the dinitro compound was obtained by simple extraction with solvent and crystallisation in 54% yield. The authors (*loc.cit*) had to resort to a complicated process of purification by solutions, precipitations, evaporations and sublimation, and obtained yields of 49%. Lungi, Mascarelli, Longo and Ravera (*Gazz.chim.ital.*, 1937,*67*,33) give 144° as the temperature which gives the optimum yield in an analogous reaction for the 6,6'-dinitro compound.

The bromination of 2,2'-dimethyl-4,4'-dinitro-biphenyl was carried out with N-bromosuccinimide in the presence of benzoyl peroxide and in carbon tetrachloride as solvent. After heating under reflux for 30 hours a bromo compound, m.p.156-158° which proved to be mostly the monobromo derivative (16) was isolated in 64% yield. It was re-treated with N-bromosuccinimide for a further 14 hours and gave a solid, m.p. 115°, in 64% yield. This proved to be a more highly brominated compound. It contained 35.6% bromine, the dibromo compound (17) requiring 37.2%. The reaction was repeated but the initial heating was continued for 48 hours in an attempt to obtain the dibromo derivative in one operation. This however was not successful. The product was re-treated and though a more fully brominated product was obtained which was repeatedly crystallised to obtain a pure sample of the dibromo compound a satisfactory analysis for the latter was not obtained.

(c) Quaternary Salts formed from 2,2'-Bisbromomethylbiphenyl: (i) Their Synthesis ; (ii) their Hofmann degradation ; (iii) Infrared and Ultraviolet Spectra of the Tertiary Amines Isolated and of some Byproducts.

(i)



2,2'-Bisbromomethylbiphenyl was prepared by the method of Hall, Lesslie and Turner (J., 1950,711), Diphenic acid was esterified and the dimethyl ester was reduced to the diol with lithium aluminium hydride in dry ether. Treatment of the diol with boiling hydrobromic acid gave the 2,2'-bis-bromomethylbiphenyl (21).

Condensation of the 2,2'-bisbromomethylbiphenyl with N-methylephedrine in dry benzene was not successful. Most of the reactants were recovered together with some N-methylephedrine hydrobromide. Other solvents were tried but neither carefully purified dry nitromethane nor 96% ethanol promoted the reaction beyond the stage of some formation of base hydrobromide. However, some quaternarisation occurred in hot, dry acetone but the product was difficult to crystallise and was contaminated with N-methylephedrine hydrobromide. As the quaternary dibromide readily hydrated on standing in the air, it was converted into the di-iodide (22 ; X = I), which crystallised easily and was not solvated.

The time of the quatern~~ary~~isation reaction was shortened and yields were improved when acetone was replaced by nitrobenzene (freshly distilled and dried over calcium chloride), and the temperature of the reaction was raised to 130°. Under these conditions the dibromide separated out after 20 mins. and gave pure di-iodide, after crystallisation, in 75% yield. The di-iodide was examined polarimetrically at 21.5°, 0° and -15° but no mutarotation was observed.

2,2'-Bisbromomethylbiphenyl was condensed with trimethylamine. In order to find the optimum conditions, the reaction was carried out using the same quantities of reactants (1 mol.bromo compound, 2.2 mols.base) and the same temperature and time, but in three different solvents : dry benzene, dry acetone and 96% ethanol. The yields were respectively 64%, 89% and 72%. Acetone was therefore used in further preparations. The dibromide was obtained as the monohydrate. Its ultraviolet spectrum was determined in methanol and found to be that of a highly sterically hindered biphenyl compound and very similar to that of 2,2'-ditolyl (in 96% ethanol), (Beaven, Hall, Lesslie and Turner, J., 1954, 131).

Some of the dibromide was converted into the di-iodide, which also crystallised as the monohydrate. The dipicrate (unsolvated) was prepared by treatment with picric acid in ethanol. The (+)-camphorsulphonate of 2,2'-bis(trimethylammoniomethyl)biphenyl was prepared. It crystallised with difficulty after several weeks. It was examined polarimetrically, at-24.5°, -14° and + 22° but no evidence of unstable optical activity was obtained. It showed no change of rotation with temperature.

2,2'-Bisbromomethylbiphenyl was also condensed with pyridine in absolute alcohol. An 85% yield of the quaternary salt was obtained. The (+)-camphorsulphonate prepared from it proved deliquescent and difficult to handle. An attempt was therefore made to prepare the (+)-bromocamphor-π-sulphonate in the hope that it would be less deliquescent and that it would be easier to investigate its optical properties.

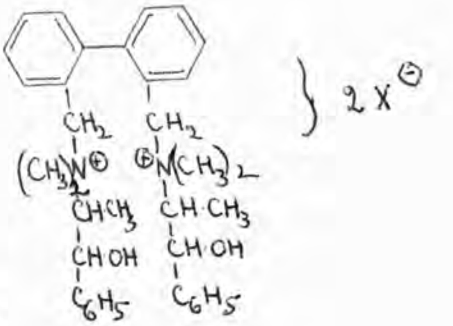
The (+)-bromocamphorsulphonate was however also deliquescent. It was eventually recrystallised with difficulty from dry acetone. It was examined polarimetrically in dimethyl formamide but no unstable optical activity could be detected. It showed a small variation of rotation with temperature:

$$[\alpha]^{-24.5^\circ}_{5461} + 108.6^\circ; \; [\alpha]^{-14.6^\circ}_{5461} + 94^\circ; \; [\alpha]^{+14.7^\circ}_{5461} + 89.6^\circ.$$

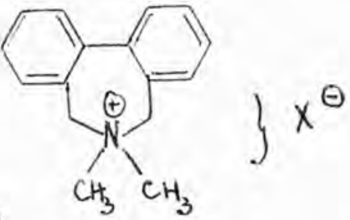
2,2'-Bisbromomethylbiphenyl was condensed with dimethylamine in ether as described by Hori, Abe, Yamakawa and Fujimira, (*Gifu Yakka Daigaku Kiyo* 1958, 8, 65, ~~and Hori~~, *Chem.Abs.*, 1959, 53, 10148). The azepinium bromide obtained had m.p. 285-287°. The authors state only that it melts > 250° ; Wenner (*J.Org.Chem.*,1951,16,1475) gives 276-277°. The bromide was converted into the iodide which had m.p.294-303°(decomp.) varying with the rate of heating. Wenner gives 287-288°. The picrate was made by treating the aqueous solution of the bromide with aqueous sodium picrate. It had m.p.285-286°. (decomp.).

(c) Hofmann Degradation of Hydroxides of

(ii)



(22)



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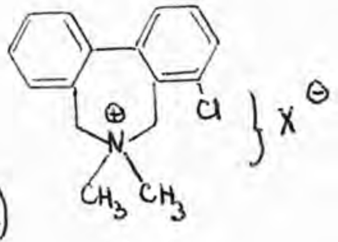
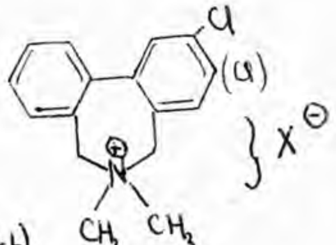
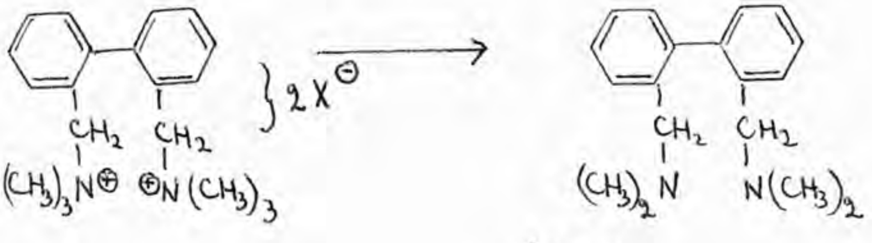


(24a)



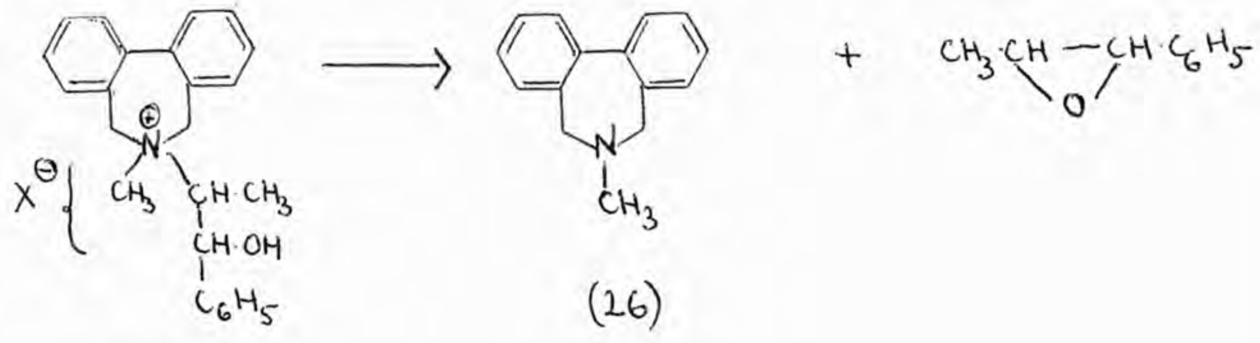
(24b)



(23) (23a)

Normal Hofamnn degradation of the bis-ephedrinium salt (22; X = OH) should give 2,2'-bis (dimethylaminomethyl)biphenyl (23a). The diamine on treatment with methyl iodide would then give a quaternary salt (23 ; X = I) identical with that synthesised directly from 2,2'-bisbromomethylbiphenyl and trimethylamine.

Hofmann elimination reaction of the cyclic compound (25, X = OH) (Beaven, Hall, Leslie and Turner, *J.*,1952, 854) proceeds normally (Hall, in the press) to give the 2,7-dihydro-1-methyl-3,4:5,6-dibenzazepine (26) and (+)-*trans*-1-methyl-2-phenylethylene oxide, the normal non-basic product from such reactions with ephedrinium compounds (Miller, *Arch.Pharm.*1902, *240*,481 ; Rabe, *Chem.* *Ber.*, 1911, *44*, 824; Emde, *Arch.Pharm.*, 1906,*244*, 241 ; Witkop and Foltz, *J.Amer.Chem.Soc.*, 1957,*79*,197).



(25)

(26)

Similar reactions on the cyclic ephedrinium compounds containing _ortho_ nitro or fluoro groups have also given the corresponding N-methylazepines (Ahmed and Hall, _J._, 1958, 3043).

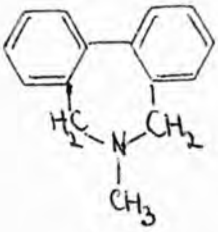
The Hofmann degradation of the unbridged bis-ephedrinium compound (22 ; X = OH) was therefore carried out as for the cyclic ephedrinium compounds (Ahmed, Ph.D. Thesis, 1959).A solution of the iodide in alcohol was boiled under reflux and a suspension of silver oxide in water was added to it during 1 hour. Most of the alcohol and water was distilled off and the residue was extracted with ether. The distillate had a strong characteristic smell of 1-methyl-2-phenylethylene oxide. The residue was only partly soluble in ether and the base obtained proved to be N-methylephedrine. This suggested that the quaternary cation was undergoing attack at the (benzyl) α-carbon as well as or instead of as expected at the hydrogen of the β-hydroxyl group. No 2,2'-bis(dimethylaminomethyl)-biphenyl (23a) was isolated.

In view of the unexpected product, the small yield of the basic material and the presence of some original iodide the experiment was repeated, the heating before distillation was however continued for 1 hour 45 minutes and the filtrate was re-treated with fresh silver oxide till no more silver iodide was seen to be formed. Both the water soluble and ether soluble parts of the residue in the flask after distillation were carefully examined, as well as the distillate. The reaction product was worked up by adding water and ether to the residue, separating and back extracting.

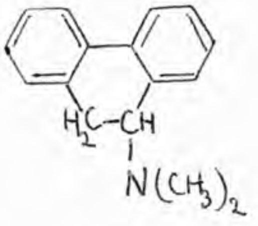
The aqueous layer was evaporated to dryness on a water bath. A solid was obtained which was partly soluble in chloroform. After washing well with chloroform a white solid was filtered off which gave precipitates with calcium chloride and silver nitrate, both soluble in acid, which indicated a carbonate or hydrogen carbonate. Its infrared spectrum had a band at 834 $cm.^{-1}$. Miller and Wilkins (<u>Analyt.Chem.</u>, 1952, <u>24</u>,1253) examined three hydrogen carbonates and they all showed a typical band in the region 832-838 $cm.^{-1}$. The carbonates examined by them had this band displaced to higher frequency at 855-877 $cm.^{-1}$. It thus seemed that the water soluble part of residue was a hydrogen carbonate.

The solid was analysed and showed a nitrogen to oxygen ratio of one to four. On standing in air its melting point went up, there was less softening and a definite loss of weight. This suggested that the solid might be hydrated. It was therefore dried for 11 hrs. at 98° and for 6.5 hrs. at 68° and at 10 cm. pressure. It lost 5% of weight and had a m.p. 206-207°(decomp.). Elementary analysis now showed a nitrogen to oxygen ratio of one to three.

In order to show whether the solid was a salt of a base or a quaternary compound an attempt was made to liberate the free base from the residue. The residue was treated with aqueous potassium hydroxide and the solution extracted with ether, but the removal of the latter gave no residue. An attempt was also made to prepare carbonates or hydrogen carbonates of 1-methyl-2,7-dihydro-3,4:5,6-dibenzazepine (26) and of 9,10-dihydro-9-dimethylaminophenanthrene (27) which might have been possible products of the degradation reaction if ring closure took place during it.



(26)



(27)

Each base was covered with water and a stream of carbon dioxide was passed into it for several hours. The bases were removed unchanged after evaporation to dryness on a water bath.

All the above facts indicated that the residue contained quaternary nitrogen but as the aqueous solution was optically inactive the cation could not be that of the starting material nor of a partially decomposed intermediate either of which would contain the asymmetric centres of ephedrine. The residue was treated in aqueous solution with sodium picrate and gave a picrate m.p. 285-286°. The high melting point indicated a quaternary compound and analysis gave the empirical formula $C_{16}H_{17}N\cdot C_6H_3N_3O_7$.

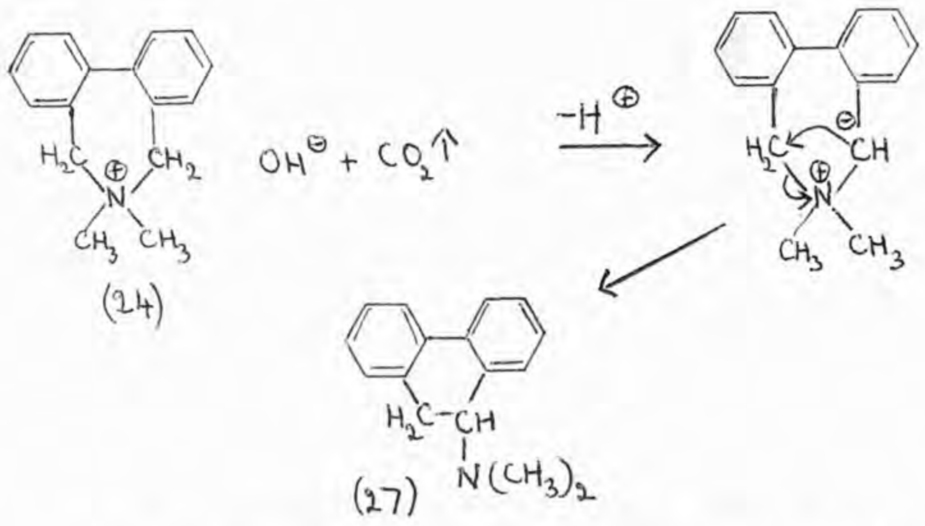
It was thought that examination of ultraviolet absorption spectra of a series of 2,2'-disubstituted biphenyls both unbridged and bridged with a 6 and 7-membered bridge would help to elucidate the structure of the organic cation. The azepinium compounds (24,26) were already available, as well as the unbridged ones (23) and 9,10-dihydro-9-dimethylaminophenanthrene (27) was synthesised for the purpose by the method of Hori <u>et al.</u> (<u>loc.cit.</u>). Its picrate was also prepared.

The ultraviolet spectra are summarised in Table 1. The spectrum of the unknown picrate in 96% ethanol was typically that of a 2,2'-bridged biphenyl with a 7-membered bridging ring (λ_{max} 245 mμ; ε_{max} 22,700) and the hydrogen carbonate in water had a similar spectrum (λ_{max} 248 mμ; ε_{max} 14,000). The corresponding bromide (24,X=Br), synthesised directly had λ_{max} at 249 mμ and ε_{max} 14,200. The displacement of the band in the picrate and the high intensity must be due to the superimposition of picrate ion absorption on that of the biphenyl system. Picric acid has ε 10 000 at 245 mμ in 95% ethanol (Friedel and Orchin, "Ultraviolet Spectra of Aromatic Compounds", Wiley, New York, 1951, No.93) and the picrate ion is probably similar.

2,7-Dihydro-1,1-dimethyl-3,4:5,6-dibenzazepinium bromide (24 ; X = Br) synthesised already, was converted into the picrate which proved by m.p. and mixed m.p. to be identical with the picrate obtained from the water soluble part of the residue.

The residue was thus identified as 2,7-dihydro-1,1-dimethyl-3,4:5,6-dibenzazepinium hydrogen carbonate (24;X $=HCO_3$) and this was confirmed by the elementary analysis of the dried solid.

The hydrogen carbonate melted at 206-207° with vigorous decomposition to a yellow liquid. A sample of it was placed in a tube fitted with a condenser and heated at 210-212° for 45 minutes. The residue had an infra-red spectrum of 9,10-dihydro-9-dimethylaminophenanthrene. It gave a picrate identical with that of this base. The experiment was repeated but heating was continued for 3 hr~~s~~. and the alkaline fumes (pH8) evolved during decomposition were dissolved in ethanol. Again the above base was obtained. The ethanol was added to saturated alcoholic picric acid but no picrate was obtained. It seems that at 210-212° the hydroxyl ions from decomposition of hydrogen carbonate are a sufficiently strong base to bring about a Stevens rearrangement on the azepinium cation.



The chloroform-soluble part of the residue also appeared to be quaternary. Its aqueous solution treated with potassium iodide or sodium picrate gave 2,7-dihydro-1,1 -dimethyl-3,4: 5,6-dibenzazepinium iodide or picrate respectively. The infrared spectrum showed a hydroxyl band and the compound gave a precipitate of mixed silver oxide and carbonate with silver nitrate. It seems likely that this part of the residue contained undecomposed quaternary azepinium hydroxide which had failed to absorb carbon dioxide during the working up.

The distillate obtained during the Hofmann degradation ot the compound (22 ; X = OH) was redistilled using a Vigreux column and fractions of 20 to 50 c.c. were collected and examined polarimetrically. Those with positive rotation contained (+)-<u>trans</u>-1methyl-2-phenylethylene oxide and the concentration of the oxide (0.217g.) was worked out using Rabe's figure (Chem. Ber.,1911,44,826) for the sepcific rotation of the oxide. This represents about 9% yield as compared with that (2.25g.) expected from a total normal Hofmann degradation.

The higher fractions had a negative rotation owing to the presence of N-methylephedrine which is moderately steam volatile.

The basic fraction obtained from the ether was identified as N-methylephedrine by m.p. and mixed m.p., by elementary analysis and by infrared spectroscopy. Its methiodide was identical with that prepared from the pure base. The basic product had $[\alpha]^{218}_{5461}$ -32.3° (c 2.9955) which agreed fairly well with Nagaio and Kanao's (Annalen, 1929, 470, 157) figure $[\alpha]_{D}$ -29.2° (c 3.32505) (both in methanol).

Isolation of N-methylephedrine from the basic products suggested that the quaternary cation was undergoing attack at the (benzyl) α -carbon atom as well as at the hydrogen of the β - hydroxyl group. A bimolecular displacement reaction (Hanhart and Ingold, J., 1927, 997 ; Ingold et al., J., 1933,68; J.,1933,69 ; J., 1933, 526) at the α -carbon atom is the process most commonly competing with bimolecular Hofmann elimination (Cope and Turnbull, Ed.Cope, "Organic Reactions", Wiley, New York, 1960, vol XI, p.317) and it has been shown (Hanhart and Ingold, J., 1927,997) that the use of anions less basic than OH^{-} favours the displacement reaction at the expense of the elimination reaction. Thus the exclusion of carbon dioxide (and hence of $CO_3^{=}$) is likely to reduce the amount of the displacement reaction byproduct (Hanhart and Ingold loc.cit ; von Braun, Tenffert, Weissbach, Annalen, 1929,472,121).

The degradation was therefore repeated (Experiment III) in an atmosphere of nitrogen, with the exclusion as far as possible of carbon dioxide throughout the decomposition. At the same time the solvent was changed from aqueous ethanol to water to avoid the further complication of attack by alkoxide ions. As the iodide was only sparingly soluble in water it was first converted into the chloride in aqueous methanol and the methanol was then removed by distillation. Under these condition 2,2'-bis(dimethylaminomethyl)biphenyl (23a) was isolated as its picrate together with 9,10-dihydro-9-dimethylaminophenanthrene (27) (also as the picrate) which formed the main product. The basic fractions contained still some N-methylephedrine.

Separation of the bases was achieved through picrates since N-methylephedrine does not give a precipitate of the picrate in ethanol. This does however crystallise eventually on prolonged standing from very concentrated solutions (Smith, J., 1927, 2056). The picrate of the phenanthrene base was identified by preparing an authenic sample of the base (Hori et.al., loc.cit.) by the action of phenyl-lithium in ether on 2,7-dihydro-1,1-dimethyl-3,4:5,6-dibenzazepinium bromide

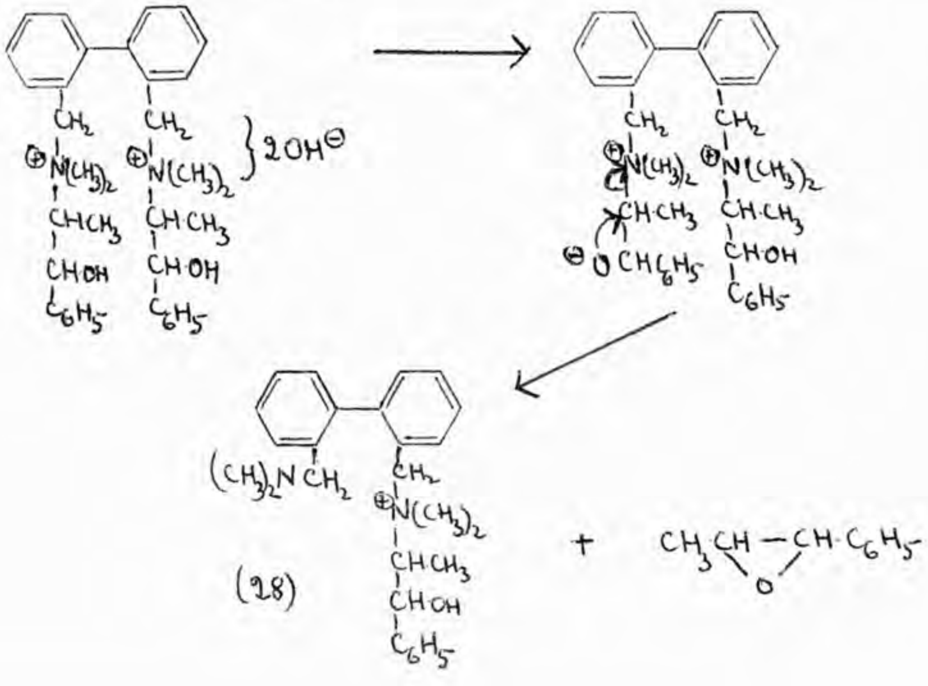
(24 ; X = Br) and converting it into a picrate identical with that isolated in this experiment.

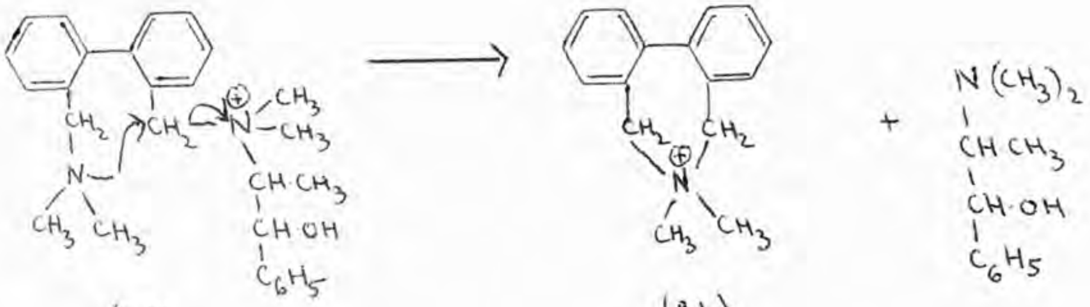
The picrate of 2,2-bis(dimethylaminomethyl)-biphenyl was decomposed by sodium hydroxide and the free base extracted with ether. Its infrared spectrum was examined. The base was then converted into its methiodide by treatment with methyl iodide in nitrobenzene in a sealed tube at 100°. It was identical (m.p. and mixed m.p.) with that synthesised directly from 2,2'-bisbromomethylbiphenyl and trimethylamine.

Some phenanthrene was isolated from the neutral ether-soluble residue . The aqueous layer from the distillate contained (+)-*trans*-1-methyl-2-phenylethylene oxide which was identified by its refractive index and infrared spectrum. The aqueous layer from the residue on evaporation yielded the hydrogencarbonate of 2,7-dihydro-1,1-dimethylazepinium cation, identified as its picrate.

Hall has investigated the action of heat on 2,2'-Di[N-(β-hydroxy-α-methylphenylethyl)-NN-dimethylammoniomethyl] biphenyl dihydroxide (22; X = OH) under similar conditions to those of experiment III described above. All the products described were isolated in the two experiments but the yield of the 2,2'-dimethylaminomethylbiphenyl base in Hall's experiment was considerably higher. It seems probable that the balance of the competing reactions is very delicate and factors such as the dilution at a particular temperature which are difficult to control during slow distillation at a particular temperature, are of critical importance.

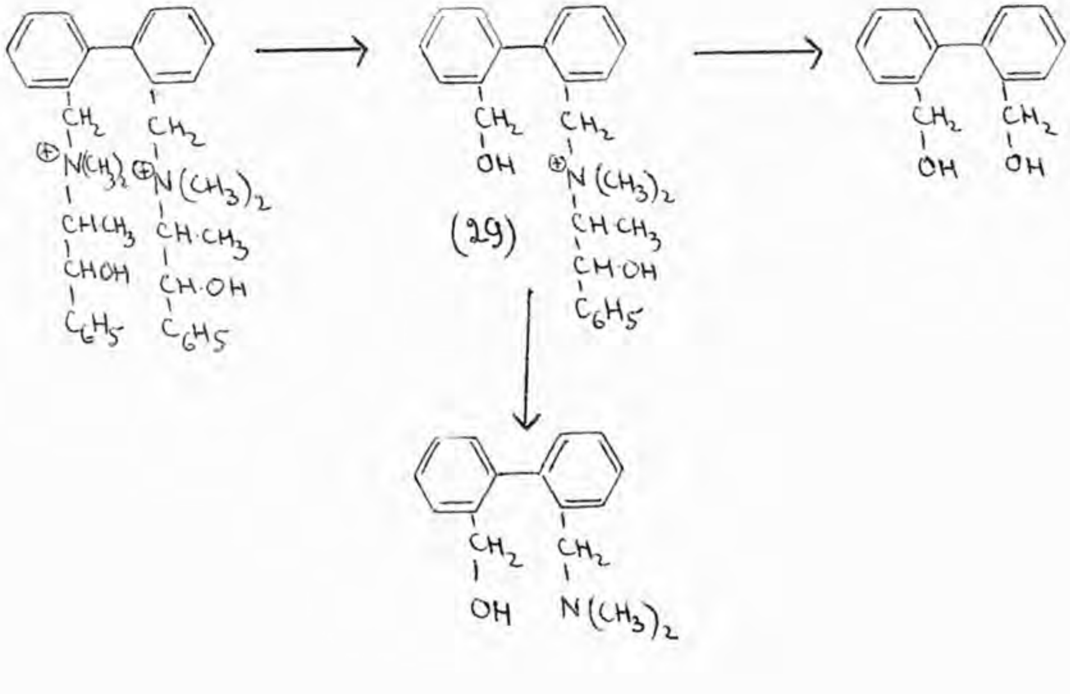
Three ways of reaction of the bis-ephedrinium cation with hydroxyl ions can be envisaged (<u>A</u>) Proton loss at one β-hydroxyl group will give an alkoxide ion which can form the ethylene oxide and the amine on one side only. Attack at the other β-hydroxyl group would lead to the elimination in the other side chain in which case 2,2'-bis(dimethylaminomethyl)biphenyl (23a) will be formed. However, a nucleophilic replacement at the benzyl α-carbon atom of positive quaternary nitrogen by neutral tertiary nitrogen in the intermediate ion (28) formed after elimination in one side chain only is a most likely route to the azepinium hydrogen carbonate and to the N-methylephedrine.





(28) (24)

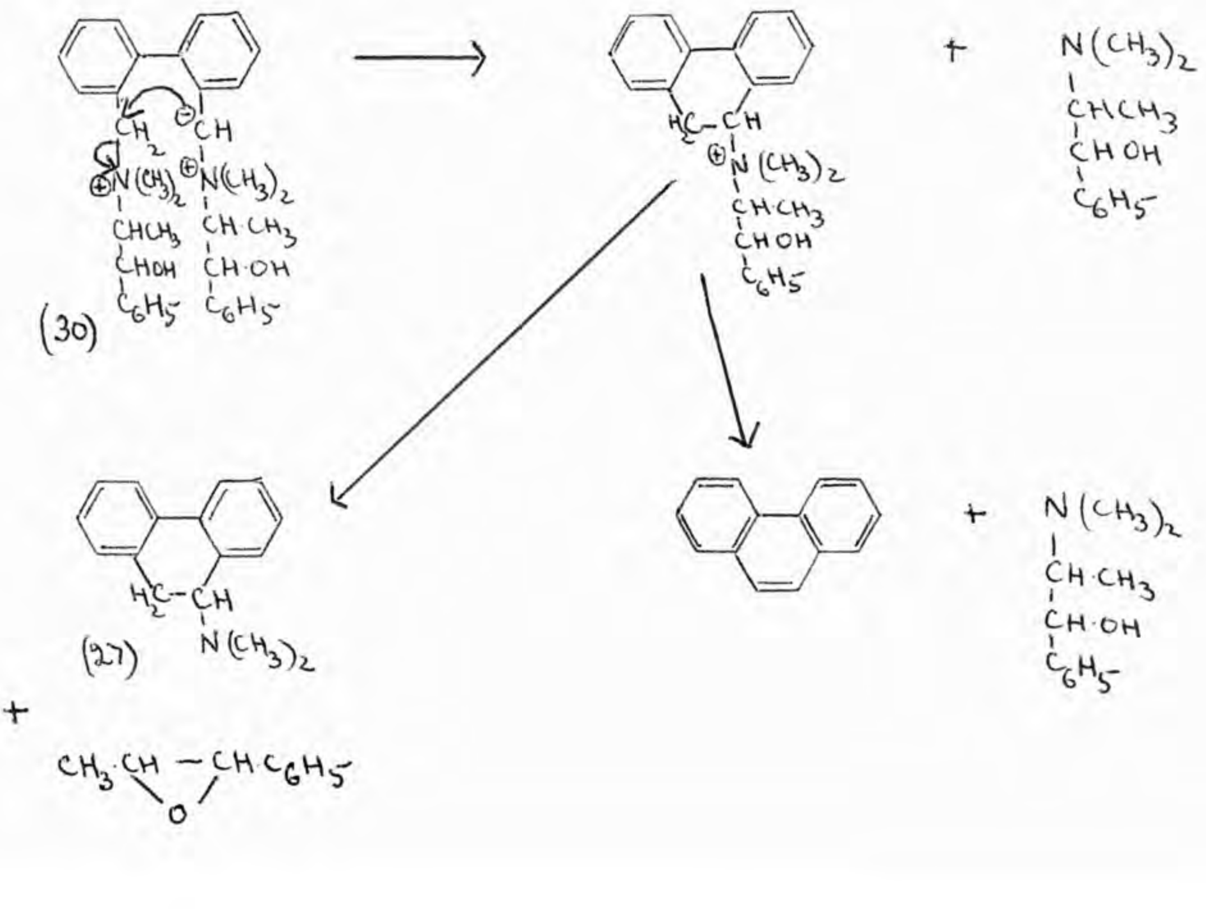
(B) Nucleophilic displacement at benzyl α-carbon atoms by hydroxyl ions or by carbonate ions would lead to the diol or to the hydroxy-amine. Cyclisation of the latter or of the intermediate mono hydroxy ion with elimination of water may be a route to the 9,10-dihydro-9-dimethylaminophenanthrene.



(29)

(C) An attack by hydroxyl ions at the benzyl methylene group may lead to proton loss and give an ylide intermediate of a type which plays an essential part in the Stevens rearrangement Such an ion may attack the benzyl carbon atom attached to the other positive nitrogen thus forming a six-membered ring. The ease of formation of 6- and 7-membered rings in 2,2'-substituted biphenyls has frequently been observed (Kenner, J., 1913, 103, 613) (Hall, Lesslie and Turner, J., 1950, 711; Beaven, Bird, Hall, Johnson, Ladbury, Lesslie and Turner, J., 1955, 2708; Hall, Ladbury, Lesslie, and Turner, J., 1956, 3475).

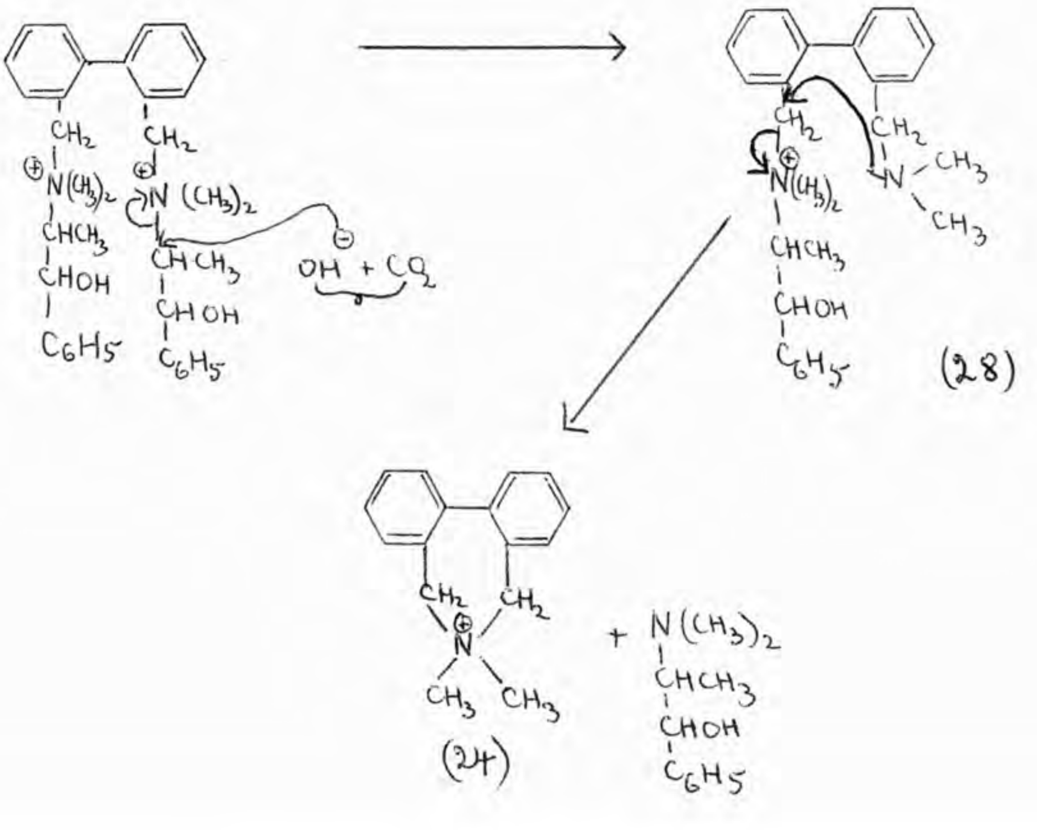
The bridged ion formed could loose a proton either at the β-hydroxyl group and give 9,10-dihydro-9-dimethylamino-phenanthrene or at the β-carbon atom in the saturated ring and give phenanthrene.



In order to compare the relative importance of the three possible ways of attack on the bis-ephedrinium cation the decomposition of the quaternary hydroxide was repeated four times under varying conditions. The decomposition was carried out (i) (Exp.IV) under nitrogen, conditions as in the third Exp.; (ii) (Exp.V) under nitrogen, heating under reflux without distillation; (iii) (Exp. VI) under nitrogen, with added potassium hydroxide ; and (iv) (Exp.VII) under carbon dioxide.

The decomposition (Exp.IV) gave results in agreement with Exp. III. The decomposition (Exp.V) carried out in dilute solution at 100°, gave N-methylephedrine, none of 2,2'-dimethylaminomethylbiphenyl and only a trace of 9,10-dihydro-9-dimethylaminophenanthrene ; the large residue still had a slight optical activity which showed that the decomposition was incomplete. Accordingly the residue was re-treated with fresh silver oxide and decomposed under conditions of (Exp.IV). No characteristic smell of ethylene oxide was detected this time but some 9,10-dihydro-9-dimethylaminophenanthrene was obtained. It seems that under conditions of (Exp.V) reaction (A) was occuring in one side chain, followed by formation of the azepinium cation. Evaporation of the water soluble residue on a water bath would lead to absorption of carbon dioxide from the air and give the hydrogen carbonate. The weights obtained corresponded to 84% of N-methylephedrine and 113% of azepinium hydrogen carbonate. The discrepancy in the latter yield is probably due to the presence in the residue of some optically active starting material.

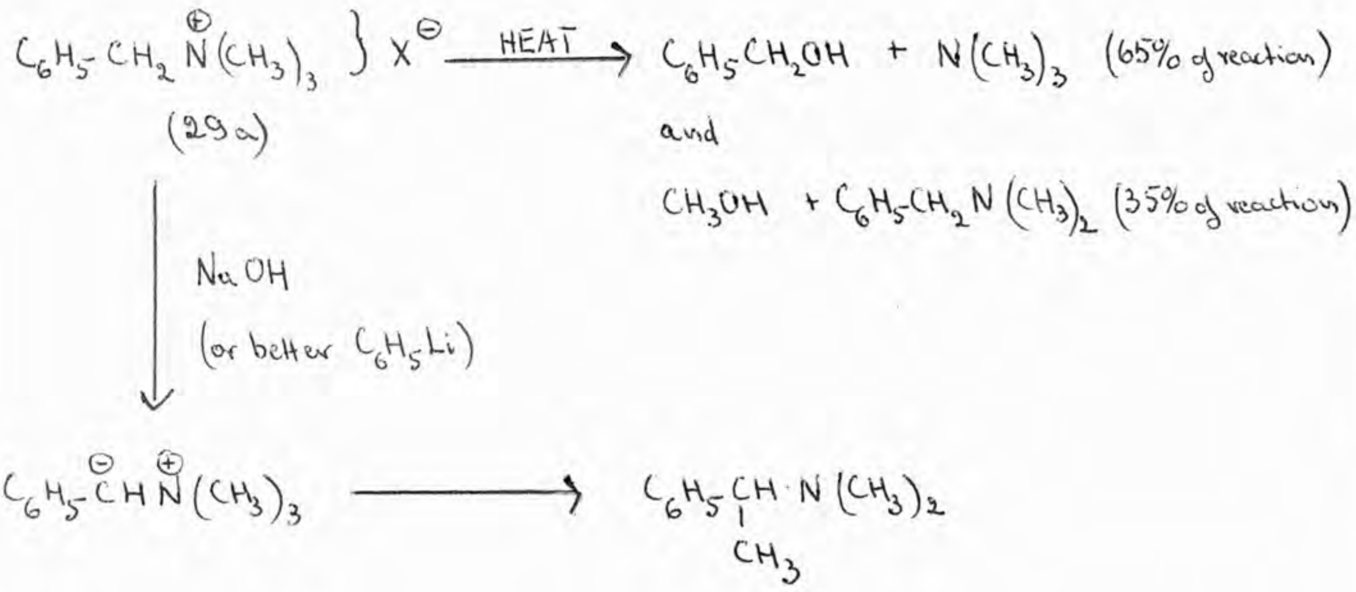
The presence of carbon dioxide (Exp. VII) has reduced the yields of both amines (23a) and (27) to negligible proportions. Bimolecular displacement at the benzyl α-carbon atom, followed by cyclisation, cannot therefore be a source of 9,10-dihydro-9-dimethylaminophenanthrene in normal experiments. However such a reaction at the isopropyl carbon atom in one side chain under these conditions where the basicity of the solution is so reduced would give the mono-ephedrinium ion, which could then give the azepinium ion (24) by a replacement of quaternary nitrogen by neutral nitrogen.



It is possible however that in spite of the presence of carbon dioxide there are enough hydroxyl ions present to give the mono-ephedrinium (28) cation by proton loss from the β -hydroxyl group, as in (Exp. V). Added potassium hydroxide (Exp.VI) has greatly increased the yield of 9,10-dihydro-9-dimethylaminophenanthrene (27) thus providing strong support for the route involving a type of Stevens rearrangement.

This arrangement was originally carried out (Stevens, Creighton, Gordon and MacNicol, J., 1928, 3193 ; Stevens, J., 1930, 2107) with quaternary compounds derived from phenacylamines and using hydroxide or alkoxide ions to remove a proton from the phenacyl group. Wittig and his co-workers (Wittig, Mangold and Felletschin, Annalen, 1948, 560, 116 ; Wittig and Zimmermann, Chem.Ber., 1953, 86, 629) used stronger bases such as phenyl-lithium and were able to bring about the rearrangement with compounds containing less readily ionised hydrogen.

Thus with quaternary compounds of suitable structure, the incursion of the rearrangement into the decomposition of quaternary ammonium hydroxides is possible and has, for example, been observed (Hughes and Ingold, J., 1933, 69) in the decomposition of benzhydryltrimethylammonium hydroxide (29_a; X = OH) in the presence of a high concentration of potassium hydroxide.



The situation of (benzyl) α-hydrogen atoms in the benzhydryl compound (29a) and in the biphenyl di-ephedrinium (22) compound is rather similar. However these carbon atoms in the di-ephedrinium compound (22) are subject to considerable steric hindrance to S_N2 reactions, since it is to be expected that both the other part of the biphenyl system and the bulky ephedrine side-chain are bound to interfere in the formation of the transition state. Thus if steric hindrance prevents nucleophilic displacement, reaction dependent on ylide formation is possible even without presence of a stronger base than hydroxyl ions.

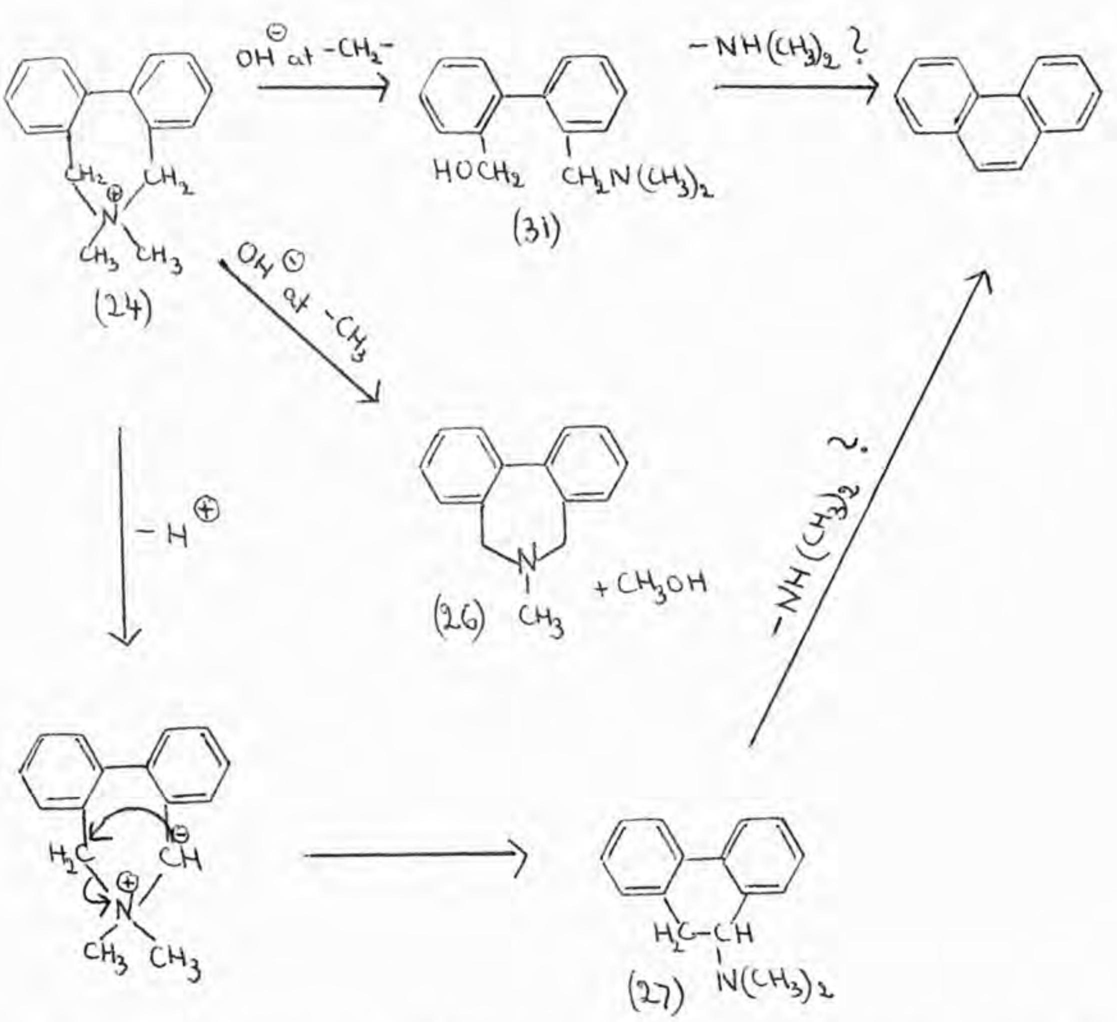
The 2,2'-dihydroxymethylbiphenyl (20) was not detected among the products of degradation reactions. It is stable to hot potassium hydroxide so can not have been formed and then destroyed. All neutral ether-soluble residues (always less than 0.2g.) were examined by infrared spectroscopy and in some cases phenanthrene was isolated from them. The diol could be easily detected spectroscopically in a 1:1 mixture with phenanthrene so that if any was formed it could not be more than 0.08g.

The formation of 9,10-dihydro-9-dimethylaminophenanthrene during the Hofmann degradation of the ephedrinium compound (22 ; X = OH) and also during the decomposition of the azepinium hydrogen carbonate (24 ; X = HCO_3) at 210° suggests that in this type of compound and under the experimental conditions described the hydroxyl ion might be a strong enough base to remove a hydrogen atom from the α (benzyl) carbon atom and bring about a Stevens rearrangement of the involved cation.

In order to test the effectiveness of the hydroxyl ion under the conditions of reactions described above, Hofmann degradation was carried out on 2,7-dihydro-1,1-dimethyl-3,4:5,6-dibenzazepinium hydroxide (24 ; X = OH) under the conditions of experiment (IV), the temperature not being allowed to rise above 135°. The 9,10-dihydro-9-dimethylaminophenanthrene (27) was obtained but it was accompanied by 2,7-dihydro-1-methyl-3,4:5,6-dibenzazepine (26) (the result of hydroxyl attack at the methyl α-carbon atoms) and by phenanthrene isolated in 32-40% yield. A similar decomposition carried out in the presence of potassium hydroxide gave a similar yield of phenanthrene (33%); the aminodihydrophenanthrene (27) but none of the azepine (26). Neither the azepine nor the phenanthrene had been detected when the hydrogen carbonate was decomposed at 210°.

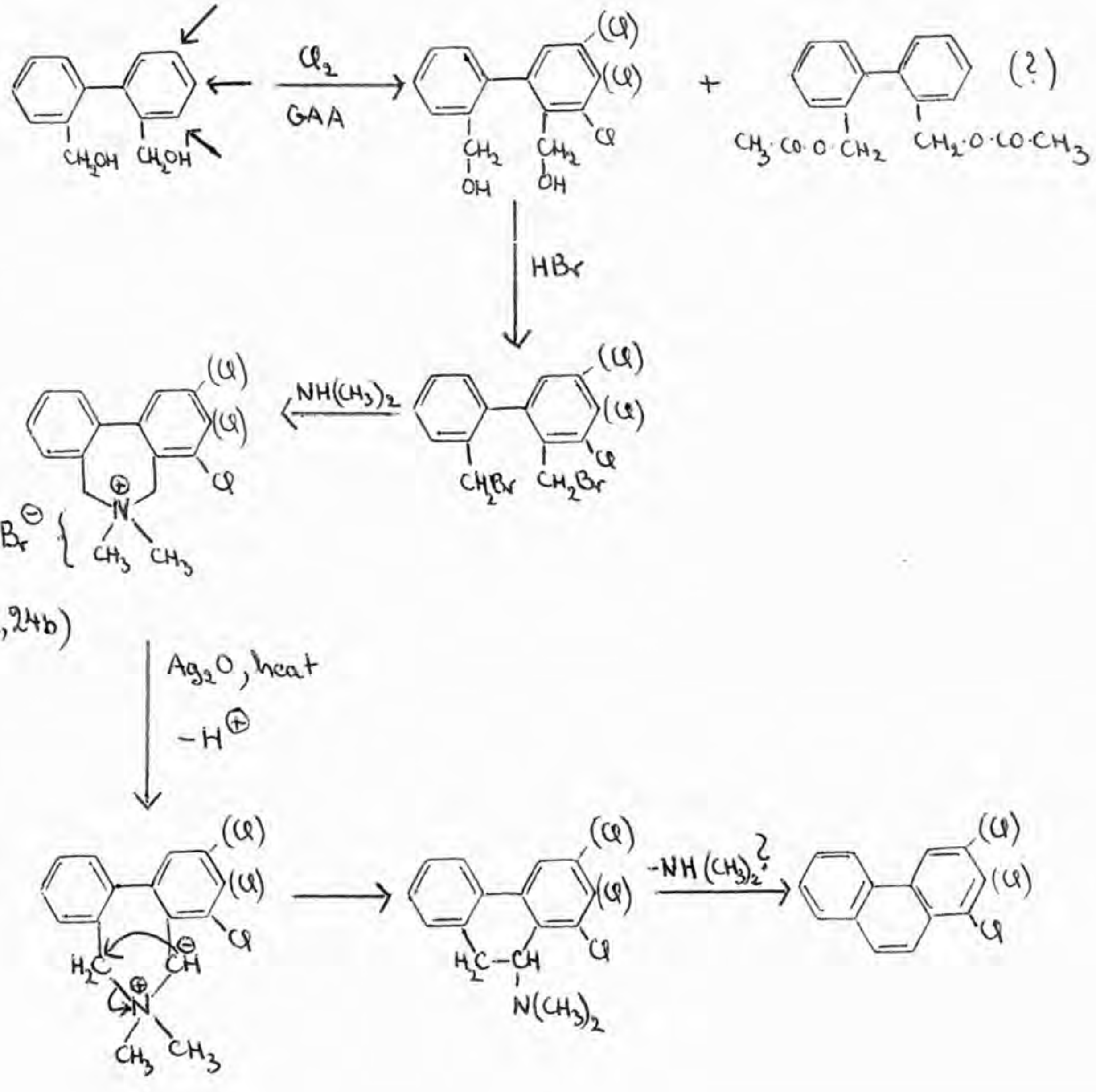
The formation of appreciable amounts of phenanthrene during the degradation of the azepinium hydroxide (24 ; X = OH) suggests that the formation of 9,10-dihydro-9-dimethylaminophenanthrene (27) during the degradation of the bis-ephedrinium hydroxide (22 ; X = OH) is derived principally from a Stevens rearrangement on the original ion (22 → 30) and not via the azepinium ion. Any amine (27) produced <u>via</u> the azepinium ion would have to be accompanied by considerable amounts of phenanthrene. Phenanthrene was detected only in reactions where a good yield of the amine (27) was obtained but in the most favourable case (Exp. VI ; added alkali) only in 19% yield. No azepine picrate (26 ; $C_6H_3N_3O_7$) was isolated but small amounts of it could easily have been missed during the fractional crystallisations of the picrate mixtures.

The considerable amount of phenanthrene obtained from the degradation of the azepinium hydroxide (24 ; X = OH) suggests that dimethylamine had been eliminated during the reaction either from the 9,10-dihydro-9-dimethylaminophenanthrene (27) or from a possible intermediate (31).



During the decomposition an alkaline gas was evolved with characteristic smell as soon as the temperature reached 80° but several attempts to isolate it as its picrate were unsuccessful. During the distillation an alcohol trap was placed before the receiving flask and the alcoholic solution treated with picric acid. An attempt was also made to salt out the highly water soluble base from the aqueous layers obtained on working up. The amine (27) appeared to be stable both to heat (it could be distilled at 183° / 1mm.) and to alkali (the yield of phenanthrene was not increased by added potassium hydroxide). The hydroxy-amine (31) is not known ; the corresponding diol is stable to alkali.

In view of the considerable yields of phenanthrene obtained during the degradation of the azepinium hydroxide it seemed interesting to find out whether Hofmann degradation of related compounds might not prove a route to certain substituted phenanthrenes which are otherwise difficult to synthesise.



Accordingly 2,2'-bishydroxymethyl biphenyl was chlorinated with free chlorine in glacial acetic acid (de la Mare, Bedford College). The product was converted into the corresponding mixture of chloro-2,2'-bisbromomethyl biphenyls which were bridged by condensation with dimethylamine. The resulting quaternary bromides were converted into the hydroxides and distilled under the conditions of experiment (IV). The product was worked up as described in previous experiments and the ether soluble non-basic fraction was analysed by vapour phase chromatography.

Vapour-phase chromatography on a packed column showed that this consisted of about equal parts of phenanthrene and chlorophenanthrene and the chlorophenanthrene band appeared to be a partially resolved doublet.

On a capillary column with greater resolution than the packed column the chlorophenanthrene band was resolved into three. The peak heights in order of increasing retention time were <u>ca.</u> 7,$^{(A)}$ 4$^{(B)}$ and 2,$^{(C)}$ the last two overlapping considerably. If phenanthrene = 1, retention times are approximately A = 2.2 ; B = 2.32 ; C = 2.37 on Apiezon L at 190°. The major components were expected to be 1 -(B) and 3-(A) chlorophenanthrene. It seemed likely that C was the 2-chloro isomer, since the 4-chloro isomer would not be expected on steric grounds.

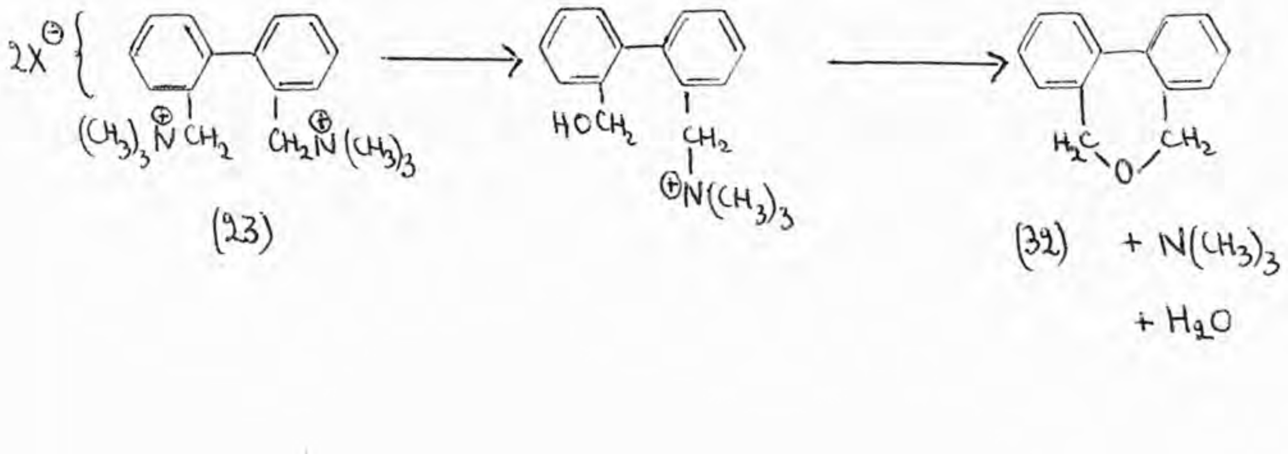
The product was re-examined on a 50 foot Apiezon L column at 203° and the retention times of the components were compared with available pure samples of 1-, 2-, 3-, 4- chlorophenanthrenes. It was found that the 3-chloro isomer, with ~~slowest~~ shortest retention time was the main product, but there was more of the 2- than of the 1- isomer present, the latter emerging last. The order of increasing retention times for the five possible isomers is :

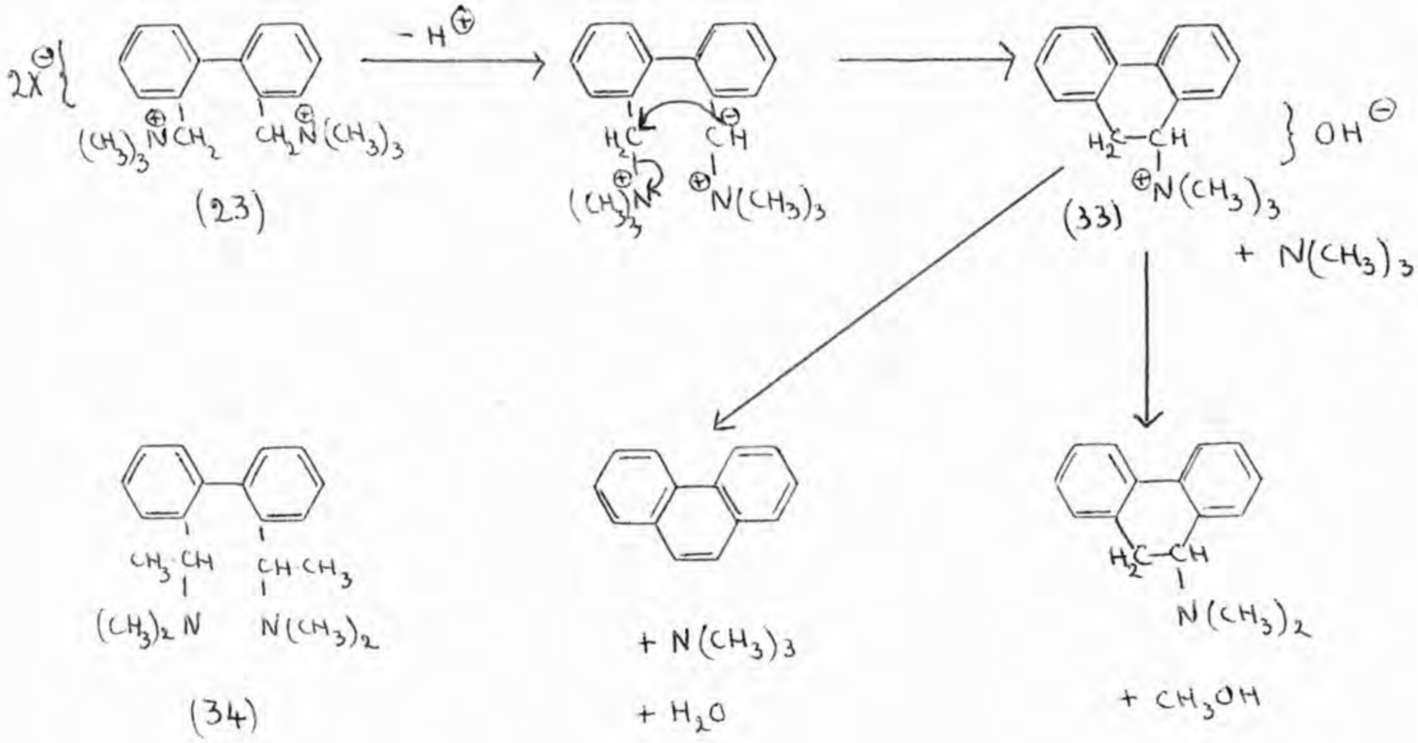
3- < 4- < 2- < 9- < 1- .

The presence of phenanthrene is due to the fact that chlorination of the diol was only partial (50%) and part of the intermediate product consisted of the unsubstituted azepinium compound (24). It seems probable that under the conditions used for chlorination (pure glacial acetic acid, no water) the diol was partly acetylated, the acetylation stopping further chlorination. The ester would have been hydrolysed to the diol in subseuqent treatment of the intermediates.

The behaviour of the bisephedrinium compound (22;X=OH) suggested that the hydroxides of other unbridged 2,2'-bis-quaternary biphenyls, in which simple olefin formation would be difficult or impossible, might give bridged compounds under Hofmann degradation conditions. Accordingly an aqueous solution of 2,2'-bis(trimethylammoniomethyl)biphenyl hydroxide (23;X=OH) was slowly distilled under reduced pressure in an atmosphere of nitrogen. 9,10-Dihydro-9-dimethylaminophenanthrene (27) and trimethylamine were detected among the products by isolation of their known picrates, as well as one other unidentified base. Non-basic products, including phenanthrene and 2,7-dihydro-3,4:5,6-dibenzoxepin (32) were also obtained. The oxepin was not isolated in a pure condition but was detected spectroscopically in a mixture with phenanthrene (infrared).

Nucleophilic displacement by hydroxyl ions at one of the benzyl α-carbon atoms, followed, by cyclisation, seems to be the most likely route to the oxepin. Proton loss from a benzyl methylene group followed by rearrangement gives an ion (33) which can give either 9,10-dihydro-9-dimethylaminophenanthrene by a displacement at a methyl group or phenanthrene by elimination.





The unidentified base was obtained as its picrate, m.p. 240° (decomp.); the analysis gives the empirical formula $C_{20}H_{29}N_2,2C_6H_3N_3O_7$, if the biphenyl skeleton is still present, or $C_{10}H_{14-15}N_1,C_6H_3N_3O_7$ if it is not. The picrate was decomposed by cold alkali and gave a little free base, the infrared spectrum of which showed the C-H stretching frequencies of NMe_2 (at 2760 and 2811 cm.$^{-1}$) and of CH_2 (at 2857 and 2918 cm.$^{-1}$). No peaks for $C-CH_3$ were found, although two slight shoulders (at 2884 and 2970 cm.$^{-1}$) on the CH_2 bands were at the CH_3 stretching frequencies. It does not seem that a "normal" Stevens rearrangement has taken place to give (34). Too little of the base was isolated to elucidate its structure.

c (iii) Infrared and Ultraviolet Spectra of the Tertiary Amines Isolated and of some Byproducts:

Both ultraviolet and infrared spectra have been used extensively for the identification of the products obtained in the Hofmann degradations.

Ultraviolet Spectra. The final identification of the unknown hydrogen carbonate (24; $X=HCO_3$) as the azepinium salt was achieved by comparing the ultraviolet spectra of a series of related 2,2'-di-substituted biphenyls, both unbridged and bridged with a 2- or 3-atom bridge. The following were studied:

9,10-dihydro-9-dimethylaminophenanthrene (27) and its picrate,

2,7-dihydro-1-methyl-3,4:5,6-dibenzazepine (26),

2,7-dihydro-1,1-dimethyl-3,4:5,6-dibenzazepinium bromide (24; X = Br) and picrate,

2,2'-bis(trimethylammoniomethyl)biphenyl dibromide monohydrate (23; X = Br).

The main features of the spectra of these compounds are given in Table I (graphs V and VI); the spectrum of the hydrogen carbonate (24; $X = HCO_3$) is also included.

The unknown hydrogen carbonate had a conjugation band at λ_{max} 248 mμ with $\mathcal{E}_{max}$ 14,000 and the longwave features were two inflections at λ 271 mμ ($\mathcal{E}_{inf.}$ 4,430) and at

λ 281 mμ (ε_{inf} 2,380). The spectrum was almost identical with the spectrum of the directly synthesised azepinium bromide (24; X = Br). This showed a conjugation band at λ_{max} 248 mμ (ε_{max} 14,200) and two inflections in the longwave region at 275 mμ ($\varepsilon_{inf.}$ 4,270) and at 280 mμ ($\varepsilon_{inf.}$ 3,050). Both the above spectra show the large measure of conjugation between the two aromatic rings which exists in the biphenyl compounds bridged with a 3-atom saturated bridge. Replacement of the tetrahedral quaternary nitrogen in the bridging ring by the pyramidal tertiary nitrogen as in (26) leads to a considerable shift of the conjugation band to shorter wavelength (λ_{max} 241 mμ) and to a further reduction in intensity of the band (ε_{max} 12,800) as compared with biphenyl (ε_{max} 17,300) and with the corresponding quaternary salt. This indicates reduction in conjugation. The spectrum of compound (26) shows a shortwave band at λ_{max} 206 mμ (ε_{max} 41,600) and has only one inflection at λ_{max} 281 mμ ($\varepsilon_{inf.}$ 3,030). The quaternary picrate (24; $X = C_6H_2N_3O_7$) shows a shortwave band with two maxima at 206 mμ and 212 mμ. The conjugation band is here at λ_{max} 245 and has a high intensity (ε_{max} 22,700). This is due to the superposition of the picrate ion absorption on that of the azepinium compound. This can also be seen in the longwave region which shows in addition to the two inflections a strong band at λ_{max} 357 mμ and 360 mμ typical of the picrate ion absorption. (Schroeder, Wilcox, Trueblood and Dekker, Analyt. Chem., 1951, 23, 1740). The superposition of the picrate ion absorption onto that of the bridged biphenyl is also evident when spectra of the 6-membered ring compound (27) and of its picrate are compared.

The spectrum of (27) shows a higher degree of conjugation than those of the biphenyls with a 3-atom bridge. The conjugation band is here shifted to longer wavelength as compared with biphenyl. It is resolved into 3 maxima at λ 252 mμ 260 mμ and 265.5 mμ with molecular extinction coefficients of 15,700, 16,000 and 15,900. The longwave region shows three inflections. 9,10-Dihydrophenanthrene (Beaven, Hall, Lesslie, and Turner, J., 1952, 854) shows single peaks both in the conjugation band region and in the longwave region, and in the latter it has a well resolved broad band. Its conjugation band at λ_{max} 263,5 mμ is of higher intensity ($\mathcal{E}_{max}$ 18,000) than in biphenyl ($\mathcal{E}_{max}$ 17,300). The spectrum of the unbridged 2,2'-disubstituted biphenyl (23 ; X = Br) is typically that of a highly sterically hindered biphenyl and resembles the spectrum of 2,2'-ditolyl (Beaven, Hall, Lesslie and Turner, J.,1954, 131). The conjugation band is left here only as an inflection at 233 mμ ($\mathcal{E}_{inf.}$ 8,980).

TABLE 1. ULTRAVIOLET ABSORPTION SPECTRA

(The Spectra were measured on a Unicam S.P. 500 spectrophotometer).

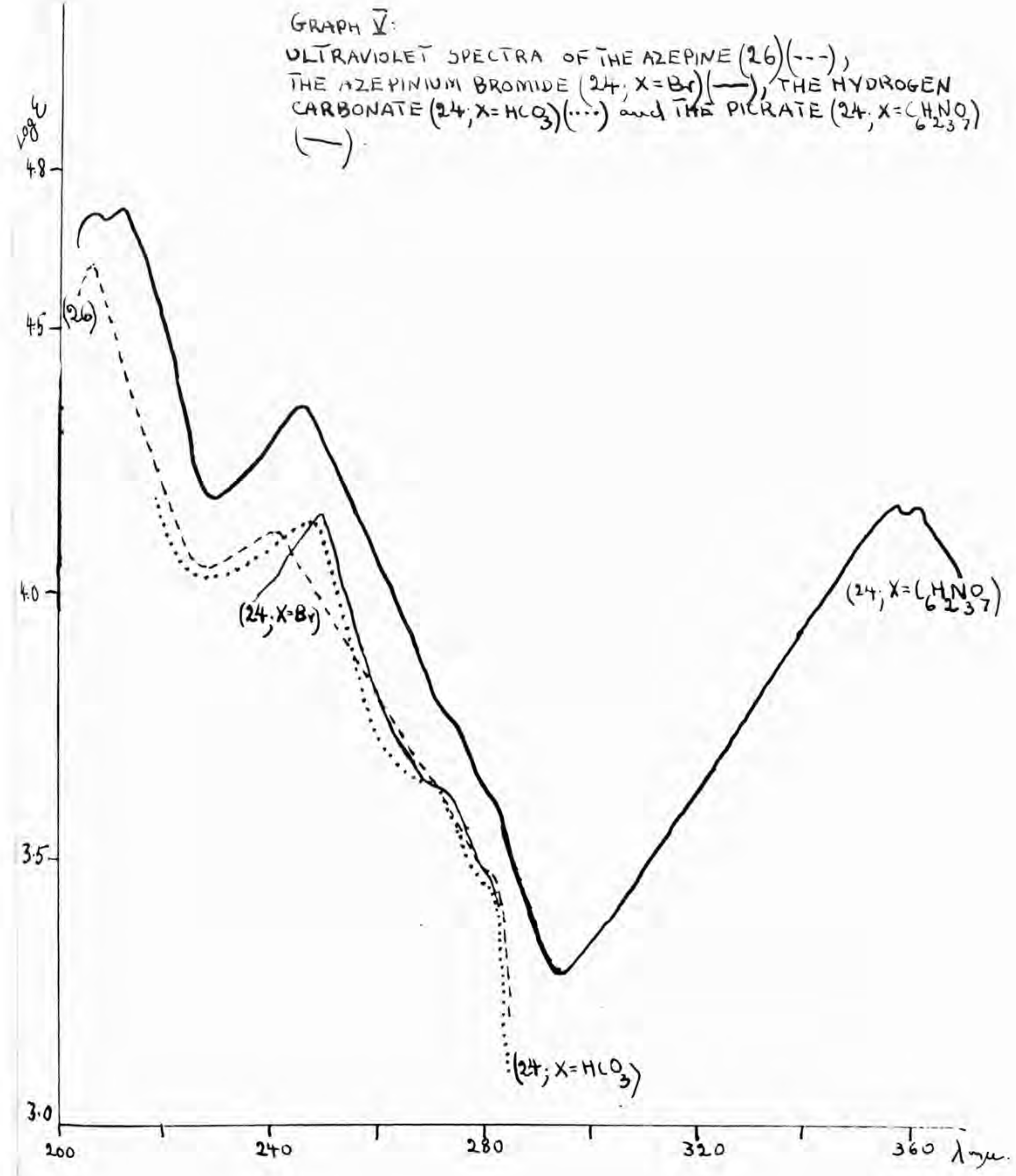
Compound	Shortwave Band		Conjugation Band		Longwave Features			
	λ_{max}	ε_{max}	λ_{max}	ε_{max}	λ_{max}	ε_{max}	λ_{max}	ε_{max}
$(23; X=Br), H_2O$ [a]			(233)	8,980	268.5	2050		
(26)	206	41,600	241	12,800	(281)	3.030		
(24; X=Br)			249	14,200	(275) (280)	4270 3050		
$(24; X=C_6H_2N_3O_7)$	206 212	51,500 52,900	245	22,700	(274) (281)	5850 4140	357 360	14,750 14,650
$(24; X=HCO_3)$			248	14,000	(271) (281)	4470 2380		
(27)	211	39,900	252 260 265.5	15,700 16,000 15,900	(274) (282) (292)	14.500 9,720 4.180		
Picrate of (27)	208 212	54,400 53,500	260 261.5	20,900 20,800	(270) (280)	18.800 11.800	357.5	16,200
Picric acid [b]			[245	10,000 [c]]			360	16,600
Na picrate [d]							358	14,100

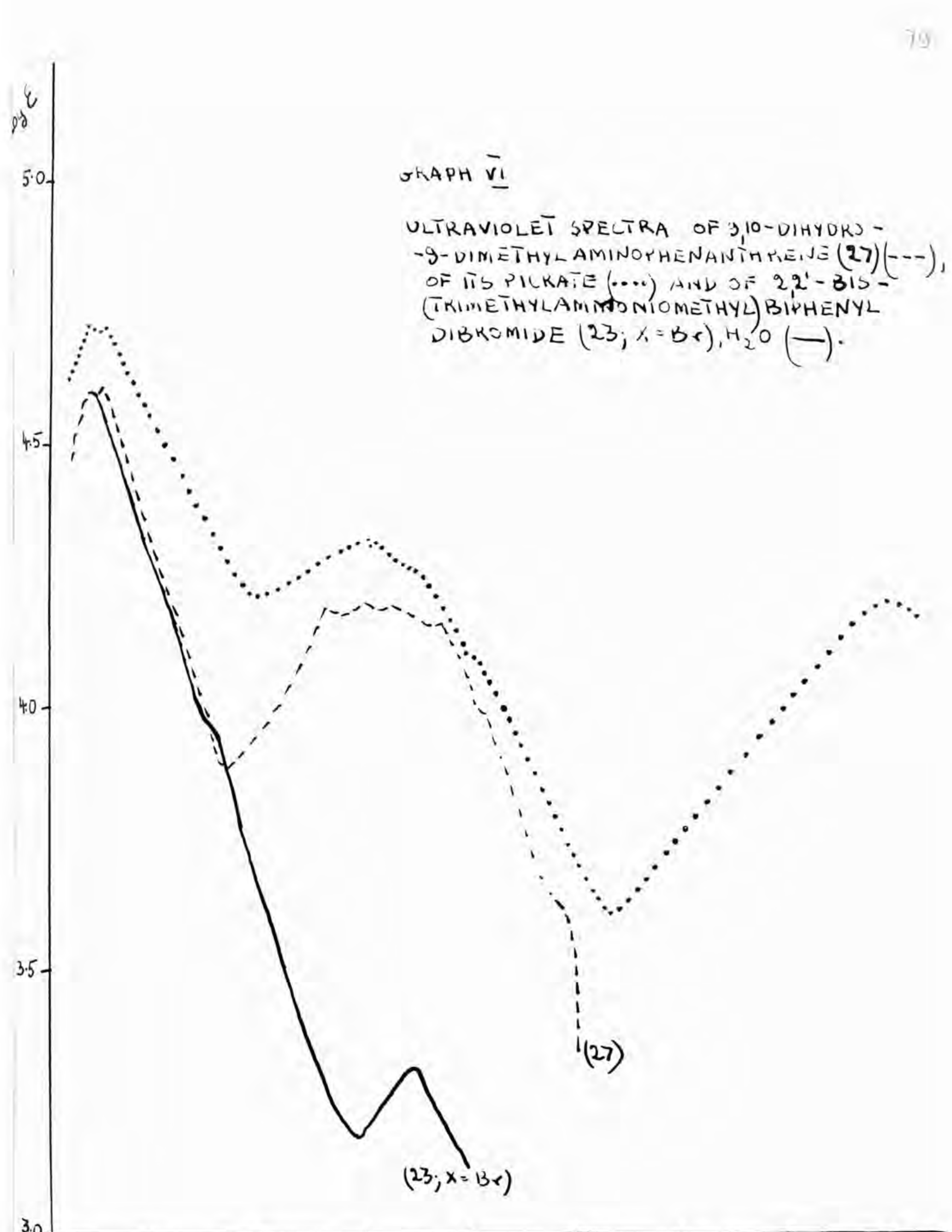
Solvent, 96% ethanol, except where otherwise stated; wavelength in mμ ; values in parentheses denote inflections.

a In methanol ; b Friedel and Orchin, "Ultraviolet Spectra of Aromatic Compounds," Wiley, New York, 1951, No 93.

c Not a maximum or point of inflection. d The acid in ethanol containing aqu. sodium hydroxide; Schroeder, Wilcox, Trueblood and Dekker, Analyt Chem. 1951, 23, 1740.

GRAPH V: ULTRAVIOLET SPECTRA OF THE AZEPINE (26)(---), THE AZEPINIUM BROMIDE (24; X=Br)(——), THE HYDROGEN CARBONATE (24; X=HCO_3)(····) and THE PICRATE (24; X=$C_6H_2N_3O_7$) (——).





GRAPH VI

ULTRAVIOLET SPECTRA OF 9,10-DIHYDRO-
-9-DIMETHYLAMINOPHENANTHRENE (27) (---),
OF ITS PICRATE (....) AND OF 2,2'-BIS-
(TRIMETHYLAMMONIOMETHYL) BIPHENYL
DIBROMIDE (23; X = Br), H_2O (—).

Infrared Spectra

The main features of the infrared spectra of the four tertiary amines, (23a), (26), (27) and N-methylephedrine are given in tables 2 and 3. The spectrum of the unidentified base (l), the picrate of which had m.p. 240°, is also included, as well as part of the spectrum of a non-basic reference compound 9,10-dihydrophenanthrene. The spedtra are reproduced in graphs I, II and III. A sharp band at 1004-1007 cm.$^{-1}$ (at 1001 cm.$^{-1}$ in $C_{14}H_{10}$) in all the above compounds except N-methylephedrine and the unidentified base, supports Beaven and Johnson's ("Conference on Molecular Spectroscopy",Ed.Thornton and Thompson, Pergamon Press, London 1959,p.78) view that the biphenyl structure has a characteristic band at 1010 cm.$^{-1}$. It is not clear whether the unknown base contains still a biphenyl skeleton - its infrared spectrum shows a weak shoulder at 1004 cm.$^{-1}$ and not a clear resolved band. However it is possible that the biphenyl absorption is here obscured by the very strong band at 1019 cm.$^{-1}$.

All the amines show a strong band at 2764 ± 9 cm.$^{-1}$ and a second (medium to strong) at 2815 ± 12 cm.$^{-1}$, which is weakest in the azepine (26). 9,10-Dihydrophenanthrene also shows a weak band here. Absorption in this region has been correlated (Hill and Meakins, J., 1958, 760 ; Braunholtz, Ebsworthy, Mann and Sheppard, J, 1958, 2780 ; Wright, J.Org.Chem., 1959, 24, 1362 ;

Katritsky and Jones, J., 1959, 3674); with the C-H stretching vibration of an N-Me group and Hill and Meakins (loc.cit.) have classified the absorption pattern according to the situation of the basic group and the number of the methyl groups attached to the nitrogen.

When the $N-Me_2$ group is not attached directly to an aromatic system two bands occur (in the 2825-2810 cm.$^{-1}$ and 2775-2765 cm.$^{-1}$ regions) and this is shown in the spectra of the three amines examined (23a, 27 and N-methylephedrine) which contain these groups and also in the spectrum of the unidentified base. The N-Me group not attached to an aromatic system gives a single band between 2805-2780 cm.$^{-1}$ and the methylazepine (26) has a strong band just outside this range at 2773 cm.$^{-1}$, the second band at 2827 cm.$^{-1}$ of lower intensity is probably due to the $-CH_2-$ groups as a similar weak band is found also in the non-basic 9,10-dihydropenanthrene.

The spectra of 2,2'-bishydroxymethylbiphenyl, of the oxepin and of phenanthrene were used in the attempt to identity the non-basic, ether-soluble products of the Hofmann degradations. All three compounds have quite characteristic absorption bands of high intensity which permit detection of anyone of them in a complex micture. The spectra are reproduced in Graph IV.

The spectrum of phenanthrene shows two outstanding bands the very strong band at 731 cm.$^{-1}$ due to the CH out of plane deformations characteristic of aromatic compounds with four adjacent free hydrogen atoms, and the strong band at 808cm.$^{-1}$ due to the same type of vibration but in presence of two adjacent free hydrogen atoms. The rest of the spectrum is uninterestingly flat and contains weak bands only. There is no band here in the region of 1010 cm.$^{-1}$ characteristic of the biphenyl skeleton structure.

The spectrum of the diol has a broad band with a maximum at 3210 cm.$^{-1}$, which can be assigned to the stretching frequency of -OH groups which are intramolecularly hydrogen bonded. The absence of this band can always be taken to indicate the absence of the diol, but the presence of the hydroxyl band in this region may also be encountered in material exposed to moisture. A strong band is present at 1033 cm.$^{-1}$ which can probably be assigned to the C-O stretching frequency of the CH_2OH group. Lecomte (Tout and Lecomte, <u>Bull.Soc., Chim.France</u> 1943, 10,542) established that a band near 1050 cm.$^{-1}$ occurs in primary alcohols. Stuart and Sutherland (<u>J.Chem.Phys.</u>, 1956, <u>24</u>, 559) showed the sensitivity of this adsorption to structural changes - there is a shift towards lower frequencies in unsaturated alcohols, and this is found greater for aryl than for alkenyl unsaturation.

The region 772-722 cm.$^{-1}$ contains three bands at 772 cm.$^{-1}$ (M), at 755 cm.$^{-1}$ (S) due to CH out of plane deformations with four free adjacent hydrogen atoms and at 722 cm.$^{-1}$ (M), which together with the two bands cited above can be used successfully for detection of the diol. The biphenyl absorption band is present here at 1001 cm.$^{-1}$.

The oxepin shows a broad strong band at 749 cm.$^{-1}$ with a shoulder at 757 cm.$^{-1}$ which can be assigned to the CH out of plane deformation vibration of the four adjacent free hydrogen atoms. Orr and Thompson (<u>J.</u>, 1950,218) have traced a strong band near 750 cm.$^{-1}$ in a considerable number of 1,2-disubstituted polynuclear structures. Two further regions are characteristic of the oxepin spectrum : two medium strong closely spaced bands at 901 cm.$^{-1}$ and 888 cm.$^{-1}$ and a strong doublet with maxima at 1081 cm.$^{-1}$ and 1072 cm.$^{-1}$ So far little infromation is available for correlation of absorptions in cyclic ethers. However it is thought that cyclic ethers containing four-, five- or six-membered rings have multiple absorption bands in these regions which can be attributed to the C-O-C stretching vibrations.

Table 2. Infrared Spectra (cm.$^{-1}$; range 600-1650) of some Tertiary Amines.

(26)	(?) (picrate, m.p.240°)	(23a)	(27)	ME^{a}
605 m				
617 m		619 sh	619 m	
632 sh			627 sh	630 m
				656 m
667 w			667 w	
			678 m	
		697 w	699 m	705 vs
711 w		711 sh	711 w	
730 m	730 vs	720 sh	728 sh	729 sh
749 vs		736 sh	737 vs	744 vs
		753 sh		
	757 m	757 vs	752 vs	
776 m	763 m	781 sh	777 s	779 s
	787 vs		790 sh	
825 w		812 w	814 m	810 m
833 w	847 vs	839 sh	833 w	835 w
849 m	862 sh	851 m	861 m	
870 w				
885 w	877 w	873 m	879 m	881 m
934 m	885 w		936 m	920 w
947 m	909 w	942 w	952 m	956 m
977 w	971 m	972 w		978 sh
	990 m		990 w	996 s
1006 w	1004 sh(?)	1007 m	1004 w	
1022 m	1019 vs	1027 s	1025 s	1030 sh
	1039 s	1041 s	1041 s	1041 s
1047 w			1047 sh	1055 s
1078 s	1078 m	1075 w		1067 sh
	1094 m	1095 m	1096 m	1095 m
1114 sh		1107 w		
1120 m				
1127 sh	1127 w		1125 w	1127 s
	1145 m	1145 m	1143 w	
1157 w		1153 m	1155 m	1157 sh
	1171 s	1172 m	1167 s	1170 s
1182 m		1189 w	1183 m	
1195 m			1200 sh	1200 m

(contd)

Table 2 continued.

Infrared Spectra (cm.$^{-1}$; range 600-1650) of some Tertiary Amines.

(26)	(?) (picrate m.p. 240°)	(23a)	(27)	ME[a]
1235 m	1231 m		1238 w	
1250 w	1255 s	1253 m		1247 sh
		1261 sh	1261 w	1267 s
	1289 m	1284 w	1277 m	1282 sh
1307 w		1297 m	1314 m	1305 sh
1333 w		1337 sh	1333 sh	1325 sh
				1355 sh
1366 m	1357 s	1361 s	1361 m	1368 s[b]
1389 w				
1416 sh	1401 w	1401 w	1404 w	1418 sh
		1439 sh	1439 sh	
1443 s	1441 vs	1449 s	1451 s	1447 s[b]
1462 m	1451 sh	1460 sh	1471 sh	1460 sh
1475 m			1481 s	
	1460 sh	1490 sh	1493 sh	1493 sh
1550 w			1563 w	
	1582 m		1587 sh	
1605 sh		1592 w	1597 w	1600 w
1637 m		1629 w		1631 w

[a] N-Methylephedrine, spectrum Nujol mull.

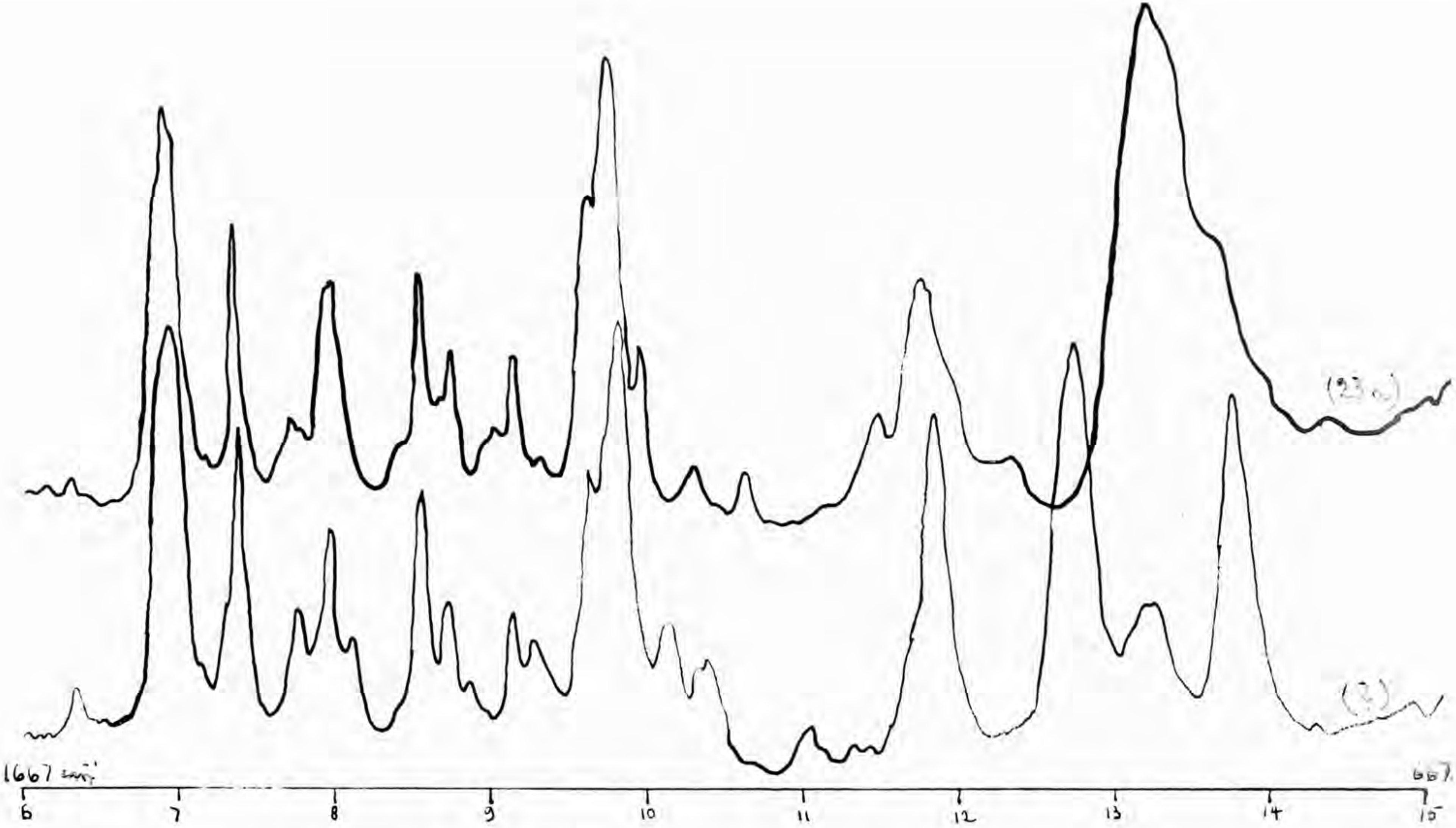
[b] Nujol peaks.

Table 3. C-H Stretching Vibrations (cm.$^{-1}$) in some Tertiary Amines and in 9,10-Dihydrophenanthrene.

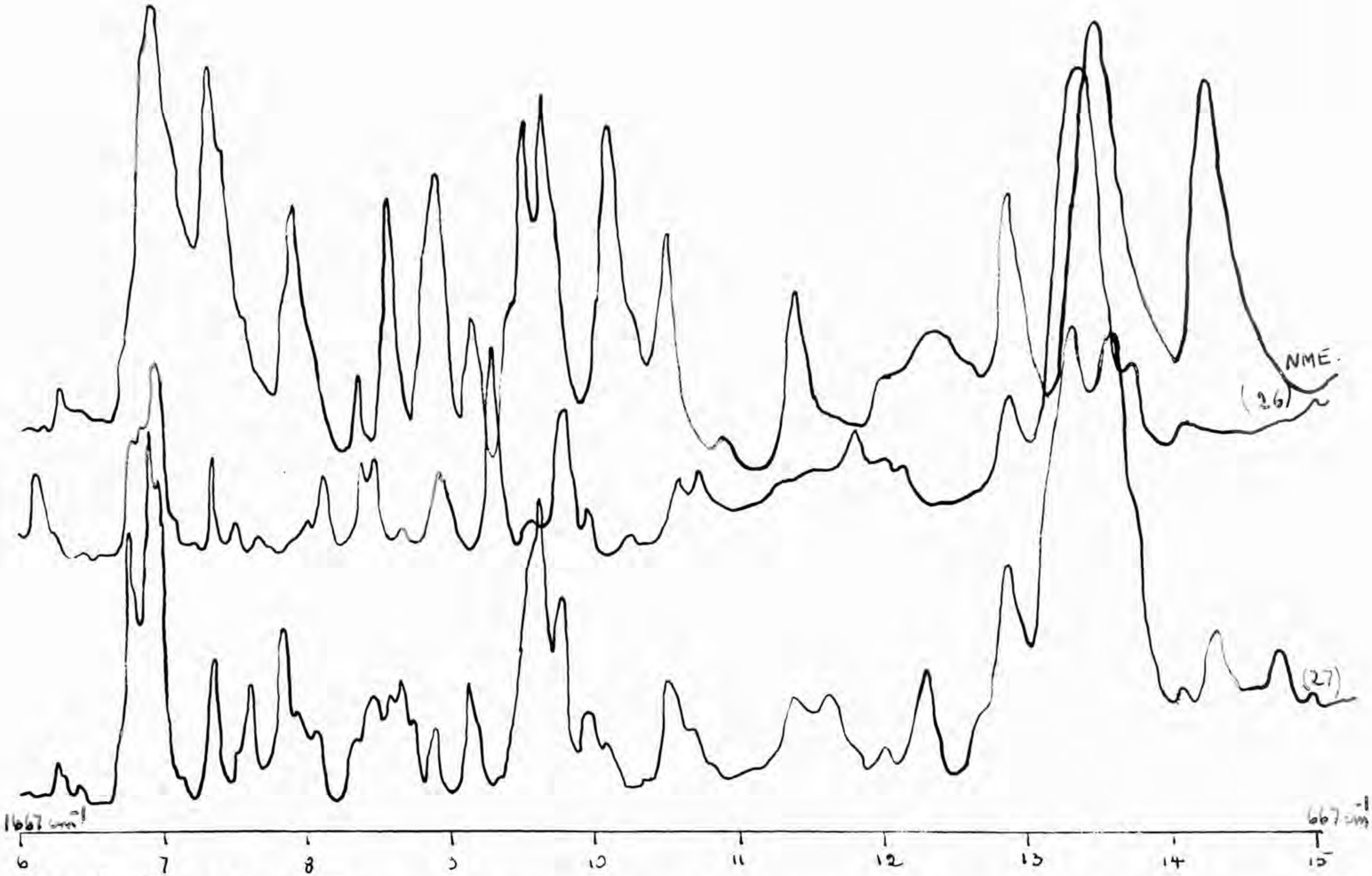
(?) (picrate m.p.240°)	(26)	(23a)	(27)	ME	DHP[b]	Probable assignment
2697 m						
2760 s	2773 s	2755 s	2768 s	2772 s		$N-CH_3$
2812 s		2803 s	2811 m	2817 s		$N-CH_3$
	2827 m				2819 m	?
2853 s	2859 m	2843 m	2851 m		2874 m	CH_2
				2867 s		CH_3
	2887 sh		2884 m			? CH
2924 s	2924 s	2927 s	2930 s		2921 s	CH_2
				2941 sh		
	2953 sh	2959 sh	2956 sh	2956 s		? CH_3
				2979 s		? CH_3
3010 sh	3006 m	3012 m	3012 m	3021 m	3008 s	CH (aromatic)
3020 sh						
3049 sh	3051 m	3046 m	3053 m	3058 m	3051 m	CH (aromatic)
				3084 sh		? CH (aromatic)

[a] *N*-Methylephedrine, spectrum in carbon tetrachloride solution.

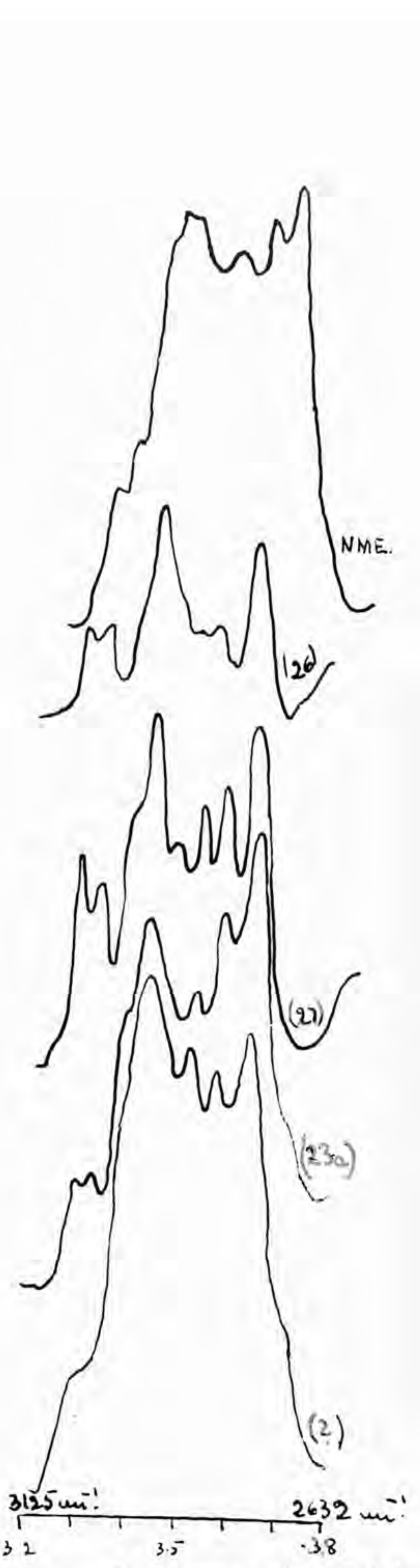
[b] 9,10-Dihydrophenanthrene, spectrum of molten material.



GRAPH I : INFRARED SPECTRA of 2,2'-BIS (DIMETHYLAMINOMETHYL) BIPHENYL (23a) and of the unidentified base (?).

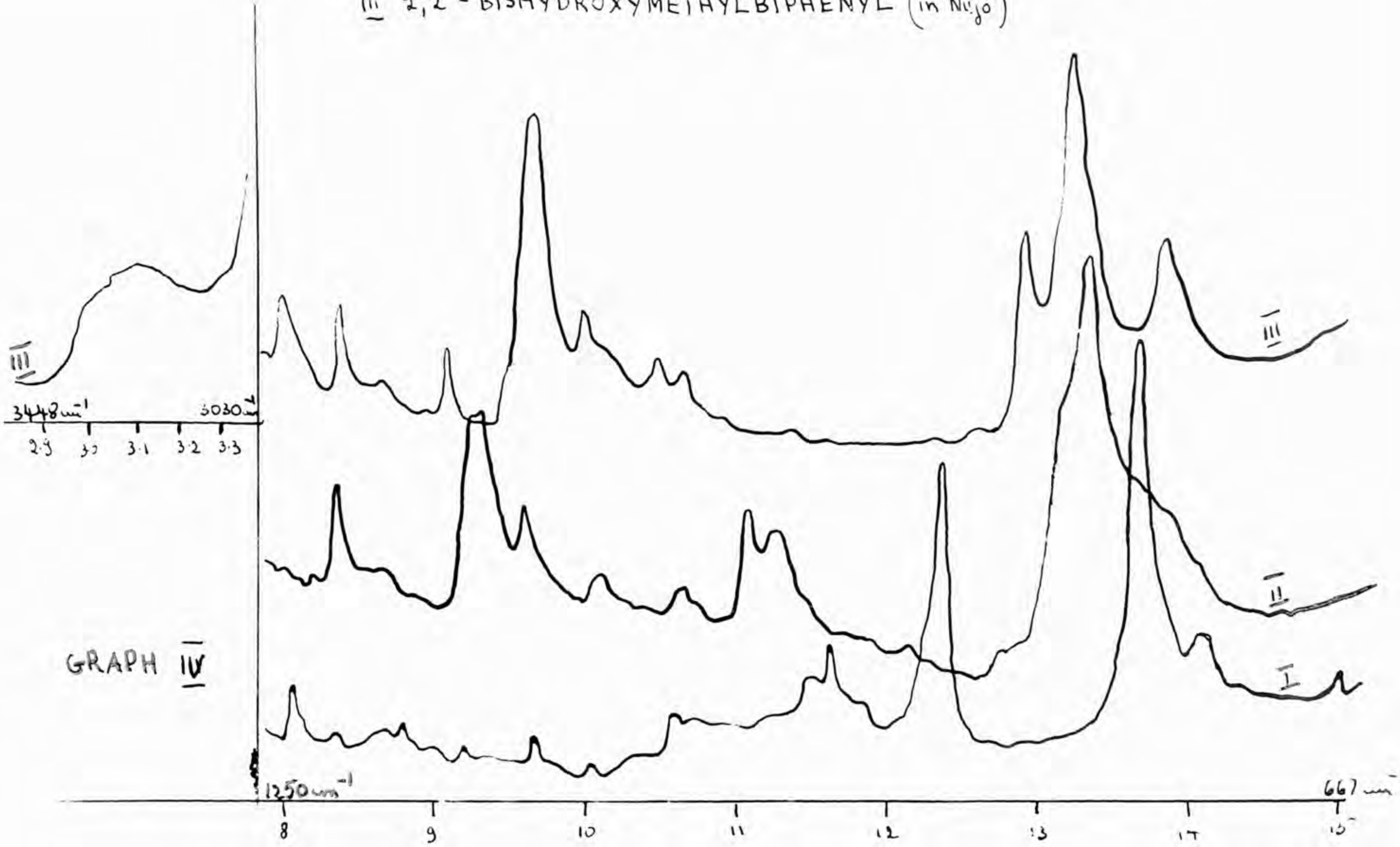


GRAPH II: INFRARED SPECTRA OF 9,10-DIHYDRO-9-DIMETHYLAMINOPHENANTHRENE (27), of 9,10-DIHYDRO-1-METHYL-AZEPINE (26) and of N-METHYLEPHEDRINE (NME.)



GRAPH III : INFRARED SPECTRA of (NME), (26), (27), (23a) & (?)

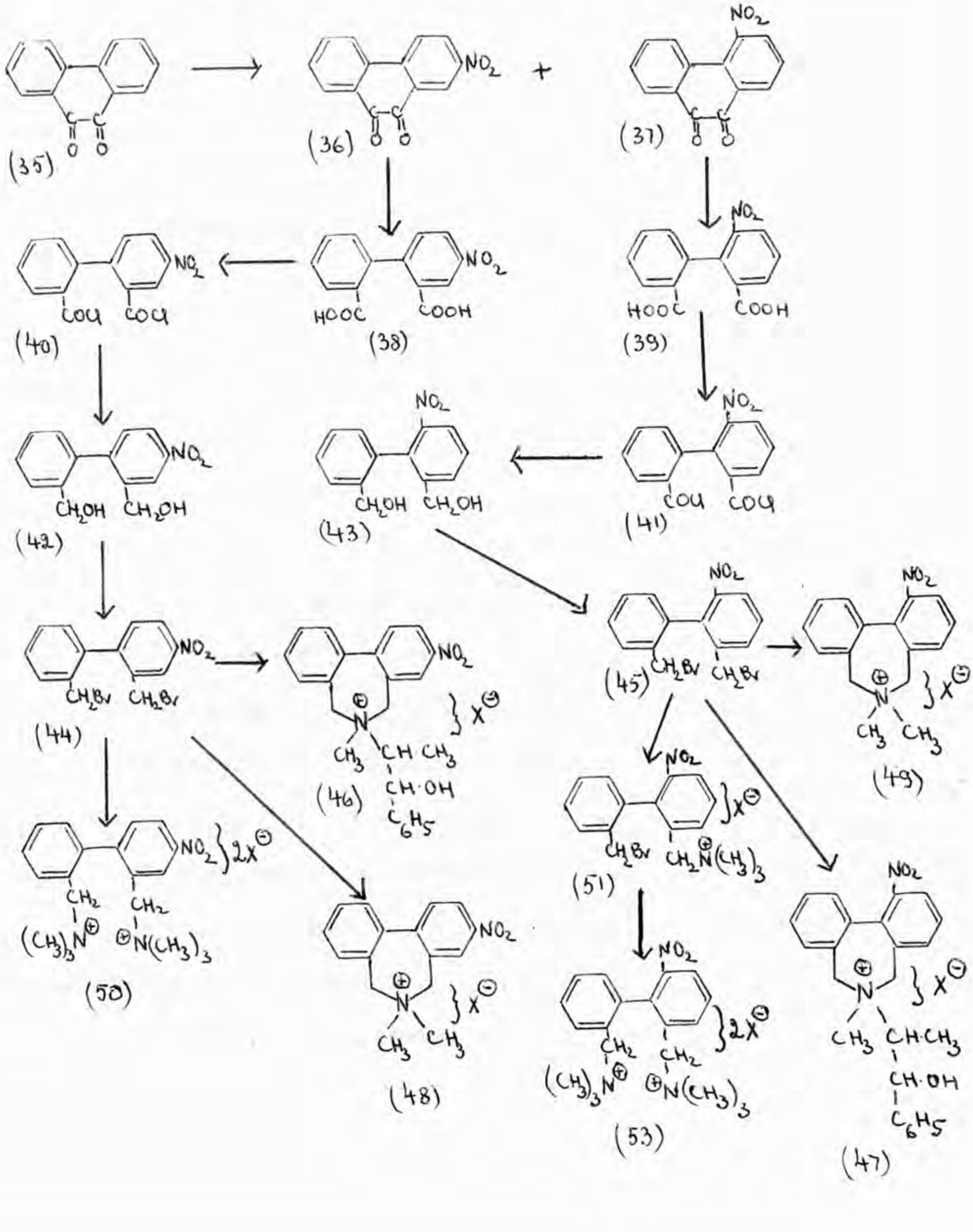
INFRARED SPECTRA OF : I PHENANTHRENE, II OXEPIN,
III 2,2'-BISHYDROXYMETHYLBIPHENYL (in Nujol)



GRAPH IV

(d) Quaternary Salts formed from 2,2'-Bisbromomethyl-6-nitro- and -4-nitro-biphenyl.

The general scheme of synthesis was as follows:



The 2-nitro-(36) and 4-nitro-phenanthraquinone (37) were prepared by mononitration of phenanthraquinone according to Schmidt and Spoun (Chem. Ber., 1922, 55, 1194). Oxidation of the 2-nitro compound with hydrogen peroxide in glacial acetic acid (Labriola and Felitte, J.Org.Chem., 1943, 8, 537) gave a strongly coloured product which on purification gave a 54% yield of the acid (38). A better yield of pure acid (38) was obtained using Moore and Huntress method (J.Amer.Chem.Soc., 1927, 49, 1328) in which the quinone is oxidised by potassium dichromate in sulphuric acid (80% crude, 66% very pure 1st crop). The 6-nitrobiphenic acid (39) was obtained by similar oxidation of the corresponding quinone in 74% yield after crystallisation. Reduction of the acids to the corresponding diols presented some difficulty as it was necessary to find conditions under which the nitro group would not be reduced, It was first attempted to approach the problem by reducing the corresponding ester. The pilot experiments were carried out using the 4-nitrobiphenic acid, since mono nitration of phenanthraquinone gives 54% of 2-nitroquinone to only 28.6% of the 4-nitro compound. The dimethyl ester was 1st prepared using methanol and sulphuric acid but only a 60.5% yield was obtained. Esterification in the presence of hydrogen chloride (Labriola and Felitte, loc.cit.) gave much better yields (90%). An attempt to reduce the ester with sodium borohydride and aluminium trichloride in 1,2-dimethoxyethane with previously carefully purified reagents (Brown, Mead, and Subba Rao, J.Amer.Chem.Soc., 1955, 6209) failed. The intense orange colour of the residue suggested that the reduction went beyond the stage of the diol formation to the azo compound.

Another attempt was made to reduce the ester by the method of Paul and Joseph (Bull.Soc.Chim.France, 1952,19,550). The authors reduced ethyl p-nitrobenzoate to the p-nitrobenzyl alcohol with potassium borohydride and lithium chloride in tetrahydrofuran at 25° and obtained an 86% yield. Using our reagents and repeating their procedure a yield of only 29% was obtained in the same reaction. However an attempt was made to reduce the dimethyl 4-nitro-biphenate in this way. At room temperature the unchanged ester was recovered, while at higher temperature (60-64°) a bright yellow gum was obtained which could not be made to solidify.

A number of authors (Ann.Reports, 1955, 52, 153 ; Nystrom, Chaikin and Brown, J.Amer.Chem.Soc., 1949, 71, 3245; Kollonitsch, Fuchs and Gabor, Nature, 1954, 173, 125) reported successful reductions of nitro-esters to the corresponding nitro-alcohols with lithium borohydride (Hydroselector) in tetrahydrofuran. An attempt to reduce the dimethyl 4-nitro-biphenate in this way at room temperature yielded orange-brown gum indicating at least partial reduction to the azo compound. The gum in chloroform was put through an alumina column but no separation was obtained.

Another approach to the reduction of acid derivatives to alcohols without reduction of the nitro groups present, can be made *via* the acid chlorides (Gaylord, Reduction with Complex Metal Hydrides ; Metal Hydrides Inc., Beverley, Mass., Bulletin 402-B, $LiBH_4$). Very few such reactions have so far been described but the general scheme is

$$\begin{tikzcd} 2LiBH_4 + 4RCOCl \arrow[r] & LiCl + BCl_3 + LiB(OCH_2R)_4 \arrow[d, "H_2O"] \\ & LiBO_2 + 4RCH_2OH \end{tikzcd}$$

The 4-nitro- (40) and the 6-nitro-(41) acid chlorides were therefore prepared by heating under reflux the corresponding acids with an excess of thionyl chloride, which was then removed by distillation at reduced pressure. The crude chlorides were fairly easily hydrolysed in air and were therefore used directly for the reduction without being first purified. Their melting points (87° for 6-nitro and 90-92° for 4-nitro) were very much lower than those of the corresponding acids and in cases where those were much higher the product was retreated with thionyl chloride. No acid anhydrides were isolated (see Bell and Robinson, J., 1927, 1695).

The 4-nitro acid chloride (40) was used in the pilot experiments in an attempt to find optimum conditions for reduction with lithium borohydride. The first two experiments were carried out in tetrahydrofuran. An excess of the hydride was used and the reagent was dissolved in the solvent at -10° to -8°. The reactions were carried out under nitrogen. In the first experiment (4 hours, room temperature) a pale yellow gum was obtained which yielded 0.5 g. (12.5%) of the required diol (42) after treatment with charcoal and benzene. Some 4-nitrodiphenic acid was also recovered. An orange solid was also isolated, which was proved by analysis to be mainly the azo compound. In the second experiment (2.5 hr.) only a 5% yield of diol (42) was obtained.

It was decided to use less stringent conditions and to carry out the reaction in ether. The hydride was dissolved in ether (Na dried) at -8° and a cold solution of the acid chloride in ether was added over 0.5 hour. The temperature rose gradually and the reactants were heated under reflux for a further 0.5 hour at 34°. A 31% yield of diol was obtained. A second attempt gave a 40% yield. By using 5 times the required amount of the lithium borohydride in a 1M ethereal solution and by carrying out the reaction at room temperature for 2 hours and at 34° for 15 minutes the yield was increased to 62.5%. This was further improved to 79% by using 4.3 times required amount of hydride in ether and adding the acid chloride solid at room temperature without any external heating. Some of the crude gum was esterified with p-nitro-benzoyl chloride in pyridine and gave the required di-ester. The ester was hydrolysed with potassium hydroxide, and the resulting gum converted into the dibromide (44) by boiling with 50% hydrobromic acid. A gum was obtained which reacted vigorously with piperidine in dry benzene to give a pale yellow solid, m.p. 302°, which must have been the quaternary piperidinium salt of (44). However too little was obtained to recrystallise or analyse.

2,2'-bishydroxymethyl-6-nitrobiphenyl (43) was prepared from the corresponding acid chloride by the method used for the 4-nitro/compound. It was found however that analogous high yields could be obtained by using a slightly lower excess of lithium borohydride (3.65 ml. instead of 4.3 mol.). The 6-nitro compound crystallised from benzene as solvate but could be obtained unsolvated by drying for 3 days at 60-80° or by allowing it to stand in air for a long time. Solvated it had m.p. 84-85° but dried it had m.p. 96-98°, which was very similar to the 4-nitro diol (42), (m.p. 95-97°). However the two compounds were not identical as shown by mixed m.p. and infrared spectra, as well as by the two different 2,2'-bisbromomethyl-nitrobiphenyl compounds (44 and 45) obtained in good yields from the two diols by the action of hot hydrobromic acid.

2,2'-Bisbromomethyl-4-nitrobiphenyl (44) was used in pilot experiments to obtain quaternary salts by condensation with (-) ephedrine to obtain (46; X=Br), with dimethylamine to obtain (48; X=Br), and with trimethylamine to obtain (50; X=Br). In all three cases quatern~~ar~~isation was very rapid. The isolated quaternary bromides were all solvated, the one with (-) ephedrine was difficult to handle and was converted into the corresponding unsolvated iodide. The salt 2,7-dihydro-1-(β-hydroxy-α-methyl-β-phenylethyl)-1-methyl-2'-nitro-3,4:5,6-dibenzazepinium bromide (46; X=Br) obtained on condensation of the 4-nitro compound (44) with (-) ephedrine contains besides the two resolved asymmetric carbon atoms of the (-) ephedrine a new stable asymmetric centre in the quaternary nitrogen atom and might be expected to separate under favourable conditions into the two diastereoisomers. However crystallisation from ethanol yielded only one (dextrorotary) form with $[\alpha]^{22}_{5461}$ $+ 30.74^{\circ}$ (methanol).

The salt showed no mutarotation at the above temperature. Condensation of (-) ephedrine with 2,2'-bisbromomethylbiphenyl (Beaven, Hall, Lesslie and Turner, J., 1952, 854) yields a quaternary salt which is also dextrorotary and in which no unstable optical activity has been detected in the range of 0°--30° (methanol). It thus seems that in both the above quaternary salts the twisted biphenyl part of the molecule which could give rise to labile optical activity, has too low an energy barrier to passage through the symmetrical state for the activity to be detected under the experimental conditions used.

The 2,2'-bisbromomethyl-6-nitrobiphenyl (45) was condensed like the 4-nitro compound (44) with the same three bases: (-) ephedrine, dimethyl- and trimethylamines. In all cases it was found that it reacted more slowly than the 4-nitro compound (44), an effect which might be expected in the sterically hindered 6-nitro biphenyl derivative.

Condensation of the 6-nitro compound (45) with (-) ephedrine lead to isolation of 2,7-dihydro-1-(β-hydroxy-α-methyl-β-phenylethyl)-1-methyl-4'-nitro-3,4:5,6-dibenzazepinium bromide (47; X = Br). The presence of the nitro group in the 6-position of the biphenyl nucleus increases the energy barrier to passage through the symmetrical transition state in salt (47) as compared with (46) and might be expected to lead to detectable optical activity due to the labile biphenyl asymmetric centre. The asymmetric centres in (47) are :

a) 2 asymmetric carbon atoms of the ephedrine part which represent stable resolved centres; as in (46) ;
b) 1 asymmetric quaternary nitrogen atom, representing an optically stable unresolved centre; as in (46) ;

c) the twisted biphenyl skeleton, sterically hindered by substitution in the 6-position, unresolved, and optically labile.

Both b) and c) can under favourable circumstances separate into the dextro and leavo forms and the total number of possible combinations could lead to separation of the four diastereoisomers (-,+,+,), (-,+,-), (-,-,+) and (-,-,-), where the first negative sign of each form represents the contribution of both the asymmetric carbon atoms of the ephedrine part of the molecule.

The 2,7-dihydro-1-(β-hydroxy-α-methyl-β-phenylethyl)-1-methyl-4'-nitro-3,4:5,6-dibenzazepinium bromide (47;X=Br) was found to mutarotate in methanol at room temperature and since the 2'-nitro quaternary bromide (46) was optically stable under similar conditions, this activity could be attributed to the labile biphenyl centre. An attempt was made to separate by crystallisation the four possible optical isomers. This proved difficult and only one isomer was obtained really or nearly pure. Its mutarotation from a large (-)ve angle ($[\alpha_0]^{24}_{5461}$ - 446°, $[\alpha_0]^{23.5}_{5461}$ -389°) to a smaller (-)ve angle ($[\alpha_\infty]^{24}_{5461}$ - 113°, $[\alpha_\infty]^{23.5}_{5461}$ -109°) with half-life of 10 and 8 minutes respectively would suggest that this represents the optical isomer containing the (-)ve biphenyl form and the (-)ve quaternary nitrogen form. Two preparations were carried out and the above isomer constituted 25-33% of the total product.

The crude residue after separation of the above isomer was found to mutarotate from $[\alpha_0]^{22}_{5461}$ -71° to $[\alpha_\infty]^{22}_{5461}$ -85° with half life of 15 minutes. This residue was treated differently in experiments I and II. In one (experiment II) it was dissolved in water and after many days crystals of hydrated salt were isolated. This crop mutarorated from $[\alpha_0]^{26}_{5461}$ - 81° to $[\alpha_\infty]^{26}_{5461}$ - 90.5° with half life of 11 minutes. At 21.3° the half life was 12 minutes, $[\alpha_0]^{21.3}_{5461}$ - 78.5° and $[\alpha_\infty]^{21.3}_{5461}$ -89°.

In the 2nd case (experiment I) the crude residual bromide was converted into the iodide by treatment with potassium iodide and the iodide was crystallised from water. The hydrated salt isolated was found to mutarotate with half life of 16 minutes from $[\alpha_0]^{22}_{5461}$ - 60° to $[\alpha_\infty]^{22}_{5461}$ -88°. It thus appears that some separation into two further isomers was taking place. The mother liquor from crystallisation of the iodide was evaporated to dryness and the impure residue was examined polarimetrically. At 22° it mutarotated with half life of 4 minutes from $[\alpha_0]_{5461}$ - 78° to $[\alpha_\infty]_{5461}$ -53°. Various solvents were tried in an attempt to effect satisfactory fractional crystallisation but this did not prove possible. However the experiments on the quaternary bromide (47) demonstrated that this type of biphenyl structure with a 6-nitro substituent is sufficiently sterically hindered to lead to detectable optical activity at room temperature.

Condensation of 2,2'-bisbromomethyl-6-nitrobiphenyl with dimethylamine proved facile and the pure 2,7-dihydro-1,1-dimethyl-4'-nitro-3,4:5,6-dibenzazepinium bromide (49 ; X=Br) was obtained after one crystallisation in 68% yield. The (+)-camphorsulphonate prepared from the bromide (49; X=Br) was examined polarimetrically at -4° and at 23° (methanol) and showed no mutarotation or change of rotation with temperature. It had $[\alpha]_{5461}$ $+ 23.5^{\circ}$ at both temperatures. The (+)-α-bromocamphor-$\bar{\pi}$-sulphonate of the azepinium ion (49) was prepared and its solution in methanol was found to mutarotate at 22° (and 24°) with half-life of 50.15 minutes from $[\alpha_0]_{5461}$ -250° (-251°) to $[\alpha_\infty]_{5461}$ $+ 66^{\circ}$ (Tables XI, XII ; graph VIII). Attempts to prepare the active iodide from the (+)-α-bromocamphor-$\bar{\pi}$-sulphonate were not successful as the solubilities of the two salts were alike. The (-) picrate (49 ; $X = C_6H_2N_3O_7$) was however obtained by decomposition at -10° of the bromocamphorsulphonate in methanol with saturated picric acid in ethanol. The (-) picrate had extrapolated $[\alpha_0]^{26.1^{\circ}}_{5791}$ -243° (acetone) and half-life of 21.5 minutes.

At 35.8° the half-life was 5.9 minutes.

The (-) picrate was very insoluble and its racemisation could only be studied in one solvent. Rates of racemisation in acetone were studied in the range 17.2° - 41.2° and the straight line plot of $\log_{10} k_{rac.}$ against 1/T gave the value of (E) of 25.2 kcal.mole.$^{-1}$ and that of (A) of $10^{15.1}$ sec.$^{-1}$ (Table XVIII, graph X).

As would be expected the introduction of the nitro group in the ortho position of the biphenyl nucleus increased the specific rotation of the azepinium compound (49) as compared with the unsubstituted diester (60, Introduction) of Iffland and Siegel (loc.cit), $[\alpha]_D^{32.5^\circ} + 2.25^\circ$, while presence of only one nitro group as compared with Ahmed and Hall's (loc.cit.) dinitro azepine (56, Introduction) with $[\alpha]_{5461}^{19^\circ} + 1333^\circ, -1343^\circ$, has lead to smaller specific rotation.

The 4'-nitro azepinium picrate is optically highly labile. It is less stable than Ahmed and Hall's dinitro azepine which had (E) (benzene) of 30 kcal.mole.$^{-1}$ with half-life of 16 hr. at 125° and 2.6 hr. at 145°. The decrease of the optical stability in (49) results from decrease in the blocking effect of the ortho-positions. The valency state of nitrogen in the two compounds is different but Ahmed and Hall have shown that the methiodide of their base (47, Introduction) is more stable than the base itself. The mono-nitro compound is also less stable than Ahmed and Hall's difluoro azepine (46, Introduction), the hydrochloride of which had half-life of _ca._ 6.5 hr. at 80°. Rather surprisingly the mono-nitro compound (49) appears less stable than the hydrocarbon di-ester of Iffland and Siegel (_loc.cit._) which was inactive after 5 hr. at 32.5°.

The Arrhenius parameter (A) of the (-) picrate has a rather high value of $10^{15.1}$ sec.$^{-1}$ ($\Delta S^{\ddagger}$ + 8.6 e.u.) and in fact appears to be the second highest known for racemisation of compounds of this type (compare Hall and Harris, _J._, 1960, 490). It is not clear why the value is so high though in being $> 10^{13}$ sec.$^{-1}$ it conforms to the general pattern for the following reasons: _a_) high values of (A) with positive entropy factors are associated with bridged biphenyls ; _b_) Brooks, Harris and Howlett (_loc.cit._) have shown that introduction of nitro groups into the biphenyl nucleus lowers the value of (A), though in their diphenic acid series the situation is not strictly comparable as the further nitro groups were introduced in the _para_ positions. Accordingly one would expect the value for the mono-nitro compound to be higher than that in Ahmed and Hall's dinitro azepine ((A) $10^{11.5}$ sec.$^{-1}$, ($\Delta S^{\ddagger}$) - 8.3 e.u.). Unfortunately no figures are available for their dinitro azepinium iodide which is more strictly comparable with the mono-nitro picrate ;

c). Frequency factors (A) are higher for ionised compounds than for unionised ones, an effect probably associated with solvation. This can be observed both in the unbridged and the bridged compounds. For example 6,6'-dimethoxy-diphenic acid (Greybill and Leffler, *J.Phys.Chem.*, 1959, 63, 1461) has in ethanol (A), $10^{9.8}$ sec.$^{-1}$; ($\Delta S^{\ddagger}$), -15.5 e.u.; while its sodium salt in water (Greybill and Leffler, *ibid.*,1457) has (A), $10^{10.6}$sec.$^{-1}$; ($\Delta S^{\ddagger}$), -12.3 e.u.. The same effect can be observed in the 8-atom ring bridged biphenyl di-acid of Dworken, Smyth and Mislow (loc.cit.) : in ethanol the acid had (A) $10^{12.5}$ sec.$^{-1}$; ($\Delta S^{\ddagger}$) -3.5 e.u., and in 2.32N-NaOH (A) was $10^{14.5}$sec.$^{-1}$ and ($\Delta S^{\ddagger}$) + 5.8 e.u.

Synthesis of pure 6-nitro-2,2'-bis(trimethylammoniomethyl)biphenyl dibromide proved unexpectedly difficult. Condensation of the corresponding bromide (45) with trimethylamine in dry acetone yielded the mono-quaternary salt (51;X=Br) with m.p. 243° (decomp.) which on treatment with saturated potassium iodide yielded the mono-quaternary iodide with the bromo-methyl group in the other *ortho* position. Since nitrobenzene proved in previous experimental work a suitable solvent for the quaternisation of similar compounds it was attempted to carry out the reaction in it. The main crop was again the mono compound, but some impure solvated di-quaternary compound

(53) was also isolated as intermediate crops with m.p. ca.170° (decomp.) with strong softening at 145 - 150°. Its infrared spectrum was markedly different from that of the mono compound (51). The C-Br band at 615.4 cm.$^{-1}$ present in the mono-quaternary compound (51) was here absent. Two additional bands were present : a hydroxyl band at 3371.5 cm.$^{-1}$ and a broad band with fine structure with maxima at ca. 1667 cm.$^{-1}$ and 1605cm.$^{-1}$ and a minimum at 1587 cm.$^{-1}$ Ethyl acetate used in recrystallisation has a broad band in the latter region with maximum at 1724 cm.$^{-1}$ and a definite minimum at 1587 cm.$^{-1}$ This band was diminished in intensity on drying for 14 hrs. at 100-120°/9 cm. but became very weak only after prolonged drying in vacuum at 155-160°. The intensity of the hydroxyl band was hardly at all reduced on drying as in the above cases.

It was hoped that a purer product could be obtained by using more stringent conditions. The mono-quaternary salt (51) was used as starting meterial and the reactants in nitrobenzene were sealed in a tube and heated at 100°. This time the main product was the di-quaternary salt (53; X=Br) but some of the mono-compound (51) was also recovered. In an attempt to complete the reaction in one step the 2,2'-bisbromomethyl-6-nitrobiphenyl (45) was heated with trimethylamine in nitrobenzene in a sealed tube for 17 hours at 138°. The product seemed to be the di-quaternary salt. Crude it had m.p. 251°. However the anhydrous salt could not be obtained pure as on contact with air or on crystallisation it solvated. Recrystallised it had m.p. 175° (decomp.) with shrinking at ca. 150-155°. Repeated analysis gave unsatisfactory and varying results. The solvated di-bromide (53;X=Br) was purified by converting it into the corresponding picrate by treating its aqueous solution with aqueous sodium picrate. The pure diquaternary picrate had m.p. 205.5° - 207.5°. It was treated in water with 48-50% hydrobromic acid and the more soluble solvated dibromide (m.p. 175° (decomp.), strong shrinking 155-157°) was isolated from the mother liquor. After subjecting the salt to prolonged drying in vacuum, a satisfactory analysis was eventually obtained for it (53; X=Br ; $\frac{1}{2}H_2O$). The dibromide was converted into the (+)-α-bromocamphor-π-sulphonate by treatment with the silver salt of the latter in aqueous alcohol. This would not crystallise and the (+)-camphorsulphonate was therefore prepared. This crystallised easily from acetone.

EXPERIMENTAL

2-Methyl-1-nitronaphthalene (2)

Fiertz-David, Manhart, Helv.Chim.Acta, 1937, 20, 1024.

2-Methylnaphthalene (71 g., 1 mol.) was dissolved in glacial acetic acid (110 g., 3.66 mol.) and the solution was stirred mechanically and cooled to 0° - 5° in an ice and salt mixture. Fuming nitric acid (29 g., 0.92 mol.) was added from a dropping funnel at such a rate that the temperature remained below 5°. Addition took 50 minutes, stirring being continued throughout and for 2½ hr. after. The reaction mixture was allowed to warm to room temperature and then slowly heated to 80° during 4 hr. The mixture (poured into a beaker) was left overnight at ca. 0°. The yellow nitro compound was filtered off and the filtrate was treated with ice and cooled in ice till no more solid separated. The combined precipitates were washed well with sodium hydroxide and water, dried and recrystallised from half their weight of methylated spirit. Yield 40 g., 43%. Pale yellow needles, m.p. 80°.

The preparation was repeated 5 times and 219.5 g., of 2-methyl-1-nitronaphthalene were obtained. The yields varied between 37% and 43%. Attempts were made to increase the yield to the 60% reported by the authors but were not successful. Thus 2-methylnaphthalene obtained from 3 different sources was used as the starting material, temperature and time of reaction were strictly controlled to follow **Fiertz**- David and Manhart and the filtrates and washings were examined and worked up carefully : the filtrates were in each case re-treated with ice and kept at 0° till no more nitro compound separated out ; the sodium hydroxide and aqueous washings were also examined a) by acidifying and treating with ice, b) by evaporation to dryness (which gave only sodium acetate). No nitro compound was being lost in this way.

1-Amino-2-methylnaphthalene (3)

a) Adams and Albert, J.Amer.Chem.Soc., 1942,64,1475.

A suspension of 2-methyl-1-nitronaphthalene (25 g.) and Raney nickel catalyst (5 g.) in 95% ethanol (75 cc.) was shaken under hydrogen at room temperature and at 3 atm. pressure for 12 hr. The reaction mixture was warmed and the catalyst filtered off. On cooling, yellow needles of the unchanged nitro compound crystallised out (18 g.). They were filtered off and the filtrate was distilled to remove the ethanol. The residue solidified on cooling. On recrystallisation from light petroleum (b.p. 60 - 80°) reddish brown needles were obtained melting at 72 - 75°. 1-Amino-2-nitronaphthalene melts at 31°.

b) Wertheim, Organic Synth., 1943, 471, (Collective Vol.2. ed. Blatt).

Coarse iron fillings (50 g.) were placed in a 2 litre flask, covered with water and heated under reflux on a vigorously boiling water bath. A few c.c. of glacial acetic acid were added and when the evolution of hydrogen was rapid the melted 2-methyl-1-nitronaphthalene (50 g.) was added. The reaction mixture was kept boiling vigorously under reflux for five hours, boiling water being added to keep the reaction mixture mobile.

500 C.c. of hot methylated spirit were added and the reaction mixture was boiled under reflux for a further 10 min. It was then filtered hot on a thick pad and allowed to stand overnight. Unreduced nitro compound (10 g.) separated out and was filtered off. Concentrated hydrochloric acid was added to the filtrate till no more base hydrochloride was precipitated. The greenish-grey hydrochloride was filtered off, washed with water and then with ether. Evaporation of the latter gave a further 7.5 g. of unchanged nitro compound. The base hydrochloride (35 g.) was treated with sodium hydroxide, the liberated base was extracted with ether and the latter was distilled off. The residue, a brown oil, was kept at ca.0° but did not solidify. It was purified by using Lesser's method (Annalen, 1913, 402, 38) i.e. the base was converted into the hydrochloride and steam

distilled to remove the unchanged nitro compound. The residue in the flask was then treated with 30% sodium hydroxide and the liberated base was steam distilled. It solidified on standing in ice and was recrystallised from light petroleum (b.p. 60-80°). White crystals rapidly turning purplish were obtained with m.p. 31-32°.

Two such preparations were carried out and 36.5 g. of 2-methyl-1-nitronaphthalene were recovered and 27 g. (51% on the basis of nitro compound used up) of 1-amino-2-methylnaphthalene were obtained from the steam distillation.

c) Lesser and Aczel, <u>Annalen</u>, 913, <u>402</u>, 30.

Coarse iron filings (12 g., 3.5 g.atoms) were added gradually to a hot suspension of 2-methyl-1-nitronaphthalene (11.5 g., 1 mol.) in 140 c.c. of 50% acetic acid. The reaction was continued by boiling under reflux for 1½ hr. The dark brown oily base which separated out on cooling was converted into the solid greyish-green hydrochloride by the addition of concentrated hydrochloride acid. The mixture was then steam distilled to remove the unreduced nitro compound (1 g.). The base was liberated by the addition of sodium hydroxide and steam distilled. A white oil was obtained which solidified on standing in ice. It was filtered off and recrystallised from light petroleum (b.p. 60-80°). White crystals which rapidly turned purple were obtained m.p. 31-32°. Yield 8.5g. (88%).

The quantities used in this preparation represent the optimum conditions. On using twice the stated amount the yield was reduced to 73%, while a fourfold increase reduced the yield still further to 66%.

Lesser obtained yields of 60 - 70%. A total of 102 g. of 1-amino-2-methylnaphthalene was prepared by all methods.

1-Iodo-2-methylnaphthalene (4)

a) Diazotisation method :

1-Amino-2-methylnaphthalene (24 g.,1 mol.) was dissolved with warming in concentrated sulphuric acid (10.5 cc., 1.25 mol.) diluted with 165 c.c. water. The solution was cooled to 0° in an ice-salt mixture. Sodium nitrite solution (10.5 g., 1 mol., in 21 c.c. water) was added dropwise with stirring at such a rate that the temperature remained between 5° - 10° throughout diazotisation which took 30 minutes.

Addition of the diazo solution to the solution of potassium iodide (37.5 g., 1.5 mol., in 60 c.c. of water) did not result in evolution of nitrogen and formation of iodo compound till the solution was warmed to 50°- 60°. The two solutions were mixed over a period of 30 mins. with shaking and warming. The reaction mixture was left to stand for 1 hr. at room temperature and overnight on the water bath at ca. 30°.

3.5 G. of sodium bisulphite were added to remove free iodine and the iodo compound was steam distilled. It appeared as a brown oil in the distillate. The distillate was washed with 10% sodium hydroxide solution to remove any remaining free iodine. The iodo compound was allowed to settle and the top layer of liquid was decanted. The rest was extracted with ether and dried over anhydrous sodium sulphate. Removal of ether by distillation and subsequent distillation of the residue under reduced pressure yielded 27 g. (66%) of the golden yellow liquid, b.p. 148/ 2 mm. The preparation was repeated and in all 90 g. of the 1-iodo-2-methylnaphthalene were prepared in this way.

b) Direct Iodination with Iodine and Iodic Acid:

Adoptation of Wirth, Konigstein and Kern (*Annalen*, 1960, *634*, 84), method used for iodonaphthalene by the authors.

2-Methylnaphthalene (11.8 g., 0.125 mol.) was dissolved in glacial acetic acid (100 c.c.) in a 250 c.c. round bottomed flask fitted with a condenser, calcium chloride tube, stirrer and thermometer. The solution was stirred vigorously throughout the preparation. It was warmed to 50° and water (5.c.c.) and carbon tetrachloride (5 c.c.) were added, the latter to prevent sublimation of iodine. The solution was cooled and concentrated sulphuric acid (5 c.c.), iodine (10.2 g., 0.08 g.atom) and iodic acid (4.1 g.,0.023 mol.) were added. The reaction mixture was warmed to 55°- 60° and kept at this temperature. After 12 hr. the very dark iodine-coloured mixture began to look paler. A further 1 g. of iodic acid was then added and 2 c.c. of water, the amount of the latter determining the amount of iodic acid taking part in the reaction, since the iodic acid is soluble in water but not in acetic acid.

After a total of 20 hr. at 55°- 60° the reaction mixture was steam distilled and the distillate was washed with sodium hydroxide. The iodo compound was allowed to settle and most of the aqueous acid layer was decanted ; the rest was extracted with ether and dried over calcium chloride. The ether was distilled off and the residue was distilled under reduced pressure. 22 G. (65.8%) of 1-iodo-2-methylnaphthalene b.p. 162°/ 5 mm ., were obtained.

o- Iodotoluene.

o-Toluidine (107 g., 1 mol.) was dissolved in concentrated sulphuric acid (77 c.c., 1.25 mol.) diluted with 250 c.c. of water and cooled in ice to room temperature. 250 g. of ice were added and the sulphate was cooled in an ice-salt mixture to 0°- 3°. Sodium nitrite solution (69 g., 1 mol. in 140 c.c. of water) was added slowly through a dropping funnel, with stirring, at such a rate that the temperature remained below 10°. The diazonium solution was filtered through a Buchner funnel cooled in ice and added slowly to a solution of potassium iodide (249 g., 1.5 mol., in 400 c.c. water). After the addition was completed the reaction mixture was allowed to stand for 1 hr. at room temperature after which it was heated gently on the water bath till evolution of nitrogen stopped. o-Iodotoluene was then steam distilled, the distillate was washed well with 10% sodium hydroxide solution and the top aqueous layer was decanted. The o-iodotoluene was dried over calcium chloride and distilled. 146 G. (67% yield) b.p. 208°- 212° were obtained.

1-Bromo-2-methylnaphthalene (9)

Adams and Binder, J. Amer. Chem. Soc., 1941, 63, 2773, modified Hall and Mitchell, J., 1951, 1375.

2-Methylnaphthalene (142 g., 1 mol.) was dissolved in 300 c.c. of carbon tetrachloride and a crystal of iodine and a pinch of iron powder were added as catalysts. The solution was cooled to 0° in an ice and salt mixture. Throughout the reaction light was excluded and the reactants were stirred mechanically. Bromine (160 g., 1 mol.) was dissolved in 300 c.c. of carbon tetrachloride and added to the 2-methylnaphthalene during 20 minutes the temperature being kept at $\nless 5^{\circ}$. After the addition was completed, the reaction mixture was stirred for a further 40 mins. It was then filtered, washed with 400c.c. of a 10% sodium hydroxide solution and with water, and dried over calcium chloride. The solvent was distilled off and the residue was distilled under reduced pressure. Yield 201 g. (91%), b.p. 128°/ 4 mm. The preparation was repeated five times and 966 g. of 1-bromo-2-methylnaphthalene were prepared in all with an average yield of 88%.

Attempted Synthesis of 2,2'-Dimethyl-1,1'-binaphthyl by the action of copper bronze on 1-iodo-2-methylnaphthalene.

a) Copper bronze was activated (Kleiderer and Adams, J.Amer.Chem.Soc., 1933, 55, 4219) by treatment with a 2% solution of iodine in acetone, followed by filtering and washing with hydrochloric acid and acetone and drying in a vacuum desiccator.

1-Iodo-2-methylnaphthalene (40 g., 1 mol.) was heated on a metal bath to 240-250° and the copper bronze (24 g.,2.5 atoms) was added during 2 hr. At this stage the temperature rose rapidly to 300° and a rapid evolution of iodine vapour was observed. The reactants were cooled rapidly and extracted with hot toluene, filtered, washed with sodium hydroxide and water and dried over calcium chloride. The toluene was distilled off and the residue distilled at reduced pressure:

(37.5%) 1st fraction,b.p. 98-102° /3 mm., 8 g. of 2-methylnaphthalene.

2nd fraction,b.p. 148° /3 mm., 4 g.of 1-iodo-2-methylnaphthalene.

A tar residue was rejected.

b) The synthesis was repeated using copper bronze not activated. The 1-iodo-2-methylnaphthalene (20 g., 1 mol.) was heated with copper bronze (20 g. 4.23 atoms) at 180-190°, the addition of copper being continued for 3 hours. The product after cooling was extracted with toluene and the latter was distilled off. A brown viscous oil was obtained. An attempt to separate and purify the products by passing a 2% acetone solution through a silica gel column was not successful. Crystallisation from light petroleum, acetone and alcohol also failed.

2-Methyl-1-o-tolylnaphthalene (5)

a) Ullman method: action of copper bronze on o-iodotoluene and 1-iodo-2-methylnaphthalene.

1-Iodo-2-methylnaphthalene (10g., 1 mol.) and o-iodotoluene (16 g.,2 mol.) were heated to 210-225° in a metal bath. An air condenser was fitted to the tube containing the reactants as both are volatile at this temperature. Copper bronze (26 g., 11 atoms) was added with stirring over a period of two hours. The reaction mixture was then kept for another hour at 210-225°.

It was cooled and extracted with hot toluene. This was distilled off and the product was distilled under reduced pressure. Three main fractions were obtained:
the first, b.p. 110°/3 mm., (mostly 2-methylnaphthalene),
the second, b.p. 110-140°/3 mm., (unchanged reactants).
the third, b.p. 160-185°/3 mm., 2-methyl-1-*o*-tolylnaphthalene).
The third fraction was redistilled and 2 g. (23%) b.p. 150-160°/3mm, of pure 2-methyl-1-*o*-tolylnaphthalene were obtained. The composition of the fractions was elucidated by vapour phase chromatography using Apiezon M on celite columns at *ca.* 200° and 1.7-1.9 l./hr. flow rate. A large tarry residue was also obtained.

2-Methyl-1-o-tolylnaphthalene from 1-lithio-2-methylnaphthalene and 2-methylcyclohexanone.

1-Bromo-2-methylnaphthalene (100 g., 0.9 mol.), dried over calcium chloride and freshly distilled, was added slowly from a dropping funnel to finely divided lithium (6.8 g., 0.97 g. atom) placed in 180 c.c. of dry ether in a flask swept throughout the experiment with dry nitrogen. The reaction mixture was stirred mechanically. When the addition of the bromo compound was completed (45 minutes), the reactants were heated under reflux for 1 hr. They were then cooled and

2-methyl-cyclohexanone (46 g., 0.82 mol.) was added dropwise to the 1-lithio-2-methylnaphthalene. When all the ketone had been added the reaction mixture changed colour from dark brown to pale yellow-green. The reactants were heated for 1 hr. under reflux, cooled and filtered through glass wool into a 500 c.c. conical flask containing crushed ice. The product was stirred well, more water and a few c.c. of dilute hydrochloric acid were added to dissolve all the solid and the ether layer was separated. The aqueous layer was extracted with ether, the combined ether extracts were washed with brine and with water and dried over anhydrous sodium sulphate.

Ether was distilled off and 2 g. of naphthalene - β -sulphonic acid were added to the carbinol and the mixture was warmed gently. After 30 mins. the reactants were cooled, ether and water were added and the two layers were separated. The aqueous layer was extracted with ether and the combined ether extracts were dried over calcium chloride. Ether was then distilled off and the dehydration of the carbinol was completed by adding another 2 g. of naphthalene - β - sulphonic acid to the residue and warming gently for 1 hour. The product was then treated as at the first stage of dehydration. After removal of ether the product was distilled under reduced pressure. Three fractions were obtained : (1) b.p. 42 - 82° /4 mm., 22 g., consisted of the unchanged ketone; (2) b.p.82-100° / 3 mm., 22.8g., consisted of 2-methylnaphthalene ; (3)b.p.140-162°/3mm., contained mainly the desired mixture of 1:2 and 1:6 olefins. This fraction was redistilled and gave 5 g.,b.p. 128/132°/2 mm. of 2-methylnaphthalene and 24 g.,b.p.142-148°/2mm. of the olefins, (48% based on the ketone actually used). The reaction was carried out six times in all with an average yield of 62%.

Dehydrogenation:

Palladium-charcoal 5% (1 g.) was added to 10 g., of the olefin and the mixture was heated slowly on a metal bath during 3 hr. to 300° and kept at this temperature for a further 3¾ hr. The product was cooled and extracted with hot benzene, filtered twice and dried over calcium chloride. The solvent was distilled off and the product was distilled twice under reduced pressure to give 5.5 g., (64%) b.p. 151-158°/3 mm. 57.5 G. of the hydrocarbon were synthesised in all, the average yield over 8 preparations being 46-47%. (Found: C,92.6 ; H, 7.2 ; Calculated for $C_{18}H_{16}$: C, 93.0 ; H, 6.9 %). The purity of the hydrocarbon was strictly controlled by using vapour phase chromatography. 6 Foot columns of 30% Silicone E 301 on Celite 545 at 227-229° and a flow rate of 1.7 litres per hr. were found most satisfactory for these high boiling hydrocarbons.

2-Bromomethyl-1-(o-bromomethylphenyl-)naphthalene. (6)

2-Methyl-1-*o*-tolylnaphthalene (5g., 1 mol.) was dissolved in 25 c.c. of dry carbon tetrachloride. N-Bromosuccinimide (7.7 g., 2 mol.) and benzoyl peroxide (0.05 g.) were added. The mixture was heated under reflux for 3½ hr. More carbon tetrachloride (10 c.c.) was added and the reaction mixture was heated to boiling and filtered hot through a preheated Buchner funnel. The insoluble succinimide was washed with hot solvent and the filtrate was filtered again when cool to remove the rest of the succinimide. The yellow solution was concentrated by distilling off most of the solvent. The rest of the solvent was removed by gently warming on a hot plate while stirring and finally by drying in a vacuum desiccator. 7 G. of dark brown viscous liquid were obtained. This was used crude for the attempted preparation of quaternary salts. Seven such preparations were carried out and 61 g. of the impure dibromo compound were prepared in all.

2,2'-Bis(N-pyridiniummethyl)-5,6-benzbiphenyl Dibromide (7;X=Br)

2,2'-Bisbromomethyl-1-phenylnaphthalene (3.5 g., 1 mol.) and pure dry pyridine (1.6 g., 2.2 mol.) were dissolved separately in dry benzene. The two solutions were mixed and warmed gently for 15 min. at which point a gum begun to separate.

The warming was continued for a further 30 min., the reactants being stirred vigorously. On cooling, the gum started to solidify. The solvent was decanted and the semi-solid gum was washed several times with dry benzene till it all solidified. The solid was filtered rapidly, washed with dry acetone and placed in a vacuum desiccator as it was deliquescent. Crystallisation proved difficult but eventually 1 g. (20% yield) was obtained from methanol-acetone as a microcrystalline pale yellow monohydrate, m.p. 264° (decomp.). (Found: C, 59.3 ; H, 4.4 ; N, 5.1 ; Br, 28.2 $C_{30}H_{26}ON_2Br_2$ requires C, 59.3 ; H, 4.6; N, 5.0 ; Br, 28.2%).

2,2'-Bis(N-pyridiniummethyl)-5,6-benzbiphenyl Di-(+)-camphorsulphonate.

2,2'-Bis(N-pyridiniummethyl)-5,6-benzbiphenyl dibromide monohydrate (0.566 g., 1 mol.) and silver (+) camphorsulphonate (0.678 g., 2 mol.) were dissolved separately in water and heated. The hot solutions were mixed and boiled to coagulate the silver bromide. The solution was left overnight and then filtered twice using a sintered glass funnel containing some chromatographic alumina. The filtrate was evaporated on a water bath and gave a glassy solid very soluble in methanol and chloroform but insoluble in light petroleum. The camphorsulphonate has failed to crystallise during 2½ years.

2',7-Dihydronaphtho(2',1':3,4)-5,6-benzazepinium-1-spiro-1'''-piperidinium Iodide (8; X=I)

2-Methyl-1-o-tolylnaphthalene (5 g., 1 mol.) was brominated as before and the freshly prepared dibromide was dissolved in a few c.c. of dry benzene. Piperidine (4 g., 2.2 mol.) was added. Immediate reaction took place, a gum separated and the reaction mixture became very hot. It was left overnight in a vacuum desiccator. Water and benzene were then added till a clear solution was obtained ; the two layers were separated and back extracted and the aqueous layer was concentrated in a vacuum evaporator. On cooling no solid crystallised out so the bromide was converted into the less soluble iodide by the addition of a cold saturated solution of potassium iodide. The quaternary iodide separated as a gum which became crystalline under aqueous ethanol on standing at 0°. The crude product (1.3 g., 15%) was recrystallised from 96% ethanol and had m.p. 178-180° (softening 170°), (1.1g., 12.5%). The iodide was solvated. It was recrystallised also from dry acetone and it crystallised with 1 molecule of solvent. M.p. 155° (decomp.) (Found: C, 62.4 ; H, 6.2 ; N, 3.0 ; O, 3.6 ; I, 25.0. $C_{23}H_{24}NI.C_3H_6O$ requires C, 62.5 ; H, 6.05 ; N, 2.8 ; O, 3.2 ; I, 25.4%).

2-Iodo-5-nitrotoluene (14)

Carlin and Foltz, *J.Amer.Chem.Soc.*, 1956, *78*, 1997.

2-Amino-5-nitrotoluene (25 g., 1 mol.) was dissolved in hot glacial acetic acid (200 c.c.) and the solution was cooled with stirring to 15° in an ice-bath. Concentrated sulphuric acid (92.5 c.c.) was cooled to 0° and sodium nitrite (16.5 g., 1.45 mol.) was dissolved in it slowly. The temperature rose during the addition but the mixture was cooled to 15° before it was added slowly and with constant stirring to the nitroamine solution. The temperature was not allowed to rise above 25° throughout the addition. The diazo solution was poured with stirring into 750 c.c. of ice-water and urea (16.5 g. 1.67 mol.) was added to destroy excess nitrous acid. Potassium iodide solution (39.5 g., 1.44 mol., in 200 c.c. water) was then added gradually and with stirring and the iodo compound separated as a solid. Solid sodium bisulphite was added to remove free iodine. The product was filtered, washed well with water, then with 10% sodium hydroxide and again with water. It was dried in a vacuum desiccator and recrystallised from aqueous ethanol. 27 G., m.p. 103-105°, small pale yellow needles, were obtained as first crop. Concentration of the mother-liquor gave a further 4 g., m.p. 100-105°. Yield 72% . 75.5 G. of the compound were prepared altogether.

2,2'-Dimethyl-4,4'-dinitrobiphenyl (15)

2-Iodo-5-nitrotoluene (25 g., 1 mol.) was dissolved in 25 c.c. hot dimethylformamide which has been previously dried over calcium oxide and distilled. The solution was heated to 160° in a metal bath. Copper bronze (28 g., 4.6 atoms) was added all at once with stirring and an air condenser was placed over the tube containing the reactants. The mixture was kept refluxing at 153-160° for one hour. It was then cooled, extracted with boiling dimethylformamide and filtered. The solvent was distilled off at 80°/11-17 mm. till the residue was almost solid. Light petroleum (800 c.c.) (b.p. 60-80° and 80-100°, 1:1 mixture) was added and the solid was dissolved by boiling under reflux. The solution was filtered and cooled. After a time crystals separated and 3.3 g., m.p. 169-170° were obtained as first crop, while concentration of the mother liquor yielded a further 3.65 g. (total yield 54%). Recrystallised from alcohol the compound had m.p. 171-172° (6.0 g., 46%).

4,4'-Dinitro-2,2'-bisbromomethylbiphenyl (17)

A solution of 4,4'-dinitro-2,2'-dimethylbiphenyl (5.4 g., 1 mol.) in dry carbon tetrachloride (51 c.c.) was heated under reflux for 30 hr. with N—bromosuccinimide (7.2 g., 2 mol.) and benzoyl peroxide (0.1 g. + 0.1 g.). The mixture was filtered hot on a preheated Buchner funnel, washed with hot carbon tetrachloride and the filtrate was cooled overnight. A solid separated out which was filtered off, ground with ice-water to remove the soluble succinimide, filtered again and dried in a vacuum desiccator (4.5 g.). The product was crystallised twice from benzene-cyclohexane mixture giving 3.2 g. of mainly monobromo compound m.p. 156-158° (Found: C,46.8; H, 3.1 ; N,7.0 ; Br, 19.9. $C_{14}H_{11}N_2O_4Br$ requires: C, 47.9 ; H, 3.15 ; N, 8.0 ; Br, 22.75%).

The product (1.22 g., 1 mol.) was re-treated with N-bromosuccinimide (1.5 g., 1 mol.) and benzoyl peroxide (0.1 g.) in carbon tetrachloride (30 c.c.). The mixture was heated under reflux for 14 hr. and worked up as above except that crystallisation took place after standing for two days at 0°. The crude product (1.5 g., m.p. 113-114°) was recrystallised as above to give 1.0 g. m.p. 115° (Found: Br, 35.6 ; $C_{14}H_{10}N_2O_4Br_2$ requires Br, 37.2%). Thus after two treatments the bromination was still not complete.

Dimethyl-2,2'-diphenate (19)

Hall, Lesslie and Turner,(J., 1950, 711).

Diphenic acid (202 g.) was placed in a 5 litre flask fitted with a reflux condenser and a calcium chloride tube. Concentrated sulphuric acid (110 c.c., 202 g., d. 1.834) and methyl alcohol (2550 c.c., 2020 g., d. 0.7928) were added and the mixture was boiled for 6 hr. It was cooled, poured into water and the acid was neutralised with sodium bicarbonate. The ester was filtered off, washed well with water and dried in air. It was recrystallised from methyl alcohol and 176 g., m.p. 74-75°, were obtained as first crop and 19.2 g., m.p. 73-75°, as second crop. Total yield 87%.

2,2'-Bishydroxymethylbiphenyl (20)

Hall, Lesslie and Turner, (*loc.cit.*)

Dimethyl-2,2'-diphenate (38 g., 1 mol.) was dissolved in 350 c.c of dry ether and the solution was added as fast as refluxing permitted to a solution of lithium aluminium hydride (8.5 g., 1.59 mol.) in 300 c.c. dry ether. Water and dilute sulphuric acid (2N) were then added cautiously to decompose the excess of reagent and the alkoxides formed. A certain amount of solid remained in the reaction flask and this was filtered off. The ethereal layer was separated and the solvent was evaporated on a water bath. The white solid diol which remained as residue was recrystallised from benzene. 25 G., m.p. 113-114°, were obtained (80% yield). The preparation was repeated twice and 75g. of the diol were prepared altogether.

2,2'-Bisbromomethylbiphenyl (21)

Hall, Lesslie and Turner, (loc.cit.)

2,2'-Bishydroxymethylbiphenyl (19 g.) was added gradually at 90° to 46-50% hydrobromic acid (950 c.c.). The mixture was then heated to boiling and boiled for 20 min.. On cooling a solid separated out. It was filtered off, washed with water and dried in a vacuum desiccator. The bromide was dissolved in boiling light petroleum (b.p. 60-80°) and a little charcoal was added just before filtering. On cooling, crystals of the dibromide separated out. 25 G., (91%) m.p. 91-93°, were obtained as first crop, and 4 g., m.p. 89-91° as second crop. The preparation was repeated and 100 g. of the dibromide were prepared in all.

Attempted Synthesis of 2,2'-Di[N-(β-hydroxy-α-methylphenyl)-N,N-dimethylammoniomethyl] biphenyl Dibromide (22 ; X = Br)

(a) Quaternarization in benzene :

The corresponding dibromide (21) (0.7 g., 1 mol.) and N-methylephedrine (0.8 g., 2.2 mol.) were dissolved in dry warm benzene, the solutions were mixed and heated for 1 hr. at 60-70°. The mixture was kept 18 hr.. at room temperature (calcium chloride tube) and the solid was filtered off, washed with dry benzene and dried in air. It melted from 78-80° to 170-174°. It was washed with warm carbon tetrachloride and N-methylephedrine, m.p. 86° (after crystallization from aqueous alcohol), was obtained on evaporation of the washings. The remaining solid, insoluble in carbon tetrachloride, had m.p. 172-174°, not depressed by mixed m.p. with base hydrobromide m.p. 174°.

(b) Quatern~~ar~~ization in acetone:

The dibromide (1.4 g., 1 mol.) and N-methylephedrine (1.6 g., 2.2 mol.) were dissolved in dry hot acetone, mixed and heated under reflux for 7 hr.. The solid was filtered off, washed with dry acetone. The acetone on evaporation yielded unreacted base. The product (2 g.) recrystallised from acetone-methanol mixture gave base hydrobromide (m.p. 174°) as first crops, and the expected quaternary dibromide (m.p. 202-208°) as latter crops. The dibromide was impure and hygroscopic. It was converted into the di-iodide with aqueous potassium iodide and yielded on one crystallisation from ethanol 1 g., m.p. 207-209° (32%).

(c) Quatern~~ar~~ization in 96% ethanol:

The bromide (1.4 g., 1 mol.) and N-methylephedrine (1.6 g., 2.2 mol.) were dissolved in hot alcohol, mixed and heated under reflux for 12 hr. On working up the unchanged reactants were recovered.

(d) Quatern~~ar~~ization in nitromethane:

The reactants in proportions used in (c) were dissolved in hot dry nitromethane (purified by heating under reflux, under nitrogen and over charcoal for 4 hr., filtering and drying over calcium chloride and distilling through a Dufton column). The solutions were mixed and heated under reflux for 10 hr. On working up the unchanged reactants were recovered.

(e) Quatern~~ar~~ization in nitrobenzene:

The reactants in proportions used in (c) were dissolved in 10c.c. nitrobenzene (freshly distilled and dried over $CaCl_2$) and heated with stirring to 130°. The mixture became opaque almost at once and solid begun to separate rapidly. This was filtered and washed with acetone. The crude bromide was pink and turned easily into a gum. It was converted into the iodide with ~~separated~~ aqueous potassium iodide. Crude yield 1.4 g., m.p. 208-209°. Recrystallised from ethanol it had m.p.209-211°. (1.25 g., 25%).

2,2'-Di[N-(β-hydroxy-α-methylphenyl)-NN-dimethylammoniomethyl] biphenyl Di-iodide (22; X = I).

2,2'-Bisbromomethylbiphenyl (13.6 g., 1 mol.) and (−)-N-methylephedrine (15.8 g., 2.2 mol.) were dissolved separately in dry warm nitrobenzene (35 c.c. in all). The solutions were mixed at 120° and the temperature rose to *ca.* 150°. The mixture was kept at ca. 130° for 20 min. during which time solid separated and the whole became very thick. It was allowed to cool, the solid was filtered off and washed with dry nitrobenzene, followed by dry benzene and dry acetone. The crude quaternary dibromide (26 g.) so obtained had m.p. *ca.* 206°. The dibromide had a varying melting point as it hydrated easily even on standing in air. It was difficult to crystallise to constant melting point and it was therefore converted into the di-iodide. The dibromide was dissolved in a large volume of water, treated with aqueous potassium hydroxide to liberate any unreacted tertiary base and the aqueous layer was extracted with benzene or carbon tetrachloride to remove the base. Addition of the benzene precipitated the dibromide in a hydrated form and much water was required to redissolve it. The aqueous solution was neutralised with hydrobromic acid and concentrated below 35° to *ca.* 1500 c.c. Attempts to concentrate the solution further resulted in crystallisation of the hydrated dibromide. A cold saturated solution of potassium iodide was added and the precipitate di-iodide was collected. Two crystallisations from aqueous ethanol gave 23.8 g.,(75%) of the di-iodide, m.p. 214-215°. (Found: C, 54.7 ; H, 5.9 ; I, 31.8 ; N, 3.45. $C_{36}H_{46}I_2N_2O_2$ requires C, 54.5 ; H, 5.85 ; I, 32.0 ;

N, 3.5%). It had $[\alpha]^{21.5}_{5461}$ − 127.5° (c. 1.006, in methanol). The preparation was repeated several times and 72 g. of the di-iodide were prepared in all.

Polarimetric Examination of the Quaternary Di-iodide (22; X=I)

Methanol (21 c.c.) was cooled to ca. −20° and added to the quaternary ephedrinium iodide (0.2146 g.) cooled to the same temperature. The solution was filtered rapidly into a jacketted polarimeter tube (Harris and Mitchell, J., 1960, 1905) round which cooling liquid was circulating. The temperature of the solution rose rapidly to −15° and remained there. The first good readings were obtained 4½ min. after wetting the solid with solvent and no change in rotation was observed during 1½ hr. Experiments at −30° and at 0° were carried out similarly, only in the first case solvent and iodide were pre-cooled to −40° (acetone + solid CO_2) and in the second case to −2° to 0° (ice). In neither case was any mutarotation observed.

2,2'-Bis(trimethylammoniomethyl)biphenyl Dibromide (23; X = Br)

(a) 2,2'-Bisbromomethylbiphenyl (13.6 g., 1 mol.) was dissolved in 50 c.c. dry acetone and cooled to −15° in an ice-salt bath. Liquid trimethylamine (25 c.c., 7 mol., d. 0.673) was added and the mixture was kept in a flask fitted with a drying tube ($CaCl_2$) at −15° to −10° for 3 hr. It was then allowed to warm up to room temperature and was left overnight. The quaternary dibromide was filtered off, washed well with dry acetone and dried in a vacuum desiccator over potassium hydroxide. 18 G. of the crude bromide were obtained. It crystallised from ethanol as a monohydrate, m.p. 219-221° (decomp.), (14 g., 74%). (Found : Br, 33.4 ; $C_{20}H_{30}Br_2N_2,H_2O$ requires Br, 33.55%). A further 5 g. of the dibromide were obtained from reactions carried out in 96% ethanol and in dry benzene.

2,2'-Bis(trimethylammoniomethyl)biphenyl Di-iodide (23 ; X = I).

The dibromide monohydrate (0.5 g.) was dissolved in water (7 c.c.) and a cold saturated aqueous solution of potassium iodide was added. The di-iodide separated as a solid, m.p. 240° (decomp.), 0.55 g. (92%). It crystallised from ethanol as a monohydrate, m.p. 245°, (decomp.). (Found: C, 42.4 ; H, 5.65 ; I 44.2 ; N, 4.9. $C_{20}H_{30}I_2N_2,H_2O$ requires C, 42.1 ; H, 5.65 ; I, 44.5 ; N, 4.9%).

2,2'-Bis(trimethylammoniomethyl)biphenyl Dipicrate (23; X = $C_6H_2N_3O_7$).

2,2'-Bis(trimethylammoniomethyl)biphenyl dibromide (0.3 g., 1 mol.) was dissolved in a few c.c. of ethanol and added with stirring to a cold saturated solution of picric acid (0.6 g., 4.15 mol.) in ethanol. A crystalline solid appeared almost at once and was filtered off and dried in air (0.49 g., 65%). It crystallised from aqueous ethanol in fine pale yellow needles, m.p. 245°. (Found: C, 51.2 ; H, 4.5 ; N, 14.5 ; $C_{32}H_{34}N_8O_{14}$ requires C, 50.9 ; H, 4.5 ; N, 14.8%).

2,2'-Bis(trimethylammoniomethyl)biphenyl (+)-Dicamphorsulphonate.

2,2'-Bis(trimethylammoniomethyl)biphenyl dibromide (0.476 g., 1 mol.) and silver (+)-camphorsulphonate (0.679 g., 2 mol.) were dissolved separately in hot water. The solutions were mixed and boiled for ½ hr. The coagulated silver bromide was filtered off and washed well with boiling water. The filtrate and washings were concentrated to 30 c.c. by evaporation on a water bath. The filtrate was then left to stand for 2 weeks at room temperature and some more silver bromide had to be filtered off. The solvent was removed at reduced pressure and a white deliquescent solid was obtained, part of which, dissolved in aqueous ethanol, became crystalline after prolonged exposure to the atmosphere. Only 0.25 g. (32%) were obtained crystalline. The rest, in spite of seeding with the crystals, remained syrupy.

A solution of the camphorsulphonate in dimethylformamide was examined polarimetrically at -24.5°, at -14° and at 22°.

It was found to be optically stable and showed no change of rotation with temperature. $[\alpha]_{5461}^{22^\circ}$ + 26.5°. Not enough of the salt was obtained to have it analysed. The experiment was repeated but again the camphorsulphonate failed to crystallise.

2,2'- Bis(N-pyridiniummethyl)biphenyl Dibromide (25)

2,2'-Bisbromomethylbiphenyl (13.6 g., 1 mol.) in absolute alcohol and pyridine (dried over potassium hydroxide) (2.76 g., 3.5 mol.) were mixed with vigorous stirring and warmed on the water bath. Solid begun to separate after a very short time. The reaction flask was shaken very vigorously It was then closed with a calcium chloride tube and heated on the water bath for 45 min. to complete the reaction. The solid was filtered off, washed well with absolute alcohol and dry acetone and dried in a vacuum desiccator. The crude yield was 17 g. (85%). The salt was recrystallised from methanol and had m.p. 295-300° (decomp.) (14 g., 70%) (Found: C, 57.7 ; H, 4.4 ; N, 5.4 ; Br, 32.3. $C_{24}H_{22}N_2Br_2$ requires : C,57.85 ; H, 4.45 ; N, 5.6 ; Br, 32.1%).

2,2'-Bis(N-pyridiniummethyl)biphenyl Di-(+)-camphorsulphonate.

The corresponding quaternary dibromide (25, X=Br) (4.98 g., 1 mol.) and silver (+)-camphorsulphonate (6.78., 2 mol.) were dissolved separately in hot water, the solutions were mixed and boiled to coagulate the precipitated silver bromide. The precipitate was filtered off, washed well with boiling water and the filtrate was evaporated to dryness on a water bath. The residue solidified under dried acetone but proved deliquescent and could not be recrystallised.

2,2'-Bis(N-pyridiniummethyl)biphenyl Di(+)-α-Bromocamphor-π-sulphonate.

The (+)-α-bromocamphor-π-sulphonate was prepared in the same way as the camphorsulphonate. The quaternary dibromide (4.98 g., 1 mol.) and the silver (+)-α-bromocamphor-π-sulphonate (8.72 g., 2 mol.) gave 9.20 g. (100%) of non-crystalline solid which was deliquescent. It was eventually recrystallised from acetone (dried $CaCl_2$) giving needles m.p.255° (softening 197°). These could be exposed to air for a short time but became syrupy after about 1 hr. The solid m.p. 255° was sent for analysis according to which it was solvated with two molecules of water. (Found: C, 53.7 ; H, 5.5 ; O, 16.2 ; $C_{44}H_{50}N_2O_8Br_2S_2.2H_2O$ requires C, 53.0 ; H, 5.7 ; O, 16.0%).

2,7-Dihydro-1,1-dimethyl-3,4:5,6-dibenzazepinium Bromide (24 ; X = Br).

Hori, Abe, Yamakawa and Fujimura, Gifu Yakka Daigaku Kiyô, 1958 8, 65 ; Chem.Abs., 1959, 53, 10148).

2,2'-Bisbromomethylbiphenyl (11.3 g., 1 mol.) was dissolved with heating under reflux in 40 c.c. of sodium-dried ether. The solution was cooled to room temperature and dimethylamine (5.4 g., 3.6 mol., d. 0.6804) cooled in an ice-salt mixture was added to it. A vigorous reaction was observed at once - the solution turned milky and the ether boiled. The reaction mixture was kept at room temperature for 24 hr.. The precipitated bromides were filtered off an dissolved in smallest amount of water. Sodium hydroxide solution (30%) was then added to decompose the dimethylamine hydrobromide and to precipitate the azepinium bromide. The latter was filtered off, washed with water and dried in air. The crude product (10 g.) had m.p. 281-283°. It was recrystallised from methanol-ethylacetate and had m.p. 285-287° (9 g., 90% yield).

2,7-Dihydro-1,1-dimethyl-3,4:5,6-dibenzazepinium Iodide (24;X=I).

The above bromide (0.4g.) was dissolved in 5 c.c. of water and a saturated aqueous solution of potassium iodide was added to it to precipitate the less soluble iodide (0.45 g., 98%). This had m.p. 294-303° (decomp.) after one crystallisation from ethanol.

2,7-Dihydro-1,1-dimethyl-3,4:5:6-dibenzazepinium Picrate (24 ; $X = C_6H_2N_3O_6$).

The corresponding bromide (0.2g., 1 mol.) was dissolved in a few c.c. of water and added to an aqueous solution of sodium picrate (0.2 g., 1.2 mol.). The precipitated picrate was filtered off washed with a little water and recrystallised from aqueous ethanol giving 0.17 g. (57%). It had m.p. 285-286° (decomp.) (Found: C, 56.4 ; H, 4.4 ; N, 12.4. $C_{22}H_{20}N_4O_7$ requires C, 56.4 ; H, 4.5 ; N, 12.4 %).

Action of heat on 2,2'-Di [N-(β-hydroxy-α-methylphenylethyl)-NN-dimethylammoniomethyl]-biphenyl Dihydroxide. (22 ; X = OH). Experiments I to VII.

Experiment I.

A solution of the corresponding iodide (3.96 g., 1 mol.) in *ca.* 60 c.c. alcohol was boiled under reflux on a water bath and a suspension of silver oxide in water was added to it during one hour. The moist silver oxide was prepared by mixing hot aqueous solutions of silver nitrate (1.275 g., 1.5 mol.) and sodium hydroxide (0.3 g., 1.5 mol.), filtering off the precipitated oxide and washing it well with boiling water. After 1 hr. the reaction mixture was filtered hot and the filtrate, which had a strong characteristic smell of 1-methyl-2-phenylethylene oxide, was distilled from a water bath at reduced pressure. When all the water and alcohol have been distilled off, a little more alcohol was added to the residue and then distilled off as before to remove the last trace of the oxide. The residue (1.3 g.,) was a solid which melted at 78° with trace melting > 200°. The solid was only partly soluble in cold water or ether but dissolved in hot water. Treated with dilute nitric acid and silver nitrate it gave a precipitate of silver iodide indicating the presence of some of the original undecomposed iodide. The residue was treated with water and ether, the layers separated and the aqueous layer back extracted with more ether. Dilute hydrochloric acid was then added to the ether and the two layers separated. The basic fraction was liberated from the hydrochloride by the addition of 30% sodium hydroxide and extraction with ether. On removal of the latter 0.85 g. of a solid were obtained which recrystallised from ethanol had m.p. 88-90°. This was proved by mixed melting point to be N-methylephedrine (not depressed).

Experiment II

A sample of freshly prepared, twice recrystallised iodid (5 g., 1 mol.) was dissolved in 100 c.c. alcohol and heated under reflux for 1 hr. with moist silver oxide (silver nitrate 1.91 g., 1.5 mol.; sodium hydroxide 0.45 g., 1.5 mol.). The reaction mixture was filtered and the filtrate tested with more silver oxide. Silver iodide was still being formed so the filtrate was heated under reflux for a further 45 min. while ca. 0.5 mol. of silver oxide was added to it. The filtrate did not then react with fresh silver oxide and the alcohol and water were distilled off, together with the ethylene oxide at reduced pressure from a water bath. The distillate was redistilled using a Vigreux column. Fractions of 20 to 50 c.c. were collected and examined polarimetrically at 21° and λ 5461Å using a 20 cm. tube :

1.	b.p.	79°	+0.145	22c.c. ≡ 0.024g.
2.		80°	+0.400	34 c.c. ≡ 0.103g.
3.		82-95°	+0.0590	20 c.c ≡ 0.090g.
4.		100°	-0.040	50 c.c
5.		100°	-0.070	50 c.c.

1-methyl-2-phenylethylene oxide 0.217g.

The weights of the (+)-trans-oxide were worked out on the basis of Rabe's figure (Ber., 1911, 44, 826) for specific rotation of the oxide $[\alpha]_D^{16^\circ}$ + 65.84 (c 2.954) and are approximate as the temperatures and wavelengths of light used are different. The residue in the flask was worked up by adding water and ether, separating and back extracting. The aqueous layer was examined polarmetrically and had a small negative rotation indicating the presence of the original cation with the asymmetric ephedrine centres.

The ether soluble part of the residue was treated with dilute hydrochloric acid. Ammonium hydroxide was then added to the acid extract and the liberated base was extracted with ether and dried over potassium carbonate. After the ether was distilled off 0.4 g. of base were obtained. Recrystallised from ligroin (40-60°) it had m.p. 89-90°. Elementary analysis showed it to be N-methylephedrine. This was further confirmed by preparing the methiodide - the base dissolved in dry ether was warmed gently and methyl iodide was added. An immediate white precipitate was obtained which, after recrystallisation from methanol, melted at 212° (Smith, J., 1927, 2056, gives m.p. 212-213° from ethanol). A sample of the methiodide was prepared using already available pure N-methylephedrine and the mixed melting point of the two methiodides was not depressed. Infrared spectra of N-methylephedrine and base derived from the Hofmann degradation, and also of the corresponding methiodides were examined and showed the compounds to be identical.

The identification of the base as N-methylephedrine was further confirmed by checking its rotation in methanol : $[\alpha]_{5461}^{21^\circ}$ -32.3° (c 2.9955). Nagaio and Kanao (Annalen, 1929, 470, 157) give $[\alpha]_D$ -29.2° (c 3.32505) in methanol.

The water soluble part of the residue was obtained as a yellowish solid (1.5 g.) by evaporating the aqueous layer to dryness on the water bath. The solid was soluble in water, ethanol, methanol and partly soluble in chloroform. It was insoluble in other organic solvents. It's aqueous solution had pH 7-8. The solid was washed well with chloroform and the insoluble part was filtered off. 0.7 G. of a white solid m.p. ca. 205-207° (with strong softehing from 95°) were obtained. Its aqueous solution was examined polarimatrically and had no rotation. Sodium fusion gave a positive test for nitrogen and negative for iodine. Precipitates were obtained with calcium chloride and silver nitrate which were both soluble in acid. Elementary analysis showed a nitrogen to oxygen ratio of one to four (N, 4.74 ; O, 22.6%). However the solid seemed to be hydrated as on standing in air its melting point went up and it underwent loss of weight. It was dried for 11 hr. at 98° and had then m.p. 205.5 - 206.6° with only slight softening at 195°. It was further dried in a vacuum pistol at 68°/10cm. for 6.5 hr. and underwent a total loss of weight of 5%. Elementary analysis showed a one to three ratio of nitrogen to oxygen (N, 5.1 ; O, 17.6%). It had m.p. 206-207° (decomp.). The infrared spectrum of the solid in nujol had a characteristic band at 834 cm.$^{-1}$. The ultraviolet spectrum of the solid in water had λ_{max} at 248 mμ with ε_{max} 14,000. The spectrum was similar to spectra of biphenyl compounds bridged with a 3-atom bridge across the 2,2'-positions of biphenyl (7-ring).

A picrate was prepared from the solid by dissolving 0.2g. in water and adding a concentrated solution of 0.2g. of sodium picrate in water. The solid picrate separated almost at once and was filtered, dried in air and recrystallised from aqueous alcohol. It had m.p. 285-286° (decomp.) which was not depressed in mixed m.p. with 2,7-dihydro-1,1-dimethyl-3,4:5,6-dibenzazepinium picrate (24; $X=C_6H_2N_3O_7$).

The experimental evidence given in previous pages lead to identification of the water soluble solid m.p.206-207° (decomp.) as the hydrogen carbonate of the above azepinium cation (24; $X= HCO_3$). This was confirmed by elementary analysis (Found: C,70.9 ; H, 6.65; N, 5.1; O,17.6; $C_{17}H_{19}NO_3$ requires C,71.6 ; H, 6.7 ; N, 4.9 ; O, 16.8%).

The chloroform soluble part of the water soluble residue was examined after removal of the solvent. The total residue (1.0118 g.) yielded 0.1783 g. of the chloroform soluble part, which softened at 75°, went liquid at 125° and begun to decom-

-pose rapidly till it was complete at 150°. The infrared spectrum showed a hydroxyl band. An aqueous solution (pH 7-8) gave with silver nitrate a mixed yellow and brown precipitate of silver carbonate and silver oxide. Sodium fusion of the solid gave a positive test for nitrogen and also a trace of iodine. The aqueous solution of the solid gave with potassium iodide solution a precipitate of quaternary iodide (24; X = I) m.p. 297-303° (decomp.) and with sodium picrate, a precipitate of the quaternary picrate (24; $X = C_6H_2N_3O_7$) m.p. 284-285°, (mixed m.p. 285-286°).

The above results showed this part of the water soluble residue to contain 2,7-dihydro-1,1'-dimethyl-3,4:5,6-dibenzazepinium hydroxide and hydrogen carbonate together probably with a trace of the original undecomposed di-ephedrinium compound (22)

Experiment III.

The quaternary di-iodide (7.9 g., 1 mol.) was dissolved in methanol (80 c.c.) and water (40 v.c.) and shaken with freshly precipitated silver chloride for 1 hr. The silver chloride was prepared by dissolving silver nitrate (6.8 g.,4 mol) and sodium chloride (2.34 g., 4 mol.) separately in ca.130 c.c. hot water, mixing the solutions, boiling to coagulate the precipitated chloride. The precipitate was then filtered, washed well with hot water and used straightaway. Methanol was removed from the filtered solution of the quaternary dichloride by distillation under reduced pressure. Subsequent operations were, as far as possible carried out in an atmosphere of nitrogen with water free of carbon-dioxide. Freshly precipitated silver oxide (from silver nitrate 6.8 g., 4 mol. and sodium hydroxide, 1.6 g., 4 mol.) was added to the aqueous solution of the chloride and the mixture shaken for 1 hr. The filtered solution was tested with more silver oxide and was fouhd to be chloride free. The solution was distilled under reduced pressure from a water bath at 60°. Owing to bumping over in the early stage some air was admitted and more water was added from the washings. When most of the water has been removed the bath temperature was slowly raised to 100°, oil distilling with the water. Finally the mixture was heated under reduced pressure at 120-125° for 15 min.

The distillate and residue in the flask were worked up separately, a procedure followed throughout this and subsequent experiments since N-methylephedrine proved to be more steam volatile than the other bases and was thus partially separated from them.

Ether was added to the distillate; water and ether were added to the residue. Both lots were separated and extracted and the ethereal layers then extracted with dilute hydrochloric acid. The resulting neutral (dextrorotary) ethereal solutions were treated separately. They were dried over magnesium sulphate, filtered through sintered glass and the ether was removed using a Dufton column. The residue from the distillate (1 g.) was transferred to a micro vacuum apparatus and vacuum distilled, the receiver being placed in ice. 0.29 G., b.p. $57^{\circ}/_{13}$ mm., of the (+)-oxide were obtained. The infrared spectrum showed that it was slightly contaminated (hydroxyl band at 3472 cm.$^{-1}$). It was therefore dissolved in 10 c.c. of sodium dried ether, dried over magnesium sulphate and the ether was removed in vacuum desiccator over calcium chloride at 40 mm. The oxide had $[\alpha]_{D}^{21.4^{\circ}}$ 1.5201 ; Fisher (<u>Chem.Ber.</u>, 1961, <u>94</u>, 893) gives $[\alpha]_{D}^{20^{\circ}}$ 1.5198. Evaporation of the aqueous layer from the residue in the distilling flask gave 0.38g. of the azepinium hydrogen carbonate, identified as its picrate as in the previous experiment.

The neutral ethereal solution from the residue gave a solid m.p. 60-85° (0.10 g.) and m.p. 98-100° after one crystallisation from ethanol, shown by mixed m.p. and infrared spectrum to be phenantherene.

After removal of ether from the two basic fractions the whole of each was treated with alcoholic picric acid using in each case twice the weight of acid to the weight of basic residue. The distillate fraction (1.36 g.,solid) gave 0.32 g. of picrate of 2,2'-bis(dimethylaminomethyl)biphenyl m.p. *ca* 206° and 0.04 g. of impure picrate m.p. 168-174°. The residue fraction (1.6 g., liquid) gave 2.31 g. of picrate m.p.165-178° which on fractional crystallisation from acetone-methanol mixture gave: 1.64 g., m.p. 173-176° (picrate of 9,10-dihydro-9-dimethylaminophenanthrene (27)); 0.17 g., m.p. 169-174° and 0.03 g. m.p. 206°, together with low melting mixtures containing picric acid. The picrate m.p. 206° was recrystallised again from acetone-methanol and was obtained as pale yellow needles m.p. 207-208° (but depending partly on the rate of heating). This was identified as 2,2'-bis(dimethylaminomethyl)biphenyl dipicrate (23a. $2C_6H_3N_3O_7$) (Found: C,49.9 ; H, 4.3 ; N, 15.35 ; $C_{30}H_{30}N_8O_{14}$ requires C, 49.6 ; H, 4.2 ; N, 15.4%).

Experiments IV to VII

The quaternary di-iodide (15.8 g., 1 mol.) was converted into the hydroxide via the dichloride as in experiment III and the total volume was made up to 350 c.c. and divided into four lots which were decomposed under following conditions:-

(Exp.IV). The solution was slowly distilled at reduced pressure under nitrogen at 70-100° for 95 min. and finally heated at 125-130° for 15 min; (Exp. V) the solution was boiled under reflux under nitrogen for 3 hr.; (Exp.VI) potassium hydroxide (2.8 g.) was added and the solution was then treated as in (exp.IV); (Exp.VII) the solution was treated as in (exp.IV) except that carbon dioxide was used instead of nitrogen.

In all four experiments (IV to VII) the smell of the methylphenylethylene oxide was detected indicating that some decomposition of a normal type occurred. Distillate and residue fractions were treated separately (except in V): working up as in experiment (III) lead after removal of solvents to the isolation of (a) basic product from distillate, (b) basic product from residue, (c) water soluble part of the residue, (d) neutral ether soluble part of the residue. The basic fractions were converted into the picrates. Part of the residue (0.2 g.) from the aqueous layer was in each case dissolved in water and treated with aqueous sodium picrate (0.2 g.), the precipitated picrate being crystallised from aqueous alcohol.

The results of experiments IV to VII are given below:

Exp. IV.

(a) Bases from distillate 0.0698 g.(solid) were treated with alcoholic picric acid (0.14 g.) and gave less than 0.01 g. picrate m.p. 213° (23a).

(b) Bases from residue 1.1391 g.(solid) treated with alcoholic picric acid (2.28 g.) gave 1.4425 g. picrate m.p. 187-190°. Crystallisation gave 0.326 g., m.p. 205-207° (23a), 0.226 g. m.p. 173-174° (27), 0.186 g., m.p. 146-154° and 0.088 g., m.p. 143-144° (N-methylephedrine). The third crop (0.186 g., m.p. 146-154° was recrystallised again and gave 0.0729 g., m.p. 174-175° (27).

(c) Water-soluble residue 0.60 g. Picrate from 0.2 g. had m.p. 285-286° (24; X = $C_6H_2N_3O_7$) after crystallisation.

(d) Neutral ether-soluble residue (0.06 g.) had m.p.71-80°. It was not possible to crystallise it.

Exp. V:

The reaction was carried out by heating under reflux so that there was no distillate to work up separately.

(a) -

(b) Bases from residue (0.7592 g.) (solid) treated with alcoholic picric acid (1.52 g.) gave 0.01g.picrate m.p.174-176° (27). The rest must have been N-methylephedrine, which does not give a picrate under conditions used.

(c) Water-soluble residue (1.6 g.) melted over a wide range softening at 60-95°, decomposing at 145° slowly, and rapidly at 195-215°. The decomposition was incomplete and the residue was re-treated with fresh silver oxide under conditions of experiment IV. There was no smell of ethylene oxide this time. The bases from residue (0.1814 g.) (semi liquid) on treatment with alcoholic picric acid (0.36 g.) yielded 0.285 g. of picrate m.p. 165-170° (27). The water-soluble residue (0.9g.) gave a picrate m.p. 285-286°. (24 ; X = $C_6H_2N_3O_7$).

(d) Neutral ether-soluble residue (semi liquid) was small (0.015 g.).

Exp. VI :

(a) Bases from distillate (0.3530 g.) (solid) gave on treatment with alcoholic picric acid (0.71 g.) a picrate (0.0377 g.) m.p. 206°. (23a).

(b) Bases from residue (0.9990 g.) (liquid) gave with picric acid (2 g.) in alcohol 1.6694 g., of picrates m.p. 154-166°. Crystallisation gave 0.610 g., m.p. 174-176° (27), 0.493 g., m.p. 158-174° (27 mostly), and 0.206 g., m.p. 137-142° (N-methylephedrine).

(c) Water-soluble residue (4.0230 g.) includes the 2.8 g. of added potassium hydroxide. The picrate obtained melted explosively at 334° ($C_6H_2N_3O_7K$).

(d) Neutral ether soluble residue (0.1705 g.) had m.p.97-98°, mixed m.p. with phenanthrene (m.p. 100-101°) was 99°.

Exp. VII :

(a) Bases from distillate (0.110 g.) gave no picrate on treatment with alcoholic picric acid (0.22 g.). Mostly N-methylephedrine. Reduction of mother liquor to half volume gave 0.1376 g. of picric acid (m.p. 122°).

(b) Bases from residue (0.6644 g.) (solid) yielded with alcoholic picric acid 0.05 g. of picrate m.p. 212-214° (23a) and 0.8398 g. of picrate m.p. 140-142° (N-methylephedrine). The latter picrate was obtained from a very concentrated solution on prolonged standing. After recrystallisation from ethanol it had m.p. 143.5-144° and analysis confirmed it to be the picrate of N-methylephedrine (Found: C, 49.6 ; H, 5.1 ; N, 13.9 ; O,31.7: Calc.for $C_{17}H_{20}N_4O_8$: C,50.0; H, 4.9; N, 13.7; O, 31.3%). Smith (J., 1927,2056) gives m.p. 144°.

(c) The water-soluble residue (1.215 g.) gave a picrate m.p. 285-286° (24 ; X = $C_6H_2N_3O_7$).

(d) Neutral ether-soluble residue (0.131 g.) was partly liquid The infrared spectrum showed probable presence of phenanthrene. There was an intense band in the phenanthrene region but the substitution pattern in the 770-690 cm.$^{-1}$ region corresponded to that of a monosubstituted benzene; the residue might have consisted mainly of 1-phenylpropan-1,2-diol derived from acid catalysed hydration of the ethylene oxide.

Action of hot concentrated potassium hydroxide on 2,2'-bis-hydroxymethylbiphenyl:

The diol (2.14 g., 1 mol.) was added to an aqueous solution of potassium hydroxide (5.6 g., 10 mol. in 15 c.c.) and the mixture was heated for 40 min. in a metal bath kept at ca.120°

The mixture was cooled and the solid filtered off, washed well with water and dried in a vacuum desiccator. Most of the diol (2.1 g.) was recovered. It had m.p. 105° (soft. ~ 90°); mixed m.p. with pure diol (m.p. 112°) was 110-112°, and with phenanthrene (m.p. 100°) it was depressed to 85-90°; recrystallised from benzene (m.p. 112°) it had an infrared spectrum identical with that of the diol.

Action of Heat on 2,7-Dihydro-1,1-dimethyl-3,4:5,6-dibenzazepinium Hydrogen Carbonate (24 ; X = HCO_3).

The hydrogen carbonate melted with strong decomposition to give a yellow liquid. 1) A sample of the carbonate (0.45 g.) was placed in a tube fitted with a reflux condenser and was heated on a metal bath at 210-212° for 40 min. At this stage evolution of alkaline fumes (pH 8) was rather strong and the heating was stopped. The infrared spectrum of the residual liquid (0.25 g.) was identical with that of 9,10-dihydro-9-dimethylaminophenanthrene. The rest of the residue was dissolved in a few c.c. of ethanol and added to a saturated solution of picric acid in ethanol. A picrate crystallised almost at once. Recrystallised from acetone it had m.p. 176° and was proved by mixed m.p. (176°) to be identical with the picrate of the above mentioned phenanthrene base.

2) 0.2 g. of the carbonate were heated at 210-212° for 3 hr. in a tube connected to a flask containing 3 c.c. of ethanol. The residue was cooled and dissolved in ether. The base was extracted with dilute hydrochloric acid and liberated with sodium hydroxide solution. It was extracted with ether, dried over potassium carbonate. Removal of solvent gave 0.1077 g. (70%) of liquid base which yielded 0.2118 g. (83%) of picrate m.p. 170-174° (softening 155-160°). This was recrystallised twice from ethanol and gave picrate m.p. 176°.

0.0355 G. of non basic fraction was isolated and its infrared spectrum was examined but this was not identified. The alcohol in which were collected the alkaline fumes from the decomposition of the carbonate was added to saturated alcoholic picric acid but no picrate was obtained.

9,10-Dihydro-9-Dimethylaminophenanthrene (27)

(Hori, Abe, Yamakawa and Fujimura, Giju Yakka Daigaku Kiyô, 1958, 8, 65 ; Chem.Abs., 1959, 53, 10148).

Finely divided lithium (1 g., 5g.atoms) was added to 30 c.c of dry ether placed in a flask fitted with a stirrer, a reflux condenser and kept under nitrogen. Phenyl bromide (11.7g. 2.5 mol.) was added to the lithium at such a rate that the ether was refluxing gently. When the addition was completed 9 g.(1 mol.) of 2,7-dihydro-1,1-dimethyl-azepinium bromide were added and the mixture was stirred under nitrogen at room temperature for 8 hr. Water was then added and some more ether till no solid remained in the flask. The two layers were separated, back extracted and the ethereal layer was dried over anhydrous sodium sulphate. The ether was distilled off and the residue was distilled at reduced pressure and gave 4 g. (60.6%) of the base b.p. 183°/1 mm.

9,10-Dihydro-9-Dimethylaminophenanthrene Picrate ($27 \cdot C_6H_3N_3O_7$).

The above amine (1 g., 1 mol.) was dissolved in 3 c.c. ethanol and added to a saturated solution of picric acid (2 g., 2 mol.) in ethanol and the mixture was stirred vigorously, corked and left to stand for 1 hour. The precipitated solid was filtered, washed with ethanol and recrystallised from acetone and gave 1.7 g.(84%), m.p. 175-176° (Found: C, 58.5 ; H, 4.6 ;

N, 12.4 ; O, 25.0. $C_{22}H_{20}N_4O_7$ requires C, 58.5 ; H, 4.5 ; N, 12.4 ; O, 24.8%).

2,2'-Bis(dimethylaminomethyl)biphenyl (23a).

The base picrate (0.6086 g.) was treated at room temperature with 10 c.c. of 10% sodium hydroxide. Water (30 c.c.) and ether (20 c.c.) were added and the mixture was stirred till all solid dissolved. The solution was filtered and the two layers were separated. The aqueous layer was extracted 3 times with ether and the ether layer was washed with water till colourless and dried over potassium carbonate. The solvent was removed using a Dufton column and the base (23a) was obtained as a viscous liquid (0.1592 g., 71%). The infrared spectrum of the base was examined, and the rest was converted into the methiodide (23 ; X = I):

the base (0.15 g.) was dissolved in 2 c.c. of nitrobenzene freshly distilled and dried over calcium chloride) and 2 c.c. of methyl iodide were added. The mixture was placed in a water bath in a sealed tube and heated to 100° over a period of 1 hr. It was then kept at this temperature for 4.5 hr. and allowed to cool overnight. The precipitated quaternary iodide was filtered off washed with acetone and dried in air. The yield was 0.1658 g. (52%) and m.p. 240° (decomp.). Recrystallised from methanol it had m.p. 245.5° (decomp.); mixed m.p. with the directly synthesised iodide was not depressed.

Action of heat on 2,7-Dihydro-1,1-dimethyl-3,4:5,6-dibenzazepinium Hydroxide (24 ; X = OH)

The azepinium bromide (4.25 g., 1 mol.) was shaken in aqueous solution with silver oxide (silver nitrate 5.1 g., 2 mol; sodium hydroxide 1.2 g., 2 mol.) for 1 hr. The filtered solution was distilled under reduced pressure, in an atmosphere of nitrogen, from a water bath at 70-100° for 95 min. and was finally heated at 130-135° for 15 min. Ether and water were added to the residue and ether to the distillate, the combined ethereal extracts were separated as usual into a neutral and a basic fraction. From the neutral fraction 0.989 g. (40%) of phenanthrene, m.p. 97-99°, was obtained. The basic fraction gave 1.320 g. of a liquid, from which 2.155 g. of picrate m.p.163-170°, with previous softening were obtained. Crystallisation of the picrate from methanol yielded 1.185 g. of 9,10-dihydro-9-dimethylaminophenanthrene picrate (27) m.p. and mixed m.p. 175-176°, 0.5795 of 2,7-dihydro-1-methyl-3,4:5,6-dibenzazepine picrate (26)m.p. mainly 158-161°, but slightly contaminated with the higher melting picrate, and 0.103 g. of mixed picrates, m.p. 155-160°. Recrystallisation of the second crop from ethanol gave the picrate with m.p. 159-161°, not lowered by mixing with an authentic sample (m.p. 162°). Recrystallisation of the third crop from ethanol gave 0.055 g., m.p. 174°, softening at 155°.

The experiment was repeated using 2.25 g. of the bromide and 0.456 g. (35%) of phenanthrene were isolated.

Action of heat on 2,7-Dihydro-1,1-dimethyl-3,4:5,6-dibenzazepinium Hydroxide with added Potassium Hydroxide.

The azepinium bromide (1.5 g., 1 mol.) was converted into the hydroxide with silver oxide and potassium hydroxide (2.8 g., 21 mol.) was added. The solution was distilled as usual under reduced pressure and in an atmosphere of nitrogen. The neutral fraction (0.296 g.; 34%) was phenanthrene, m.p. 100-101°. The basic fraction (0.440g.) gave a picrate (27) (0.852 g., 38%) m.p. 175-176°.

It was noticed during the above three experiments that during the distillation as soon as temperature reached 80° basic fumes (pH 10) with typical ammoniacal smell were evolved. Attempts were made to isolate the volatile base as it's picrate. Parts of the distillate after ether extraction were treated with a) a concentrated aqueous solution of sodium picrate, b) solid sodium picrate, c) a concentrated aqueous solution of sodium picrate in the presence of ethanol d) a saturated solution of picric acid in ethanol. No precipitate was obtained on mixing so the solutions were concentrated by evaporation on a water bath. In no case was the dimethylamine picrate isolated. The solid obtained eventually on total evaporation was picric acid with m.p. not changed. An attempt was also made to salt out the base by adding a large excess of solid sodium chloride to the distillate and by heating the mixture on a water bath at reduced pressure. A trap containing ethanol was attached to the distillation flask. After several hours the flask was disconnected and the ethanol was added to saturated alcoholic picric acid. No picrate was obtained.

A sample of the dimethylamine picrate was prepared from an aqueous solution of the base and from alcoholic picric acid Crude it had m.p. 159-161°, recrystallised from alcohol-acetone m.p. 160-161°. (Walden, Ulich and Birn, *Zeitschrift fur Physicalische Chemie*., 1927, *130*, 502, gives m.p. 160-161°; Ries (*Zeitschrift Fur Krystallographie und Mineralogie*, *55*, 466) m.p. 158-159° ; Jerusalem, *J.*, 1909, *95*, 1275 m.p. 165-166°). Mixed m.p. with picrates isolated from the degradation of the 2,7-dihydroazepinium compound was in each case highly depressed so that if any trace of the dimethylamine picrate was obtained in the basic fraction it must have been very small indeed.

Action of heat on 3'- and, 2'- and 1'-Chloro-2,7-dihydro-3,4:5,6-dibenzazepinium Hydroxides (24a and b; X = OH).

The hydroxides were prepared in a series of reactions. The products were used directly for the next step without purification. 2,2'-Dihydroxydimethylbiphenyl (5 g., 1 mol.) was chlorinated in glacial acetic acid with free chlorine (de la Mare, Bedford College). Chlorination stopped when *ca.* ½ the diol was chlorinated. The product, a pale green syrup, was dried for 16 hr. in a vacuum desiccator. It was then converted into the dibromide by adding it at 90° to 48-50% hydrobromic acid (250 c.c.) and boiling for 20 mins. On cooling a brown gum was obtained, which solidified on scratching. This was filtered, washed well with water and dried for several days in a vacuum desiccator over calcium chloride (yield 6.5 g.). The filtrate was extracted with benzene and the latter evaporated but no residue was obtained.

The mixture of dibromides (6.5 g., 1 mol.) was quaternarised in dry ether (30 c.c.) and dry benzene (20 c.c.) with dimethylamine (5 c.c. $\equiv$ 3.4 g., *d.* 0.6804, 6.4 mol.). The mixture was kept at room temperature for 24 hr. in a flask fitted with a reflux condenser and a calcium chloride tube. Reaction started almost at once on mixing and a white solid begun to separate. At the end of 24 hr. the solvent was still strongly brown in colour. The solid bromides were filtered off, washed well with dry benzene and dried in air (6 g., m.p. softening from 134-244°, then strongly decomposing 259-277°). The filtrate on evaporation gave 1.6238 g. of dark brown gum.

The bromides (6 g., 1 mol.) were dissolved in 70 c.c. of carbon dioxide free water and silver oxide (silver nitrate 6.8 g., sodium hydroxide 1.6 g., 2.5 mol.) was added. The mixture was shaken at room temperature and under nitrogen for 1.5 hr. Addition of silver oxide produced a strong smell of dimethylamine indicating the presence of it's hydrobromide. The solution of hydroxides (150 c.c.) was filtered off from the silver bromide and distilled from a water bath under nitrogen at reduced pressure. For the 1st hour the temperature was kept at 70-80°, and then it was allowed to rise to 100° during 30 min. The decomposition was completed by heating for 15 min. at 125-130°. The residue was partly liquid and partly solid. Water and ether were added and the basic and neutral fraction were separated in the usual way. The basic fraction yielded 0.8083 g. The non-basic fraction (0.5463 g.) had m.p. 82-86° (softening at 66°). It was examined by vapour phase chromatography and showed a 1:1 mixture of phenanthrene and chloro-phenanthrenes. The 1- , 2- and 3- chloro-phenanthrenes were identified in the mixture. The vapour phase chromatography was done on a 50 ft. long stainless steel capillary column using Apiezon L at 203°.

The retention times were as follows :

Phenanthrene	ca.	8.2 min.
1-Chlorophenanthrene		18.75min.
2-Chlorophenanthrene		18.35min.
3-Chlorophenanthrene		17.4 min.

The main product was the 3-isomer, and there was more of the 2-isomer than of the 1-. The vapour phase chromatography was done by Dr. E.A. Johnson of the Medical Research Council.

Action of heat on 2,2'-Bis(trimethylammoniomethyl)biphenyl Dihydroxide (23 ; X = OH).

The corresponding dibromide (23 ; X = Br) (9.52 g., 1 mol was converted into the dihydroxide (silver nitrate 13.6 g., sodium hydroxide 3.2 g., 2 mol.) and the aqueous solution was distilled under reduced pressure in an atmosphere of nitrogen at 70-100° for 90 min. and finally at 125-130° for 15 min. Decomposition was accompanied by a strong smell of trimethylamine. The products were worked up as usual, a very small basic fraction (0.030 g.) and a neutral fraction (0.184 g.) were obtained from the distillate.

The basic fraction from the residue (1.476 g.) was converted into a mixture of picrates (2.1095 g.) which solidified during several days. This mixture was difficult to separate, crystallisation from ethanol and various ethanol-acetone mixtures giving gums and crops melting over wide ranges, but a small quantity (0.425 g.) of 9,10-dihydro-9-dimethylaminophenanthrene picrate (27) m.p. 175°, mixed m.p. 175-176° was isolated. 0.1525 G. of a new picrate was also obtained. It had m.p. 240° (decomp.), mixed m.p. with 2,2'-bis(dimethylaminomethyl)biphenyl dipicrate (23a ; $2C_6H_3N_3O_7$) depressed to 178-190° ; mixed m.p. with 2,2'-bis(trimethylammoniomethyl)biphenyl dipicrate (23; X = $C_6H_2N_3O_7$) depressed to 226-227°. (Found C, 51.5 ; H, 4.7 ; N, 14.4 ; O, 29.8. Calc. for $C_{20}H_{29}N_2$, $2C_6H_3N_3O_7$: C, 50.9; H, 4.7 ; N, 14.8 ; O, 29.6 %).

The above unknown picrate (.0477 g.) was treated with 3 c.c. of 10% sodium hydroxide. 10 C.c. of water were added, and also some ether till a clear solution was obtained. The alkaline solution was extracted with ether, the extracts washed with water and dried over potassium carbonate. The solution was filtered and the ether removed by evaporation with slight warming. The base (0.0187 g.) was a liquid. The infrared spectrum shows bands characteristic of N-CH_3 and C-CH_2, but not of C-CH_3 which could be expected in case of rearrangement of methyl groups from the nitrogen to the α (benzyl) carbon atoms.

The neutral ether-soluble fraction from the residue (1.537 g.) was crystallised from ethanol and gave phenanthrene (0.355 g.), m.p. 99°, a solid (0.570 g.) m.p. 75-90° (softening ~50°), and a liquid (0.492 g.). Both the solid and the liquid were separated by crystallisation and chromatography on alumina into phenanthrene and impure 2,7-dihydro-3,4:5,6-dibenzoxepin. The best sample had m.p. 51-67°; the pure compound (Wittig, Davis and Koenig, <u>Chem.Ber.</u>, 1951, <u>84</u>, 627) has m.p. 72.5-73°. Its infrared spectrum closely resembled that of pure oxepin but still showed some phenanthrene peaks, which have however decreased in intensity during the stages of purification. One, less pure sample, which crystallised in long needles and had m.p. 45-55°, had an analysis corresponding to a 1:1 mixture (Found: C, 89.4 ; H, 6.15 ; O, 4.4. Calc. for $C_{14}H_{10}$, $C_{14}H_{12}O$: C, 89.8 ; H, 5.9 ; O, 4.3%). No evidence of the presence of 2,2'-bishydroxymethylbiphenyl was found in any of the fractions.

The aqueous solution of the residue after ether extraction was taken down to dryness under reduced pressure in a stream of nitrogen. The residual solid (1.40 g.) gave a picrate <u>(23; X = $C_6H_2N_3O_7$)</u> m.p. 245°, not depressed by the picrate of the quaternary starting material. The distillate from this operation was saturated with sodium chloride and trimethylamine distilled off it, collected in ethanol and made into the picrate, m.p. 224° (from ethanol) isolated after partial evaporation of the solvent (½). The m.p. was not depressed by the picrate synthesis directly from trimethylamine and alcoholic picric acid.

<u>2- and 4- Nitrophenanthraquinones</u> (36), (37).

(Schmidt and Spoun, Chem. <u>Ber</u>., 1922, <u>55</u>, 1194).

Phenanthraquinone (60 g., 1 mol.) was nitrated in two batches by boiling with concentrated nitric acid (<u>d</u>. 1.42 g./c.c.) (1,800 c.c.) for twenty minutes. The cooled reaction mixture was poured into <u>ca</u>. 5 litres of ice-water. The product was filtered off, washed with water, dried in air and boiled with 1 litre alcohol. The insoluble 2-nitrophenanthraquinone (36) was filtered off (38 g., 54.3%, crude m.p. 250-259°). The filtrate was cooled and a little of the mixture of the 2- and the 4- nitrophenanthraquinones was filtered off. The filtrate was concentrated to <u>ca</u>. 400 c.c. and allowed to cool ; the 4-nitrophenanthraquinone (37) crystallised out (20 g., 28.6%. crude m.p. 168-170°).

The 4-nitrophenanthraquinone was recrystallised from glacial acetic acid and 15 g. (21.4%) m.p. 172-175° were obtained, as first crop, (+ 4 g. m.p. 168-170° as second crop); the 2-nitro compound was also recrystallised from glacial acetic acid and 28 g., 40%, m.p. 262-264° were obtained as 1st crop, and 10 g. m.p. 250-260° as 2nd crop. The synthesis was repeated six times and altogether 182 g. of pure 2-nitro- and 80 g. of pure 4-nitro-phenanthraquinone were prepared.

4-Nitrodiphenic Acid (38)

(a) Labriola and Felitte, J. Org. Chem., 1943, 8, 537.

The 2-nitrophenanthraquinone (18 g., 1 mol.) was heated under reflux for 3 hr. in 150 c.c. of glacial acetic acid and 150 c.c. of hydrogen peroxide (20 volume). The mixture was cooled, made slowly alkaline with 30% sodium hydroxide and filtered. The filtrate was acidified with dilute sulphuric acid to pH 5 (Congo Red) and the precipitated acid was filtered off. (16 g., 78% m.p. 210-212°). The acid was strongly coloured so it was purified according to Moore and Huntress, (J.Amer.Chem.Soc., 1927, 49, 1328) by covering it with smallest amount of water and adding solid sodium bicarbonate till there was no more effervescence. The solution was filtered to remove the unchanged quinone and boiled with charcoal ; it was then filtered again and acidified as before to reprecipitate the acid. This was filtered and recrystallised from water, when an almost white solid was obtained m.p. 215-216° (11 g., 54%).

(b) Method of Moore and Huntress, loc.cit.

The 2-nitrophenanthraquinone (10 g., 1 mol.) was dissolved in 30 c.c. of concentrated sulphuric acid and added to 100 c.c. of water with vigorous stirring. A hot aqueous solution of potassium dichromate (40 g., 3.3 mol., in 400 c.c. H_2O) was added and the mixture was stirred mechanically for 2.5 hr. at boiling point. The reaction mixture was cooled, filtered and the acid washed with water till the washings were colourless. The crude acid was dissolved in minimum amount of water by gradual addition of solid sodium bicarbonate, the unchanged quinone was removed by filtration and the filtrate boiled with charcoal and filtered. The warm, clear bright yellow filtrate was then slowly acidified with 50% sulphuric acid and gave an almost white acid m.p. 210-216° (10 g., 80%). Recrystallised from water it had m.p. 214-216° (7.5 g., 1st crop, 66%) (2nd crop 2 g. m.p. 204-208°).

The preparation was repeated and 78.5 g. of the acid were obtained altogether.

6-Nitrodiphenic Acid (39)

(Schmidt and Kämpf, Chem.Ber., 1903, 36, 3737, modified according to Moore and Huntress, loc.cit.)

4-Nitrophenanthraquinone (12 g., 1 mol.) was boiled under reflux for 1 hr. with an aqueous solution of potassium dichromate (33 g., 2.36 mol., in 450 c.c. water) and concentrated sulphuric acid (30 c.c.). The reaction mixture was cooled, the product filtered off and washed well with water. It was purified by dissolving in dilute ammonium hydroxide, filtering and acidifying with dilute sulphuric acid. The 6-nitrodiphenic acid crystallised from the hot acid solution. It crystallised from aqueous alcohol in white plates m.p. 249-251° (10 g., 74%). Altogether 70.5 g. of the pure acid were prepared.

Dimethyl 4-nitrobiphenate

(*a*) The corresponding acid (5 g., 1 mol.) was esterified in the standard way by dissolving it in 10 times its weight of methanol (50 g., 63 c.c.) and adding its own weight (5 g., 2.7 c.c.) of concentrated sulphuric acid and heating under reflux for 6 hr. The mixture was then cooled, poured into 200 c.c. of water and neutralised with solid sodium bicarbonate. The ester appeared as a pale green gum. The liquid was decanted and the ester solidified in ethanol (3.3 g., 60.5%, m.p.93-95°). The decanted liquid was concentrated by distillation to 50 c.c. but gave no more ester.

(b) (Labriola and Felitte, *loc.cit*)

The acid (5 g., 1 mol.) was dissolved in cold methanol (50 g., 63 c.c.) and hydrogen chloride was passed through the solution for 5 hr. The mixture was allowed to stand for 24 hr.

It was concentrated to half its original volume by evaporation on a water bath and the ester appeared as a green oil. Water was added and the acid was neutralised with solid sodium bicarbonate. The liquid was decanted and the ester solidified under ethanol. On recrystallisation from ethanol 4.8 g., (90%) m.p. 93-95°, were obtained.

14.7 g. of the ester were prepared altogether.

Attempted reduction of dimethyl 4-nitrobiphenate with $NaBH_4$ and $AlCl_3$.

2,2'-Dimethoxyethane (digol) was used as solvent. It was purified by distillation from calcium hydride and then from lithium aluminium hydride under nitrogen. Aluminium trichloride was sublimed and the sodium borohydride recrystallised under nitrogen from digol (Brown, Mead, Subba Rao, loc.cit.). The sodium borohydride (0.85 g., 1.25 mol.) was dissolved in 25 c.c. of solvent (1M solution) and the ester (6.3 g., 1 mol.) was added. A suspension of aluminium trichloride (1.12 g.,0.42 mol.) in digol was added and the reactants were stirred under nitrogen for 1 hr. at room temperature and for 1 hr. at 70-74°.On cooling and hydrolysing with 2N hydrochloric acid an orange oil was obtained which could not be crystallised.

Attempted reduction of dimethyl 4-nitrobiphenate with KBH_4 and LiCl

Tetrahydrofuran, left for 12 hrs. over potassium hydroxide and then distilled from lithium aluminium hydride, was used as solvent. The lithium chloride was dried at 130° for 4 hr. The ester (1 g., 1 mol.) was placed in the solvent and potassium borohydride (0.18 g., 1.03 mol.) and lithium chloride (0.15 g., 1.11 mol.) were added with stirring. The reactants were stirred for 6 hr. at 25-30°. Water and sulphuric acid were added and unchanged ester (0.5 g.) was recovered from the tetrahydrofuran layer. Extraction of the aqueous layer with benzene and removal of the latter gave only a trace of solid. The reaction was repeated at higher temperature (60-64°) but the product was a yellow gum which would not solidfy.

Reduction of ethyl *p*-nitrobenzoate to the *p*-nitro-benzyl alcohol

(Paul and Joseph,
Bull.Soc.Chim.France, 1952, 19,550).

The ester (7.5 g., 1 mol.) was dissolved in pure, freshly distilled tetrahydrofuran (24 c.c.) and potassium borohydride (2.2 g., 1.05 mol.) was added and the mixture stirred mechanically. Ground lithium chloride (1.8 g., 1.1 mol.) was then added and the temperature went up by *ca.* 3 degrees. Stirring was continued for 6.5 hr. Water (40 c.c.) was added and the solution extracted with ether, dried over sodium sulphate and the ether evaporated to the point of crystallisation when 5.5g., of mixed ester and alcohol m.p. 50-90° were obtained. On recrystallisation from boiling water 2.8 g.(29%) m.p.88-92° of the alcohol were obtained as first crop. Successive crops yielded the unchanged ester.

Attempted reduction of dimethyl 4-nitrobiphenate with $LiBH_4$

The ester (4.7g., 1 mol.) was dissolved in purified tetrahydrofuran (10 c.c.) and added to a solution of lithium borohydride (0.328 g., 1 mol.) in tetrahydrofuran (8-10 c.c.) in a flask fitted with a condenser and calcium chloride tube. The mixture was stirred for 6 hr. It was then hydrolysed with water and dilute hydrochloric acid. The tetrahydrofuran layer was separated, dried over magnesium sulphate and the solvent distilled off at reduced pressure. A very dark brown gum was obtained. The aqueous layer was extracted with ether, treated as above and gave more brown-orange gum. A solution of the gum in chloroform was put through an alumina column but no separation was obtained.

4-Nitrobipenoyl dichloride (40)
(Bell and Robinson, J., 1927, 1695).

The acid (29 g., 1 mol.) was covered with thionyl chloride (75 c.c, 123 g., 10 mol.) and the mixture heated under reflux for 72 hr. (calcium chloride tube). The excess of thionyl chloride was removed by distillation at reduced pressure under dry nitrogen. When most of the liquid had been removed, the residue was transferred to an evaporating dish and placed in a vacuum desiccator over potassium hydroxide till it went solid. The crude chloride (30 g., 92% yield) had m.p. 84-88°. Attempts to recrystallise it resulted in partial hydrolysis so it was used directly for the reduction to the diol. A sample was crystallised with difficulty from benzene-light petroleum and had m.p. 88-90°. Bell and Robinson give the m.p. as 90-92°. 55.4 g. of the acid chloride were prepared altogether.

<u>6-Nitrobiphenoyl dichloride</u> (41)
(Bell and Robinson, <u>J</u>., 1927, 1695).

The 6-nitro biphenic acid (16g., 1 mol.) was covered with thionyl chloride (40 c.c., 65.6 g., 10 mol.) and the mixture was heated under reflux for 72 hr. Excess of thionyl chloride was removed as in the above experiment. The crude dichloride (17 g., 94.5%) had m.p. 84-85°. A sample was crystallised from benzene-light petroleum and had m.p. 86-87°. (Bell and Robinson give the same m.p.) Altogether 50 g. of the acid chloride were prepared.

2,2'-Bishydroxymethyl-4-nitrobiphenyl (42)

(a) 1st experiment:

The corresponding acid chloride (5 g., 1 mol.) was dissolved in 10 c.c. of purified tetrahydrofuran and added slowly at room temperature to a solution of lithium borohydride (2 g., 5.9 mol.) in 40 c.c. of tetrahydrofuran prepared at -8° and allowed to warm up to room temperature. The reaction was exothermic and at first very vigorous. The mixture was stirred mechanically for 4 hr. at room temperature and under nitrogen. It was hydrolysed with water and 1N hydrochloric acid and the two layers were separated. The top tetrahydrofuran layer was washed with water and dilute acid and dried over magnesium sulphate. The solvent was distilled off and the residue (5 g.) was a dark orange gum. This was partly dissolved in benzene and the solution passed through a layer of charcoal placed in a sintered glass funnel. The benzene was evaporated and gave a pale yellowish glass which crystallised on being covered with fresh benzene. Recrystallised from benzene it had m.p. 97-98° (0.5 g., 12.5 % yield). (Found: C, 64.4 ; H, 5.1 ; N, 6.0 ; O, 24.3 % ; $C_{14}H_{13}NO_4$ requires C, 64.8 ; H, 5.05 ; N, 5.4 ; O, 24.7%).

The charcoal was washed well with acetone, the latter evaporated and the residue treated with benzene as above gave some more diol, which was recrystallised with the main crop.

The part of the gum insoluble in benzene was hydrolysed by boiling with 10% sodium hydroxide. Part dissolved and on acidifying gave 0.6g. of 4-nitro-diphenic acid. The remaining part of the gum solidified and was recrystallised from glacial acetic acid (m.p. 170-270°) The solid was orange in colour and contained a large proportion of the azo compound. The azo compound $C_{28}H_{26}N_2O_4$ requires C, 76.0 ; H, 5.8 ; N, 6.2 ; O,14.1% and the isolated solid, was found on analysis to contain C, 71.0 ; H, 4.1 ; N, 5.6 ; O, 18.8%.

(b) <u>2nd Experiment</u>:

The above experiment was repeated but the stirring of the reactants was continued for only 2.5 hr. A 5% yield of diol was obtained.

(c) <u>3rd Experiment</u>:

Sodium dried ether was used as solvent. Lithium borohydride (1 g., 7.3 mol.) was dissolved in 50 c.c. ether at -8° with stirring and under nitrogen. It was warmed to room temperature and a suspension of the 4-nitrobiphenoyl dichloride (2 g., 1 mol.) in 15 c.c. ether was added during 0.5 hr. at such a rate that the temperature of the reactants remained 4-6° above room temperature. The mixture was stirred for another 0.5 hr. at 34°, cooled and hydrolysed with water and 1N hydrochloric acid. The two layers were separated, the ether layer dried over magnesium sulphate and the solvent distilled off.

The gum was treated as in the previous experiments and 0.5g (31%) of the diol was obtained. The experiment was repeated and a 40% yield was obtained. This was further increased to 62.5% when 5 times the required amount of hydride was used and the reactants were stirred for 2 hr. at room temperature and heated for only 15 min. at 34°.

(d) Standard procedure for preparation of 2,2'-bishydroxymethyl-4-nitrobiphenyl (42).

Lithium borohydride (10 g., 4.3 mol.) was dissolved at -8° in 500 c.c. sodium dried ether with stirring under nitrogen and allowed to warm to room temperature. The solid 4-nitrobiphenoyl dichloride (34 g., 1 mol.) was added at such a rate that temperature was 7-8° above room temperature and the addition took about 45 min. The reactants were stirred for another hour, hydrolysed with 75 c.c water and with 50 c.c. dilute hydrochloric acid. The ether layer was separated, washed with 10% sodium hydroxide to remove any unreacted acid chloride, then with water and filtered through charcoal. Most of the ether was distilled off and the residue dried on a water bath. The gum was solidified under benzene. Crude yield 27 g.(100%)

m.p. 87-93°. Recrystallised twice from benzene it had m.p. 95-97° (21.5 g., 79%).

Altogether 25 g. of the 4-nitro diol were synthesised.

Di-p-nitrobenzoate of 2,2'-bishydroxymethyl-4-nitrobiphenyl.

Impure 2,2'-bishydroxymethyl-4-nitrobiphenyl (42) (0.4g.) was dissolved in 8 c.c. of pyridine (dried over potassium hydroxide) and 1.6 g. of *p*-nitrobenzoyl chloride were added. The mixture was warmed gently for 10 min. and stirred. A solid was formed which was filtered off after cooling, washed well with sodium carbonate solution and water and dried. (0.8 G., m.p. 186-188° were obtained). It was crystallised from 1,2-dimethoxyethane and 0.4 g., m.p. 204°, were obtained as the first crop. (Found: C, 60.4 ; H, 3.3 ; N, 7.7 ; $C_{28}H_{19}N_3O_{10}$ requires C, 60.3 ; H, 3.4 ; N, 7.5 %).

2,2'-Bishydroxymethyl-6-nitrobiphenyl (43)

Lithium borohydride (6 g., 3.65 mol.) was dissolved at -8° in 400 c.c. sodium dried ether with stirring under nitrogen and allowed to warm to room temperature. The solid 6-nitrobiphenyl dichloride (41) (24 g., 1 mol.) was added during 1 hour so that the temperature remained at 27-30°. The reactants were stirred for 1 hour, hydrolysed and worked up as in preparation of the 4-nitro diol above. Evaporation of residual ether on the water bath gave a yellow liquid residue. This was dissolved in a little benzene and allowed to stand overnight. A solid m.p. 92-95° was obtained, 20 g. (74%). On recrystallisation from benzene it was found that the melting point went down to 84-85°, which however went up again on standing in air to 92-95°. On drying for 3 days at 60-80° in an electric oven the melting point was 96-98°. (Found C, 64.7 ; H, 5.2 ; O, 24.7 ; N, 5.6. ; $C_{14}H_{13}O_4N$ requires C, 64.8 ; H, 5.05 ; O, 24.7 ; N, 5.4 %).

Solid m.p. 84-85° showed a strong infrared absorption band at 14.9 μ (CH wagging vibration in benzene); in solid m.p. 92-95° this band was much weaker and in solid m.p. 96-98° the band di~~s~~sappeared. Examination of the crystals under microscope showed white transparent rods in the low melting point solid which on standing became opaque while still retaining the rod shape. Comparison of the infrared spectra of the 4-nitro and 6-nitro diols shows different absorption in the 13.0 - 14.0 μ region as would be expected with the two different substitution patterns in the two compounds. Mixed m.p. of the 4-nitro and 6-nitro (dried) diols (softening at 76-78°) m.p. 80°. Altogether 35 g. of the 6-nitro diol were prepared, the average yield of three preparations being: crude 80%; recrystallised from benzene and dried 75%.

2,2'-Bisbromomethyl-4-nitrobiphenyl (44)

The corresponding diol (21.5 g., 1 mol.) was added to 48-50% hydrobromic acid (967.5 c.c., *d* 1.5) at 90°, the mixture was heated to boiling and allowed to boil for 20 minutes. On cooling a heavy gum was obtained. The acid layer was decanted and the gum solidified under light petroleum (80-100°). It was filtered and dried in a vacuum desiccator. Yield 20 g.(62.5%), m.p. 81-83°. Recrystallised from light petroleum (b.p.80-100°) with charcoal the 1st crop, 13 g.,had m.p. 83-85° and the 2nd crop, 7 g., had m.p. 81-84°.

(Found:C, 43.5 ; H, 2.9 ; N, 3.7 ; O, 8.4 ; Br, 41.4 ; $C_{14}H_{11}NO_2Br_2$ requires : C, 43.7 ; H, 2.9 ; N, 3.6 ; O, 8.3 ; Br, 41.5 %).

2,2'-Bisbromomethyl-6-nitrobiphenyl (45)

The corresponding diol (10 g., 1 mol.) was added to 48-50% hydrobromic acid (450 c.c.) at 90° and boiled for 2o min. On cooling a solid was obtained, which was filtered off and dried. Yield 15 g. (100%) m.p. 101-105°. Recrystallised from light petroleum(b.p.80-100°) with charcoal the 1st crop, 13.0 g., had m.p. 104.5-105°, and the 2nd crop, 0.5 g., had m.p.102-105°. Total yield 90%. On 2nd recrystallisation the m.p. was 106-107°. (Found: C,43.6; H,2.9; N,3.5; O,8.4; Br,41.45; $C_{14}H_{11}NO_2Br_2$ requires: C, 43.7; H, 2.9; N,3.6; O,8.3; Br,41.5%). The preparation was repeated and 35.6 g. of the dibromide were synthesised.

(+)-2,7-Dihydro-1-(2-hydroxy-1-methyl-2-phenylethyl)-1-methyl-2'-nitro-3,4:5,6-dibenzazepinium Bromide (46; X = Br) and Iodide (46 ; X = I).

(-)Ephedrine hemihydrate (4.0 g., 2.3 mol.) was dissolved in a few c.c. of dry benzene and dried over anhydrous sodium sulphate. 2,2'-Bisbromomethyl-4-nitrobiphenyl (3.85 g., 1 mol.) was dissolved in 10 c.c. dry benzene with warming and the filtered (-)ephedrine solution was added to it at 50°. The mixture was kept at this temperature for 14 hr. and at 60° for 1 hr. (calcium chloride tube). The solution went cloudy after 5 minutes and a gum started to separate which solidified after some time. The reaction mixture was cooled and the solid filtered off. It was washed with warm dry benzene when it turned again into a gum, which would not solidify on trituration with ice-cold water. Liquid was decanted and the gum was dried in a vacuum desiccator over calcium chloride. A semi-solid was obtained (4.3 g., 91.5% yield) which could not be obtained crystalline. It was sparingly soluble in water, quite insoluble in ethyl acetate and acetone, it was soluble in methanol and ethanol. The bromide was converted into the iodide by adding saturated potassium iodide solution in water to a solution of the bromide in water.

1.25 G., of the bromide gave 1.4 g.(100%) of the iodide. Recrystallised from ethanol, the iodide was obtained as daffodil yellow clusters of rods m.p. 229° (decomp.).Yield 1.05g., (76% on the bromide used). (Found: C,55.9; H, 4.8 ; N, 5.3 ; O, 9.5 ; I, 24.8 ; $C_{24}H_{25}N_2O_3I$ requires : C,55.8 ; H, 4.9 ; N, 5.4 ; O, 9.3 ; I, 24.6%). The iodide had $[\alpha]^{22^\circ}_{5461}$ $+30.74^\circ$ (methanol, c 0.9840). The first reading was taken 4¼ minutes after wetting and the rotation of the solution remained constant.

2,7-Dihydro-1,1-dimethyl-2'-nitro-3,4:5,6-dibenzazepinium Bromide (48)

2,2'-Bisbromomethyl-4-nitrobiphenyl (0.6 g., 1 mol.) was dissolved in 5 c.c. dry benzene and 5 c.c dry ether and cooled to 0°. Dimethylamine (1.5 c.c., 14.6 mol., d 0.6804) cooled in an ice-salt mixture was added and the reactants were allowed to warm to room temperature. Reaction was instantaneous and a white solid was formed. This was filtered off after 30 min. and washed with dry benzene. It was purified by dissolving in smallest amount of water and adding a few c.c. of 30% sodium hydroxide (to decompose any dimethylamine hydrobromide) till the quaternary bromide was reprecipitated. This was filtered off and dried in a vacuum desiccator 0.4 g.(74%), m.p. 241° (decomp.) with some previous softening, was obtained. After three recrystallisations from ethyl acetate-ethanol it had m.p. 246-248° (decomp.); 0.15 g. were obtained as 1st crop. (Found: C, 50.6 ; H, 5.2 ; O, 15.0 ; Br, 21.5 ; $C_{32}H_{34}N_4O_4Br_2.3H_2O$ requires: C, 51.0 ; H, 5.35 ; O, 14.9; Br21.2%)

2,2'-Bis(trimethylammonio)methyl-4-nitrobiphenyl Dibromide (50).

The corresponding bromide (3.85 g., 1 mol.) was dissolved in 10 c.c. dry benzene and cooled in ice. Anhydrous trimethylamine (5 c.c., 5.7 mol., d 0.673) cooled in an ice-salt mixture was added and the mixture was allowed to warm to room temperature. Reaction was very rapid and vigorous - a pink solid separated out almost at once. The reactants were allowed to stand at room temperature for 48 hr., then the solid was filtered off, washed with dry acetone and dried in a vacuum desiccator. Yield 4g.(80%). The quaternary bromide was deliquescent in air at first, but after standing for a while it solidified again. It was recrystallised from methylated spirit and 2.4g., m.p. 233-235° (decomp.) were obtained as 1st crop. (Found: C, 45.9; H, 6.0 ; Br., 31.6 ; $C_{20}H_{29}N_3O_2Br_2.H_2O$ requires C, 46.1 ; H, 6.0 ; Br, 31.0%).

2,7-Dihydro-1-(2-hydroxy-1-methyl-2-phenylethyl)-1-methyl-4'-nitro-3,4:5,6-dibenzazepinium Bromide (47 : X = Br)

Experiment I

The (-) ephedrine hemihydrate (4.0 g., 2.3 mol.) was dissolved in dry benzene and dried over anhydrous sodium sulphate. The filtered solution was added at 50° to the 6-nitro bromide (3.85 g., 1 mol.) dissolved in 10 c.c. dry benzene (calcium chloride tube). After about 15 min. the mixed solution became slightly cloudy and after 0.5 hr. a gum begun to separate which started solidifying after 3 hr. The mixture was kept 24 hr. at 50°, 1 hr at 60° and 24 hr. at room temperature. The solid was filtered off and washed with dry benzene. On washing with water it turned into a gum which would not solidify on trituration. The gum was dried in a vacuum desiccator and went solid. 3.45 G. (73.5% yield) m.p. $225\text{-}230^\circ$ (decomp.)(softening 125°) were obtained. The solid was recrystallised from ethanol. The 1st crop (0.85 g., 25% of crude product) had m.p. 233° (decomp.). (Found: C, 61.3 ; H, 5.3 ; N, 5.8 ; O, 9.9 ; Br, 170; $C_{24}H_{25}N_2O_3Br$ requires C, 61.4 ; H, 5.4 ; N, 5.9 ; O, 10.2 ; Br, 17.0%). This crop was examined polarimetrically and mutarotated in methanol at 24° from $[\alpha_0]_{5461}$ -446° to $[\alpha_\infty]_{5461}$ -113° (Table IV ; Graph VIIa). No more crops could be obtained from ethanol so the solution was evaporated on a water bath. Attempts to recrystallise the residue were not successful. The crude product was examined polarimetrically at 22° (methanol) and it mutarotated from $[\alpha_0]_{5461}$ -71° to $[\alpha_\infty]_{5461}$ -85° (Table VI ; graph VIIc). The crude bromide (residue) was dissolved in water and purified by adding potassium hydroxide solution to liberate any unchanged (-) ephedrine, extracting the latter with ether and neutralising the aqueous layer with dilute hydrobromic acid (1 drop phenolphtalein as indicator). The 6-nitro quaternary bromide separated out at this stage and was filtered off and dried in vacuum. The crude bromide was converted into the iodide by treating its aqueous solution with aqueous potassium iodide. The crude iodide (2g.) had m.p. 218-219° (decomp.) with previous softening. It crystallised with difficulty from water - 1st crop, 0.6 g., had m.p.175-190° (decomp.) with softening at ca.155°. (Found: C, 53.9 ; H, 5.2 ; N, 5.1 ; O, 11.7 ; I, 24.1 ; $C_{24}H_{25}N_2O_3I \cdot H_2O$ requires C,53.9 ; H, 5.1 ; N, 5.2 ; O, 12·0; I, 23.7%). This mutarotated in methanol at 22° from $[\alpha_0]_{5461}$ -60° to $[\alpha_\infty]_{5461}$ -88° (Table IX ; Graph VIIf.). Evaporation of the mother liquor yielded a solid m.p. 223-226° (decomp.) with softening at ca.155°. This impure residue mutarotated in methanol at 22° from $[\alpha_0]_{5461}$ -78° to $[\alpha_\infty]_{5461}$ -53° (Table X ; Graph VIIg). Too little was available to try to purify it.

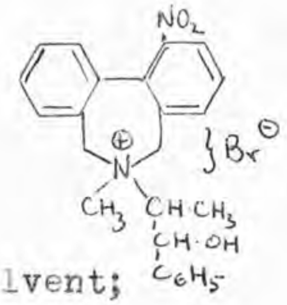
Experiment II

The preparation of the (-) ephedrinium quaternary salt was repeated using the same quantities as in the 1st experiment but heating for 54 hr. at 50-60°. A higher yield 3.8g.(82%) was obtained. 33% (1.15 g.) of the crude product crystallised from ethanol and had m.p. 233-235° (decomp.) The bromide mutarotated at 23.5° from $[\alpha_0]_{5461}$ -389° to $[\alpha_\infty]_{5461}$ -109°, (Table V ; Graph VIIb). The mother liquor was evaporated to dryness on a water bath. The residue was dissolved in hot water and after two weeks transparent plate crystals were obtained: 0.8g., m.p. 190-195° (decomp.) with softening at *ca.* 105°. The bromide mutarotated in methanol at 21.3° and 26° in an opposite way to the main crop (Tables VII and VIII ; graphs VII d and VII e). (Found: C, 59.9 ; H, 5.7 ; N, 5.5 ; O, 13.1 ; Br, 16.3 ; $C_{24}H_{25}N_2O_3Br.H_2O$ requires C, 59.1 ; H, 5.6 ; N, 5.7 ; O, 13.1 ; Br, 16.4%).

Polarimetric Experiments on the (-) ephedrinium salts (47; X=Br or I)

All solutions were examined in a jacketted tube on the mercruy green line (λ 5461 Å). All were made up in methanol. The results are given below:

Exp.	Substance Examined	T	c	$[\alpha_0]$	$[\alpha_\infty]$	k min^{-1}	$t_{\frac{1}{2}}$min.	Graph
I	Bromide m.p.233° (decomp.)	24°	1.004	-446°	-113°	6.97×10^{-2}	10	VII a
II	Bromide m.p.233-235° (decomp.)	23.5°	1.004	-389°	-109°	8.53×10^{-2}	8	VII b
I	Bromide residue crude	22°	1.008	-71°	-85°	4.606×10^{-2}	15	VII c
II	Bromide; 1st crop H_2O	21.3°	1.110	-78.5°	-89°	5.905×10^{-2}	12	VII d
II	Bromide; 1st crop H_2O	26°	1.0225	-81°	-90.5°	6.14×10^{-2}	11	VII e
I	Iodide; 1st crop H_2O	22°	1.027	-60°	-88	4.38×10^{-2}	16	VII f
I	Iodide; impure residue	22°	1.0115	-78°	-53°	16.25×10^{-2}	4	VII g

Table IV (Graph VIIa) Mutarotation of 

(m.p.233°) in MeOH

t = 24° ; l = 2; c = 1.004 g./100c.c. solvent;

λ = 5461 Å ; Zero at 180.085° ;

(Solution cloudy: had to be filtered again)

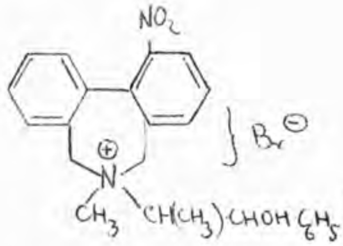
Time mins.	Polarimetric reading.	$(\alpha_t - \alpha_\infty)$	$\text{Log}(\alpha_t - \alpha_\infty)$
15.5	175.770	2.040	0.3096
16.45	.990	1.820	.2601
16.85	176.020	1.790	.2529
19.00	.210	1.600	.2041
20.15	.385	1.425	.1538
20.65	.420	1.390	.1430
21.00	.465	1.345	.1287
21.50	.500	1.310	.1173
22.00	.555	1.255	.0986
23.30	.675	1.135	.0550
24.50	.750	1.060	.0253
25.00	.770	1.040	.0170
25.75	.830	0.980	-.0088
26.50	.900	0.910	-.0410
27.00	.920	0.890	-.0606
29.00	177.040	0.770	-.1135
30.00	.090	0.720	-.1427
30.50	.160	0.650	-.1871
32.00	.190	0.620	-.2076
32.65	.210	0.600	-.2218
33.00	.265	0.545	-.2636
34.50	.325	0.485	-.3143
35.60	.370	0.440	-.3565
37.50	.395	0.415	-.3820
38.40	.410	0.400	-.3979
39.75	.440	0.370	-.4318
41.15	.490	0.320	-0.4949
42.50	.530	0.280	-0.5528
44.50	.565	0.245	-0.6108
46.00	.600	0.210	-0.6778
53.50	.690	0.120	-0.9208
∞	.810		

extrapolated $[\alpha_0]^{24}_{5461}$ = -446° ; $[\alpha_\infty]^{24}_{5461}$ = -113°

k = 6.97×10^{-2} min.$^{-1}$; $t_{\frac{1}{2}}$ = 10 mins.

Table V (Graph. VII b)

Mutarotation of



(m.p. 233-235° decomp.)

$t = 23.5^{\circ}$; $c = 1.004$g. ; $l = 2$; $\lambda = 5461$ Å ; Zero at 180.1°

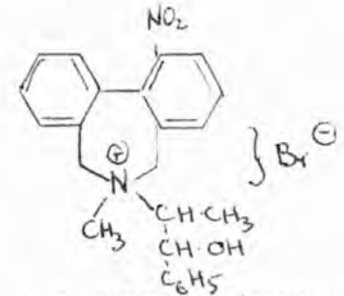
Time mins.	Polarimetric reading.	$(\alpha_t - \alpha_\infty)$	$\text{Log}(\alpha_t - \alpha_\infty)$
3.55	174.070	3.84	0.5843
4.35	.280	3.63	0.5599
5.35	.590	3.32	0.5211
6.30	.830	3.08	0.4885
7.50	175.105	2.805	0.4479
8.20	.260	2.650	0.4233
9.10	.500	2.410	0.3820
10.15	.700	2.210	0.3444
11.00	.840	2.070	0.3160
12.00	.990	1.920	0.2833
14.00	176.275	1.635	0.2135
15.00	.435	1.475	0.1688
16.00	.590	1.320	0.1206
18.00	.760	1.150	0.0607
20.00	.965	0.945	-0.0246
21.00	177.040	0.870	-0.0605
22.00	.090	0.820	-0.0862
23.00	.190	0.720	-0.1427
24.00	.260	0.650	-0.1871
27.50	.400	0.510	-0.2924
32.00	.550	0.360	-0.4437
33.00	177.650	0.260	-0.5850
42.00	.810	0.100	-1.0000
∞	.910		

Extrapolated $[\alpha_0]^{23.5}_{5461} = -389^{\circ}$; $[\alpha_\infty]^{23.5}_{5461} = -109^{\circ}$;

$k = 8.53 \times 10^{-2}$ min.$^{-1}$; $t_{\frac{1}{2}} = 8$ min.

Table VI (Graph VIIc)

Mutarotation of



in MeOH

(crude residue after removal of the 1st crop with m.p. 233°)

$t = 22^\circ$; $l = 2$; $c = 1.003$ g./100 c.c. solvent ;

$\lambda = 5461$ Å ; Zero at 180.09° ;

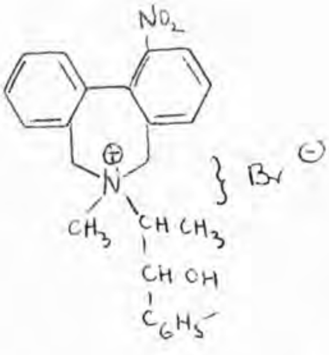
Time mins.	Polarimetric reading	$(\alpha_\infty - \alpha_t)$	$\mathrm{Log}(\alpha_\infty - \alpha_t)$
4.05	178.615	0.220	-.6576
5.25	.605	0.210	-.6778
5.65	.595	0.200	-.6980
6.25	.590	0.195	-.7100
7.40	.580	0.185	-.7328
8.45	.575	0.180	-.7447
10.15	.560	0.165	-.7825
12.50	.545	0.150	-.8239
17.25	.510	0.115	-.9393
21.50	.490	0.095	-1.0223
24.00	.480	0.085	-1.0706
25.50	.475	0.080	-1.0969
27.50	.470	0.075	-1.1249
28.30	.465	0.070	-1.1549
29.50	.460	0.065	-1.1871
32.00	.455	0.060	-1.2218
35.00	.450	0.055	-1.2596
54.00	.415	0.020	-1.6990
∞	.395		

$k = 4.606 \times 10^{-2}$ min.$^{-1}$; $t_{\frac{1}{2}} = 15$ min. ;

Extrapolated $[\alpha_0]^{22^\circ}_{5461} = -71^\circ$; $[\alpha_\infty]^{22^\circ}_{5461} = -85^\circ$

Table VII (Graph VII d).

Mutarotation of



in MeOH

(1st crop from water)

$t = 21.3^{\circ}$; $l = 2$; $c = 1.1100$ g./100 c.c. solvent ;
$\lambda = 5461$ Å ; Zero at 180.11°

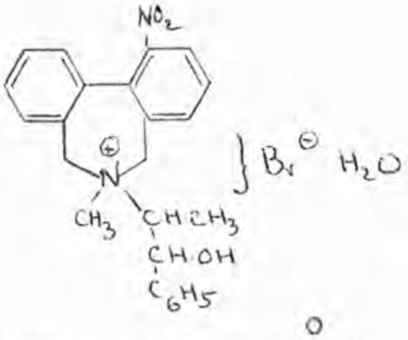
Time mins.	Polarimetric reading	$(\alpha_\infty - \alpha_t)$	log $(\alpha_\infty - \alpha_t)$
3.50	178.340	.210	-.6778
4.60	.320	.190	-.7212
6.20	.310	.180	-.7447
6.55	.300	.170	-.7695
8.00	.290	.160	-.7958
10.00	.270	.140	-.8539
13.00	.250	.120	-.9208
14.40	.240	.110	-.9586
15.50	.230	.100	-1.0000
16.50	.220	.090	-1.0458
20.50	.205	.075	-1.1249
22.00	.200	.070	-1.1549
28.00	.180	.050	-1.3010
35.00	.160	.030	-1.5229
∞	.130		

$k = 5.905 \times 10^{-2}$ min.$^{-1}$; $t_{\frac{1}{2}} = 12$ min. ;

Extrapolated $[\alpha_0]^{21.3}_{5461}$ -78° ; $[\alpha_\infty]^{21.3}_{5461} = -89^{\circ}$.

Table VIII (Graph VIIe)

Mutarotation of



in MeOH

c = 1.0225 g./100 c.c. solvent ; t = 26° ; l = 2 ;

λ = 5461 Å ; Zero at 180.09° .

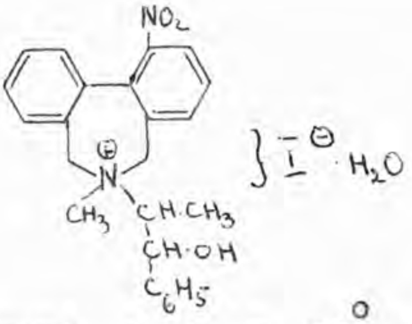
Time mins.	Polarimetric reading	$(\alpha_\infty - \alpha_t)$	$\mathrm{Log}(\alpha_\infty - \alpha_t)$
5.45	178.375	.135	-.8697
6.20	.365	.125	-.9031
6.65	.360	.120	-.9208
7.20	.350	.110	-.9586
11.00	.330	.090	-1.0458
12.50	.325	.085	-1.0706
15.10	.320	.080	-1.0969
16.00	.310	.070	-1.1549
18.50	.300	.060	-1.2218
21.25	.290	.050	-1.3010
∞	.240		

k = 6.14 x 10^{-2} min. ; $t_{\frac{1}{2}}$ = 11 min.

Extrapolated $[\alpha_0]^{26}_{5461} = -81^\circ$; $[\alpha_\infty]^{26}_{5461} = -90.5^\circ$.

Table IX (Graph VII f)

Mutarotation of



in MeOH

c = 1.027 g./100 c.c. solvent ; t = 22° ; l = 2 ;
λ = 5461 Å ; Zero at 180.1° .

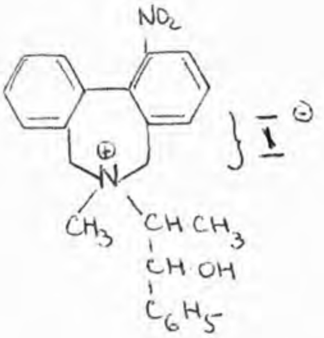
Time min.	Polarimetric reading	$(\alpha_\infty - \alpha_t)$	$\text{Log}(\alpha_\infty - \alpha_t)$
2.75	178.815	.515	-0.2882
3.50	.810	.510	-0.2924
4.00	.800	.500	-0.3010
4.50	.790	.490	-0.3098
5.25	.750	.450	-0.3468
6.30	.745	.445	-0.3516
9.50	.680	.380	-0.4202
10.90	.650	.350	-0.4559
12.15	.635	.335	-0.4749
13.25	.620	.320	-0.4948
14.60	.600	.300	-0.5229
15.50	.595	.295	-0.5302
16.70	.585	.285	-0.5452
17.30	.580	.280	-0.5528
23.00	.520	.220	-0.6576
24.35	.515	.215	-0.6676
25.65	.480	.180	-0.7447
26.90	.470	.170	-0.7695
28.25	.465	.165	-0.7825
29.45	.457	.157	-0.8041
30.35	.455	.155	-0.8097
31.55	.452	.152	-0.8182
40.25	.400	.100	-1.000
∞	.300		

$k = 4.38 \times 10^{-2}$ min.$^{-1}$; $t_{\frac{1}{2}}$ = 16 min. ;

Extrapolated $[\alpha_0]^{22}_{5461} = -60^\circ$; $[\alpha_\infty]^{22}_{5461} = -88^\circ$.

Table X (Graph VII g)

Mutarotation of



(impure residue)

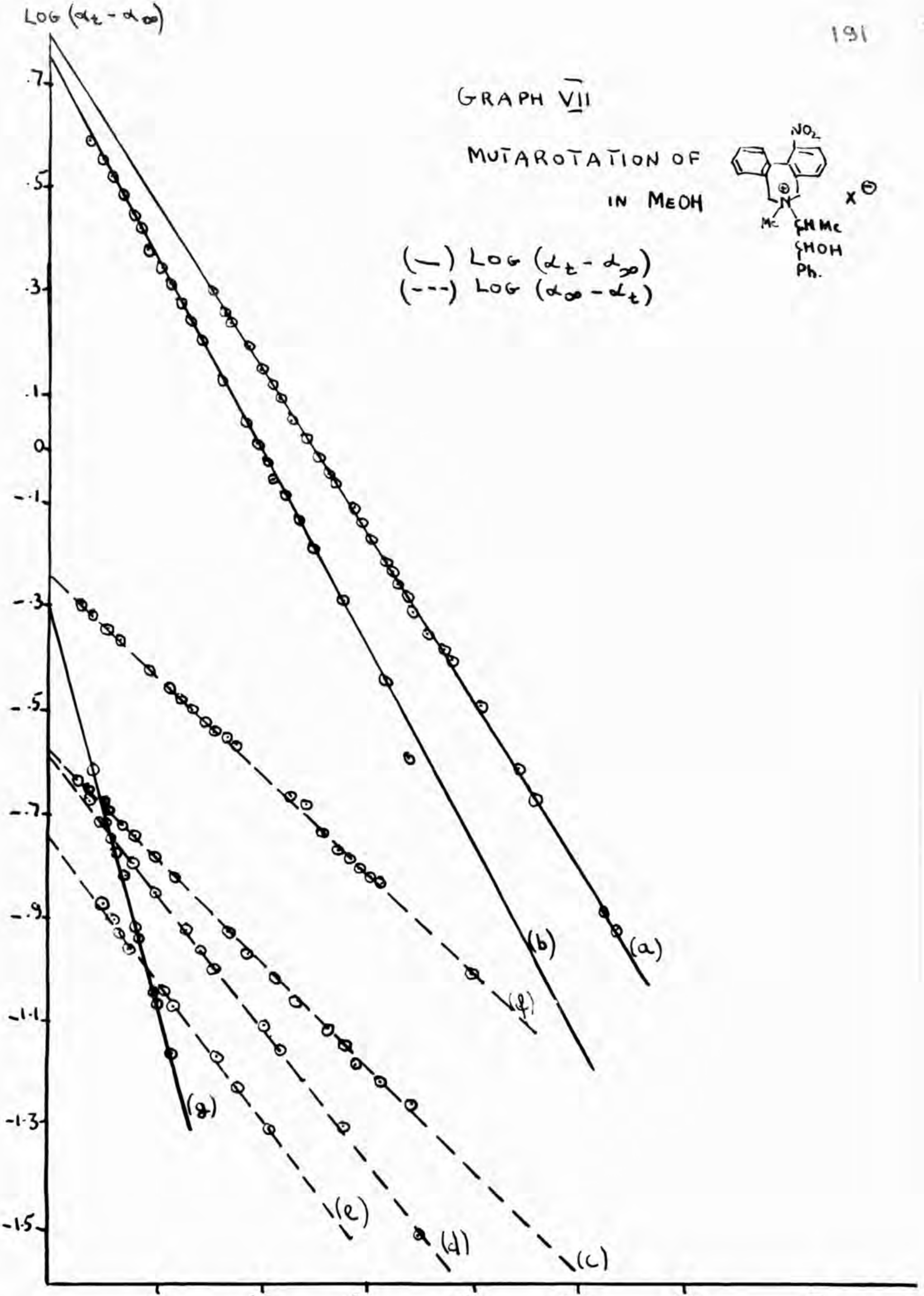
in MeOH

c = 1.0115 g./100 c.c. solvent ; t = 22° ; 1 = 2 ;
λ = 5461 Å ; Zero at 180.1° .

Time mins.	Polarimetric reading	$(\alpha_t - \alpha_\infty)$	$\mathrm{Log}(\alpha_t - \alpha_\infty)$
4.25	178.790	0.240	-0.6198
5.35	.840	0.190	-0.7214
5.90	.850	0.180	-0.7447
6.40	.860	0.170	-0.7695
7.30	.880	0.150	-0.8239
8.10	.910	0.120	-0.9208
8.50	.915	0.115	-0.9393
10.25	.940	0.090	-1.0458
10.50	.945	0.085	-1.0706
11.75	.963	0.067	-1.1739
∞	179.030		

k = 16.25 x 10^{-2} min.$^{-1}$; $t_{1/2}$ = 4 min. ;

Extrapolated $[\alpha_0]^{22}_{5461}$ = -78° ; $[\alpha_\infty]^{22}_{5461}$ = -53° .



GRAPH VII

MUTAROTATION OF IN MeOH

2,7-Dihydro-1,1-dimethyl-4'-nitro-3,4:5,6-dibenzazepinium Bromide (49 ; X = Br)

2,2'-Bisbromomethyl-6-nitro-biphenyl (3.85 g., 1 mol.) was dissolved in 10 c.c. dry benzene and 5 c.c. sodium dried ether and an excess of dimethylamine (10 c.c.,14.6 mol.,*d* 0.6804) previously cooled in ice was added. The solution went cloudy rapidly and a pinkish gum begun to separate which went solid after 1 hr. The mixture was left at room temperature (calcium chloride tube) for 24 hr. The solid was filtered off and washed well with dry benzene. It was then covered with *ca.*10 c.c. water and triturated for ½ hr. - the resulting solid was filtered off, and dried on a water bath. The white crystalline solid was recrystallised from acetonitrile and had m.p. 137-140° (decomp.). The yield was 2.5 g.(68%). (Found : C, 52.65 ; H, 5.2 ; N, 7.4 ; O, 12.9 ; Br, 22.2 ; $C_{16}H_{17}N_2O_2Br.H_2O$ requires C, 52.3 ; H, 5.2 ; N, 7.6 ; O, 13.1 ; Br, 21.8 %).

The preparation was repeated using 1 g. of the 6-nitro biphenyl compound and 0.9 g. (95%) of the pure azepinium bromide was obtained.

2,7-Dihydro-1,1-dimethyl-4'-nitro-3,4:5,6-dibenzazepinium (+)-Camphorsulphonate.

The above azepinium bromide (49 ; X = Br) (0.54 g., 1 mol.) and silver (+)-camphorsulphonate (0.51 g., 1 mol.) were dissolved separately in 50% alcohol, the solutions were mixed and boiled for ½ hr. The precipitated silver bromide was filtered off and washed well with hot water. The filtrate was evaporated to dryness on a water bath and a glassy solid was obtained. This was recrystallised from ethyl acetate and 0.5 g. (36%) were obtained as 1st crop, m.p.160° (decomp.) with softening at 120°. The solid was examined polarimetrically in methanol at + 23° and at -4°. The rotation of its solution was constant and unchanged $[\alpha]_{5461}^{23^\circ, -4^\circ} \neq + 23.5^\circ$. The camphorsulphonate was recrystallised again but this time from ethanol-ethyl acetate mixture. It crystallised slowly in fine plates grouped into stars. It had m.p. 139-141° (decomp.). Examined polarimetrically in methanol at 23° it had $[\alpha]_{5461}^{23^\circ} + 23.4^\circ$.

<u>Preparation of (+)-Silver α-Bromocamphor-π-sulphonate.</u>

Water at 60-70° was gradually added with stirring to ammonium (+)-α-bromocamphor-π-sulphonate (22 g., 1 mol.) to obtain a saturated solution. About 90 c.c. were added and the resulting solution was at 45-50°. A warm concentrated solution of silver nitrate (11.5 g., 1 mol., in *ca.* 5 c.c. water) was added with stirring. The silver (+)-α-bromocamphor-π-sulphonate was cooled in ice, filtered in the dark-room and dried over calcium chloride in a desiccator, also in the dark-room. Crude yield 19 g. This was added to *ca.* 100 c.c. hot water and the hot solution was filtered through a sintered glass funnel and 2 pieces of No. 50 filter paper. White needles separated from the clear solution on cooling. They were filtered off and dried in a vacuum desiccator in the dark-room. Yield 14.5 g. (52%)

2,7-Dihydro-1,1-dimethyl-4'-nitro-3,4:5,6-dibenzazepinium α-Bromocamphor-π-sulphonate.

a) Preparation from the corresponding azepinium camphorsulphonate :

The camphorsulphonate (0.5g.) was dissolved in water and a saturated solution of potassium iodide was added. The precipitated iodide was filtered off and dried in a vacuum desiccator. The dried iodide (0.293 g., 1 mol.) and (+) silver α-bromocamphor-π-sulphonate (0.327 g., 1 mol.) were dissolved separately in aqueous alcohol and the solutions were mixed with stirring and heated for ½ hr. The precipitated silver iodide was filtered off and the filtrate was evaporated on a water bath. The solid residue (0. 4g., 93% on the iodide) was recrystallised from methanol-ethyl acetate mixture. Fine white needles, m.p. 264° (decomp.) were obtained as 1st crop (0.15 g., 35%). (Found: C, 53.6 ; H, 5.4 ; N, 4.5 ; Br, 13.7 ; $C_{26}H_{31}N_2O_6SBr$ requires C, 53.9 ; H , 5.4 ; N, 4.8 ; Br, 13.8%).

b) Preparation from the corresponding azepinium bromide:

Solutions of the azepinium bromide (1.83 g., 1 mol.) and the (+) silver α-bromocamphor-π-sulphonate in aqueous alcohol were mixed and treated as above. The solid residue, 2.7 g., was recrystallised from methanol-ethyl acetate and gave 2.4 g. (86%) m.p. 267° - 269° (decomp.). Mixed m.p. with salt from 1st preparation not depressed (depends on rate of heating).

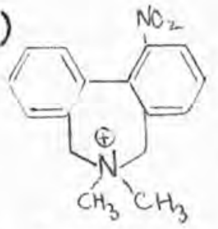
Mutarotation of 2,7-dihydro-1,1-dimethyl-4'-nitro-3,4:5,6-dibenzazepinium α-Bromocamphor-π-sulphonate (49)

The salt was found to mutarotate in methanol solution at 22° and 24° with half life time in each case of 50.2 minutes.

$[\alpha]_{5461}^{22^\circ, (24^\circ)}$ initial, by extrapolation -250° (-251°) and

$[\alpha]_{5461\ \mathrm{final}}^{22^\circ (24^\circ)}$ + 66°. (Tables XI and XII, Graph VIII).

Table XI (Graph VIII)

Mutarotation of  (+)-α-bromocamphor-π-sulphonate in methanol.

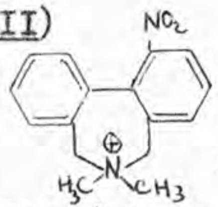
l = 2 ; c = 0.5975 g./100 c.c. of solvent ; t = 24° ;
λ 5461 Å ; Zero 180.08°.

Time mins.	Polarimetric reading	$(\alpha_\infty - \alpha_t)$	$\text{Log}_{10}(\alpha_\infty - \alpha_t)$
3.20	177.405	3.465	0.5397
5.60	.452	3.418	0.5337
7.20	.530	3.340	0.5237
8.00	.565	3.305	0.5191
9.50	.630	3.240	0.5105
11.20	.700	3.170	0.5010
12.50	.740	3.130	0.4955
15.00	.865	3.005	0.4778
16.50	.925	2.945	0.4690
20.00	178.055	2.815	0.4494
23.00	.170	2.700	0.4313
27.20	.305	2.565	0.4090
30.25	.385	2.485	0.3953
35.25	.575	2.295	0.3600
45.50	.870	2.000	0.3010
50.50	179.005	1.865	0.2706
54.25	.100	1.770	0.2479
62.50	.300	1.570	0.1959
71.25	.480	1.390	0.1430
75.50	.560	1.310	0.1172
90.00	.850	1.020	0.0086
125.50	180.210	0.660	1.81954 -.1805
140.25	.362	0.508	1.70586 -.2941
159.25	.475	0.395	1.59660 -.4034
195.50	.630	0.240	1.38021 -.6198
∞	.870	0	

$k = 1.38 \times 10^{-2}$ min.$^{-1}$ $t_{\frac{1}{2}} = 50.2$ min.

Table XII (Graph VIII)

Mutarotation of

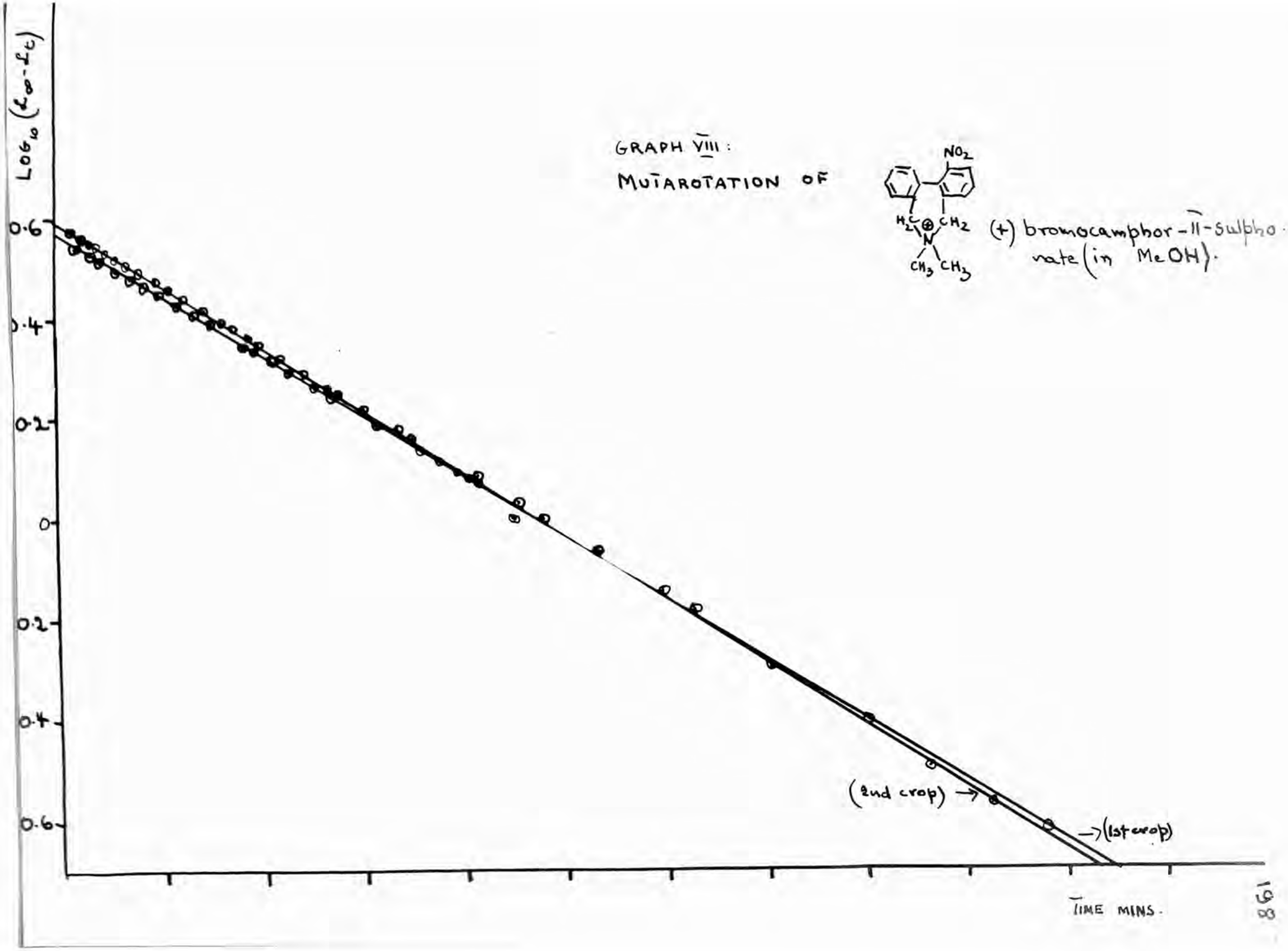


(+)-α-bromocamphor-$\overline{\pi}$-sulphonate in methanol.

l = 2 ; c = 0.6155g./100 c.c. of solvent ; t = 22° ;
λ = 5461 Å ; Zero at 180-08°.

Time mins.	Polarimetric reading	$(\alpha_{\infty}-\alpha_{t})$	$\log_{10}(\alpha_{\infty}-\alpha_{t})$
2.75	177.130	3.760	0.5751
3.25	.135	3.755	0.5746
4.25	.160	3.730	0.5717
5.10	.220	3.670	0.5647
6.00	.265	3.625	0.5593
7.50	.325	3.565	0.5521
8.00	.345	3.545	0.5496
9.50	.430	3.460	0.5391
10.00	.455	3.435	0.5359
11.00	.505	3.385	0.5296
12.75	.575	3.315	0.5213
14.50	.660	3.230	0.5092
16.25	.720	3.170	0.5011
17.50	.775	3.115	0.4935
19.75	.885	3.005	0.4778
22.50	.970	2.920	0.4654
25.00	178.080	2.810	0.4487
29.50	.245	2.645	0.4224
35.50	.460	2.430	0.3856
40.00	.615	2.275	0.3570
45.00	.760	2.130	0.3284
54.25	179.040	1.850	0.2672
61.00	.175	1.715	0.2342
67.50	.340	1.550	0.1903
70.50	.400	1.490	0.1732
83.50	.650	1.240	0.0934
92.50	.775	1.115	0.0462
96.25	.875	1.015	0.0064
100.00	.915	0.975	-0.0110
104.50	.975	0.915	-0.0386
108.00	180.020	0.870	-0.0605
120.00	.165	0.725	-0.1397
142.50	.380	0.510	-0.2924
172.25	.570	0.320	-0.4948
185.00	.620	0.270	-0.5686
212.50	.730	0.160	-0.7959
∞	.890	0	

$k = 1.38 \times 10^{-2}$ min.$^{-1}$; $t_{\frac{1}{2}}$ = 50.2 min.

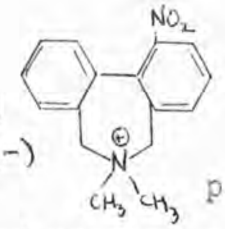
 GRAPH VIII:
MUTAROTATION OF (+) bromocamphor-π-sulphonate (in MeOH).

(-)2,7-Dihydro-1,1-dimethyl-4'-nitro-3,4:5,6-dibenzazepinium Picrate (49 ; X = $C_6H_2N_3O_7$)

The corresponding (α)bromocamphor - π -sulphonate (0.3846 g., 1 mol.) finely ground was dissolved at ca. -10° in 20 c.c methanol and a saturated solution of picric acid (0.3040 g., 2 mol.) in ethanol at -10° was added to it with stirring. The mixture was placed in an evaporating dish in an ice-salt mixture and air was blown over the surface to reduce the volume of the liquid. Solid begun to appear after 20 minutes and the stirring was continued for another 10 minutes. The solid picrate was filtered on a precooled funnel and dried in a vacuum desiccator. Total time of preparation was 35 minutes. The yield was 0.2g. (61%) and the m.p. 178°. (Found: C, 53.3 ; H, 3.7 ; N, 14.2 ; O, 28.4 ; $C_{22}H_{19}N_5O_9$ requires C, 53.1 ; H, 3.85 ; N, 14.2 ; O, 28.9%).

The preparation was repeated four times and 0.65 g. of the active picrate were prepared altogether. Crops from the various preparations were checked polarimetrically and it was found that they were the same. Racemisation of the picrate in acetone was studied over the range of 17° to 41° and the energy of activation (E) and the Arrhenius parameter (A) were derived from the experimental plots (Tables XIII to XVIII, Graphs IX and X).

Table XIII, Graph IXa)

Racemisation of (-) 

picrate in acetone.

l = 2 cm ; c = 0.3490g/100 c.c. of solvent ; t = 17.15° ;

λ 5791 Å ; Zero at 177.32.

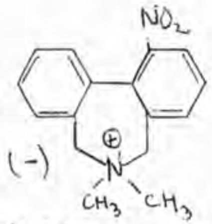
Time mins.	Polarimetric reading	α observed	$\text{Log}_{10}\alpha$
5.50	175.685	1.635	0.2135
6.50	.700	1.620	0.2095
7.50	.725	1.595	0.2028
8.50	.730	1.590	0.2014
10.00	.745	1.575	0.1973
14.00	.800	1.520	0.1818
15.00	.835	1.485	0.1718
16.00	.845	1.475	0.1687
17.00	.870	1.450	0.1614
19.50	.880	1.440	0.1584
22.00	.900	1.420	0.1523
24.00	.920	1.400	0.1461
28.00	.930	1.390	0.1430
38.00	176.080	1.240	0.0934
45.00	.145	1.175	0.0701
50.00	.200	1.120	0.0492
56.00	.225	1.095	0.0395
64.00	.290	1.030	0.0128
72.50	.380	0.940	-0.0269
80.50	.420	0.900	-0.0458
90.00	.480	0.840	-0.0757
100.00	.550	0.770	-0.1135
108.00	.605	0.715	-0.1397
132.00	.710	0.610	-0.2147
143.00	.760	0.560	-0.2518
150.0	.790	0.530	-0.2757
165.0	.850	0.470	-0.3279
180.0	.900	0.420	-0.3768
190.0	.940	0.380	-0.4202
220.0	177.030	0.290	-0.5376
230.0	.040	0.280	-0.5528
254.0	.090	0.230	-0.6383
285.0	.140	0.180	-0.7447
∞	.320	0	

$k = 7.876 \times 10^{-3}\ \text{min.}^{-1}$ $t_{\frac{1}{2}} = 88$ minutes.
$= 1.312 \times 10^{-4}\ \text{sec.}^{-1}$

Extrapolated value of $[\alpha_0]$ 5791 -243°

initial

Table XIV, (Graph IXb).

Racemisation of  picrate in acetone.

l = 2 ; c = 0.4545 g./100 c.c. solvent ; t = 19.65°.

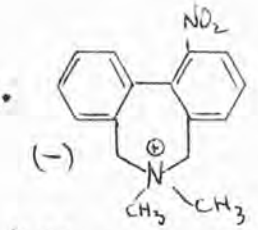
λ 5791 Å ; Zero at 177.32° .

Time mins.	Polarimetric reading	α observed	$\log_{10} \alpha$
4.00	175.05	2.280	0.3579
5.15	.085	2.235	0.3493
6.50	.110	2.210	0.3444
9.50	.170	2.150	0.3324
10.25	.190	2.130	0.3284
12.45	.250	2.070	0.3160
13.25	.270	2.050	0.3118
15.40	.310	2.010	0.3032
17.80	.360	1.960	0.2923
20.00	.390	1.930	0.2856
23.00	.445	1.875	0.2730
24.70	.490	1.830	0.2625
26.25	.520	1.800	0.2552
28.35	.565	1.755	0.2443
29.75	.580	1.740	0.2406
31.50	.615	1.705	0.2317
45.50	.860	1.460	0.1643
48.00	.940	1.380	0.1399
55.00	176.160	1.160	0.0645
60.25	.230	1.090	0.0374
64.25	.280	1.040	0.0170
69.75	.355	0.965	-0.0155
74.25	.400	0.920	-0.0362
76.00	.420	0.900	-0.0458
78.75	.450	0.870	-0.0605
86.50	.520	0.800	-0.0969
129.50	.840	0.480	-0.3188
250.00	177.210	0.110	-0.9586
∞		0	

k = 1.227 x 10^{-2} min.$^{-1}$ = 2.045 x 10^{-4} sec.$^{-1}$; $t_{\frac{1}{2}}$ = 54.3 minutes

Extrapolated initial $[\alpha]_{5791}$ -263° ;.

Table XV. (Graph IXc).

Racemisation of  picrate in acetone.

l = 2 ; c = 0.4050 g./100 c.c. of solvent ; t = 26.12° ;

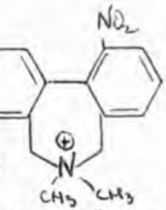
λ 5791 Å ; Zero at 180.09°.

Time mins.	Polarimetric reading	α observed	$\log_{10} \alpha$
2.25	178.340	-1.750	0.2430
3.00	.370	1.720	0.2355
3.50	.390	1.700	0.2305
4.00	.405	1.685	0.2240
4.50	.460	1.630	0.2122
5.00	.495	1.595	0.2028
5.50	.520	1.570	0.1959
6.50	.550	1.540	0.1875
7.50	.605	1.485	0.1718
8.50	.665	1.425	0.1538
9.00	.670	1.420	0.1523
10.50	.730	1.360	0.1335
11.50	.785	1.305	0.1155
13.50	.860	1.230	0.0899
15.50	.945	1.145	0.0588
17.00	.980	1.110	0.0453
18.00	179.040	1.050	0.0212
19.00	.065	1.025	0.0107
20.00	.085	1.005	0.0021
23.00	.175	0.915	-0.0386
24.00	.215	0.875	-0.0578
26.00	.260	0.830	-0.0809
28.00	.320	0.770	-0.1135
29.50	.355	0.735	-0.1137
31.00	.380	0.710	-0.1487
33.00	.430	0.660	-0.1805
34.50	.460	0.630	-0.2008
37.00	.505	0.585	-0.2328
42.50	.590	0.500	-0.3010
44.50	.630	0.460	-0.3372
47.50	.675	0.415	-0.3819
50.50	.720	0.370	-0.4318
52.50	.750	0.340	-0.4685
54.50	.770	0.320	-0.4948
60.00	.820	0.270	-0.5686
62.50	.850	0.240	-0.6198
65.50	.880	0.210	-0.6778
78.00	.930	0.160	-0.7969
90.00	180.000	0.090	-1.0458
∞	180.090	0	

$k = 3.224 \times 10^{-2}\,\text{min.}^{-1}$; $t_{\frac{1}{2}}$ = 21.5 min.

$= 5.373 \times 10^{-4}\,\text{sec.}^{-1}$; initial extrapolated $[\alpha]_{5791}$ -243°

Table XVI.(Graph IX d).



Racemisation of (-) picrate in acetone.

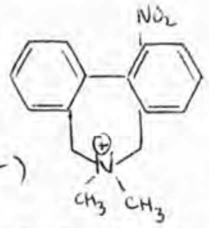
$l = 2$; $c_o = 0.3865$ g./100 c.c. of solvent ; $t = 35.76^{\circ}$;
λ 5791 Å ; Zero at 180.09°.

Time mins.	Polarimetric reading	α observed	$\text{Log}_{10}\,\alpha$
3.75	178.900	1.190	0.0756
4.00	.940	1.150	0.0607
4.40	.960	1.130	0.0531
4.65	.980	1.110	0.0453
4.90	179.05	1.040	0.0170
5.50	.060	1.030	0.0128
6.00	.145	0.945	-0.0246
6.50	.190	0.900	-0.0458
6.90	.210	0.880	-0.0555
7.25	.250	0.840	-0.0757
7.45	.265	0.825	-0.0835
7.75	.300	0.790	-0.1024
8.10	.330	0.760	-0.1192
8.40	.370	0.720	-0.1427
8.70	.420	0.670	-0.1739
9.00	.440	0.650	-0.1871
9.50	.410	0.680	-0.1675
9.75	.430	0.660	-0.1805
10.35	.470	0.620	-0.2076
10.80	.560	0.530	-0.2757
11.60	.590	0.500	-0.3010
12.50	.630	0.460	-0.3372
13.00	.670	0.420	-0.3768
13.70	.700	0.390	-0.4089
14.20	.735	0.355	-0.4498
15.50	.780	0.310	-0.5086
16.00	.800	0.290	-0.5376
16.65	.840	0.250	-0.6021
17.50	.850	0.240	-0.6198
17.90	.870	0.220	-0.6576
19.50	.900	0.190	-0.7213
21.50	.920	0.170	-0.7695
22.50	.950	0.140	-0.8539
23.70	.970	0.120	-0.9208
25.25	.990	0.100	-1.0000
∞	180.090	0	

$k = 11.810 \times 10^{-2}\,\text{min.}^{-1} = 1.968 \times 10^{-3}\,\text{sec.}^{-1}$ $t_{\frac{1}{2}} = 5.86$ minutes ;

Extrapolated initial $[\alpha]_{5791}$ -255° .

Table XVII. (Graph IX e).

Racemisation of (-) 

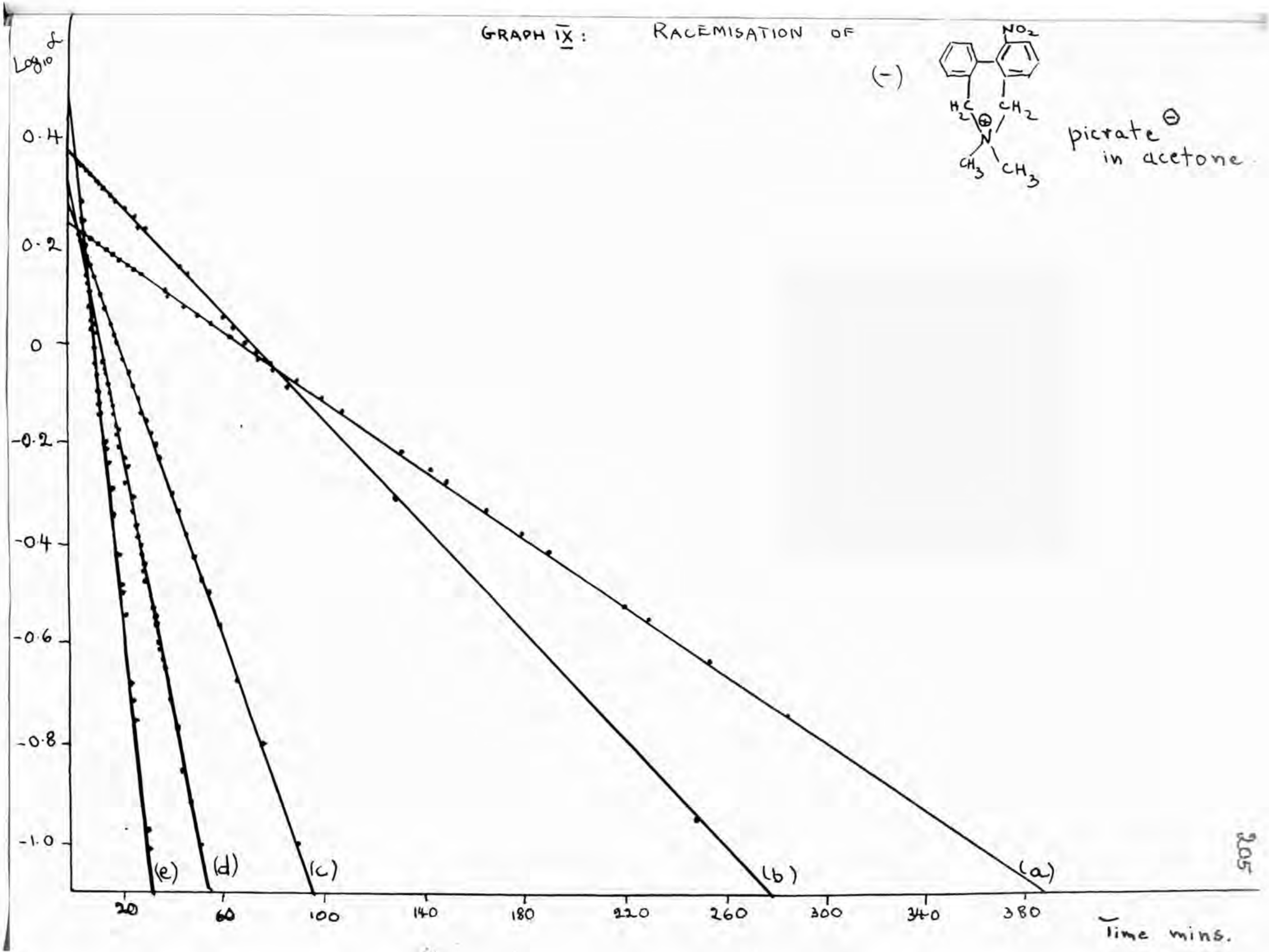
picrate in acetone.

1 = 2 ; c = 0.5190 g./100 c.c. of solvent ; t = 41.19° ;
λ 5791 Å ; Zero at 180.09 .

Time mins.	Polarimetric reading	α observed	$\log_{10} \alpha$
2.45	178.150	1.940	0.2878
3.15	.340	1.750	0.2430
3.65	.545	1.545	0.1889
3.90	.615	1.475	0.1688
4.45	.795	1.295	0.1123
5.00	.945	1.145	0.0588
5.25	179.000	1.090	0.0374
5.65	.125	0.975	-0.0110
5.95	.175	.915	-0.0386
6.25	.210	.880	-0.0555
6.55	.290	.800	-0.0969
7.25	.350	.740	-0.1308
7.50	.380	.710	-0.1487
8.20	.480	.610	-0.2147
8.60	.515	.575	-0.2403
8.90	.570	.520	-0.2840
9.40	.640	.450	-0.3468
10.40	.720	.370	-0.4318
10.80	.770	.320	-0.4949
11.00	.775	.315	-0.5017
11.45	.800	.290	-0.5376
12.25	.885	.205	-0.6883
12.75	.895	.195	-0.7100
13.25	179.915	.175	-0.7570
15.65	.985	.105	-0.9788
15.85	180.010	.080	-1.0970
∞	180.090	0	

$k = 21.931 \times 10^{-2}\ \text{min.}^{-1}$; $t_{\frac{1}{2}} = 3.2$ minutes ;
$= 3.655 \times 10^{-3}\ \text{sec.}^{-1}$

initial extrapolated $[\alpha]_{5791}$ -341° .



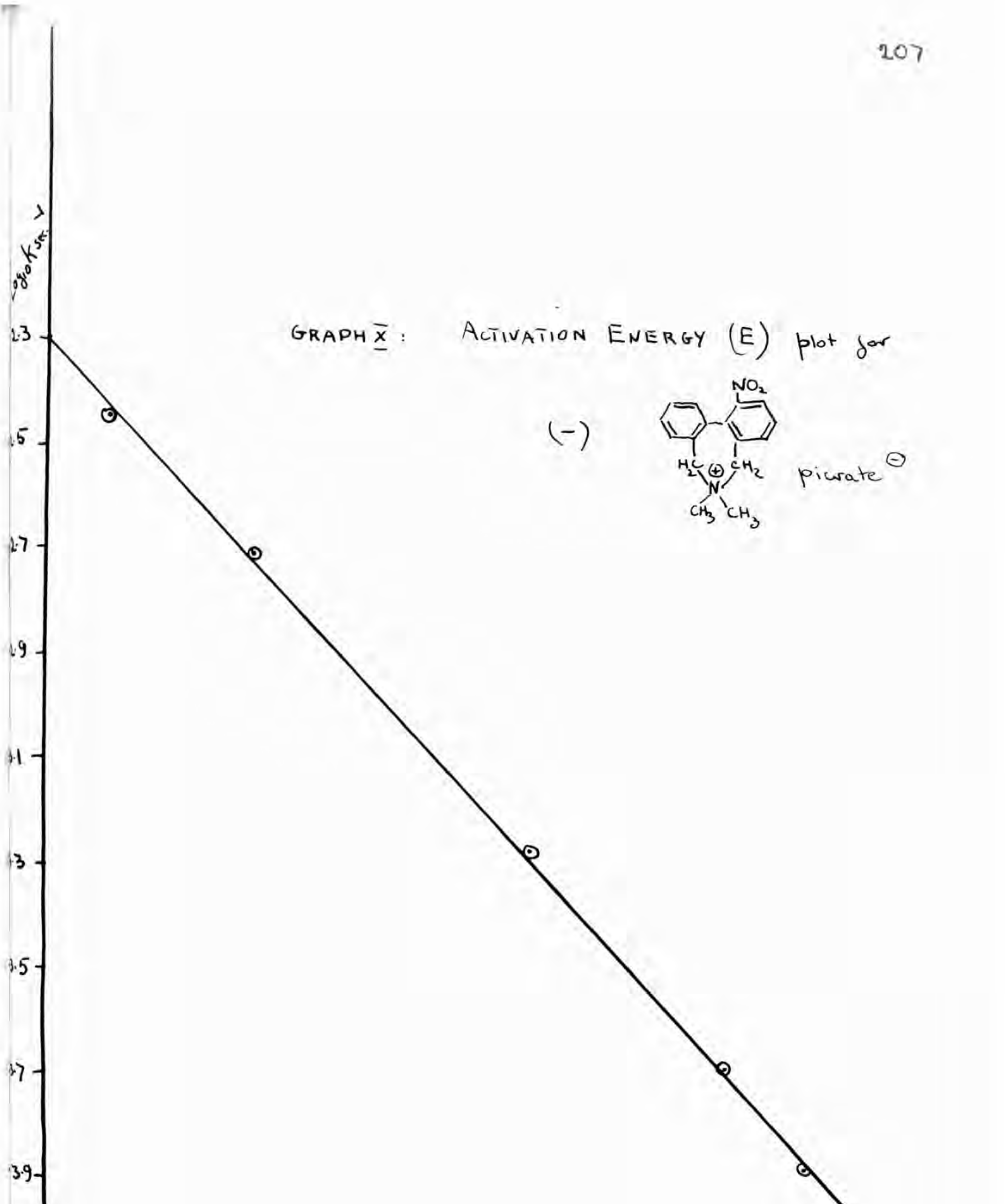
GRAPH IX: RACEMISATION OF (−) picrate$^{\ominus}$ in acetone

Table XVIII, (Graph X).

$\log_{10} k / \frac{10^3}{T}$

	T(A°)	$\frac{10^3}{T}$	k sec.$^{-1}$	$\log_{10}$ k	$\log_{10}$A(sec.$^{-1}$)	$\Delta S^{\ddagger}$ e.u.
1.	290.35	3.444	1.312×10^{-4}	-3.8821	15.12	+ 8.6
2.	292.85	3.415	2.045×10^{-4}	-3.6893	15.15	+ 8.7
3.	299.32	3.341	5.373×10^{-4}	-3.2698	15.09	+ 8.7
4.	308.96	3.237	1.968×10^{-3}	-2.7060	15.15	+ 8.6
5.	314.39	3.181	3.655×10^{-3}	-2.4371	15.11	+ 8.4
				Mean value	15.1	+ 8.6

The straight line plot of $\log_{10}k$ against $10^3/T$ is given in graph (X). The value of E comes to 25.2 kcal.mole^{-1}, that of A to $10^{15.1}$sec.$^{-1}$ and that of $\Delta S^{\ddagger}$ to + 8.6 e.u. Values of A were computed by using the Arrhenius equation in the form : $\log_{10}A = \log_{10}k + \frac{E}{4.576} \; \frac{1}{T}$ and values of $\Delta S^{\ddagger}$ by using the Glasstone, Leidler and Eyring absolute reaction rate equation in the form : $\Delta S^{\ddagger} = 4.576 \; \log_{10} \text{krac.}/T + E/T - 49.20$.



GRAPH X̲ : ACTIVATION ENERGY (E) plot for (−) picrate$^{\ominus}$

2-Bromomethyl-2'-trimethylammoniomethyl-6-nitrobiphenyl Bromide (51 ; X = Br)

The 2,2'-bisbromomethyl-6-nitrobiphenyl (3.85 g.,1 mol.) was dissolved in 10 c.c of dry acetone and cooled in an ice-salt mixture. Trimethylamine (5 c.c., 3.36 g., 5.6 mols.), also cooled to ca. -10°, was added and the mixture was allowed to warm to room temperature (calcium chloride tube). After ca. 15 minutes a very slight cloudiness appeared and after 48 hours there was quite a lot of solid. The mixture was left at room temperature for a week to complete the reaction, the solid was filtered off, washed with dry acetone and dried in a vacuum desiccator (3.5 g.), m.p. 225-226°(decomp.) The crude solid was recrystallised from methanol (2.7 g., 61%) and had m.p. 243° (decomp.) (Found: C, 46.1 ; H, 4.5; N, 6.1 ; O, 7.0 ; Br, 36.2 ; $C_{17}H_{20}N_2O_2Br_2$ requires C, 46.0 ; H, 4.5 ; N, 6.3 ; O, 7.2 ; Br, 36.0%).

2-Bromomethyl-2'-trimethylammoniomethyl-6-nitrobiphenyl Iodide (51 ; X = I)

The above bromide (1.1 g.) was dissolved in water and treated with saturated potassium iodide solution in water. The precipitated iodide (1.1 g., 91%) was recrystallised from methanol and had m.p. 231-232° (decomp.) (Found: I, 41.8 ; $C_{17}H_{20}N_2O_2BrI$ requires I, 42.1%).

2,2'-Bis(trimethylammoniomethyl)-6-nitrobiphenyl Dibromide (53 ; X = Br)

a) The corresponding bromide (45) (3.85 g., 1 mol.) was dissolved in dry nitrobenzene (10 c.c.) and cooled in ice. Trimethylamine (5 c.c., 5.6 mol.) at *ca.* -10° was added and the mixture was allowed to warm slowly to room temperature. A solid started to form after 1 hour and after 3 hours the reaction seemed complete. The mixture was left for another 24 hr., the solid was filtered off and washed well acetone. It was dried in air and had m.p. 230° (decomp.) (crude yield 4.0 g.). Recrystallisation from methanol gave 2.0 g.,m.p.243° (decomp.) as first crop, 0.7 g., m.p. 243° (decomp.) as second crop and on evaporation of the mother liquor a residue (1.3 g.) m.p. 170° (decomp.) with shrinking at 145-150° was obtained. This, unlike the solid m.p. 243°, was entirely insoluble in nitrobenzene. The solid m.p. 243° proved to be the mono-quaternary salt (51). The residue (1.3 g.) obtained by evaporation of the mother liquor was recrystallised from methanol-ethyl acetate and gave 0.8 g., m.p. 170° (decomp.) with shrinking at 150-155° (53). Evaporation of the mother liquor from this crystallisation gave a solid m.p. 215-220°(decomp.) which was a mixture of the mono-(51) and di-(53) quaternary salts.

The infrared spectra of (51) and (53) were examined. A band at 615.4 cm.$^{-1}$ present in (51) in the C-Br absorption region was absent in the spectrum of (53). The latter contained also two additional bands : a strong hydroxyl band at 3371.5 cm.$^{-1}$ and a broad band with maxima at 1667 cm.$^{-1}$ and 1605 cm.$^{-1}$, both probably due to solvate molecules. Both peaks were hardly reduced in intensity after drying the compound for 14 hr. at 100-120°/9 cm. and were still present especially the 3371.5 cm.$^{-1}$ band after drying at 155-160° in a vacuum oven. Owing to the tenacity with which the solvent molecules are held there was difficulty in obtaining a satisfactory repeatable analysis for the di-quaternary salt and therefore in deciding whether it was pure. The identity of (53) was however finally established by obtaining a satisfactory analysis for it after prolonged drying in vacuum : (Found: C, 47.05 ; H, 6.0 ; Br, 31.0 ; $C_{20}H_{29}N_3O_2Br_2\frac{1}{2}H_2O$ requires C, 46.9 ; H, 5.9 ; Br, 31.2%) and for the di-picrate obtained from it.

b) The mono-quaternary salt (51 ; X = Br) (1.8 g., 1 mol.) was dissolved in 15 c.c. dry nitrobenzene and cooled to *ca.* -10°. Trimethylamine (1.5 c.c., 4.0 mol.) cooled to -10° was added and the mixture was sealed in a hard glass tube. It was heated to 100° for 14 hr. and then kept for 4 days at room temperature. The product was filtered, washed well with dry nitrobenzene and dry acetone and dried in a vacuum desiccator (1.75 g.). After recrystallisation from methanol-ethyl acetate, 0.75 g., m.p. 170° (decomp.) with shrinking at 155-160°, was obtained. The rest would not recrystallise so the solvent was evaporated and the solid recrystallised from methanol alone, when 0.1 g.,m.p.240-241° (decomp.) of the mono-quaternary salt (51) was obtained.

c) 2,2'-Bisbromomethyl-6-nitrobiphenyl (4 g., 1 mol.) was dissolved in 20 c.c. dry nitrobenzene and cooled to -10°. Trimethylamine (6 c.c., 6.4 mol.) cooled to -10°, was added and the mixture was sealed in a hard glass tube. It was heated in boiling chlorobenzene (138°) for 17 hr. and then kept at room temperature for 3 days, the tube being shaken from time to time. The solid was filtered off, washed with dry acetone and dried in a vacuum desiccator (4.4 g.). It had m.p. 251° (decomp.), mixed m.p. with solid (51) m.p. 243° (decomp.) depressed to 231-233° (decomp.). On exposure to air or on crystallisation from methanol-ethyl acetate the unhydrous impure solid m.p. 251° solvated and its m.p. changed to 175° (decomp.) with shrinking at *ca.* 155°. Yield 3.55 g.(68%).

d) The quaternary dibromide was purified by converting it into the dipicrate and decomposing the latter. In a typical experiment the dipicrate (1 g.) was covered with 10 c.c. water and 2 c.c. of 48-50% hydrobromic acid were added. The mixture was stirred vigorously and the bright yellow picrate disappeared and was replaced by a faintly yellow solid. The solid picric acid (m.p. 120°) was filtered off and the mother liquor was evaporated on the water bath. The residue was washed well with ethyl acetate in which both the picric acid and the picrate are soluble. Recrystallisation from methanol -ethyl acetate mixture gave 0.4 g.(64.5%) m.p. 175° (decomp.) with shrinking at 155-157°.

2,2'-Bis(trimethylammoniomethyl)-6-nitrobiphenyl Dipicrate (53 ; $X = C_6H_2N_3O_7$).

The dibromide (43 ; X = Br) (4 g.) was dissolved in 30 c.c. aqueous methanol and 4 g. of sodium picrate dissolved in *ca.* 100 c.c. water were added to it with stirring. A gum started to separate which solidified on standing in ice. The filtered solid (6.3 g., 100%) was recrystallised from acetone-ethanol mixture and gave 5.6 g. (89%) m.p. 205.5 - 207.5°. (Found : C, 47.9 ; H, 4.3 ; N, 15.8 ; O, 31.9 ; $C_{32}H_{33}N_9O_{16}$ requires C, 48.1 ; H, 4.2 ; N, 15.8 ; O, 32%).

2,2'-Bis(trimethylammoniomethyl)-6-nitrobiphenyl (+)-Dicamphorsulphonate (53 ; X = $C_{10}H_{15}SO_4$).

The corresponding quaternary dibromide (0.5 g., 1 mol.) and (+) silver camphorsulphonate (0.66 g., 2 mol.) were dissolved separately in hot water and the hot solutions were mixed with stirring. The precipitated silver bromide was filtered off and the filtrate was evaporated on a water bath. The crude salt (0.65 g.) was recrystallised from acetone and 0.3 g. m.p. 183-185° (decomp.) with softening at 174-176° were obtained as first crop, and 0.15 g., m.p. as above, as second crop. (Yield 56%) (Found : C, 57.4 ; H, 7.7 ; N, 4.9 ; S, 7.7 ; $C_{40}H_{59}N_3O_{10}S_2.2H_2O$ requires C, 57.05 ; H, 7.5 ; N, 5.0 ; S, 7.6%).

HOFMANN DEGRADATION OF SOME QUATERNARY EPHEDRINIUM COMPOUNDS

BY
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AND
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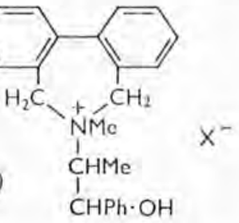
Preprinted from the
Journal of the Chemical Society, January 1963, pages 268—280.

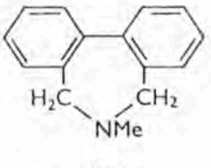
44. *Hofmann Degradation of Some Quaternary Ephedrinium Compounds.*

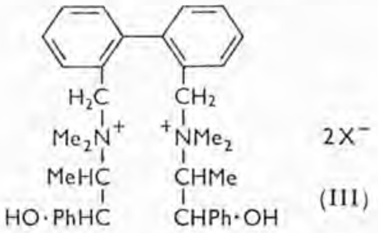
By D. MURIEL HALL and TERESA M. POOLE.

Hofmann degradation proceeds normally with the (+)-dibenzazepinium hydroxide (I; X = OH), to give the dibenzazepine (II) and (+)-*trans*-1-methyl-2-phenyloxiran. However, the analogous biphenyl bisquaternary dihydroxide (III; X = OH) gives an appreciable yield of the ditertiary base (IV) only if carbon dioxide is excluded; the diamine is accompanied by (−)-*N*-methylephedrine, 9-dimethylamino-9,10-dihydrophenanthrene, and the 2,7-dihydro-1,1-dimethyl-3,4:5,6-dibenzazepinium cation. Possible reaction paths are discussed.

HOFMANN degradation of (+)-2,7-dihydro-1-(β-hydroxy-α-methylphenethyl)-1-methyl-3,4:5,6-dibenzazepinium hydroxide[1] (I; X = OH), without special precautions to exclude carbon dioxide, proceeded normally to give 2,7-dihydro-1-methyl-3,4:5,6-dibenzazepine (II), identified as its methiodide,[2] and (+)-*trans*-1-methyl-2-phenyloxiran, the normal non-basic product from such reactions with ephedrinium compounds.[3] Similar reactions of the cyclic ephedrinium compounds containing *o*-nitro- or *o*-fluoro-groups had also given the corresponding *N*-methylazepines.[4]

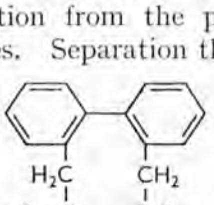

(I)

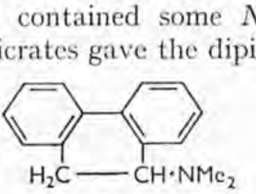

(II)


(III)

However, when the unbridged compound (III; X = OH), prepared from 2,2′-bis-bromomethylbiphenyl and (−)-*N*-methylephedrine in nitrobenzene at 130°, was subjected to Hofmann degradation under similar conditions (Experiment 1), *N*-methylephedrine was isolated from the basic products, suggesting that the quaternary cation was undergoing attack at the (benzyl) α-carbon atom as well as at the hydrogen of the β-hydroxyl group. A bimolecular displacement[5,6] at the α-carbon atom is the process most commonly competing with bimolecular Hofmann elimination,[7] and it has been shown[5] that the use of anions less basic than hydroxyl favours the displacement at the expense of the elimination. Thus exclusion of carbon dioxide (and hence of CO_3^{2-}) is likely to reduce the amount of the displacement by-product.[5,8]

The degradation of the bisquaternary dihydroxide (III; X = OH) was therefore repeated (Experiment 2) in an atmosphere of nitrogen (with exclusion of carbon dioxide); water was used instead of aqueous ethanol to avoid attack by alkoxide ions. The basic fraction from the products still contained some *N*-methylephedrine, but also other bases. Separation through the picrates gave the dipicrate of the expected amine (IV) as the main product, accompanied by smaller quantities of the picrate of 9-dimethylamino-9,10-dihydrophenanthrene (V).[9] Relevant ultraviolet absorption spectra are given in Table 1.


(IV)


(V)

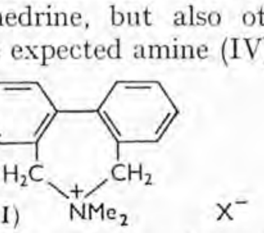

(VI)

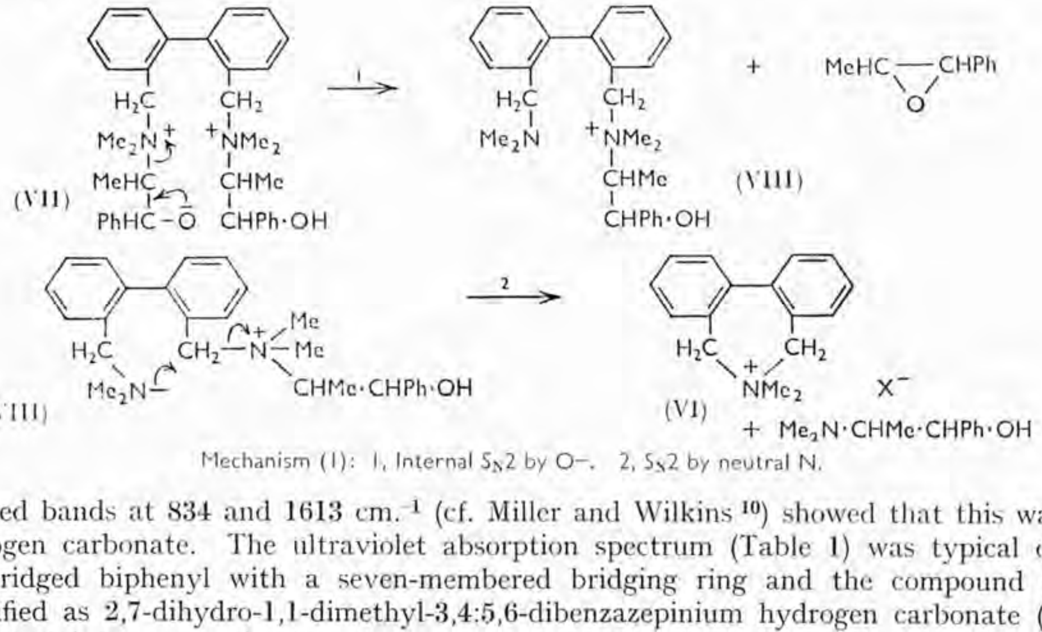
TABLE 1.

Ultraviolet absorption spectra (λ in mμ) of solutions in 96% EtOH (values in parentheses are inflections).

Compound	Short-wave band λ		Conjugation band		Long-wave features			
	$\lambda_{max.}$	ε	$\lambda_{max.}$	ε	$\lambda_{max.}$	ε	$\lambda_{max.}$	ε
V)	211	39,900	252	15,700	(274)	14,500		
			260	16,000	(282)	9720		
			265·5	15,900	(292)	4180		
Picrate of (V)	208	54,400	260	20,900	(270)	18,800	357·5	16,200
	212	53,500	261·5	20,800	(280)	11,800		
(II)	206	41,600	241	12,800	(281)	3030		
(VI; X = HCO_3)			248	14,000	(271)	4430		
					(281)	2380		
(VI; X = Br)			249	14,200	(275)	4270		
					(280)	3050		
(VI; X = $C_6H_2N_3O_7$)	206	51,500	245	22,700	(274)	5850	357	14,750
	212	52,900			(281)	4140	360	14,650
(XVII; X = Br),H_2O *			(233)	8980	268·5	2080		
Picric acid †			[245	10,000] ‡			360	16,600
Na picrate §							358	14,100

* In MeOH. † Friedel and Orchin, "Ultraviolet Spectra of Aromatic Compounds," Wiley, New York, 1951, No. 93. ‡ Not a maximum or point of inflection. § The acid in ethanol containing aqueous sodium hydroxide; Schroeder, Wilcox, Trueblood, and Dekker, *Analyt. Chem.*, 1951, **23**, 1740.

The residue from this decomposition (Experiment 2) was treated with ether and water. Evaporation of the aqueous solution, after thorough washing with ether, gave a small residue, part of which was a white solid, insoluble in chloroform. Qualitative tests and infrared bands at 834 and 1613 cm.$^{-1}$ (cf. Miller and Wilkins [10]) showed that this was a hydrogen carbonate. The ultraviolet absorption spectrum (Table 1) was typical of a 2,2′-bridged biphenyl with a seven-membered bridging ring and the compound was identified as 2,7-dihydro-1,1-dimethyl-3,4:5,6-dibenzazepinium hydrogen carbonate (VI; X = HCO_3) by conversion into the picrate, identical with that made from the corresponding bromide. (The high intensity and slight displacement of the conjugation band in the ultraviolet absorption spectrum of the picrate are due to superimposition of picrate absorption on that of the biphenyl system. Picric acid has ε 10,000 at 245 mμ in 95% ethanol [11] and the ion is probably rather similar.) The chloroform-soluble part of the residue also contained the 2,7-dihydro-1,1-dimethyl-3,4:5,6-dibenzazepinium cation and appeared (from the infrared spectrum and qualitative tests) to contain the quaternary hydroxide (VI; X = OH), which had failed to absorb dioxide during the working up.



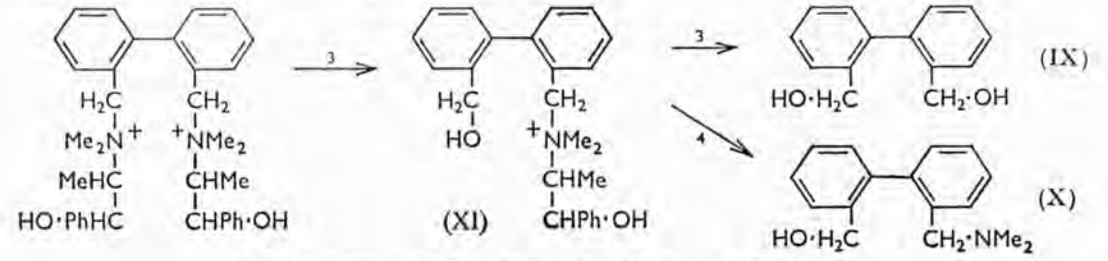
Mechanism (I): 1, Internal S_N2 by O−. 2, S_N2 by neutral N.

The Hofmann degradation of compound (III; X = OH) was carried out for a third time (Experiment 3). Owing to bumping in the early stages, a little carbon dioxide was allowed to enter and a more dilute solution was used; otherwise, conditions were as in

Experiment 2. The main picrate this time was that of the aminodihydrophenanthrene (V), accompanied by very small amounts of the dipicrate of base (IV). The ethereal extract of the reaction products remaining in the flask yielded phenanthrene.

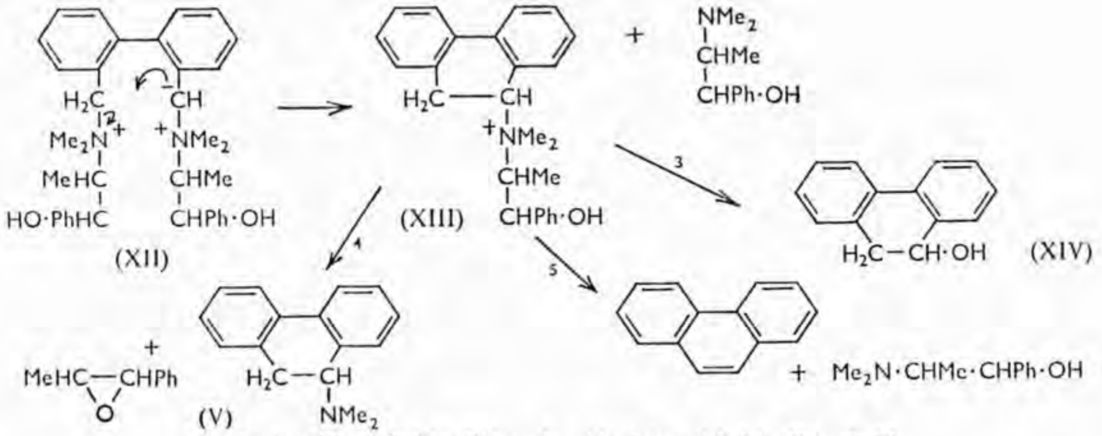
Three modes of reaction * of the cation (III) with hydroxyl ions can be envisaged. (1) Proton loss at the β-hydroxyl group will give an alkoxide ion (VII), which can form the oxiran (ethylene oxide) and the ion (VIII) by an internal nucleophilic substitution. This process can occur in both side chains, in which case 2,2′-bisdimethylaminomethylbiphenyl (IV) will be formed. On the other hand, nucleophilic replacement (at the benzyl α-carbon atom) of positive (quaternary) nitrogen by neutral (tertiary) nitrogen in the ion (VIII) is the most likely route to the azepinium hydrogen carbonate (VI; $X = HCO_3$).

(2) Nucleophilic displacement at benzyl α-carbon atoms by hydroxyl ions (or by carbonate ions in experiments where carbon dioxide is not excluded) would lead to the diol (IX) or the hydroxy-amine (X). Cyclisation of the hydroxy-amine (X) or of the intermediate ion (XI), with loss of water, is a possible but rather unlikely route to 9-dimethylamino-9,10-dihydrophenanthrene (V).



Mechanism (2): 3, S_N2 by OH^-. 4, $-H^+$, internal S_N2 by O^-.

(3) Attack by hydroxyl ions at a benzyl methylene group may lead to proton loss rather than to substitution. This would give an ylide intermediate (XII) of a type which plays an essential part in the Stevens rearrangement. In view of the frequently observed[12] ease of 6- and 7-membered ring formation among 2,2′-substituted biphenyls it seems possible that, once formed, such an ion might preferentially attack the benzyl carbon atom attached to the other positive nitrogen, thus forming a six-membered ring, rather than a methyl or isopropyl carbon atom attached to its own nitrogen. The ion (XIII) so formed could undergo proton loss either at the β-hydroxyl group, leading to 9-dimethylamino-9,10-dihydrophenanthrene (V), or at the β-carbon atom in the saturated ring, leading to phenanthrene; nucleophilic displacement by hydroxyl at the α-carbon atom would give 9,10-dihydro-9-hydroxyphenanthrene (XIV), which was not detected. If formed, therefore, it must have undergone ready dehydration to phenanthrene.



Mechanism (3): 3, S_N2 by OH^-. 4, $-H^+$, internal S_N2 by O^-. 5, E2.

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* Probable mechanisms are indicated in the reaction schemes, but in no case has a bimolecular mechanism been unequivocally proved for these particular compounds.

The relative importance of the three modes of attack on the cation (III), and whether (2) followed by cyclisation or (3) is a source of (V), can be found by studying the effect of changes in hydroxyl-ion concentration and of added carbon dioxide on the reaction products. Change in hydroxyl-ion concentration should have little effect on process (1), since proton loss at the hydroxyl group cannot be rate-determining, but reduction in hydroxyl-ion concentration (by heating the solution under reflux instead of distilling it) might be expected to decrease processes (2) and (3), whereas added hydroxyl ions should promote them. Carbon dioxide might be expected to promote (2) at the expense of (1) and (3), since carbonate ions are nucleophilic but only weakly basic.

Accordingly, the decomposition of the quaternary hydroxide (III; X = OH) was carried out (*a*) under nitrogen, in conditions as before, (*b*) under nitrogen, but with heating under reflux without distillation, (*c*) under nitrogen with added potassium hydroxide, and (*d*) under carbon dioxide. The results are detailed in Tables 2 and 3.

TABLE 2.

Products of Hofmann degradation of the dihydroxide (III; X = OH).
[Citations in parentheses are m. p.s. Others are yields in g.].

			Distillate		Residue		Bases present				
Expt.	Iodide (g.)	Condns.	Bases	Picrates	Bases	Picrates	(IV)	(V)	ME [1]	Neutral Et_2O-sol. residue	H_2O-sol. residue (g.) (picrate,[2] m. p.)
2	7·9	N_2, CO_2-free air	0·43 (solid)	0·14 (195—205°)	2·37	0·1 (170—205°) 2·17 [3] (190—208°) ~0·1 (170—176°)	+	+ (less)	+	— [4]	0·4 (278—281°)
3	7·9	N_2	1·36 (liquid)	0·32 (~206°) 0·04 (168—174°)	1·60	2·31 [5] (165—178°)	+	+ (more)	+	0·10 [6] (60—85°)	0·38
(*a*)	3·95	N_2	0·698 (solid)	<0·01 (213°)	1·14 (solid)	1·44 [7] (187—190°)	+	+	+	0·06 (71—80°)	0·60 (279—282°)
(*b*)	,,	N_2, ≯100° dil. soln.	—	—	0·759 (solid)	<0·01 (174—176°)	—	Trace	+	0·015	1·60 [8] (285°)
(*c*)	,,	N_2, +KOH	0·353 (solid)	0·038 (206°)	0·999 (liquid)	1·67 [9] (155—166°)	Trace	+	+	0·1705 (97—98°)	4·02 [10] (200—320° [11])
(*d*)	,,	CO_2	0·110	—	0·664 (solid)	0·05 (212—214°) 0·84 (140—142°) [12]	Trace	—	+	0·131 [13] (partly liquid)	1·215 (285°)

[1] *N*-Methylephedrine. [2] In all cases a single crystallisation raised the m. p. to 285—286°. [3] The base was distilled and only part made into the picrate. Crystallisation of this crop gave 0·90 g. of m. p. >200° and 0·37 g. of m. p. 170—174°. [4] Not isolated separately. [5] Crystallisation gave 1·64 g. of m. p. 173—176°, 0·17 g. of m. p. 169—174°, and 0·03 g. of m. p. 206°. [6] M. p. 98—100° after crystallisation. [7] Crystallisation gave 0·326 g. of m. p. 205—207°, 0·226 g. of m. p. 173—174°, 0·186 g. of m. p. 146—154°, and 0·088 g. of m. p. 143—144°. [8] Incompletely decomposed. On re-treatment with fresh Ag_2O under the conditions of (*a*) it gave 0·181 g. of bases, yielding 0·285 g. of picrate, m. p. 165—170°, and 0·90 g. of water-soluble residue. [9] Crystallisation gave 0·610 g. of m. p. 174—176°, 0·493 g. of m. p. 158—174°, and 0·206 g. of m. p. 137—142°. [10] Includes the added potassium hydroxide and its carbonate. [11] Mainly potassium picrate, melting explosively at 334° after crystallisation. [12] *N*-Methylephedrine picrate, obtained from highly concentrated mother-liquor. [13] Probably mainly 1-phenylpropan-1,2-diol (see Experimental).

The decomposition (*b*), carried out in dilute solution at 100°, gave *N*-methylephedrine, none of the base (IV) and only a trace of the aminophenanthrene (V); it was incomplete and the large residue was mainly the azepinium hydrogen carbonate (formed from the hydroxide during the subsequent working-up and evaporation). Thus, here, reaction (1) must be occurring in one side-chain, followed by nucleophilic replacement by neutral nitrogen in the other, leading to the cation of compound (VI). The weights obtained correspond to an 84% yield of *N*-methylephedrine and 113% of azepinium hydrogen

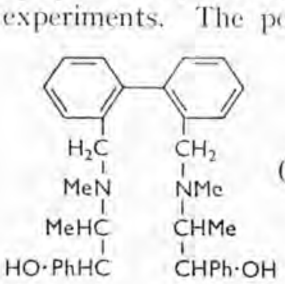
TABLE 3.

Melting points of picrates used for identifications.

Tertiary amine	Picrate	Quaternary cation	Picrate
(II)	162°	(VI)	285—286°
(IV)	207—208	(XVII)	245
(V)	175—176		
N-Methylephedrine	143·5—144		
Trimethylamine	224		

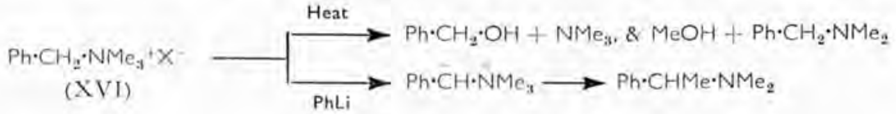
carbonate, the discrepancies being partly accounted for by the presence of a little (optically active) undecomposed starting material. The residue was treated with fresh silver oxide and re-treated under conditions (*a*). Some of the amine (V) was obtained.

The presence of carbon dioxide (*d*) reduced the yields of both amines (IV) and (V) to negligible proportions. Bimolecular displacement at the benzyl α-carbon atom, followed by cyclisation, cannot, therefore, by the source of the aminophenanthrene (V) in the normal experiments. The possibility of similar reaction at one of the other α-carbon atoms (methyl or isopropyl) in *both* side chains is also eliminated, since this would give either a new tertiary amine (XV) (not observed) or (IV) (of which only a trace was obtained). However, such reaction at the isopropyl carbon atom in *one* side chain would give the ion (VIII), which could then give the azepinium ion (VI) by a replacement reaction. It is possible that this is indeed the route to (VI) under these conditions, where the basicity of the solution is so much reduced. Alternatively, there may be sufficient hydroxyl ions present to produce (VIII) by proton loss from the β-hydroxyl group, as in (*b*).


(XV)

Added potassium hydroxide (*c*) has greatly increased the yield of 9-dimethylamino-9,10-dihydrophenanthrene (V), thus providing strong support for process (3), the route involving a type of Stevens rearrangement. This rearrangement, originally[13] carried out with hydroxide or alkoxide ions on phenacylamines and later with phenyl-lithium[14,15] on compounds containing less readily ionised hydrogen, can occur during the decomposition of quaternary ammonium hydroxides of suitable structure and has been observed[6b] in, for example, the decomposition of diphenylmethyltrimethylammonium hydroxide in the presence of a high concentration of potassium hydroxide.

However, benzyltrimethylammonium hydroxide (XVI; X = OH) is decomposed when heated in aqueous solution[6b] into benzyl alcohol and trimethylamine (65% of the reaction) and methyl alcohol and benzyldimethylamine (35% of the reaction), whereas treatment of the quaternary bromide (XVI; X = Br) with phenyl-lithium in ether[14] gives the rearrangement product, *NN*-dimethyl-α-methylbenzylamine.



$$\underset{\text{(XVI)}}{\mathrm{Ph{\cdot}CH_2{\cdot}NMe_3{}^+X^-}} \begin{cases} \xrightarrow{\text{Heat}} \mathrm{Ph{\cdot}CH_2{\cdot}OH + NMe_3,\ \&\ MeOH + Ph{\cdot}CH_2{\cdot}NMe_2} \\ \xrightarrow[\text{PhLi}]{} \mathrm{Ph{\cdot}\bar{C}H{\cdot}NMe_3} \longrightarrow \mathrm{Ph{\cdot}CHMe{\cdot}NMe_2} \end{cases}$$

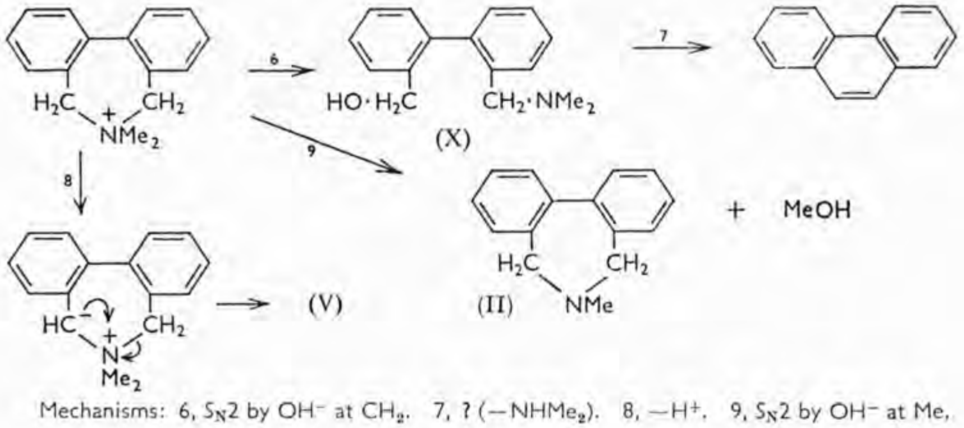
The situation of (benzyl) α-hydrogen atoms in (III) is formally rather similar to that of (benzyl) α-hydrogen atoms in (XVI), but the benzyl α-carbon atoms in the cation of (III), unlike those in (XVI), are subject to considerable steric hindrance to S_N2 reactions, since both the other part of the biphenyl system and the bulky ephedrine side-chain interfere with the formation of the transition state. If steric factors hinder nucleophilic displacements in (III), the way is open for reaction dependent upon ylide formation, even without use of a stronger base than hydroxyl ions. [Indeed the necessity to use phenyl-lithium to form an ylide from (XVI) may be only partly due to the greater basic strength of the reagent and partly due to its weak nucleophilic power.]

The diol (IX) has not been detected among the degradation products. It is stable to hot potassium hydroxide, so cannot have been formed and then destroyed. All neutral ether-soluble residues (always very small) were examined by infrared spectroscopy and in some cases phenanthrene was isolated from them. The diol was easily detectable spectroscopically in a 1 : 1 mixture with phenanthrene so that, if any was formed, it was only in very minor amount.

Thus all the evidence points to the Stevens rearrangement as the source of the aminophenanthrene (V), and to the unimportance of bimolecular displacements by hydroxyl ions at the benzyl α-carbon atoms in (III).

However, during the investigation of the quaternary hydrogen carbonate, another possible source of the 9-dimethylamino-9,10-dihydrophenanthrene (V) was revealed. The hydrogen carbonate melted with vigorous decomposition at 206°; a sample kept at 210° for 40 minutes gave 9-dimethylamino-9,10-dihydrophenanthrene. It thus appeared that at 210° the hydroxyl ion (from the decomposing hydrogen carbonate) was a sufficiently strong base to bring about a Stevens rearrangement of the cation (VI). In order to test the effectiveness of the hydroxyl ion under the conditions of the reactions described above, Hofmann degradation was carried out on 2,7-dihydro-1,1-dimethyl-3,4:5,6-dibenzazepinium hydroxide (VI; X = OH) under the conditions of experiment (*a*), the temperature not being allowed to rise above 135°. As expected, the aminophenanthrene (V) was obtained but it was accompanied by 2,7-dihydro-1-methyl-3,4:5,6-dibenzazepine (II) (the result of hydroxyl attack at the methyl α-carbon atoms) and by phenanthrene, isolated in 32—40% yield. A similar decomposition in the presence of potassium hydroxide gave a similar yield of phenanthrene (33%), and the amine (V), but none of the azepine (II). Neither the azepine nor the phenanthrene had been detected when the hydrogen carbonate was decomposed alone at 210°.

Thus the Stevens rearrangement of the azepinium ion is favoured by a high concentration of hydroxyl ions and a high temperature. Under somewhat less favourable conditions ($\ngtr$135° and no added potassium hydroxide) some substitution to give azepine occurs as well. At lower temperatures and with low concentrations of hydroxyl ions no rearrangement occurs, as shown by the products of decompositions (*b*) and (*d*) (see Table 2); in (*b*) the temperature was $\ngtr$100° and the hydroxyl-ion concentration was not increased by distillation of the water; in (*d*) the temperature was higher but the hydroxyl-ion concentration was very greatly reduced by the presence of carbon dioxide.



Mechanisms: 6, S_N2 by OH^- at CH_2. 7, ? (—$NHMe_2$). 8, —H^+. 9, S_N2 by OH^- at Me.

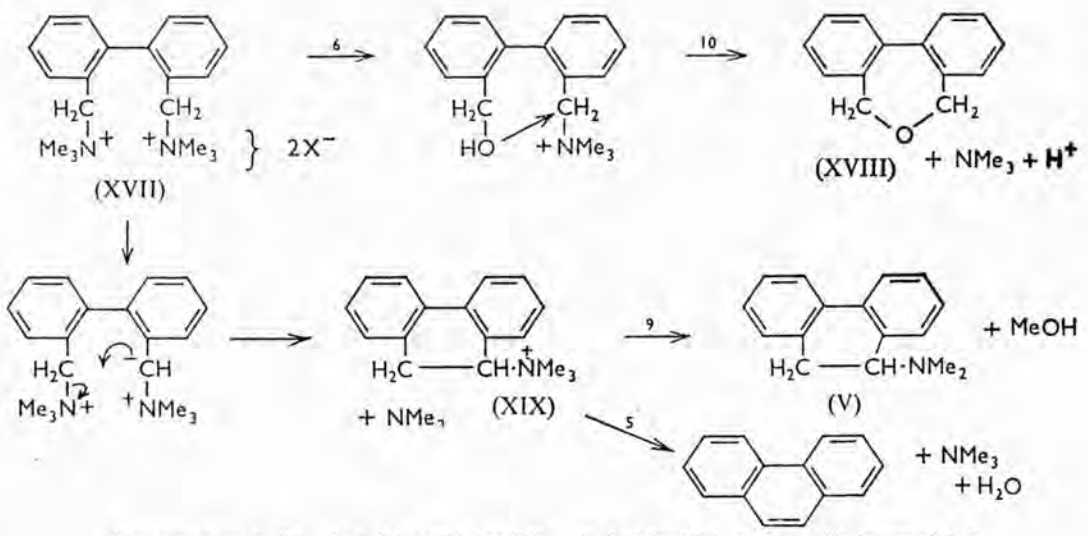
Some of the 9-dimethylamino-9,10-dihydrophenanthrene (V) produced in the other decompositions of the bisephedrinium compound (III; X = OH) may have come from the azepinium ion. However, it is considered that most of it is formed by the Stevens rearrangement on the original ion (III ⟶ XII ⟶ XIII ⟶ V), for the following reason. Any amine (V) produced *via* the azepinium ion will be accompanied by appreciable amounts of phenanthrene (and some azepine). Phenanthrene was detected among the decomposition products only in reactions where a good yield of the amine (V) was obtained but, in the most favourable case (reaction *c*; added alkali) only in 19% yield and some of this may have come from elimination reactions of compounds (XIII) or (XIV). No azepine picrate was isolated, but this is less valuable evidence since small amounts could have been missed among the other picrates.

The mode of formation of phenanthrene by the action of hydroxyl ions on the azepinium cation (VI) is not so far understood. It appears to involve elimination of dimethylamine from the benzylamine analogue (X) or from (V) and, during the decomposition, an alkaline gas (almost certainly dimethylamine) was evolved as soon as the temperature reached 80°. However, the amine (V) appeared to be stable both to heat (since it could be distilled at 183°/1 mm.) and to alkali (since the yield of phenanthrene was not increased by added potassium hydroxide). The hydroxy-amine (X) is not known; the corresponding diol is stable to hot alkali.

It is not clear why, in the original decomposition of the bisephedrinium compound (III), smaller yields of the diamine (IV) were obtained in Experiment 3 and in decomposition (*a*) than in Experiment 2. Perhaps the balance of competing reactions is very delicate and factors such as the dilution at a particular temperature (difficult to control during slow distillation at a gradually rising temperature) are of critical importance.

In view of the behaviour of the dihydroxide (III), it seemed possible that the hydroxides of other unbridged 2,2′-bisquaternary biphenyls, in which simple olefin formation would be difficult or impossible, might give bridged compounds under Hofmann degradation conditions. Accordingly, an aqueous solution of the hydroxide (XVII; X = OH) was slowly distilled under reduced pressure in an atmosphere of nitrogen. 9-Dimethylamino-9,10-dihydrophenanthrene (V) and trimethylamine were isolated as picrates. At least one other (unidentified) base was present. Non-basic products, including phenanthrene and 2,7-dihydro-3,4:5,6-dibenzoxepin (XVIII) were also obtained. The oxepin was not isolated in a pure condition but was detected spectroscopically in a mixture with phenanthrene.

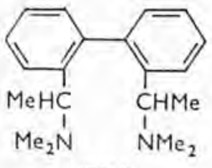
Again, several competing processes must operate. Nucleophilic displacement by hydroxyl ions at one of the benzyl α-carbon atoms, followed by cyclisation, seems the most likely route to the oxepin. Cyclisation involving alkylation of a hydroxyl group by the methylene group of $^-CH_2\cdot NMe_3^+$ in a rather similar situation has been observed by Easton and Fish.[16]



Mechanisms: 5, E2. 6, S_N2 by OH^- at CH_2. 9, S_N2 by OH^- at Me. 10, Internal S_N2.

Proton loss from a benzyl methylene group, followed by rearrangement, gives an ion (XIX) which can undergo either bimolecular displacement at a methyl group, giving (V), or elimination involving a β-hydrogen atom, giving phenanthrene.

The unidentified base was obtained as its picrate, m. p. 240° (decomp.); the analysis gives the formula $C_{20}H_{28}N_2,2C_6H_3N_3O_7$, if the biphenyl skeleton is still present, or $C_{10}H_{15}N,C_6H_3N_3O_7$ if it is not. The possibility that " normal " Stevens rearrangement without cyclisation) had occurred to give the diamine (XX) was considered; decomposition of the picrate by cold alkali gave a little free base, the infrared spectrum of which showed the C–H stretching frequencies of NMe_2 (at 2760 and 2811 cm.$^{-1}$) and of CH_2 (at 2857 and 2918 cm.$^{-1}$). No peaks for C–CH_3 were found, although two slight shoulders (at 2884 and 2970 cm.$^{-1}$) on the CH_2 bands were at the CH_3 stretching frequencies. It thus appears that the base contains CH_2 groups rather than CH·CH_3 groups and so cannot have structure (XX). It has not proved possible to elucidate the structure with the small amount available.



(XX)

The pure amine (IV) was obtained from its dipicrate and gave a dimethiodide identical with (XVII; X = I), prepared from 2,2'-bisbromomethylbiphenyl and trimethylamine. The ultraviolet absorption spectrum of the dimethobromide (XVII; X = Br) (Table 1) is that of a highly hindered 2,2'-disubstituted biphenyl (compare, for example, the spectrum of 2,2'-dimethylbiphenyl [17,18]).

Infrared Spectra.—The main features of the infrared spectra of the four tertiary amines, (II), (IV), (V), and *N*-methylephedrine, are given in Tables 4 and 5. Part of the spectrum of a non-basic reference compound, 9,10-dihydrophenanthrene, is included. A sharp band at 1004—1007 cm.$^{-1}$, found in the first three compounds, is also present in the spectrum of 9,10-dihydrophenanthrene (at 1001 cm.$^{-1}$) but not in that of *N*-methylephedrine; this supports the view of Beaven and Johnson [18] that a band at 1010 cm.$^{-1}$ is characteristic of the biphenyl structure.

TABLE 4.

Infrared spectra (cm.$^{-1}$; 600—1650 cm.$^{-1}$) of some tertiary amines.

(II)	(IV)	(V)	ME *	(II)	(IV)	(V)	ME *	(II)	(IV)	(V)	ME *
605m				934m		936m	920w	1250w	1253m		1247sh
617m	619sh	619m		947m	942w	952m	956m		1261sh	1261w	1267s
632sh		627sh	630m	977w	972w		978sh		1284w	1277m	1282sh
			656m			990w	996s	1307w	1297m	1314m	1305sh
667w		667w		1006w	1007m	1004w		1333w	1337sh	1333sh	1325sh
		678m		1022m	1027s	1025s	1030sh				1355sh
	697w	699m			1041s	1041s	1041s	1366m	1361s	1361m	1368s†
			705vs	1047w		1047sh	1055s	1389w			
711w	711sh	711w		1078s	1075w		1067sh	1416sh	1401w	1404w	1418sh
730m	720sh	728sh	729sh		1095m	1096m	1095m		1439sh	1439sh	
749vs	736sh	737vs	744vs	1114sh	1107w			1443s	1449s	1451s	1447s†
	753sh			1120m				1462m	1460sh	1471sh	1460sh
	757vs	752vs		1127sh		1125w	1127s	1475m		1481s	
776m	781sh	777s	779s		1145m	1143w			1490sh	1493sh	1493sh
		790sh		1157w	1153m	1155m	1157sh	1550w		1563w	
825w	812w	814m	810m		1172m	1167s	1170s			1587sh	
833w	839sh	833w	835w	1182m	1189w	1183m		1605sh	1592w	1597w	1600w
849m	851m	861m		1195m		1200sh	1200m	1637m	1629w		1631w
870w				1235m		1238w					
885w	873m	879m	881m								

* *N*-Methylephedrine, spectrum of Nujol mull. † Nujol peak.

A few of the C–H stretching frequencies require comment. One of the CH_2 bands in 9,10-dihydrophenanthrene occurs at a rather high frequency (2874 cm.$^{-1}$ instead of the usual [19] 2853 ± 10 cm.$^{-1}$) and one of the C–CH_3 bands in *N*-methylephedrine is apparently double (2956 and 2979 cm.$^{-1}$). The γ-hydroxyl group may be responsible for a shift to higher frequency in this band, although this effect is much more marked with isopropyl-O than with n-propyl-O compounds.[20]

All the amines show a strong band at 2764 ± 9 cm.$^{-1}$ and a second band (medium to strong) at 2815 ± 12 cm.$^{-1}$, which is least prominent in the azepine (II) and is also present

Table 5.

C–H Stretching vibrations (cm.$^{-1}$) in some tertiary amines and in 9,10-dihydrophenanthrene.

(II)	(IV)	(V)	ME *	DHP †	Probable assignment
2773s	2755s	2768s	2772s		N–CH_3
	2803s	2811m	2817s		N–CH_3
2827m				2819m	?
2859m	2843m	2851m		2874m	CH_2
			2867s		CH_3
2887sh		2884m			?CH
2924s	2927s	2930s		2921s	CH_2
			2941sh		
2953sh	2959sh	2956sh	2956s		?CH_3
			2979s		?CH_3
3006m	3012m	3012m	3021m	3008s	CH (arom.)
3051m	3046m	3053m	3058m	3051m	CH (arom.)
			3084sh		?CH (arom.)

* *N*-Methylephedrine, spectrum in CCl_4. † 9,10-Dihydrophenanthrene, spectrum of molten material.

as a weak band in 9,10-dihydrophenanthrene. A number of workers [21,22] have correlated absorption in this region with the C–H stretching vibration of an $>$NMe group, and Hill and Meakins [21] have classified the absorption pattern according to the situation of the basic group and the number of methyl groups attached to the nitrogen. With an NMe_2 group not directly attached to an aromatic system two bands occur in the 2825—2810 and 2775—2765 cm.$^{-1}$ ranges. This is borne out by the spectra of the three amines containing NMe_2 (IV, V, and *N*-methylephedrine) in the present work. For amines containing an NMe group not directly attached to an aromatic system, Hill and Meakins [21] found a single band between 2805 and 2780 cm.$^{-1}$. The methylazepine (II) has a strong band just outside this range (2773 cm.$^{-1}$); the second band (at 2827 cm.$^{-1}$) is weaker than for the other amines and it is presumably due to the CH_2 groups rather than the NMe group, especially as a similar band is found in the non-basic 9,10-dihydrophenanthrene.

EXPERIMENTAL

Action of Heat on 2,7-*Dihydro*-1-(β-*hydroxy*-α-*methylphenethyl*)-1-*methyl*-3,4:5,6-*dibenzazepinium Hydroxide* (I; X = OH).—The corresponding (solvated) (+)-bromide [1] (9·1 g.) was shaken in aqueous-ethanolic solution with silver oxide for 1 hr. The filtered solution was distilled at atmospheric pressure; ethanol and water containing (+)-*trans*-1-methyl-2-phenyloxiran were collected. The residue was extracted with ether, and the ethereal solution washed with hydrochloric acid. Aqueous ammonia was added to the acid solution and the free base extracted with ether, dried (K_2CO_3), and distilled, giving 2,7-dihydro-1-methyl-3,4:5,6-dibenzazepine [2] (2·2 g., 53%), b. p. 150—160°/2 mm. [methiodide (from ethanol), m. p. 294° (decomp.), not depressed by authentic specimen (see below); *picrate*, m. p. 162° (from ethanol) (Found: C, 57·9; H, 4·25; N, 12·6. $C_{21}H_{18}N_4O_7$ requires C, 57·5; H, 4·1; N, 12·8%)].

2,2′-*Di*-[NN-*dimethylammoniomethyl*-N-(β-*hydroxy*-α-*methylphenethyl*)]*biphenyl Di-iodide* (III; X = I).—2,2′-Bisbromomethylbiphenyl (13·6 g., 1 mol.) and (−)-*N*-methylephedrine (15·8 g., 2·2 mol.) were dissolved separately in dry warm nitrobenzene (35 c.c. in all). The solutions were mixed at 120° and the temperature rose to *ca.* 150°. The mixture was kept at *ca.* 130° for 20 min. during which solid separated and the whole became very thick. It was allowed to cool and the solid filtered off and washed with dry nitrobenzene, followed by dry benzene and dry acetone. The crude quaternary dibromide (26 g.) so obtained had m. p. *ca.* 206°. In some preparations a small amount of another solid separated from the washings but was not identified. The dibromide was dissolved in a large volume of water, treated with aqueous potassium hydroxide, and extracted with benzene or carbon tetrachloride to remove any unchanged tertiary base. Addition of the benzene precipitated the dibromide in a hydrated form and much water was required to redissolve it. The aqueous solution was neutralised with hydrobromic acid and concentrated below 35° to *ca.* 1500 c.c. (Hydrated anhydrous carbonate) was 9-dimethylamino-9,10-dihydrophenanthrene (infrared spectrum and picrate, m. p. 176°). No phenanthrene was detected.

Action of Heat on 2,7-*Dihydro*-1,1-*dimethyl*-3,4:5,6-*dibenzazepinium Hydroxide* (VI; X = OH).—The azepinium bromide (4·25 g.) was shaken in aqueous solution with silver oxide for 1 hr. The filtered solution was distilled under reduced pressure, in an atmosphere of nitrogen, from a water-bath at 70—100° for 95 min. and was finally heated at 130—135° for 15 min. Ether and water were added to the residue, and ether to the distillate; the combined ethereal extracts were separated as usual into a neutral and a basic fraction. From the neutral fraction, 0·989 g. (40%) of phenanthrene, m. p. 97—99°, was obtained. The basic fraction gave 1·320 g. of a liquid, from which 2·155 g. of picrate, m. p. 163—170° with previous softening, were obtained. Crystallisation of the picrate from methanol yielded 1·185 g. of 9-dimethylamino-9,10-dihydrophenanthrene picrate, m. p. and mixed m. p. 175—176°, 0·5795 g. of 2,7-dihydro-1-methyl-3,4:5,6-dibenzazepine picrate, m. p. mainly 158—161° (slightly contaminated with the higher-melting picrate), and 0·103 g. of mixed picrates, m. p. 155—160°. Recrystallisation of the second crop from ethanol gave the picrate with m. p. 159—161°, not lowered on admixture with an authentic sample. Recrystallisation of the third crop from ethanol gave 0·055 g., m. p. 174°, softening at 155°.

In a second experiment 2·25 g. of bromide gave 0·438 g. (33%) of phenanthrene.

Action of Heat on 2,7-*Dihydro*-1,1-*dimethyl*-3,4:5,6-*dibenzazepinium Hydroxide with Added Potassium Hydroxide.*—The azepinium bromide (1·50 g.) was converted into the hydroxide, and potassium hydroxide (2·8 g.) was added. The solution was distilled as usual under reduced pressure and in an atmosphere of nitrogen. The neutral fraction (0·296 g.; 34%) was phenanthrene, m. p. 100—101°. The basic fraction (0·440 g.) gave a picrate (0·852 g., 38%), m. p. 175—176°.

2,2′-*Bis(trimethylammoniomethyl)biphenyl Di-iodide* (XVII; X = I).—(*a*) 2,2′-Bisbromomethylbiphenyl (13·6 g.) in dry acetone (50 c.c.) was cooled to −15°. Liquid trimethylamine (25 c.c.) was added and the mixture kept (drying tube) at −15° to −10° for 3 hr., then allowed to warm to room temperature and left overnight. The quaternary *dibromide* (18 g.) was collected and crystallised from ethanol as a monohydrate, m. p. 219—221° (decomp.) (14 g., 74%) (Found: Br, 33·4. $C_{20}H_{30}Br_2N_2,H_2O$ requires Br, 33·55%). Some of the dibromide was converted (by treatment with aqueous potassium iodide) into the *di-iodide*, which crystallised from ethanol as a monohydrate, m. p. 245° (decomp.) (Found: C, 42·4; H, 5·65; I, 44·2; N, 4·9. $C_{20}H_{30}I_2N_2,H_2O$ requires C, 42·1; H, 5·65; I, 44·5; N, 4·9%). The *dipicrate* had m. p. 245° (from aqueous ethanol) (Found: C, 51·2; H, 4·5; N, 14·5. $C_{32}H_{34}N_8O_{14}$ requires C, 50·9; H, 4·5; N, 14·8%).

(*b*) 2,2′-Bis(dimethylaminomethyl)biphenyl (IV) was liberated from its dipicrate and heated with an excess of methyl iodide in nitrobenzene in a sealed tube at 100° for 5 hr. The di-iodide was collected, washed with acetone, and crystallised from ethanol: it had m. p. and mixed m. p. 245° (decomp.).

Action of Heat on 2,2′-*Bis(trimethylammoniomethyl)biphenyl Dihydroxide* (XVII; X = OH).—The above dibromide (9·52 g.) was converted into the dihydroxide, and the aqueous solution thereof was distilled under reduced pressure in nitrogen at 70—100° for 90 min. and finally at 125—130° for 15 min. Decomposition was accompanied by a strong smell of trimethylamine. The products were worked up as usual; a very small basic fraction (0·030 g.) and a neutral fraction (0·184 g.) were obtained from the distillate.

The basic fraction from the residue (1·476 g.) was converted into a mixture of picrates which solidified during several days. This mixture was largely intractable, crystallisation giving gums and crops melting over wide ranges, but a small quantity (0·425 g.) of 9-dimethylamino-9,10-dihydrophenanthrene picrate, m. p. 175°, mixed m. p. 175—176°, was isolated. 0·1525 G. of a new but unidentified *picrate* was also obtained. It had m. p. 240° (decomp.) (Found: C, 51·5; H, 4·7; N, 14·4; O, 29·8. $C_{20}H_{28}N_2,2C_6H_3N_3O_7$ requires C, 50·9; H, 4·5; N, 14·8; O, 29·7%).

The neutral ether-soluble fraction from the residue (1·537 g.) crystallised from ethanol and gave phenanthrene (0·335 g.), m. p. 99°, a solid (0·570 g.), m. p. 75—90° (softening at $\sim$50°), and a liquid (0·492 g.). Both the solid and the liquid were separated (by crystallisation and chromatography on alumina) into phenanthrene and impure 2,7-dihydro-3,4:5,6-dibenzoxepin. The best sample of the oxepin had m. p. 51—67° (the pure compound [25] has m. p. 72·5—73°). Its infrared spectrum closely resembled that of the pure oxepin but still showed some phenanthrene peaks (which had decreased in intensity during the purification). One (less pure) sample had m. p. 45—55° and its analysis corresponded to a 1 : 1 mixture (Found: C, 89·4; H, 6·15; O, 4·4. Calc. for $C_{14}H_{10},C_{14}H_{12}O$: C, 89·8; H, 5·9; O, 4·3%). There was no evidence of the presence of any 2,2′-bishydroxymethylbiphenyl in any of the fractions.

The aqueous solution of the residue after ether extraction was taken down to dryness under reduced pressure in a stream of nitrogen. The residual solid (1·40 g.) gave a picrate, m. p. 245°, not depressed by the picrate of the quaternary starting material. The distillate from this operation was saturated with sodium chloride, and trimethylamine distilled off from it, collected in ethanol, and made into the picrate, m. p. 224°, isolated after evaporation of the solvent (Delépine[26] gives m. p. 216°).

Spectra.—Ultraviolet absorption spectra were measured on a Unicam S.P. 500 spectrophotometer. Infrared spectra were measured on a Grubb–Parsons GS 2A double-beam recording spectrometer.

We thank Professor P. B. D. de la Mare for valuable discussions. We gratefully acknowledge the support of a research grant from the Department of Scientific and Industrial Research and we are indebted to the Central Research Funds Committee of the University for a grant for the purchase of a spectrophotometer.

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[*Received, February 15th*, 1962.]

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