SOME BIPHENYLS DERIVED FROM THEBAINE.

A thesis submitted for the degree
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by

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ABSTRACT.

(+)-3,4-Dimethoxy-2-(5-methoxy-2-vinylphenyl)-stilbene has been prepared from thebaine. This is a biphenyl with a "buttressed" ortho-methoxyl group, as well as being substituted in the 6,6'-positions by vinyl groups. The rates of racemisation of this compound and of the dibenzyl, obtained by saturating the vinyl groups, give information about this "buttressing" effect. The ultraviolet spectra are also studied.

Reaction of thebaine with anhydrous magnesium iodide and reduction of the product with lithium aluminium hydride is found to give (+)-2,3,8,9-tetrahydro-4'-hydroxy-3',2"-dimethoxy-N-methyl-4,5:6,7-dibenzazonine and not the N-demethylated compound, as had been thought at one time. A number of derivatives have been prepared and characterised. The N-methyl azonine is a 2,2'-bridged biphenyl with a nine-membered heterocyclic bridging ring, and its methyl ether has also a "buttressed" ortho-methoxyl group. For these reasons, the ultraviolet spectrum and the optical stability of this ether are of interest. Exhaustive methylation of the methyl ether methiodide gives (+)-2,3,3'-trimethoxy-6,6'-divinylbiphenyl, which polymerises too readily for investigations concerning its optical stability to be carried out. Measurements have been made, however, of the rates of racemisation of the diethylbiphenyl, obtained by hydrogenation of the vinyl groups.

The results obtained from the racemisation experiments and the determinations of the ultraviolet spectra of the above compounds are compared with those for related compounds.

The above stilbene, dibenzyl, and the diethylbiphenyl are also amongst the very few known optically active biphenyls with *ortho*-alkyl groups, and would be very inaccessible by processes requiring optical resolution.

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ACKNOWLEDGEMENTS.

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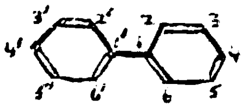
INTRODUCTION

The Stereochemistry of the Biphenyls

The Biphenyl Molecule.



(I)

Electron diffraction studies show that the biphenyl molecule is non-planar in the vapour state[1,2], the most recent data[2] indicating that the rings are at about 42° to one another, with a $C_1-C_{1'}$ distance of 1.49 Å. The molecular conformation in the liquid state is not known with certainty[3]. X-Ray evidence[4,5] shows that the molecule is planar in the solid state and that the length of the $C_1-C_{1'}$ bond in this state[6,7,5] is 1.50 Å, there being no conjugation between the benzene rings[6]. The 2,2',6,6' hydrogen bond angles are slightly deformed in the plane of the rings[6,5]. The most probable conformation in solution has an angle of about 20° between the planes of the two benzene rings[8] as shown by analysis of and the similarity between the ultraviolet spectra in solution[8] and in the solid state[9]. This agrees with the inference of Dale[9], from comparison of the results of measurements of the infrared absorption spectrum in solution and in the solid state, that the molecule is slightly non-planar.

Ultraviolet absorption spectroscopy gives information about conjugation between the two phenyl rings and analysis of the spectra and of the changes observed on the introduction of substituents may lead to conclusions relating resonance and the conformation of the biphenyl skeleton. Biphenyl itself shows a high intensity band at 249 mμ, often termed the conjugation band, with an intensity, or molecular extinction coefficient, ϵ, of 17,300 (in ethanol), which arises as a result of resonance between the two aromatic nuclei, the C_1-$C_{1'}$ bond acquiring some double bond character. According to calculations by Guy[10], in biphenyl derivatives in solution, the angle of twist between the planes of the two benzene rings may be as large as 22° before the resonance energy is appreciably reduced, and somewhere between 45 and 68° before it reaches zero. This decrease in resonance energy results in a hypsochromic shift (a decrease in wavelength) of the conjugation band accompanied by a decrease in intensity.

Ortho Substitution

Introduction of substituents into the biphenyl nucleus has effects which depend on their nature and the position of introduction. Any ortho substituent will raise the energy barrier to inversion of conformation, and if this barrier is raised sufficiently so that the molecule cannot become coplanar at room temperature, the possibility of stable optical activity will occur. Many derivatives have been resolved, and the energy barrier to the passage through the transition state, which need not necessarily be planar, although the rings have to pass one another, has been found to be in the order of 18 to 35 kcal. mole^{-1}, compared with that calculated for biphenyl itself (Howlett[11], 1960): 3.9 kcal. mole^{-1}. In some cases, compounds have been optically activated (asymmetric transformation) but not resolved, and in compounds without, or with only small <u>ortho</u>-substituents, the passage through the coplanar state is so facile, that they cannot be optically activated.

The rate constant for racemisation (k_{rac}) depends on the energy of activation (E) for configurational change, and on the non-exponential term (A), often called the frequency factor, of the Arrhenius equation:-

$$k_{rac} = Ae^{-E/RT}.$$

Values of 10 to 12.5 sec.$^{-1}$ for $\log_{10}$ A are common for these reactions[12], although 13 sec.$^{-1}$ is typical for unimolecular reactions, values above 13 sec.$^{-1}$ generally giving rise to positive values for $\Delta S^{\ddagger}$, the entropy of activation[13]. Ortho-substituents can be arranged in order of decreasing effectiveness in preventing racemisation in unbridged biphenyls[14]:

$$Br > Me > Cl > NO_2 > CO_2H > OMe > F.$$

Although the ultraviolet spectrum of a biphenyl may show a decrease in conjugation in the biphenyl system when compared with biphenyl itself, optical activity may not necessarily occur. For this, an approximate minimum value of E of about 18 kcal. mole^{-1} is necessary[15]. Biphenyls may be conveniently divided into the following loose categories:-

(a) Those which spectroscopically show considerable conjugation and are optically inactive, e.g. 2-fluorobiphenyl and some bridged biphenyls (p. 15). The former shows a shift in the conjugation band[16] to λ_{max} 241.5mμ (ε 16,500) and a calculated interplanar angle of 49°, from the assumed geometry of the molecule[16].

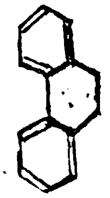
(b) Those which spectroscopically show negligible conjugation but do not show optical activity or are optically unstable. 2,2'-Difluoro and 2,2'-dichlorobiphenyl show shifts in the conjugation band to λ_{max} 233.5 mμ (ε 13,800) and λ_{inf} 230 mμ (ε 6,600) respectively[16], with calculated interplanar angles of 55 and 79° (both in a <u>cis</u> conformation), from the assumed geometry[16]. Dipole moment measurements[17,16] give values of 77 and 81° respectively for these interplanar angles. It has not been possible to achieve optical activation of compounds with these <u>ortho</u>-substituents and calculated values for E are 6 and 18 kcal.mole^{-1} respectively[11].

(c) Those which spectroscopically show negligible conjugation and which show, by exhibiting stable optical activity, that they cannot pass through a coplanar transition state. Examples here are very numerous, but in continuing the above series of dihalogeno biphenyls, the 2,2'-dibromo derivative has λ_{inf} ca. 228 mμ (ϵ 12,000) and the conjugation band is absent in the di-iodo compound[16]. The interplanar angle of each has been calculated as before and found to be 83 and 91° respectively[16], and dipole moment measurements[17] gave 85 and 84°. 2,2'-Dibromobiphenyl-4,4'-dicarboxylic acid exhibits optical activity, with a half-life of 7.3 min. at 5.6°. The energy of activation for racemisation[18] was found to be 19 kcal. mole^{-1}. The corresponding di-iodo-compound has also been obtained optically active[19], the energy of activation for racemisation[20] being 21.6 kcal. mole^{-1}, with a half-life of 104 min. at 25°.

Substitution of methyl groups in the o-positions of biphenyl gives a considerable diminution in conjugation e.g. for 2-methylbiphenyl, λ_{max} 235 mμ (ϵ 10,500)[21,22,23] and in 2,2'-dimethylbiphenyl, the band has almost vanished[24]. Replacement of methyl by ethyl, n-propyl, or n-butyl has little effect as the larger alkyl group can take up a position in which it contributes little additional overlap[22,25].

o-Hydroxyl and o-methoxyl substituents produce a decrease in the extinction coefficient of the conjugation band of biphenyl, but the hypsochromic shift[21,23] is only about 5 mμ. In conjugated systems, bathochromic shifts of this order are usual[26,27], and so the "theoretical" hypsochromic shift of about 10 mμ is comparable with that due to alkyl substituents[22]. The hypsochromic shifts produced by two *o*-methyl or *o*-methoxyl groups are approximately twice as great as for one (λ_{max} 227 and $<$ 230 mμ respectively[24,28]).

These hypsochromic shifts are regarded as being steric in origin[22] there being an overlap between a group in one of the *ortho*-positions and the *o*'-hydrogen on the other ring. In the *ortho*-methoxy[21,23] and hydroxy[21] and the *o*,*o*'- and *m*,*m*'-dimethoxy[28] and dihydroxy[28] compounds, long-wavelength phenoxy bands are also present at about 280 to 295 mμ (ε 5,000 to 6,000).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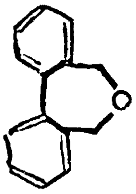
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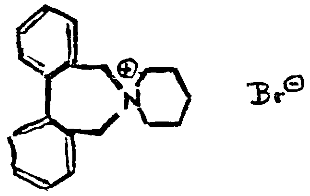

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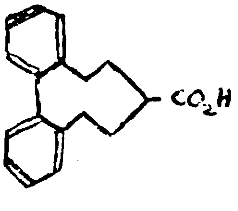

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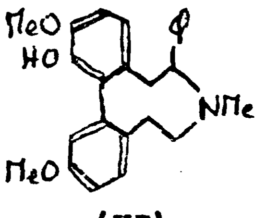


(VI)

The conjugation bands of the bridged biphenyls 9,10-dihydrophenanthrene (II), 2,7-dihydro-3,4:5,6-dibenzoxepin (III) and the azepinium salt (IV) occur at λ_{max} 264 (ε 17,000), 250 (ε 16,500) and 248 mμ (ε 15,000) respectively[29]. The introduction of two methoxyl groups

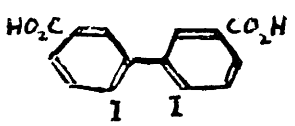
into the o,o'-positions produces a decrease in intensity in all three cases but no hypsochromic shift in the case of the first two compounds (to λ_{max} 272, ϵ 13,500, and 253 mμ ϵ 8,700, respectively[29]), because, according to Braude and Forbes[22], the "locking-effect" of the ethane bridge is sufficient to enforce a near planar configuration in the excited state, contrary to the expectation that the interplanar angle should be increased by the effect of the methoxyl group. For steric effects to operate in which a decrease in intensity with no hypsochromic shift occurs, steric hindrance to planarity should not exceed ca. 3 kcal. mole^{-1} (Braude and Sondheimer[25]). Howlett[30] calculated this for (II) to be 1.4 but according to Mislow[31] it is 4 kcal. mole^{-1}. In the case of the azepinium salt[29] (λ_{max} 237.5 mμ, ϵ 11,500), a hypsochromic effect results as the system is sufficiently flexible to have non-coplanarity in the excited state[22].
A long-wave band, due to hyperconjugative interaction of the two rings through the bridge[32] occurs in the spectrum[29] of (II), at λ_{max} 299.5 mμ (ϵ 4,500). There is no long-wave band in that of (III), but it occurs at 272 mμ (ϵ 4,800) in that[29] of (IV). Introduction of the methoxyl groups enhances absorption in all cases, together with increases in wavelength, where applicable, to λ_{max} 304.5 (ϵ 9,300); 293.5 (ϵ 10,000); and 297.5 mμ (ϵ 10,500), respectively[29]. The effect can be regarded

as being due to superposition of absorption due to the phenoxy chromophores[22] in the cases of (II) and (IV), as 3,3'-dimethoxybiphenyl absorbs in the long-wave region[28] at λ_{max} 285 mμ (ε 6,000).

The cyclononadiene acid (V) has no band due to hyperconjugation through the bridging ring, and the conjugation band is vestigial[33] at λ_{inf} 231 mμ (ε 5,550), but phenyldihydrothebaine (VI) has a band[34] at λ_{max} 281 mμ (ε 5,600) due only to the phenoxy chromophores[57,35] (p. 22).

The "Buttressing" Effect.

Meta-substituents exert indirect steric effects by "buttressing" *ortho*-substituents against in-plane bending away from the biphenyl link. This is reflected in measurements on racemisation rates on 2,2'- and 2,2',3,3'-substituted biphenyls[36,35]. According to Braude and Forbes[22], even in biphenyl itself there is a slight interference between the *o*-hydrogen atoms, which are therefore susceptible to the "buttressing" effect.



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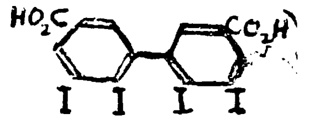
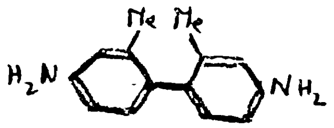


(VIII)

Rieger and Westheimer[35] calculated the activation energies for the racemisation of 2,2'-di-iodo- (VII) and 2,2',3,3'-tetraiodo-5,5'-dicarboxybiphenyl (VIII), the difference being due to the "buttressing" effect. The calculated difference agreed well with the experimental value of 6.4 kcal. mole^{-1}.



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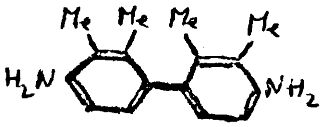


(X)

2,2'-Dimethylbenzidine (IX) has not been obtained in an optically active state, but 2,2',3,3'-tetramethylbenzidine (X) was found to have an activation energy[37] of 17.7 kcal. mole^{-1}. This approximates to the minimum value of 18 kcal. mole^{-1} normally required before optical activity is experimentally detectable[15].

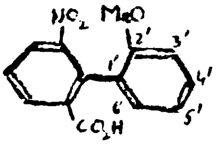
Substituents in the 4'- or 5'-positions in biphenyls such as (XI) have only a small effect in comparison with those in the 3'-position, as is shown[13] in table (1):-

Table (1).

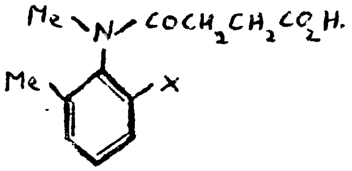
Half-lives of the Racemisation of Derivatives of 6-Carboxy-2'-methoxy-2-nitrophenyl (XI).

Substituent	NO_2	Br	Cl	Me	MeO
Position 3'	1905	827	711	331	98
4'	115	25	12	2.5	3.6
5'	35	32	31	12	11

Values of $t_{\frac{1}{2}}$ in min. at 25°.



(XI)



(XII)

The abnormal effect of the nitro-group, in view of its size, does not seem to be fully understood. It sometimes has the reverse effect as in derivatives of the type[33,13] (XII). Here, optical activity occurs owing to the restricted rotation about the link between the aromatic ring and the nitrogen atom.

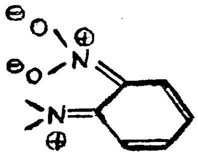
Table (2).

Half-lives for the Racemisation of Compounds of Type (XII).

X	I	Br	Cl	OMe	NO_2
$t_{\frac{1}{2}}$ (117°)	21.5	3.1	0.6	-	-
$t_{\frac{1}{2}}$ (57°)	-	-	63	2.7	0.6

Values of $t_{\frac{1}{2}}$ in hr.

It has been proposed[33] that the effect of the nitro-group in compounds of type (XII) is due to contributions from structures such as (XIII), which favour coplanarity.



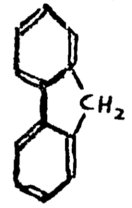
(XIII)

Bridged Biphenyls.

Suitable bridging of the 2,2'-positions of biphenyl retains the basic collinear biphenyl structure, but twisting and dissymmetry occur in order to accommodate the strainless multiplanar bridge, except in the first member of the series, fluorene (XIV), which has a strained coplanar configuration. Thus, except in the case of fluorene, optically active enantiomers should exist, even if the 6,6'-positions are unsubstituted. The energy barrier to racemisation depends on the distortion of the bond angles, the stretching and bending of bonds, and on non-bonded interaction in the transition state. Dreiding models show that the hydrogens on one α-carbon atom of the bridge eclipse those on the other α-carbon atom, in the transition state. As the size of the bridge increases from a seven- to an eight-membered ring, the angle strain in the transition state decreases at the expense of increased non-bonded interaction of opposed α-hydrogens until in the nine-membered ring, the barrier arises largely from the interaction of the non-bonded hydrogens, on the α-carbon atoms, which are almost exactly opposed[x], and "cogwheeling" is prevented by the conformation of the bridge[33].

[x] The direct non-bonded interaction of hydrogen in rigid bicyclic systems has been studied by L. de Vries and S. Winstein, _J. Amer. Chem. Soc._, 1960, _82_, 5363; S. Winstein and R.L. Hansen, _ibid._, 1960, _82_, 6206; L. de Vries and P.R. Ryanson, _J. Org. Chem._, 1961, _26_, 621; D. Kivelson, S. Winstein, P. Bruck, and R.L. Hansen, _J. Amer. Chem. Soc._, 1961, _83_, 2938.

Neglecting solvent effects, the activation energy for racemisation remains approximately constant for seven-, eight- and nine-atom bridged compounds, which do not have other substituents on the benzene rings[33].



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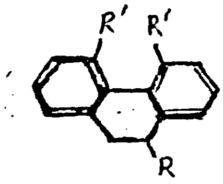
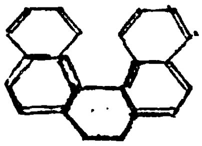


(XV)

The first in this series of bridged biphenyls is fluorene (XIV) which shows absorption in the ultraviolet region[39] of a typical planar o,o'-disubstituted biphenyl at λ_{max} 260 mμ (ϵ 19,000), which is the so-called conjugation band, and at λ_{max} 300 mμ (ϵ 10,000), which is due to the hyperconjugative interaction of the two rings through the methylene bridge[32]. More recent data[40], however, have the values λ_{max} 261 (ϵ 17,500) and 300.5 mμ (ϵ 9,030) in iso-octane solution. The molecule is planar[41] although not completely collinear[41,42].

9,10-Dihydrophenanthrene (II), the next in the series, is optically inactive, owing to the low energy of activation for racemisation. This has been calculated by Mislow[31] as 4 kcal. mole^{-1} and the interplanar angle as 15.3° from the assumed geometry of the molecule. Braude and Forbes[22] used the relationship $\cos^2\theta = \epsilon/\epsilon_0$, where θ is the interplanar angle, ϵ is the molar extinction coefficient of the conjugation band, and ϵ_0 that of this band[39] in the spectrum of fluorene. They obtain the value 18° for ϑ, the conjugation band[29] being at λ_{max} 264 mμ (ϵ 17,000). The long-wave hyperconjugation band has decreased in intensity[29] to ϵ 4,500 at λ_{max} 299.5 mμ.

The 4,5-dimethyl derivative (XV, R = H; R' = CH_3) has been obtained optically active and the energy of activation for racemisation found to be[43] 23.1 kcal. mole^{-1}. The interplanar angle has increased to 24°, as calculated by Braude and Forbes[22] using the relationship $\cos^2\vartheta = \epsilon/\epsilon_0$, for the conjugation band[44] at λ_{max} 260 mμ (ϵ 16,000). The 9-dimethylamino-4,5-dimethyl derivative (XV, R = $N(CH_3)_2$; R' = CH_3) was obtained optically active by Mislow and Joshua[45], who obtained a value for E of 22 to 23 kcal. mole^{-1}. The two methyl groups in compounds (XV) appear to be less effective as blocking groups than the two benzo groups in (XVI), which has an energy of activation[46] of 30.8 kcal. mole^{-1}.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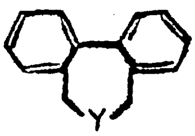
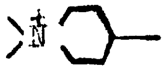
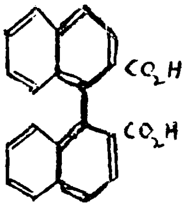

(XVII)

The calculated activation energy[33] for the three-atom bridged biphenyl (XVII, Y = CH_2) is 21 kcal. mole^{-1} but attempts to resolve the related compounds[29,47,48] where Y =  Br^- and  C_6H_5 Br^-; $>CHCO_2H$; $>CHCH_2OH$; $>CHCO_2CH_3$ and $>C(CO_2H)_2$ were unsuccessful, presumably owing to optical instability. The dextrorotatory cycloheptadiene ester (XVII,Y = $>C(CO_2Et)_2$) was obtained by Iffland and Siegel[49], and has a half-life of 80 min. at 32.5°, giving a value[33] for E which will lie between 20.8 and 26.2 kcal. mole^{-1} for reasonable values of A. Many related compounds, with substituents in the <u>ortho</u>-positions have since been obtained optically active. For the compounds (XVII, Y = $>CHCO_2H$, $>CHCO_2CH_3$ and $>CHCH_2OH$) the conjugation bands are all[48] at 249 mμ (ϵ <u>ca</u>. 15,000; cf. for biphenyl ϵ 17,000); for[50] (XVII, Y =$>CH_2$), λ_{max} 247 mμ (ϵ 15,700); and for[29] (XVII, Y = $>O$), λ_{max} 250 mμ (ϵ 16,500). The long-wave features of these compounds are barely discernible inflections at[29,48,50] <u>ca</u>. 275 mμ (ϵ 1,500 - 1,750). The angle between the ring planes in the structure (XVII, Y = $>C<$) according to a model is about 50° and direct calculation gives values of 48.6 and 49.1°, according to assumptions made with respect to bond lengths (Beaven et al.[48]).



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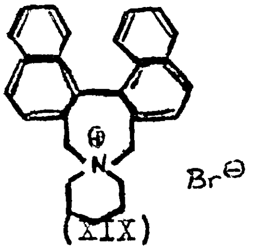

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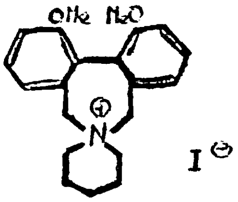
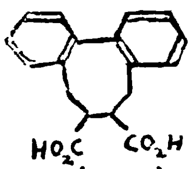
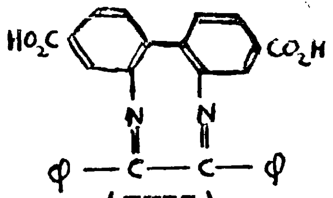


(XX)

9,10-Dihydro-3,4:5,6-dibenzophenanthrene (XVI) is more optically stable[51] than 3,4:5,6-dibenzophenanthrene-9,10-dicarboxylic acid[52]. The non-bridged compound (XVIII) is more stable optically than the seven-membered ring compound (XIX) which in turn is more optically stable[51] than the hydrocarbon (XVI). The azepinium compound (XX), though less stable optically than (XIX) is more stable than (XVI), although the blocking groups are methoxyl groups instead of benzene rings[29,51]. Thus enlargement of the bridging ring from six to seven atoms increases optical stability, but the joining of two of the ortho-blocking groups into a ring, decreases the optical stability. When the interplanar angle is already small, as in (XVI), the ease of obtaining the planar configuration, i.e. the optical instability, is increased over that when the angle is of the order of 50°, as in (XIX) and (XX)[51].



(XXI)



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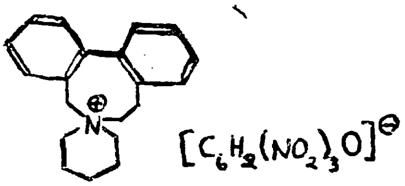
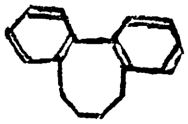


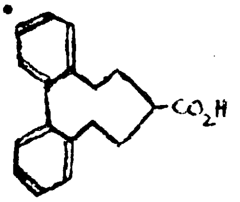
(XXIII)

The cis- and trans-dibenzocycloöctadiene acids (XXI) have been obtained in optically active forms by Mislow and his co-workers[53], the former compound racemising and the latter mutarotating at 31.5° in ethanol with half-lives of 85 and 12 min. respectively (cf. XVII, $Y = \rangle C(CO_2Et)_2$: $t_{\frac{1}{2}} = 80$ min. at 32.5°). The energy of activation for racemisation for the cis-acid was found to be 22.8 kcal. mole^{-1} in ethanol, and 25.4 kcal. mole^{-1} in sodium hydroxide solution[53]. Both acids are less optically stable than the diazocine (XXII), which was resolved by Bell[54], as the additional double bonds in[55] the diazocine confer greater rigidity. The dibenzazocine picrate (XXIII) is less stable optically[55] than Mislow's acids, with $t_{\frac{1}{2}}$ = 1.4 min. at 23° in acetone and E = 22.1 kcal. mole^{-1}.

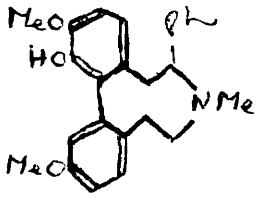


(XXIV)

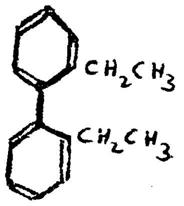
The ultraviolet spectrum[50] of the parent hydrocarbon (XXIV) shows a further reduction in conjugation as compared with the six- and seven-membered ring compounds: λ_{max} 235 mμ (ϵ 9,680). There are two long-wave inflections[50] at 265 and 275 mμ. The spectra of the methyl esters of the acids (XXI) give similar results[48], the conjugation band for each being at λ_{max} 236.5 mμ (ϵ *ca.* 12,500) and the two long-wave inflections being at *ca.* 266 and 274 mμ (ϵ *ca.* 800 and 500 respectively) for each. The inflections are resolved better than in the case of the three-atom bridged compound (XVII, Y = $>CHCO_2H$), and is therefore additional evidence for a reduction in conjugation[48]. Considerable conjugation between the benzene rings still exists, in spite of the large angle between them, which is shown by models to be either 60-65° or 75-80°. Spectral evidence favours the former[48]. The contrast between non-coplanar bridged biphenyls and those with non-bridging 2,2'-substituents is striking. In the latter, unless the 2,2'-substituents are very small (e.g. fluorine[16]), conjugation is greatly reduced and the long-wave features are more evident (cf. 2,2'-ditolyl[24]), even though transient coplanarity (in the trans-position) can undoubtedly be achieved[48].



(V)



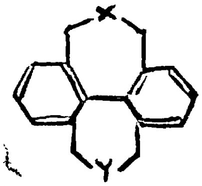
(VI)

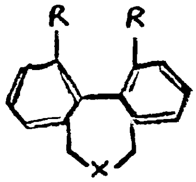


(XXV)

Phenyldihydrothebaine (VI), a five-atom bridged biphenyl, can be prepared from thebaine[56,34] and four optically active isomers have been isolated, which are also optically stable[34]. A band occurs in the ultraviolet spectrum[34] at 281 mμ (ϵ 5,600), which was thought by Braude and Forbes to be partly a conjugation band, and by using the relationship $\cos^2\theta = \epsilon / \epsilon_0$ (p. 17), they[22] calculated $\theta \geqslant 57^\circ$. However, in this type of compound, the molecule is very flexible and a number of conformations are possible. Hall and Minhaj[57] state that models show that $110^\circ > \theta > 50^\circ$ and attribute the band at 281 mμ to absorption by the methoxyphenyl partial chromophores. Mislow et al.[33] prepared the acid (V), the spectrum of which had no peak at 281 mμ, but an inflection at λ_{inf} 231 mμ (ϵ 5,550), which was a vestigial conjugation band and showed that there was very little conjugation in the molecule, confirming the assignment of the band at 281 mμ in the spectrum of (VI) to the partial phenoxy chromophores[33] (see also p.10). The long-wave[33] features in the spectrum of the acid (V) have disappeared except for two inflections at *ca.* 265 and 272 mμ (ε *ca.* 600) due, it is reasonable to assume, to the partial alkyl chromophores. This spectrum is nearly superimposable on that[58] of the open chain analogue (XXV). The laevorotatory isomer of the acid (V) was isolated by second order asymmetric transformation during crystallisation of the quinidine salt, and its half-lives at 25 and 80° were about 24 hr. and 2 min. respectively[33], showing greater optical stability than the corresponding four atom-bridged biphenyl (XXI) (p. 20). The energy of activation[33] was 24.0 kcal. mole^{-1}.

Doubly-Bridged Biphenyls.





XXVI a, X = Y = O. d, X = Y = CH_2. XXVII a, R = H.
b, X = O; Y = S. e, X = Y = CO. b, R = CH_3.
c, X = Y = NCH_3. f, X = Y = S.

A number of doubly-bridged biphenyls have been prepared by Mislow *et al.*[31]. For a given series of singly- (e.g. XXVIIa or XXVIIb) or doubly-bridged biphenyls (XXVI, X = Y), the energy of activation for racemisation parallels the interplanar angle, within each series[31]. This was shown in nuclear magnetic resonance studies[31], but it is not legitimate to compare this relationship *between* the series, e.g. the interplanar angle decreases in the compounds (XXVIIb, X = O) $>$ (XXVIIa, X = O) $>$ (XXVIa), but the optical stabilities are (XXVIIb, X = O) $>$ (XXVIa) $>$ (XXVIIa, X = O). Mislow[31] calculated the activation energies for the following, making different assumptions from those made previously in such calculations (e.g. see ref. 30) and obtained close agreement with the shown practical results:

Table (3).

Activation Energies for some Biphenyls.

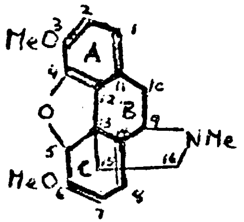
Compound	(XXVIa)	(XXVId)	(XXVIe)	(XXVIf)	(XXVIIa, X = O)	(XXVIIa X = S)
Calculated	22	29	33	37	9	17
Experimental	20.4	-	31.2	35.0	9.2*	16.1*

Activation energies in kcal. mole^{-1}

* Determind by R.J. Kurland, M.B. Rubin and W.B. Wise, *J. Chem. Phys.*, 1964, *40*, 2426, using N.M.R. Spectroscopy.

The Chemistry of Phenyldihydrothebaine.

Certain derivatives of thebaine (XXVIII) having one double bond only in ring C in the 6,7 position, react with Grignard reagents with opening of the cyclic ether and introduction of the organic radical into ring C. The presence of a second double bond in this ring, causes the reaction of Grignard reagents with thebaine to take an entirely different course.



(XXVIII)

The reaction of thebaine and phenylmagnesium bromide was first investigated by Freund[58,59], who obtained in this way, a phenolic base, the composition of which was

$$C_{25}H_{27}O_3N = \text{Thebaine} + C_6H_6,$$

and the base was accordingly named phenyldihydrothebaine.

It was found to be strongly resistant to hydrogenation and to be so stable in concentrated acids that demethylation could be accomplished without structural change, although no hydrolysis of what was then thought to be the "enol-ether" methoxyl group (that attached to C_6 in thebaine) could be effected. Exhaustive methylation resulted in loss of trimethylamine only, and retention of the residue of the basic side-chain as a vinyl group, which was unknown in any compound of the morphine series in a comparable state of saturation. These facts led Freund to postulate some formulae for thebaine which now seem unlikely. The reduction of phenyldihydrothebaine was subsequently accomplished[60], but was found to involve reductive scission of the nitrogen-containing ring, the product being a secondary amine, phenyltetrahydrothebaimine.

The problem was investigated by Small, Sargent and Bralley[34], who resolved phenyldihydrothebaine into two diastereoisomeric bases, designated (+)-α- and (+)-δ-phenyldihydrothebaine, in the ratio of approximately 10:1. They were both phenolic as well as basic, as shown by their solubility in alkalies and ready coupling with diazonium salts. As with the corresponding methyldihydrothebaines, prepared by Small and Fry[61] by the interaction of thebaine and methylmagnesium iodide, these bases were isomerised by slow distillation in a high vacuum or by heating in an evacuated sealed tube at 200°; (+)-α-phenyldihydrothebaine was recovered 75% unchanged together with 16% of a new isomer, termed by Small (-)-δ-phenyldihydrothebaine, identical with the (+)-δ-form, except for the opposite sign of optical rotation. Similarly, (+)-δ-phenyldihydrothebaine gave a fourth isomer, termed the (-)-α-form, equal and opposite in optical rotatory power to the (+)-α-form. The existence of two centres of dissymmetry is evident, the equilibrium reached from either side favouring the α-forms[34].

Thus the optical antipode of (+)-α is (-)-α by this nomenclature. Robinson[62,63] suggested that it would be preferable to term them (+)-α and (-)-δ, for then (+), (-), α, and δ could then be taken to represent left- or right-hand at two centres of dissymmetry and the partial racemisation of (+)-α by heat would then give (-)-α. However, in order to avoid confusion, the names of compounds and derivatives in this field and the designation of isomers as used by Small and his co-workers were adhered to by Bentley and Robinson[62-65] and will be used here, in spite of the fact that the anomaly exists that some compounds designated as (+), are actually laevorotatory.

Asymmetry about a carbon atom joined directly to the nitrogen atom, superimposed on the dissymmetric molecule, gives rise to the α and δ isomers (α being used for one racemic pair and δ for the other), since elimination of the nitrogen by exhaustive methylation leaves only one asymmetric centre and only one pair of enantiomers.

Any satisfactory formula for phenyldihydrothebaine must explain the following:-

(a) The resistance of the base to hydrogenation[56,34].

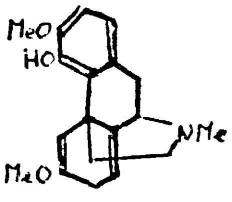
(b) The stability of what was originally thought to be the "enol ether" methoxyl group (that attached to C6 in thebaine) on treatment with concentrated acid[56,34].

(c) The Hofmann exhaustive methylation of either of the (+)-isomers results in a dextrorotatory nitrogen-free product, the residue of the basic side chain being retained as a vinyl group. Similarly, the (-)-δ-isomer gives a laevorotatory nitrogen-free product[34] (degradation of the (-)-α-isomer has not been carried out).

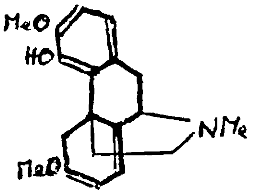
(d) Demethylation gives norphenyldihydrothebaine[56], which has the properties of a trihydric phenol and can be methylated to phenyldihydrothebaine methyl ether[66,34].

(e) Asymmetry at a carbon atom joined to the nitrogen after the entry of the phenyl group of the Grignard reagent[34].

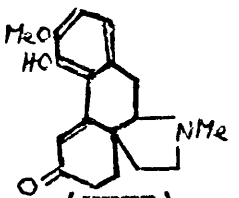
Small, Sargent and Bralley rejected the idea that the near aromatic nucleus of thebaine, which bears the hydrolysable methoxyl group, has become aromatic in phenyldihydrothebaine, in spite of (a), (b), (c), and (d), because no place could be found for two hydrogen atoms and the optical activity could not be explained[61,34].



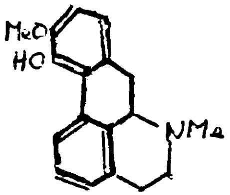
(XXIX)



(XXX)



(XXXI)

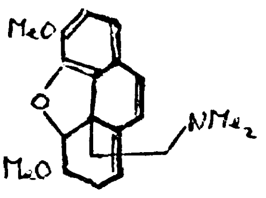


(XXXII)

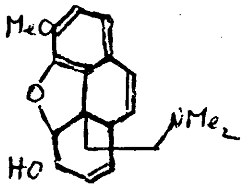
The ultraviolet absorption spectra of phenyl- and methyl-dihydrothebaine and of dihydrothebaine-φ (XXIX) (at that time believed to be (XXX), in which no structural change has occurred, have almost identical maxima and minima, whereas the spectra of metathebaine (XXXI) and apocodeine (XXXII), in which rearrangement has occurred, are different.

Also, the spectra of phenyldihydrothebaine methine and β-codeimethine (XXXIII) are similar, whilst that of α-codeimethine (XXXIV), with a non-conjugated double bond at $C_{7,8}$, is different from either of them. Small pointed out that the spectrum of phenyldihydrothebaine gave no indication of the presence of a new aromatic ring in conjugation with that already present in thebaine[34].

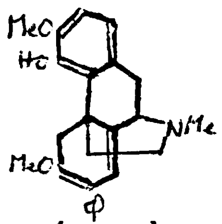
Small, Sargent and Bralley[34] advanced structure (XXXV) for phenyldihydrothebaine, which did not explain the anomalous properties of the base, and they questioned the validity of Gulland and Robinson's formulae for thebaine and morphine[67]. But structure (XXXV) is not in agreement with the ultraviolet spectrum of phenyldihydrothebaine which is not styrenoid.



(XXXIII)



(XXXIV)



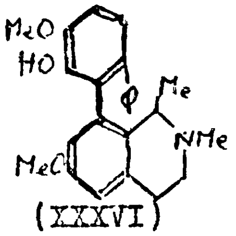
(XXXV)

It must be concluded that the near aromatic nucleus in thebaine has become fully aromatic in phenyldihydrothebaine, and the sequence leading from phenyldihydrothebaine to the optically active nitrogen-free product may be represented in the form:-

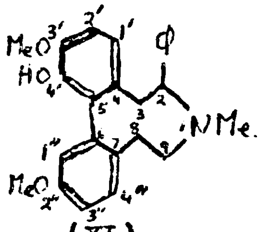
$$\text{-C-C-NMe-C-C-} \longrightarrow \text{-C=C + NMe + C=C-},$$

the presence of two double bonds in the end product being easily demonstrated.

Phenyldihydrothebaine is a C_{25} base; one carbon atom being present in an NMe group (now lost), two in OMe groups, eighteen in the three benzene rings, leaving four for the two double bonds. Hence, the product of exhaustive methylation cannot contain an asymmetric carbon atom. Thebaine is easily degraded to phenanthrene derivatives which are derived from biphenyl, certain derivatives of which exhibit optical activity due to restricted rotation of the phenyl groups in the presence of ortho-substituents of sufficient size. This explains the optical activity of the product of exhaustive methylation and there is evidence that it must be applied to phenyldihydrothebaine itself, in that the centre of dissymmetry represented by (+) and (-), gives the configuration of the biphenyl system.

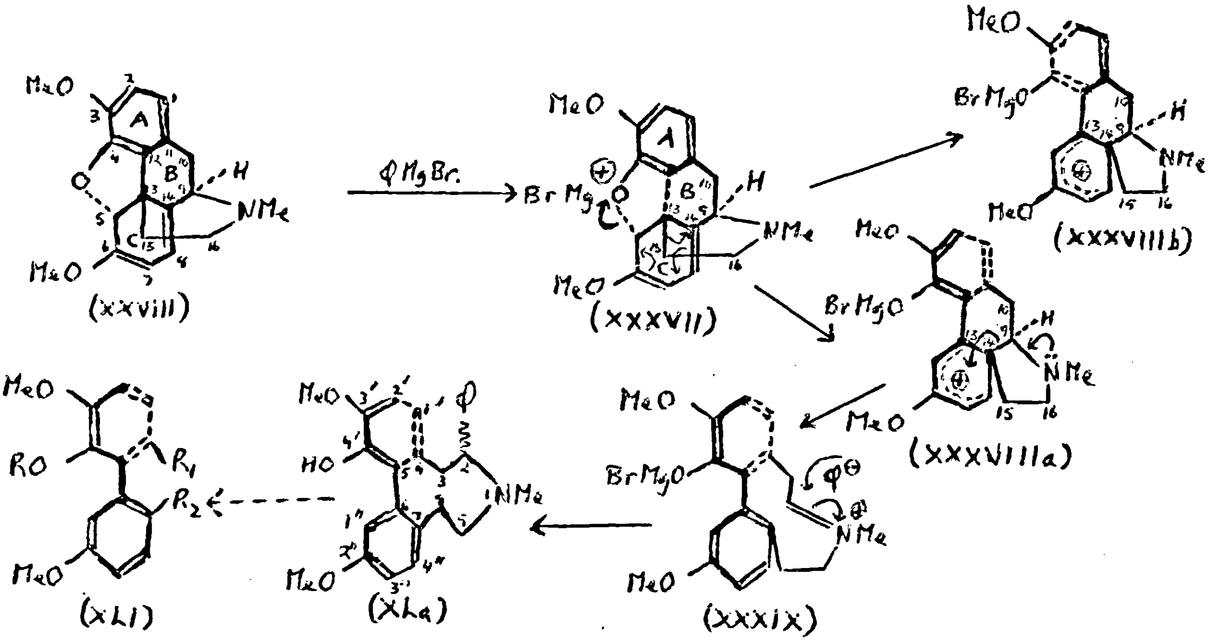


(XXXVI)



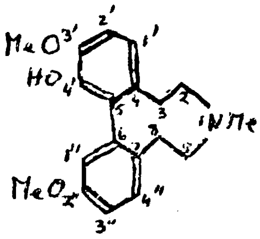
(XL)

The structure first suggested by Bentley and Robinson was (XXXVI), who rejected it later in favour[65] of (XL) because phenyldihydrothebaine does not show biphenyl bands in the ultraviolet spectrum and they then thought that (XXXVI) would represent a non-sterically hindered biphenyl system. Also (XXXVI) does not explain the formation of isomers during the entry of the phenyl group.



The formation of the (+)-isomers of phenyldihydrothebaine (XLa) from thebaine (XXVIII) is the result of a then novel type of molecular change. Attack by $MgBr^{\oplus}$ on the ether oxygen atom undoubtedly initiates the process, rather than attack by $C_6H_5^{\ominus}$ at C_9, in view of the reaction between thebaine and anhydrous magnesium iodide (p. 36). The driving force is probably the tendency of the near aromatic nucleus C to become fully aromatic. Cleavage of the magnesium-complexed oxide bridge of (XXXVII), allows the migration of the alkyl chain[62,63]. The absolute configuration of thebaine is known[68], and at or near the transition state C_{13} must be trigonal for the migration of C_{15} from C_{13} to C_{14}, and the two rings A and C approach coaxiality. Two diastereoisomeric transition states, one of which is thermodynamically preferable, are possible, and this also applies to the two possible metastable intermediates[69,70](XXXVIIIa) and (XXXVIIIb). Models show that the former is preferable, for the angle between the planes C_{15}-C_{14}-C_9 and C_{14}-C_9-N is nearly 0°, whilst in the latter it is close to 60°. If the latter were the intermediate, the five-atom ring C_{15}-C_{14}-C_9-N-C_{16} would be severely puckered. Even when the resultant release of non-bonded interaction is taken into consideration, an interplanar angle of 60° would be intolerable when the Baeyer strain-free alternative (XXXVIIIa) is possible[69]. The preferred intermediate gives way to the imonium ion (XXXIX), which then reacts with the phenyl anion[62,63] to give the (+)-isomers of phenyldihydrothebaine (XLa). Thus, the absolute configuration of the biphenyl ring system in (+)-α- and (+)-δ-phenyldihydrothebaine is as shown and the simple bicyclic derivatives (e.g. the methines and the nitrogen-free degradation products (p. 34-5), have the configuration shown[69] in (XLI).

Using the Sequence Rule of Cahn, Ingold and Prelog[71], the use of which was discussed by Cahn[72], thebaine may be completely specified as 5R, 9R, 13S., and knowing now the absolute configuration of the ring system of (+)-α-phenyldihydrothebaine, the (+)- and (-)-enantiomers may be specified as S and R respectively. The absolute configuration at the asymmetric carbon atom (C_2 in (XLa)) in the (+)-α-isomer is not known. The parent compound of the series (XLII), as well as its degradation products, and the nitrogen-free degradation products of the isomers of (XL), can exist only in the (+)- and (-)- or S- and R-forms.

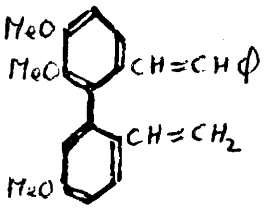


(XLII)

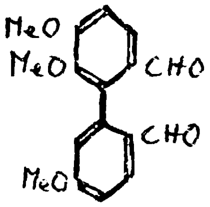
Examination of models shows that biphenyls bridged across the *o*,*o*'-positions by a nine-membered ring do not possess single conformations corresponding to minimum angles of strain. Hall and Minhaj[57] state that models show that the angle between the planes of the benzene rings may lie between 50 and 110°, a number of conformations being preferred. Biphenyls in which the rings are far removed from coplanarity, do not exhibit biphenyl absorption in the ultraviolet region; hence, as pointed out by Small, there is no indication in the ultraviolet spectrum of the appearance of a new aromatic nucleus in conjugation with that present in thebaine.

Proof of the Structure of the Phenyldihydrothebaines.

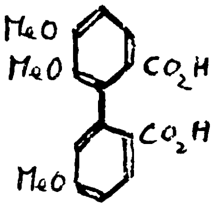
Oxidation of phenyldihydrothebaine with alkaline potassium permanganate produced benzaldehyde, benzoic acid, and 4-methoxyphthalic acid. Exhaustive methylation of the methyl ether of phenyldihydrothebaine produced (+)-3,4-dimethoxy-2-(5-methoxy-2-vinylphenyl)-stilbene (XLIII), which was prepared by Freund but stated to be optically inactive[56]. Permanganate oxidation of this gave 5,6,5'-trimethoxybiphenyl-2,2'-dialdehyde (XLIV), also obtained by ozonolysis of (XLIII), and 5,6,5'-trimethoxydiphenic acid (XLV), also obtained by oxidation of (XLIV), which was identical with an authentic specimen[62-65].



(XLIII)

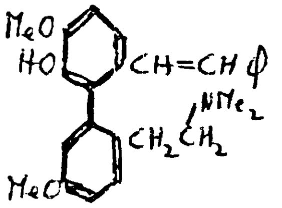


(XLIV)

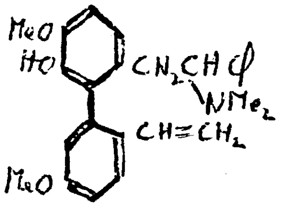


(XLV)

Small, Sargent and Bralley[34] studied the degradation of the four diastereoisomers of phenyldihydrothebaine. They are fairly resistant, but all, except for the (−)-α-isomer, have been converted into nitrogen-free substances. In the first stage of exhaustive methylation, methines, the normal- (XLVI) and iso-methines (XLVII), are produced, the latter predominating; in fact the normal-methine was only isolated during the degradation of the (+)-α-isomer. The reactions and properties of these were investigated by Small, Sargent and Bralley[34], Bentley and Robinson[65], and Fieser and Fieser[73].

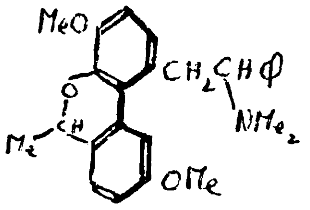


(XLVI)

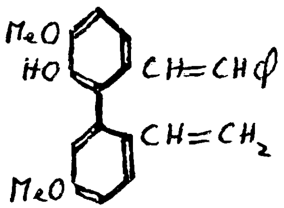


(XLVII)

The vinyl group of the iso-methine cyclises with the phenolic hydroxyl on boiling with concentrated hydrochloric acid, giving (XLVIII). This is indifferent to catalytic hydrogenation. The normal-methine cannot be cyclised in this way, and both it and the iso-methine can be catalytically hydrogenated, the side chain becoming saturated. The hydrogenated iso-methine is unaffected by hot acid[34]. In the iso-methine derivatives, the α:δ isomerism persists, but not in the normal-methines[34].

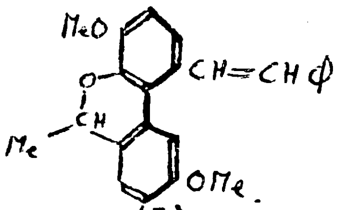


(XLVIII)

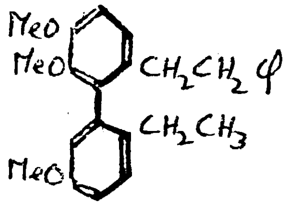


(XLIX)

Further degradation of the normal- and iso-methines gives the optically active nitrogen-free product (XLIX). Acetylation shows the presence of the free phenolic hydroxyl group, and cyclisation by hydrochloric acid to (L) shows that it contains a vinyl group[34]. The phenolic stilbene (XLIX) may be hydrogenated to a variety of products, depending on conditions[34,73,65].



(L)



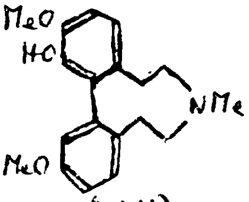
(LI)

The stilbene (XLIII), which is the methyl ether of (XLIX), is optically active and can be reduced to a tetrahydro-derivative, (+)-2-(2-ethyl-5-methoxyphenyl)-3,4-dimethoxydibenzyl[65] (LI).

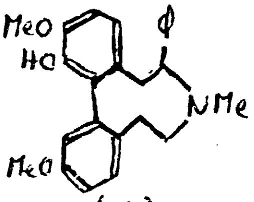
Compounds Related to Phenyldihydrothebaine.

Other compounds analogous to phenyldihydrothebaine which have been prepared so far are methyldihydrothebaine[61], and benzyldihydrothebaine[59], from the interaction of benzylmagnesium bromide and thebaine.

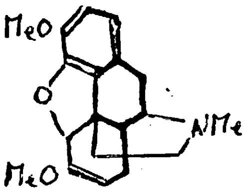
Attempts have been made to prepare[74,64,65], the parent compound (XLII) of the series, which Bentley and Robinson called "dihydrothebaine" by analogy with (XL). Since this name is already in use[75] for (LII), it will be avoided here as far as possible and systematic names used instead.



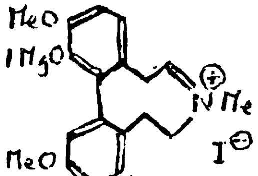
(XLII)



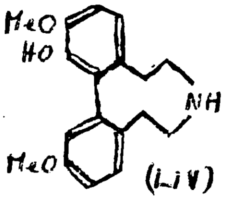
(XL)



(LII)



(LIII)



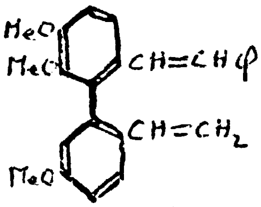
(LIV)

In the belief that the sequence of changes leading to phenyldihydrothebaine is initiated by the attack on the ether oxygen atom by $MgBr^{\ominus}$, Bentley and Robinson investigated the reaction between thebaine and anhydrous magnesium iodide. This yielded a substance, for which they suggested the structure (LIII) and which gave phenyldihydrothebaine when treated with phenylmagnesium bromide, but afforded no detectable amount of 4-methoxyphthalic acid on oxidation. Reduction with sodium in liquid ammonia was rapid but gave no definite product, whilst reduction with lithium aluminium hydride was vigorous, with the evolution of gas and with the production of a phenolic amine. The latter was thought by the authors[65] to be the secondary amine (LIV), but a reinvestigation of this product in the present work has shown it to be the desired amine (XLII).

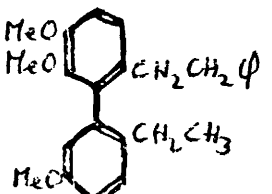
PART 1.

The Preparation of and Kinetic Racemisation Experiments on (+)-3,4-Dimethoxy-2-(5-methoxy-2-vinylphenyl)-stilbene and (+)-2-(Ethyl-5-methoxphenyl)-3,4-dimethoxydibenzyl.

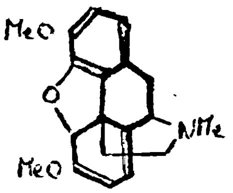
DISCUSSION.



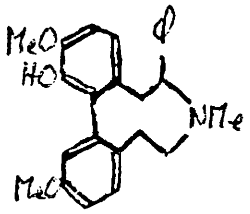
(XLIII)



(LI)



(XXVIII)



(XL)

The principle object was to prepare the sterically hindered biphenyl (+)-3,4-dimethoxy-2-(5-methoxy-2-vinylphenyl)-stilbene (XLIII) and to determine the values of E, $\log_{10}$ A, $\Delta S^{\ddagger}$, $\Delta H^{\ddagger}$, and $\Delta F^{\ddagger}$ for racemisation (p. 48, 84). The results would give additional information about the "buttressing" effect (p. 13) and the values obtained for the above thermodynamic constants could be compared to those obtained for related compounds.

The stilbene was prepared by a sequence of reactions from thebaine (XXVIII), proceeding via (+)-α-phenyldihydrothebaine (XL), its methylation product and Hofmann degradation thereof. The structures and properties of the compounds involved were all known, but many difficulties concerning the synthesis and the racemisation of the stilbene were encountered and required investigation. Information concerning the relationship of the structure of the stilbene to the ultraviolet spectrum was obtained and it was possible to make comparisons with related compounds.

By saturating the vinyl groups of the stilbene, (+)-2-(2-ethyl-5-methoxyphenyl)-3,4-dimethoxydibenzyl (LI) was obtained, and rates of racemisation were measured for this also.

The Preparation of (+)-3,4-Dimethoxy-2-(5-methoxy-2-vinylphenyl)-stilbene (XLIII).

The stilbene (XLIII) was prepared by treating thebaine with phenylmagnesium bromide, obtaining the (+)-α-phenyldihydrothebaine produced as its hydrochloride, and carrying out exhaustive methylation (two Hofmann degradations) on the methyl ether of the base.

(a) (+)-α-Phenyldihydrothebaine (XL).

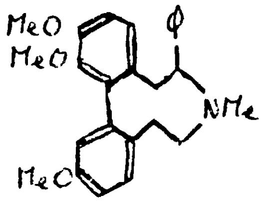
The Grignard reagent, phenylmagnesium bromide, was prepared in anhydrous ether solution by allowing bromobenzene and magnesium turnings to react together. Reaction with thebaine in benzene solution gave a mixture of (+)-α- and (+)-δ-phenyldihydrothebaine bases, the former predominating in quantity. The mixture was ultimately obtained as a purple syrup, which was converted into a mixture of the perchlorates and then crystallised from an acetone-ethanol mixture. The (+)-α-isomer was isolated by decomposing the perchlorate mixture and then converting the mixture of bases into the hydrochlorides; a precipitate of the less soluble (+)-α-phenyldihydrothebaine hydrochloride was obtained. This was laevorotatory in ethanol and melted over an extended temperature range. The precipitation of the hydrochloride was achieved by two methods, the second being that used in later preparations: (i) absolute ethanol saturated with dry hydrogen chloride was added to the mixture of the bases in ether solution[34] and (ii) dry hydrogen chloride was passed into an absolute ethanol solution of the mixture of the bases. After obtaining as complete precipitation as possible using both methods, attempts were made to isolate the (+)-δ-isomer, according to the method of Small, Sargent and Bralley[34], from the residual solutions, but in both cases, a very impure product only was obtained.

The hydrochloride prepared by method (i) was obtained in two crops, the second being obtained after evaporation of the filtrate, decomposition to the base, and reconversion into the hydrochloride. The second crop, which had a numerically higher specific rotation than the first, was again converted into the base and back into the hydrochloride, again giving two crops, the second being precipitated by dry hydrogen chloride. The first crop had a lower specific rotation, and the second an unchanged rotation. Elementary analysis of this second crop was satisfactory and showed it to be solvated with one molecule of ethanol of crystallisation. The original first crop of hydrochloride was converted into the base and dissolved in hot absolute ethanol. On cooling, a white crystalline solid was obtained, the liquors giving a second crop after three days at below 0°. This base was dextrorotatory in ethanol.

The first crop of the base, after a further crystallisation, was converted into the hydrochloride by passing hydrogen chloride through a solution in absolute ethanol. Two crops of this were obtained, the second after concentration of the mother liquor, but neither had as high a specific rotation as those obtained above.

The hydrochloride obtained by method (ii), had a specific rotation intermediate between those of the two initial crops prepared by method (i). It was regarded as being satisfactory, without further purification, for further stages in the synthesis, and this method was used in later preparations of this compound.

(b) (+)-α-Phenyldihydrothebaine Methyl Ether (LV).



(LV)

Several methods were used to prepare (LV) as its perchlorate, and all gave non-crystalline products whose appearance and melting point differed from that of the product obtained by Bentley and Robinson[65], who first prepared this compound. The methyl ether perchlorate was obtained later in two crystalline forms, one of which was similar in appearance to theirs and near it in melting point.

(i) The base was precipitated by the action of two equivalents of dimethyl sulphate in methanol solution on one equivalent of (+)-α-phenyldihydrothebaine hydrochloride in dilute sodium hydroxide solution, by a modification of Bentley and Robinson's method[65]. The perchlorate was obtained as an amorphous white solid. In two preparations, melting points of 139 and 140° were obtained and the infrared spectrum of the former product indicated some degree of solvation. Bentley and Robinson[65] obtained colourless plates, m.p.205 °. Some of the product, m.p. 140°, when recrystallised from the minimum amount of alcohol, gave an oil, which became a glass after drying overnight in an oven. This glass softened at 128 to 130°. Heating under vacuum and "crystallisation" from a variety of solvents gave no improvement in melting point, but "crystallisation" from aqueous ethanol, gave, after removing the oil which first separated out on cooling, an amorphous solid which melted at 128 to 139°. Elementary analysis gave results which were incompatible with those required by any reasonable formula, but they may have been caused by the suspected solvation.

The product m.p. 139° was converted into the base, which was treated with methyl iodide. The methiodide, obtained in good yield, was the same as that obtained by Bentley and Robinson[65], and by Small, Sargent and Bralley[34], as shown by the melting point and the specific rotation in 96% ethanol. The infrared spectrum showed the absence of a hydroxyl peak and elementary analysis was satisfactory. Hence the above perchlorate must have been a form of the required product, and later, after all other factors had been taken into consideration, this was the form of the perchlorate prepared when required.

(ii) (+)-α-Phenyldihydrothebaine hydrochloride (one equivalent) in sodium hydroxide solution and dimethyl sulphate (two equivalents) in methanol solution were heated under reflux for half an hour. An oil formed and the supernatant liquid was heated for a further period of time with more dimethyl sulphate. On cooling, an oil and solid separated. The perchlorate of the two combined was shown by infrared spectroscopy and a mixed melting point with (+)-α-phenyldihydrothebaine perchlorate to be a mixture of this and the perchlorate or the methyl ether.

Half of the oil obtained after the initial period of heating, was converted into the perchlorate which was shown by infrared spectroscopy and a mixed melting point to be the perchlorate of the starting material.

The remainder of the oil was allowed to react with a further quantity of dimethyl sulphate. The product isolated was converted into the perchlorate. The infrared spectrum, the specific rotation in 96% ethanol and a mixed melting point, indicated that this was a mixture of the perchlorates of the required product and of the starting material. Conversion into the base and reaction with methyl iodide gave a product in very poor yield, whose infrared spectrum was identical with and melting point similar to that obtained in (i) above.

(iii) Reaction in methanol solution with dimethyl sulphate in the presence of sodium methoxide, as used by Freund[56], gave a product of melting point 142 to 143°, after conversion into the perchlorate. Freund, however, prepared only the base. The infrared spectrum resembled that obtained for the product with m.p. 139° in (i); reconversion into the base and reaction with methyl iodide gave a methiodide in 55% yield, whose infrared spectrum was identical with and whose melting point was similar to those obtained in (i) and (ii) above. It appeared that this perchlorate was a form of the required product.

Some of the methyl ether perchlorate, prepared by method (i), was obtained in a crystalline form from a cooling ethanol solution, which had been seeded with some obtained previously on the small scale. A small quantity of a second crop was obtained, after concentration and seeding of the mother liquor, as colourless crystals which melted at 226 to 227°. Unfortunately, an attempted isolation of this at a later date failed. The first crop, after two further crystallisations, gave colourless plates, which melted at 197°. Elementary analysis gave good results. Bentley and Robinson[65] obtained colourless plates, which melted at 205°. Both of the crystalline perchlorates reacted with alkali with difficulty and subsequent reaction with methyl iodide gave a very poor overall yield. The melting points of both methiodides were similar to each other and to those obtained in (i), (ii), and (iii) above. In view of the difficulty encountered in trying to decompose the crystalline perchlorates with alkali and the poor yield of methiodide obtained, it was decided in future to omit this crystallisation and use only the amorphous materials as prepared in (i), when the perchlorate was required.

(+)-α-Phenyldihydrothebaine methyl ether methiodide was prepared from (+)-α-phenyldihydrothebaine hydrochloride by conversion into the methyl ether base as in method (i), followed by reaction with methyl iodide, without first isolating and purifying the methyl ether perchlorate. As good a product as that obtained by method (i) proceeding via the methyl ether perchlorate was obtained, as shown by infrared and melting point evidence and the specific rotation in 96% ethanol. For future work, this should be the adopted procedure.

The forms and characteristics of (+)-α-phenyldihydrothebaine methyl ether perchlorate may be summarised as follows:-

(i) A white non-crystalline form, for which poor analytical results were obtained, infrared spectroscopy indicating possible solvation. The apparently best sample had melting point of 142 to 143°, $[\alpha]_{5461}^{22.5}$ + 26.6°, $[\alpha]_{D}^{22.5}$ +20.3° (c, 0.56 in 96% EtOH). It reacted readily with alkali and gave the methiodide in good yield. Higher melting products were obtained, but appeared to be mixtures with the perchlorate of the starting material.

(ii) A crystalline form, white colourless plates, of melting point, 197°, $[\alpha]_{5461}^{22}$ +20.6°, $[\alpha]_{D}^{22}$ +18.8° (c, 0.27 in EtOH). Good elementary analysis was obtained. It did not react readily with alkali and the subsequent yield of the methiodide was low.

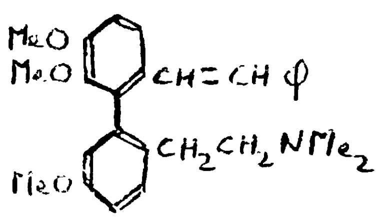
(iii) A crystalline form as a white solid, melting point 226 to 227°, $[\alpha]_{5461}^{22}$ +35.6°, $[\alpha]_{D}^{22}$ +34.4° (c, 0.23 in EtOH). It, too, did not react readily with alkali and gave a poor yield of the methiodide. An attempted isolation of this form at a later date failed.

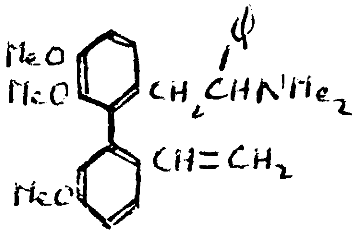
All three methiodides were the same compound.

Bentley and Robinson[65] obtained the perchlorate in the form of colourless plates, of melting point 205°, $[\alpha]_{D}^{21}$ +9.26° (in water, concentration unknown).

For future work, it is considered that it would be unnecessary to prepare the methyl ether perchlorate in any of its forms and that the methiodide could be obtained directly from the methyl ether base.

(c) The Methine Methiodides of (+)-α-Phenyldihydrothebaine Methyl Ether.


(LVI)

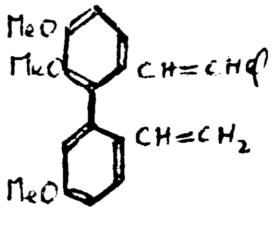

(LVII)

Bentley and Robinson[65] assume that a Hofmann degradation carried out on (+)-α-phenyldihydrothebaine methyl ether methiodide gives the normal-methine (LVI), but no reason is given for this assumption. A degradation on (+)-α-phenyldihydrothebaine methiodide itself gives a mixture of the normal- and iso-methines with the latter predominating[34]. It is not definately known why the normal-methine is not formed by the breaking of the nitrogen containing ring so that the double bond which is formed is in conjugation with the phenyl group of the vinylphenyl side chain as well as with the aromatic biphenyl nucleus[73]. However, Hofmann degradation involves the loss of a proton from the carbon atom in the β-position to the nitrogen atom and this is not under the influence of that phenyl group. Also, the environment on either side of the nitrogen atom is not the same[65]. Thus it seems unlikely that the degradation of the methyl ether methiodide would result in only the normal-methine, but should give at least mainly the iso-methine (LVII).

The degradation was carried out on the various methyl ether methiodide fractions, according to Freund's method[56]. These fractions were (i) a combination of various products, (ii) that obtained via the methyl ether perchlorate (m.p. 197°)

which had been "recrystallised" twice (p. 69), and (iii) that obtained directly from the base omitting the methyl ether perchlorate stage. In each case, the degradation product was allowed to react with methyl iodide, and evaporation of the reaction mixture gave a yellow solid and an orange oil. Recrystallisation from alcohol of the two combined gave orange needles, which were laevorotatory in alcohol. This was possibly the iso-methine methiodide and evaporation of the crystallisation liquors gave an orange oil, which, in (i) above was allowed to react with an additional quantity of methyl iodide, giving an orange coloured solid, which could not be satisfactorily crystallised. This may have been a mixture of the methiodides of the normal- and iso-methines.

(d) <u>(+)-3,4-Dimethoxy-2-(5-methoxy-2-vinylphenyl)-stilbene (XLIII)</u>



(XLIII)

A second Hofmann degradation was carried out on each of the crystalline methine methiodide products obtained above, and also on the non-crystalline product obtained from fraction (i) above, by the method of Bentley and Robinson[65]. After purification, each product was obtained as nearly colourless prisms, which were dextrorotatory in acetone solution. The specific rotations were the same within the limits of experimental error, and the melting points were similar. The infrared spectra were identical and confirmed the presence of the vinyl groups.

These results confirmed the view that it would be unnecessary to prepare the methyl ether perchlorate in future, especially, as a higher overall yield was achieved without it.

The ultraviolet spectrum of the stilbene obtained from the crystalline methine methiodide in (c) batch (iii) was determined, and an additional crystallisation gave a slight increase in melting point, satisfactory elementary analysis results, and only a small change in the ultraviolet spectrum (Fig. 3, p. 96).

Racemisation Experiments on (+)-3,4-Dimethoxy-2-(5-methoxy-2-vinylphenyl)-stilbene (XLIII).

The rate constant for racemisation depends on the energy of activation for configurational change (E) and on the non-exponential term, A, often called the frequency factor, of the Arrhenius equation:

$$k_{rac} = Ae^{-E/RT} \qquad (i).$$

For a first order reaction

$$k = \frac{2.303}{t} \log_{10} \frac{\text{initial concentration}}{\text{concentration at time } t}$$

If optical rotation is used as a measure of concentration,

$$k = \frac{2.303}{t} \log_{10} \frac{\alpha_0 - \alpha_\infty}{\alpha_t - \alpha_\infty},$$

where α_t is the optical rotation of the solution at time t, α_0 is that at time zero, and α_∞ is that at the completion of the process, i.e. at complete racemisation. Since $\alpha_{\infty} = 0$

$$k_{rac} = \frac{2.303}{t} \log_{10} \frac{\alpha_0}{\alpha_t}.$$

On plotting t against $\log_{10} \alpha_t$, a straight line is obtained, where $k_{rac} = \frac{-2.303}{\text{slope}}$.

The half-life, $t_{\frac{1}{2}} = \frac{\log_{10} 2 \times 2.303}{k_{rac}}$.

From equation (i), $\log_{10} A = \log_{10} k_{rac} + \frac{E}{4.576T}$ (ii)

(R = 1.987 cal./deg. mole),

and on plotting k_{rac} against 1/T, a straight line of slope $-\frac{E}{4.576}$ is obtained, and hence $\log_{10}$ A, which is best calculated at each temperature at which rates are measured. The mean value is then taken.

The entropy of activation $\Delta S^{\ddagger}$, may be obtained from Glasstone, Laidler and Eyring's equation[76]:

$$k_{rac} = \kappa(kT/h)e^{-\Delta F^{\ddagger}/RT} \qquad \text{(iii)}$$
$$= \kappa(kT/h)e^{-\Delta H^{\ddagger}/RT}\, e^{\Delta S^{\ddagger}/R}$$

in the form $\Delta S^{\ddagger} = 4.576 \log_{10} (k_{rac}/T) + E/T - 49.20$, where $\Delta F^{\ddagger}$ is the change in standard free energy and $\Delta H^{\ddagger}$ the change in enthalpy on reaching the transition state. κ, the transmission coefficient, is taken as unity; the Boltzmann constant, $k = 1.380 \times 10^{-16}$ erg/deg., and Planck's constant $h = 6.624 \times 10^{-27}$ erg sec. $0^{\circ}C = 273.2^{\circ}K$.

$$\Delta H^{\ddagger} = E - RT$$

$\Delta F^{\ddagger}$ is calculated from equation (iii) in the form;

$$\Delta F^{\ddagger} = 47.22T - 4.576T \log_{10} (k_{rac}/T).$$

According to Bentley and Robinson[65], (+)-3,4-dimethoxy-2-(5-methoxy-2-vinylphenyl)-stilbene (XLIII) racemises at 130° in 10 minutes, and so a solvent was required which would not boil at this temperature, was readily available and could be purified easily. p-Cymene satisfied these requirements.

Kinetic runs were carried out between 100 and 129° in p-cymene solution, and as a straight line was not obtained on plotting t against $\log_{10} \alpha_t$ at each temperature, it became obvious that a reaction, in addition to racemisation, was taking place. As the stilbene is highly unsaturated, this was then assumed to be one of polymerisation. On prolonged heating at 129°, laevorotatory solutions were obtained and the impure racemate and a polymer were isolated. The nature of these were suggested by infrared spectroscopy, the presence of the racemate being confirmed by isolation of the pure compound later.

After 15 minutes at 130°, the dry (+)-stilbene gave a dextrorotatory solution after extraction with either acetone or p-cymene, together with a white insoluble residue, which was presumably polymeric. The solutions were of a mixture of racemate, the optically active compound, and polymer. These were isolated from the p-cymene solution and identified by either melting point or infrared spectroscopy. Bentley and Robinson[65] stated that after 10 minutes at 130°, a substance was obtained which was optically inactive in acetone, together with what was presumably a polymer. The optical activity here was very low in acetone solution after the heating, and this they presumably mistook for optical inactivity.

Polymerisation in solution must take place before racemisation, as ultimately a laevorotatory solution was obtained. When heating is carried out in p-cymene solution, the polymer remains in solution, but when carried out on the solid, the polymer is only sparingly soluble. Thus, either it is more difficult to get this sparingly soluble substance into solution than to keep it there once it is formed, or the polymer may not be the same species in both cases.

Polymer formation is not prevented by heating the solid under nitrogen, but a number of studies of the prevention of polymerisation of styrene and related compounds by various inhibitors have been made[77,78]. It was decided that 10% of the weight of the optically active compound of either picric acid or trinitrobenzene[78], when added to a p-cymene solution, would be suitable, as neither would give too intense a colour at this concentration. Also, this concentration should not effect the rates of racemisation[79]. Prolonged heating of these solutions at 130° produced complete racemisation only and the purified racemate was obtained after removal of the solvent and recrystallisation of the residues. The infrared spectra so obtained were used to confirm the presence of the racemate isolated in the earlier experiments.

Kinetic Racemisation Experiments on the Stilbene in the Presence of a Polymerisation Inhibitor.

A series of kinetic runs were carried out between 101° and 135° on a p-cymene solution containing 1.5% of the (+)-stilbene and 0.15% of trinitrobenzene ($\lambda = 5890 Å$). The latter was used as a polymerisation inhibitor rather than picric acid, as it coloured the solution to a lesser degree. The technique used was that described on p. 83.

On plotting the logarithm of the rotation against time at each temperature, deviations of the points from the straight line were negligible (Fig. 1, p. 91), and duplicate experiments, when carried out, agreed well with one another. Hence it was apparent that only one reaction, namely racemisation, had occurred.

The following results were obtained:-

$E = 25.8$ kcal. mole^{-1}, $\Delta H^{\ddagger} = 25.0$ kcal. mole^{-1},

$\log_{10} A = 10.6$ sec^{-1}., $\Delta F^{\ddagger} = 30.1$ kcal. mole^{-1} at 135.3°.

$\Delta S^{\ddagger} = -12.5$ e.u.,

As $\Delta F^{\ddagger}$ is temperature dependent, the value recorded was that obtained at the highest temperature, 135.3°, at which a kinetic run was performed.

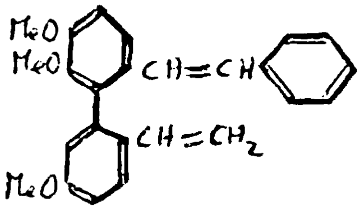
The pure racemate was isolated and after two crystallisations from methanol (43% recovery), melted at 123.5-124°. The ultraviolet spectrum was similar to that of the (+)-stilbene. A further crystallisation increased the melting point to 125°.

Bentley and Robinson[65] obtained 124°. The ultraviolet spectrum (Fig. 3, p. 96) changed little and closely resembled that of the optically active stilbene and satisfactory elementary analytical results were obtained.

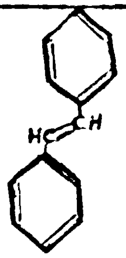
A chromatographic separation of the residue obtained by evaporation of the mother liquor from the first crystallisation gave a further small quantity of impure racemate.

It was apparent from analytical, melting point, ultraviolet spectral evidence and earlier infrared evidence, that racemisation only had occurred during the kinetic experiments.

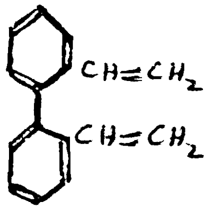
Discussion of the Ultraviolet Spectrum of the Stilbene (XLIII).



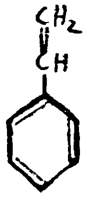
(XLIII)



(LVIII)



(LIX)



Styrene

The ultraviolet spectra of the (+)- and (±)-stilbenes (XLIII) should have been identical, the differences obtained presumably being due to experimental errors and to the previous treatment of the samples. After considering all factors involved, the true spectrum of the stilbene is regarded as being that of the (+)-isomer.

The long-wave bands (table 4) in the spectrum of trans-stilbene (LVIII) originate in an Ar-CH=CH- chromophore[80]. It is reasonable to assume that this is also true in the case of the substituted stilbene (XLIII), with effects due to the phenoxy partial chromophores.

Table (4)

Ultraviolet Absorption Spectra of the (+)- and (±)-Stilbenes (XLIII) and of trans-Stilbene (LVIII) in 96% Ethanol.

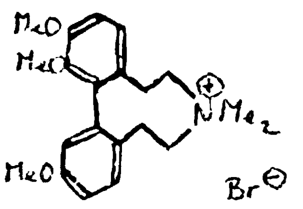
	The (+)-Stilbene.		The (±)-Stilbene.		trans-Stilbene[80].	
	λ_{max} (mμ)	ε	λ_{max} (mμ)	ε	λ_{max} (mμ)	ε
Long-wave bands			(320)	25,200	(321)	ca. 17,600
	311	27,000	310.5	26,450	307.5	28,300
					295.5	29,000
Short wave bands	(ca. 250)	22,900	(ca.250)	22,850		
	(ca. 240)	25,400	(ca.240)	25,300		
			(239)	25,700	(236)	ca. 11,100
					228.5	16,400
	(ca. 230)	27,300	(ca.225)	28,500		
					222	ca. 14,900
	205.5	38,100	205.5	37,250	210	?
	λ_{min} (mμ)	ε	λ_{min} (mμ)	ε		
	282.5	18,300	282.5	18,100		

Figures in parentheses denote points of inflection.

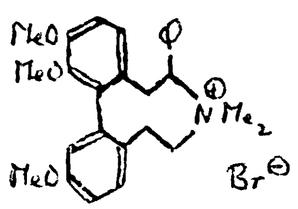
Styrene[81] and 2,2'-divinylbiphenyl[82] (LIX) have respectively three and two bands, due to styrene-like conjugation, in the 285 mμ region. The intensities of the bands in the latter spectrum (1870 and 1340) are about twice those of the corresponding bands in the former (790 and 615), but this is not so in the 250 mμ region, where these compounds have three bands each, also due to styrene-like conjugation, the bands in the former being of intensity 15,500, 15,800 and 9,800, and those of the latter 25,000, 24,000 and 17,000. The intensity of the inflection at 250 $m\mu$ (ϵ *ca.* 22,900) in the spectrum of the stilbene (XLIII) is also less than twice the intensities of the bands in this region for styrene.

The substituted stilbene (XLIII) and *trans*-stilbene each have a point of inflection in the 240 $m\mu$ region of their spectra.

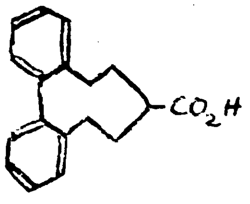
An inflection at 235 $m\mu$ (ϵ 25,300) in the spectrum of (LIX), has been attributed[82] to the vestigial conjugation band of a hindered di-*o*-substituted biphenyl (*cf.* 2,2'-dialkylbiphenyls[83], p. 10). This inflection occurs at *ca.* 230 $m\mu$ for the substituted stilbene, the lesser degree of conjugation presumably being due to the "buttressed" *ortho*-methoxyl group. This conjugation must be comparable to that between the benzene rings in the bridged biphenyls (LX), (LXI) and (V), where the conjugation bands appear at λ_{inf} *ca.* 225 (ϵ 22,050), *ca.* 230 (ϵ 26,900) [p. 124] and 231 $m\mu$ (ϵ 5,550)[33], respectively, although enhancement of the intensities due to the presence of the methoxyl groups occurs in all except that of (V).



(LX)



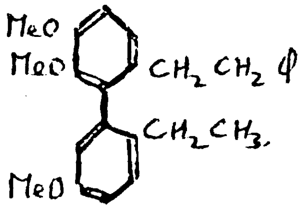
(LXI)



(V)

The bands of the substituted stilbene and of *trans*-stilbene in the 205 and 210 $m\mu$ regions are due to the benzene chromophores.

The Preparation of (+)-2-(2-Ethyl-5-methoxyphenyl)-3,4-dimethoxydibenzyl (LI).



(LI)

Three hydrogenations of (+)-3,4-dimethoxy-2-(5-methoxy-2-vinylphenyl)-stilbene (XLIII) were carried out using a hydrogen pressure of one atmosphere in the presence of a palladium-charcoal catalyst: (a) at room temperature, according to the method of Bentley and Robinson[65], (b) at -30 to -25°, as it was suspected that partial racemisation might have occurred in (a), and (c) at room temperature again on a larger scale, to see if the absorption of hydrogen was proportional to the quantities of the reactants, as it was suspected that complete hydrogenation of the vinyl groups had not occurred. None of these suspicions was confirmed, and method (a) was that used for later preparations.

The hydrogenation at room temperature gave an oil of low optical activity, but in very high yield. Elementary analysis gave acceptable results. However, the volume of gas used for the hydrogenation, appeared to be less than that theoretically required.

The product prepared at -30 to -25° was optically stable at -19° and at various temperatures up to 21.5°, although the specific rotation decreased with increase in temperature.

However, the original value was obtained again on returning to -19°. Thus in the preparation at room temperature, no partial racemisation could have occurred, or a labile asymmetric centre have been set up.

By scaling up the quantities used originally at room temperature, it was found that the quantity of hydrogen taken up was not increased proportionally and that the amount of gas absorbed was not the sum of that used in a blank experiment without the stilbene and the theoretical amount required for the hydrogenation. As palladium forms Pd_2H under a pressure of one atmosphere of hydrogen, which may be a mixture of two immiscible solid solutions or an interstitial compound[84], it seems possible that some of this hydrogen might be used in the hydrogenation without the reabsorption by the catalyst of an equivalent amount.

The infrared spectra of all the products were the same. The peaks at 10.32, 10.90, and 11.10 μ in the spectrum of the (+)-stilbene, assumed to be due to -CH=CH- (p. 79), were absent.

Additional preparations were carried out using method (a) and the products combined with that from (c).

Absorption occurred in the ultraviolet spectrum (Fig.10, p. 170) at λ_{max} 279 mμ (ϵ 4,450) and was due to the phenoxy partial chromophores (*cf.* the bridged biphenyls (LX) and (LXI) [p. 124; fig. 8, p. 160]). The vestigial conjugation band appeared at λ_{inf} *ca.* 227.5 mμ (ϵ 17,800) with minimum absorption at λ_{min} 252 mμ (ϵ 829). (*cf.* (LX), (LXI), (V), the stilbene (XLIII) and 2,2'-divinylbiphenyl (LIX) [p. 53]). Overlapping by the band due to the benzene chromophore at λ_{max} 201 mμ (ϵ 64,500) occurred. The band appearing at 311 mμ in the spectrum of the stilbene due to the combined effects of the Ar-CH=CH- and phenoxy partial chromophores was absent. Hydrogenation of the vinyl groups of (XLIII) is therefore complete and the spectrum of the product as expected.

Kinetic Racemisation Experiments on the (+)-Dibenzyl.

The dibenzyl was optically stable in p-cymene solution at 160°, but it was found to racemise at 175°. This solvent was thermally unstable at 200° and as it was clear that kinetic experiments would have to be done at up to 220°, another solvent was required. β-Phenylethyl alcohol was found to be suitable.

Kinetic racemisation experiments were carried out at 181 to 224°, using a 4.01% solution and λ=5461 Å, as described on p. 83. On plotting $\log_{10} \alpha_t$ against t, deviations of the points from the straight line were negligible. The following results were obtained:

$E = 33.45$ kcal. mole^{-1}, $\Delta H^{\ddagger} = 32.5$ kcal. mole^{-1},

$\log_{10}A = 11.4$ sec^{-1}., $\Delta F^{\ddagger} = 37.2$ kcal. mole^{-1}

$\Delta S^{\ddagger} = -9.42$ e.u., at 223.6°.

The fractions of solution obtained in the above experiments were combined and heated under vacuum until optically inactive. The racemate was recovered in 80% yield and elementary analysis gave good results. The infrared spectrum was identical with that of the active compound, and from this information, and the type of graphs obtained, showed that racemisation only had occurred.

EXPERIMENTAL

The Preparation of (+)-3,4-Dimethoxy-2-(5-methoxy-2-vinylphenyl)-stilbene (XLIII).

This was prepared by a multistage process from thebaine (XXVIII) as follows.

(a) (+)-α-Phenyldihydrothebaine (XL)

The method of preparation was that of Small, Sargent and Bralley[34]. Phenylmagnesium bromide was prepared as follows. Redistilled bromobenzene (51.6 g.) was dissolved in sodium-dried ether (100 c.c.). About a quarter of this solution was added to magnesium turnings (10.8 g.) and sodium-dried ether (65 c.c.), care being taken to exclude moisture. A crystal of iodine was added and the mixture was warmed a little to start the reaction. Once this had occurred, the remainder of the bromobenzene solution was added at a rate sufficient to keep the ether refluxing. The mixture was heated under reflux for 15 min., and then as much of the ether as possible was removed leaving behind a dark-brown solution.

Sodium-dried benzene (100 c.c.) was added to the phenylmagnesium bromide solution, and heated under reflux on a water bath. A solution of thebaine (50 g.) in warm sodium-dried benzene (950 c.c.) was added slowly with stirring over a period of two hours. Heating under reflux was continued for a further six hours; then the solution was cooled and poured into excess saturated ammonium chloride solution.

The aqueous layer was separated and extracted several times with benzene, and the combined benzene solutions were extracted several times with 2N HCl. The acid extracts were rendered alkaline, in the presence of ether, with dilute ammonium hydroxide solution. A little sodium metabisulphite was added, and after shaking, the two solvent layers were separated from one another. The aqueous layer was extracted twice more with ether and the combined ether extracts were dried and the solvent evaporated, leaving behind a purple syrup.

The Perchlorate.

The syrup was dissolved in absolute alcohol (75 c.c.) and treated, until acid to litmus, with alcoholic perchloric acid, which was made up by adding 27.5 g. (16.2 c.c.) of 60% aqueous perchloric acid to 60 g. (76 c.c.) of ice-cold absolute alcohol. It was allowed to stand overnight and the purple crystals which formed were filtered off, washed with two portions of absolute alcohol (37.5 c.c. each) to remove some of the colour, and extracted with ether, giving 74 g. (94%) of very pale violet coloured crystals, m.p. 246°. Small, Sargent and Bralley, loc. cit., give m.p. 248°. These crystals consisted of the perchlorate of (+)-α-phenyldihydrothebaine together with a little of that of the (+)-δ-isomer.

The perchlorate mixture (4 g.) was recrystallised from acetone-ethanol mixture giving 1.2 g., $[\alpha]_{5461}^{21}$ +5.60°, $[\alpha]_{D}^{21}$ +4.60°, (c, 0.98 in acetone).

0.5 G. of this was twice recrystallised from ethanol, giving 0.15 g., m.p. 246°, $[\alpha]_{5461}^{21}$ +6.66°, $[\alpha]_D^{21}$ +5.00° (c, 0.60 in acetone). $[\alpha]_{5461}^{21}$ +40.7°, $[\alpha]_D^{21}$ +35.6° (c, 0.20 in 96% ethanol).

Small, Sargent and Bralley obtained perchlorate with $[\alpha]_D^{20}$ +8.2° (c, 0.98 in acetone); $[\alpha]_D^{26}$ +35° (c, 0.21 in ethanol). Berson and Greenbaum[70] obtained perchlorate with $[\alpha]_D^{32}$ +39° (c, 0.21 in 95% ethanol); $[\alpha]_D^{32}$ +8.6° (c, 0.94 in acetone).

In our hands recrystallisation effected little improvement in specific rotation.

227.5 G. of the perchlorate mixture were prepared altogether at an average yield of 83% (the original authors: 89%).

The Hydrochloride.

The prepared perchlorate was known to contain a small proportion of the (+)-δ-isomer. Separation of the two was dependent on conversion of the perchlorate mixture into a mixture of the hydrochlorides and on the relative insolubility of the (+)-α-compound in anhydrous ethanol. The perchlorate mixture was first converted into a mixture of the bases and the (+)-α-phenyldihydrothebaine hydrochloride was precipitated by two different methods: (i) in which absolute ethanol saturated with hydrogen chloride was added to the bases in ether solution, and (ii), in which dry hydrogen chloride was passed into an absolute alcohol solution of the bases.

It was not possible to obtain the (+)-δ-isomer in a pure form by either method, presumably owing to incomplete precipitation of the (+)-α-isomer, but method (ii) was that used for subsequent preparations of (+)-α-phenyldihydrothebaine hydrochloride.

(i) Precipitation by Ethanolic Hydrogen Chloride. (Small, Sargent and Bralley[34].)

The perchlorate crystals (69 g.) were stirred with dilute ammonium hydroxide solution and extracted with ether. The aqueous solution was extracted twice more and the combined extracts dried over calcium chloride and then acidified with absolute ethanol saturated with hydrogen chloride. This was left overnight in the refrigerator and a mass of whitish crystals, a purple oil and an ethereal-alcoholic solution were obtained. The solution was poured off and the residue washed with two small amounts of dry ether, the washings and solution being combined and set aside. The residue was shaken with a little ice-cold dry methanol, which converted the oil into a further mass of white crystals all of which were filtered off and washed with two small quantities of ice-cold dry methanol. The white crystals obtained were those of (+)-α-phenyldihydrothebaine hydrochloride.

The solution was evaporated down to near dryness and the residue was dissolved in dilute ammonia solution and extracted with ether. The extracts were then re-acidified with HCl in absolute ethanol, kept at 0° for three hours, and the white crystals obtained were filtered off and washed with ice-cold dry methanol. These consisted of more of the (+)-α-compound which had been left in solution. The filtrate was put aside in order to attempt the isolation of (+)-δ-phenyldihydrothebaine.

Yield:- 1st. crop, 24.5 g., m.p. 175-184°, $[\alpha]_{5461}^{22}$ -9.4°,
$[\alpha]_{D}^{22}$ -7.43° (c, 1.01 in water).
2nd. crop, 24.0 g., m.p. 175-184°, $[\alpha]_{5461}^{22}$ -16.0°,
$[\alpha]_{D}^{22}$ -12.6° (c, 1.00 in water).
Total, 48.5 g. (76% from thebaine).

The specific rotation and melting point were not mentioned by the authors.

The second crop (22.2 g.) was stirred with ammonia, extracted with ether, and the extracts were dried overnight over calcium chloride. Hydrogen chloride dissolved in absolute alcohol was added and the resulting mixture was cooled in the refrigerator for five hours in a stoppered flask. The white solid which had formed was filtered off, washed with ice-cold methanol, and dried. Yield, 10.1 g. $[\alpha]_{5461}^{22}$ -11.9°, $[\alpha]_{D}^{22}$ -9.46° (c, 1.00 in water).

The filtrate was evaporated, extracted with ether and the syrupy residue was dissolved in acetone, which was removed under vacuum, in an attempt to obtain a crystalline solid. An attempt at recrystallisation from absolute alcohol in a stoppered flask also failed to give a crystalline solid. It was reconverted into the base and the syrup was dissolved in the minimum amount of

absolute alcohol. Dry HCl was passed through it for 4 hr. and it was then placed in the refrigerator overnight. The solid produced, after filtering, was washed with dry methanol, giving an off-white solid, 0.6 g.
$[\alpha]^{21}_{5461}$ -15.5°, $[\alpha]^{21}_{D}$ -13.0° (c, 1.00 in water).
Elementary analysis indicated that the compound was solvated with one molecule of ethanol of crystallisation. (Found: C, 68.9; H, 7.0; Cl, 7.7; N, 2.9; O, 13.5. Calculated for $C_{25}H_{28}ClNO_3$ + C_2H_5OH: C, 68.7; H, 7.3; Cl, 7.5; N, 3.0; O, 13.6%).

The original first crop of hydrochloride (16.5 g.) was converted into the base and the combined ether extracts obtained were evaporated, giving a pale yellow glass. This was dissolved in absolute alcohol and then cooled in the refrigerator, giving a white crystalline solid, 10.5 g. A second crop (5.5 g.) of the base was obtained from the filtrate after 3 days' standing in the refrigerator. $[\alpha]^{22}_{5461}$ +5.65°, $[\alpha]^{22}_{D}$ +5.15°, (c, 2.04 in ethanol). Small, Sargent and Bralley[34] obtained m.p. 40-70°, $[\alpha]^{20}_{D}$ +10.2°, (c, 1.98 in ethanol).

The first crop of base was again crystallised, giving a mass of white prisms, 9.5 g., $[\alpha]^{22}_{5461}$ +7.05°, $[\alpha]^{22}_{D}$ +6.81°,(c, 1.98 in ethanol). 8.5 G. of this was dissolved in the minimum quantity of absolute alcohol and dry hydrogen chloride was passed through the solution for nine hours. After being left in the refrigerator overnight, the liquid was decanted from the solid which had formed at the bottom of the flask and the latter was transferred to a Buchner funnel, where it was sucked as dry as possible, and the drying completed in a warm oven. Yield, 4.0 g. $[\alpha]^{21}_{5461}$ -9.75°, $[\alpha]^{21}_{D}$ -8.30° (c, 1.03 in water).

The mother liquors were evaporated to about one-third bulk and cooled to ca. 0°. More of the hydrochloride, 4.5 g. was obtained, after filtering and washing with light petroleum (b.p. 40-60°), giving a total of 8.5 g. (theoretical yield, 9.3 g.). $[\alpha]^{21}_{5461}$ -7.88°, $[\alpha]^{21}_{D}$ -6.90° (c. 1.01 in water).

(ii) Precipitation by Dry Hydrogen Chloride.

The perchlorate mixture (66 g.) was converted into the mixture of the bases as before, and the ether extract was dried over calcium chloride overnight before removal of the solvent. The solid was dissolved in the minimum quantity of absolute alcohol, and dry HCl was passed through the solution for about ½ hr., by which time it had set nearly solid. The flask was stoppered and placed in the refrigerator overnight. The solid was filtered off, washed with cold dry methanol and the filtrate set aside for the attempted isolation of the (+)-δ-isomer. Yield, 55.0 g. (81.5% from thebaine). $[\alpha]^{21}_{5461}$ -12.8°, $[\alpha]^{21}_{D}$ -10.0° (c, 1.05 in water).

This was regarded as being a satisfactory method of preparation and altogether 191.5 g. were prepared at an average yield from thebaine of 70.5%.

(+)-δ-Phenyldihydrothebaine.

The isolation of this compound was attempted on each of the solutions obtained above after the completed precipitation of (+)-α-phenyldihydrothebaine hydrochloride. This was done according to the method of Small, Sargent and Bralley[34].

Each solution was evaporated giving a brown syrup. An aqueous solution of the syrup was rendered alkaline with dilute aqueous ammonia and extracted with ether. The residue from the evaporated extract was stirred with a small amount of ethanol, but it did not crystallise. Crystallisation was attempted from various solvents, but without success. Extraction by various light petroleum fractions was of no avail. Reconversion into the hydrochloride and filtering off the small amount of precipitated (+)-α-compound before conversion into the base again was of no use. The gum finally obtained from the treated filtrate from (i) above had the following properties: it softened at about 79°, $[\alpha]^{23}_{5461}$ -35.4°, $[\alpha]^{23}_{D}$ -27.6° (c, 0.73 in acetone). The original authors obtained white needles, m.p. 143.5°, $[\alpha]^{20}_{D}$ -131° (c, 0.87 in acetone).

It appeared that there must have been some (+)-δ-compound present, but in an extremely impure state.

(b) (+)-α-Phenyldihydrothebaine Methyl Ether (LV).

The perchlorate of the methyl ether (LV) was prepared by several methods, and all gave non-crystalline products. The compound was obtained later in two crystalline forms, which were found to be of little synthetic value. Method (i) below was found to be the best method of preparation, but purification through the perchlorate was found to be unnecessary in later preparations of the stilbene.

The (+)-α-phenyldihydrothebaine hydrochloride, where used below, was that prepared by method (ii) above.

(i) <u>Preparation of the Methyl Ether Perchlorate by a Modification of the Method of Bentley and Robinson^{65}.</u>

(+)-α-Phenyldihydrothebaine hydrochloride (7 g., one equivalent) was dissolved in warm water (33 c.c.). After cooling, excess 10% sodium hydroxide solution (100 c.c.) was added, which, during the addition, gave initially a precipitate which then redissolved. A solution of dimethyl sulphate (3.1 c.c., two equivalents) in methanol (8 c.c.) was added slowly with stirring, which gave a white gummy precipitate. This was filtered off, washed with water and dried in an evacuated desiccator. Yield, 6.0 g. (90.5%). The base was dissolved in the minimum amount of warm ethanol, cooled, and 60% perchloric acid (5 c.c.) was added, followed by water, until no further precipitation was observed. The solid perchlorate was filtered off, recrystallised once from dilute perchloric acid, and twice from water containing the minimum amount of alcohol for complete solution. Yield of perchlorate: 4.5 g. (54% from the phenolic hydrochloride). M.p. 139°, $[\alpha]^{22}_{5461}$ +23.3°, $[\alpha]^{22}_{D}$ +20.8°, (c, 1.01 in 96% ethanol). $[\alpha]^{22}_{5461}$ +1.00°, $[\alpha]^{22}_{D}$ +0.05°, (c, 1.00 in acetone).

The solubility in water was too low to determine the specific rotation in this solvent.

Bentley and Robinson obtained colourless plates m.p. 205°, $[\alpha]^{21}_{D}$ +9.26° (in water, concentration unknown).

The I.R. spectrum of the perchlorate showed a broad band with two peaks in the 3 μ region which may have been due to solvation; it showed peaks at about 9.2 and 16.1 μ in common with many inorganic perchlorates.

A further quantity of perchlorate (8 g.) was prepared from (+)-α-phenyldihydrothebaine hydrochloride (14 g.) by the above method. It had m.p. 140°. A small amount of this perchlorate was crystallised from the minimum amount of ethanol, giving an oil, which, after drying overnight in an oven, gave a light brown glass which softened at about 128-130°. "Recrystallisation" from a variety of solvents and solvent mixtures, and heating under vacuum at 134° for 3½ hr. gave solids with no increase in m.p. above 140°. Some was "recrystallised" again from water containing a little ethanol, and the solution was decanted from the oil which first formed on cooling. The solid obtained on further cooling was again treated in this way. The final white solid obtained had m.p. 128-139°. Elementary analysis gave an anomalous result for carbon. (Found: C, 59.9; H, 6.4; Cl, 7.0. Calculated for $C_{26}H_{30}ClNO_7$: C, 62.0; H, 6.0; Cl, 7.0%).

The perchlorate, m.p. 139° (1.0 g.) was dissolved in glacial acetic acid and then shaken with ammonium hydroxide (s.g. 0.880) and ether, the base being extracted by the solvent as it was formed. The aqueous layer was extracted twice with ether and a solid residue which had formed on the addition of the ammonia was redissolved in acetic acid and treated again.

The ether solutions were combined and the solvent removed.

Methyl iodide (2 c.c.) and acetone (6.5 c.c.) were added to the base and heated under reflux for 4 hr., methyl iodide (*ca.* 1 c.c.) being added every hour. A white crystalline precipitate was obtained on concentrating the solution slightly, and was filtered off, washed with acetone and dried. Yield, 0.85 g. (79%), m.p. 190°. (Yield from (+)-α-phenyldihydrothebaine hydrochloride, 43%).

The methiodide was recrystallised from absolute ethanol, giving colourless plates, 0.75 g., m.p. 201°. Further crystallisation gave no increase in melting point. $[\alpha]^{22.5}_{5461}$ +26.3°, $[\alpha]^{22.5}_{D}$ +18.5° (c, 0.32 in 96% ethanol). (Found: C, 59.8; H, 5.9; I, 23.55. Calculated for $C_{27}H_{32}INO_3$: C, 59.45; H, 5.9; I, 23.3%). The infrared spectrum showed the absence of a hydroxyl peak.

Bentley and Robinson[65] obtained a product of m.p. 205°. Small, Sargent and Bralley[34] methylated (+)-α-phenyldihydrothebaine with diazomethane, and then prepared a methiodide with m.p. 196-197.5°, $[\alpha]^{28}_{D}$ +20.7° (c, 0.34 in ethanol).

A further 22.8 g. of perchlorate were obtained after two "crystallisations" from aqueous ethanol only; 15.2 g. were converted into the methiodide, giving 9.86 g., m.p. 197°.

(ii) Preparation of the Methyl Ether Perchlorate at Elevated Temperatures.

(+)-α-Phenyldihydrothebaine hydrochloride (3.5 g.), dissolved in water (16.5 c.c.) and excess 10% sodium hydroxide solution (50 c.c.), was heated under reflux for ½ hr. with a solution of dimethyl sulphate (1.6 c.c., 2 equivalents) in methanol (4 c.c.). The supernatant liquid was run off from the oil, which had formed during the period of heating, and treated as follows.

A further quantity of dimethyl sulphate (2 c.c.) was added and the solution was heated under reflux for a further 3 hr., extra dimethyl sulphate (1 c.c.) being added every ½ hr. On cooling, an oil and some solid appeared, which were dissolved in warm dilute perchloric acid. The resulting solution was filtered, cooled, and diluted with water until no further precipitation occurred, and this solid perchlorate was "recrystallised" from dilute ethanol, after the addition of a little decolourising carbon. A chocolate brown solid, 0.4 g., m.p. 208-210° was obtained. A mixed m.p. with (+)-α-phenyldihydrothebaine perchlorate (m.p. 246°) was 218°. The I.R. spectrum of the product was different from that of this perchlorate and resembled that of the product m.p. 170° below. The product m.p. 208-210° was probably a mixture of the perchlorates of the methyl ether and the starting material.

About half of the oil obtained after the first period of heating was washed twice with 10% sodium hydroxide solution and converted into the perchlorate and "crystallised" as above, giving a buff coloured solid. Yield 0.8 g., m.p. 247.5°. A mixed m.p. with (+)-α-phenyldihydrothebaine perchlorate gave no depression and the I.R. spectrum was identical with that of this compound.

The rest of the oil obtained, after the first period of heating, plus 10% sodium hydroxide solution (25 c.c.), water (8 c.c.) and dimethyl sulphate (2 c.c.), together with sufficient ethanol to keep all in solution, was heated under reflux for 4 hr. Dimethyl sulphate (ca. 1 c.c.) was added every ½ hr. A white precipitate (probably sodium sulphate) gradually formed, and after cooling the mixture, was filtered off. The ethanol was then removed from the solution and a brown precipitate was obtained, which was converted into the perchlorate, as above, but "crystallised" twice. A pale brown solid, 1.8 g. (ca. 87%), m.p. 170°, was obtained. Further crystallisation did not improve the m.p. $[\alpha]_{5461}^{22.5}$ +39.1°, $[\alpha]_{D}^{22.5}$ +33.8°, (c, 0.665 in 96% EtOH). A mixed m.p. with (+)-α-phenyldihydrothebaine perchlorate was 192-220° and this, together with the specific rotation, suggests that the product may have been a mixture of the perchlorates of the methyl ether and the starting material. This suggestion was supported by I.R. evidence. The spectrum of the product was different from that of (+)-α-phenyldihydrothebaine perchlorate, peaks at 10.8, 12.0 and 12.9 μ being either very small or absent, but was similar to that of the product m.p. 208-210° above. It resembled that of the product in (i) m.p. 139°, but was not as clear in the 10.5-15.0 μ region.

The product m.p. 170° (0.15 g.) was converted into the methiodide as in (i), using acetone (1 c.c.) and methyl iodide (1 c.c.). Yield 0.05 g. (31%, 27% calculated from (+)-α-phenyldihydrothebaine hydrochloride). Recrystallisation from absolute ethanol gave colourless plates, m.p. 196°. The I.R. spectrum was identical with that of the methiodide obtained in (i).

(iii) Preparation of the Methyl Ether in the Presence of Sodium Methoxide. Adapted from the method of Freund[56] who prepared the base only.

Sodium (0.2 g.) was dissolved in methanol (10 c.c.) and (+)-α-phenyldihydrothebaine base (2 g.) and dimethyl sulphate (1 c.c.) were added. After standing overnight, the excess methanol was removed, water was added and the solution obtained was evaporated to near dryness. The residue was dissolved in dilute acetic acid and the required product was precipitated by the addition of dilute sodium hydroxide solution. This was repeated once more and the perchlorate prepared and "recrystallised" from aqueous ethanol, giving a pale brown solid, 0.7 g. (27%), m.p. 142-143°. This was dissolved in aqueous ethanol at a little above room temperature and slowly cooled to about -10°. A white solid was obtained, but with no improvement in m.p. The I.R. spectrum was similar to those of the products obtained in (ii) of m.p. 208-210° and 170°, and resembled that of the product in (i) m.p. 139°, but was a little less clear. Peaks at 10.8 and 12.9 μ were present, as in the spectrum of (+)-α-phenyldihydrothebaine perchlorate, but that at 12.0 μ which appeared in the latter, was missing. The product appeared to be a form of the required methyl ether perchlorate. $[\alpha]_{5461}^{22.5}$ +26.6°, $[\alpha]_{D}^{22.5}$ +20.3°, (c, 0.56 in 96% EtOH).

The perchlorate m.p. 142-143° (0.1 g.) was converted into the methiodide as before, using acetone (1 c.c.) and methyl iodide (1 c.c.). 0.06 G. (55.5%) were obtained, m.p. 191°. The yield from (+)-α-phenyldihydrothebaine base was 15%.

Recrystallisation of the methiodide from absolute alcohol gave colourless plates, 0.05 g., m.p. 198°. The I.R. spectrum was similar to those of the methiodides obtained in (i) and (ii), but with differences in the 7.5-8.0 μ region. A further crystallisation gave no change in m.p., but the I.R. spectrum was now identical with those of the other methiodides.

The Crystallisation of the Methyl Ether Perchlorate.

A small part of the last batch of methyl ether perchlorate prepared in (i) above was allowed to separate from an ethanol solution on a watch glass, while being scratched by a glass rod, and a few granules of a genuinely crystalline product were obtained. 4 G. of this perchlorate were recrystallised from ethanol after being seeded with a crystal of this, giving a white crystalline mass, 2.8 g., m.p. 194-195°.

Concentration of the mother liquor followed by seeding gave, as a white crystalline solid, a second crop, 0.3 g., m.p. 226-227°, $[\alpha]_{5461}^{22}$ +35.6°, $[\alpha]_{D}^{22}$ +34.4°, (c, 0.23 in ethanol). An attempt to obtain a further quantity of this at a later date failed.

Two further crystallisations of some of the first crop gave colourless plates, m.p. 197°. (Found: C, 62.1; H, 6.3; Cl, 7.2. Calculated for $C_{26}H_{30}ClNO_7$: C, 62.0; H, 6.0; Cl, 7.0%). $[\alpha]_{5461}^{22}$ +20.6°, $[\alpha]_{D}^{22}$ +18.8°, (c, 0.27 in EtOH). Bentley and Robinson[65] obtained a crystalline product, m.p. 205°, $[\alpha]_{D}^{21}$ +9.26° (in water). The present product was not sufficiently soluble in water to determine the specific rotation in this with any degree of accuracy. It appeared to be <u>ca</u>. 8-10°.

Crystallisation of a further 3.6 g. of the non-crystalline perchlorate (prepared by method (i)) from an ethanol solution with seeding gave 0.83 g. of crystalline product, m.p. 193-194°, followed by 1.81 g. of non-crystalline product, m.p. 130-135°, after concentration of the mother liquor.

The lower melting crystalline perchlorates were combined (2.4 g.) and converted into the methiodide as follows. The perchlorate did not react with ammonia or sodium hydroxide; it was therefore dissolved in ethanol and rendered alkaline with alcoholic sodium hydroxide solution. The resulting solution was evaporated to near dryness under reduced pressure, water then being added to dissolve inorganic salts. This was then extracted three times with ether, which was then removed from the extract solution, and the base was dissolved in acetone and converted into the methiodide, 0.8 g., (30%), m.p. 196°.

The crystalline perchlorate (0.3 g.) m.p. 226-227° and of high specific rotation, was treated similarly, giving 0.04 g. (12%) of methiodide, m.p. 197-198°.

The melting points of both methiodides were similar and although the perchlorates were apparently physically different, the same compound was obtained in either case. These methiodides were also the same compound and of similar quality as the methiodides obtained from each of the non-crystalline perchlorates previously, but the yield was lower. Hence it was considered unnecessary to obtain the methyl ether perchlorate in either crystalline form in future work.

Preparation of the Methyl Ether Methiodide without First Preparing the Perchlorate.

The object of this experiment was to see whether omitting the purification of the methyl ether via the perchlorate made any difference to the quality of the methiodide obtained from it.

(+)-α-Phenyldihydrothebaine hydrochloride (7 g.) was converted into the methyl ether base by method (i), p. 67, and obtained as a white gummy precipitate, yield 4.3 g. (65%). This was then converted into the methiodide without first preparing and purifying the perchlorate, by heating it under reflux in acetone (20 c.c.) with methyl iodide (2 c.c.) for 2 hr., additional methyl iodide (1 c.c.) being added every ½ hr. After filtering off the white precipitate which formed, and washing it with acetone, 4.5 g. (77.5%) were obtained (50% calculated from the hydrochloride), m.p. 197.5°. Recrystallisation from ethanol gave colourless plates, 3.6 g., m.p. 197-198°. $[\alpha]^{23}_{5461}$ +25.3°, $[\alpha]^{23}_{D}$ +18.5°, (c, 0.30 in 96% ethanol).

A second crop of crystals was obtained, on concentrating the mother liquor, as a colourless crystalline mass, 0.7 g., m.p. 197-197.5°, $[\alpha]^{23}_{5461}$ +25.8°, $[\alpha]^{23}_{D}$ +19.4°, (c, 0.31 in 96% ethanol).

The I.R. spectra of the two crops were identical and the same as those of the methiodide obtained in (i), (ii) and (iii) above. Also, the specific rotations were identical, within the limits of experimental error, with that of the methiodide from (i), and agreed with that obtained by Small, Sargent and Bralley[34]. Hence, it was seen that the preparation of the methiodide from the base without first preparing and purifying the perchlorate gave an equally good final product and in higher yield.

A further 10.8 g., m.p. 195-197°, were prepared by this method from 14 g. of (+)-α-phenyldihydrothebaine hydrochloride.

(c) The Methine Methiodides of (+)-α-Phenyldihydrothebaine Methyl Ether. Freund[56].

(i) Various combined fractions of (+)-α-phenyldihydrothebaine methyl ether methiodide (4.5 g.) were digested with a solution of sodium (2.25 g.) in absolute ethanol (36 c.c.) on a water bath for about 1 hr., giving a clear dark solution. The alcohol was removed and an excess of a saturated aqueous solution of ammonium chloride was added and extracted with ether. The ether extracts were dried over solid potassium hydroxide and the solvent was removed, leaving a yellow oil behind.

This was allowed to react with methyl iodide (2 c.c.) after dissolving it in acetone (10 c.c.), the mixture then being heated under reflux for 2 hr., periodically adding a small quantity of methyl iodide. Excess reagent was then removed, leaving behind a yellow solid and an orange oil. A seed was obtained by recrystallising a small amount of the solid from ethanol. The oil and the remainder of the solid were crystallised by seeding and cooling, first to room temperature, and then to below 0°. Pale orange crystals were obtained, yield, 2.1 g. (46%), m.p. 207°. 0.5 G. were crystallised twice more giving pale orange needles, 0.1 g., m.p. 210°. This was probably the methiodide of the iso-methine, (LVII). $[\alpha]^{23}_{5461}$ -19.2°, $[\alpha]^{23}_{D}$ -12.8°, (c, 0.23 in EtOH). A fourth crystallisation did not change the appearance or melting point. Freund[56] gave no figures for any physical constants or analytical results.

Concentration of the mother liquor from the first crystallisation gave crystals infusible at 330°, which were probably inorganic. Evaporation of the filtrate gave an orange oil which was allowed to react with more methyl iodide, giving an orange solid, 0.31 g., m.p. 195-198°. This could not be satisfactorily crystallised from any solvent or solvent mixture, and gave only an orange oil which set solid at room temperature.

A further 3.0 g. of the methyl ether methiodide gave 1.13 g. (37%) of the crystalline methine methiodide (after one crystallisation) and 0.98 g. of orange oil from the liquor which was treated with further methyl iodide as above.

It is possible that the two fractions of non-crystalline solidified oil were mixtures of the methiodides of the normal- (LVI) and iso-methines (LVII).

(ii) 7.0 G. of the methyl ether methiodide, m.p. 197° prepared from the non-crystalline perchlorate, which had been "recrystallised" twice from aqueous ethanol only (p. 69), were converted into the crystalline methine methiodide as pale orange needles, 2.8 g. (39%), m.p. 204° after one crystallisation in addition to solidified oil from the mother liquor.

(iii) 10.8 G. of the methyl ether methiodide, m.p. 195-197°, obtained after omitting the perchlorate stage (p. 75), were converted into the crystalline methine methiodide (6.1 g), after one crystallisation, in addition to solidified oil from the mother liquor. A further crystallisation of the former product gave pale orange needles, 3.5 g., m.p. 210°.

A further quantity of the methine methiodides was prepared from 93.1 g. of (+)-α-phenyldihydrothebaine hydrochloride. After removal of the excess methyl iodide, a yellow precipitate and an orange oil were obtained. The two were stirred together with successive quantities of ether until all was converted into a yellow solid. The solid was dissolved in hot benzene and the inorganic salts were filtered off with decolourising carbon. Nothing separated from the benzene solution on cooling, and after removing the solvent, the orange syrup obtained was recrystallised from ethanol, giving a pale orange solid, 21.3 g., m.p. 210°. 1.3 G. were again crystallised giving what was probably the iso-methine methiodide as colourless needles, 1.03 g., m.p. 210.5-211°. (Found: C, 59.9; H, 6.2; I, 22.9; N, 2.5; O, 8.45. Calculated for $C_{23}H_{34}INO_3$: C, 60.1; H, 6.1; I, 22.7; N, 2.5; O, 8.6%).

(d) <u>(+)-3,4-Dimethoxy-2-(5-methoxy-2-vinylphenyl)-stilbene (XLIII).</u> Bentley and Robinson[65].

This was obtained from the various batches of the methine methiodides, as described below. The infrared spectra of all the stilbene products were identical, with peaks at 10.32, 10.90 and 11.10 μ. For trans -CH=CH-, the out of plane deformation frequency of CH normally lies between 10.31 and 10.41 μ, that of $-CH=CH_2$ between 10.05 and 10.15 μ, and the CH_2 out of plane deformation frequency of $-CH=CH_2$, between[85] 10.97 and 11.06 μ.

(i) From Crystalline Material Obtained in (c) (i) Above.

This had been prepared from various combined fractions of methyl ether methiodide. The methine methiodide (1.3 g.) was dissolved in methanol (5.3 c.c.). Sodium (0.67 g.) in methanol (13.4 c.c.) was added and the mixture was heated under reflux for 2 hr. The reaction mixture was then poured into saturated ammonium chloride solution, which resulted in the precipitation of an orange coloured gum. This was extracted three times with ether (13.4 c.c. each time), and the combined extracts were extracted three times with 2N HCl (1.5 c.c. each time), and then with water, until neutral to litmus. After drying over anhydrous sodium sulphate, the ether was removed and the crystalline residue was dissolved in alcohol (about 45 c.c.) at about 50°, to prevent possible racemisation, and allowed to cool, first to room temperature, and then to about 4°. Large pale brown prisms were obtained, 0.4 g. (46%), m.p. 113-114°. $[\alpha]_{5461}^{22}$ +80.2°, $[\alpha]_{D}^{22}$ +60.9°, (c, 1.01 in acetone).

The stilbene was crystallised again from ethanol as before, giving colourless prisms 0.1 g., m.p. 113°. $[\alpha]_{5461}^{22}$ +79.5°, $[\alpha]_{D}^{22}$ +62.0°, (c, 0.47 in acetone). The mother liquor was kept at about 4° and deposited a further crop of prisms, 0.06 g., m.p. 113°.

A second preparation from 1.13 g. of methine methiodide gave a total of 0.57 g. (76%) of product, after recrystallisation. A further crystallisation gave 0.54 g. in two crops, the best of which consisted of colourless prisms, 0.48 g., of similar m.p. and specific rotation as before.

(ii) From Crystalline Material Obtained in (c) (ii) above.

This had been prepared via the methyl ether perchlorate after two "crystallisations" from aqueous ethanol only (p. 69). 2.8 G. were converted into the stilbene giving, after recrystallisation, a total of 0.98 g. (53%) in two crops. The overall yield from thebaine was 3.25%. The best crop was as small pale orange crystals, 0.74 g., m.p. 114-115°, $[\alpha]^{20}_{5461}$ +82.1°, $[\alpha]^{20}_{D}$ +63.0°, (c, 1.02 in acetone).

(iii) From Crystalline Material Obtained in (c) (iii) above.

This had been obtained omitting the methyl ether perchlorate stage. 3.5 G. were converted into the stilbene giving orange crystals, 1.35 g., which after recrystallisation, gave a total of 1.24 g. (66.5%) in two crops. The overall yield from thebaine was 5.2%. These two crops were combined and crystallised again giving 1.19 g. in two crops, the best consisting of large pale orange crystals, 1.07 g., m.p. 114-115.5° $[\alpha]^{20}_{5461}$ +82.0°, $[\alpha]^{20}_{D}$ +62.5°, (c, 1.01 in acetone).

In a further preparation, 20.0 g. of the methine methiodide gave 5.1 g. of the stilbene in two crops, after recrystallisation The overall yield from thebaine was 4.5%. The best crop consisted of very pale yellow prisms, 4.4 g., m.p. 113°, $[\alpha]^{22}_{D}$ +64.3°, (c, 1.18 in acetone).

A further crystallisation of 0.2 g. of the first crop gave colourless prisms, 0.19 g., m.p. 113°. (Found: C, 80.1; H, 6.6; O, 13.5. Calculated for $C_{25}H_{24}O_3$: C, 80.6; H, 6.5; O, 12.9%).

The U.V. spectrum was determined and the sample was crystallised again, increasing the m.p. to 113.5-114°. (Found: C, 80.2; H, 6.7; O, 13.5. Calculated for $C_{25}H_{24}O_3$: C, 80.6; H, 6.5; O, 12.9%). Only small changes in the U.V. spectrum (Fig. 3, p. 96) were produced.

(iv) From Non-crystalline Methine Methiodide.

The two batches obtained in (c) (i) above were combined (1.29 g.) and converted into the stilbene. A total of 0.60 g. (70%) was obtained after crystallisation. A further crystallisation gave 0.55 g. in two crops, the best being as very pale yellow prisms, 0.48 g., m.p. 112-113°. $[\alpha]_{5461}^{22}$ +76.5°, $[\alpha]_D^{22}$ +62.6°, (c, 0.33 in acetone). This also appeared to be the required stilbene.

From the above results, the products obtained after omitting the methyl ether perchlorate stage were as good as those obtained after including it, but with higher overall yields. This is the recommended procedure for future preparations. Also, the main fractions prepared in (i), (ii), and (iii) were assumed to be suitable for combination for the proposed kinetic racemisation experiments.

Bentley and Robinson[65] obtained colourless prisms, m.p. 115°, $[\alpha]_D^{18}$ +59°, (c, 2.0 in acetone).

General Procedure for Racemisation Experiments.

A solution of suitable strength of the optically active compound in a purified solvent was made up, in order to give an optical rotation of about 1.0-1.2° at a convenient wavelength using a 1 d.m. semimicro polarimeter tube. Ca. 1 c.c. of the solution was sealed under vacuum in each of ten to twelve pyrex glass tubes. The tubes were suspended in a standard thermostatically controlled oil bath, equipped with a stirrer, at the required temperature. The first tube was removed after about five minutes, when it was assumed that the contents of all the tubes had reached the temperature of the bath. It was plunged into cold water, shaken, opened, and the optical rotation (α_0) of the solution was determined on a Hilger polarimeter, using the 1 d.m. semimicro tube. As racemisation takes place by a first order rate reaction, this rotation was regarded as being at zero time. The other tubes were removed from the bath one by one, and treated similarly at increasing time intervals, so as to obtain rotations decreasing by about 0.09-0.1° ($\alpha_1, \alpha_2, \alpha_3, \ldots.$), until the last, with a rotation of about 0.1°. The logarithm of the rotation was plotted against time, and the rate constant and half-life for the racemisation of the compound at that temperature was determined (p. 48).

The whole procedure was repeated at other temperatures, generally six runs being performed in all, the range of temperature giving half-lives ranging from about 20 min. to 12 hr. Duplicate runs were not normally carried out unless thought necessary.

Racemisation Experiments on (+)-3,4-Dimethoxy-2-(5-methoxy-2-vinylphenyl)-stilbene (XLIII).

p-Cymene was a suitable solvent for racemisation experiments on the (+)-stilbene, and was purified according to the method described in "Organic Solvents" by Weissberger and Proskauer, p. 110. The solvent was repeatedly shaken mechanically with concentrated sulphuric acid (50 c.c. per l.) for 3 hr., until the acid became only faintly yellow in colour. After being washed with sodium hydroxide solution and then with water, it was dried over sodium and then distilled (b.p. 175°).

(a) Attempted Racemisation and an Investigation of the Products.

Preliminary runs were carried out at 100°, 111.1° (twice), 116° (twice), 122° (twice) and 129°, using a 1.5% solution of the (+)-stilbene in *p*-cymene, and deviations from the straight line, on plotting the logarithm of the rotation against time, were observed. These deviations increased with time in each run and became more serious at the higher temperatures.

All the fractions of the solution of the partly racemised stilbene were combined, and two quantities of this were heated at 129° for 2 and 4 hr. respectively in a corked tube. The solutions then had α_D -0.10° and -0.15° (l= 1).

p-Cymene was removed from the first solution and the pale yellow solid obtained was extracted with hot ethanol, leaving behind a small amount of a white solid. A pale yellow solid, m.p. 118-120°, crystallised from the ethanol on cooling; on evaporation, the crystallisation liquors yielded a sticky yellow mass. A further crystallisation of the yellow solid gave little change in m.p. $[\alpha]_D$ -7.0°, (c, 1.01 in p-cymene).

The I.R. spectrum differed from that of the original stilbene in many ways, including the presence of a peak at 11.10 μ instead of two at 10.90 and 11.00 μ. A peak at 10.32 μ was, however present in both. For the significance of these peaks, see p. 79. This evidence indicated the presence of at least some racemate, as was confirmed later, the remainder being, most probably, a laevorotatory polymer, whose contribution to the spectrum would easily be masked by that of the racemate, as was apparent below.

The spectrum of the alcohol insoluble part was simple and nearly all the peaks had disappeared, or almost so, including those at 10.32, 10.90 and 11.00 μ. The substance was most probably a polymer of the optically active compound.

The I.R. spectrum of the substance obtained by evaporation of the crystallisation liquors had peaks at 10.32 and 11.00 μ and thus this substance appeared to be an impure form of the racemate, as was confirmed later.

The solution which had been heated for 4 hr. was treated similarly. A small amount of a white recrystallised product was obtained, which softened at about 118°, but gradually melted above 142°. The I.R. spectrum showed it to be polymeric. A larger quantity of the alcohol insoluble substance was obtained than before. Evaporation of the crystallisation liquors yielded impure racemate, as shown by the I.R. spectrum.

The (+)-stilbene (ca. 0.05 g.) was heated dry in a corked tube at 130° for 15 min. It was then extracted with acetone and a large amount of a white insoluble material was filtered off. For the solution: α_{5461} +0.025°, $[\alpha]_{5461}$ +ca. 3.3° (c, ca. 0.77 in acetone, l =1).

The acetone was removed from the solution and an attempt made to get the combined residue and the white insoluble material into p-cymene solution. A residue was obtained again, which softened at 125-128°, m.p. 215-270° and the solution had α_D +0.30° (l = 1). The solvent was removed from the latter and the I.R. spectrum of the residue showed it to be impure racemate. Extraction with hot ethanol, left a residue which gradually melted between 215 and 330°. The optically active stilbene, as shown by I.R. spectroscopy, crystallised from the alcohol solution on cooling.

(b) To Find the Conditions to Prevent the Formation of Polymer.

After 15 min. at 130° under nitrogen, the (+)-stilbene was extracted with p-cymene. A large amount of an insoluble substance was present, presumably the polymer.

The (+)-stilbene (0.05 g.) and a polymerisation inhibitor (0.005 g.), picric acid in one experiment and trinitrobenzene in another, were heated in p-cymene solution (5 c.c.) at 130 ± 0.3°. Racemisation was complete within 4½ hr. and the rotations of the solutions did not become negative after this time, and so it was assumed that polymerisation had been prevented. The solvent was removed from each of the solutions and recrystallisation of the residues retained almost all of the inhibitors in solution. The racemate crystallised from ethanol, in the case of the picric acid experiment, as a yellow solid, 0.018 g. (35% recovery), m.p. 119-120°. That crystallised from methanol, in the case of the trinitrobenzene experiment, was as a white solid, 0.028 g. (57% recovery), m.p. 121°. The latter racemate was purer than the former, and a further crystallisation gave 0.018 g., m.p. 121°. Bentley and Robinson[65] obtained m.p. 124°. The I.R. spectrum was identical with that of the racemate m.p. 119-120° above and had peaks at 10.32 and 11.10 μ (for the significance of these, see p. 79). This spectrum was used to confirm the presence of impure racemate obtained in the earlier experiments in (a) above.

(c) Kinetic Racemisation Experiments on the Stilbene in the Presence of a Polymerisation Inhibitor.

A solution in p-cymene of 1.50% of the (+)-stilbene and 0.15% of trinitrobenzene was used for kinetic runs, which were carried out according to the procedure on p. 83.

Temperature: 101.1 ± 0.1°.

Time (min.)	0	40	80	121	160	210	280	360	450	560	620	720
α_D (deg.)	1.27	1.15	1.05	0.95	0.87	0.78	0.67	0.57	0.46	0.37	0.32	0.26

$k = 3.649 \times 10^{-5}$ sec.$^{-1}$,

$t_{\frac{1}{2}} =$ 316.7 min. (317 min. from graph).

Temperature: 109.4 ± 0.2°.

Time (min.)	0	18	42	65	101	130	160	200	250	300	390	480
α_D (deg.)	1.20	1.12	1.01	0.91	0.76	0.66	0.58	0.46	0.38	0.30	0.20	0.13

$k = 7.784 \times 10^{-5}$ sec.$^{-1}$,

$t_{\frac{1}{2}} =$ 148.4 min. (148 min. from graph).

Temperature: 114.9 ± 0.2°.

Time (min.)	0	9	18	28	45	65	90	117	150	190	245	300
α_D (deg.)	1.20	1.12	1.03	0.96	0.86	0.75	0.63	0.50	0.41	0.29	0.20	0.14

$k = 1.214 \times 10^{-4}$ sec.$^{-1}$

$t_{\frac{1}{2}}$= 95.2 min. (95 min. from graph).

Temperature: $122.4 \pm 0.1^{\circ}$.

Time (min.)	0	5	11	18	25	35	45	60	75	95	125	150
α_D (deg.)	1.21	1.11	1.02	0.93	0.84	0.73	0.64	0.51	0.42	0.31	0.20	0.15

$k = 2.349 \times 10^{-4}$ sec.$^{-1}$,

$t_{\frac{1}{2}}$= 49.2 min. (49 min. from graph).

Temperature: $129.5 \pm 0.3^{\circ}$.

Time (min.)	0	2	5	9	13	18	22	27	36	40	58	70
α_D (deg.)	1.04	0.95	0.89	0.80	0.75	0.66	0.56	0.51	0.40	0.38	0.23	0.17

$k = 4.266 \times 10^{-4}$ sec.$^{-1}$,

$t_{\frac{1}{2}}$= 27.0 min. (27 min. from graph).

Temperature: $129.5 \pm 0.3^{\circ}$.

Time (min.)	0	2	6	10	14	18	23	32	42	55	75
α_D (deg.)	1.04	0.98	0.90	0.82	0.72	0.64	0.57	0.46	0.34	0.24	0.14

$k = 4.379 \times 10^{-4}$ sec.$^{-1}$,

$t_{\frac{1}{2}}$= 26.4 min. (26.2 min. from graph).

Temperature: 135.3 ± 0.2°.

Time (min.)	0	1	3	5	8	10
α_D (deg.)	1.05	1.01	0.96	0.88	0.775	0.71

Time (min.)	13	19	25	33	43	60
α_D (deg.)	0.64	0.50	0.41	0.28	0.20	0.10

$k = 6.531 \times 10^{-4}$ sec.$^{-1}$,

$t_{\frac{1}{2}}$= 17.7 min. (17.7 min. from graph).

Mean Temp. (deg. C.)	Mean Temp. (deg. K.)[T]	10^3. 1/T	Rate Const. sec^{-1}.10^5k.	Log$_{10}$ k.
101.1	374.3	2.672	3.649	$\bar{5}.5622$
109.4	382.6	2.614	7.784	$\bar{5}.8912$
114.9	388.1	2.576	12.14	$\bar{4}.0842$
122.4	395.6	2.528	23.49	$\bar{4}.3709$
129.5	402.7	2.484	43.22*	$\bar{4}.6357$
135.3	408.5	2.448	65.31	$\bar{4}.8150$

* The mean of two results.

The calculated value for E was 25.79 kcal. mole^{-1}.

Mean Temp. (deg. C.)	Log$_{10}$A sec^{-1}.	ΔS^* e.u.	ΔH^* kcal. mole^{-1}.	ΔF^* kcal. mole^{-1}.
101.1	10.62	-12.39	25.08	29.68
109.4	10.62	-12.42	25.03	29.79
114.9	10.59	-12.55	25.02	29.87
122.4	10.62	-12.49	25.00	29.95
129.5	10.63	-12.44	24.99	30.01
135.3	10.61	-12.60	24.98	30.13

Fig.1.

Racemisation of (+)-3,4-Dimethoxy-2-(5-methoxy-2-vinylphenyl)-stilbene in p-Cymene Solution.

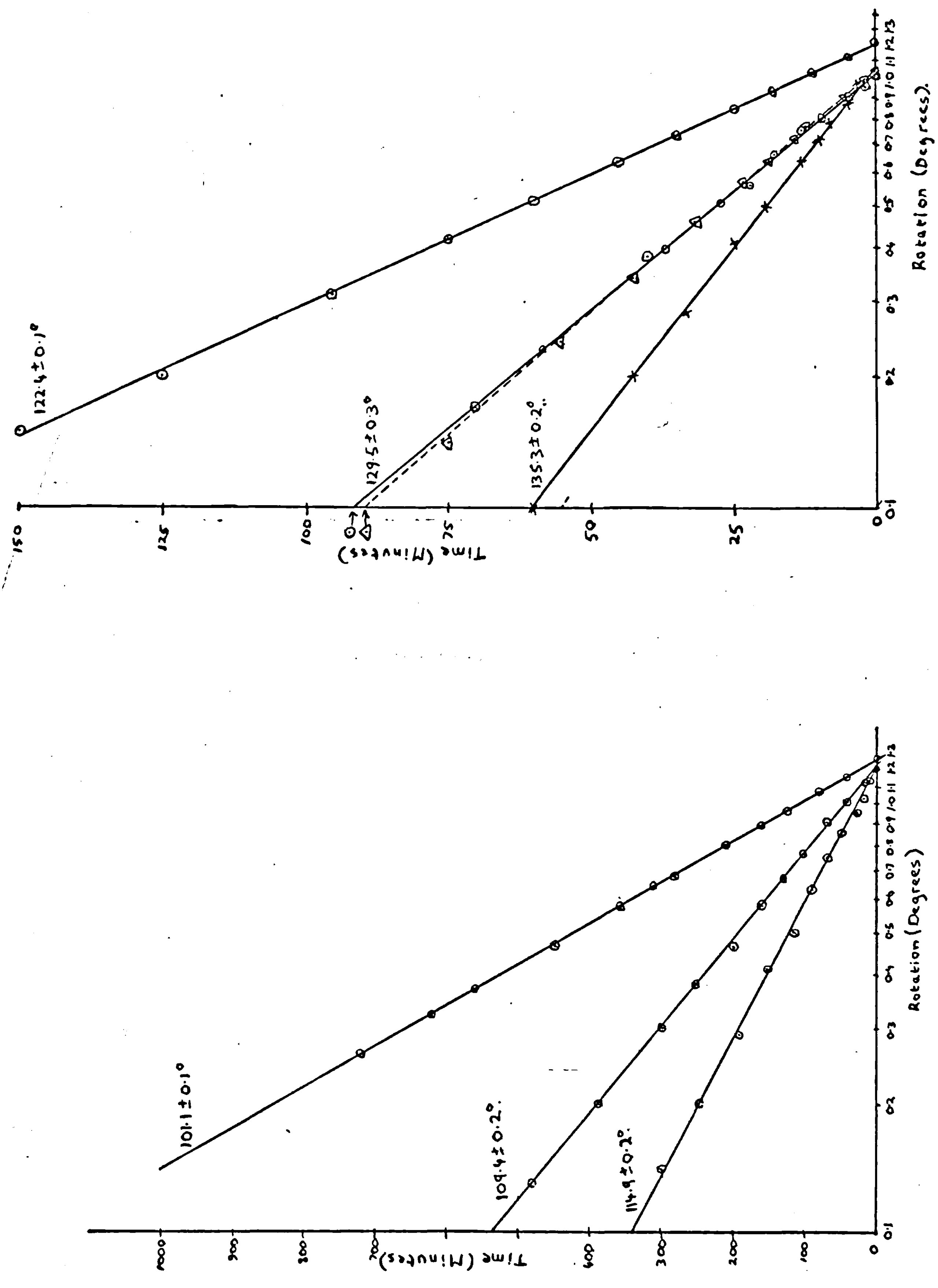
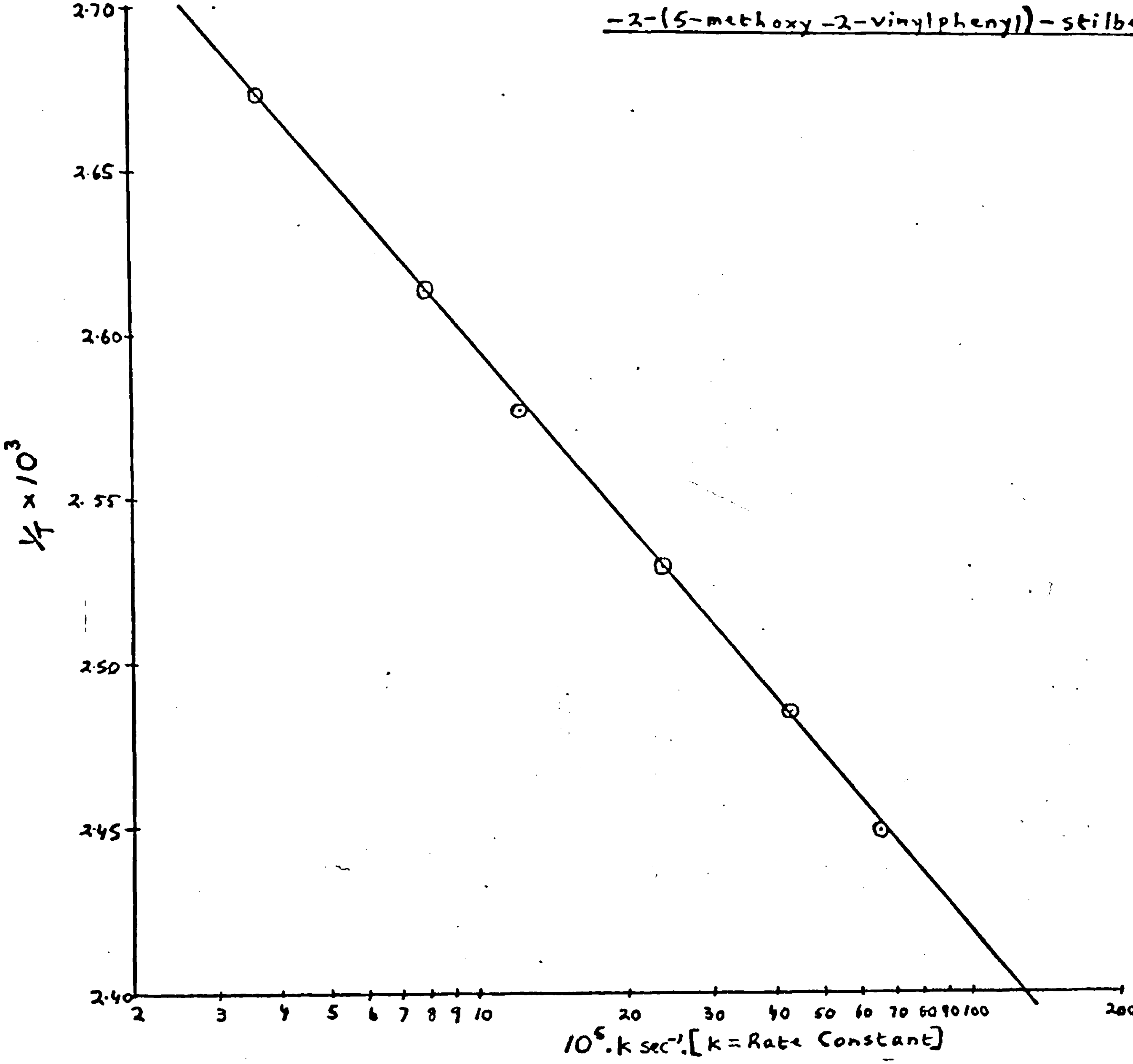


Fig. 2.

Plot of $1/T$ against the Rate Constant for the Racemisation of (+)-3,4-Dimethoxy-2-(5-methoxy-2-vinylphenyl)-stilbene.



These values were calculated as on p. 48, and the means of the results were as follows:

$E = 25.8$ kcal. mole^{-1}, $\Delta H^{\ddagger} = 25.0$ kcal. mole^{-1},
$\log_{10} A = 10.6$ sec^{-1}., $\Delta F^{\ddagger} = 30.1$ kcal. mole^{-1} at
$\Delta S^{\ddagger} = -12.5$ e.u., 135.3°.

Isolation of the Racemate.

The various fractions of solution obtained after the kinetic runs were combined and heated under vacuum at 129° until optically inactive ($4\frac{1}{2}$ hr.). The *p*-cymene was removed giving a red-brown solid, 0.74 g., which melted over the range 86-88°, 96-106.5°. This presumably contained 0.07 g. of trinitrobenzene. After recrystallisation from methanol, most of the trinitrobenzene remained in solution, pale orange prisms separating out on cooling, 0.33 g., m.p. 123-123.5°. A second crop was obtained after concentration of the filtrate, as a red-brown solid, 0.02 g., m.p. 111.5-113°, making a total of 0.35 g. (47%) recovered. The mother liquor from this was set aside.

The first crop was crystallised again, giving pale yellow prisms, 0.29 g. (43%) m.p. 123.5-124°. (Found: C, 80.15; H, 6.5; O, 13.3. $C_{25}H_{24}O_3$ requires C, 80.6; H, 6.5; O, 12.9%). The U.V. spectrum was determined. After a further crystallisation, the m.p. was increased to 125°. (Found: C, 80.4; H, 6.45; O, 13.3. $C_{25}H_{24}O_3$ requires: C, 80.6; H, 6.5; O, 12.9%). There was little change in the U.V. spectrum (Fig. 3, p. 69) and it was very similar to that finally obtained for the (+)-stilbene. Bentley and Robinson[65], obtained a product m.p. 124°.

The above mother liquor was evaporated and the residue was dissolved in benzene and passed down a silica gel column. The column was then eluted with light petroleum (b.p. 60-80°) and with methanol. An orange coloured band remained at the top of the column, and the eluants were examined as follows.

Benzene Fraction. On evaporation, a red-brown tar, 0.21 g. was obtained, which was a mixture of the racemate and trinitrobenzene, as shown by I.R. spectroscopy. These could not be separated by recrystallisation from methanol.

Light Petroleum Fraction. On evaporation, a trace of a pale yellow syrup was obtained, insufficient in quantity for either an I.R. spectrum or a m.p. determination.

Methanol Fraction. A pale brown solid, 0.01 g. was obtained on evaporation. A poor I.R. spectrum was obtained with very illdefined peaks and the substance appeared to be a polymer. On re-extraction with ethanol, a trace of a white insoluble substance remained. Almost certainly, the stilbene had polymerised in solution on standing, or on passing down the column after having been removed from the influence of the trinitrobenzene.

The Ultraviolet Spectra of the (+)- and (±)-Stilbenes (XLIII).

Blank determinations were carried out beforehand using the clean dry empty cells in the Unicam S.P.500 instrument. The optical densities at suitable wavelengths were then determined for solutions in 96% ethanol of known strength. The extinction coefficient, ϵ, was calaulated at each wavelength, after making allowances for the blank readings. The calculations were made using the formula

$$\epsilon = \frac{\text{Optical Density}}{lx},$$

where l is the path length in c.m., and x is the molar concentration. The results were plotted graphically.

Initially, 2 m.m. and 10 m.m. fused silica cells were used in turn in the instrument, and the results obtained were compared. In general, it is essential to use only 2 m.m. cells below 220 mμ to reduce errors from stray light and solvent absorption. Above this wavelength either should have been satisfactory, but in fact it was found that more consistent results were obtained when 2 m.m. cells were used throughout the entire range.

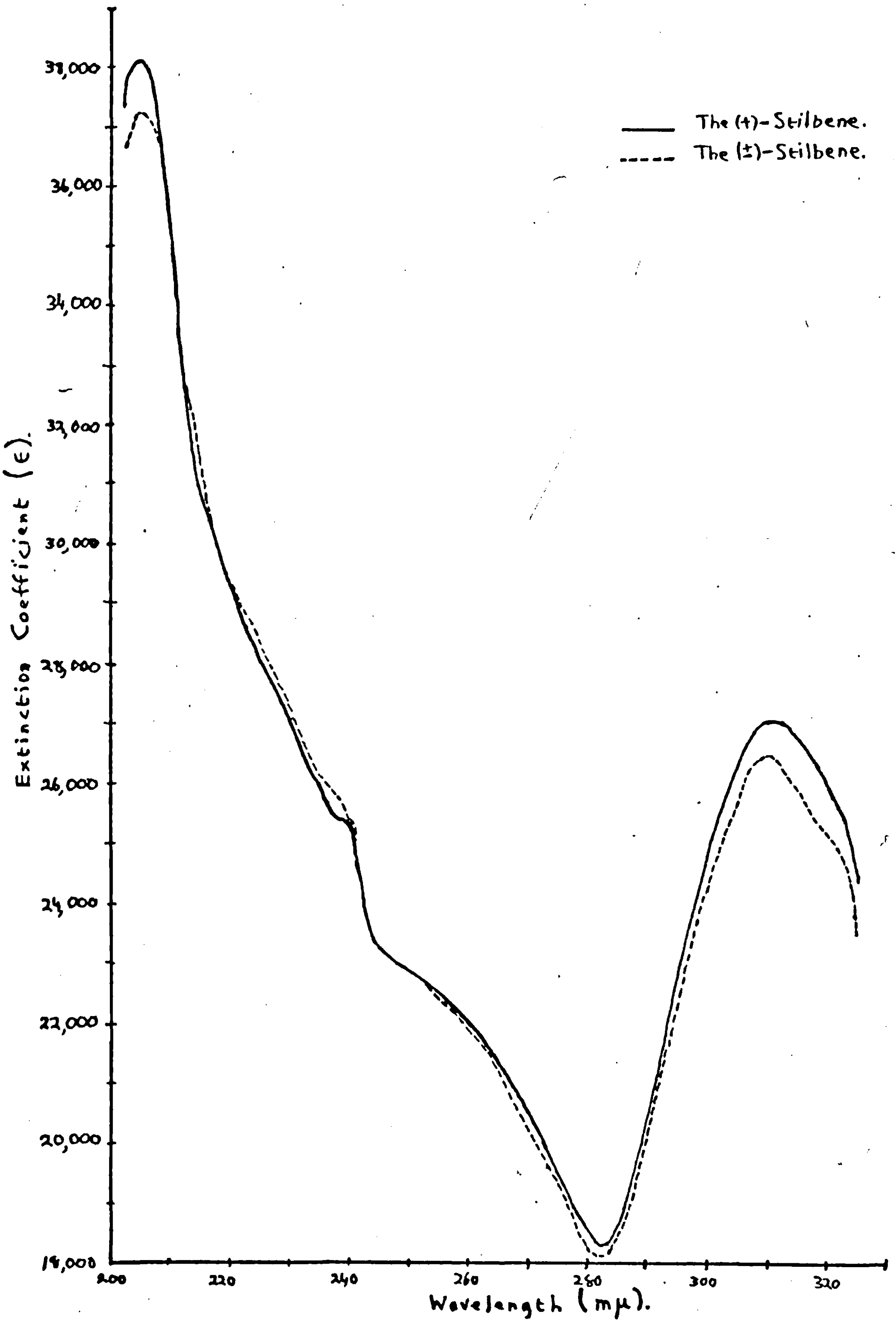
It was necessary to use each solution on the day on which it was made, otherwise a gradual change in the spectrum over a period of days occurred, presumably due to polymerisation.

(i) <u>The (+)-Stilbene.</u>

The spectrum of the sample m.p. 113°, which had been recrystallised twice (p. 82) was determined. A further crystallisation increased the m.p. to 113.5-114°, with only small changes in the U.V. spectrum. Two absorption bands occurred in this latter spectrum: a long-wave band λ_{max} 311 mμ (ϵ 27,000) and a short-wave band λ_{max} 205.5 mμ (ϵ 38,100). There was minimum absorption at 282.5 mμ (ϵ 18,300) and several points of

Fig. 3.

The Ultraviolet Spectrum of (+)- and (±)-3,4-Dimethoxy-2-(5-methoxy-2-vinylphenyl)-stilbene in 96% Ethanol.



inflection at ca. 250 (ϵ 22,900), ca. 240 (ϵ 25,400) and at ca. 230 mμ (ϵ 27,300), the last being the vestigial conjugation band.

(ii) The (±)-Stilbene.

The U.V. Spectrum of the sample m.p. 123.5-124° (p. 93), which had been recrystallised twice, was determined. A further crystallisation increased the m.p. to 125° and was accompanied by little change in the spectrum. This latter spectrum had a long-wave band at λ_{max} 310.5 mμ (ϵ 26,450) and a short-wave band at λ_{max} 205.5 mμ (ϵ 37,250). Minimum absorption occurred at 282.5 mμ (ϵ 18,100). There were points of inflection at ca. 250 (ϵ 22,850), ca. 240 (ϵ 25,300), 239 (ϵ 25,700) and at ca. 225 mμ (ϵ 28,500), the last being the vestigial conjugation band. This spectrum resembled very closely that of the (+)-stilbene.

Preparation of (+)-2-(2-Ethyl-5-methoxyphenyl)-3,4-dimethoxydibenzyl (LI).

Three methods of preparation were used, for the reasons stated on p. 56. The I.R. spectra of all three products were identical and had the characteristics expected (p. 57). As method (a) was found to give the required product, it was used for subsequent preparations.

(a) Preparation at Room Temperature. Bentley and Robinson[65].

The (+)-stilbene was hydrogenated using a low pressure (1 atmosphere) hydrogenation apparatus at room temperature.

A blank experiment was carried out beforehand, using a palladium-charcoal catalyst (0.078 g.) and ethyl acetate (20 c.c.). The apparatus was flushed out with hydrogen three times, and following the normal procedure, 25 c.c. of hydrogen were taken up. The stilbene (0.23 g.) was then added to the above catalyst suspension and 39 c.c. of hydrogen were ultimately absorbed. It thus appeared that 14 c.c. of hydrogen were used up in the hydrogenation instead of the theoretical quantity, 27.6 c.c. The mixture was then filtered and the volume adjusted accurately to 20 c.c. $[\alpha]_D^{20}$ +5.1°, (c, 1.08 in ethyl acetate).

The solution was evaporated under vacuum to constant weight, giving a white oil, 0.22 g. (92%). $[\alpha]_D^{20}$ +5.65°, (c, 1.06 in *p*-cymene).

In two later preparations, altogether 2.13 g. of the stilbene were hydrogenated, giving 1.82 g. (85.5%) of the dibenzyl. Elementary analysis of the second of these preparations gave the following results. (Found: C, 80.2; H, 7.45; O, 12.1. $C_{25}H_{28}O_3$ requires: C, 79.75; H, 7.5; O, 12.75%).

(b) Preparation at -30 to -25°.

This was carried out because it was suspected at the time that partial racemisation might have occurred at room temperature. Palladium-charcoal (0.16 g.) was suspended in ethyl acetate (15 c.c.) and the hydrogen absorption found to be 45 c.c. A fresh amount of the catalyst (0.16 g.) and solvent (15 c.c.) were taken and the stilbene (0.37 g.) was added.

A temperature of -30 to -25° was maintained by means of immersion of the reaction vessel in a solid carbon dioxide-alcohol bath, and 80 c.c. of hydrogen were ultimately taken up in 1½ hr. 35 C.c. appeared to have been used in the hydrogenation. In theory, this should have been 45 c.c., but possibly some had been absorbed during the volume and pressure adjustments. Filtration was carried out at -30° into a 20 c.c. volumetric flask, and made up to the mark. The specific rotation was determined at various temperatures and after various time intervals, using a jacketed polarimeter tube connected to a low temperature thermostat unit. At the end of these determinations, the solution was evaporated under reduced pressure. Yield, 0.30 g. (81%).

The determinations were carried out in the order shown, (c, 1.50 in ethyl acetate): $[\alpha]_D^{-19.2}$ +7.3°, no change after 105 min.; $[\alpha]_D^{-5.1}$ +4.6°, no change after standing overnight; $[\alpha]_D^{11.0}$ +3.7°, no change after 4.75 hr.; $[\alpha]_D^{21.5}$ +2.7°, no change after 4½ hr.; $[\alpha]_D^{-17.6}$ +6.7°; $[\alpha]_D^{-19.6}$ +7.3°.

As the specific rotation at about -19° was the same before and after this series of determinations, no racemisation had occurred at up to room temperature. However, $[\alpha]_D^{21.5}$ was lower than that obtained in (a), for reasons unknown (an incorrect weighing?), but $[\alpha]_{5461}^{22}$ +18.5°, (c, 5.90 in β-phenylethyl alcohol) compares favourably with values obtained later for other products.

(c) Larger Scale Preparation at Room Temperature.

So far, the volume of hydrogen used in the reaction appeared to be less than that theoretically required. It was suspected that incomplete hydrogenation may have occurred and it was necessary to see if hydrogen absorption was proportional to the quantities of the reactants present.

Palladium-charcoal (0.50 g.), ethyl acetate (105 c.c.) and the stilbene (1.00 g.) absorbed 168 c.c. of hydrogen. After having scaled up the quantities used in (a), 161 c.c. should have been absorbed by the catalyst and solvent, and 120 c.c. were calculated to have been required for the hydrogenation, making 281 c.c. in all. As only 168 c.c. were taken up, it seemed that either only 48 c.c. were taken up by the solvent and catalyst, or only 7 c.c. were used in the hydrogenation, or an intermediate situation arose. On adding 0.08 g. of catalyst to the reaction mixture, an additional 25 c.c. of gas were taken up, which was the same as that used in the blank experiment in (a). It appears that one can place no reliance in such calculations or in assuming that the amount of gas absorbed is equal to the sum of that used in a blank experiment and the theoretical amount required for the hydrogenation of the stilbene. The yield of the dibenzyl finally obtained was 0.96 g. (96%).

The following were obtained using the Zeiss polarimeter: (c, 4.735 in p-cymene), $[\alpha]_{3650}+38.6^{\circ}$; $[\alpha]_{4050}+22.2^{\circ}$;

$[\alpha]_{4360}$ +15.5°; $[\alpha]_{5460}$ +5.64°; $[\alpha]_{5780}$ +4.60°, (l = 1), and the following with the Hilger instrument:
$[\alpha]_D$ +4.80°; $[\alpha]_{5780}$ +4.60°; $[\alpha]_{5460}$ +5.80, (l = 2).

The various products prepared under (a) and (c) were combined and the U.V. spectrum was determined on a Unicam S.P. 500 spectrophotometer using fused silica cells (Fig.10, p. 170). A 6.51 x 10^{-5} molar solution in 96% ethanol was used in 10 m.m. cells between 310 and 240 mμ, and in 1 m.m. cells between 245 and 199 mμ. The following characteristics were observed: λ_{max} 279 mμ (ϵ 4,450), λ_{min} 252 mμ (ϵ 829), the vestigial conjugation band at λ_{inf} 227.5 (ϵ 17,800) and λ_{max} 201 mμ (ϵ 64,500). This spectrum was consistent with that expected for this compound. It gave no evidence of incomplete hydrogenation of the vinyl groups of (XLIII).

Racemisation Experiments on the (+)-Dibenzyl (LI).

(a) Preliminary Partial Racemisation Studies.

$[\alpha]^{20}_{5780}$ +4.23°, (c, 1.06 in p-cymene).

This was given by α_{5780} +0.045° (l = 1), using a Zeiss polarimeter. The rotation was found to be unaltered after allowing the solution (i) to stand at room temperature for 48 hr., (ii) after 30 min. at 160° under vacuum, and (iii) after 2 hr. at 175°. After 8 hr. at 175°, however, the rotation was reduced to +0.017°, or after 1 hr. at 205°, to +0.02°. This last result was accompanied by deposition on the sides of the tube and so either the solvent or the solute or both was thought to have altered in composition.

p-Cymene was heated alone under vacuum at 205° for 2 hr., and gave a precipitate which adhered to the sides of the tube. The following were heated under vacuum at 220° for 3 hr.: tetralin, ethyl benzoate, nonyl alcohol, 1-methylnaphthalene, *n*-decane, and β-phenylethyl alcohol. All, except for β-phenylethyl alcohol, had alterations in appearance. It was decided to carry out partial racemisation of the dibenzyl in this solvent, especially as I.R. spectroscopy gave no indication of any decomposition.

Owing to the low specific rotation of the dibenzyl, a fairly concentrated solution was required, which had α_{5461} +0.86° and α_{5780} +0.75° $(l = 1)$, which corresponded to $[\alpha]^{22}_{5461}$ +21.4° and $[\alpha]^{22}_{5780}$ +18.7°, (c, 4.01 in β-phenylethyl alcohol). The solution was heated under vacuum at 180 ± 0.5° for 7½ hr. and then had α_{5461} +0.51° and α_{5780} +0.425°; after 19½ hr., α_{5461} +0.23° and α_{5780} +0.20°; and after 25 hr., α_{5461} +0.16° and α_{5480} +0.13°. On plotting the logarithm of the rotation against time at each wavelength, a straight line was obtained in each case.

(b) Kinetic Racemisation Experiments.

The method was that described on p. 83, using a 4.01% solution in redistilled β-phenylethyl alcohol, λ = 5461 Å.

Temperature: 180.8 ± 0.5°.

Time (hr.)	0	$1\frac{1}{2}$	3	$4\frac{1}{2}$	6	$7\frac{1}{2}$
α_{5461} (deg.)	0.86	0.75	0.69	0.62	0.56	0.51

Time (hr.)	10	13	16	$19\frac{1}{2}$	25	30
α_{5461} (deg.)	0.42	0.35	0.29	0.23	0.16	0.11

$k = 1.853 \times 10^{-5}$ sec^{-1}.,

$t_{\frac{1}{2}}$= 10.4 hr. (10.4 hr. from graph).

Temperature: 193.1 ± 0.5°.

Time (hr.)	0.10	0.50	1.00	1.50	2.25	3.08
α_{5461} (deg.)	0.81	0.73	0.67	0.63	0.53	0.46

Time (hr.)	4.00	5.25	7.50	10.17	12.17
α_{5461} (deg.)	0.38	0.32	0.21	0.13	0.09

$k = 5.003 \times 10^{-5}$ sec^{-1}.,

$t_{\frac{1}{2}}$= 3.85 hr. (3.83 hr. from graph).

Temperature: 203.3 ± 0.5°.

Time (hr.)	0.00	0.37	0.67	1.00	1.45
α_{5461} (deg.)	0.86	0.77	0.68	0.60	0.52

Time (hr.)	1.92	2.50	3.25	4.33	6.00
α_{5461} (deg.)	0.43	0.33	0.25	0.17	0.09

$k = 1.059 \times 10^{-4}$ sec^{-1}.,

$t_{\frac{1}{2}}$= 1.82 hr. (1.82 hr. from graph).

Temperature: 214.9 ± 0.5°.

Time (min.)	0	7	15	22	32	45	65	85	115	155
α_{5461} (deg.)	0.84	0.73	0.65	0.58	0.50	0.43	0.32	0.23	0.15	0.08

$k = 2.454 \times 10^{-4}$ sec^{-1}.,

$t_{\frac{1}{2}}$= 47.1 min. (47.0 min. from graph).

Temperature: 223.6 ± 0.50.

Time (min.)	2	6	11	16	22	30	40	52	75
α_{5461} (deg.)	0.76	0.67	0.59	0.51	0.43	0.35	0.26	0.19	0.10

$k = 4.594 \times 10^{-4}$ sec^{-1}.,

$t_{\frac{1}{2}}$= 25.2 min. (25.2 min. from graph).

Mean Temp. (deg. C.)	Mean Temp. (deg. K.)[T]	10^3.1/T	Rate Const. sec^{-1}. 10^5k.	Log$_{10}$ k.
180.8	454.0	2.203	1.858	$\bar{5}.2690$
193.1	466.3	2.144	5.003	$\bar{5}.6993$
203.3	476.5	2.099	10.59	$\bar{4}.0248$
214.9	488.1	2.049	24.54	$\bar{4}.3899$
223.6	496.8	2.013	45.94	$\bar{4}.6622$

The calculated value for E was 33.45 kcal. mole^{-1}.

Fig. 4.

Racemisation of (+)-2-(2-Ethyl-5-methoxyphenyl)-3,4-dimethoxydibenzyl in β-Phenylethyl Alcohol Solution.

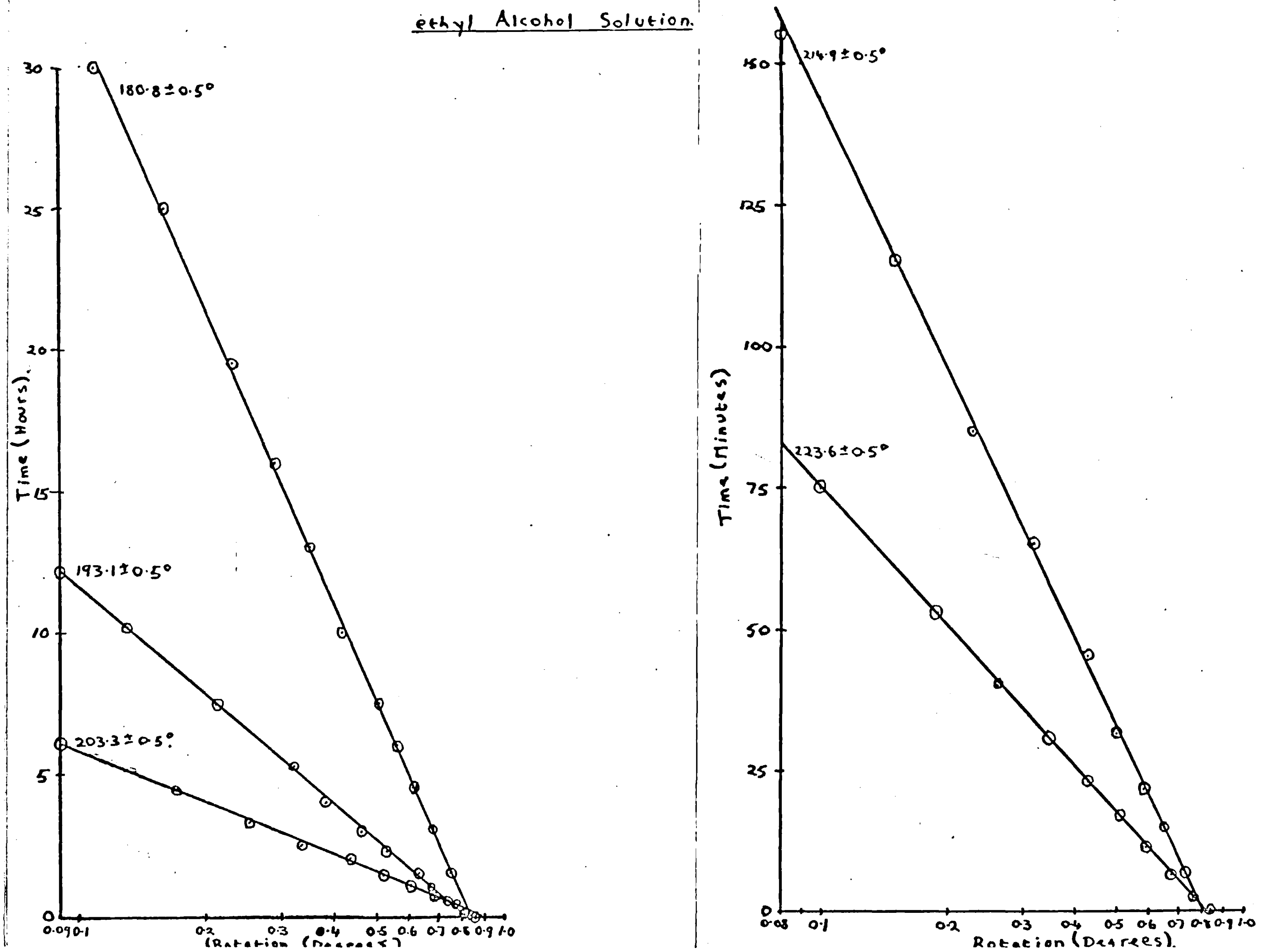
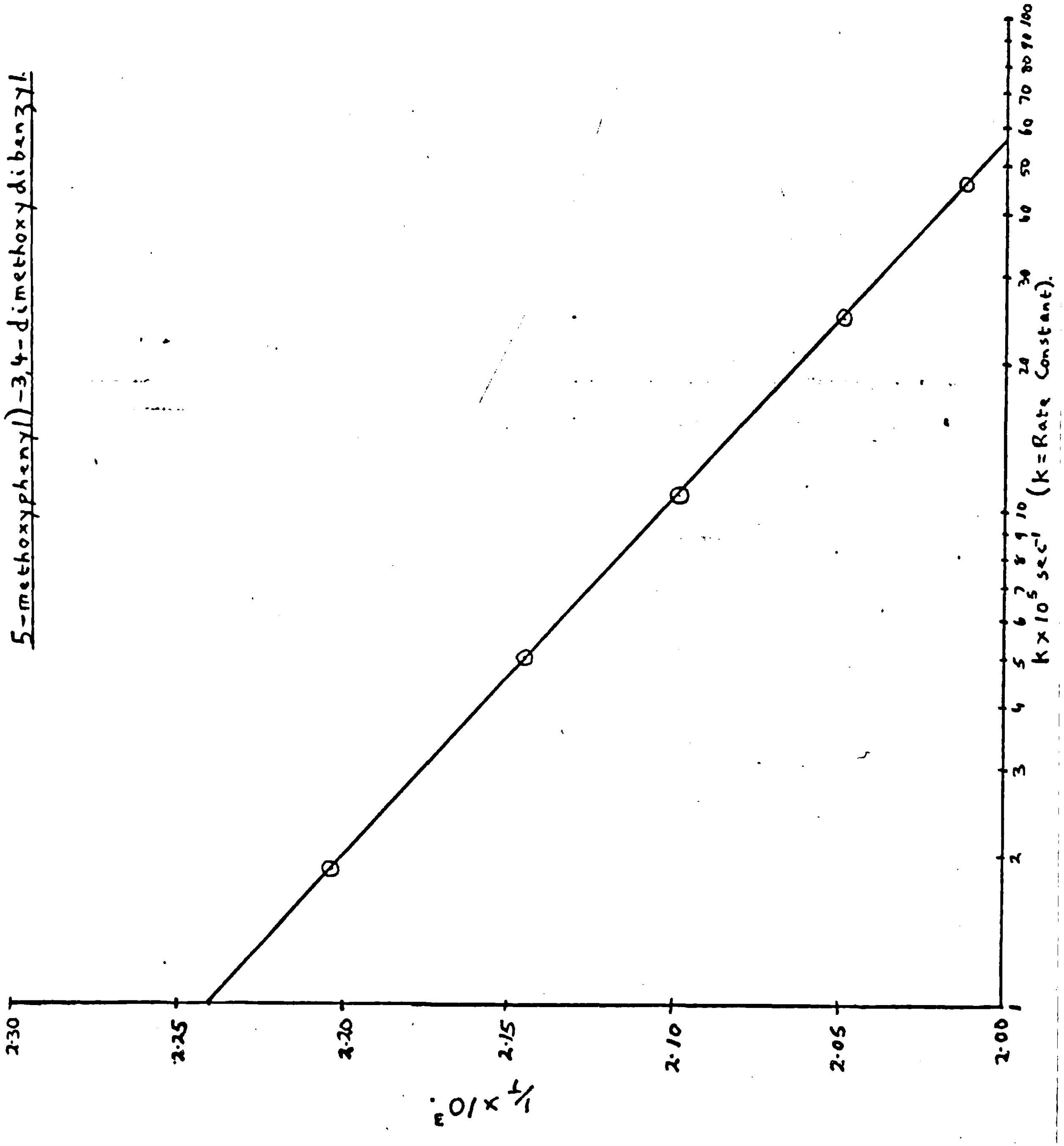


Fig. 5.



Plot of 1/T Against the Rate Constant for the Racemisation of (+)-2-(2-Ethyl-5-methoxyphenyl)-3,4-dimethoxydibenzyl.

Mean Temp. (deg. C.)	Log_{10} A sec^{-1}.	ΔS^{*} e.u.	ΔH^{*} kcal. mole^{-1}.	ΔF^{*} kcal. mole^{-1}.
180.8	11.37	-9.32	32.55	36.79
193.1	11.37	-9.37	32.52	36.89
203.3	11.37	-9.43	32.50	37.01
214.9	11.37	-9.48	32.48	37.12
223.6	11.37	-9.49	32.46	37.18

These values were calculated as on p. 48, and the means of the results were as follows:-

$E = 33.45$ kcal. mole^{-1}, $\Delta H^{\ddagger} = 32.5$ kcal. mole^{-1},
$\log_{10} A = 11.4$ sec^{-1}., $\Delta F^{\ddagger} = 37.2$ kcal. mole^{-1},
$\Delta S^{\ddagger} = -9.42$ e.u., at 223.6°.

Isolation of the Racemate.

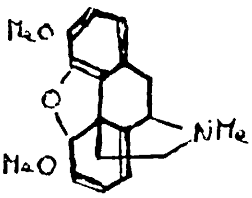
The fractions of the solution from the kinetic racemisation experiments were combined, and 6.25 c.c. (containing 0.25 g. of the dibenzyl) were heated under vacuum at 223.6° until optically inactive (24 hr.). The solvent was evaporated under reduced pressure and the residue was dissolved in acetone, which was then removed. This was repeated several times. The product was heated at a little below its b.p. under reduced pressure for 1 hr., after which time a brown oil remained, 0.20 g. (80% recovery). (Found: C, 79.9; H, 7.45; O, 12.4. $C_{25}H_{28}O_3$ requires: C, 79.75; H, 7.5; O, 12.75%).

The I.R. spectrum was identical with that of the optically active compound and from the above evidence, racemisation only and no apparent decomposition had occurred during the kinetic racemisation experiments.

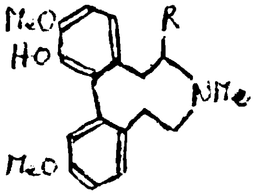
PART 2.

The Preparation and Proof of the Structure of (+)-2,3,8,9-Tetrahydro-4'-hydroxy-3',2"-dimethoxy-N-methyl-4,5:6,7-dibenzazonine and Kinetic Racemisation Experiments on its Methyl Ether and on (+)-2,3,3'-Trimethoxy-6,6'-diethylbiphenyl.

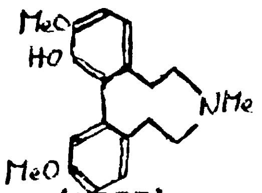
DISCUSSION.



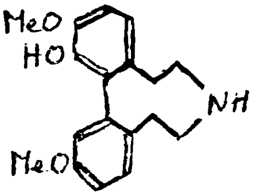
(XXVIII)



(LXII)



(XLII)



(LIV)

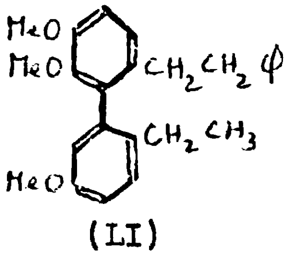
Compounds of the type (LXII) have been prepared from thebaine (XXVIII) by reaction with Grignard reagents, RMgX, where R = C_6H_5, $C_6H_5CH_2$, and CH_3 (p. 25, 35). In an attempt to prepare the parent compound of the series, 2,3,8,9-tetrahydro-4'-hydroxy-3',2"-dimethoxy-N-methyl-4,5:6,7-dibenzazonine (XLII), Bentley and Robinson[64,65] allowed thebaine and anhydrous magnesium iodide to react together; reduction of the product with lithium aluminium hydride gave a base, which they thought was the secondary amine (LIV) (p. 35).

As the N-methyl azonine is a 2,2'-bridged biphenyl with a nine-membered heterocyclic bridging ring, it was hoped to obtain this compound and its methyl ether with a view to studying the ultraviolet absorption spectrum and the optical stability of a bridged biphenyl having a nitrogen containing bridging ring of this size. These studies should also give useful information about the steric effect of a buttressed o-methoxyl group.

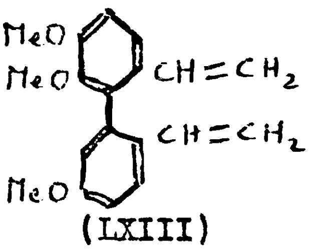
Bentley and Robinson's base was prepared and an investigation of its composition was carried out. This product was found to be the (+)-isomer of the parent member of the series, the N-methyl azonine (XLII), which was subsequently obtained in a crystalline form. No satisfactory evidence for the presence of the secondary amine (LIV) was found. Exhaustive methylation of the methyl ether methiodide of (XLII) gave the (+)-divinylbiphenyl (LXIII), in confirmation of the proposed structure.

The divinylbiphenyl polymerised too readily for racemisation rates to be determined but hydrogenation of the side chains gave (+)-2,3,3'-trimethoxy-6,6'-diethylbiphenyl (LXIV), the racemisation of which was studied in β-phenylethyl alcohol solution.

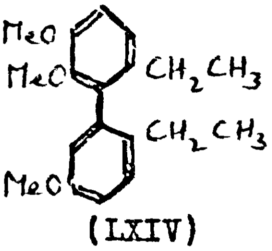
The diethylbiphenyl (LXIV) and its phenyl analogue (LI) are among the very few known optically active biphenyls with ortho-alkyl groups and would be very inaccessible by processes requiring optical resolution.



(LI)



(LXIII)

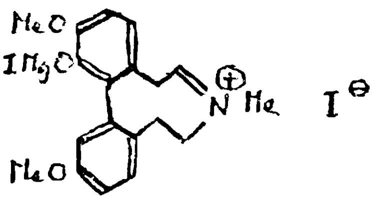


(LXIV)

The Preparation and Properties of Bentley and Robinson's Base.

Thebaine and anhydrous magnesium iodide were allowed to react together in solution under anhydrous conditions, according to the method of Bentley and Robinson[65]. The product, a light brown solid, was insoluble in ethanol, chloroform, acetone, and ether, but soluble in methanol. Addition to water produced a greenish substance immediately presumably owing to hydrolysis. It was previously reported by these authors that prolonged storage in an evacuated desiccator also produced a greenish substance, but after six month's storage we found no evidence of this, although its reactivity towards lithium aluminium hydride had diminished considerably after two weeks.

Magnesium and ionic iodine were found to be present. The infrared absorption spectrum showed a peak at 5.95 μ, which may have been due to a cyclic C=N group. Many compounds containing this absorb within the range[86] 5.9 to 6.5 μ. There was intense absorption at 2.8 to 3.2 μ which may have been due to hydroxyl[87] produced by aerial hydrolysis of -OMgI. The above evidence supported Bentley and Robinson's structure[65] (LIII) for the thebaine-magnesium iodide product.



(LIII)

In view of the large weight of the substance obtained, (234 g. from 75 g. of thebaine, the theoretical yield being 142 g.) and the fact that it progressively lost benzene on storage in an evacuated desiccator, even after a considerable time, it seems that the compound is heavily associated with benzene, on preparation.

The thebaine-magnesium iodide product was treated with lithium aluminium hydride, according to the method of Bentley and Robinson[65], with slight modifications. A large quantity of gas was evolved during the reaction which was thought to be partly methane, as suggested by these authors, as it is known that lithium aluminium hydride reduction of Schiff's base methiodides can give secondary amines with the loss of methane in certain cases, if the base is sufficiently sterically hindered[88]. However, as no secondary amine was positively identified later, it is thought that this gas must have been very largely hydrogen.

The base was obtained as a brown glass, whose infrared spectrum (fig. 6, p. 140) was similar in form to that of (+)-α-phenyldihydrothebaine (fig. 7, p. 141), except that many peaks which could be attributed to a C_6H_5 group, in that of the latter, were absent. This showed that the structure, at least, resembled that of phenyldihydrothebaine. A peak was present at 3.60 μ, as in the spectrum of phenyldihydrothebaine (NMe peaks normally appear[89] between 3.55 and 3.62 μ), and there was a double peak with a maximum at 2.85 and 2.90 μ.

This was due to the hydroxyl group[87]. At the time, part was thought to have been due to NH, the stretching frequency of which normally lies[89] between 2.86 and 3.03 μ. However, there was virtually no absorption at 6.05 μ (see later); the deformation vibration frequency of NH lies between[89] 6.06 and 6.45 μ. The peak at 5.95 μ (cyclic C=N), present in the spectrum of the thebaine-magnesium iodide product, was absent.

Nitrogen was shown to be present by the sodium fusion test, and treatment with cold nitrous acid gave an orange coloured solution, which indicated a secondary amine, whereas phenyldihydrothebaine gives a yellow solution, indicative of a tertiary amine. On rendering each of these solutions alkaline, each gave a deep red solution, which was inconsistent for either a secondary or a tertiary amine.

Nitrous acid, followed by Liebermann's reaction with concentrated sulphuric acid and phenol, gave a green-blue colour, which became purple on dilution and yellow on basification. These colourations, except the last, indicated a secondary amine.

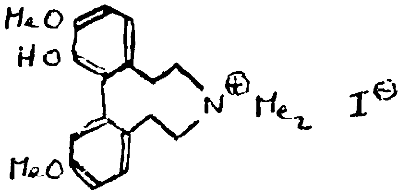
Thus, at this stage, there was no certainty whether the base was the secondary amine (LIV) or the N-methyl azonine (XLII), or a mixture of the two.

Investigation of the Composition of Bentley and Robinson's Base.

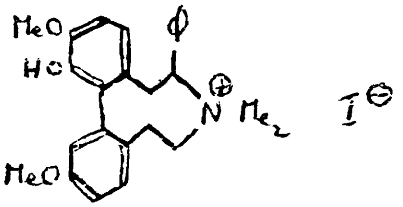
(a) Reaction with Excess of Methyl Iodide.

Reaction of the base with excess of methyl iodide, under neutral conditions, gave an optically active quaternary compound,

(+)-2,3,8,9-tetrahydro-4'-hydroxy-3',2"-dimethoxy-N, N-dimethyl-4,5:6,7-dibenzazoninium iodide (LXV), as shown by the infrared spectrum, which had a hydroxyl peak at 3.05 μ and resembled the spectrum of (+)-α-phenyldihydrothebaine methyl ether methiodide (LXVI) in the 3.2 to 3.7 μ region. Elementary analysis gave good results based on structure (LXV). Either the secondary amine or the N-methyl azonine would give this compound under these conditions.



(LXV)



(LXVI)

It is reasonable to assume that if the base, as isolated from the lithium aluminium hydride reduction, were the secondary amine (LIV), treatment with one equivalent of methyl iodide under neutral conditions would give a tertiary amine, the N-methyl azonine, whereas, if it were already the N-methyl azonine, the quaternary compound would be produced.

When this was carried out, the reaction was not quite complete and two products were obtained. One was a base, shown by the fact that it was possible to obtain a precipitate from acetone solution on the addition of a little more methyl iodide, and the other was a methiodide which did not react further with additional methyl iodide. The infrared spectrum of this base had a peak at 3.60 μ (NMe[89]), in common with that of the lithium aluminium hydride reduction product.

However, a small peak occurred at 6.05 μ, which had been virtually absent before, and was thought at the time to be due to an NH group[89] indicating the presence of some secondary amine in the original mixture. As little positive evidence was later obtained for the presence of secondary amine, the peak at 6.05 μ may have been due to moisture.

The methiodide obtained was (LXV), as shown by infrared spectroscopy, and the picrate derived from it was the same as that derived from an authentic specimen of (LXV), as shown by melting point and infrared evidence.

By calculation, if the lithium aluminium hydride reduction product is entirely the secondary amine, 1.5 g. should give either about 1.5 g. of the tertiary base, the N-methyl azonine, or about 0.75 g. of the quaternary methiodide. If it is entirely the N-methyl azonine, 1.5 g. should give about 2.25 g. of the quaternary methiodide. The combined products of two experiments were 0.2 g. of the basic product and 1.9 g. of the quaternary methiodide from 1.5 g. of starting material. These results at the time were interpreted as indicating that the N-methyl azonine predominated in the reduction product, but in fact they corresponded to a quantitative yield of methiodide on that part (1.3 g.) which had reacted, assuming for the moment, that the reduction product was entirely the N-methyl azonine.

(b) Fractional Crystallisation of the Picrate.

It was hoped that by converting some of the lithium aluminium hydride reduction product into the picrate, a separation of the two components, then thought to be present, might be achieved by fractional crystallisation.

On the addition of two equivalents of picric acid dissolved in ethanol to a solution of the base in ethanol, a yellow gum was obtained, which on crystallisation from ethanol gave an oil, which solidified on cooling, and two fractions of crystals of different melting point. After extraction of these parts with hot iso-propyl alcohol, residues less soluble in this solvent were left, which could, however, be crystallised from n-propyl alcohol. Further extraction with hot iso-propyl alcohol of the more soluble part, recovered by cooling the solution, was carried out and the less soluble part of this was crystallised as before from n-propyl alcohol. This process was repeated several times and the crystallised products from the n-propyl alcohol, crystallised further from this solvent. Finally, two fractions were obtained, whose melting points did not alter on further treatment; one from the iso-propyl alcohol crystallisations, of melting point 103-105.5°, and the second from the n-propyl alcohol crystallisations, melting point 217-218°. The former was present in a very large proportion relative to the latter. Analysis of the former seemed to indicate either the presence of the picrate of the secondary amine with one molecule of iso-propyl alcohol of crystallisation or that of the unsolvated N-methyl azonine. The melting point slowly increased on standing over a period of two weeks. The infrared spectrum of the picrate melting point 103-105.5° was identical with that of an authentic specimen of the N-methyl azonine picrate prepared later, which had been crystallised twice from iso-propyl alcohol and melted at 101-111°. Elementary analytical results for the two were similar, except those for oxygen, which in the case of the authentic specimen, rendered the results different from those required by any reasonable formula.

When some of the picrate, which melted at 103-105.5°, was converted into the base, nuclear magnetic resonance spectra[x] in chloroform and carbon tetrachloride solutions, were those to be expected for the N-methyl azonine, except for an unidentified peak in each at about τ 8.7 in addition to that at about τ 7.75 due to NMe. This unidentified peak was, at the time, thought to be due to NH, but the spectra in deuterochloroform and carbon tetrachloride solutions of the base obtained later from the picrate of an authentic crystalline specimen of the N-methyl azonine, each contained a less intense form of the unidentified peak. The spectra of (+)-α-phenyldihydrothebaine in these solvents also contained unidentified peaks at about τ 9. This phenomenon was not observed, however, in the spectrum of the crystalline N-methyl azonine (obtained later) in carbon tetrachloride solution.

Column chromatography, heating under reflux with insufficient iso-propyl alcohol for complete solution, and

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[x] I would like to thank Dr. R. Hulme of West Ham College of Technology, London, E.15, for determining these spectra and for help in the interpretation of the results.

precipitation from benzene solution by the addition of successive quantities of light petroleum (b.p. 40-60°), failed to separate the picrate m.p. 103-105.5° into two components. The use of infrared spectroscopy showed the presence only of the N-methyl azonine salt.

From its analysis, the picrate of m.p. 217-218°, could have been that of the unsolvated N-methyl azonine, but the nuclear magnetic resonance spectrum of the liberated base was unintelligible. The authentic specimen of the N-methyl azonine picrate, when crystallised twice from n-propyl alcohol, had a melting point of 111-114°. No further work was done on the above picrate, owing to insufficient quantity, and it remains unidentified.

The above results showed that the prepared base was at least predominantly the N-methyl azonine, and that no positive evidence had been obtained concerning the presence of the secondary amine.

(c) Work on the Lithium Aluminium Hydride Reduction Product.

As no success had been achieved at a separation with the picrate, attempts were made on the reduction product.

(i) Fractional Precipitation.

Fractional precipitation from acetone solution by carbon tetrachloride gave a substance, the infrared spectrum of which had no NMe peak[89] at 3.60 μ but had absorption at ca. 6 μ. At the time it was thought that the secondary amine had been obtained[89]. Exposure of this substance to air followed by extraction with acetone, left a residue of indistinct infrared spectrum. This was possibly formed by reaction with carbon dioxide in the atmosphere. The substance recovered from the carbon tetrachloride solution had an infrared spectrum resembling that of the untreated base.

(ii) Attempted Chromatographic Separation.

The reduction product in acetone solution was deposited on a silica gel column and eluted with 60% acetone + 40% carbon tetrachloride; 80% acetone + 20% carbon tetrachloride; 100% acetone; chloroform; and ethanol, in that order.

The first elution mixture gave a fraction, the infrared spectrum of which contained peaks at 6.00 and 5.90 μ. The NMe peak was absent, and these and other smaller differences between this spectrum and that of the reduction product were not altered by drying the fraction under high vacuum. There was no evidence for HCO_3^- or CO_3^{--}. Carbon dioxide was passed through a solution of the authentic N-methyl azonine (obtained later). The infrared spectrum of the vacuum dried product had a peak[89] at 6.05 μ (NH^+). The peak at 3.60 μ had diminished in size, but there was not one at 5.90 μ (C=O stretching frequency lies[90] between 5.85 and 5.92 μ) and there was no other evidence for HCO_3^- or CO_3^{--}. There were other differences between this spectrum and that of the above fraction and it would appear that the difference in composition between the fraction and the reduction product was not necessarily due to carbonate or bicarbonate formation, but may have been due to the presence of a greater proportion of the secondary amine. (Piperidine absorbs at 6.0 and 6.10 μ). However, some of the reduction product, which was stable in the second olution mixture and was recovered from it, gave partly on exposure to air, an acetone insoluble substance which absorbed weakly at 5.85 μ. (C=0 stretching frequency).

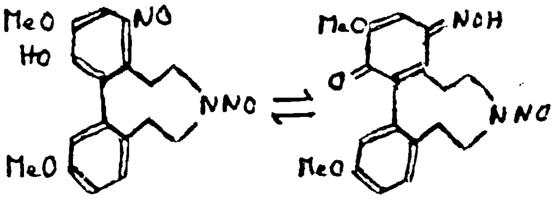
The acetone and ethanol eluants also contained the reduction product, whilst chloroform contained nothing.

(d) Attempted Separation of the Components by the Preparation of Derivatives.

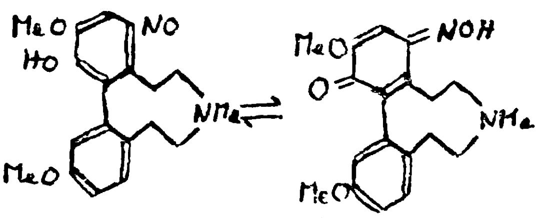
Attempts were made to separate the supposed components of the lithium aluminium hydride reduction product by the preparation and separation of suitable derivatives.

(i) Reaction with Nitrous Acid.

The base was treated with cold nitrous acid. The reaction mixture was extracted with ether, which yielded a substance which could have been either (LXVII) or (LXVIII), as shown by the infrared spectrum.



(LXVII)



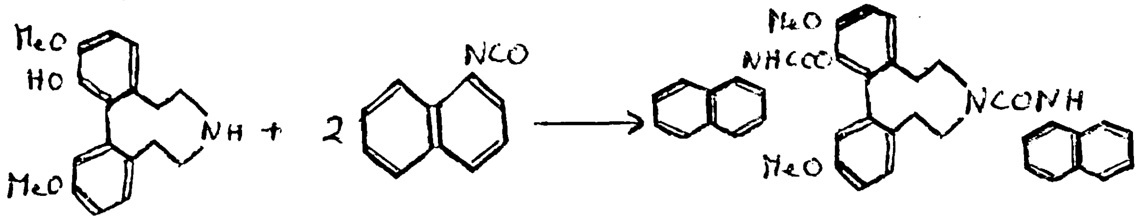
(LXVIII)

The spectrum had peaks, amongst others, at 6.10, 6.65, 7.52, 7.69, 6.73 and 12.80 μ. The first was probably due to C=0 stretching (normally[91] 5.47-6.25 μ) and the second to an aromatic nitroso group (normally[92] *ca.* 6.67 μ). The NO vibration of an N-N=O group[92] (6.85-6.94μ) could have occurred near here also. C-N Stretching vibrations occur in aliphatic amines[89] at 8.20-9.80 μ and in aromatic tertiary amines[89] at 7.35-7.63 μ. The peak at 12.80 μ was possibly due to NO stretching (normally[91] 12.32 μ). There was also a double peak with maxima at 2.96 and 3.08 μ (*cf.* at 2.85 and 2.90 μ in the base), which may have been due to the influence of an NOH group. The OH stretching frequency of this group lies in the range[92] 2.74-2.86 μ.

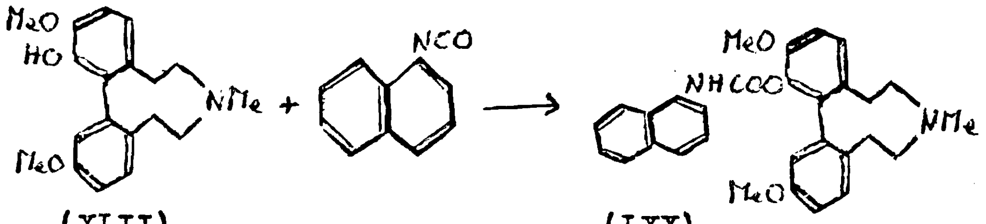
A substance isolated from the aqueous mother liquor appeared to be a less pure form of the above compound, as shown by infrared spectroscopy. It was therefore improbable that a separation had been achieved and the matter was not investigated further.

(ii) Reaction with 1-Naphthylisocyanate.

The base was heated at 80° for 20 minutes with just over one equivalent of 1-naphthylisocyanate in a stream of nitrogen, under strictly anhydrous conditions, when the components, which were then assumed to be present, should have undergone the following reactions:

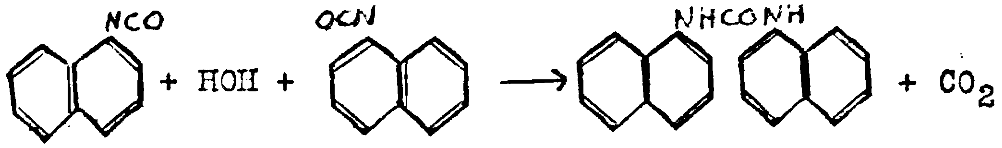


(LIV) (LXIX)



(XLII) (LXX)

Any moisture present would react in the following way:



(LXXI)

After treating the reaction mixture with a variety of dried solvents, a buff coloured solid of melting point 131-133° was isolated, the molecular weight of which was 485, as determined using a vapour pressure osmometer. The molecular weight of (LXX) is 482.6 from the formula, and on this evidence, together with that of the infrared spectrum, the buff coloured solid was assumed to be this compound, although elementary analysis gave a very poor result. Two of the most important features of the spectrum were a double peak with maxima at 5.75 and 5.85 μ, and a broad but well defined peak at 3.06μ. Urethanes have a peak within the range 5.76-5.83 μ due to the stretching vibration[90] of C=O, the peak at 3.06 was presumably due to the stretching vibration of NH, as this peak occurrs in the infrared spectrum of piperidine. This peak did not occur in the spectrum of the base.

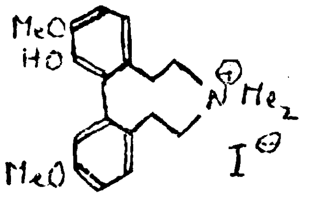
Various other products were obtained, which were either impure forms of (LXX) or of di-(1-naphthyl)-urea (LXXI) or unidentifiable. Melting point, molecular weight and infrared evidence was used in the elucidation of the nature of these products, and an authentic specimen of (LXXI) was prepared by treating 1-naphthylisocyanate with water. No derivative (LXIX) of the secondary amine was obtained and it was concluded that if the secondary amine was present in the base, it was in insufficient quantity for isolation and identification.

(e) Deuteration.

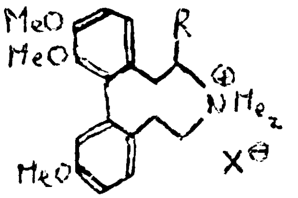
The base was shaken with deuterium oxide for two days. The infrared spectrum of the product had, in addition to the double peak with maxima at 2.85 and 2.90 µ (OH, with or without NH), a corresponding shift of this double peak to a longer wavelength region to give an additional double peak with maxima at 3.85 and 3.92 µ, due[87,89] to the formation of an OD group, with or without an ND group.

The infrared spectrum of the sodium salt of the prepared base had a low plateau in the 2.8-3.2 µ region, the hydroxyl peak having disappeared. There was no peak at 3.06 µ, as in the spectrum of piperidine, which would have been due to an NH group. The salt was dissolved in deuterium oxide and allowed to stand for three days. On recovery of the salt from solution, the infrared spectrum had no peak in the 3.85-4.15 µ region, and hence there was no identifiable quantity of the ND compound present[89], and hence no identifiable amount of the secondary amine in the prepared base.

Preparation of (+)-2,3,8,9-Tetrahydro-3',4',2"-trimethoxy-N,N-dimethyl-4,5:6,7-dibenzazoninium iodide (LXXII) and Bromide (LX).



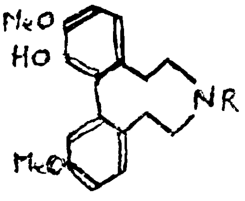
(LXV)



(LX) X = Br; R = H

(LXI) X = Br; R = C_6H_5

(LXXII) X = I; R = H.



(XLII) R = CH_3

(LIV) R = H.

It was necessary to prepare the methyl ether methiodide, the azoninium iodide (LXXII), of the lithium aluminium hydride reduction product. This base could be regarded as being the N-methyl azonine only, as little positive evidence had been found for the existence of the secondary amine. Degradation of (LXXII) and a comparison of the ultraviolet spectrum of the bromide (LX) with that of (+)-α-phenyldihydrothebaine methyl ether methobromide (LXI) and related compounds were required in order to obtain further confirmation of the structure of the reduction product. It had been hoped to carry out racemisation experiments on (LX), but this was not possible and success was achieved later with the methyl ether itself.

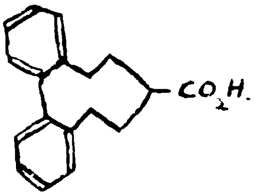
Reaction of Bentley and Robinson's base, the lithium aluminium hydride reduction product, with excess of methyl iodide under neutral conditions, gave the optically active phenolic methiodide (LXV). If any of the secondary amine had been present, this would also have been converted into this quaternary salt. This was further treated with methyl iodide in the presence of sodium methoxide, a method used by Freund[56] in the phenyldihydrothebaine series of compounds, to give the methyl ether methiodide (LXXII), which was also optically active. This compound was also prepared directly from the base using Freund's method. Elementary analysis and infrared evidence confirmed the expected result. It was impracticable to carry out the preparation using Purdie and Irvine's method[93], by treating (LXV) with methyl iodide and silver oxide.

Conversion of some of the methyl ether methiodide into the picrate gave a yellow crystalline solid, on which elementary analysis gave good results.

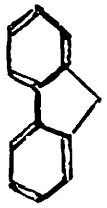
The methyl ether methobromide (LX), was prepared in good yield from (LXXII), by shaking the latter with silver bromide. Good elementary analytical results were obtained. Its ultraviolet spectrum was determined and also that of (+)-α-phenyldihydrothebaine methyl ether methobromide (LXI) (fig. 8, p. 160). The results for these two compounds were compared with those for related compounds obtained from the literature.

The Ultraviolet Spectrum of the Methyl Ether Methobromide (LX).

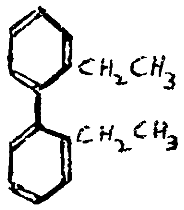
The conjugation bands of (LX) and (LXI) occur as points of inflection at λ_{inf} *ca.* 225 mμ (ε 22,050) and λ_{inf} *ca.* 230 mμ (ε 26,900) respectively. This compares with that of the acid[33] (V), λ_{inf} 231 mμ (ε 5,550), and with that of 2,2'-diethylbiphenyl[58] (XXV), λ_{inf} *ca.* 227 mμ (ε 6,000). The conjugation bands in all these four compounds overlap with those due to the separate benzene rings.



(V)



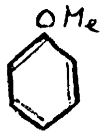
(XIV)



(XXV)

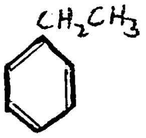
Thus a large hypsochromic shift in each of these conjugation bands has occurred, when compared with the position of that in the spectrum of fluorene[39] (XIV), in which[22] $\theta = 0^{\circ}$, λ_{max} 260 mμ (ϵ 19,000). It should be born in mind that biphenyls bridged across the <u>o</u>,<u>o</u>'-positions to make nine-membered rings, do not possess single conformations corresponding to minimum angles of strain[57]. For the above two methobromides, the <u>ortho</u>-methoxyl group, which is also buttressed, must play a part in diminishing the conjugation between the benzene rings. These effects for biphenyls in general are discussed more fully in the introduction.

The long-wave band of fluorene[32], λ_{max} 300 mμ (ϵ 10,000), due to the hyperconjugative interaction of the two benzene rings through the bridge, is absent in the spectrum[33] of the acid (V), but the two methobromides have maxima at 280.5 (ϵ 4,145) and 282 mμ (ϵ 4,290) respectively. These are not conjugation bands[57,33] as was thought at one time[22] for the case of phenyl-dihydrothebaine, but are due to the phenoxy chromophores, $MeO.C_6H_4$-. Anisole[94] (LXXIII) and <u>p</u>-cresol methyl ether[95] (LXXIV), have maxima at 277.5 (ϵ 1,510) and 279.5 mμ (ϵ 2,425) respectively.



(LXXIII)

(LXXIV)



(LXXV)

Superimposed on the phenoxy chromophore band in the spectrum of (LX) is a small point of inflection at 253.5 mμ (ϵ 692) and in the spectrum of (LXI) are two at 265 (ϵ 2,020) and 271 mμ (ϵ 2,840). In that of 2,2'-diethylbiphenyl (XXV), the alkyl benzene partial chromophores give rise to peaks[58] at 263.5 (ϵ 730) and 271 mμ (ϵ 560). The spectrum of the acid (V) also has two small peaks at about 265 and 271 mμ, with extinction coefficients[33] of about 600. The spectrum of toluene[96] contains peaks at λ_{inf} _ca_. 248 (ϵ 126) and 253 mμ (ϵ 178), λ_{max} 260 (ϵ 224) and λ_{inf} 263 mμ (ϵ 159), that of ethylbenzene[97] (LXXV) at λ_{max} 253 (ϵ 131), 255 (ϵ 131), 262 (ϵ 218), 264.5 (ϵ 173) and 267.5 mμ (ϵ 178), amongst others, and that of _p_-cresol methyl ether[95] at λ_{max} 270.5 (ϵ 1,620) and λ_{inf} 273.5 mμ (ϵ 1,920). Anisole, however, has[94] λ_{inf} 264 (ϵ 1,220) and λ_{max} 271 mμ (ϵ 1,830).

Just as the spectrum of the acid (V) resembles very closely that of 2,2'-diethylbiphenyl[58,33], so those of the methobromides (LX) and (LXI) resemble that of diethylbiphenyl with bands due to the phenoxy chromophores superimposed, although masking of some of the inflections due to the alkylbenzene partial chromophores undoubtedly occurs in the spectrum of (LX).

All the above spectroscopic evidence supports structure (LX) for the methyl ether methobromide and hence structure (XLII) for the lithium aluminium hydride reduction product.

Crystallisation of the N-Methyl Azonine.

The lithium aluminium hydride reduction product was crystallised, with some difficulty, from light petroleum (b.p. 60-80°) giving white globular crystals, which were dextrorotatory in ethanol solution and which melted at 103.5-104.5°. Good elementary analytical results were obtained based on structure (XLII). The infrared spectrum of a mull (fig. 9, p. 162) had the following differences from that of an evaporated acetone solution of the non-crystalline reduction product (fig. 6, p. 140): there was a single strong hydroxyl peak at 2.90 μ instead of the double peak at 2.85 and 2.90 μ, and nine peaks between 3.3 and 3.6 μ instead of only four. In addition, there were other splittings between 5 and 13 μ. The peak due to the NMe group still appeared at 3.60 μ. There was no evidence for an NH group. However, the spectrum of a mull of the non-crystalline reduction product, after prolonged drying under vacuum, closely resembled that of the former. The nuclear magnetic resonance spectrum in deuterochloroform solution had peaks at chemical shifts of τ 4.65 (OH), τ 7.73 (NMe) and at τ 6.17 and 6.28 (the two methoxyl groups), using tetramethylsilane as the standard*. There was no evidence

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*I would like to thank Dr. R.F.M. White of Sir John Cass College, London, for the determination of this spectrum and for the interpretation of the results.

of an NH group, and the crystalline substance was the N-methyl azonine (XLII).

Summary of the Evidence for the Structure of Bentley and Robinson's Base.

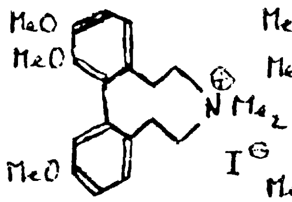
This base, the lithium aluminium hydride reduction product, was obtained initially as a brown glass, the infrared spectrum of which resembled that of (+)-α-phenyldihydrothebaine basically, and hence was of similar structure. Nitrogen was shown to be present and reaction with one equivalent of methyl iodide gave only the quaternary azoninium salt (LXV) together with some unreacted base. Fractional precipitation of the picrate of the reduction product gave two fractions, one in far greater proportion to the other. Nothing positive was identified in the smaller fraction, and the larger was found by various techniques, including nuclear magnetic resonance spectroscopy, to be the picrate of the N-methyl azonine (XLII) only, with no conclusive evidence to support the presence of any secondary amine salt. An attempted column chromatographic separation of the base gave a fraction which could have contained some of the secondary amine (LIV), but the evidence was inconclusive. Reaction of the base with nitrous acid, and with 1-naphthylisocyanate, and also treatment of the sodium salt with deuterium oxide, gave results consistent with the presence of the N-methyl azonine only. Crystallisation of the base gave a product which was dextrorotatory in solution. Thus the base is (+)-2,3,8,9-tetrahydro-4'-hydroxy-3',2"-dimethoxy-N-methyl-4,5;6,7-dibenzazonine (XLII) only and is not a mixture with the secondary amine, unless this is present in an unidentifiably small proportion.

The ultraviolet spectrum of the quaternary azoninium bromide confirmed structure (XLII) for the base, and the nuclear magnetic resonance spectrum of the crystalline compound was consistent with this structure.

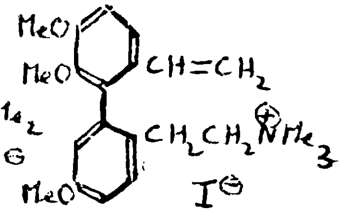
The Exhaustive Methylation of the Methyl Ether Methiodide (LXXII).

For the final confirmation that the base had the tetrahydrodibenzazonine structure, it was necessary to carry out an exhaustive methylation; this structure would give a 2,2'-divinylbiphenyl.

(a) Hofmann Degradation to (+)-2,3,3'-Trimethoxy-6 (or 6')-(2-trimethylammonioethyl)-6' (or 6)-vinylbiphenyl Iodide (LXXVI).

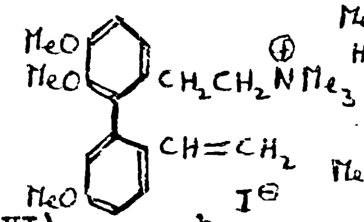


(LXXII)

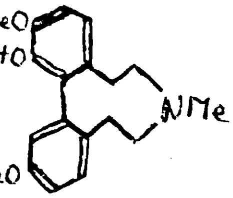


a

(LXXVI)



b



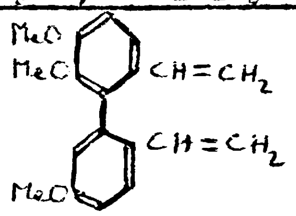
(XLII)

The methyl ether methiodide (the azoninium iodide) (LXXII) was subjected to a Hofmann degradation, by the method which Freund[56] had used on phenyldihydrothebaine, i.e. it was allowed to react with sodium ethoxide in ethanol. The product was treated with methyl iodide and gave what appeared to be a mixture of two methine methiodides. A series of crystallisations from ethanol and from ethanol-light petroleum (b.p. 80-100°)

yielded eventually, A, m.p. ca. 200° (in 25% yield) and B, m.p. ca. 180° (in 50% yield). The best fraction of A consisted of laevorotatory white feathery crystals, m.p.203.5-204°, and that of B of dextrorotatory colourless needles, m.p. 182-183°. A gave good elementary analytical results, for the expected methine methiodide, but those for B were very poor and did not correspond to figures based on any reasonable formula. The infrared spectrum of B resembled that of the methiodide of (+)-α-phenyldihydrothebaine methyl ether iso-methine (LVII) (allowing for the absence of the third benzene ring); A, to a lesser extent. The spectra of both had peaks at about 10.95 μ which may have been due to the CH_2 out of plane deformation vibration of $CHR{=}CH_2$, which normally lies between[91,98] 10.93 and 11.05 μ. One of the methine methiodides was probably the 6-vinyl-biphenyl iodide derivative (LXXVIa) and the other the 6'-vinyl-biphenyl iodide derivative (LXXVIb), as was shown below.

A later preparation gave only the higher melting compound.

(b) Hofmann Degradation of the Methine Methiodides (LXXVI) to (+)-2,3,3'-Trimethoxy-6,6'-divinylbiphenyl (LXIII).



(LXIII)

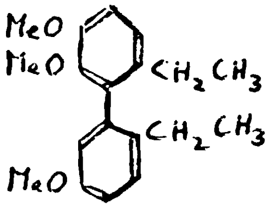
A second Hofmann degradation was carried out on each of the products obtained in (a), by the method of Bentley and Robinson[65], as used in the phenyldihydrothebaine series of compounds. They both gave identical products, which were uncrystallisable oils, and of the same dextrorotatory power in 96% ethanol solution. The infrared spectra were also identical and had peaks at 6.10, 10.10 and 11.10 μ. The C=C stretching vibration in $CHR=CH_2$ normally occurs between 6.08 and 6.10 μ, the CH out of plane deformation frequency between 10.05 and 10.15 μ, and the CH_2 out of plane deformation frequency between 10.93 and 11.05 μ for alkenes[98]. Poor elementary analytical results were obtained, possibly because the compound could not be crystallised or distilled. Catalytic hydrogenation gave the expected diethylbiphenyl, however (see below).

After standing in an evacuated desiccator for three weeks, both batches of the oil were partly converted into infusible white solids, which were assumed to be polymers of the compound, as the infrared spectra had either a diminution in size or a disappearance of some of the supposed peaks due to vinyl groups. This polymerisation also took place in solution.

From the above evidence, it appeared that the expected (+)-2,3,3'-trimethoxy-6,6'-divinylbiphenyl (LXIII) had been obtained. This, together with the evidence from the ultraviolet spectrum of the methyl ether methobromide (LX) confirms the structure of Bentley and Robinson's lithium aluminium hydride reduction product as a tetrahydrodibenzazonine.

Preparation of (+)-2,3,3'-Trimethoxy-6,6'-diethylbiphenyl (LXIV).

The freshly prepared (+)-divinylbiphenyl (LXIII) was hydrogenated to the diethylbiphenyl (LXIV) using a palladium-charcoal catalyst and a hydrogen pressure of one atmosphere. A dextrorotatory white viscous oil was obtained in good yield. Good elementary analytical results were obtained. The infrared spectrum had no peaks at 6.10, 10.10 and 11.10 μ, which were the peaks assumed to be due to the vinyl groups in the spectrum of (LXIII).

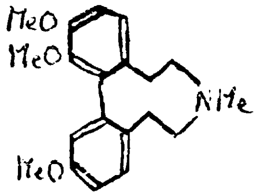


(LXIV)

The ultraviolet spectrum in 96% ethanol resembled very closely that of the methobromides (LX) and (LXI) (p. 124, also fig. 8, p. 160) and that of (+)-2-(2-ethyl-5-methoxyphenyl)-3,4-dimethoxydibenzyl (LI) (p. 57, also fig. 10, p. 170). The peak due to the phenoxy chromophore occurred at 279 mμ (ϵ 4,710) and the vestigial conjugation band at λ_{inf} ca. 227.5 mμ (ϵ 16,700), which was overlapped by the peak due to the benzene chromophore at 201 mμ (ϵ 60,200) (cf. also the spectrum of 2,2'-divinylbiphenyl, p. 53). There was no trace of any peak at 310 mμ, which was present in the spectrum of the stilbene (XLIII) and due to the presence of the vinyl groups (p. 53). Hence, complete hydrogenation of the vinyl groups of (LXIII) had occurred and the spectrum of (LXIV) was as expected.

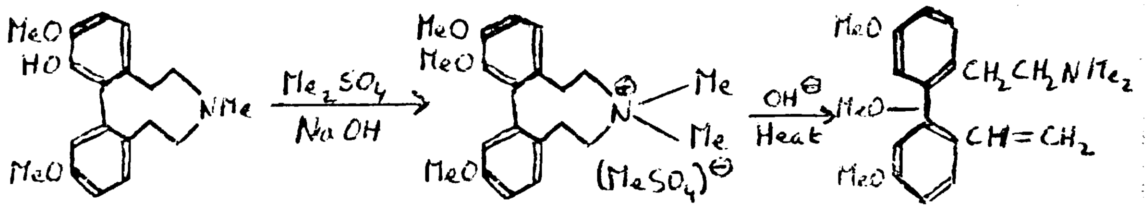
Preparation of (+)-2,3,8,9-Tetrahydro-3',4',2"-trimethoxy-N-methyl-4,5:6,7-dibenzazonine (LXXVII).

It was originally hoped to perform kinetic racemisation experiments on the methyl ether methobromide (LX), in order to compare the results with those for other related bridged biphenyls especially in view of the fact that it has a "buttressed" methoxyl group. Attempts were made in various solvents, but in every case decomposition as well as racemisation occurred. In view of the general greater stability of tertiary amine bases than of the corresponding quaternary salts, it was decided to prepare the methyl ether base (LXXVII) and determine its optical stability.



(LXXVII)

It was necessary to methylate the phenolic hydroxyl group of the N-methyl azonine without quaternising the nitrogen atom. The crystalline N-methyl azonine did not react with diazomethane. Reaction with dimethyl sulphate in sodium hydroxide solution was carried out at an elevated temperature, and a viscous oil, dextrorotatory in β-phenylethyl alcohol solution, was obtained, whose infrared spectrum had no hydroxyl peak. The substance was basic in nature, and some was reacted with picric acid and also with methyl iodide. The former product could not be obtained crystalline, but the latter could and was shown to be a mixture of the methine methiodides (LXXVI), which had been prepared previously (p. 129). It was apparent that the N-methyl azonine had been initially converted into the methyl ether of the quaternary methyl methosulphate (LXVIII), which, under the prevailing hot alkaline conditions, had degraded to the methine bases (LXXIX).



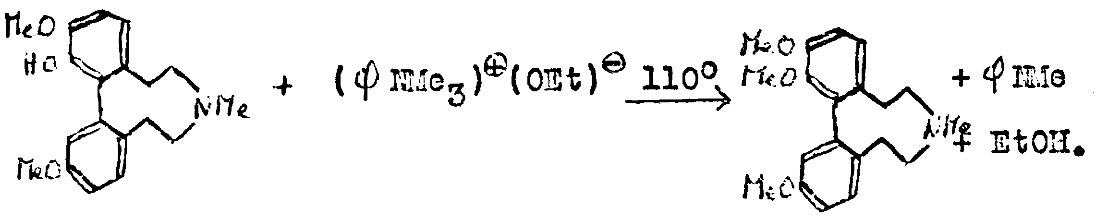
(XLII) (LXXVIII) (LXXIX)

The desired product (LXXVII) was obtained by the method which Rodionov[99] used to convert morphine into thebaine. Phenyltrimethylammonium p-toluene sulphonate was prepared by allowing p-methyltoluene sulphonate and dimethyl aniline to react together. Reaction with sodium ethoxide in ethanol solution gave phenyltrimethylammonium ethoxide and this was used to convert the N-methyl azonine into its methyl ether.

$$\phi NMe_2 + (p\text{-})\ MeC_6H_4SO_3Me \rightarrow (\phi NMe_3)^{\oplus}(MeC_6H_4SO_3)^{\ominus} \xrightarrow{EtONa}$$

(LXXX)

$$(\phi NMe_3)^{\oplus}(OEt)^{\ominus} + MeC_6H_4SO_3Na.$$



(XLII) (LXXVII)

The dimethyl aniline, which was liberated, cannot attack NMe groups, and as it is too weakly basic to form a salt with acetic acid, was steam distilled off from the reaction mixture in acetic acid solution. Isolation of the methyl ether (LXXVII) and distillation under reduced pressure gave an uncrystallisable viscous oil, in good yield. The infrared spectrum showed the absence of a hydroxyl group and nuclear magnetic resonance spectroscopy in deuterochloroform solution[*] confirmed this absence and also the presence of an additional methoxyl group (for the three methoxyl groups: τ 6.15, 6.25 and 6.47) as well as the presence of an NMe group (τ 7.73). Tetramethyl silane was used as the standard. Elementary analysis was not completely satisfactory, owing possibly to the fact that the base soon became discoloured on standing, even under vacuum.

The oil in β-phenylethyl alcohol solution was dextrorotatory; after it had been heated at 193° for 4½ hours until optically inactive, it yielded the racemate without decomposition, as shown by infrared spectroscopy.

Reaction of the optically active compound with methyl iodide gave the methiodide (LXXII), with melting point, and infrared spectrum identical with those of an authentic specimen described above (p. 123).

The tertiary picrate was obtained in the solid state, but the melting point was not sharp. Elementary analysis gave a good result and the infrared spectrum resembled that of the picrate

[*] See footnote, p. 127.

of the phenolic N-methyl azonine, which melted at 103-105.5° (p. 114), in the 3.2-3.6 μ region; the hydroxyl peak was absent.

All the above evidence confirms that the oil obtained is the methyl ether (+)-2,3,8,9-tetrahydro-3',4',2"-trimethoxy-N-methyl-4,5:6,7-dibenzazonine (LXXVII).

Kinetic Racemisation Studies.

The sealed tube technique was used as described on p. 83. The graphs plotted and calculations were as described on p. 48, giving the results as stated below, for the given compounds.

(a) (+)-2,3,3'-Trimethoxy-6,6'-divinylbiphenyl (LXIII).

Although a *p*-cymene solution of the vinylbiphenyl and picric acid (to act as polymerisation inhibitor) gave no precipitation after standing for several months, it was decided that kinetic racemisation experiments would give unreliable results, and hence were not carried out.

(b) (+)-2,3,3'-Trimethoxy-6,6'-diethylbiphenyl (LXIV).

A 1.975% solution in β-phenylethyl alcohol was used, between the temperature range 181.5-228.9°, $\lambda = 5780$ Å.

$E = 33.8$ kcal. mole^{-1}, $\Delta H^{\ddagger} = 32.8$ kcal. mole^{-1},
$\log_{10} A = 11.5$ sec^{-1}., $\Delta F^{\ddagger} = 37.3$ kcal. mole^{-1} at
$\Delta S^{\ddagger} = -8.94$ e.u., 228.9°.

The racemate was isolated with 100% recovery; it gave acceptable results on elementary analysis, and the infrared spectrum was identical with that of the optically active compound. Hence, the kinetic measurements had been concerned with racemisation only and no decomposition had occurred.

(c) (+)-2,3,8,9-Tetrahydro-3',4',2"-trimethoxy-N-methyl-4,5:6,7-dibenzazonine (LXXVII).

A 3.49% solution in β-phenylethyl alcohol solution was used in the temperature range 145.0-191.5°, λ = 5780 Å..

$E = 31.5$ kcal. mole^{-1}, $\Delta H^{\ddagger} = 30.9$ kcal. mole^{-1},

$\log_{10} A = 11.7$ sec^{-1}., $\Delta F^{\ddagger} = 34.5$ kcal. mole^{-1} at 191.5°.

$\Delta S^{\ddagger} = -7.60$ e.u.,

The racemate was isolated with 69% recovery, after heating the combined fractions of solution from the kinetic runs until optically inactive. Elementary analysis gave satisfactory results, and together with infrared evidence, showed that racemisation only, with no decomposition, had occurred.

EXPERIMENTAL.

The Preparation and Properties of Bentley and Robinson's Base.

Sodium dried solvents were used where anhydrous conditions were required.

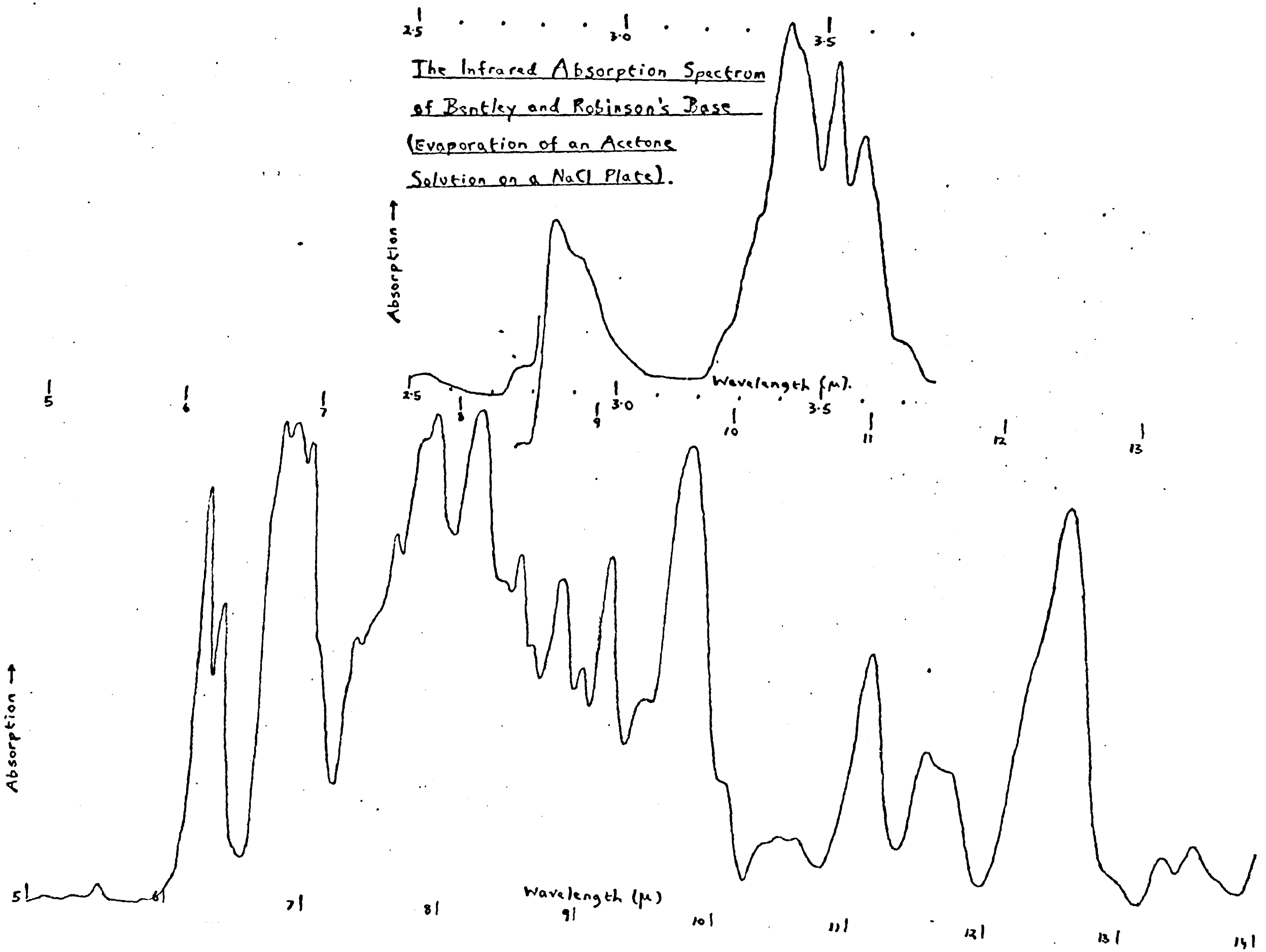
Anhydrous magnesium iodide was prepared as follows. Iodine (9.15 g.) was added to a slight excess (ca. 1 g.) of magnesium turnings in a mixture of benzene (80 c.c.) and ether (20 c.c.). Precautions were taken to ensure the exclusion of moisture. Slight warming was needed to start the reaction and when the latter had finished, the mixture was heated under reflux on a water bath until the distinctive colour of iodine had been replaced by a muddy-brown colour (ca. 1½ hr.).

Thebaine and the magnesium iodide were then allowed to react together, by the method of Bentley and Robinson[65]. Thebaine (10 g.) was dissolved in benzene (200 c.c.) and the anhydrous magnesium iodide suspension was added slowly to the refluxing, vigorously stirred solution over a period of 1 hr., care being taken to exclude moisture. A dark brown precipitate immediately formed, which soon became green and eventually light brown. Heating under reflux and stirring were continued for a further 4 hr.; the solid was then rapidly filtered off, washed with hot benzene, then ether, and stored in an evacuated desiccator. Yield 27.2 g. of material which was still heavily solvated with benzene; this was gradually liberated on storage even after a considerable time. No green substance was produced even after six months' storage, as previously stated by Bentley and Robinson. Altogether 234 g. were prepared in this way.

The product was insoluble in ethanol, chloroform, acetone, and ether, but soluble in methanol. The addition of water immediately produced a greenish substance. The infrared spectrum showed a peak at 5.95 μ, possibly due to a cyclic C=N group[86], and there was intense absorption at 2.8-3.2 μ which may have been due to hydroxyl[87] produced by some aerial hydrolysis of the -OMgI. On testing for Mg and I^-, positive results were obtained. The above evidence supported Bentley and Robinson's structure (LIII) for this product.

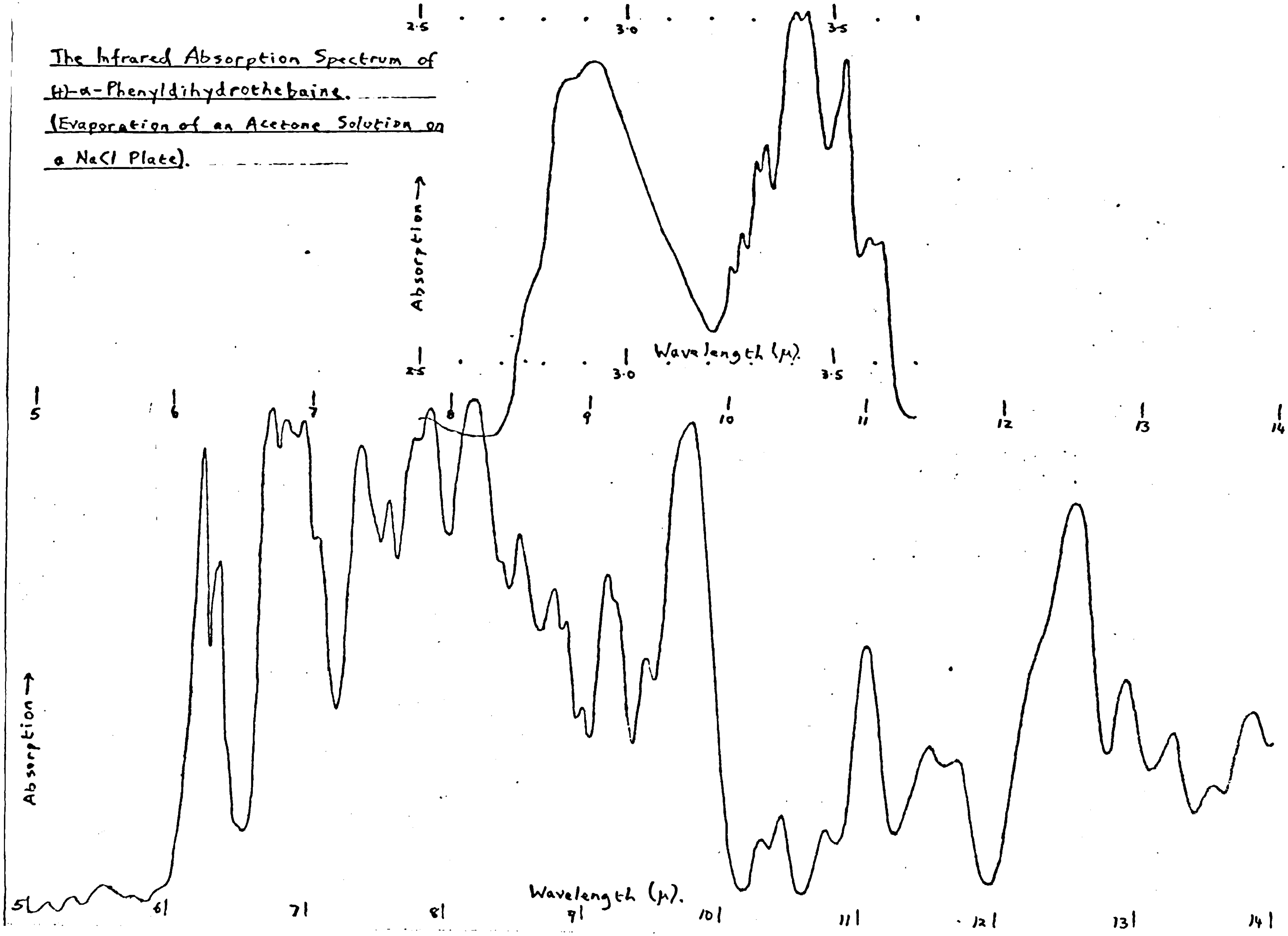
The above thebaine-magnesium iodide product was reduced with lithium aluminium hydride, by a modification of Bentley and Robinson's method[65]. 13.6 G. of the freshly prepared product were suspended in ether (75 c.c.). Lithium aluminium hydride (1.6 g.) was suspended in ether (45 c.c.) and added slowly to the above suspension. The mixture was heated under reflux and vigorously stirred, precautions being taken to eliminate moisture. A large volume of gas was evolved during the addition. Heating was continued for a further 1½ hr., the pale-brown solid initially present giving way to a white one. The mixture was cooled and hydrolysis of the product started by the addition of wet ether. It was completed with a 33% aqueous solution of

Fig. 6.



The Infrared Absorption Spectrum of Bentley and Robinson's Base (Evaporation of an Acetone Solution on a NaCl Plate).

Fig. 7.



The Infrared Absorption Spectrum of (+)-α-Phenyldihydrothebaine. (Evaporation of an Acetone Solution on a NaCl Plate).

Rochelle's salt. About 1 litre of water was added to the thick emulsion produced and the latter was extracted three times with ether. The combined extracts were dried over anhydrous sodium sulphate and the ether was evaporated, the last traces being taken off under vacuum. Yield 3.85 g., ca. 80% based on thebaine. Altogether 39 g. were prepared.

The substance was in the form of a dark-brown glass of softening point ca. 50-53°. The infrared spectrum of an evaporated acetone solution was similar in form to that of one of (+)-α-phenyldihydrothebaine (VI) which had been treated similarly, indicating that the two compounds had the same basic structure. However, the latter spectrum had additional peaks at 3.25, 3.27, 3.31, 8.85, 9.20, 12.90 and 13.85 μ which could have been due to an extra phenyl group[100]. Each spectrum contained a peak at 3.60 μ, presumed to be due to an NMe group[89]. That of the prepared base showed virtually no absorption at 6.05 μ (see later) which could have been due to NH had it been present[89], and a double peak with maxima at 2.85 and 2.90 μ occurred, which was due[87] to OH but part was then thought to be due to NH.

Nitrogen was present (Lassaigne test) and cold nitrous acid gave an orange-red solution, whereas the phenyldihydrothebaine gave a yellow solution. Each gave a deep red solution on basification. Nitrous acid and the performance of Liebermann's test with concentrated sulphuric acid and phenol gave a green-blue colour which became purple on dilution and yellow on basification. At this stage it was uncertain whether this prepared base was the secondary amine (LIV) or the N-methyl azonine (XLII).

On standing in air, the base assumed a bluish colouration, but when kept in an evacuated desiccator, it does not happen, and hence it was stored in this way.

Reduction of the thebaine-magnesium iodide product with lithium aluminium hydride after two weeks' storage, proved more difficult and needed a much longer period of heating under reflux. Yield 2.81 g., 58.5% based on thebaine.

Investigation of the Composition of Bentley and Robinson's Base.

(a) Reaction with Methyl Iodide.

(i) With Excess of Reagent.

The base (3.75 g.) was dissolved in acetone (7.5 c.c.) and methyl iodide (5 c.c.) added. A white precipitate slowly formed and the mixture was heated under reflux for 1½ hr. The acetone and most of the excess methyl iodide were removed, a little acetone was added and the mixture was filtered, the solid then being washed with acetone. Yield 4.6 g. (81%). The product was crystallised from ethanol, giving (+)-2,3,8,9-tetrahydro-4'-hydroxy-3',2"-dimethoxy-N,N-dimethyl-4,5:6,7-dibenzazoninium iodide (LXV) as small pale yellow crystals, m.p. 218-218.5°. $[\alpha]_D$ +44.6°, $[\alpha]_{5461}$ +54.8°, (c, 0.25 in ethanol).

(Found: C, 52.5; H, 5.9; I, 27.7; N, 3.2; O, 10.6. $C_{20}H_{26}INO_3$ requires C, 52.8; H, 5.75; I, 27.9; N, 3.1; O, 10.5%).

The infrared spectrum contained a hydroxyl peak at[87] 3.05 μ. In the 3.2-3.7 μ region, it resembled in outline the spectrum of (+)-α-phenyldihydrothebaine methyl ether methiodide (LXVI). Together with the analysis, this showed the presence of an $\overset{\oplus}{N}Me_2$ group and supported structure (LXV) for the compound. Both secondary amine and N-methyl azonine would give this compound under the above conditions of preparation.

Some of the methiodide (0.22 g.) was dissolved in dilute aqueous sodium hydroxide solution and dilute acid was added until precipitation just commenced. One drop of the sodium hydroxide solution was then added, followed by an aqueous solution of 0.33 g. of sodium picrate. On adjusting the pH to between 5 and 7, a yellow precipitate (0.28 g.) was obtained of the picrate. This was crystallised from iso-propyl alcohol, filtered, and washed with light petroleum (b.p. 40-60°). After the picrate had been dried under vacuum for one day at 60-70°, its m.p. was 102.5-104°. A further crystallisation, and period of drying under vacuum as before, gave 0.12 g. of (+)-2,3,8,9-tetra-hydro-4'-hydroxy-3',2"-dimethoxy-N,N-dimethyl-4,5:6,7-dibenzazoninium picrate, m.p. 96-98°. (Found: C, 56.1; H, 5.2; N, 9.9; O, 28.7. $C_{26}H_{28}N_4O_{10}$ requires C, 56.1; H, 5.1; N, 10.1, O, 28.75%). Precipitation from iso-propyl alcohol solution by pouring this into ether, increased the m.p. to 104.5-107.5°.

(Found: C, 56.05; H, 5.1; N, 10.3. $C_{26}H_{28}N_4O_{10}$ requires: C, 56.1; H, 5.1; N, 10.1%). It seems that melting point depends on particle size or crystal structure.

(ii) Reaction with one Equivalent of Methyl Iodide.

The base (1.0 g.) was dissolved in acetone (2 c.c.) and one equivalent (0.21 c.c.) of methyl iodide was pipetted into the mixture. A whitish precipitate slowly formed, and the mixture was heated under reflux for 2 hr. on a low temperature water bath. A little unreacted methyl iodide and acetone were boiled off. Water was added to the residue which was then extracted with benzene six times. The combined extracts were dried over calcium chloride and evaporated, leaving a brown gum (0.1 g.). The addition of a small quantity of methyl iodide in acetone to this product gave a white precipitate.

The aqueous solution was evaporated and the residue was dissolved in acetone, which was then removed. Solution in acetone again gave, on standing, a white precipitate (1.15 g.), m.p. 215-215.5°. This was filtered off and the filtrate was evaporated, giving a residue (0.35 g.). Neither reacted further with methyl iodide. The infrared spectrum of the precipitate was identical with that of the methiodide (LXV) of the lithium aluminium hydride reduction product, prepared in (i) above, and was thus the quaternary salt. The spectrum of the residue from the mother liquor was very similar but not so clear, as the residue must have been less pure.

Another experiment, using half the above quantities of reagents yielded 0.1 g. of the brown gum and 0.4 g. of the quaternary salt. Deductions obtained from the various I.R. spectra are discussed on p. 113.

Each batch of quaternary methiodide, obtained above, was converted into the picrate, as in (i). Comparison of the infrared spectrum and melting point of each batch with those of the authentic specimen, showed that the same compound had been obtained. This was confirmed by mixed melting point evidence.

(b) Fractional Crystallisation of the Picrate of the Base.

The base (5.0 g.) was dissolved in ethanol and two equivalents (7.5 g.) of picric acid in ethanol solution were added, giving a yellow gum. Crystallisation from ethanol gave an oil, which solidified on cooling, and two crops of crystals: (i) 2.21 g., m.p. 107-144°, and (ii) 0.85 g., m.p. 83-105°, 135-140°, on concentration of the mother liquor. Further crystallisation of these fractions from ethanol always gave an oil and a crop of crystals. From methanol an oil only was obtained, but n- and iso-propyl alcohols gave only solid and the substance was less soluble in the latter solvent.

After a further crystallisation of the fractions from ethanol, extraction of each with hot iso-propyl alcohol gave a solution and a much less soluble residue. The more soluble fraction was recovered on cooling, and re-extracted with hot iso-propyl alcohol, and the less soluble was crystallised from n-propyl alcohol. The crystallised products from n-propyl alcohol were crystallised further from this solvent. This process was continued until fractions were obtained which did not alter in melting point on further treatment. That finally obtained from iso-propyl alcohol had m.p. 103-105.5° and was in high yield; that from n-propyl alcohol, m.p. 217-218°, was very small in quantity.

The former picrate appeared at the time to be either the solvated derivative of the secondary amine or that of the unsolvated N-methyl azonine, as the following results indicated: (Found: C, 55.4; H, 5.3; N, 9.8; O, 29.45. $C_{24}H_{24}N_4O_{10}$ + C_3H_7OH requires: C, 55.1; H, 5.5; N, 9.5; O, 29.9. $C_{25}H_{26}N_4O_{10}$ (N-methyl azonine picrate) requires: C, 55.35; H, 4.8; N, 10.3; O, 29.5%). After standing for two weeks this picrate had m.p. 106-119°. An authentic specimen (obtained later) of the N-methyl azonine was converted into the picrate, and, after two crystallisations from iso-propyl alcohol, the (+)-2,3,8,9-tetrahydro-4'-hydroxy-3',2"-dimethoxy-N-methyl-4,5;6,7-dibenzazoninium picrate had m.p. 101-111°. (Found: C, 55.7; H, 5.7; N, 9.9; O, 28.5. $C_{25}H_{26}N_4O_{10}$ requires: C, 55.35; H, 4.8; N, 10.3; O, 29.5%). The result for oxygen was anomalous. The infrared spectra of this and the picrate m.p. 103-105.5° were identical.

The following were prepared in order to record their N.M.R. spectra:

(i) Some of the picrate, m.p. 103-105.5°, was extracted from sodium hydroxide solution at pH 5-6 with ether, and after drying the extract over anhydrous sodium sulphate, the ether was removed. The base obtained was dried under vacuum.

(ii) The picrate of authentic crystalline N-methyl azonine (obtained later) was converted into the base, which was dried overnight, under vacuum, in contact with a molecular sieve at the temperature of liquid nitrogen.

(iii) Authentic crystalline N-methyl azonine (obtained later, p. 159).

(iv) Solvated phenyldihydrothebaine was crystallised twice from light petroleum (b.p. 40-60°) and obtained unsolvated, as shown by the I.R. spectrum. It had m.p. 38-54°.

The n.m.r. spectra were determined, using tetramethylsilane as standard, at 60 Mc/sec. The peaks at the given chemical shifts were identified as shown, amongst others, and the significance of the unidentified peaks are discussed on p. 116.

Specimen	Solvent	OH	MeO	NMe	Unidentified
(i)	$CHCl_3$	-	6.10, 6.22	7.73	8.78
(i)	CCl_4	4.75	6.12, 6.22	7.77	8.69
(ii)	$CDCl_3$	-	6.08, 6.20	7.73	8.76*
(ii)	CCl_4	4.85	6.15, 6.25	7.80	8.71*
(iii)	CCl_4	4.66	6.16, 6.26	7.80	-
(iv)	$CDCl_3$	4.54	6.02, 6.17	7.71	8.97, 9.14
(iv)	CCl_4	4.60	6.10, 6.25	7.81	9.10

*small peaks.

Column chromatography failed to give more than one substance from the picrate m.p. 103-105.5°. Heating under reflux with insufficient iso-propyl alcohol for complete solution gave, after recovery of that in solution, two fractions of different melting point. However, after precipitation of each of these from either hot benzene or hot iso-propyl alcohol by the addition of light petroleum (b.p. 60-80°), products of similar m.p. (*ca.* 120°) and of identical I.R. spectra were obtained. Precipitation of some of the picrate, m.p. 103-105.5°, from benzene solution by the addition of successive quantities of light petroleum (b.p. 40-60°) gave fractions of different m.p., between 128 and 155°. However, the I.R. spectra were identical. All the spectra obtained here were identical with that of the picrate, m.p. 103-105.5°, with peaks at 3.67 μ (NMe) but none at *ca.* 6 μ (NH).

The picrate, m.p. 217-218°, appeared to be the unsolvated N-methyl azonine, by analysis. (Found: C, 55.65; H, 4.8; N, 10.3; O, 29.4. $C_{25}H_{26}N_4O_{10}$ requires: C, 55.35; H, 4.8; N, 10.3; O, 29.5%). On conversion into the base, n.m.r. spectroscopy gave unintelligible results. The authentic specimen of the N-methyl azonine picrate, when crystallised twice from *n*-propyl alcohol, had m.p. 111-114°. No further work was done on the picrate, m.p. 217-218°, owing to insufficient sample.

(c) Work on the Lithium Aluminium Hydride Reduction Product.

(i) Fractional Precipitation.

The reduction product was extracted with carbon tetrachloride giving a pale brown residue. This residue was fractionally precipitated from acetone solution three times with carbon tetrachloride. The infrared spectrum of the final precipitate had no peak[89] at 3.60 μ (NMe), but absorption occurred at ca. 6 μ, suspected of being due to an NH group[89]. Exposure of this fraction to air and extraction with acetone, gave a brown residue of indistinct I.R. spectrum. The parts soluble in carbon tetrachloride, had I.R. spectra resembling that of the untreated base.

(ii) Attempted Chromatographic Separation.

Some of the reduction product was dissolved in a small quantity of acetone and deposited on a silica gel chromatographic column and eluted with the following, in the order shown: 60% acetone + 40% carbon tetrachloride; 80% acetone + 20% carbon tetrachloride; 100% acetone; chloroform; and ethanol.

The first eluant gave a substance whose I.R. spectrum was somewhat different from that of the reduction product, the main differences being the presence of peaks at 6.00 μ and 5.90 μ but not at 3.60 μ. There was no evidence for the presence of HCO_3^- or CO_3^{--}. No change in the spectrum occurred on drying the substance under vacuum in contact with a molecular sieve at the temperature of liquid nitrogen. Carbon dioxide was passed through a solution of the authentic N-methyl azonine (obtained later) in aqueous acetone, for 6 hr. After drying the product under vacuum as above, a mauve solid was obtained. The I.R. spectrum was different from that of the fraction from the column. Although there was a peak at 6.05 μ (probably[89] $NH^{\oplus}$) and that at 3.60 μ (NMe) was very small, there was not one at 5.90 μ (C=O stretching frequency[90]) nor was there any other evidence for HCO_3^- or CO_3^{--}. There were also other smaller differences.

The second eluant on evaporation yielded a substance whose I.R. spectrum resembled that of the reduction product, but on standing in air, the substance gave partly an acetone insoluble residue which absorbed weakly at 5.85 μ in the I.R. region. This substance was stable in the eluant, however.

The other eluants yielded the reduction product, except for the chloroform, which gave no product.

(d) Attempted Separation of the Components by the Preparation of Derivatives.

(i) Reaction with Nitrous Acid.

Reaction of the original base with cold nitrous acid produced an orange coloured solution. Excess acid was removed by the addition of a little urea, and the solution was extracted with ether. The extract was washed with water and evaporated. The I.R. spectrum suggested that it could be either a derivative of the secondary amine (LXVII) or of the N-methyl azonine (LXVIII) (p. 119).

The aqueous solution was rendered basic with sodium carbonate and extracted with chloroform. The I.R. spectrum of this product was similar to but less clear than that obtained above, and suggested that the product was a less pure form of the same compound.

(ii) Reaction with 1-Naphthylisocyanate. Dried solvents were used throughout.

The original base (2.0 g.), 1-naphthylisocyanate (1 c.c., just over one equivalent), and one drop of triethylamine dissolved in ether to act as a catalyst, were heated in a nitrogen atmosphere at 80° for 20 min., care being taken to exclude moisture, within which time the originally obtained molten mass had become solid. After cooling, the reaction mixture was extracted successively with the following solvents.

(1) Cold light petroleum (b.p. 40-60°). After evaporation of the extract, a white solid, insufficient in amount for further investigation, was obtained.

(2) Cold light petroleum (b.p. 80-100°). This yielded a white solid after evaporation, which had, after recrystallisation from light petroleum (b.p. 100-120°), m.p. 95-100°. This was regarded as being an impure form of the N-methyl azonine derivative (LXX).

(3) Cold light petroleum (b.p. 100-120°). Evaporation of this extract gave a solid, which after two crystallisations from this solvent, gave pale yellow crystals, m.p. 100-110°. The molecular weight in 96% ethanol solution was found to be 467, using a vapour pressure osmometer previously calibrated with benzil in 96% ethanol solution. The molecular weight of (LXX) is 482.6, and hence this substance was considered to be an impure form of the N-methyl azonine derivative.

(4) Hot light petroleum (b.p. 100-120°). After allowing this extract to cool, the substance which precipitated was filtered off and crystallised again, giving an off-white solid

m.p. 100-130°. The crystallisation liquor was combined with the cooled extract and set aside. The solid was extracted with ether, giving a violet coloured residue of m.p. <u>ca</u>. 195°. The extract was set aside for further treatment.

Di-(1-naphthyl)-urea (LXXI) and the impure N-methyl azonine derivative (LXX) were isolated from the residue, m.p. <u>ca</u>. 195°, the former being identified by comparing the melting point and I.R. spectrum with those of an authentic specimen, prepared by the action of water on 1-naphthylisocyanate. The latter was identified by I.R. evidence.

The ether extract, after filtering off the solid, m.p. <u>ca</u>. 195°, was evaporated, yielding a brown gum. After two crystallisations from a mixture of acetone and light petroleum (b.p. 100-120°), the N-methyl azonine derivative was obtained as a buff coloured solid, m.p. 131-133°. The molecular weight in 96% ethanol was determined using the osmometer, at the following molarities: 0.0377, 0.0189, 0.0074 M, giving the results: 482, 482, and 492 respectively, the mean being 485 [(LXX) = 482.6]. Infrared spectral evidence supported this conclusion, and details are given on p. 121. (Found: C, 75.0; H, 5.8; N, 6.5; O, 12.0. $C_{30}H_{30}N_2O_4$ requires: C, 74.7; H, 6.3; N, 5.8; O, 13.3%).

The combined liquors from (4) were evaporated. The residue was found to be a mixture of impure (LXX) and various unidentified substances, as shown by m.p. and I.R. evidence, and molecular weight determinations.

No trace of the secondary amine derivative (LXIX) had been found, and if present at all, the amine must have been present with the N-methyl azonine in a very small amount only.

(e) Deuteration.

The base, as isolated from the lithium aluminium hydride reduction, was shaken with deuterium oxide for 2 days, occasionally heating the mixture to 30°. The base was dried under vacuum. Together with the double peak with maxima at 2.85 and 2.90 μ (OH with or without NH), there was now one with maxima at 3.85 and 3.92 μ, due to[87,89] OD with or without ND.

The original base (0.25 g.) was dissolved in a little ethanol and aqueous sodium hydroxide solution (8.0 c.c. of N/10, the theoretical quantity) was added. Unchanged base was extracted with ether and the aqueous solution was evaporated under vacuum. Twice acetone was added and removed and then the residue was finally dried by warming under vacuum. The sodium salt was obtained as a green solid. The infrared spectrum contained no hydroxyl peak, although there was a low plateau in the 2.8-3.2 μ region. There was no NH peak at 3.06 μ as in the spectrum of piperidine, and the NMe peak at 3.60 μ was of moderate intensity.

The salt was dissolved in deuterium oxide and allowed to stand for 3 days. The solution was evaporated and the residue was dried under vacuum. The I.R. spectrum had no peak in the 3.85-4.15 μ region and the above plateau was retained and hence there was no identifiable quantity of the ND compound present[89].

(+)-2,3,8,9-Tetrahydro-3',4',2"-trimethoxy-N,N-dimethyl-4,5:6,7-dibenzazoninium Iodide (LXXII).

(i) Purdie and Irvine[93]. Methyl iodide (1 c.c., ca. 0.0165 mole) and silver oxide (1.92 g., 0.0082 mole) were added to (+)-2,3,8,9-tetrahydro-4'-hydroxy-3',2"-dimethoxy-N,N-4,5:6,7-dibenzazoninium iodide (LXV) (0.75 g., 0.00165 mole) dissolved in methanol (8 c.c.). The mixture was heated under reflux for 1 hr. and then filtered. The solid residue was extracted five times with hot methanol and the combined filtrate and extracts were evaporated, giving red crystals, 0.15 g. This product was crystallised from ethanol, and after washing with ether, pale pink crystals were obtained, 0.03 g., m.p. 219-221°. No hydroxyl peak was apparent in the infrared spectrum. This was the required product but in very poor yield.

The solids from the reaction mixture were extracted with water, but only inorganic salts were obtained.

This, then, was not a suitable method of preparation.

(ii) Adapted from Freund's[56] method for the phenyldihydrothebaine series.

The theoretical quantity of sodium (0.04 g.) was dissolved in ethanol (5 c.c.) and the (+)-2,3,8,9-tetrahydro-4'-hydroxy-3',2"-dimethoxy-N,N-4,5:6,7-dibenzazoninium iodide (LXV) (0.75 g.) added, followed by methyl iodide (1.c.c.). The mixture was digested for 1 hr. and precipitation started by the addition of a few drops of ether. A white precipitate slowly formed, and excess ether was added to complete the process; 0.79 g. (104%), m.p. 219-220°, were obtained. Recrystallisation from ethanol gave small cream coloured crystals of the azoninium iodide, the methyl ether methiodide, 0.51 g. (66%), m.p. 221-222°. After a second crystallisation: fine white needles, m.p. 227-227.5°. (Found: C, 53.5; H, 6.45; I, 26.7. $C_{21}H_{28}INO_3$ requires: C, 53.7; H, 6.0; I, 27.0%). No hydroxyl peak occurred in the I.R. spectrum, which was the same as that of the product m.p. 219-221°, obtained in very small yield in (i) above. This appeared to be the required product and in good yield.

(iii) The lithium aluminium hydride reduction product (11.1 g.) was gently heated under reflux with methyl iodide (7.5 c.c.) for 1½ hr., a little methyl iodide being added periodically, by which time the initially red solution had become deep yellow. A solution consisting of sodium (0.9 g.) in ethanol (15 c.c.) and methyl iodide (22.5 c.c.) in ethanol (25 c.c.) was added and the mixture was digested on a warm water bath for 1 hr. After cooling, ether was added until no further precipitation occurred. A pale brown solid, 16 g. (96%), m.p. 218-221°, was obtained. Three crystallisations from ethanol raised the melting point to 226.5-227° and gave colourless needles, the infrared spectrum of which was identical to that obtained in (ii) above. $[\alpha]_D^{19}$ +43.0°, $[\alpha]_{5461}^{19}$ +61.5° (c, 0.24 in ethanol).

In a further preparation by this method, 30 g. (80%) were prepared from 25 g. of the reduction product, which had been obtained from 50 g. of thebaine (overall yield 60%).

(+)-2,3,8,9-Tetrahydro-3',4',2"-trimethoxy-N,N-dimethyl-4,5:6,7-dibenzazoninium Picrate (LX).

(+)-2,3,8,9-Tetrahydro-3',4',2"-trimethoxy-N,N-dimethyl-4,5:6,7-dibenzazoninium iodide (LXXII) (0.15 g.) was dissolved in the minimum quantity of warm water and sodium picrate (0.22 g.) was added. The yellow precipitate which quickly formed was filtered off and recrystallised from iso-propyl alcohol. After filtering, the solid was washed with light petroleum (b.p. 40-60°) but soon degenerated into a gum. This was extracted with hot iso-propyl alcohol, cooled and precipitated by pouring the solution into ether. A brilliant yellow powder, 0.12 g. (66%), m.p. 143-144°, was obtained. Recrystallisation from iso-propyl alcohol, filtering and washing with ether, gave yellow crystals, 0.10 g., m.p. 144-145°. (Found: C, 56.3; H, 5.2; N, 9.9; O, 28.7. $C_{27}H_{31}N_4O_{10}$ requires: C, 56.8; H, 5.3; N, 9.8; O, 28.0%).

(+)-2,3,8,9-Tetrahydro-3',4',2"-trimethoxy-N,N-dimethyl-4,5:6,7-dibenzazoninium Bromide (LX).

(+)-2,3,8,9-Tetrahydro-3',4',2"-trimethoxy-N,N-dimethyl-4,5:6,7-dibenzazoninium iodide (LXXII) (5 g.) was dissolved in aqueous ethanol. Excess of freshly prepared silver bromide (4 g.) was added and the mixture was shaken periodically during several days, by which time some of the pale yellow silver bromide had been converted into the yellow iodide, and was afterwards filtered off. The solution was concentrated until a cloudiness appeared and was filtered whilst hot. As no solid appeared on cooling, the solvent was removed. The residue was dissolved in hot methanol-acetone mixture and the product was obtained in three crops, after cooling the solutions to ca. 0° each time. The addition of ether to the final filtrate gave pale brown crystals 0.4 g., m.p. 230°. The total yield was 3.9 g. (87%).

Further crystallisation of the first three crops from a mixture of methanol and acetone gave various crops, all of m.p. 238°. These final crops were combined and the I.R. spectrum was identical with that of the iodide from which this bromide was prepared. (Found: C, 59.8; H, 6.8; Br, 18.9; N, 3.2; O, 11.4. $C_{21}H_{23}BrNO_3$ requires: C, 59.7; H, 6.7; Br, 18.9; N, 3.3; O, 11.4%)

(+)-α-Phenyldihydrothebaine Methyl Ether Methobromide (LXI).

(+)-α-Phenyldihydrothebaine methyl ether methiodide (LXVI) (0.07 g.) was dissolved in aqueous ethanol and shaken with silver bromide (0.10 g.) for 3 hr. The silver salts were filtered off, the solvent was removed, and the residue was dissolved in hot acetone containing just sufficient ethanol for complete solution. Light petroleum (b.p. 60-80°) was added to the boiling mixture until a cloudiness appeared. On cooling, colourless crystals, m.p. 181-182°, were obtained.

The Ultraviolet Spectrum of the Methyl Ether Methobromides (LX) and (LXI).

The ultraviolet spectra were determined, as on p. 94, of a 3.900×10^{-5} molar solution of (LX) and a 3.870×10^{-5} molar solution of (LXI), in 96% ethanol, using the Unicam S.P. 500 spectrophotometer. Fused silica cells were used, 2 m.m. between 200 and 250 mμ, and 10 m.m. between 240 and 300 mμ, the larger cells because of the low optical densities in the latter region. The following results were obtained.

	(LX)		(LXI)	
	Wavelength (mμ)	ϵ	Wavelength (mμ)	ϵ
λ_{max}	280.5	4,150	282	4,290
λ_{inf}	-	-	(271)	2,840
λ_{inf}	-	-	(265)	2,020
λ_{inf}	(253.5)	692	-	-
λ_{min}	255	667	260.5	1,730
Conjugation band	(ca. 225)	22,050	(ca. 230)	26,900
λ_{max}	203	67,950	207.5	59,950

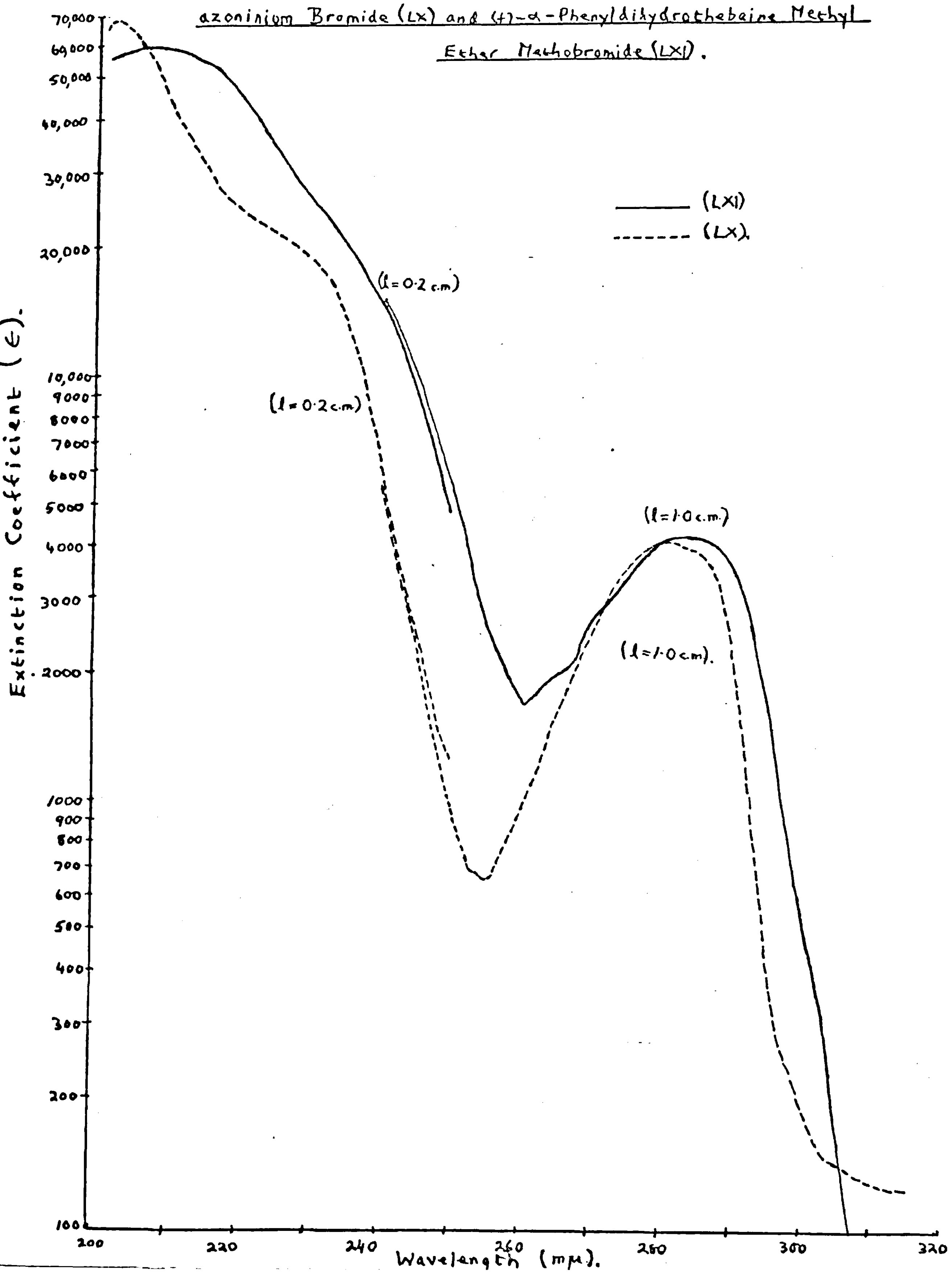
Crystallisation of the N-Methyl Azonine.

When a solution in ether of some of the lithium aluminium hydride reduction product was allowed to stand, a white crystalline precipitate slowly formed. This could then be crystallised from light petroleum (b.p. 60-80°). The remainder of the base was recrystallised from this solvent, after being seeded with the crystals obtained above, giving:

crop (1), yellow crystals, which softened at 84°,

Fig. 8.

The Ultraviolet Spectra of (+)-2,3,8,9-Tetrahydro-3′,4′,2″-trimethoxy-N,N-dimethyl-4,5:6,7-dibenzazoninium Bromide (LX) and (+)-α-Phenyldihydrothebaine Methyl Ether Methobromide (LXI).



m.p. 94-105°. Concentration of the mother liquor gave, on cooling:

crop (2), small grey crystals, m.p. 81-105°, and a red oil insoluble in the petroleum.

The red oil was dissolved in benzene and passed down a silica gel column which removed most of the colour. After evaporation of the eluant, the residue was recrystallised from the light petroleum, giving:

crop (3), as a brown amorphous solid together with some crystals. The ratio of the quantities of the three crops obtained was 8:0.78:1.

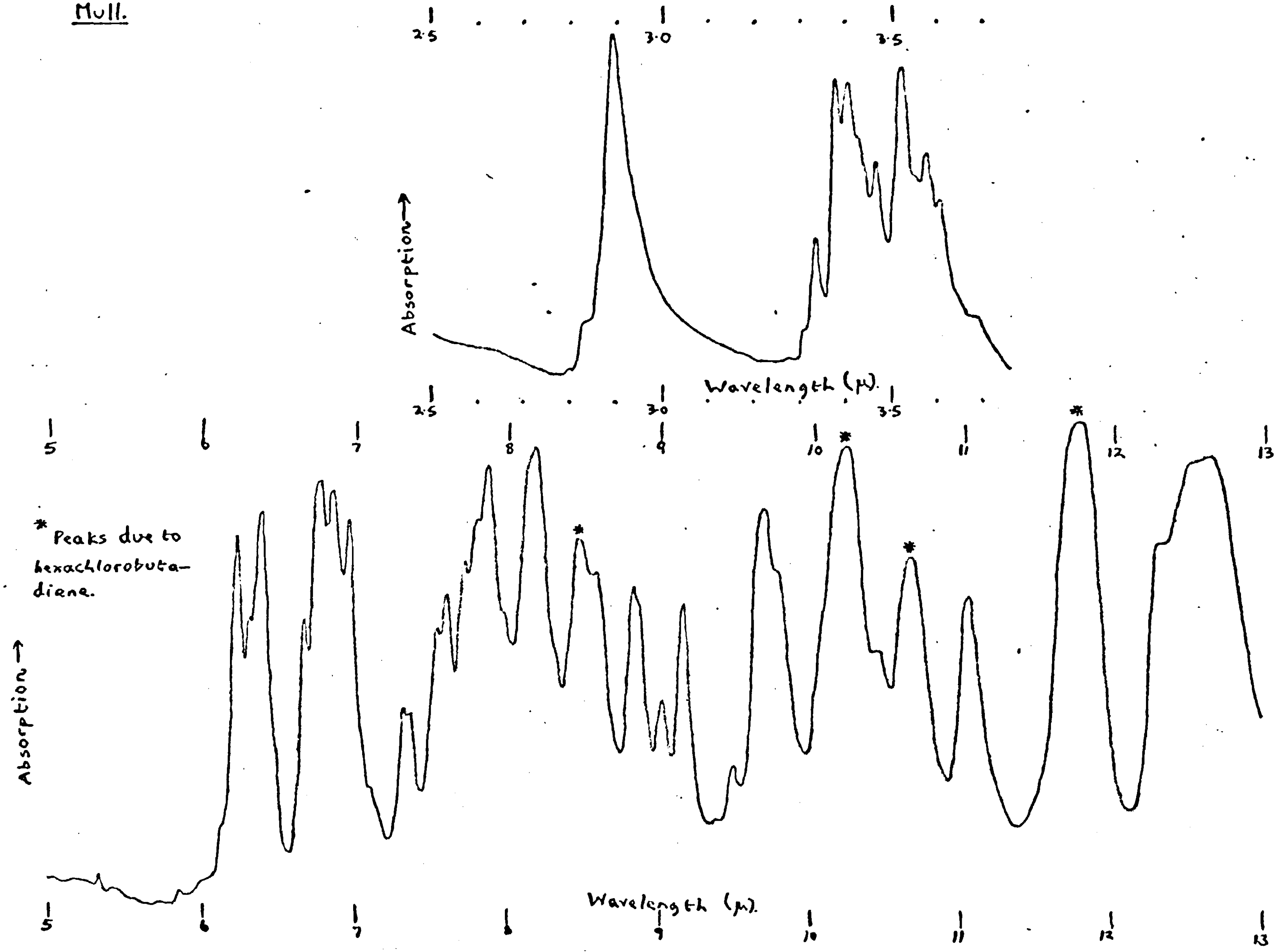
The I.R. spectrum of crop (1) in hexachlorobutadiene mull was different from that of an evaporated acetone solution of the material before crystallisation. However, it closely resembled that of a hexachlorobutadiene mull of the non-crystalline material, which had been dried overnight under vacuum in contact with a molecular sieve at the temperature of liquid nitrogen. There was no evidence for an NH group in the crystalline compound. The details are discussed on p. 127.

The I.R. spectrum of crop (3) resembled that of the material before crystallisation and was mainly non-crystalline.

A further crystallisation of crop (1) gave white globular crystals, m.p. 103.5-104.5°. (Found: C, 72.6; H, 7.7; N, 4.6; O, 15.2. $C_{19}H_{23}NO_3$ requires: C, 72.8; H, 7.4; N, 4.5; O, 15.3%). $[\alpha]_D^{21.5}$ +72.9° (c, 0.28 in EtOH). The result of the n.m.r. spectrum in deuterochloroform is discussed on p. 127.

Fig. 9.

The Infrared Absorption Spectrum of the Crystalline Lithium Aluminium Hydride Reduction Product ((+)-2,3,8,9-Tetrahydro-4'-hydroxy-3',3"-dimethoxy-N-methyl-4,5;6,7-dibenzazonine). Hexachlorobutadiene Mull.



The Exhaustive Methylation of (+)-2,3,8,9-Tetrahydro-3',4',2"-N,N-dimethyl-4,5:6,7-dibenzazoninium Iodide (LXXII).

(a) Hofmann Degradation to (+)-2,3,3'-Trimethoxy-6 (or 6')-(2-trimethylammonioethyl)-6' (or 6)-vinylbiphenyl Iodide (LXXVI).

Adapted from the method of Freund[56] for the phenyldihydrothebaine series of compounds.

(+)-2,3,8,9-Tetrahydro-3',4',2"-trimethoxy-N,N-dimethyl-4,5:6,7-dibenzazoninium iodide (LXXII) (3.9 g.) was digested with a solution of sodium (2.25 g.) in absolute alcohol (36 c.c.) on a warm water bath for about ½ hr., when a clear dark solution was obtained. The alcohol was removed and a saturated aqueous solution of ammonium chloride was added. The mixture was extracted with ether, dried over potassium hydroxide, and evaporated, leaving a dark brown oil.

The oil was dissolved in acetone (10 c.c.) and methyl iodide (2 c.c.), and heated under reflux for 1 hr., periodically replenishing the methyl iodide. The volatile components were removed, acetone was added, and the solid which formed was filtered off and washed with more acetone. A white solid, 2.2 g., m.p. 229-237° (with decomposition) and a red coloured filtrate were obtained.

Treatment of the Solid.

Recrystallisation from ethanol gave cream coloured feathery crystals, 0.4 g., m.p. 199.5-200.5°, and concentration of the mother liquor gave inorganic salts, which were removed. A further crystallisation gave one of the methine methiodides, or vinylbiphenyl iodide derivatives, (LXXVI) in two crops, the best of which was as white silky crystals, 0.05 g., m.p. 203.5-204°. $[\alpha]_D^{20}$ -26.6°, $[\alpha]_{5461}^{20}$ -36.7°, (c, 0.27 in ethanol). (Found: C, 54.5; H, 6.3; I, 26.25; N, 3.1; O, 10.1. $C_{22}H_{30}INO_3$ requires: C, 54.7; H, 6.25; I, 26.25; N, 2.9; O, 9.9%). The I.R. spectrum resembled that of the methiodide of (+)-α-phenyldihydrothebaine methyl ether iso-methine (LVII) (allowing for the absence of the third benzene ring) and a peak at 10.95 μ was most probably due to a vinyl group[91,98].

Treatment of the Filtrate and Washings.

Evaporation gave an orange residue which was recrystallised from ethanol, giving small pale orange needles, 0.6 g., m.p. 198.5-199.5°. Addition of ether to the mother liquor gave an orange precipitate, 2.0 g., m.p. 177-179°.

A further crystallisation of the orange needles (m.p. 198.5-199.5°), increased the m.p. to 202-203° (0.5 g.). This compound was the same as that m.p. 203.5-204° above. A further crystallisation of the precipitate, m.p. 177-179°, from ethanol-light petroleum (b.p. 80-100°) mixture gave:

crop (1), which after a further crystallisation, was obtained as 0.9 g. of yellow needles, which melted over the range 171-175.5°, 179-184°. Addition of light petroleum to the hot mother liquor gave on cooling:

crop (2), which was filtered off and washed with ethanol-light petroleum mixture and then with ether. Pale yellow crystals,

0.3 g., m.p. 179.5-182° were obtained. This was extracted with hot light petroleum (b.p. 80-100°) containing insufficient ethanol for complete solution. The extract was cooled, and the crystals obtained were subjected to a further extraction. That which was probably the other vinylbiphenyl iodide derivative, or methine methiodide, was obtained. The product, colourless needles, 0.06 g. had m.p. 182-183°. (Found: C, 52.2; H, 6.5; N, 3.2; O, 10.2. $C_{22}H_{30}INO_3$ requires: C, 54.7; H, 6.25; N, 2.9; O, 9.9%). Although the analytical results do not correspond to those for any reasonable product, it is predominantly either (LXXVIa) or (LXXVIb), as was shown below.
$[\alpha]_D^{20}$ +12.7°, $[\alpha]_{5461}^{20}$ +22.1°, (c, 0.24 in ethanol). The I.R. spectrum resembled that of the methiodide of (+)-α-phenyldihydrothebaine methyl ether iso-methine (LVII) even more closely than that of the product m.p. 203.5-204° above, and also had a peak at 10.93 μ (a vinyl group[91,98]) (p. 130).

The various fractions of high melting product were combined, as also were the low melting fractions:

Yield of product m.p. ca. 200°: 1.0 g. (25%)
m.p. ca. 180°: 2.0 g. (50%).

A repeated preparation, starting from 30 g. of (LXXII) gave only fractions of product of m.p. ca. 200° totalling 26.2 g. (85%). No lower melting product was obtained.

(b) Hofmann Degradation of the Methine Methiodides (LXXVI) to (+)-2,3,3'-Trimethoxy-6,6'-divinylbiphenyl (LXIII).

Degradation of each of the above methine methiodides was carried out using the method of Bentley and Robinson[65], as in the phenyldihydrothebaine series.

The high melting methine methiodide (0.7 g.) was dissolved in methanol (3.3 c.c.) and a solution of sodium (0.42 g.) in methanol (8.5 c.c.) was added. The mixture was heated under reflux for 2 hr. The reaction mixture was then poured into water, which was then saturated with ammonium chloride, and resulted in the precipitation of an orange gum. The mixture was extracted three times with ether (9 c.c. each time) and the combined extracts were washed three times with 2N HCl (1 c.c. each time) and about six times with water (2 c.c. each time), the final washings then being neutral to litmus. After drying over anhydrous sodium sulphate, the ether was removed giving a yellow oil, which was only solid below 0°. Crystallisation having been attempted three times from light petroleum (b.p. 80-100°) the oil only was obtained, 0.33 g. (77%), and many solvents including ethanol, were tried, but none gave a solid product. The I.R. spectrum contained peaks at 6.10, 10.10 and 11.10 μ, which were assumed to be due to the vinyl groups[98] (p. 131) $[\alpha]_D^{19}$ +25.2°, $[\alpha]_{5461}^{19}$ +35.9°, (c, 1.58 in 96% EtOH).

After standing in an evacuated desiccator for three weeks, 0.23 g. of the oil gave a quantity of a white solid. Extraction with hot ethanol gave 0.06 g. of insoluble matter, which was infusible at 300°. The I.R. spectrum of this solid showed some changes, including the disappearance or diminution in size of some of the supposed peaks due to the vinyl groups. It was assumed to be a polymer of the required product.

The ethanol extracts were evaporated and the residue was dissolved in benzene and passed down a silica gel column, which removed most of the colour. After evaporation of the eluant, extraction with ether again left behind an insoluble white residue (0.01 g.), which melted with decomposition over the range 159-170.5°, 222-233°. The I.R. spectrum was the same as that of the previous insoluble component; this substance was also assumed to be polymeric. The ether solution was evaporated, giving (+)-2,3,3'-trimethoxy-6,6'-divinylbiphenyl. (Found: C, 73.4; H, 7.3; O, 16.6. $C_{19}H_{20}O_3$ requires: C, 77.0; H, 6.8; O, 16.2%). Rapid polymer formation after drying prior to analysis occurred, but poor results were probably obtained as the compound had been neither crystallised nor distilled.

The low melting methine methiodide (0.8 g.), obtained in (a) above, was treated similarly with the same results. The I.R. spectrum of the oil obtained was identical with that of the oil obtained previously. $[\alpha]_D^{19}$ +25.2°, $[\alpha]_{5461}^{19}$ +36.5°, (c, 1.58 in 96% ethanol).

A further 25 g. of the high melting methine methiodide was degraded to the biphenyl. The yellow oil obtained was dissolved in benzene and passed down a silica gel column. Evaporation of the eluant gave a yellow viscous liquid, 6.46 g. of which were ether soluble and the required product. Yield, 41%; 14% from thebaine. This was the procedure for future preparations.

Catalytic hydrogenation of the oil gave (+)-2,3,3'-trimethoxy-6,6'-diethylbiphenyl (LXIV), thus confirming that the oil was the required divinylbiphenyl (LXIII).

(+)-2,3,3'-Trimethoxy-6,6'-diethylbiphenyl (LXIV).

(+)-2,3,3'-Trimethoxy-6,6'-divinylbiphenyl (LXIII) (3.09 g.), freshly prepared, was dissolved in ethyl acetate (300 c.c.). Palladium-charcoal (2.0 g.) was added and hydrogenation was carried out at 1 atm. pressure. The volume of hydrogen taken up was 595 c.c. The mixture was filtered, and the solvent was removed giving a white viscous liquid, 2.85 g. (92.5%). (Found: C, 75.8; H, 8.0; O, 15.9. $C_{19}H_{24}O_3$ requires: C, 76.0; H, 8.05; O, 16.0%).

$[\alpha]_D^{21}$ +62.2°, $[\alpha]_{5461}^{21}$ +71.1° (c, 2.81 in β-phenylethyl alcohol).

The I.R. spectrum showed the loss, amongst other differences, of the peaks due to the vinyl groups at 6.10, 10.10 and 11.10 μ, when compared with the spectrum of the divinylbiphenyl.

The ultraviolet spectrum was determined, as on p. 94, of a 1.012×10^{-4} molar solution in 96% ethanol, using the S.P. 500 spectrophotometer. Fused silica cells were used, 1 m.m. between 199 and 245 mμ, and 10 m.m. between 240 and 310 mμ. The following characteristics were observed: λ_{max} 279 mμ (ε 4,710), λ_{min} 252 mμ (ε 692), the vestigial conjugation band at ca. 227.5 mμ (ε 16,700) and λ_{max} 201 mμ (ε 60,200). The spectrum was consistent with that expected for the required compound.

Attempted Racemisation of (+)-2,3,8,9-Tetrahydro-3',4',2"-trimethoxy-N,N-dimethyl-4,5:6,7-dibenzazoninium Bromide (LX).

The above compound was heated between 180° and 220° until optically inactive, in various solvents. After the experiment in every case, either dilution of the solution with ether followed by water extraction, or evaporation of the solution, gave only a gum and no solid product. It was possible to obtain the optically active compound in a solid state by these methods from these solutions prior to heating. Hence, decomposition, in addition to racemisation, had occurred in these experiments. The solvents used were β-phenylethyl alcohol, methyl benzoate, resorcinol diacetate and nitrobenzene.

(+)-2,3,8,9-Tetrahydro-3',4',2"-trimethoxy-N-methyl-4,5:6,7-dibenzazonine (LXXVII).

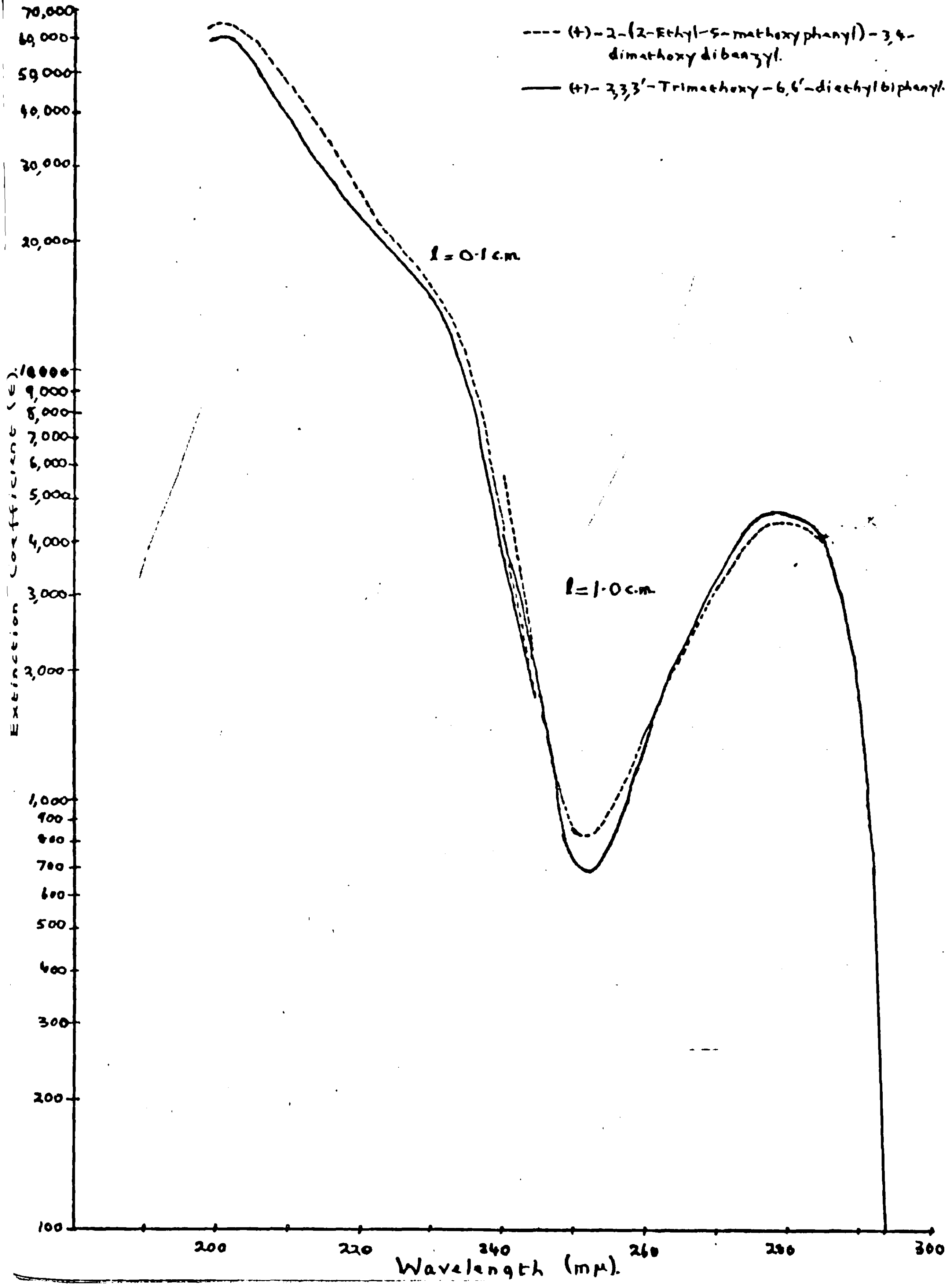
Three methods of preparation were tried, only the last, that using phenyltrimethylammonium ethoxide being successful.

(a) Diazomethane.

The crystalline (+)-2,3,8,9-tetrahydro-4'-hydroxy-3',2"-dimethoxy-N-methyl-4,5:6,7-dibenzazonine (XLII) in methanol solution, did not react with a solution of diazomethane in ether,

Fig. 10.

The Ultraviolet Spectra of (+)-2-(2-Ethyl-5-methoxyphenyl)-3:4-dimethoxydibenzyl and (+)-2,3,3'-Trimethoxy-6,6'-diethylbiphenyl in 96% Ethanol Solution.



as shown by I.R. spectroscopy and melting point evidence concerning the solid isolated.

(b) Dimethyl Sulphate.

Crystalline N-methyl azonine (1.0 g.) in 2.5 c.c. of 2N sodium hydroxide solution, did not react with one equivalent (1.5 c.c. of a solution consisting of 3 c.c. of dimethyl sulphate in 8 c.c. of methanol) of dimethyl sulphate during 3 hr. at room temperature. The I.R. spectrum of the substance isolated showed that it was unreacted N-methyl azonine.

Crystalline N-methyl azonine (4.0 g.) in a large excess of 2N sodium hydroxide solution (40 c.c.), and excess of a solution of dimethyl sulphate (7.5 c.c.) in methanol (20. c.c.), were heated under reflux for 1 hr., extracted with ether, and the extracts dried over solid potassium hydroxide, which also removed unreacted starting material. Removal of the solvent gave 2.72 g. of a brown oil. Distillation of the oil under reduced pressure, gave a colourless oil with a blue fluorescence, 1.3 g., b.p. 189°/0.9 m.m. The I.R. spectrum had no hydroxyl peak and was different in other respects to that of non-crystalline N-methyl azonine.

$[\alpha]^{22}_{5780}$ +25.6°, $[\alpha]^{22}_{5461}$ +31.0°, (c, 1.37 in β-phenylethyl alcohol). The above solution had α_{5461} +0.425°; after 50 min. at 193° under vacuum, it then had α_{5461} +0.14°; after 5 hr., α_{5461} +0.01°, (l = 1). Evaporation of the final solution gave a brown oil whose I.R. spectrum was the same as that of the optically active compound, with some solvent peaks superimposed.

Hence, partial racemisation and not decomposition had occurred.

The optically active oil (0.1 g.) was dissolved in ethanol, and picric acid (one equivalent, 0.07 g.) in ethanol solution was added. A yellow glass precipitated (0.10 g.), which failed to give a crystalline picrate from any solvent tried.

The optically active oil (0.1 g.), acetone (1 c.c.) and methyl iodide (0.5 c.c.) were heated under reflux for 3 hr. Volatile components were then removed and ether added, giving a white solid, 0.08 g. Recrystallisation from ethanol gave fine colourless needles, 0.02 g., m.p. 202.5-203.5°. A second crop, after concentration of the mother liquor, was obtained, 0.02 g., m.p. 168-172°. This substance melted over the range 171-172°,180-184° after a further crystallisation.

The I.R. spectrum of the first crop was identical with that of the methine methiodide, m.p. 203.5-204°, prepared previously (p. 163). A mixed melting point confirmed that it was the same compound. The second crop was presumably mainly the methine methiodide, m.p. 182-183°. Thus, it is certain that in the process of methylation under hot alkaline conditions, degradation to the methines (LXXIX) also occurs.

(c) <u>Phenyltrimethylammonium Ethoxide.</u> Rodionov[99].

p-Methyltoluenesulphonate (0.1 mole, 18.6 g.) and dimethylaniline (0.1 mole, 12.1 g.) were warmed together in a 100 c.c. bolt-head flask, on a water bath. A mass of turquoise coloured plates were obtained, which, when recrystallised from a little ethanol, gave crystalline flakes of the quaternary salt (LXXX), 26.7 g. (87%), m.p. 156-159° (Rodionov obtained m.p. 160-161°).

Sodium (0.004 mole, 0.1 g.) was dissolved in ethanol (1 c.c.) and a solution of the prepared quaternary ammonium salt (0.004 mole, 1.19 g.) in ethanol (2.8 c.c.) was added. The precipitated sodium p-toluenesulphonate was filtered off and washed several times with small amounts of ethanol, the washings being added to the filtrate. The crystalline N-methyl azonine (0.003 mole, 1.0 g.) was dissolved in this quaternary ammonium ethoxide solution, which then became dark brown in colour. The alcohol was removed and the brown residue was heated at 110° for 1 hr. 15% Acetic acid solution was added until acidic and precipitated dimethylaniline was filtered off, that remaining in solution being removed by steam distillation; dimethylaniline is so feebly basic that it forms no salt with acetic acid. The solution was cooled, filtered, and rendered alkaline with sodium hydroxide pellets. It was extracted with ether and the extracts were dried over solid potassium hydroxide; unchanged phenol precipitated on the walls of the vessel as a blue deposit. Evaporation left behind a green oil which was dissolved in hot light petroleum (b.p. 60-80°) and filtered. A green oil was again obtained on cooling, and so the solvent was removed and the product, 0.90 g. (86%) was quickly distilled under reduced pressure to give minimal racemisation. The methyl ether, (+)-2,3,8,9-tetrahydro-3',4',2"-trimethoxy-N-methyl-4,5:6,7-

dibenzazonine was obtained as a colourless viscous oil, 0.58 g. (56%), b.p. 178°/0.1 m.m.

The I.R. spectrum was similar to that of the N-methyl azonine before crystallisation except that there was no hydroxyl peak. The n.m.r. spectrum showed the absence of the hydroxyl group and the appearance of an additional methoxyl group. Other details are discussed on p. 158. (Found: C, 72.7, 74.6; H, 7.7, 8.0; N, 4.3, 4.0; O, 15.3, 13.8. $C_{20}H_{25}O_3$ requires: C, 73.4; H, 7.7; N, 4.3; O, 14.7%). The product discoloured on standing even under vacuum. $[\alpha]_D^{18.5}$ +22.0°, $[\alpha]_{5461}^{18.5}$ +36.0°, (c, 1.00 in β-phenylethyl alcohol).

The above solution had α_D +0.22° and α_{5461} +0.36°. After 30 min. at 193° under vacuum, the solution had α_D +0.10° and α_{5461} +0.17°; after 4½ hr., α_D and α_{5461} 0.00°. The solvent was then removed under ca. 3 m.m. pressure, and the brown gum obtained was distilled under this pressure. The pale yellow viscous distillate had an infrared spectrum which was identical with that of the optically active compound, but with some β-phenylethyl alcohol peaks superimposed.

A further 3.20 g. (77%) of this methyl ether were prepared from 4.0 g. of crystalline N-methyl azonine. The product distilled at 176-180°/0.2 m.m. to give 2.62 g.

The methyl ether (0.1 g.), acetone (1 c.c.) and methyl iodide (0.5 c.c.) were heated under reflux for 3 hr. Volatile components were removed, more acetone was added, and the white precipitate was filtered off, 0.07 g. (49%). Recrystallisation from ethanol gave fine white needles, m.p. 224-225°, and a mixed melting point with an authentic specimen of the methyl ether methiodide (LXXII) prepared previously (p. 156, method (iii)) gave no depression. The I.R. spectra of both were identical, thus confirming the identity of this compound and the methyl ether itself.

The methyl ether (0.1 g.) in ethanol solution (1 c.c.) was added to picric acid (1 equivalent, 0.07 g.) dissolved in ethanol (1 c.c.). A yellow gum precipitated. It was only obtained in a solid state by cooling an iso-propyl alcohol solution, which gave 0.09 g. (53%), m.p. 90-95°, but which softened between 60° and 75°. It was then dissolved in a further quantity of warm iso-propyl alcohol and a large excess of light petroleum (b.p. 40-60°) was added. After cooling to below 0°, a pale yellow solid (0.05 g.), which softened between 81° and 88° m.p. 90-93°, was obtained: (+)-2,3,8,9-tetrahydro-3',4',2"-trimethoxy-N,N-dimethyl-4,5:6,7-dibenzazoninium picrate. (Found: C, 55.8; H, 5.2; N, 10.0; O, 28.8. $C_{26}H_{28}N_4O_{10}$ requires: C, 56.1; H, 5.1; N, 10.1; O, 28.75%). The I.R. spectrum resembled that of the picrate m.p. 103-105.5° obtained from the lithium aluminium hydride reduction product (p. 146), except that the hydroxyl peak was absent. The 3.2-3.6 μ region was identical.

Kinetic Racemisation Studies.

The method used was that described on p. 83, and the values of the various thermodynamic constants for the racemisations of the given compounds, were calculated as on p. 48.

(a) (+)-2,3,3'-Trimethoxy-6,6'-divinylbiphenyl (LXIII).

No polymer was precipitated from a *p*-cymene solution containing 12.87% of the divinylbiphenyl and 1.29% of picric acid (polymerisation inhibitor), on standing for several months. However, from observations made during the preparation (p. 166), it was decided that polymerisation would occur too readily, especially at the higher temperatures, to make the results of kinetic racemisation experiments reliable.

(b) (+)-2,3,3'-Trimethoxy-6,6'-diethylbiphenyl (LXIV).

A 1.975% solution in redistilled β-phenylethyl alcohol was used, λ= 5780 Å.

Temperature: 181.5 ± 0.5°.

Time (hr.)	0	1	3	4.25	6	7.75
α_{5780} (deg.)	1.19	1.14	0.99	0.91	0.81	0.72

Time (hr.)	10	12.5	15	18.5	23.5	32.5
α_{5780} (deg.)	0.645	0.54	0.46	0.37	0.26	0.15

$k = 1.778 \times 10^{-5}$ sec.$^{-1}$

$t_{\frac{1}{2}}$ = 10.83 hr. (10.83 hr. from graph).

Temperature: $191.0 \pm 0.5^{\circ}$.

Time (hr.)	0.00	0.33	0.75	1.25	1.87	2.33
α_{5780} (deg.)	1.24	1.16	1.08	1.00	0.92	0.87

Time (hr.)	3.50	4.83	6.33	8.00	10.75	15.00
α_{5780} (deg.)	0.73	0.605	0.50	0.39	0.28	0.16

$k = 3.736 \times 10^{-5}$ sec^{-1}.

$t_{\frac{1}{2}}$ = 5.15 hr. (5.15 hr. from graph).

Temperature: $201.8 \pm 0.3^{\circ}$.

Time (hr.)	0.00	0.33	0.75	1.34	1.83	2.42
α_{5780} (deg.)	1.26	1.15	1.02	0.82	0.73	0.63

Time (hr.)	3.00	3.80	4.75	5.75	6.80
α_{5780} (deg.)	0.52	0.41	0.31	0.22	0.17

$k = 8.150 \times 10^{-5}$ sec^{-1}.

$t_{\frac{1}{2}}$ = 2.36 hr. (2.35 hr. from graph).

Temperature: $211.6 \pm 0.3^{\circ}$.

Time (min.)	0	10	22	35	55	78
α_{5780} (deg.)	1.135	1.04	0.90	0.79	0.63	0.50

Time (min.)	95	110	135	165	200	250
α_{5780} (deg.)	0.42	0.36	0.28	0.20	0.14	0.09

$k = 1.729 \times 10^{-4}$ sec^{-1}.

$t_{\frac{1}{2}}$ = 66.85 min. (66.5 min. from graph).

Temperature: 223.7 ± 0.4°

Time (min.)	0	4	9	15	20	25	33	40	50	65	80	95
α_{5780} (deg.)	1.02	0.915	0.82	0.70	0.63	0.55	0.455	0.38	0.295	0.20	0.135	0.095

$k = 4.191 \times 10^{-4}\ sec^{-1}$.

$t_{\frac{1}{2}}$ = 27.6 min. (27.5 min. from graph).

Temperature: 228.9 ± 0.4°.

Time (min.)	0	2	5	8	12	17	22	30	40	53	60
α_{5780} (deg.)	1.025	0.94	0.83	0.74	0.635	0.53	0.43	0.33	0.23	0.14	0.11

$k = 6.210 \times 10^{-4}\ sec^{-1}$.

$t_{\frac{1}{2}}$ = 18.6 min. (18.7 min. from graph).

Mean Temp. (deg. C.)	Mean Temp. (deg. K) [T]	10^3. 1/T	Rate Const. sec^{-1}. 10^5k.	Log_{10} k
181.5	454.7	2.199	1.778	$\bar{5}.2500$
191.0	464.2	2.154	3.736	$\bar{5}.5723$
201.8	475.0	2.105	8.150	$\bar{5}.9112$
211.6	484.8	2.063	17.29	$\bar{4}.2377$
223.7	496.9	2.012	41.91	$\bar{4}.6223$
228.9	502.1	1.992	62.10	$\bar{4}.7931$

The calculated value for E was 33.79 kcal. mole^{-1}.

Mean Temp. (deg. C.)	Log_{10} A (sec^{-1}.)	$\Delta S^{\ddagger}$ (e.u.)	$\Delta H^{\ddagger}$ (kcal. (mole^{-1}).	$\Delta F^{\ddagger}$ (kcal. mole^{-1}).
181.5	11.49	-8.80	32.89	
191.0	11.48	-8.88	32.87	
201.8	11.46	-9.03	32.85	
211.6	11.47	-8.99	32.83	
223.7	11.43	-9.01	32.80	
228.9	11.50	-8.92	32.79	37.28

The following mean results were obtained:

E = 33.8 kcal. mole^{-1},
$\log_{10}$ A = 11.5 sec^{-1}.,
$\Delta S^{\pm}$ =-8.94 e.u.,
$\Delta H^{\pm}$ = 32.8 kcal. mole^{-1},
$\Delta F^{\ddagger}$ = 37.3 kcal. mole^{-1} at 228.9°.

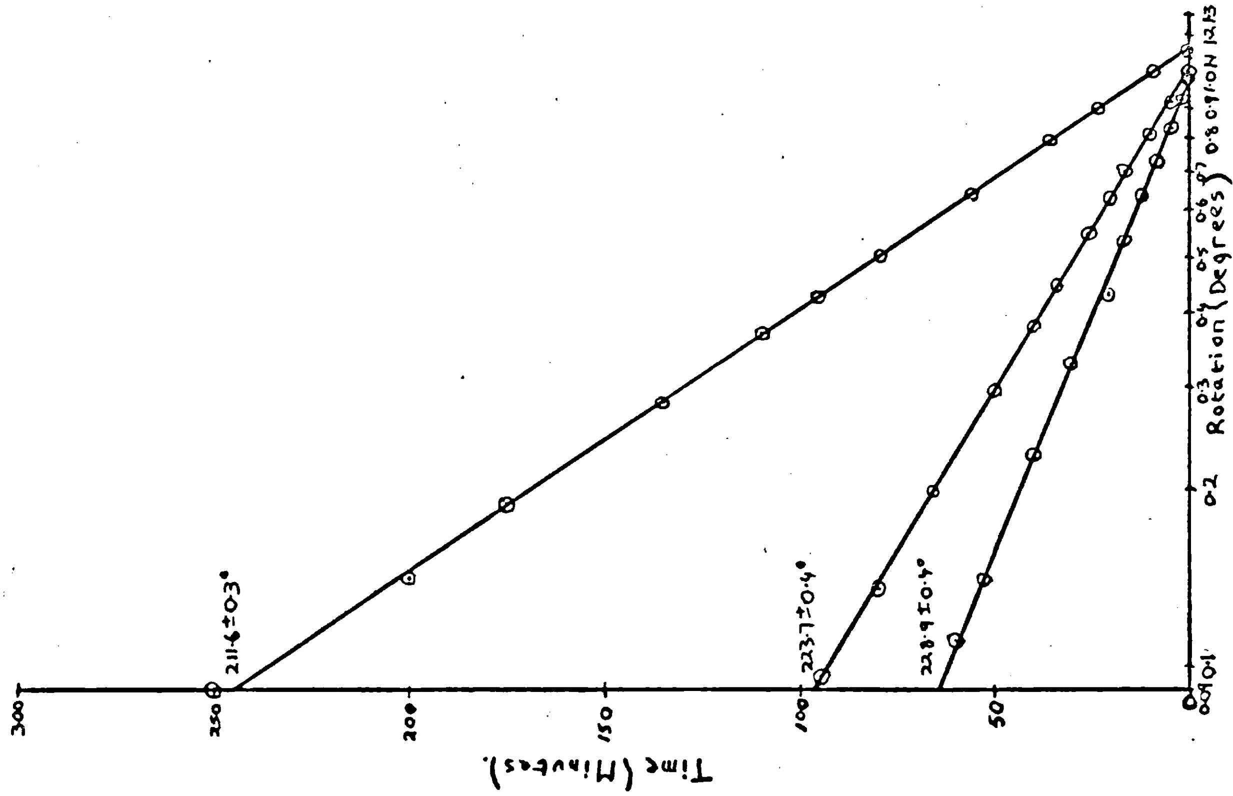
Isolation of the Racemate.

The solution residues from the above experiments were combined and 30 c.c. (containing 0.59 g. of the compound), were heated under vacuum at 210° overnight. The solution was then optically inactive, and removal of the solvent under reduced pressure left a pale brown oil, 0.71 g. Distillation under reduced pressure gave a pale yellow oil, 0.59 g. (100% recovery), b.p. 152-155°/ 0.4 m.m. (Found: C, 76.4; H, 7.8; O, 15.9. $C_{19}H_{24}O_3$ requires: C, 76.0; H, 8.05; O, 16.0%).

The infrared spectrum was identical with that of the optically active compound, and hence it was assumed that racemisation only had been obtained with no decomposition.

Fig. 11.

Racemisation of (+)-2,3,3'-Trimethoxy-6,6'-diethylbiphenyl in β-Phenylethyl Alcohol Solution.



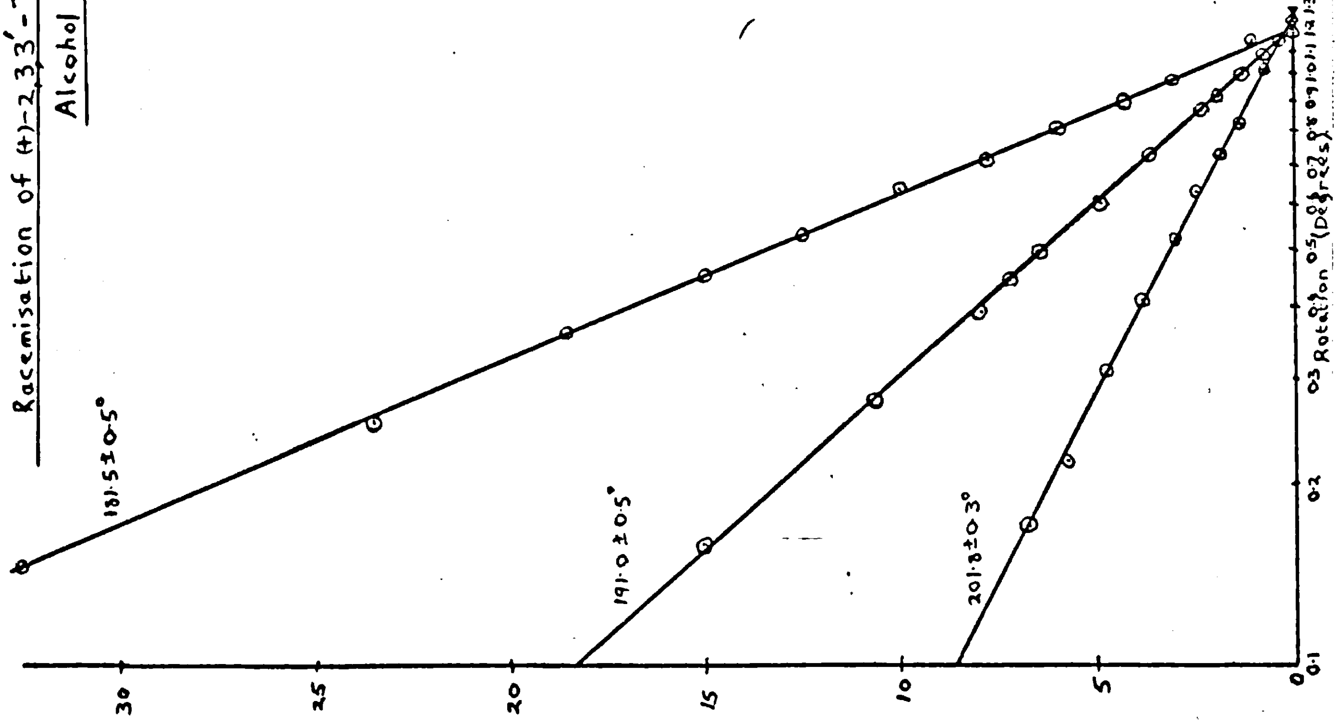
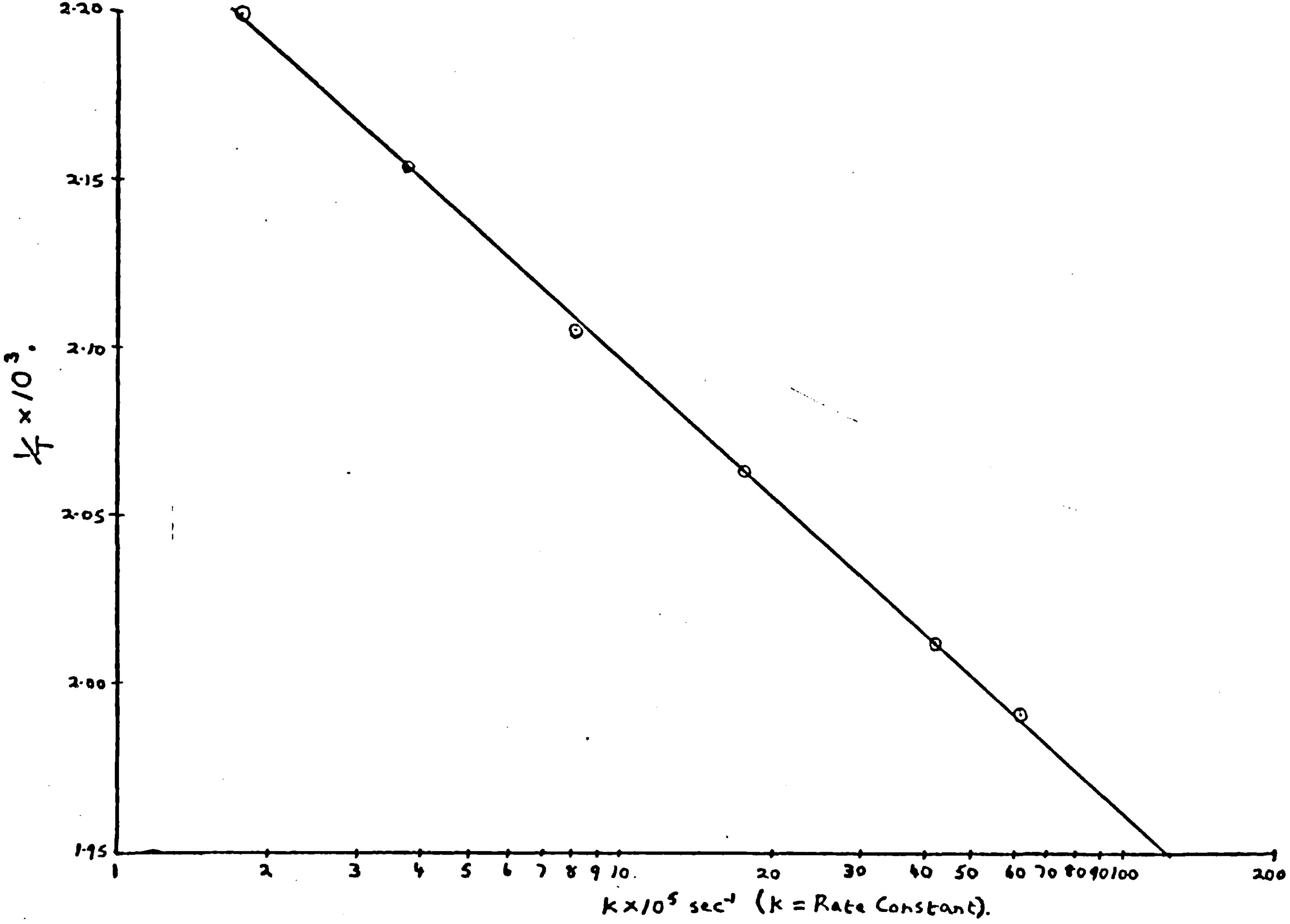


Fig. 12.

Plot of $1/T$ Against the Rate Constant for the Racemisation of (+)-2,3,3'-Trimethoxy-6,6'-diethylbiphenyl.



(c) (+)-2,3,8,9-Tetrahydro-3',4',2"-trimethoxy-N-methyl-4,5:6,7-dibenzazonine (LXXVII).

A 3.49% solution in redistilled β-phenylethyl alcohol was used, $\lambda = 5780$ Å.

Temperature: 145.0 ± 0.5°.

Time (hr.)	0.00	0.75	1.83	3.34	5.00	7.50	10.00	12.50	15.50	19.92	30.42
α_{5780} (deg.)	0.80	0.73	0.67	0.57	0.59	0.52	0.46	0.40	0.34	0.28	0.17

$k = 1.374 \times 10^{-5}$ sec^{-1}.

$t_{\frac{1}{2}}$ = 14.02 hr. (14.05 hr. from graph).

Temperature: 155.0 ± 0.2°.

Time (hr.)	0.00	0.34	0.75	1.42	2.50	4.08	6.00	8.00	11.02	15.00
α_{5780} (deg.)	0.83	0.76	0.72	0.66	0.56	0.45	0.35	0.27	0.175	0.11

$k = 3.756 \times 10^{-5}$ sec^{-1}.

$t_{\frac{1}{2}}$ = 5.13 hr. (5.08 hr. from graph).

Temperature: 167.0 ± 0.5°.

Time (hr.)	0.00	0.33	0.67	1.02	1.57	2.00	2.60	3.60	5.00	6.00
α_{5780} (deg.)	0.76	0.68	0.59	0.51	0.435	0.38	0.31	0.23	0.14	0.095

$k = 9.616 \times 10^{-5}$ sec^{-1}.

$t_{\frac{1}{2}}$ = 2.00 hr. (1.98 hr. from graph).

Temperature: 172.4 ± 0.1°.

Time (min.)	0	13	26	40	60
α_{5780} (deg.)	0.77	0.675	0.60	0.52	0.42

Time (min.)	95	120	140½	192	240
α_{5780} (deg.)	0.30	0.23	0.19	0.12	0.08

$k = 1.635 \times 10^{-4}$ sec^{-1}.

$t_{\frac{1}{2}}$ = 70.7 min. (70 min. from graph).

Temperature: 180.6 ± 0.4°.

Time (min.)	0	6	13	21	32
α_{5780} (deg.)	0.79	0.70	0.615	0.55	0.46

Time (min.)	44½	65	85	115	140
α_{5780} (deg.)	0.36	0.26	0.175	0.09*	0.03*

$k = 2.850 \times 10^{-4}$ sec^{-1}.

$t_{\frac{1}{2}}$ = 40.55 min. (40.5 min. from graph).

Temperature: 191.5 ± 0.1°.

Time (min.)	0	2	5	10	14½	18
α_{5780} (deg.)	0.71	0.65	0.59	0.475	0.42	0.37

Time (min.)	22	27	36	49	60
α_{5780} (deg.)	0.32	0.26	0.20	0.09*	0.045*

$k = 5.917 \times 10^{-4}$ sec^{-1}.

$t_{\frac{1}{2}}$ = 19.2 min. (19.4 min. from graph).

On plotting the logarithm of the rotation against time at each temperature, a straight line resulted in each case, but the points given by (*) were off their respective lines and were ignored.

Mean Temp. (deg. C.)	Mean Temp. (deg. K.)[T]	10^3 1/T	Rate Const. (sec^{-1}.) 10^5k.	Log$_{10}$ k
145.0	418.2	2.391	1.374	$\bar{5}.1380$
155.0	428.2	2.335	3.756	$\bar{5}.5747$
167.0	440.2	2.272	9.616	$\bar{5}.9830$
172.4	445.6	2.239	16.35	$\bar{4}.2137$
180.6$^+$	453.8	2.204	28.50	$\bar{4}.4548$
191.5$^+$	464.7	2.152	59.17	$\bar{4}.7721$

On plotting the logarithm of the rate constant against the reciprocal of the temperature, two straight lines were possible: (1), taking all six points into consideration, and (2), by ignoring points at temperatures ($^+$), because of the deviation at (*) above, some decomposition presumably having occurred in addition to racemisation. Values of E obtained from the two straight lines were 31.35 and 31.74 kcal. mole^{-1}.

Mean Temp. (deg. C.)	Mean Temp. (sec^{-1}.)	$\Delta S^\ddagger$ (e.u.)	$\Delta H^\ddagger$ (kcal. mole^{-1})	$\Delta F^\ddagger$ (kcal. mole^{-1}).
145.0	11.72	-7.55	30.91	
155.0	11.77	-7.38	30.89	
167.0	11.74	-7.57	30.87	
172.4	11.74	-7.58	30.85	
180.6	11.74	-7.63	30.84	
191.5	11.70	-7.88	30.82	34.48

The following mean results were obtained:

$E = 31.5$ kcal. mole^{-1}, $\Delta H^{*} = 30.9$ kcal. mole^{-1},

$\log_{10} A = 11.7$ sec^{-1}., $\Delta F^{*} = 34.5$ kcal. mole^{-1} at 191.5°.

$\Delta S^{*} = -7.60$ e.u.,

Isolation of the Racemate.

The fractions of solution from the racemisation experiments were combined, and 21 c.c. (containing 0.73 g. of the methyl ether) were heated overnight at 167° under vacuum, which rendered the solution optically inactive. Several times the volume of ether was added and the resulting solution was extracted with dilute hydrochloric acid five times. The combined acid extracts were themselves extracted with ether twice, and the acid solution was rendered alkaline with solid potassium hydroxide. This was extracted three times with ether, and the combined extracts were dried over calcium chloride, after adding a little hydrosulphite. Evaporation then yielded 0.50 g. of racemate (69% recovery). (Found: C, 73.4; H, 8.1; O, 14.5. $C_{20}H_{25}NO_3$ requires: C, 73.4; H, 7.7; O,14.7%).

The infrared spectrum was almost identical with that of the optically active compound. The differences were due to a little β-phenylethyl alcohol which were present in spite of the treatment carried out.

Fig. 13.

Racemisation of (+)-2,3,8,9-Tetrahydro-3′,4′,2″-trimethoxy-N-methyl-4,5:6,7-dibenzazonine (LXXXII) in β-Phenylethyl Alcohol.

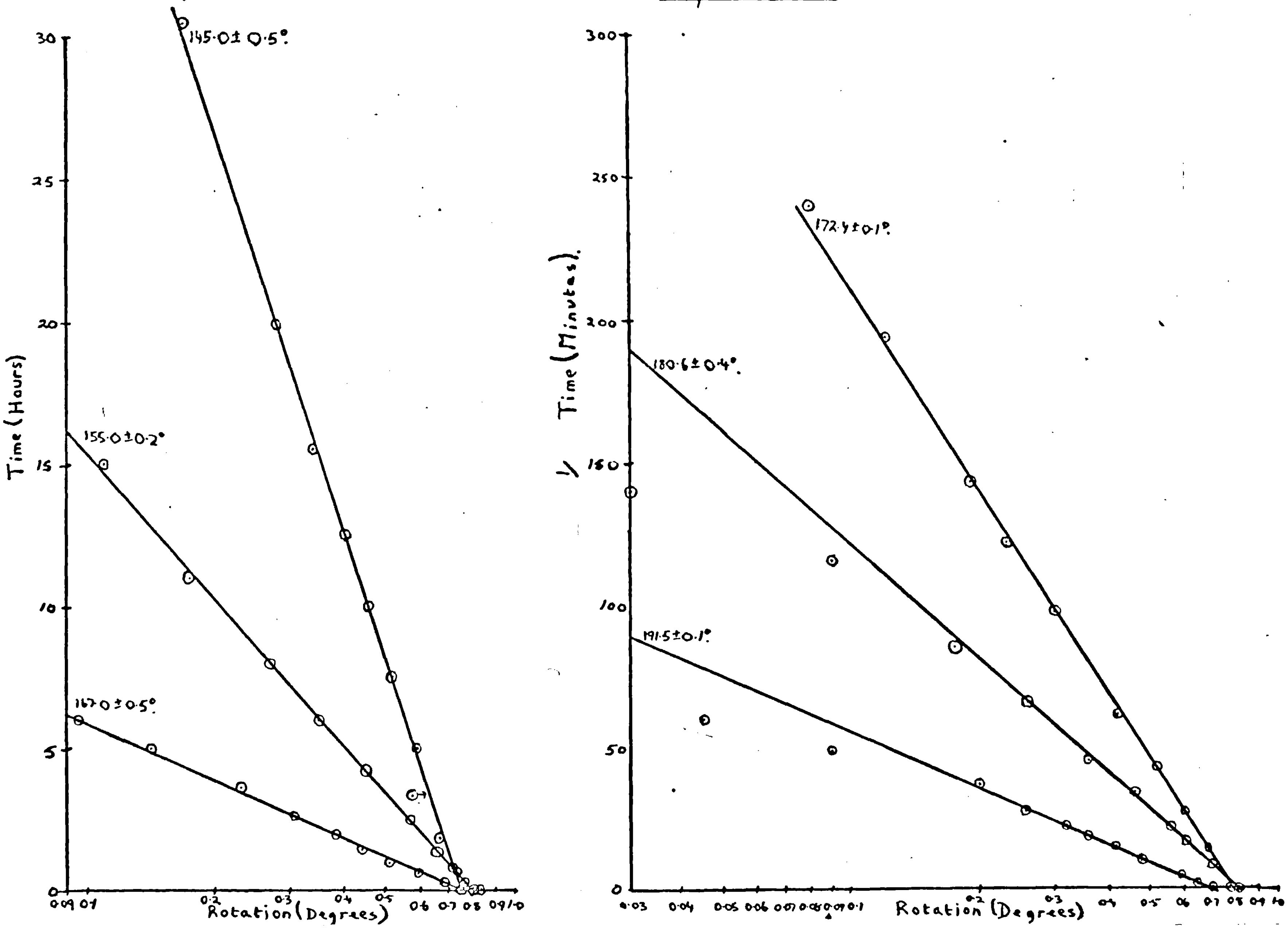
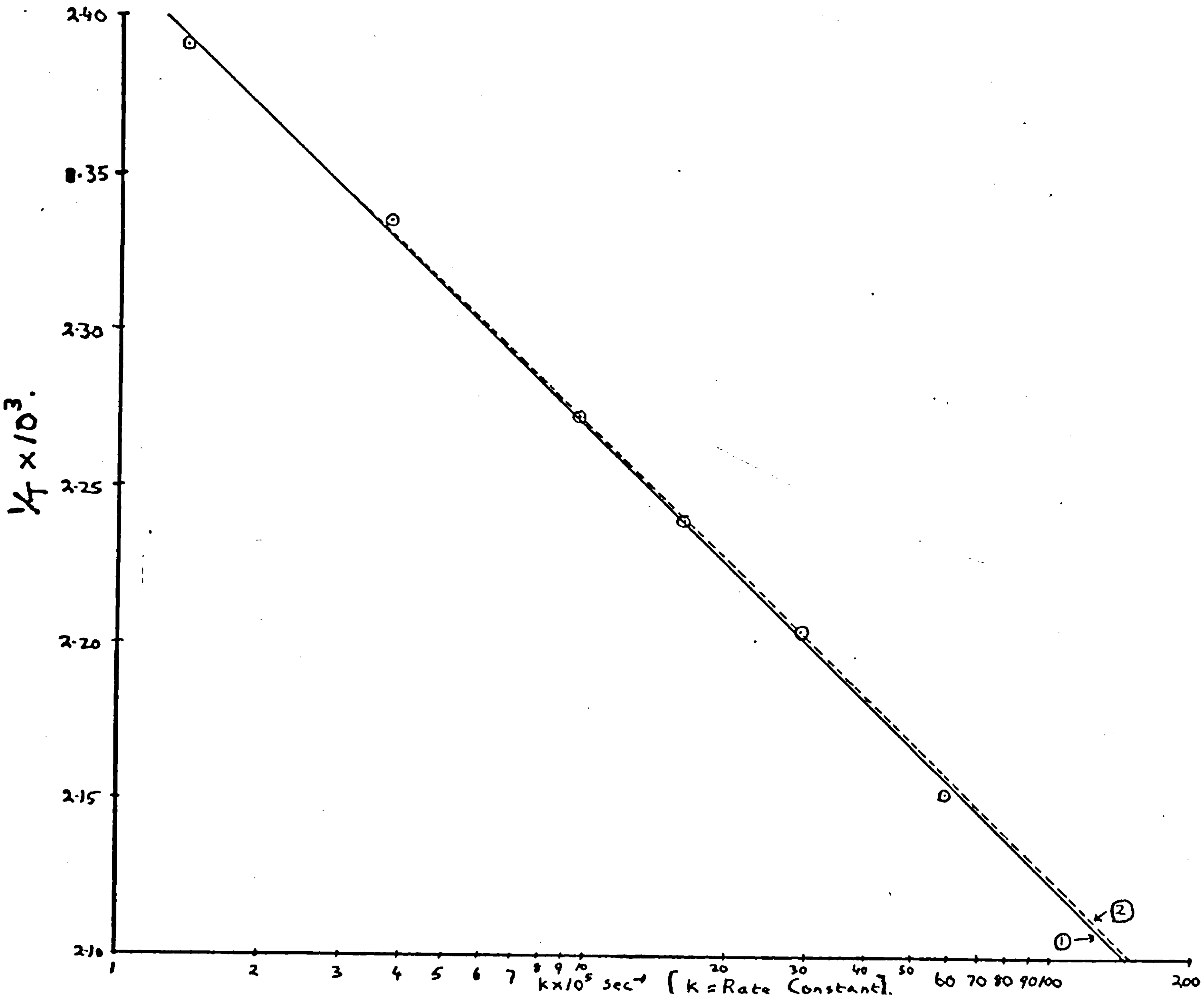


Fig. 14.

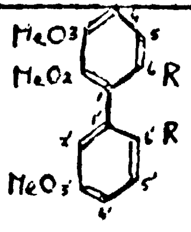
Plot of $\frac{1}{T}$ against the Rate Constant for the Racemisation of (+)-2,3,8,9-Tetrahydro-3',4',2''-trimethoxy-N-methyl-4,5:6,7-dibenzazonine.



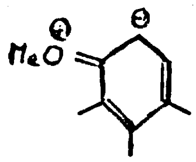
PART 3.

DISCUSSION OF RESULTS.

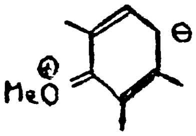
Kinetic Racemisation Experiments.



(LXXXI)



(LXXXII)



(LXXXIII)

In the 2,3,3'-trimethoxybiphenyl derivatives (LXXXI), the methoxyl group in the 3-position can rotate freely if that in the 2-position is favourably orientated. However, any contributions by the canonical structure (LXXXII) to the mesomeric state of the molecule will tend to orientate the 3-methoxyl group in the plane of the ring. The methoxyl group in the 2-position is subject to the "buttressing" effect (p. 13) by that in the 3-position against in-plane bending away from the biphenyl link, but in cases where the two benzene rings are coplanar, models show that the direction of the C-O bond of this 2-methoxyl group cannot make an angle of less than $\alpha = \beta = 42^{\circ}$ with the plane of the benzene ring in the direction of the biphenyl link, owing to the hydrogen atom in the 2'-position (fig. 15). However, any contributions by the canonical structure (LXXXIII) to the mesomeric state will tend to orientate the 2-methoxyl group in the plane of the ring, presumably in the position away from the hydrogen atom in the 2'-position. As the carbon atom of this 2-methoxyl group will lie close to the oxygen atom of the methoxyl group in the 3-position in structure (LXXXIII), distortion of the geometry of this 2-methoxyl group may occur. Hence, it is not known whether any contributions by (LXXXIII) will tend to diminish or increase the interaction between the 2-methoxyl group and the 2'-hydrogen atom. The methoxyl group in the 3'-position can rotate freely, but is subject to contributions by structures such as (LXXXII). These effects may be illustrated as in fig. 15, neglecting contributions by the above canonical structures, for cases in which the benzene rings are coplanar.

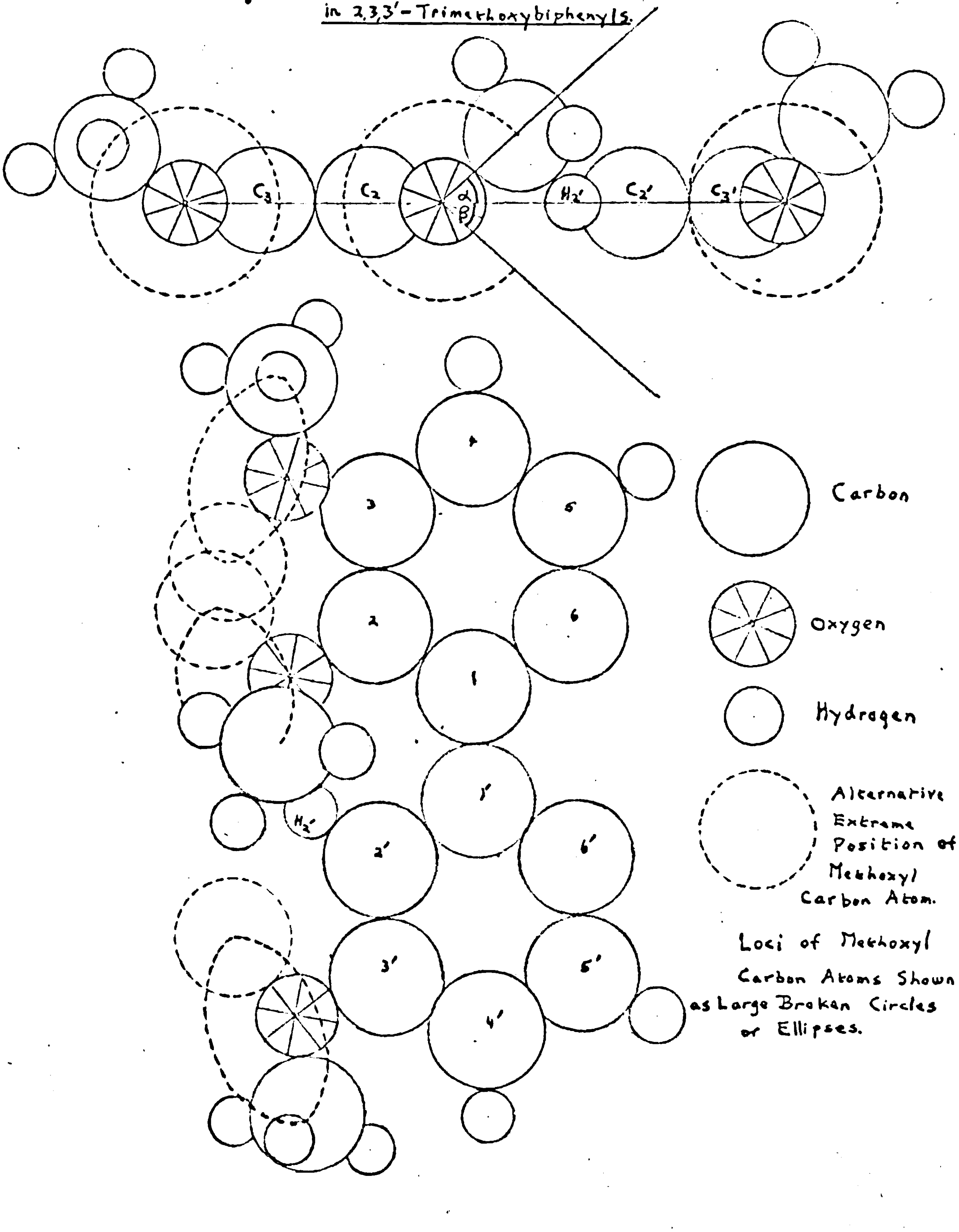
If the angle between the planes of the benzene rings is increased, α, for example, increases to a maximum of 52° at an interplanar angle of 25°, whilst β decreases numerically until interaction between the methoxyl group in the 2-position and the hydrogen atom in the 2'-position eventually disappears.

Effects due to hydrogen bonding or to other forces are not taken into account in this discussion.

The results obtained from work carried out on the (+)-isomers below are in table (5). The high optical stabilities of the compounds are due to steric hindrance to free rotation of the benzene nuclei about the biphenyl linkage by the groups in the 6,6'-positions, in the cases of (XLIII), (LI) and (LXIV),

Fig. 15b

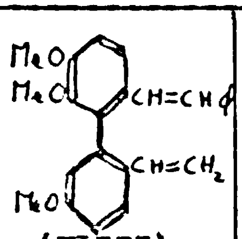
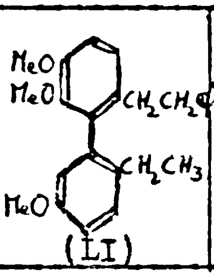
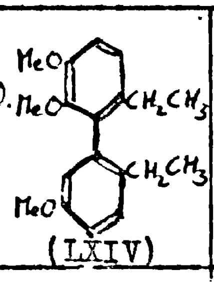
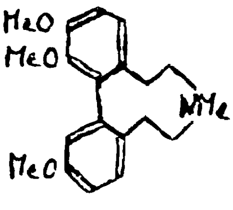
Illustration Showing the Positions and Loci of the Methoxyl Groups in 2,3,3'-Trimethoxybiphenyls.



together with the steric effect of a "buttressed" ortho-methoxyl group which may incorporate contributions by the canonical structures (LXXXII) and (LXXXIII) mentioned above. This steric effect also plays a part in the optical stability of the bridged compound (LXXVII), together with the non-bonded interaction of opposed hydrogens on the α-carbon atoms of the five-atom bridge, in the transition state for racemisation[33].

Table (5).

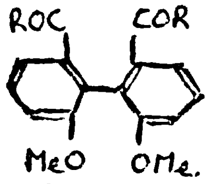
Results of the Kinetic Racemisation Experiments.

	 (XLIII)	 (LI)	 (LXIV)	 (LXXVII)
Solvent	p-cymene	β-phenylethyl alcohol		
E (kcal. mole^{-1})	25.8	33.45	33.8	31.5
Log$_{10}$ A (sec^{-1}.)	10.6	11.4	11.5	11.7
ΔS* (e.u.)	-12.5	- 9.42	- 8.94	- 7.60
ΔH* (kcal. mole^{-1})	25.0	32.5	32.8	30.9
ΔF* (kcal. mole^{-1})	30.1	37.2	37.3	34.5
	at 135.3^o	at 223.6^o	at 223.9^o	at 191.5^o

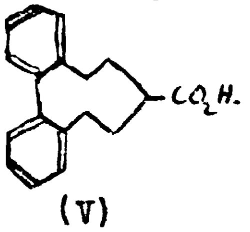
Saturation of the vinyl groups of the stilbene (XLIII) to give the dibenzyl (LI), increases the optical stability considerably, as is to be expected from the examination of models, but the absence of the phenyl group in the side-chain in the diethyl biphenyl (LXIV), does not give a decrease relative to (LI). This is to be expected from the conformation of these side-chains.

Models show that if the "buttressing" effect has a reasonably large effect on the conformation of the ortho-methoxyl group, the transition state for racemisation for the four compounds is slightly non-planar but symmetrical and that racemisation takes place with the methoxyl group in the 2-position passing the hydrogen atom in the 2'-position. However, if the "buttressing" effect has only a small effect on the conformation of the ortho-methoxyl group, this group will pass the ethyl group in the 6'-position in (LI) and (LXIV) and the transition state will be planar for these two compounds.

The difference in the activation energies for racemisation of (V) and (LXXVII) is 7.5 kcal. mole^{-1}, which is due to the effect of the "buttressed" ortho-methoxyl group in the latter. It is interesting to compare the energies of activation for racemisation for (LI) and (LXIV) with the figures obtained for the non-buttressed biphenyls (LXXXIV) with methoxyl groups in the 2,2'-positions (table 6). A difference of about 7.7 kcal. mole^{-1} for the activation energies occurs between the two groups of compounds.



(LXXXIV)



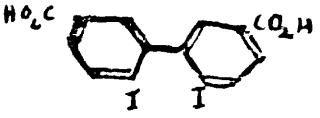
(V)

Table (6).

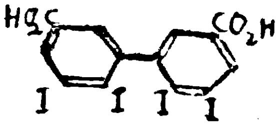
The Activation Energies for Racemisation for Compounds (LXXXIV).

R	E (kcal. mole^{-1})	Reference
$Na^+ O^-$	25.9	101
NH_2	27.85	102
CH_3O	25.5	102
HO	24.5	102

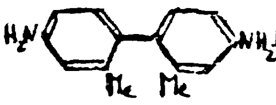
The "buttressing" effect also accounts for the difference of 6.4 kcal. mole^{-1} in the activation energies[35] of the non-bridged biphenyls (VII) and (VIII), and the fact that (X) has been obtained in an optically active state, whereas (IX) has not[37] (p. 13).



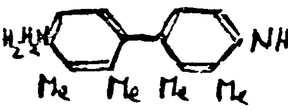
(VII)



(VIII)



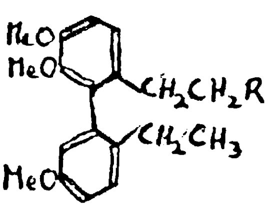
(IX)



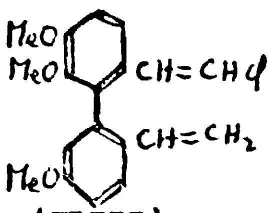
(X)

Ultraviolet Spectra Determinations.

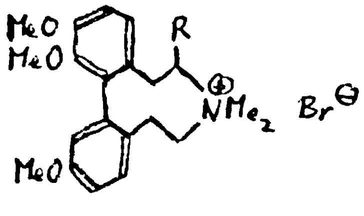
In the course of the work, the ultraviolet spectra of the compounds below were determined in 96% ethanol solution with the following results.



(LI) R = C_6H_5
(LXIV) R = H



(XLIII)



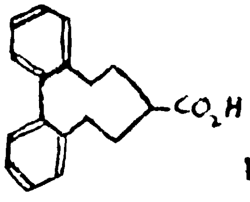
(LX) R = H
(LXI) R = C_6H_5

Table (7).
(XLIII)

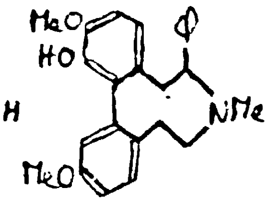
Chromophore	λ_{max} (mμ)	ε
Ar-CH=CH- + ArO-	311	27,000
Styrene-like conjugation	(ca. 250)	22,900
Other short-wave bands	(ca. 240)	25,400
Biphenyl Conjugation	(ca. 230)	27,300
Phenyl	205.5	38,100

	(LI)		(LXIV)		(LX)		(LXI)	
Chromophore	λ_{max}(mμ)	ε	λ_{max}(mμ)	ε	λ_{max}(mμ)	ε	λ_{max}(mμ)	ε
Phenoxy	279	4450	279	4710	280.5	4150	282	4290
Alkylbenzene	-	-	-	-	(253.5)	692	(271) (265)	2840 2020
Biphenyl conjugation	(ca. 227.5)	17800	(ca. 227.5)	16700	(ca. 225	22050	230	26900
Phenyl	201	64500	201	60200	203	67950	207.5	59950

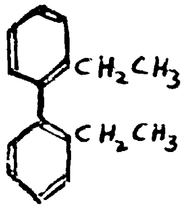
Figures in parentheses denote points of inflection.



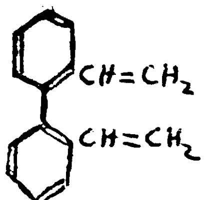
(V)



(VI)



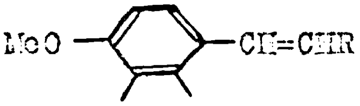
(XXV)



(LIX)

The wavelengths of the conjugation bands in the spectra of (LI), (LXIV), (LX) and (LXI) are fairly close to one another, showing small hypsochromic shifts relative to that for the acid (V) at 231 mμ (ε 5,550). The presence of the methoxyl groups brings about a large enhancement of the intensities. The conjugation band of the stilbene (XLIII) also shows a hypsochromic shift relative to that for 2,2'-divinylbiphenyl (LIX), together with a small enhancement of intensity, this band in the spectrum of the latter compound occurring[82] at λ_{inf} 235 mμ (ϵ = 25,300). Presumably, these shifts, where they occur, must be the result of additional steric hindrance caused by the "buttressed" methoxyl group in the <u>ortho</u>-position.

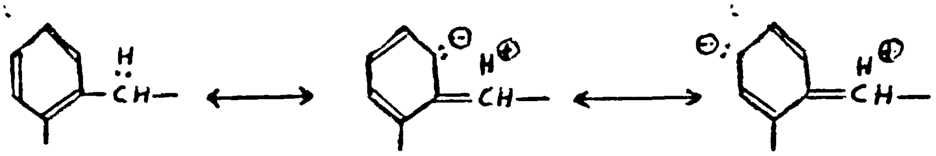
The methiodides (LX) and (LXI), phenyldihydrothebaine[34,57,33] (VI), and the unbridged compounds (LI) and (LXIV), each have a band in their spectra which must be due to the phenoxy chromophores at about 280 mμ (ϵ 4,150 - 5,600). 2,2'-Divinylbiphenyl (LIX) has two bands in its spectrum in the 285 mμ region (ϵ 1,870 and 1,340) due to styrene-like conjugation, but in the stilbene (XLIII), these chromophores and also the phenoxy chromophores have a combined effect due to the possibility of resonance through the system



(R = H or C_6H_5)

which increases the wavelength to 311 mμ and the extinction coefficient to 27,000.

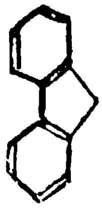
Points of inflection occur at 253.5 mμ (ϵ 692) in the spectrum of (LX) and at 265 mμ (ϵ 2,020) and 271 mμ (ϵ 2,840) in that of (LXI) some others being masked in both cases. Inflections also occur at 265 and 272 mμ (ϵ <u>ca</u>. 600) in that[33] of (V). Analogy of these spectra with those of 2,2'-diethylbiphenyl[58] (XXV), λ_{max} 263.5 (ϵ 730) and 271 mμ (ϵ 560) and with those of toluene[96], ethylbenzene[97] and p-cresol methyl ether[95], which all have absorption in this region (p. 126), leads to the conclusion that the inflections in the spectra of (V), (LX) and (LXI) are due to the partial alkylbenzene chromophores. Alternatively, in all these spectra, it could be said that the above regions of absorption are due to hyperconjugation between the aromatic rings and the α-methylene groups of the side-chains or bridge.



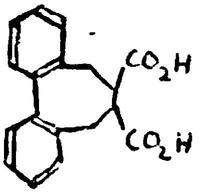
Only the first two structures apply in the cases of (LX), (LXI) and p-cresol methyl ether.

In bridged biphenyls without substituents on the benzene rings, as the size of the bridge increases, the wavelength of the long-wave band in each of the spectra decreases from that for fluorene[40] (XIV) at λ_{max} 300.5 mμ (ϵ 9,080) to those for the methyl esters of the cis- and trans-acids (XXI), which occur at λ_{inf} ca. 266 and 274 mμ (ϵ ca. 800 and 500 respectively) in both spectra[48]. In going through the series, the wavelengths tend towards those of the long-wave inflections for the above five-atom bridged biphenyls and the intensities towards those for (V). According to Braude[32], the long-wave band in each of the spectra of the one- (XIV) and two-atom bridged biphenyls (II) is due to the hyperconjugative interaction of the phenyl rings through the bridge, this effect presumably decreasing as the size of the bridge increases. However, it is more reasonable to assume that the long-wave band in each of the spectra of the bridged biphenyls, except in the case of fluorene (XIV), is due to the partial alkylbenzene chromophores, or in other words, to hyperconjugation between the aromatic rings and the α-methylene groups of the bridge.

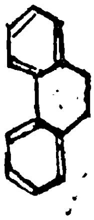
Just as the spectrum of (V) resembles that of 2,2'-diethylbiphenyl[58,33], so the spectra of the methobromides (LX) and (LXI) resemble that of the diethylbiphenyl with the band due to the phenoxy chromophores in the spectrum of 3,3'-dimethoxybiphenyl superimposed. This also applies to the spectra of (LI) and (LXIV), as well as to that of phenyldihydrothebaine, except that the long-wave inflections are missing or they may be masked. Except for this absence, the spectra of (LI) and (LXIV) resemble those of the methobromides. However, superimposition of the band due to the phenoxy chromophores on the spectrum of 2,2'-divinylbiphenyl does not give rise to the spectrum of the stilbene (XLIII).



(XIV)



(XXI)



(II)

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The Preparation of Bentley and Robinson's "Dihydrothebaine" and Proof of its Structure

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The Preparation of Bentley and Robinson's "Dihydrothebaine" and Proof of its Structure

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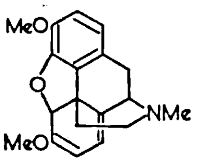
THE action of phenylmagnesium bromide on thebaine (I) gives phenyldihydrothebaine, shown by Bentley and Robinson[1] to have the structure (II; R=Ph). By treating thebaine with anhydrous magnesium iodide Bentley and Robinson[1] hoped to prepare the unsubstituted "dihydrothebaine" (II; R=H), which Schmid and Karrer[2] had also tried to make by direct reduction of thebaine. Bentley and Robinson obtained a light brown solid, for which they tentatively suggested structure (III); reduction with lithium aluminium hydride gave a gas (assumed to be methane) and what appeared to be a phenolic secondary amine from which they could obtain no crystalline derivatives. They considered that demethylation accompanying reduction might have given (IV).

We have reinvestigated these reactions and have now shown that the main product of the lithium aluminium hydride reduction is the tertiary amine, (+)-2,3,8,9-tetrahydro-4′-hydroxy-3′,2″-dimethoxy-*N*-methyl-4,5 : 6,7-dibenzazonine (II; R=H). We were unable to detect methane among the gases evolved during the reduction and could find no evidence for the presence of the secondary amine (IV). The reaction with nitrous acid on which Bentley and Robinson based their assignment is probably a *C*-nitrosation of the phenolic aromatic ring.

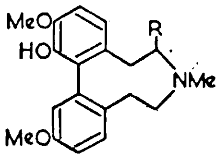
The azonine (II; R=H) was obtained as a crystalline solid, m.p. 103·5—104·5°. Infrared and nuclear magnetic resonance spectra are consistent with the suggested structure, both showing the presence of a hydroxyl and an *N*-methyl group. The methiodide, the methyl ether (V), and the methyl ether methiodide (VI; X=I) have all been prepared and characterised. The methyl ether methobromide (VI; X=Br) has an ultraviolet spectrum (λ_{inf} 225 mμ, λ_{max} 280·5, ϵ_{max} 4145) closely resembling that of phenyldihydrothebaine methyl ether methobromide (λ_{inf} 230 mμ, λ_{max} 282, ϵ_{max} 4290) both in 96% ethanol.

Two Hofmann degradations of the methyl ether methiodide (VI; X=I) gave a nitrogen-free product, considered to be (VII), which polymerised readily and could be hydrogenated to (+)-6,6′-diethyl-2,3,2′-trimethoxybiphenyl (VIII). This compound and the azonine methyl ether (V) racemise on heating in solution at rates consistent with their hindered biphenyl structures.

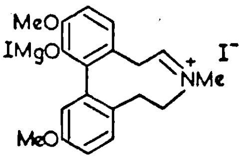
We conclude that the secondary amine (IV) is



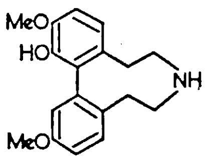
(I)



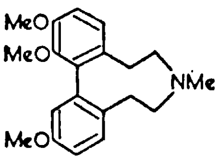
(II)



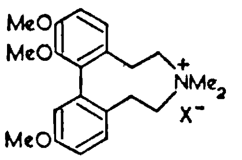
(III)



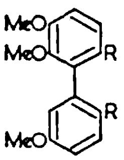
(IV)



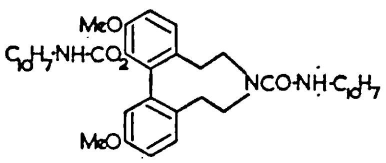
(V)



(VI)



(VII) R=CH:CH_2
(VIII) R=Et



(IX)

absent from the lithium aluminium hydride reduction product for the following reasons: (*a*) we failed to separate the product into two components, (*b*) we were unable to detect any of the substituted urea (IX), when the crude reduction product was treated with α-naphthyl isocyanate, although the α-naphthylurethane of (II; R=H) was readily obtained, and (*c*) we did not observe any shifts in the infrared spectrum after treatment of the sodium salt of (II; R=H) with deuterium oxide; the phenol itself readily underwent *O*-deuteration under the same conditions.

Full details, including a study of the optical stability of (V), will be published elsewhere.

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[1] K. W. Bentley and R. Robinson, *J. Chem. Soc.*, 1952, 947.
[2] H. Schmid and P. Karrer, *Helv. Chim. Acta*, 1950, 33, 863.