# STERIC EFFECTS IN SOME 2,2'-BRIDGED BIPHENYLS.

A Thesis submitted to the University

of London for the Degree of

Doctor of Philosophy.

By:

JOAN MARGARET INSOLE.

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ABSTRACT.

Two types of bridged biphenyls are discussed in this thesis, 3,4:5,6-dibenzazepinium compounds and 5,6:7,8-dibenzo-1,4-diazocines.

An attempt to synthesise 2,7-dihydro-4'-methoxy-3.4:5,6-dibenzazepinium-1-spiro-1'"-piperidinium bromide is described. 2,7-Dihydro-4',1"-dimethoxy-3,4:5,6-dibenzazepinium-1-spiro-1'"-piperidinium iodide was synthesised in an optically active condition, but attempts to obtain it in an optically and chemically pure state were not completely successful. The optical stability of the impure product was determined. Attempts to resolve or activate optically 6-methoxydiphenic acid were unsuccessful.

4',1"-Dimethyl-2,3-diphenyl-5,6:7,8-dibenzo-1,4-diazocine was obtained optically active and an estimation of its optical stability was made. 2,3-Dimethyl-5,6:7,8-dibenzo-1,4-diazocine-2',3"-dicarboxylic acid was synthesised but attempts to resolve it were unsuccessful. The optical stability of 2,3-diphenyl-5,6:7,8-dibenzo-1,4-diazocine-2',3"-dicarboxylic acid was determined.

2,3,4',1"-Tetramethyl-5,6:7,8-dibenzo-1,4-diazocine and 2,3-dimethyl-5,6,:7,8-dibenzo-1,4-diazocine were synthesised. Attempts to obtain 1,2,3,4-tetrahydro-2,3-dimethyl-5,6:7,8-dibenzo-1,4-diazocine by reduction of the latter diazocine appeared to be successful, but the product was chemically unstable.

## ACKNOWLEDGMENTS.

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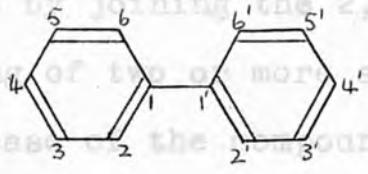
# C O N T E N T S.

## INTRODUCTION.

In the biphenyl molecule (1), which is collinear, the two benzene rings can rotate about the 1,1'-bond with only a small energy barrier (e.g. Howlett, J., 1960, 1055, has calculated the energy barrier to be 3.9 k.cal/mole), and so the molecule in solution can easily assume the coplanar configuration.



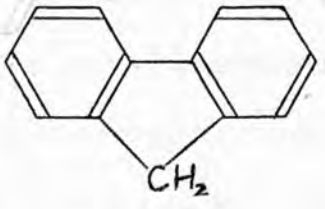

(I)

However, the introduction of ortho-substituents in the biphenyl molecule can bring about restriction of the rotation about the 1,1'-bond. The amount of restriction depends mainly on the number of substituent groups and their relative sizes. If the restriction in rotation makes it difficult for the molecule to pass through the coplanar configuration, then the compound will exist in two stereoisomeric forms, one being the mirror image of the other. Such compounds can be resolved into their optically

active enantiomers, provided that (a) each benzene ring is unsymmetrically substituted, (b) a resolving group is present, and (c) the restriction in rotation is large enough for the enantiomers to be comparatively stable optically under experimental conditions. As one isomer will be converted into the other isomer simply by passing through the coplanar configuration, the optical stability of any such compound will depend on the ease with which the molecule can attain coplanarity and, therefore, on the amount of restriction of rotation.

Restricted rotation about the 1,1'-bond can also be brought about by joining the 2,2'-positions with a bridge consisting of two or more atoms.

In the case of the compound containing a 2,2'-bridge of one carbon atom, i.e., fluorene (2), there can be no

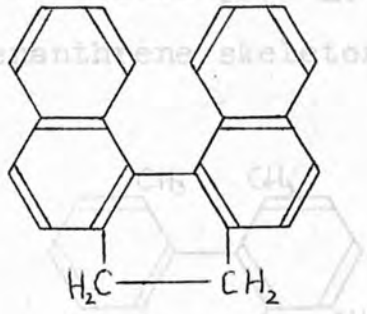



(2)

possibility of optical isomerism as the molecule is planar (Brown and Bortner, Acta Cryst., 1954, 7, 139; Burns and Iball, Nature, 1954, 173, 635).

In compounds where the bridging chain is composed of two atoms another factor may contribute to the asymmetry

of the molecule. This other factor is "intramolecular overcrowding." In compounds such as (3) (Hall and Turner, J., 1955, 1242), (4) (Wittig and Zimmermann, Chem.Ber., 1953, 86, 629) and (5), (6), (7) and (8), (Armarego and Turner, J., 1956, 3668; 1957, 13), where the calculated angles between the planes of the ring systems are not large enough to accommodate the o,o'-substituents, these substituents may be bent out of the planes of the benzene rings. However, it

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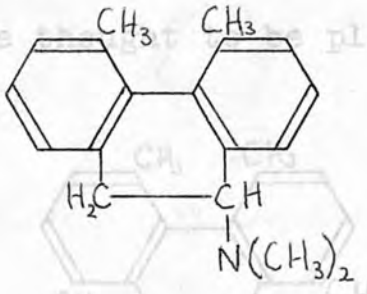


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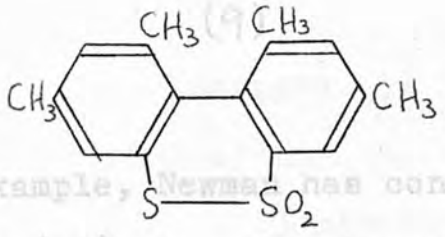


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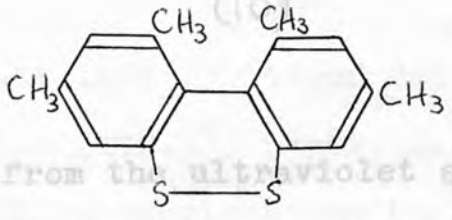


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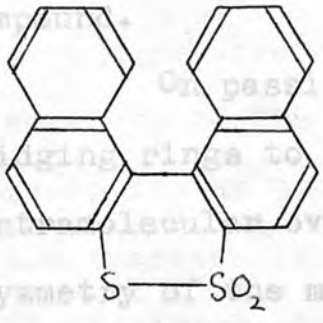
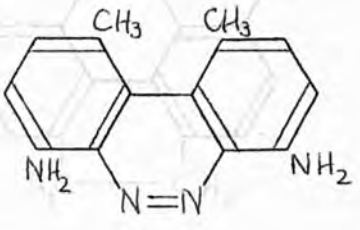



(7)


(8)

is not certain that this bending occurs and it is possible that the angles of twist between the ring systems are increased to accommodate the substituent groups.

The asymmetry of molecules such as (9) (Theilacker and Baxmann, Naturwiss., 1951, 38, 156; Annalen, 1953, 581, 117), and (10) (Newman and Hussey, J.Amer.Chem.Soc., 1947, 69, 978, 3023) is due entirely to "intramolecular overcrowding", as the benzo [3,4-c] cinnoline skeleton of (9) and the phenanthrene skeleton of (10) are thought to be planar. For

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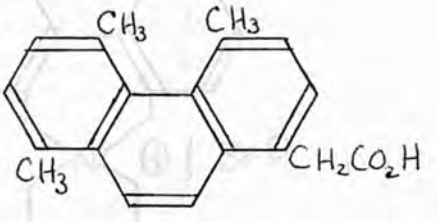


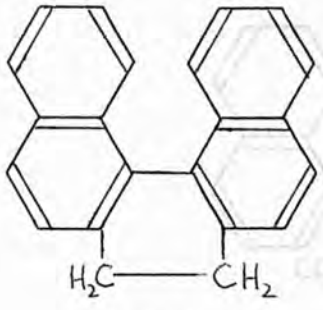

(10)

example, Newman has concluded from the ultraviolet spectrum of (10) that the phenanthrene skeleton is not distorted enough to produce the optical isomerism observed in this compound.

On passing from compounds containing six-membered bridging rings to those containing seven-membered rings, "intramolecular overcrowding" no longer contributes to the asymmetry of the molecules because the increase in the size of the bridging chain allows the angle between the planes

of the benzene rings to be large enough to accommodate o,o'-substituents without strain. Thus in such molecules containing seven-membered bridging rings, asymmetry is due entirely to the twisted conformation.

It has been observed that enlargement of the bridging ring from six to seven atoms leads to an increase in optical stability, this being demonstrated by compounds (3) and (11) (Hall and Turner, J., 1955, 1242).

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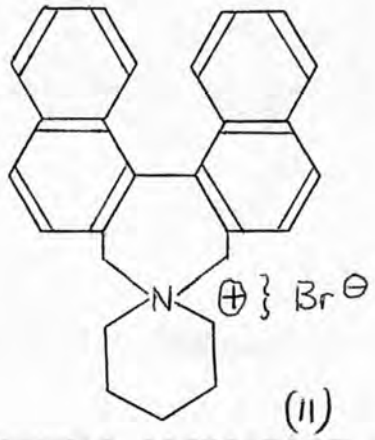
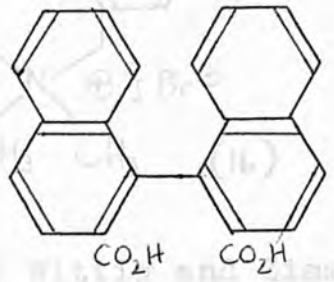



(11)

Compound (3) has a half life period of racemisation of 158 minutes in boiling toluene (110.5°) (Hall, J., 1956, 3674), and of 13 minutes in boiling ethylbenzene (~136°), while compound (11) has a half life period of racemisation of the order of 26 hours at 172° in ethylene glycol. Thus (11) is much more optically stable than (3). The steric effects due to the substituent groups (in this case, benzene rings acting as substituents) must be the same in both cases, so the increase in stability must be due to the greater configurational stability of the seven-membered ring, in which a greater distortion is required in order to pass

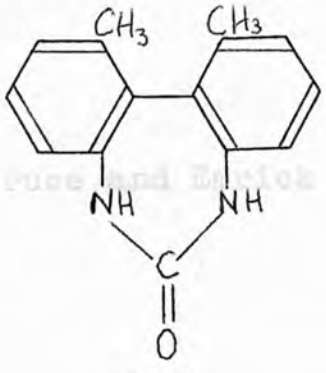
through the coplanar configuration.

However, both these bridged compounds are less stable than 1,1'-binaphthyl-2,2'-dicarboxylic acid (12). The rotation of a solution of the diacid in N-methylformamide was unchanged after being heated at $\sim 175^{\circ}$ for 8 hours (Hall and Turner, loc.cit.). In general, bridged biphenyls are less optically stable than the corresponding unbridged compounds in the few cases in which direct comparison can be made.




(12)

Many 2,2'-bridged biphenyls containing seven-membered bridging rings have been obtained optically active. Examples of these are given below:-

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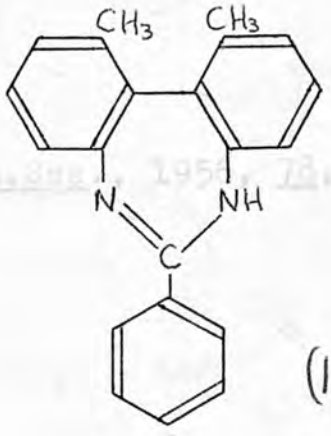


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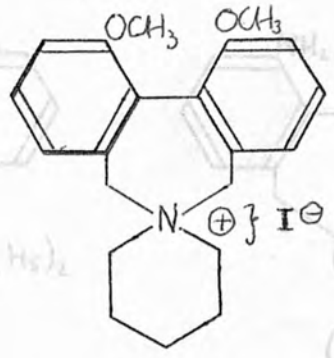
(13) and (14) Sako (Mem.Coll.Eng. Kyushu Imp.Univ., 1932, 6,283)



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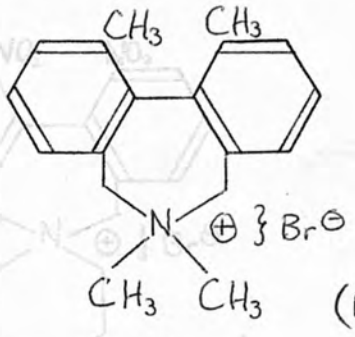
(15) Beaven, Hall, Lesslie and Turner, (J., 1952, 854)



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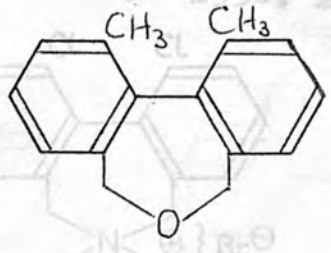

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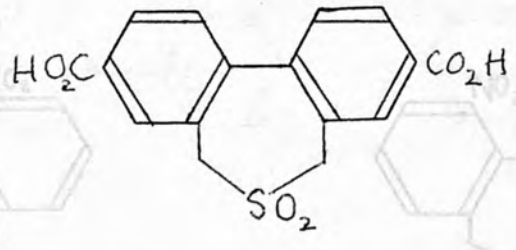
(16) and (17) Wittig and Zimmermann (Chem.Ber., 1953, 86, 629).



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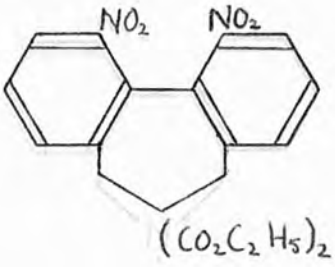
(18) Truce and Emrick (J.Amer.Chem.Soc., 1956, 78, 6130).

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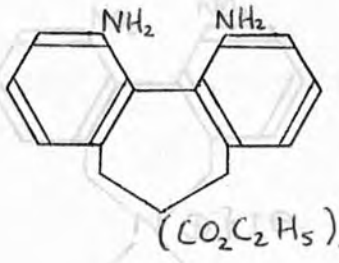


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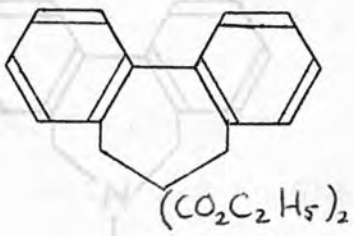


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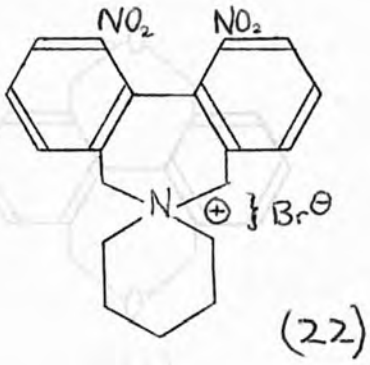
(19), (20) and (21) Iffland and Siegel (J.Amer.Chem.Soc., 1958, 80, 1947).

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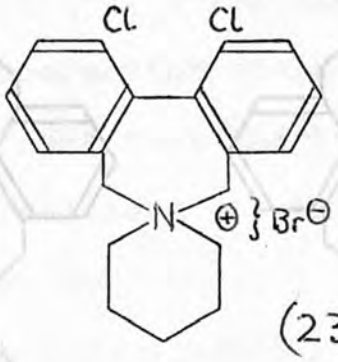


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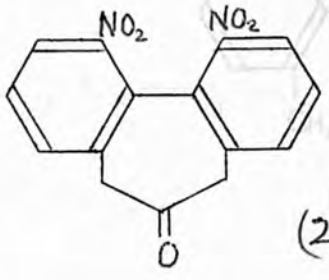
(22) and (23) Fitts, Siegel and Mislow (J.Amer.Chem.Soc., 1958, 80, 480).

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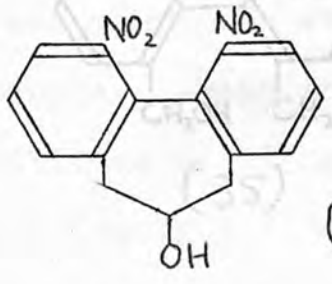


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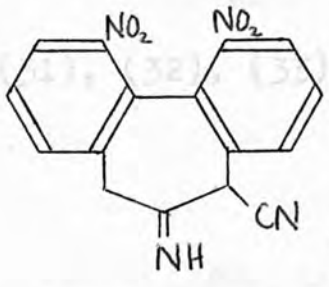


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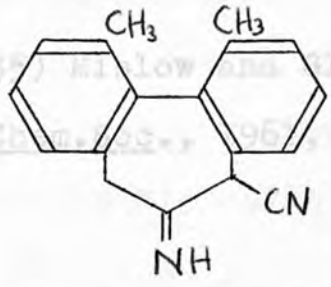


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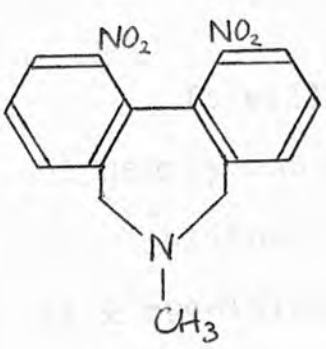
(24), (25), (26) and (27) Newman, Rutkin and Mislow (J.Amer.Chem.Soc., 1958, 80, 465).



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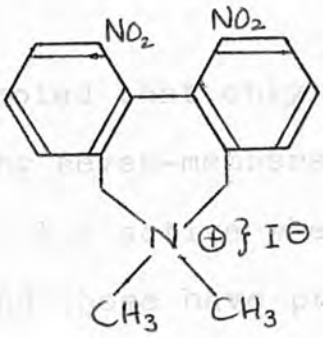

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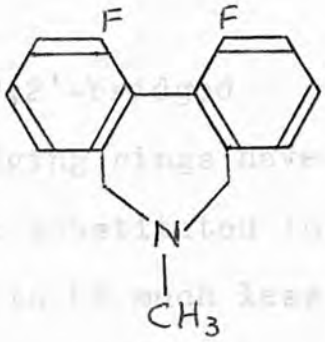
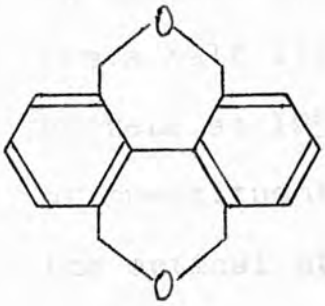


(30)

(28), (29) and (30) Ahmed and Hall (J., 1958, 3043).



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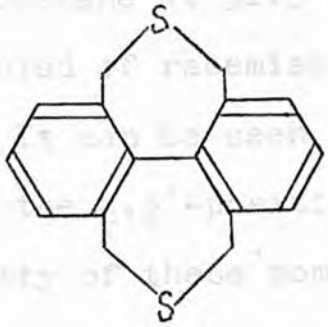

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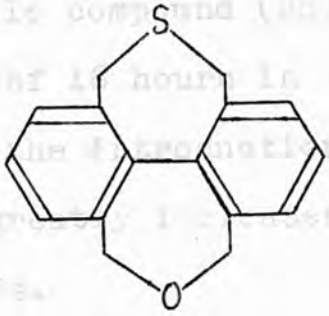

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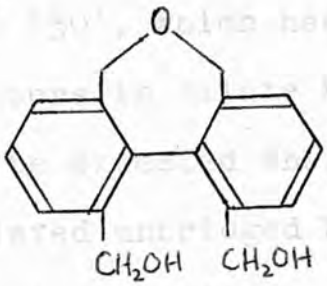

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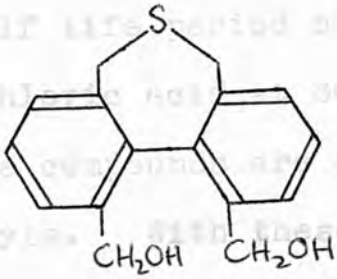


(35)

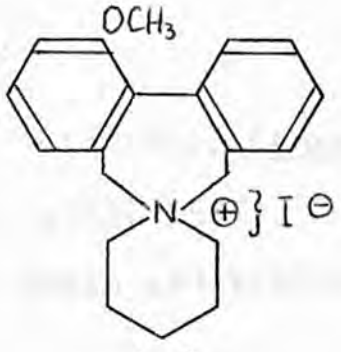
(31), (32), (33), (34) and (35) Mislow and Glass, (J.Amer. Chem.Soc., 1961, 83, 2780).

It will be noted that only two 2,2'-bridged biphenyls containing seven-membered bridging rings have been obtained optically active when not substituted in the o, o'-positions, and those have proved to be much less optically stable than related compounds containing substituents in the o,o'-positions. For example, compound (21) has a half life period of racemisation of 80 minutes in cyclohexane at 31.5°, while compound (28) has a half life period of racemisation of 16 hours in benzene at 125°. It can be seen that the introduction of substituents in the o,o'-positions greatly increases the optical stability of these compounds.

Compound (28) is much more optically stable than compound (30), which has a half life period of racemisation of 6.5 hours in dilute hydrochloric acid at 80°. This is only to be expected when these compounds are compared with related unbridged biphenyls. With these it has been found that the optical stabilities of biphenyls substituted in the ortho positions depend mainly on the relative sizes of these substituents. The relative sizes (or steric effects) of different groups are generally accepted to be in the order of $NO_2 > OCH_3 > F$, in the case of the racemisation of optically active biphenyls (Adams and Yuan, Chem.Rev., 1932, 12, 261).

However, when the optical stabilities of compounds (28) and (30) were compared with that of (15), it appeared that the stabilities were in the order of $OCH_3 > NO_2 > F$. Compound (15) was only partially racemised when a cyclohexanol solution of it was boiled (160°) for eight hours. The difference in the valency states of the nitrogen atoms in the compounds (28) and (15) might be the cause of this anomaly. Accordingly, the methiodide (29) of (28) was made. It had a half life period of racemisation of 4.75 hours in acetone at 145°. Thus it is nearly twice as stable as the dinitroazepine (28) but still not as stable as the dimethoxyazepinium compound (15).

For this present work, it was thought that the optical stability of the dimethoxyazepinium compound needed investigating more fully and that the problem would be further clarified if the unsymmetrical monomethoxy-azepinium iodide (36) could be obtained optically active.




(36)

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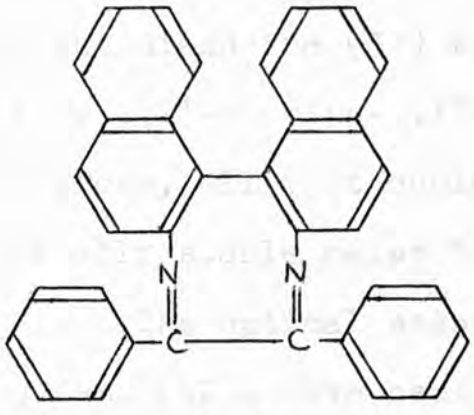
This would give a clear/picture of the effect of the

methoxyl group on the optical stability of these types of compound.

A few bridged biphenyls with an eight-membered bridging ring have been obtained optically active. These are given below.



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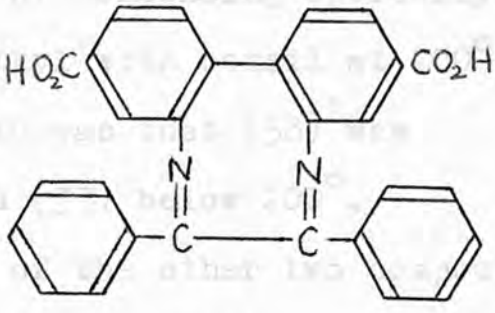

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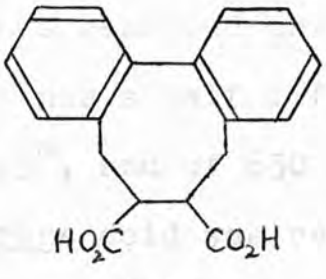
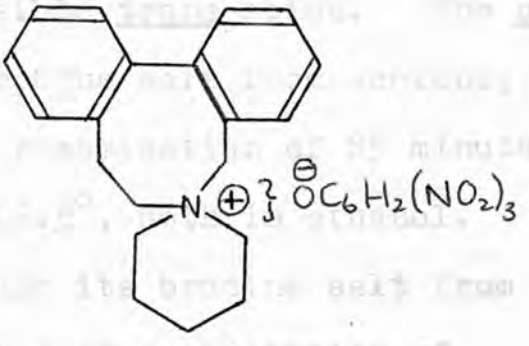


(39)



(40)

(37) Kuhn and Goldfinger (Annalen, 1929, 470, 183).

(38) Bell (J., 1952, 1527).

(39) Dvorken, Smyth and Mislow (J.Amer.Chem.Soc., 1958, 80, 486).

(40) Ahmed and Hall (J., 1959, 3383).

Little was known about the optical stability of compounds (37) and (38) and, therefore, how their stabilities compared with those of the eight-membered saturated ring compounds (39) and (40). The diazocine (38) was resolved by recrystallisation of its brucine salt from ethanol, and the diazocine (37) was made by condensing optically active 2,2'-diamino-1,1'-binaphthyl with benzil at 200°. Therefore, all that could be said was that (38) was optically stable below ~ 80° and (37) below 200°.

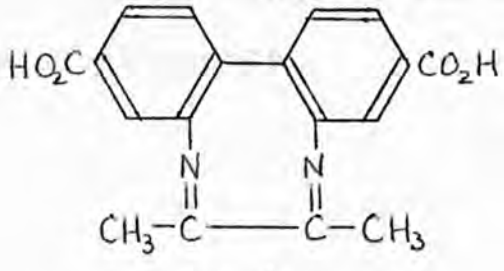
The optical stabilities of the other two compounds, (39) and (40), have been studied more fully. The diacid (39) was obtained in two forms, one from being the cis acid and the other one of the two possible trans acids. The cis acid was resolved through its morphine salt from acetone, and it has a half life period of racemisation of 85 minutes at 31.5°, and of 630 minutes at 16.5°, both in ethanol. The trans acid was resolved through its brucine salt from acetone, and has a half life period of mutarotation of 12 minutes at 31.5° in ethanol. The (+)- α-bromocamphor-$\pi$-sulphonate of (40) underwent an asymmetric transformation by crystallisation from ethanol-ethyl acetate. The azocine picrate has a half life period of racemisation of 3.5 minutes at 16° in acetone.

Thus the *cis* diacid is more optically stable than the azocine picrate although both are unsubstituted in the *o*,*o*'-positions. This may be due partly to the presence of the smaller nitrogen atom in the bridging ring of the azocine picrate and partly to the use of different solvents in the determination of these rates. It is also to be expected that the tendency of the azocine picrate, unlike the diacid, to be ionised to some extent under these conditions must affect the rate of racemisation. This is borne out by the fact that the diacid has a half life period of racemisation of 610 minutes at 16.5° in 2.32N sodium hydroxide solution. Thus it is slightly less stable in sodium hydroxide than in ethanol. However, at the same time it shows that this factor must contribute very little to the optical stabilities of these compounds and it does not account for the large difference between the optical stability of the azocine picrate and that of the *cis* acid.

Even from the little information available it appeared that the diazocines were much more stable than the compounds containing the saturated bridges, and that this increase in optical stability was due to the presence of the double bonds in the bridging rings of the diazocines. The double bonds would tend to make the whole structure

more rigid and therefore would make it more difficult for the molecule to attain coplanarity.

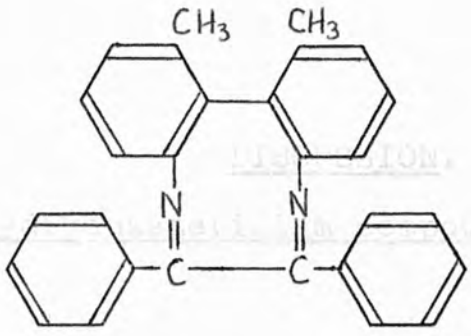
It was decided to investigate the optical stabilities of some diazocine compounds and to compare them with compounds (39) and (40). For purposes of comparison it would be necessary to investigate the optical stability of a diazocine unsubstituted in the o,o'-positions. The diazocine (41) seemed to be ideal for this purpose.




(41)

Accordingly, it was decided to attempt to synthesise it and to resolve it. Failing this, the investigations would be carried out on the compound (38).

The presence of substituents in the o,o'-positions would be expected to increase the optical stabilities of these diazocines. It was thought necessary to obtain such a compound in an optically active condition in order to examine the effect of the substituent groups on the optical stability. The diazocine (37) appeared to be too stable for this purpose so it was decided to attempt to prepare compound (42) in its optically active forms.



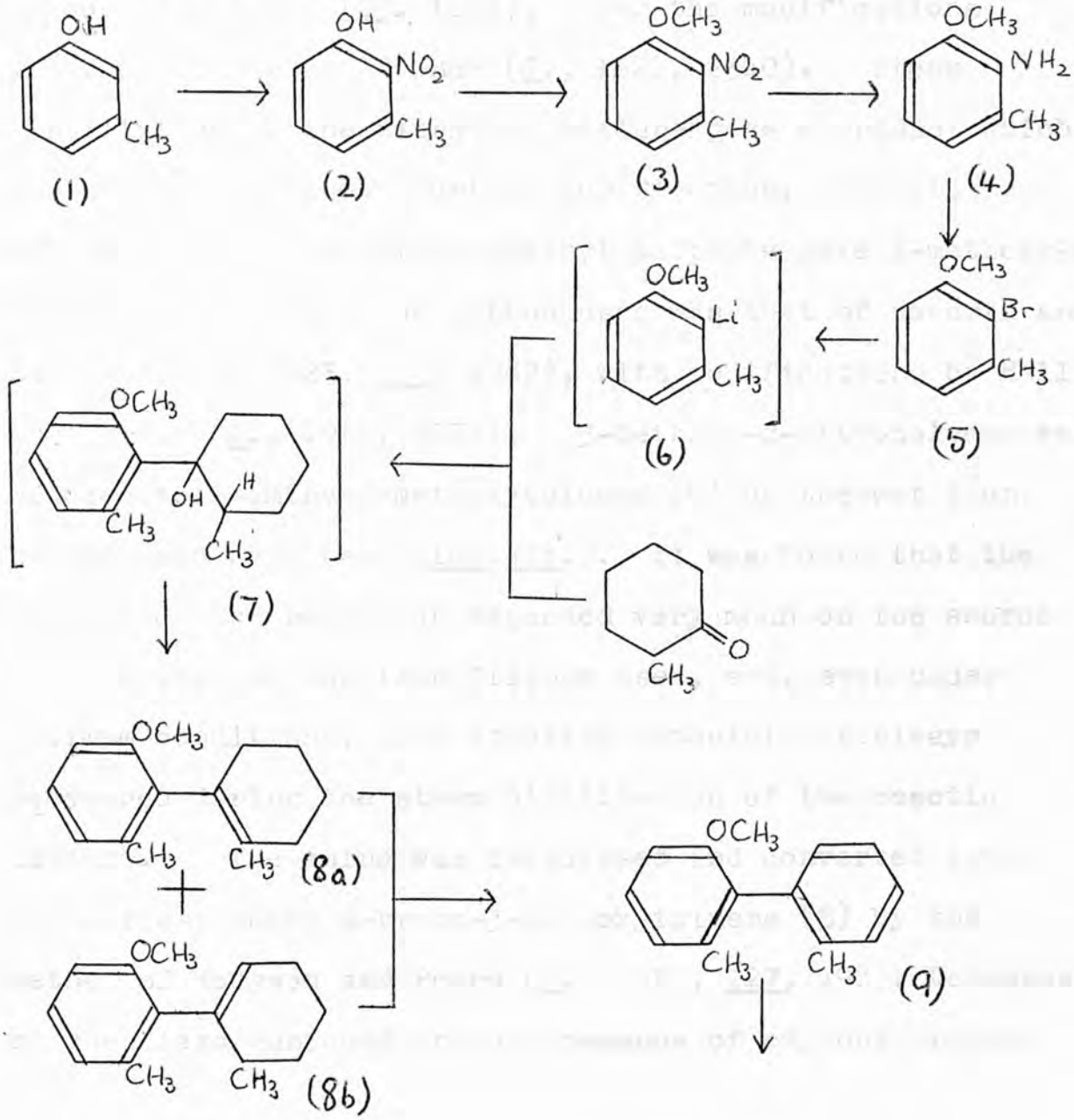
(42)

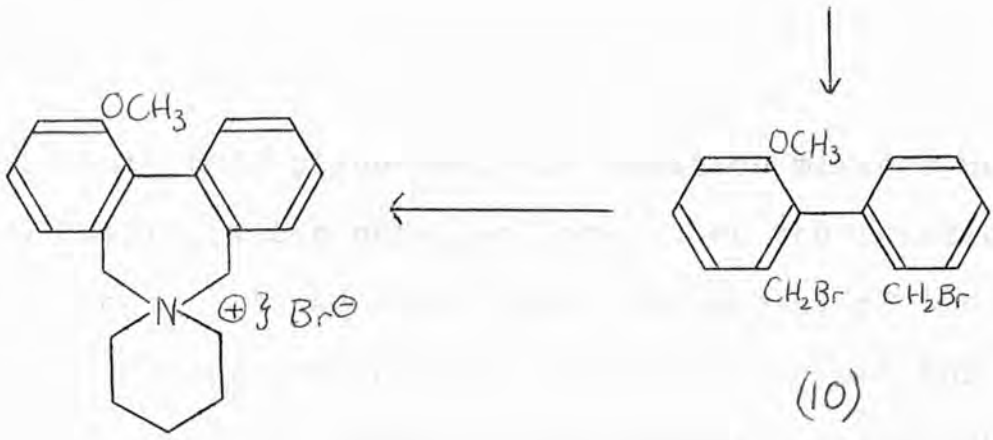
The methyl groups should not have such a large steric effect as the benzene rings of the binaphthyl compound, which act as substituents.

## DISCUSSION.

(a) Methoxydibenzazepinium compounds.

An attempt was made to obtain 2,7-dihydro-4'-methoxy-3,4:5,6-dibenzazepinium-1-spiro-1"-piperidinium bromide (11) by the following synthesis.





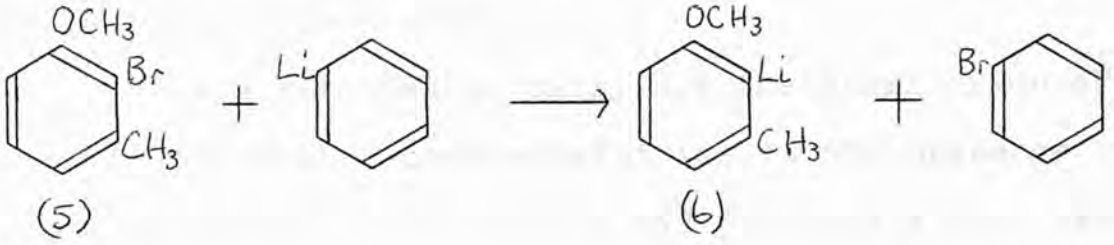

(10)

(11)

2-Nitro-m-cresol(2) was prepared by the method of Gibson (J., 1923, 123, 1269), using the modifications given by Kenner and Turner (J., 1928, 2340). Steam distillation of the nitration mixture gave a product which could be used without further purification. Methylation of 2-nitro-m-cresol with dimethyl sulphate gave 3-methoxy-2-nitrotoluene (3). The method used was that of Haworth and Lapworth (J., 1923, 123, 2982), with modifications by Hall and Turner (J., 1951, 3072). 3-Methoxy-2-nitrotoluene was reduced to 2-amino-3-methoxytoluene (4) by the wet iron method used by Gibson (loc.cit.). It was found that the success of the reduction depended very much on the source and the size of the iron filings used, and, even under optimum conditions, some starting material was always recovered during the steam distillation of the reaction mixture. The amine was diazotised and converted into the corresponding 2-bromo-3-methoxytoluene (5) by the method of Hodgson and Beard (J., 1925, 127, 498). Decomposition of the diazo compound in the presence of cuprous bromide

would only take place when the reaction mixture was heated on a boiling water bath, and even then the reaction was very slow. It was found that the removal of the product by steam distillation could be started before the decomposition of the diazo compound had ceased, and that the decomposition was completed during the steam distillation. The bromo compound was then converted into its corresponding lithium compound (6).

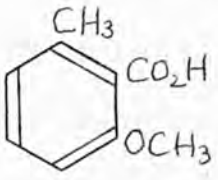
There are two possible methods of making a lithium compound like 2-lithium-3-methoxy-toluene (6). The first method is a direct reaction of the bromo compound with free lithium. The second method involves the preparation of phenyl-lithium from bromobenzene. Then, under suitable conditions, an exchange reaction can take place between the bromo compound and phenyl-lithium to give the required lithium compound and bromobenzene.




(5) (6)

Accordingly, the preparation of the lithium compound was attempted by both methods and the success of each method was determined by pouring the resulting ethereal solution of the lithium compound on to a mixture of solid carbon dioxide and ether. 3-Methoxy-o-toluic acid (12) was

isolated from both products. It was found that the first




(12)

method using free lithium gave a better yield (50%) than the second method using phenyl-lithium (31%). Therefore, it was decided to prepare the lithium compound (6) by the direct reaction of the bromo compound (5) with lithium. Then, without isolating the product, 2-methylcyclohexanone was added to an ethereal solution of the lithium compound. The product (7) of this reaction was isolated and was dehydrated by heatingtwice with naphthalene-β-sulphonic acid, at a temperature above 100°, to give a mixture of 2'-methoxy-6'-methylphenyl-2-methylcyclohex-1-(and-6-)ene(8a and 8b). 2,2'-Dimethyl-6-methoxybiphenyl (9) was prepared by dehydrogenating the above mixture of phenylcyclohexenes with 5% palladium-charcoal.

It was intended to carry out the bromination of the above bitolyl with N-bromosuccinimide in the presence of benzoyl peroxide. This method had previously been used successfully by Wenner (J.Org.Chem., 1952, 17, 523), and by Ahmed and Hall (J., 1958, 3043) to brominate other bitolyls.

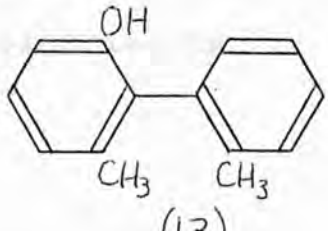
A solution of the bitolyl (1 mol.) in dry carbon tetrachloride was heated under reflux with N-bromosuccinimide (2 mol.) and a small amount of benzoyl peroxide. The heating was carried out on a water bath kept at ~90° and

was continued for eight hours. After only a few minutes heating, the solution went a dark red-brown as free bromine was liberated, and the solution remained this colour throughout. The crystals of N-bromosuccinimide gradually disappeared from the bottom of the flask and different crystals appeared floating on the surface of the solution. After eight hours, the reaction mixture was filtered hot and the filtrate was evaporated to dryness. A brown gum was obtained. The crystalline solid, which had been filtered off , was identified by its melting point as succinimide. All attempts to isolate a solid from the gum mentioned above failed. Therefore, the gum was dissolved in benzene, the benzene solution was dried over calcium chloride, and was filtered. A slight excess of piperidine was added and the solution was warmed at $\sim 50^{\circ}$ for five hours. During this time, needle-like crystals mixed with a sticky gum appeared at the bottom of the flask containing the solution. The solution was decanted off and the residue was washed several times with warm, dry benzene. The sticky gum dissolved up completely leaving white needles of piperidine hydrobromide. Had the azepinium compound (11) been formed, it would have been insoluble in benzene. The rapid appearance of free bromine in the reaction mixture made it seem likely that the bromination was not proceeding satisfactorily. Therefore, a method of Looker and Holm

(J.Org.Chem., 1959, 24, 567) for the removal of excess bromine by distillation was adopted, carbon tetrachloride and bromine being slowly distilled off during the reaction. At the same time, more carbon tetrachloride was added to keep the volume of the reaction solution constant. However, once again no azepinium compound was obtained from the reaction with piperidine. Finally, bromination was attempted with free bromine at 120°. A reaction took place and acidic fumes were evolved but no azepinium compound could be isolated as a result of the reaction with piperidine.

From these experiments, it was concluded that little or none of the dibromo compound had been formed. However, it did appear that some reaction was taking place. It seems probable that nuclear rather than side-chain bromination was taking place in all the experiments carried out.

As it appeared to be impossible to obtain 2,2'-bisbromomethyl-6-methoxybiphenyl (10) from the bitolyl (9), it was decided to attempt to demethylate the bitolyl, and then to attempt to resolve the product, 6-hydroxy-2,2'-dimethylbiphenyl (13), through its (-)-menthoxy-acetate.




(13)

The following attempts were made to affect this demethylation.

(1) A solution of the bitolyl (4 g.) in a mixture of hydrobromic acid (10 c.c.; d 1.49) and glacial acetic acid (40 c.c.) was boiled under reflux for $9\frac{1}{2}$ hours.

(2) A solution of the bitolyl (5 g.) in a mixture of hydriodic acid (10 c.c.), which had been shaken with red phosphorus to remove most of the free iodine, and acetic anhydride (40 c.c.) was boiled under reflux for six hours.

(3) A mixture of the bitolyl (4 g.) and pyridine (1 g.) was heated at 200-210° for five hours in the presence of hydrogen chloride gas.

(4) A solution of the bitolyl (4 g.) in a mixture of hydriodic acid (6 c.c.), which had been boiled under reflux for $\frac{1}{2}$ hour with red phosphorus to remove all traces of free iodine, and glacial acetic acid (30 c.c.) was heated at 80-100° for $1\frac{1}{2}$ hours.

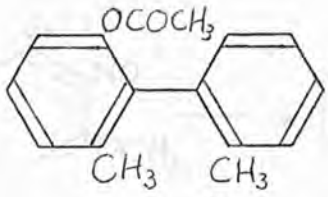
(5) A solution as used in experiment (4) was heated at 140° for four hours.

(6) A solution of the bitolyl (2.9 g.) in iodine-free hydriodic acid (6 c.c.) and acetic anhydride (30 c.c.) was boiled under reflux for one hour.

No demethylation took place in experiments (2), (4) and (5). In experiments (1) and (3), demethylation did

take place and some 6-hydroxy-2,2'-dimethylbiphenyl, m.p. 41-43° (after recrystallisation), was obtained. (Found: C, 84,5; H, 7.1. $C_{14}H_{14}O$ requires C, 84.8; H, 7.1%.) The phenol was recrystallised from methanol in an acetone-solid carbondioxide freezing mixture, and was filtered off under the same low temperature conditions. However, the amount of product in both cases was very small ( $<0.5$ g.), and most of the starting material was recovered unchanged. Attempts to make the demethylation go to completion under the conditions of experiments (1) and (3), by heating for much longer periods, were unsuccessful.

In experiment (6), the reaction mixture was poured into cold water and a yellow oil was obtained. The oil was extracted with ether. The ethereal layer was washed twice with acidic sodium metabisulphite solution, and then $\sim$ 15 times with luke-warm water until the aqueous extracts were only slightly acid to litmus. The ethereal solution was dried over calcium chloride, and then the ether was removed by distillation. The residue was a pale orange oil, which crystallised after standing for four days. The solid was recrystallised from ethanol giving colourless needles with a melting point of 70-72°. On analysis, this solid was found to be the acetate of 6-hydroxy-2,2'-dimethyl-biphenyl (14). Found: C, 79.8; H, 6.6. $C_{16}H_{16}O$ requires C, 80.0; H, 6.7%.). Hydrolysis of this acetate with



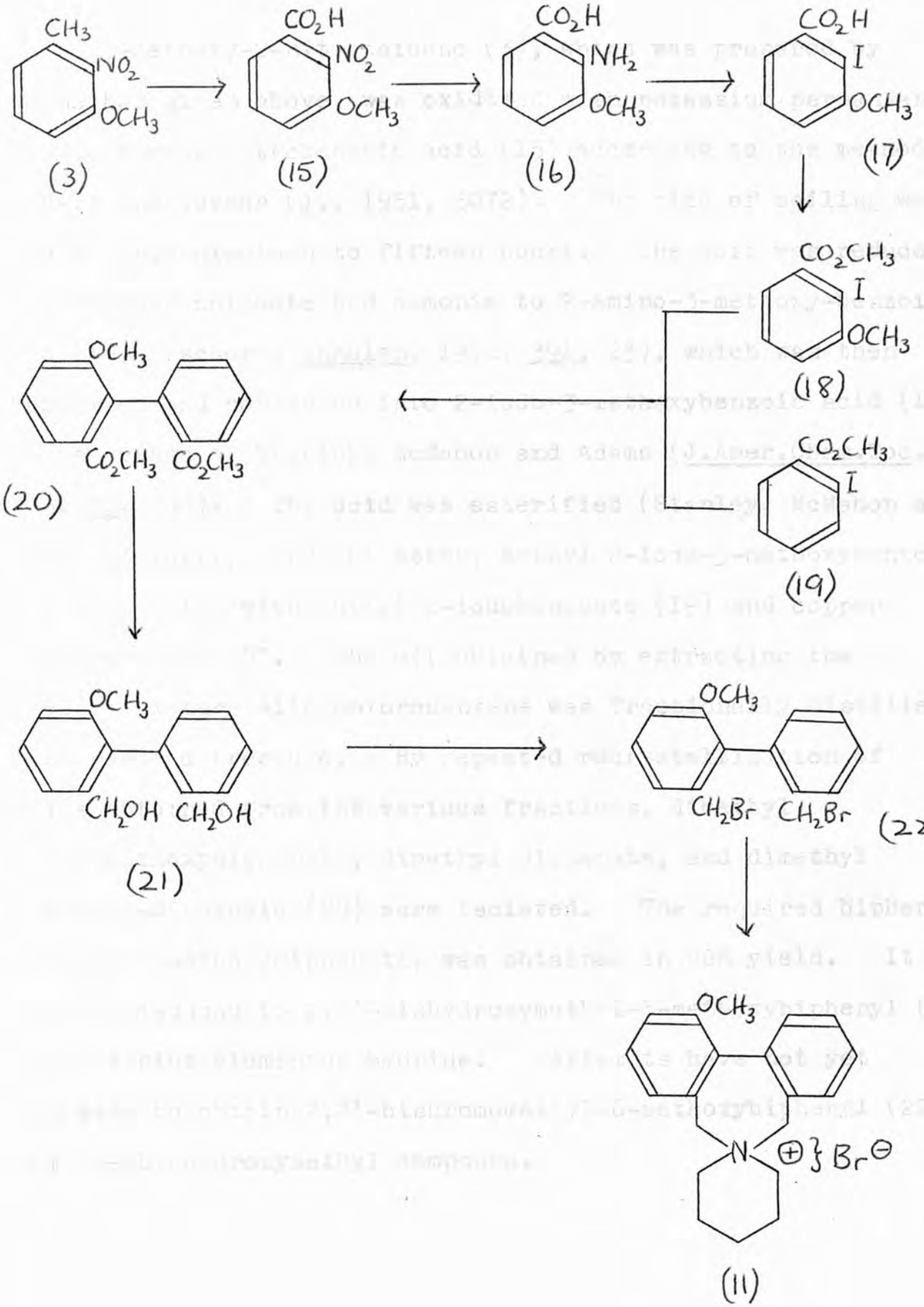

(14)

alcoholic potassium hydroxide gave the required phenol (13).

Attempts to repeat this demethylation under the same conditions failed to give any trace of the acetate or of the phenol. The original experiment had been carried out with some bitolyl which previously had been recovered from unsuccessful demethylation experiments using hydrobromic acid and glacial acetic acid. It is thought probable that this sample contained a slight trace of an impurity, possibly hydrobromic acid, which had a catalytic effect on the reaction when carried out under the conditions of experiment (6). When using freshly-prepared bitolyl, this catalyst would not be present, and so the demethylation would not proceed as expected.

Thus attempts to find a satisfactory method of demethylating 6-methoxy-2,2'-dimethylbiphenyl failed and the project was abandoned.

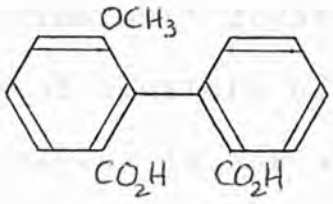
An attempt was made to obtain 2,7-dihydro-4'-methoxy-3,4:5,6-dibenzazepinium-1-spiro-1'"-piperidinium bromide (11) by a different route. The general scheme of this synthesis is given below.


CH3
NO2
OCH3
(3)
CO2H
NO2
OCH3
(15)
CO2H
NH2
OCH3
(16)
CO2H
I
OCH3
(17)
CO2CH3
I
OCH3
(18)
CO2CH3
I
(19)
OCH3
CO2CH3 CO2CH3
(20)
OCH3
CH2OH CH2OH
(21)
OCH3
CH2Br CH2Br
(22)
OCH3
N ⊕ } Br⊖
(11)

3-Methoxy-2-nitrotoluene (3), which was prepared by the method given above, was oxidised with potassium permanganate to 3-methoxy-2-nitrobenzoic acid (15) according to the method of Hall and Turner (J., 1951, 3072). The time of boiling was reduced from nineteen to fifteen hours. The acid was reduced with ferrous sulphate and ammonia to 2-amino-3-methoxy-benzoic acid (16) (Pschorr, Annalen, 1912, 391, 23), which was then diazotised and converted into 2-iodo-3-methoxybenzoic acid (17) by the method of Stanley, McMahon and Adams (J.Amer.Chem.Soc., 1933, 55, 706). The acid was esterified (Stanley, McMahon and Adams, loc.cit.), and the ester, methyl 2-iodo-3-methoxybenzoate (18) was heated with methyl 2-iodobenzoate (19) and copper bronze at 245-255°. The oil obtained by extracting the reaction mixture with chlorobenzene was fractionally distilled under reduced pressure. By repeated recrystallisation of solids obtained from the various fractions, dimethyl 6,6'-dimethoxydiphenate, dimethyl diphenate, and dimethyl 6-methoxy-diphenate (20) were isolated. The required biphenyl, dimethyl 6-methoxydiphenate, was obtained in 20% yield. It was then reduced to 2,2'-bishydroxymethyl-6-methoxybiphenyl (21) using lithium aluminium hydride. Attempts have not yet been made to obtain 2,2'-bisbromomethyl-6-methoxybiphenyl (22) from the bishydroxymethyl compound.

6-Methoxydiphenic acid.

Since dimethyl 6-methoxydiphenate (20) was available in some quantity, it was decided to hydrolyse it to 6-methoxydiphenic acid (23) and to attempt to obtain this acid in an optically active condition.




(23)

Resolution was attempted by the crystallisation of the quinine, brucine, strychnine, ephedrine and cinchonine salts of the acid from such solvents as absolute ethanol, acetone, ethyl acetate and ethyl cellosolve.

The brucine salt crystallised from absolute ethanol in the form of clusters of fine, white needles. A solution of the brucine salt in chloroform showed no mutarotation at $0^{\circ}$, $21^{\circ}$ and $40^{\circ}$. The salt was decomposed by shaking the chloroform solution of the salt with dilute hydrochloric acid. The chloroform solution of the free acid was found to be optically inactive at $17^{\circ}$. The rotation of this solution could not be observed at a lower temperature because the acid began to crystallise out of solution on cooling.

The quinine salt crystallised from acetone in the form of clusters of needles. A chloroform solution of the salt showed no mutarotation at 0.2°, 20.7°, 40° and 60.5°. Decomposition of the salt in chloroform at 20° gave an optically inactive solution of the free acid.

The strychnine salt crystallised from absolute alcohol in the form of clusters of needles. The salt was decomposed immediately. It was dissolved in ice-cold formic acid (100%) and then the solution was poured into a mixture of concentrated hydrochloric acid and ice. White crystals of the free acid came down after standing for 1-2 minutes in ice. A solution of the free acid in acetone was inactive. Crystalline cinchonine and ephedrine salts could not be obtained.

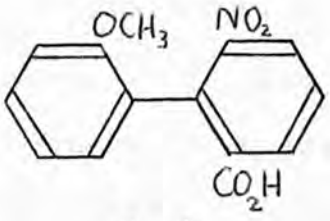
Attempts were made to effect the optical activation of the acid in acetone using nor-(+)-ψ-ephedrine according to the method of ~~Glazer, Harris~~ Jamison and Turner (J., ~~1950~~, ~~1753~~ 1938, 1646). The alkaloid was found to mutarotate in acetone so the acetone solution of it was allowed time to reach optical equilibrium before being mixed with the acetone solution of the acid. All this was carried out at a temperature below -30° and the polarimetric readings were taken at -30.2°. No mutarotation was observed after the addition of the acid.

An attempt was also made using chloroform instead of acetone as the solvent. Acetone had been used first because

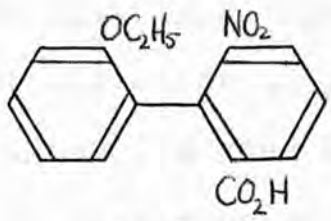
the acid is very soluble in this solvent while it is not readily soluble in chloroform. Using chloroform, no mutarotation was observed at -26.2°, -4.7° and 17.3°. On lowering the temperature again to -29.9°, the rotation was found to be unchanged. The chloroform solution was shaken with dilute hydrochloric acid to remove the alkaloid. This procedure was carried out at a temperature below -30° as before. The chloroform solution of the free acid was found to be optically inactive at -25°. The experiment was repeated but no mutarotation was observed at -10°, 0°, and 40°. The chloroform solution of the free acid was found to be inactive.

One experiment was conducted in chloroform using cinchonidine instead of nor-(+)-ψ-ephedrine. No evidence of any optical activation was obtained.

When comparing 6-methoxydiphenic acid with similar substituted biphenyls, e.g. 2'-methoxy-2-nitrobiphenyl-6-carboxylic acid (24) (Li and Adams, J.Amer.Chem.Soc., 1935, 57, 1565), and 2'-ethoxy-2-nitrobiphenyl-6-carboxylic acid (25), (Li and Adams, loc.cit.), it does appear that this acid should




(24)




(25)

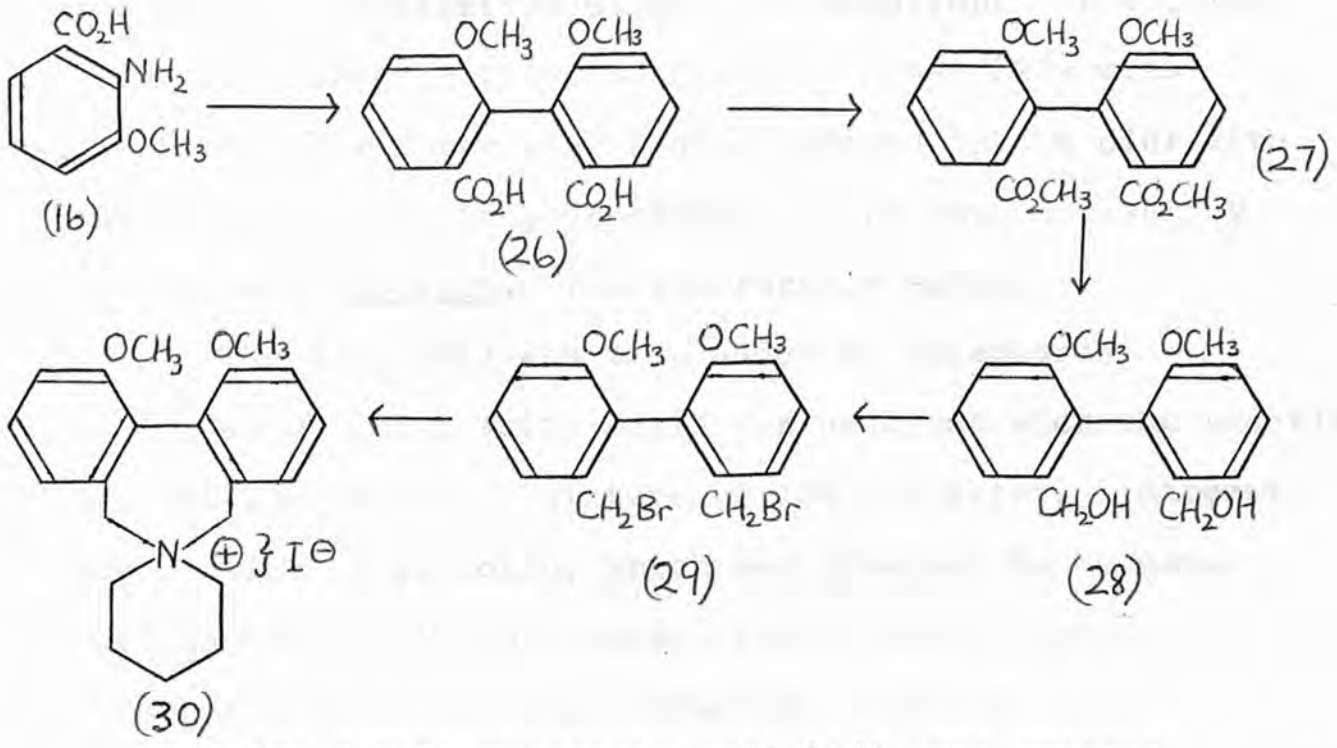
be obtainable in an optically active condition. However, it would probably be optically unstable at temperatures a little above room temperature. Therefore, the failure to obtain it optically active does not provide proof that it cannot be optically activated in any way but only that the right conditions have not been found.

An attempt was also made to activate optically the ester (20), according to the method of Buchanan and Graham (J., 1950, 500). Dimethyl 6-methoxybiphenyl (1 g.) was dissolved in ethyl-(+)-tartrate (40 c.c.) at 80°. The solution was cooled rapidly to 25° and was kept at this temperature for 30 minutes. Ice-cold water was then added to precipitate an oil, which gradually solidified during three hours. The solid ester was filtered off and washed well with cold water. A solution of the dry ester in chloroform was optically inactive.

2,7 -Dihydro-4',1"-dimethoxy-3,4:5,6-dibenzazepinium-1-spiro-1'"-piperidinium iodide.

The azepinium bromide had previously been synthesised by Beaven, Hall, Lesslie and Turner (J., 1952, 854), who then resolved it by the repeated recrystallisation of its camphor-sulphonate from acetonitrile. The synthesis used by the above co-workers was followed, in general, in the present work. The

general scheme of the synthesis is set out below.




2-Amino-3-methoxybenzoic acid (16), the general synthesis of which has already been described, was diazotised and converted into 6,6'-dimethoxydiphenic acid (26) by the method of Wittig and Petri (Annalen, 1933, 505, 17) with the modifications of Hall and Turner (J., 1951, 3072). It was decided to synthesise the azepinium iodide in an optically active condition. Accordingly, the 6,6'-dimethoxydiphenic acid was resolved by the method of Kenner and Turner (J., 1928, 2340) and Stanley, McMahon and Adams (J.Amer.Chem.Soc., 1933, 55, 706) through its diquinine salt. Preparation of optically active 2,2'-bishydroxymethyl-6,6'-dimethoxybiphenyl (28) was attempted by the reduction of the optically active acid with lithium aluminium hydride. However, on no occasion did the

reduction go to completion and the recovered acid had always undergone some racemisation during the reaction. Therefore, the acid was converted into its dimethyl ester (27) with diazomethane. The ester was readily reduced to the diol with lithium aluminium hydride, according to the method given by Hall and Turner (loc.cit.) for the racemic ester.

The diol (28) was then added to phosphorus tribromide at $0^{\circ}$ and a white solid was obtained when the reaction mixture was poured into a mixture of ice and water. Attempts to recrystallise this solid, which was presumed to be crude, optically active 2,2'-bisbromomethyl-6,6'-dimethoxybiphenyl (29), were unsuccessful. It was, therefore, dissolved in benzene, the benzene solution was dried and piperidine was added. A yellow gum, insoluble in benzene, was obtained. This gum solidified on exposure to air and was recrystallised from acetone-light petroleum. Two crops with different optical rotations were obtained. These two crops of the azepinium bromide were subsequently converted into the corresponding azepinium iodide.

Both crops showed anomalous optical dispersion, and the azepinium iodide obtained from the first crop of bromide failed to give a satisfactory analysis result. The azepinium iodide obtained by Beaven, Hall, Lesslie and Turner (J., 1952, 854) did not show anomalous dispersion. The infra-red and ultra-violet spectra of the first crop of

azepinium iodide and those of the azepinium iodide obtained by Beaven *et al.* were compared. They had many similarities but were not exactly identical. It was therefore concluded that the product obtained in the present work was chemically and, therefore, optically impure. Attempts to purify further the first crop of the azepinium iodide by recrystallisation failed. It was thought that the presence of the impurity was perhaps the result of the failure to recrystallise the bisbromomethyl compound ( 29 ). The above authors were able to recrystallise the racemic bisbromomethyl compound and, even if that had not removed the impurity, the repeated recrystallisations of their azepinium camphorsulphonate, during the resolution, probably eliminated it at any early stage.

Both the resolved azepinium iodide and the optically impure product obtained in the present work showed the same order of optical stability. As the prospect of obtaining the azepinium iodide in a pure state seemed remote at the time, it was decided to carry out racemisation experiments on solutions of the impure product in dimethyl formamide. The apparatus used for the racemisations was the same as that described on p.45. Racemisation rates were determined at 140.3° (using xylene as the constant boiling liquid), 156.2° (using cyclohexanone), 160.0° and 162.5° (using cyclohexanol), and 172.2° (using phenetole).

At no time during these experiments was there any indication that two different rates of racemisation were being observed. In the experiment carried out at 162.5°, during 5½ hours the rotation of the solution of azepinium iodide changed from +0.47° to +0.15°. These readings were taken on the mercury green line ( $\lambda$ = 5461 Å), but readings were taken at the same time on the mercury yellow line ( $\lambda$ = 5791 Å). The anomalous dispersion could be seen throughout the 5½ hours. In the same experiment, one of the tubes was heated for more than thirty hours and the solution at the end of this time was found to be optically inactive.

The racemisation experiments were carried out with samples of azepinium iodide with very different optical rotations. Therefore, samples of varying degrees of purity were used. A plot of $\log_{10}k$ against $\frac{1}{T}$ was made and a reasonably good straight line was obtained. Values of the activation energy, E, and of the non-exponential term, A, in the Arrhenius equation were calculated. E was found to be 34.1 kcal./mole, and A to be $10^{12.9}$ sec.$^{-1}$.

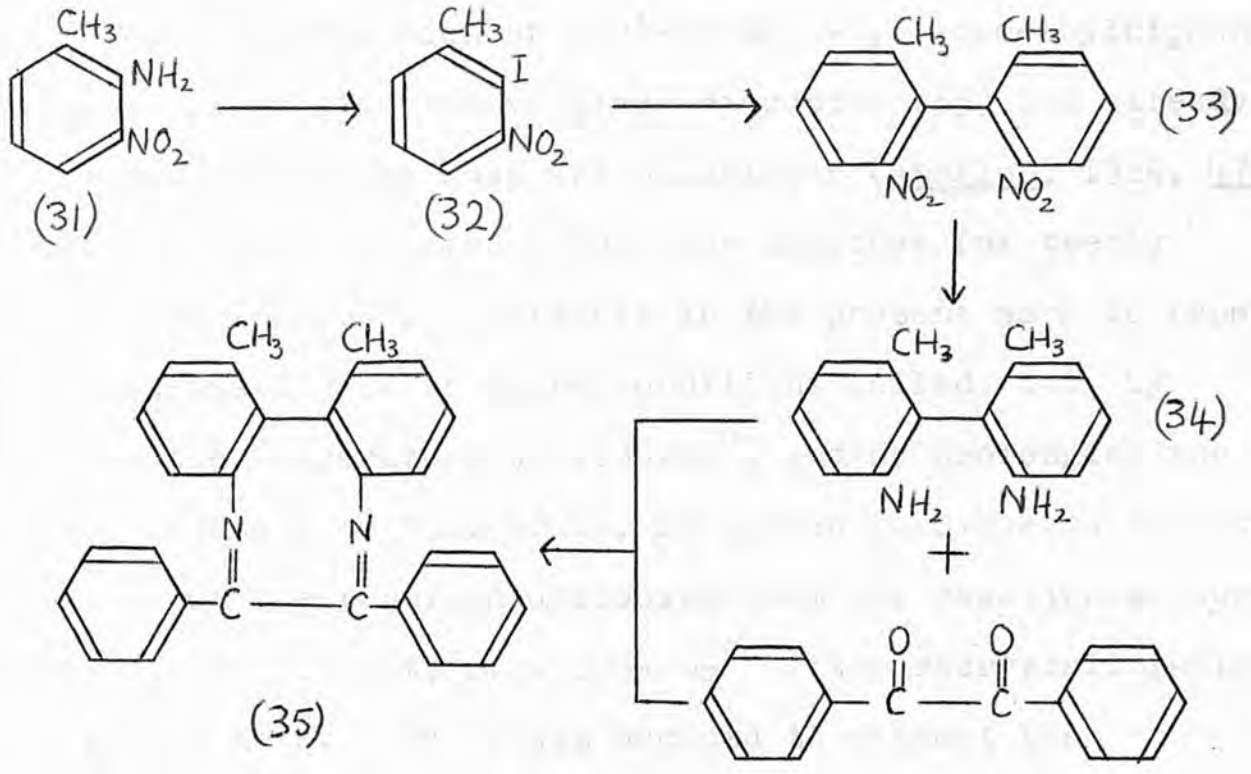
From all the observations made during these racemisation experiments, it seems probable that the two components present in the supposed azepinium iodide were racemising at almost, if not exactly, the same rate.

Since these experiments were carried out, it has been found that recrystallisation of the azepiniumbromide from ethanol-ethyl acetate greatly improves its purity. After two recrystallisations, the optical rotation was found to be very much higher than had ever been obtained before, and the dispersion was found to be normal. It is proposed to convert this sample into the azepinium iodide. If a satisfactory analysis result for the iodide is obtained, it is then proposed to carry out a racemisation experiment on it to determine its optical stability. If it proves to racemise at the same rate as the impure samples, it must be concluded that the racemisation experiments already carried out give a good estimation of the optical stability of 2,7-dihydro-4',1"-dimethoxy-3,4:5,6-dibenzazepinium-1-spiro-1'"-piperidinium iodide (30).

(b) Diazocines.

4'1"-Dimethyl-2,3-diphenyl-5,6:7,8-dibenzo-1,4-diazocine.

This diazocine (35) was made by the following synthesis.

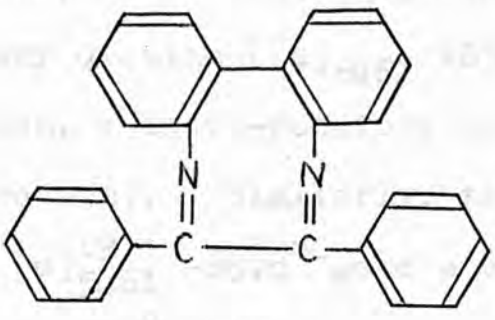



2-Amino-3-nitrotoluene (31) was diazotised and converted into 2-iodo-3-nitrotoluene (32) by the addition of potassium iodide. The method used was that of Carlin and Foltz (J.Amer.Chem.Soc., 1956, 78, 1997), but it was modified on the suggestion of Pal (Ph.D. Thesis, London University, 1959, p.15), who left the iodo-compound to separate overnight, thereby increasing the yield. 2,2'-Dimethyl-6,6'-dinitrobipheyl (33) was prepared by the reaction of 2-iodo-3-nitrotoluene with copper bronze at 140-150°. This method is a modified version by Ahmed and Hall (J., 1958, 3043)

of that used by Carlin and Foltz (loc.cit.). The reduction of 2,2'-dimethyl-6,6'-dinitrobiphenyl to 2,2'-diamino-6,6'-dimethylbiphenyl (34) was carried out according to the method of Kenner and Stubbings (J., 1921, 119, 593).

The condensation of 2,2'-diamino-6,6'-dimethylbiphenyl with benzil to give the required diazocine (35) had already been accomplished by Kuhn and Goldfinger (Annalen, 1929, 470, 183), who heated the two substances together for twenty minutes at 180-200°. Attempts in the present work to repeat the condensation under these conditions failed, but, by raising the temperature to 220-230°, and by prolonging the time of heating to four hours, it proved possible to isolate a little of the required diazocine from the reaction mixture. However, the product, m.p. 208-209° (after recrystallisation), was rather dark. So it was decided to attempt the condensation under different and much milder conditions.

A simple method from the preparation of 2,3-diphenyl-5,6:7,8-dibenzo-1,4-diazocine (36), by condensing 2,2'-diaminobiphenyl with benzil in boiling




(36)

glacial acetic acid, had recently been announced by Allinger and Youngdale (J.Org. Chem., 1959, 24, 306). An attempt was made to condense the dimethyl-diamine (34) with benzil under the same conditions, but no condensation product could be isolated after boiling the glacial acetic acid solution of the reactants under reflux for nineteen hours. However, by using propionic acid (b.p. 141°) instead of glacial acetic acid (b.p. 118°), the required condensation took place. The product, obtained in a similar yield, was much paler than before and had a slightly higher melting point of 209-210°.

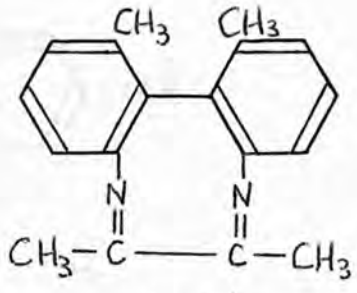
It was proposed to carry out this condensation using optically active 2,2'-diamino-6,6'-dimethylbiphenyl. This diamine was resolved by the method of Meisenheimer and Höring (Ber., 1927, 60, 1429), and the condensation was carried out under the conditions given above for the racemic diamine. An optically active condensation product was isolated which, after recrystallisation from ethanol and from light petroleum, had a melting point of 179-180°. The dextro-rotatory diamine ($[\alpha]_{5461}^{20}$ +63.7°, in chloroform) gave, on condensation, a laevo-rotatory diazocine ($[\alpha]_{5461}^{22}$ -2,080°, also in chloroform). Similarly, the laevo-rotatory diamine with $[\alpha]_{5461}^{19}$ -63.8° gave a condensation product with $[\alpha]_{5461}^{19}$ +2,060°.

This diazocine proved to be exceedingly optically stable. The rotation of a tetralin solution of the diazocine was unchanged after boiling under reflux ($207^{\circ}$) for $9\frac{1}{2}$ hours, and that of a diphenyl ether solution unchanged after boiling under reflux ($259^{\circ}$) for four hours. Therefore, a diphenyl ether solution of the optically active diazocine was heated in a sealed tube, in an electrically-heated furnace. After five hours at $372^{\circ}$ ($\pm 2^{\circ}$), the diazocine had lost 24% of its optical activity, and, after five hours at $446^{\circ}$ ($\pm 3^{\circ}$) the loss of optical activity was 64%. For these experiments, the sealed tubes were put into the furnace while it was still cold, and the times given above refer to the period of heating after the furnace had reached the required temperature. At the end of the five hours, the tubes were removed from the furnace and were allowed to cool down to room temperature. The solutions darkened while being heated, and it is thought that there was some slight decomposition of the diazocine, and, possibly, of the solvent. However, it was considered that the loss of optical activity was due almost entirely to racemisation of the diazocine. The main sources of error in these experiments were thus uncertainties in the times of heating and in the exact temperatures.

By comparison with the results obtained by Kistiakowsky and Smith (J.Amer.Chem.Soc., 1936, 58, 1043) when racemising 2,2'-diamino-6,6'-dimethylbiphenyl, it was found that the diazocine is more optically stable than the diamine. Kistiakowsky and Smith (loc.cit.) heated diphenyl ether solutions of the optically active diamine in sealed tubes at various temperatures. The decrease in optical activity of the diamine, after being heated at 356° for four hours, was 33%, and 30% after 31 minutes at 385°. Thus the introduction of the bridging ring increases the configurational stability of the molecule.

4'1"-Dimethyl-2,3-dimethyl-5,6:7,8-dibenzo-1,4-diazocine.

2,2'-Diamino-6,6'-dimethylbiphenyl was also condensed with diacetyl. The condensation was carried out in ethylene glycol at 160-170°. A brown gum was obtained after pouring the reaction mixture into cold water and extracting with ether. From this gum the required product, 4',1"-dimethyl-2,3-dimethyl-5,6:7,8-dibenzo-1,4-diazocine (37), was isolated by passing a benzene solution of it through an

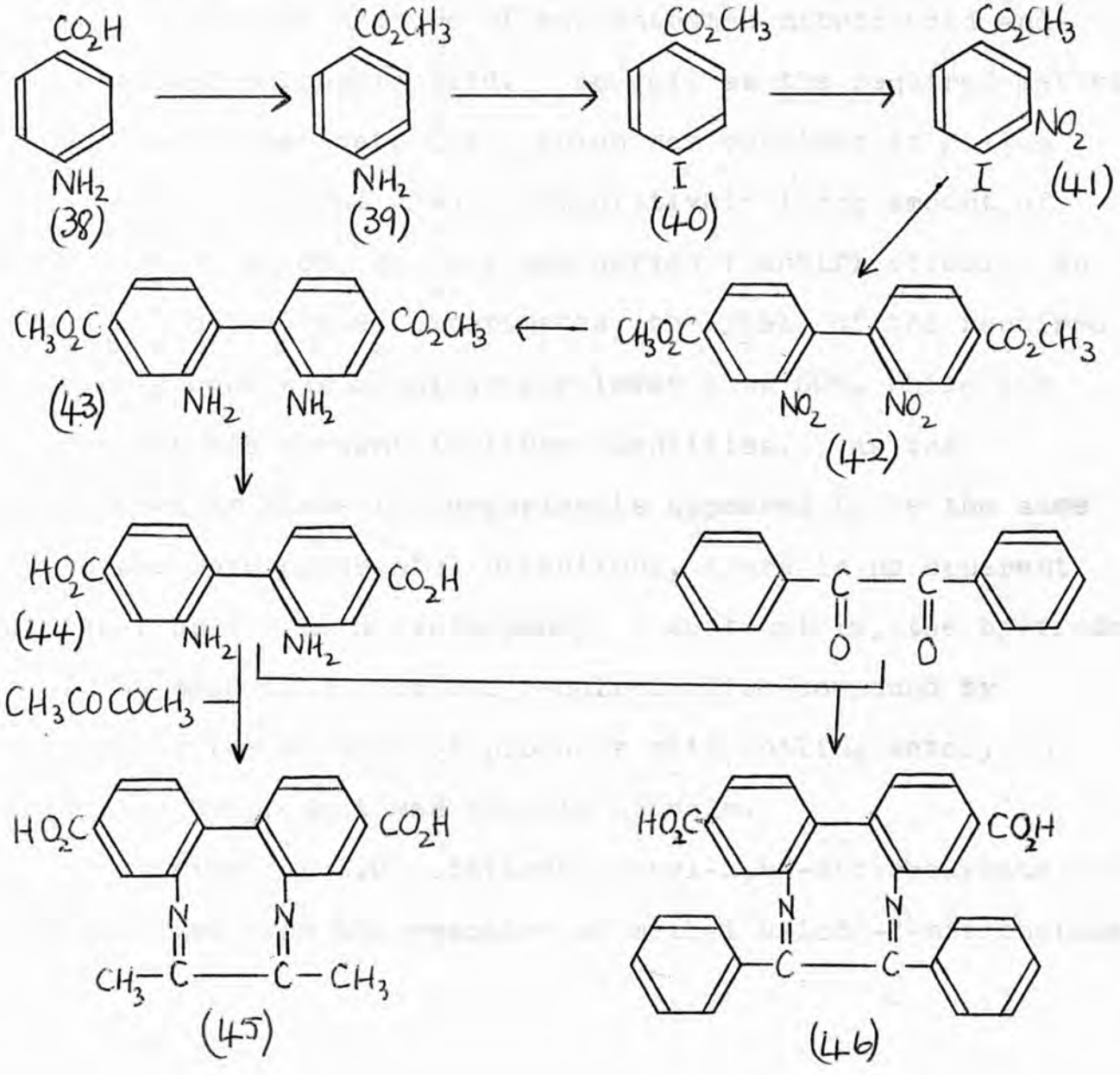


(37)

alumina column. However, the yield was so small (~5%) that it was considered impractical to attempt to obtain this diazocine in an optically active condition.

2,3-Diphenyl-5,6:7,8-dibenzo-1,4-diazocine-2'3"-dicarboxylic acid (and the corresponding 2,3-dimethyl compound).

These diazocines were synthesised in the following way.



Methyl p-aminobenzoate (39) was obtained by esterifying p-aminobenzoic acid (38) by the method of Reigel and Buchwald (J.Amer.Chem.Soc., 1929, 51, 484). The amino-ester was diazotised and converted into methyl p-iodobenzoate (40) using potassium iodide. The method used was one developed by Cheung King Ling (unpublished). An unpublished method by Cheung King Ling was also used for the nitration of methyl p-iodobenzoate. This was carried out below 5° using a nitration mixture of concentrated nitric acid and concentrated sulphuric acid. As well as the required methyl 4-iodo-3-nitrobenzoate (41), which was obtained in yields of 60-65%, there was also a comparatively large amount of a by-product which, so far, has defied identification. In two or three isolated experiments, the yield of the required nitro-compound was considerably lower than 60%, while the by-product was present in large quantities. As the conditions in these few experiments appeared to be the same as in the more successful nitrations, there is no apparent explanation for this discrepancy. Fortunately, the by-product could be separated from the required nitro-compound by extracting the mixture of products with boiling water, in which the by-product was readily soluble.

Dimethyl 2,2'-dinitrobiphenyl-4,4'-dicarboxylate (42) was obtained from the reaction of methyl 4-iodo-3-nitrobenzoate

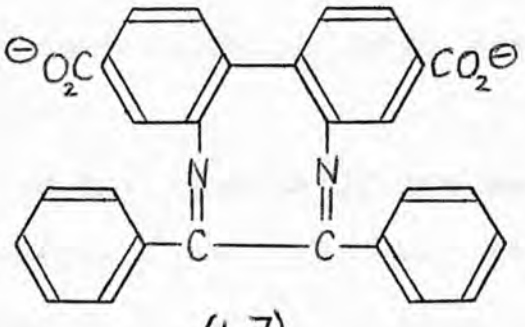
with copper bronze at 180-190°, and was reduced to dimethyl 2,2'-diaminobiphenyl-4,4'-dicarboxylate (43) using hydrazine hydrate in the presence of Raney nickel. The methods for both Ullmann reaction and the reduction were those of Cheung King Ling (unpublished work). Dimethyl 2,2'-diaminobiphenyl-4,4'-dicarboxylate was hydrolysed with alcoholic potassium hydroxide to give the corresponding dicarboxylic acid (44). This acid, 2,2'-diamino-biphenyl-4,4'-dicarboxylic acid, was condensed with diacetyl in ethylene glycol at 130-140°, to give 2,3-dimethyl-5,6:7,8-dibenzo-1,4-diazocine-2'3"-dicarboxylic acid (45). Attempts to resolve this acid through its brucine, ephedrine, quinine and strychnine salts have, so far, been unsuccessful because the salts have failed to crystallise from such solvents as ethanol, acetone, ethyl acetate, ethylene glycol monoethyl ether and ethylene glycol.

2,2'-Diaminobiphenyl-4,4'-dicarboxylic acid was also condensed with benzil. Bell's method (J., 1952, 1527) of heating the acid with benzil at 260° failed to work satisfactorily, so the condensation was carried out by heating the acid with a boiling solution of benzil in glacial acetic acid, in which the dicarboxylic acid was almost insoluble, for 25 hours. 2,3-Diphenyl-5,6:7,8-dibenzo-1,4-diazocine-2'3"-dicarboxylic acid (46) was obtained by filtering the hot acetic acid solution, concentrat-

ing the filtrate to small bulk and adding hot water. The required product crystallised out from the aqueous acetic acid solution. The diazocine-dicarboxylic acid was resolved through its brucine salt from ethanol according to the method given by Bell (loc.cit.).

The diazocine-dicarboxylic acid in ethyl benzoate solution was very optically stable and did not racemise at an observable rate below 240°. A solution of it in ethyl benzoate was sealed up in a number of glass tubes. The tubes were evacuated immediately before sealing and hooks were made at the ends of the tubes at the time of sealing. By means of pieces of wire threaded through these hooks, the tubes were suspended down a long, wide air condenser into a flask containing a liquid with a suitable boiling point. The liquid was heated to boiling and, when its temperature had become constant, the tubes were removed at suitable intervals of time. They were immediately chilled by plunging them into hot, then cold, water, and polarimetric readings were taken at room temperature. Racemisation rates were determined in this way at five different temperatures using 1-methylnaphthalene (247.0°), diphenyl ether (261.5°), diphenylmethane (268.5°), ethyl cinnamate (274.0°) and dimethyl phthalate (288.0°) as the constant boiling solvents.

In earlier attempts to racemise this compound, N,N'-dimethyl formamide was used instead of ethyl benzoate as the solvent. It was found that racemisation began to occur at a lower temperature ( $\sim 210^{\circ}$), and, at $245^{\circ}$ (1-methylnaphthalene), the diazocine had a half life period of racemisation of the order of 350-400 minutes. In ethyl benzoate, at $247^{\circ}$, the half life period of racemisation was 52.6 hours. The racemisation in N,N'-dimethylformamide went rather erratically and was not reproducible. The solvent appeared to be decomposing on heating as there was a great increase in pressure inside the tubes during the experiments. It is thought that decomposition of the solvent produced gaseous amines. The diazocine-dicarboxylic acid, in the presence of these amines, would be partially ionised and the resulting ions, for example (47), would have




(47)

rates of racemisation different from that of the unionised acid.

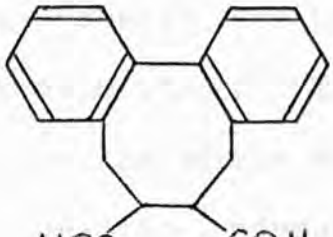
An attempt was made to test the validity of this hypothesis by racemising the disodium salt of the diazocine-

dicarboxylic acid in water at 245°. At this temperature, the tubes could not stand up to the great pressure exerted by the water vapour inside them and they exploded.

When ethyl benzoate was first used, the solutions of the diazocine-dicarboxylic acid in this solvent darkened considerably after being heated at 247° for a few hours. Removal of air from the tubes before sealing eliminated this trouble. It therefore appears that the diazocine-dicarboxylic acid had been decomposing slightly in the presence of the air remaining in the tubes after sealing. After many hours' heating at these high temperatures, there was also a tendency for the readings to deviate slightly from the straight line plot of $\log_{10}(\alpha_t - \alpha_\infty)$ against time. It had been noticed with these particular tubes that there was a slight increase in pressure inside them, and that a few bubbles of gas had appeared in the solutions when the tubes were opened. It was concluded that there had been a slight decomposition of the ethyl benzoate.

From the results of the racemisation experiments using ethyl benzoate as a solvent, the values of the activation energy, E, and of A (the non-exponential term in the Arrhenius equation, $k = Ae^{-E/RT}$) for the diazocine-dicarboxylic acid (46) were calculated. E was found to have a value of 36.5 kcal./mole, and A was calculated to be $10^{10}$ sec.$^{-1}$.

Thus 2,3-diphenyl-5,6:7,8-dibenzo-1,4-diazocine-2'3"-dicarboxylic acid is exceedingly optically stable in comparison with cis-1,2:3,4-dibenzo-1,3-cyclooctadiene-6,7-dicarboxylic acid (48) and 1,2,7,8-tetrahydro-3,4:5,6-

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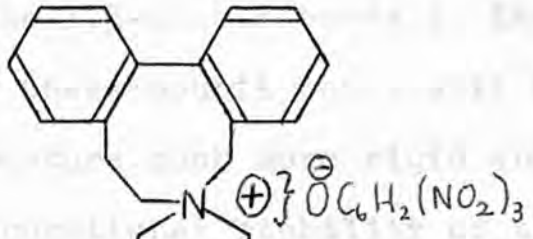



(49)

dibenzazocine-1-spiro-1'-piperidinium picrate (49). Mislow's cis-acid (48) (J.Amer.Chem.Soc., 1958, 80, 486) has an activation energy, E, of 22.8 kcal./mole, and a value of A of $10^{12.5}$ sec.$^{-1}$ in ethanol, while in 2.32 N sodium hydroxide solution, the value of E was found to be 25.4 kcal./mole and of A, $10^{14.6}$ sec.$^{-1}$. Ahmed's azocine picrate (49) (J., 1959, 3383) has an activation energy, E, of 22.0 kcal./mole, and a value of A of $10^{14.05}$ sec.$^{-1}$ in acetone. The cis-acid is thus slightly more optically stable than the azocine picrate, and, as was stated in the Introduction, this may be partly due to the replacement of a nitrogen atom for a carbon atom in the bridging ring. However, the presence of two nitrogen atoms in the bridging ring of the diazocine-dicarboxylic acid might, if anything, be expected to make this compound less optically stable than the compounds (48) and (49). Even so, the difference

would be comparatively slight. The great difference in optical stability observed between the compounds (48) and (49), and the diazocine-dicarboxylic acid must be due to some other difference between them. This difference is most probably the presence of the 1,3-double bonds in the diazocine ring. The effect of these double bonds will be to make the whole molecular structure much more rigid and thus greatly increase the configurational stability of the molecule.

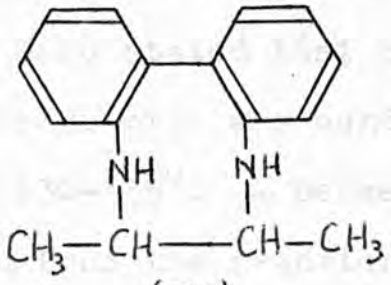
The difference in optical stability observed between 4',1"-dimethyl-2,3-diphenyl-5,6:7,8-dibenzo-1,4-diazocine (35) and 2,3-diphenyl-5,6:7,8-dibenzo-1,4-diazocine-2',3"-dicarboxylic acid (46) must be due to the presence of the o,o'-methyl groups in the compound (35). However, the difficulty of accurately assessing the optical stability of this diazocine makes any detailed comparison between them impossible.

Before the present work was carried out, the effect of the presence of the 1,3-double bonds in the diazocine ring on the optical stability of this type of bridged biphenyl could not be predicted. It was already known that bridged biphenyls are less optically stable than the corresponding unbridged compounds in the few cases in which direct comparison can be made. So far, direct comparison had only been possible in the case of biphenyls

containing saturated bridging chains. It appears, in the case of the diazocines, that the decrease in optical stability, which would be expected from the bridging of the biphenyl, is more than compensated for by the great increase in optical stability associated with the unsaturated state of the bridging chain because, not only are the diazocines much more optically stable than the compounds (48) and (49), which contain saturated bridging chains, but the diazocine (35) appears to be much more optically stable than the corresponding unbridged biphenyl. Therefore, the presence of the double bonds in the bridging chain seems to have a very much greater effect on the optical stabilities of such bridged biphenyls than the actual bridging of the biphenyl in the first place.

1,2,3,4-Tetrahydro-2,3-dimethyl-5,6:7,8-dibenzo-1,4-diazocine.

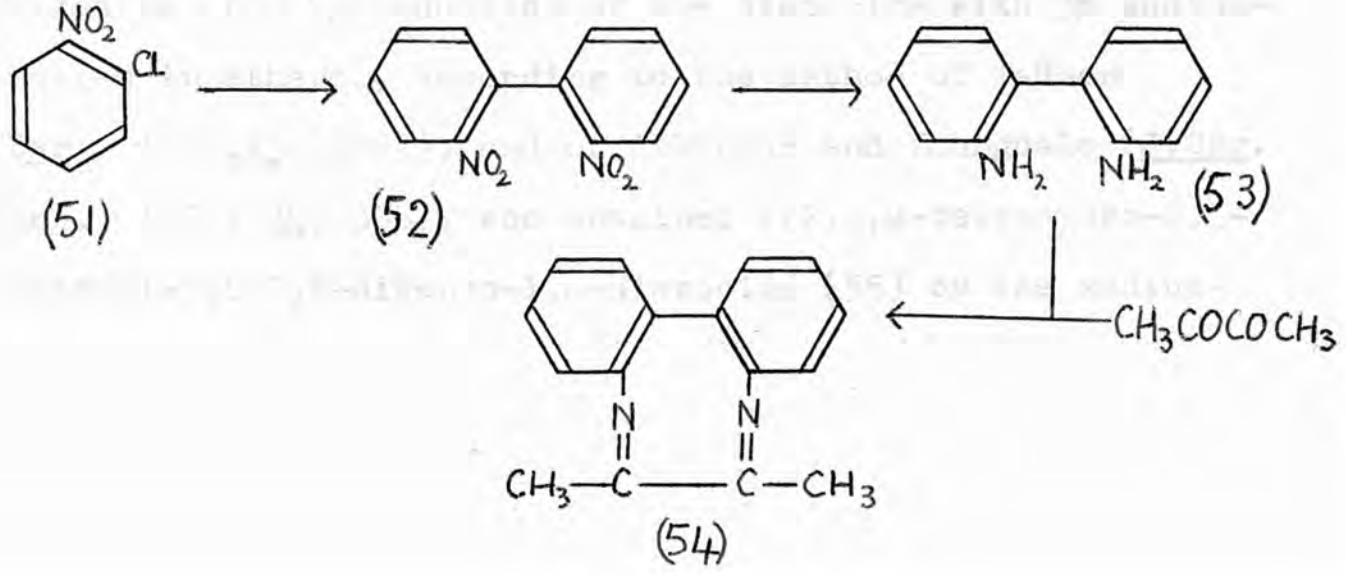
There are only two bridged biphenyls with a saturated four-membered bridging chain which have been obtained optically active. These are Mislow's acid (48) and Ahmed's azocine picrate (49). It was decided that it would be interesting to compare the optical stabilities of these two compounds with the optical stability of a compound like 1,2,3,4-tetrahydro-2,3-dimethyl-5,6:7,8-dibenzo-1,4-diazocine (50). If the imino groups in the bridging ring



(50)

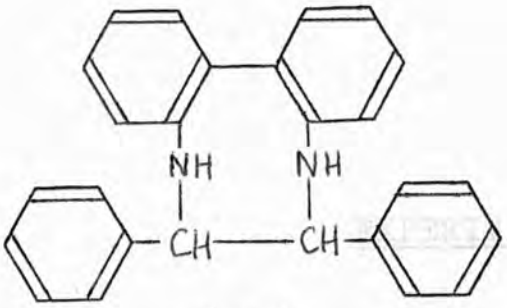
proved to be basic it was thought likely that they could be used as resolving groups. It was therefore decided to attempt to synthesise this compound.

2,3-Dimethyl-5,6:7,8-dibenzo-1,4-diazocine (54) was prepared in the following way.



2,2'-Dinitrobiphenyl (52) was prepared by heating o-chloronitrobenzene (51) with copper bronze at 250-260° (Shaw and Turner, J., 1933, 135). It was then reduced to 2,2'-diaminobiphenyl (53) using stannous chloride and concentrated hydrochloric acid. An attempt to carry out an iron-water reduction by the method of Shaw and Turner (loc.cit.) failed and the starting material was recovered unchanged. This was due probably to the type of iron filings used. The method of Sako (Mem.Coll.Eng.Kyushu Imp.Univ., 1932, 6, 263) was also tried but the yield was only 50%, whereas Sako stated that he obtained the diamine in 95% yield. The diamine was condensed with diacetyl in ethyleneglycol at 130-135°. A benzene solution of the brown gum obtained from the reaction was passed through an alumina column. The diazocine (54) was isolated from one of the fractions as a pale yellow crystalline solid, which became white on recrystallisation from light petroleum.

Attempts were made to obtain the tetrahydro-diazocine (50) by reduction of the diazocine with 3% sodium-amalgam in ethanol, according to the method of Taüber (Ber., 1892,25, 3287), and of Allinger and Youngdale (J.Org. Chem., 1959, 24, 306), who obtained 1,2,3,4-tetrahydro-2,3-diphenyl-5,6:7,8-dibenzo-1,4-diazocine (55) by the sodium-

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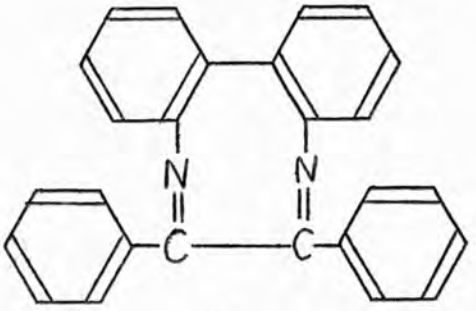



(36)

amalgam reduction of 2,3-diphenyl-5,6:7,8-dibenzo-1,4-diazocine (36). In the case of compound (54), a reaction occurred and a white solid was obtained when the alcoholic solution was poured into cold water. This solid recrystallised from light petroleum in needles, m.p.161-163°. However, on standing for a few hours, the solid began to go yellow and sticky, and no satisfactory analysis result for it could be obtained.

It was concluded that the reduction had been satisfactory, but that the reduced compound was unstable and was very readily oxidised. Accordingly, it was decided to go no further in the attempt to reduce the diazocine.

## EXPERIMENTAL.

(a) Methoxydibenzazepinium compounds.

2-Nitro-m-cresol. (Gibson, J., 1923, 123, 1269; Modified by Kenner and Turner, J., 1928, 2340).

m-Cresol (106 c.c.) dissolved in oleum (6-7%; 400 c.c.) was cooled to 0° in an ice-salt mixture. To this was added a mixture of fuming nitric acid (d=1.5; 46.5 c.c.) in oleum (6-7%; 106.5 c.c.), keeping the temperature below 10°. The addition took 2-2½ hours. After leaving overnight, half the nitration mixture was diluted with 125 c.c. of water, and was steam distilled in superheated steam at 125°. The other half was treated in the same way. The orange-coloured oil so obtained was separated from the aqueous distillates and was used without further purification for the next stage. The aqueous distillates were extracted once with carbon tetrachloride. The carbon tetrachloride solution was dried over calcium chloride, and the solvent was distilled off to give a little more 2-nitro-m-cresol.

3-Methoxy-2-nitro-toluene.

(Haworth and Lapworth, J., 1923, 123, 2982; Modified by Hall and Turner, J., 1951, 3072).

Crude 2-nitro-m-cresol (75 g.), dissolved in m-xylene (100 c.c.) and dried over freshly dried sodium sulphate, was diluted with more m-xylene (300 c.c.), which had been dried over potassium carbonate. This solution was boiled under reflux with potassium carbonate (110 g.) in a metal bath kept at 150-160°. Dimethyl sulphate (60 c.c.) was added, with shaking, in four lots over a period of approx. four hours. An extra 10 c.c. of dimethyl sulphate were added near the end of the reaction, which took five hours to complete, and during which the colour of the m-xylene solution changed from red to yellow. The mixture was made alkaline with 10% sodium hydroxide solution and was steam distilled. m-Xylene distilled over first, followed by 3-methoxy-2-nitro-toluene, which was filtered off, washed with water and recrystallised from methanol. The m-xylene solution was separated from the aqueous distillate, and dried over potassium carbonate. m-Xylene was distilled off at 51-2°/33 mm., and the 3-methoxy-2-nitro-toluene, which remained, was distilled at 117-8°/3 mm.

The yield, based on m-cresol, was 45%; m.p. 50-1°.

2-Amino-3-methoxytoluene.

(Gibson, J., 1923, 123, 1269).

3-Methoxy-2-nitrotoluene (80 g.) was melted and added to iron filings (80 g.), a little water, and glacial acetic acid (1 c.c.), which were being heated under reflux on a boiling water bath. After heating for five hours, the reaction appeared to have finished. The mixture was made alkaline with 10% sodium hydroxide solution and was steam distilled. At first, the yellow oil that came over went solid on cooling, but towards the end of the distillation, no solid was obtained even on cooling in ice. The solid was filtered off, and pressed free of excess oil. It was dissolved in dilute hydrochloric acid, the solution was filtered to remove any insoluble 3-methoxy-2-nitrotoluene, and then was made alkaline to reprecipitate the amine. The amine was filtered off and dried. The oil obtained from the steam distillation was extracted with ether. The ethereal solution was washed three times with dilute hydrochloric acid, once with water, and was dried over calcium chloride. The ether was distilled off, and the solid 3-methoxy-2-nitrotoluene remaining was recrystallised from methanol. The aqueous solution from the ether extraction was made alkaline to precipitate the amine, which was filtered off and dried. Both crops of amine were distilled at 100-105°/10 mm. The amine came over as a yellow oil, which

solidified on cooling, m.p. 30-31°. In a typical experiment, 42 g. of amine were obtained and 19 g. of 3-methoxy-2-nitrotoluene were recovered. Total yield of amine, based on nitro-compound used up, was 85%.

2-Bromo-3-methoxytoluene (Sandmeyer's method).
(Hodgson and Beard, J., 1925, 127, 498).

A solution of 2-amino-3-methoxytoluene (40 g.; 1 mol.) in 40% hydrobromic acid was cooled, with stirring, to 0° in an ice-salt mixture. A solution of sodium nitrite (21 g.; 1 mol.) in water (38 c.c.) was added keeping the temperature below 3°. The addition took 1½ hours. The diazo solution was added to cuprous bromide (21 g.; 0.5 mol.) dissolved in 40% hydrobromic acid in a 500 c.c. flask fitted with a reflux condenser. No violent reaction was observed. The flask was heated on a boiling water bath for 2½ hours and, although the decomposition of the diazo compound was not complete, the mixture was then steam-distilled. Decomposition was completed during the distillation. The distillate was made alkaline to remove traces of bromine. The yellow oil in the distillate solidified on cooling in ice. The solid was filtered off, washed with water and recrystallised from aqueous alcohol. Yield of 2-bromo-3-methoxytoluene, m.p. 41-42°, was 80%.

3-Methoxy-o-toluic acid. (Method I).

A 3-necked, 250 c.c. flask was set up on a water bath and was fitted with a dropping funnel, a reflux condenser and an inlet for nitrogen. A calcium chloride tube was placed in the top of the condenser. After the air in the apparatus had been replaced by nitrogen, dry ether (10 c.c.) and lithium wire (0.4 g.; 2.1 atoms), which had been cut up into small pieces, were placed in the flask. 2-Bromo-3-methoxytoluene(5 g.; 1 mol.), dissolved in dry ether, was added, by means of the dropping funnel, over a period of ½-hour. During this time, the flask was warmed to keep the ethereal solution gently refluxing and nitrogen was continuously passed through the apparatus. After being heated for a short time more, the solution became cloudy and yellow. The flask was removed from the water bath and, when the reaction had stopped, the solution was decanted through a plug of glass wool onto a mixture of Drikold and ether. When all the carbon dioxide had come off, cold water was added to dissolve a white solid which had precipitated out, and the two layers were separated. The aqueous layer was washed twice with ether, was filtered, and was acidified with dilute sulphuric acid. The white solid so obtained was filtered off, washed with water, and recrystallised from water, giving white needles of 3-methoxy-o-toluic acid, m.p. 139-140°. The yield was 50%.

3-Methoxy-o-toluic acid. (Method II).

Phenyl-lithium was prepared from bromobenzene (4.0 g.; 1 mol.) and lithium (0.4 g.; 2.1 atoms) by the method described in the preceding experiment. The solution containing phenyl-lithium was decanted through a plug of glass wool into another 250 c.c. flask, through which nitrogen was being passed. 2-Bromo-3-methoxytoluene (5 g.; 1 mol.) in dry ether was added gradually and the mixture was heated for an hour. On cooling, it was poured into a mixture of Drikold and ether and, after all the carbon dioxide had come off and water had been added, was filtered to remove some insoluble material. It was worked up as in the preceding experiment.

The yield of 3-methoxy-o-toluic acid, m.p. 139°, was 31%.

The products of these two experiments were shown to be identical by doing a mixed m.p., which was 139-140°.

The two compounds were shown to be free from bromine by the Lassaigne Sodium Test. Therefore, in both cases, the point of attack was the 2-position and bromine was eliminated from the benzene ring.

2'-Methoxy-6'-methylphenyl-2-methylcyclohex-1-(and-6-)ene.

2-Lithium-3-methoxy-toluene was prepared, as in a preceding experiment, from 2-bromo-3-methoxytoluene (50.0 g.; 1 mol.) and lithium wire (3.8 g.; 2.1 atoms). The reaction was carried out in a 1-litre flask and the reaction mixture was stirred mechanically. 30 C.c. of dry ether were allowed for each gram of lithium. This stage of the preparation took 1½ hours. The flask was then cooled and freshly-distilled 2-methylcyclohexanone (21 g.; 0.8 mol.) was added gradually. The reaction became vigorous at times. Heating was continued for another hour. A little more 2-methylcyclohexanone (1 g.) was added on cooling but no further reaction took place. The solution was decanted through a plug of glass wool on to crushed ice. Dilute sulphuric acid was added until the aqueous layer became colourless. The two layers were separated and the aqueous layer extracted once with ether. The combined ethereal extracts were washed once with brine, and then with a little water, and were dried over sodium sulphate. Ether was distilled off and the residue was heated under reflux for an hour with naphthalene-β-sulphonic acid (1.5 g.), in an oil bath kept at 100-105°. On cooling, water and ether were added. The two layers were separated, the aqueous layer was washed once with ether, and the ethereal extracts were dried over calcium chloride. The ether was distilled off and the

residue was heated with more naphthalene-β-sulphonic acid (1.5 g.) at 120-125° for one hour. The mixture was worked up as before and the residue was distilled under reduced pressure. 2-Methylcyclohexane distilled over first at 60-70°/12 mm., followed by a colourless liquid, which was 2'-methoxy-6'-methylphenyl-2-methylcyclohex-1-(and-6-)ene, at 130-135°/5 mm. Yield, based on 2-methylcyclohexanone, was 61%. (Found: C, 83.2; H, 9.2. $C_{15}H_{20}O$ requires C, 83.3; H, 9.3%).

2,2'-Dimethyl-6-methoxybiphenyl.

The above phenylcyclohexene (25 g.) was heated under reflux with palladium-charcoal (5%; 4 g.) in a metal bath. The temperature of the bath was raised from 140° to 240° over a period of 3 hours and then it was kept at 240-250° for a further 3½ hours. The mixture was cooled and extracted with hot benzene. The benzene solution was filtered, benzene was distilled off and the residue was distilled under reduced pressure. The 2,2'-dimethyl-6-methoxybiphenyl came over as a colourless liquid at 131-136°/4 mm. (Found: C, 84,8; H, 7.5. $C_{15}H_{16}O$ requires C, 84.9; H, 7.6%).

3-Methoxy-2-nitrobenzoic acid.

(Hall and Turner, J., 1951, 3072).

A solution of potassium permanganate (20 g.) in 500 c.c. of water was added to a mixture of 3-methoxy-2-nitrotoluene (15 g.) and hydrated magnesium sulphate (36 g.) in a five-litre, round-bottomed flask. The solution was boiled under reflux until the purple colour of the solution had disappeared. Then another solution of potassium permanganate (20 g.) in 500 c.c. of water was added and boiling was continued. The process was repeated until 80 g. of potassium permanganate in 2,000 c.c. of water had been added. The purple colour disappeared completely after boiling for fifteen hours. Sulphur dioxide was passed through the alkaline solution to dissolve the precipitate of manganese dioxide which had formed during the reaction, and to precipitate a pale yellow, crystalline solid, which was 3-methoxy-2-nitrobenzoic acid. The solid was filtered off and recrystallised from aqueous alcohol. The yield of 3-methoxy-2-nitrobenzoic acid, m.p. 251-252°, was 8.3 g. (47%).

2-Amino-3-methoxybenzoic acid.

(Pschorr, Annalen, 1912, 391, 23).

A solution of 3-methoxy-2-nitrobenzoic acid (10 g., 1 mol.) in dilute ammonia solution (70 c.c.) was added, with stirring, to a boiling solution of ferrous sulphate (100 g.; 7 mol.) in 220 c.c. of water. The ferrous sulphate solution had previously been acidified with a few drops of dilute sulphuric acid to prevent oxidation of the ferrous ions to ferric. Ammonia (d 0.88) was then added to the boiling mixture until the thick precipitate, which had been formed when the two solutions were mixed, changed colour from brown to black. The solution at this point was strongly alkaline. It was boiled for a further five minutes and was filtered while hot. The filtrate was neutralised with glacial acetic acid to precipitate the buff-coloured 2-amino-3-methoxybenzoic acid, which was filtered off and recrystallised from aqueous alcohol ($\sim$2:1). The yield of 2-amino-3-methoxybenzoic acid, m.p. 169-170°, was 6 g. (71%).

2-Iodo-3-methoxybenzoic acid.

(Stanley, McMahon and Adams, J.Amer.Chem.Soc., 1933, 55, 706).

A suspension of 2-amino-3-methoxybenzoic acid (60 g.; 1 mol.) in a mixture of water (500 c.c.) and concentrated sulphuric acid (51 c.c.) was cooled to 0° in an ice-salt mixture. A solution of sodium nitrite (24.8 g.; 1 mol.) in 60 c.c. of water was added, with stirring, keeping the temperature of the mixture below 3°. The mixture was stirred at this temperature for a further thirty minutes, after which it was poured into a three-litre, three-necked, round-bottomed flask containing a boiling solution of potassium iodide (60 g.; 1 mol.) in 200 c.c. of water. The mixture was boiled under reflux, with stirring, for thirty minutes. On cooling, the solid 2-iodo-3-methoxybenzoic acid was filtered off and recrystallised from aqueous ethanol. The yield of 2-iodo-3-methoxybenzoic acid, m.p. 148-150°, was 68 g. (68%).

Methyl 2-iodo-3-methoxybenzoate.

(Stanley, McMahon and Adams, J.Amer.Chem.Soc., 1933, 55, 706).

2-Iodo-3-methoxybenzoic acid (96 g.) was dissolved in methanol (1,206 c.c.) in a five-litre, round-bottomed flask. Concentrated sulphuric acid (48 g.) was added cautiously and the solution was boiled under reflux for six hours. Most of the methanol was then distilled off and the remaining solution was poured into ~3 litres of cold water. Solid sodium bicarbonate was added to remove any unchanged acid and the pale brown solid ester was filtered off. It was recrystallised from aqueous alcohol. The yield of methyl 2-iodo-3- methoxybenzoate, m.p. 54-56°, was 80 g. (80%).

Methyl 2-iodobenzoate.

2-Iodobenzoic acid (175 g.) was dissolved in methanol (2,200 c.c.) in a five-litre, round-bottomed flask. Concentrated sulphuric acid (87.5 g.) was added cautiously and the solution was boiled under reflux for six hours. Most of the methanol was distilled off and the remaining solution was poured into ~ 2 litres of cold water. Solid sodium bicarbonate was added to dissolve any unchanged acid. The solution was extracted with ether to remove the liquid ester. The ethereal extracts were washed once with sodium bicarbonate solution, once with water, and then were dried over magnesium sulphate. The ether was distilled off and the residual oil was distilled under reduced pressure. The yield of methyl 2-iodobenzoate, b.p. 116-120°/4 mm.. was 171 g. (92%).

Dimethyl 6-methoxydiphenate.

Copper bronze (30 g.) was added gradually to methyl 2-iodobenzoate (32.4 g.; 2 mol.) and methyl 2-iodo-3-methoxybenzoate (18 g.; 1 mol.) in a boiling tube, which was being heated at 230° in a metal bath. The copper bronze was added at such a rate that the temperature of the mixture was kept at 245-255°. The addition took 25 minutes and then

the mixture was heated at 245-255° for a further 10 minutes. on cooling to ~160°, the mixture was extracted with boiling chlorobenzene. The solution was filtered and most of the solvent was distilled off. Some methanol, enough to double the volume, was added, with stirring, to the residue. This mixture was left in the refrigerator for two days, by which time a solid had crystallised out. This solid was filtered off and washed with a little ice-cold methanol. It was recrystallised from methanol and a white crystalline solid (1.8 g.), m.p. 131-134°, was obtained. By means of a mixed melting point it was found to be dimethyl 6,6'-dimethoxydiphenate. The original filtrate was evaporated down to dryness and the residual oil was distilled under reduced pressure. Two fractions of boiling points 154-180°/2-3 mm., and 180-195°/2-3 mm., were obtained. The residue remaining in the distilling flask was discarded. The first fraction (10.9 g.) was mixed with a little methanol (3-5 c.c.) and, after leaving in the refrigerator for a few days, a white solid crystallised out. It was filtered off and recrystallised (6.1 g.) from methanol. The white, crystalline solid (4.2 g.) so obtained was found to be dimethyl diphenate by means of a mixed melting point. The second fraction (9.9 g.) was stirred with small amounts of light petroleum (b.p. 40-60°) until the oil solidified. The solid was filtered off and washed with more light petroleum (b.p. 40-60°). It was recrystallised from light petroleum (b.p. 60-80°). The product had a m.p. of 64-68°, but was

found to be contaminated with some high melting dimethyl 6,6'-dimethoxydiphenate. Accordingly it was dissolved up in boiling cyclohexane from which the impurity crystallised out first. As soon as the low melting product was seen to be coming out of solution, the solution was quickly filtered. The low melting product came out of solution as an oil which solidified on standing. It was recrystallised from methanol. The yield of dimethyl 6-methoxydiphenate, m.p. 66-68°, was 3.6 g. (20%). (Found: C, 68.15; H, 5.7. $C_{17}H_{16}O_5$ requires C, 68.0; H, 5.4%).

2,2'-Bishydroxymethyl-6-methoxybiphenyl.

Sodium-dried ether (30 c.c.) and lithium aluminium hydride (0.4 g.; 3 mol.) were placed in a 3-necked, 250 c.c., round-bottomed flask, fitted with a reflux condenser and a dropping funnel. A calcium chloride tube was placed in the top of the condenser. A solution of dimethyl 6-methoxydiphenate (1 g.; 1 mol.) in ether (70 c.c.) was added gradually, by means of the dropping funnel, to the mixture in the flask over a period of one hour. The solution was washed in with 30 c.c. of fresh ether. The ethereal solution was boiled under reflux for one hour, and, on cooling, water and then 2N sulphuric acid were added to decompose the lithium salts. The two layers were separated and the aqueous layer was washed twice with fresh ether. The ethereal extracts

were combined and the ether was distilled off. The white crystalline residue was recrystallised from a mixture of carbon tetrachloride and light petroleum (60-80°). The yield of 2,2'-bishydroxymethyl-6-methoxybiphenyl, m.p. 79-81°, was 0.5 g. (62%). (Found: C, 73.6; H, 6.55. $C_{15}H_{16}O_3$ requires C, 73.75; H, 6.6%.)

6-Methoxydiphenic acid.

Dimethyl 6-methoxydiphenate (5 g.; 1 mol.) was added to a solution of potassium hydroxide (4.4 g.; 4 mol.) in water (4 c.c.) and ethanol (33 c.c.) in a 100 c.c., round-bottomed flask. The mixture was warmed to dissolve the ester and the solution was boiled under reflux for three hours. Most of the ethanol was distilled off and the residue was poured into cold water. The solution was acidified with dilute hydrochloric acid. The precipitated acid was filtered off and recrystallised from water. The yield of 6-methoxydiphenic acid, m.p. 219-221°, was 3.6 g. (80%). (Found: C, 66.2; H, 4.6. $C_{15}H_{12}O_5$ requires C, 66.2; H, 4.4%.)

6,6'-Dimethoxydiphenic acid.

(Wittig and Petri, Annalen, 1933, 505, 17; Modified by Hall and Turner, J., 1951, 3072).

2-Amino-3-methoxybenzoic acid (33.5 g.; 1 mol.) and sodium nitrite (14 g.; 1 mol.) were dissolved in 200 c.c. of 1N sodium hydroxide solution and the solution was cooled to 0° in an ice-salt mixture. To this solution was added 292 g. of 10% hydrochloric acid, keeping the temperature below 5°. When the addition of hydrochloric acid was complete, sodium metabisulphite (110 g.) and ammonia (110 c.c.; d 0.88) were added to a solution of copper sulphate (48.5 g.) in water (275 c.c.) and ammonia (55 c.c.; d 0.88). This catalytic solution was cooled to below 30° and the diazonium solution was added to it, with stirring. Then another solution of anhydrous ferric chloride (72 g.) in concentrated hydrochloric acid (360 c.c.) and water (110 c.c.) was added to precipitate the 6,6'-dimethoxydiphenic acid, which was filtered off when cold, washed with water and then redissolved in sodium bicarbonate solution. This solution was filtered and then acidified with dilute hydrochloric acid to reprecipitate the 6,6'-dimethoxydiphenic acid, which was filtered off, washed with water and dried. The yield of 6,6'-dimethoxydiphenic acid, m.p. 291-292°, was 23.6 g. (78%).

Resolution of 6,6'-dimethoxydiphenic acid.

(Kenner and Turner, J., 1928, 2340; Stanley, McMahon and Adams, J.Amer.Chem.Soc., 1933, 55, 706).

Diquinine salts.

A boiling solution of anhydrous quinine (64.4 g.; 2 mol.) in methanol (300 c.c.) was added to a boiling solution of 6,6'-dimethoxydiphenic acid (30 g.; 1 mol.) in methanol (800 c.c.). On cooling, the methanol was evaporated off, under reduced pressure, keeping the temperature of the solution below 40°. The last traces of methanol were removed in a vacuum desiccator. The solid residue was boiled under reflux with one litre of dry acetone for half an hour. On cooling, some of the solid, which had not dissolved in the acetone, was filtered off and washed with ~ 50 c.c. of cold, dry acetone. This salt (49 g.) was recrystallised from dry acetone to give a white, crystalline product. The yield of this less soluble diquinine salt, m.p. 171-173°, was 43 g. $[\alpha]_D^{19}$ = +122.3° (c. 1.0345, in chloroform).
Kenner and Turner report that this salt has a $[\alpha]_D$ of +126° in chloroform, and Stanley, McMahon and Adams give a value of +111.0° for $[\alpha]_D^{20}$, in the same solvent.

The mother liquor from the first filtration was evaporated down to ~ 250 c.c. by distilling under reduced pressure. A small amount of solid (1 g.), which had crystallised out, was filtered off. The remainder of the

solvent was allowed to evaporate in the open at room temperature. Last traces were removed in a vacuum desiccator. A glass-like solid, which could be ground up into a pale brown powder, was obtained. The yield of this more soluble diquinine salt, m.p. $\sim 135^{\circ}$, was 44 g.
$[\alpha]_D^{21.5} = -66.0^{\circ}$ (c, 0.9775, in chloroform).

Kenner and Turner report that this salt, m.p. $\sim 60^{\circ}$, has a $[\alpha]_D$ of $-68^{\circ}$ in chloroform, and Stanley, McMahon and Adams give a $[\alpha]_D^{20}$ value for this salt, m.p. 98-100°, of $-60^{\circ}$ in the same solvent.

(-)-6,6'-Dimethoxydiphenic acid.

A solution of the less soluble diquinine salt (20 g.) in chloroform was extracted with three 100 c.c. portions of 5% sodium hydroxide solution. The combined aqueous extracts were extracted twice with small amounts of chloroform and nitrogen was bubbled through the aqueous solution to blow off the chloroform dissolved in it. The solution was filtered and dilute hydrochloric acid was added to precipitate the free (-)-6,6'-dimethoxydiphenic acid. The acid precipitated as a gel, which gradually went solid. It was filtered off, washed with a little cold water and dried. Another 20 g. of the less soluble diquinine salt was treated in the same way. The total yield of (-)-6,6'-dimethoxydiphenic acid, m.p. 291-292°, was 7.2 g.
$[\alpha]_D^{20.5} = -117.8^{\circ}$ (c, 0.8830, in acetone).

Kenner and Turner report that this acid has a $[\alpha]_D$ of $-115^\circ$ in acetone, while Stanley, McMahon and Adams report a value for $[\alpha]_D^{20}$ of $-114.9^\circ$ in acetone.

(+)-6,6'-Dimethoxydiphenic acid.

The more soluble diquinine salt (40 g.) was decomposed in the same way. The yield of (+)-6,6'-dimethoxydiphenic acid, m.p. 290-292°, was 8.2 g.
$[\alpha]_D^{23} = +115.1^\circ$ (c, 1.0035, in acetone).
Kenner and Turner do not appear to have obtained the free (+)-acid, but Stanley, McMahon and Adams report that the free (+)-acid has a $[\alpha]_D^{20}$ of $+108.5^\circ$ in acetone.

Dimethyl (+)-6,6'-dimethoxydiphenate.

(+)-6,6'-Dimethoxydiphenic acid (4.5 g.; 1 mol.) was added gradually to an ice-cold, ethereal-alcoholic solution of diazomethane, containing 1.5 g. (2.4 mol.) of diazomethane. When the effervescence had stopped, a little glacial acetic acid was added to decompose any excess diazomethane. The white, solid ester, which had crystallised out, was filtered off. More solid was obtained on evaporating the mother liquor to dryness. Dimethyl (+)-6,6'-dimethoxydiphenate, m.p. 104-106°, had $[\alpha]_D^{20}$ $+154.3^\circ$ (c, 0.9460, in A.R. acetone). (Found: C, 65.6; H, 5.5. $C_{18}H_{18}O_6$ requires C, 65.45; H, 5.5%).

Dimethyl (-)-6,6'-dimethoxydiphenate.

Dimethyl (-)-6,6'-dimethoxydiphenate, prepared in the same way from (-)-6,6'-dimethoxydiphenic acid, had a m.p. of 105-106°.

$[\alpha]_D^{21}$ = -158.6° (c, 0.9835, in acetone).

(Found: C, 65.2; H, 5.35. $C_{18}H_{18}O_6$ requires C, 65.45; H, 5.5%).

(+)-2,2'-Bishydroxymethyl-6,6'-dimethoxybiphenyl.

Sodium-dried ether (75 c.c.) and lithium aluminium hydride (1.2 g.; 3 mol.) were placed in a 3-necked, 500 c.c. round-bottomed flask, fitted with a dropping funnel and a reflux condenser. A calcium chloride tube was placed in the top of the condenser. Dimethyl (+)-6,6'-dimethoxydiphenate (3.5 g.; 1 mol.) was gradually washed into the flask, from the dropping funnel, with more sodium-dried ether (160 c.c.). The solution was boiled under reflux for thirty minutes and, on cooling, water and then 2N sulphuric acid were added to decompose the lithium salts. The two layers were separated and the aqueous layer was washed once with fresh ether. The ethereal extracts were combined and, without first being dried, the ether was distilled off. The white, crystalline product was recrystallised, with rapid cooling, from boiling water. The yield of (+)-2,2'-bishydroxymethyl-6,6'-dimethoxybiphenyl, m.p. 135-137°, was 1.8 g. (62%). $[\alpha]_D^{18}$ = 98.0°

(c, 0.9545, in A.R. acetone). (Found: C, 69.9; H, 6.5; O, 23.5. $C_{16}H_{18}O_4$ requires C, 70.1; H, 6.6; O, 23.3%).

(-)-2,2'-Bishydroxymethyl-6,6'-dimethoxybiphenyl.

(-)-2,2'-Bishydroxymethyl-6,6'-dimethoxybiphenyl, prepared in the same way from dimethyl (-)-6,6'-dimethoxydiphenate, had a m.p. of 134-136°. $[\alpha]_D^{19.5} = -98.7°$ (c, 1.0185 in A.R. acetone).
(Found: C, 70.1; H, 6.6. $C_{16}H_{18}O_4$ requires C, 70.1, H, 6.6%).

(+)-(or (-)-) 2,2'-Bisbromomethyl-6,6'-dimethoxybiphenyl.
(Adapted from Hall and Turner, J., 1951, 3072).

Phosphorus tribromide (6 c.c.; 6 mol.) was poured into a 25 c.c. round-bottomed flask and the flask was fitted with a calcium chloride tube. The flask was cooled to 0° in an ice-water mixture and (+)-2,2'-bishydroxymethyl-6,6'-dimethoxybiphenyl (2.95 g.; 1 mol.) was added gradually, the calcium chloride tube being removed for each addition. The flask was shaken from time to time. The addition of all of the hydroxy compound took 35 minutes. The mixture was allowed to warm up to room temperature and was then warmed at 30-35° for twenty minutes. It was poured, with stirring, on to crushed ice. The aqueous layer was decanted and the residue was stirred with large volumes of fresh, ice-cold water.

During this treatment the product, a pale yellow oil, solidified. The white solid was filtered off and was washed thoroughly with cold water. On contact with the air, it began to go sticky again and attempts to recrystallise it from light petroleum (b.p. 60-80°) were unsuccessful. Accordingly, it was decided to proceed to the next stage without further purification. The product was dissolved in benzene, the benzene solution was shaken three times with cold water to remove all traces of phosphorus compounds, and then was dried over calcium chloride.

(-)-2,7-Dihydro-4'1"-dimethoxy-3,4:5,6-dibenzazepinium-1-spiro-1'"-piperidinium iodide.

(Adapted from Beaven, Hall, Lesslie and Turner, J., 1952, 854).

The benzene solution of (+) - ~~(or (-))~~ 2,2'-bisbromomethyl-6,6'-dimethoxybiphenyl from the previous experiment was filtered into a conical flask and piperidine (2.3 g.; 2.2 mol.) was added. The solution was left to stand overnight, during which time a mixture of a yellow gum and white needles appeared on the bottom of the flask. The solution was decanted and the residue was washed several times with fresh benzene. On the addition of one or two drops of water the yellow gum solidified. The solid was filtered off, dried and

recrystallised from a mixture of acetone and light petroleum (b.p. 60-80°). White needles (1.0 g.) crystallised out and were filtered off.

$[\alpha]^{21}_{4358}$ +1.7°
$[\alpha]^{21}_{5461}$ -15.6°
$[\alpha]^{21}_{5791}$ -16.2°
(c, 2.6565, in acetonitrile).

A second crop (0.56 g.) was also obtained. It came down as an oil which gradually solidified.

$[\alpha]^{22}_{4358}$ +22.1
$[\alpha]^{22}_{5461}$ -8.0°
$[\alpha]^{22}_{5791}$ -9.6°
$[\alpha]^{22}_{6907}$ -10.6°
(c, 1.5600, in acetonitrile)

Both crops were converted into the corresponding azepinium iodide by the following procedure.

The bromide was dissolved in the least volume of cold water and a saturated solution of potassium iodide was added. The white precipitate of the iodide was filtered off, washed with water and dried. The iodide obtained from the first crop of the bromide was recrystallised from ethanol. The recrystallised product (0.53 g.) had a melting point of 246-248° and went yellow on exposure to light.

$[\alpha]^{22}_{4358}$ + 3.1°
$[\alpha]^{22}_{5461}$ -22.9°
$[\alpha]^{22}_{5791}$ -23.5°
(c, 2.7050, in acetonitrile)

Further recrystallisation from ethanol did not improve the melting point or change the optical rotation.

The iodide obtained from the second crop of bromide was not recrystallised. It had a melting point of 235-238°.

$[\alpha]^{22}_{5461}$ -7.9° )
$[\alpha]^{22}_{5791}$ -10.2° ) (c, 1.9560, in acetonitrile.)

The optically active 2,7-dihydro-4',1"-dimethoxy-3,4:5,6-dibenzazepinium-1-spiro-1'"-piperidinium iodides obtained by Beaven, Hall, Lesslie and Turner (loc.cit.) had a melting point of 242-245° and of 215-218° (they were dimorphic) and $[\alpha]^{22}_{5461}$ +4.0° and -3.8°.

The supposed azepinium iodide with $[\alpha]^{22}_{5461}$ -22.9°, did not give a satisfactory analysis result. (Found: C, 55.0; H, 5.6; N, 3.4; O, 7.5; I, 28.8. $C_{21}H_{26}NO_2I$ requires C, 55.9; H, 5.8; N, 3.1; O, 7.1; I, 28.1%). It has the same (high) melting point as the resolved azepinium iodide, but the optical rotation is much higher and shows anomalous dispersion. The dispersion of the compound obtained by Beaven et al. was normal. The physical properties of the compound obtained in the present work were further investigated. The infra-red spectra of the two compounds are very similar but are not completely identical, and the ultra-violet spectra show the same maxima (237.5 mμ and 296.5 mμ) and minima (233.5 mμ and 261.0 mμ). (Beaven, Hall, Lesslie and Turner, loc.cit.). However, all the intensities in the ultra-violet spectrum of the supposed azepinium bromide are considerably lower than those given in the above paper for

the racemic azepinium bromide. Finally, both compounds show the same order of optical stability. From these observations, it was concluded that the compound obtained in the present work is the required azepinium iodide, but that it is contaminated with a small amount of an optically active impurity.

It is thought that the impurity is probably present because the optically active dibromo-compound could not be recrystallised. Beaven et al. recrystallised the racemic dibromo-compound and, in the process of resolving the azepinium compound, recrystallised its camphorsulphonate many times. Any impurity formed during the preparation of the dibromo-compound or of the racemic azepinium bromide would probably have been removed by these repeated recrystallisations.

In a later experiment, the bromide was recrystallised from ethanol-ethyl acetate, after being recrystallised from acetone-light petroleum (b.p. 60-80°). White needles, with no trace of any oil, were obtained. The melting point of the bromide, recrystallised in this way, was 230-232°, with softening at 180°, probably owing to some solvation. Further recrystallisation did not change the melting point. After the second recrystallisation from ethanol-ethylacetate, the bromide had -

$[\alpha]^{21}_{5461}$ $-46.9^{\circ}$ )
$[\alpha]^{21}_{5791}$ $-43.2^{\circ}$ ) (c, 0.6715, in acetonitrile).

Before recrystallisation from ethanol-ethylacetate, the azepinium bromide had

$[\alpha]^{25}_{5461}$ $-16.5^{\circ}$ )
$[\alpha]^{25}_{5791}$ $-17.7^{\circ}$ ) (c, 2.6290, in acetonitrile).

Thus the recrystallisation had increased the optical rotation threefold, and had changed the ratio $\frac{\alpha 5461}{\alpha 5791}$ from 0.93 to 1.09.

It is propose to convert this sample of azepinium bromide into its iodide and then to have it analysed in the hope that the required compound has, at last, been obtained in a pure state.

**Analysis Result for the Iodide.**

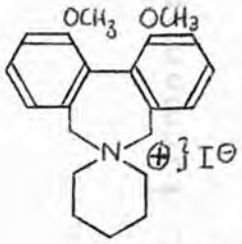
**Found:** C, 55.7; H, 6.1; N, 2.9; O, 6.9; I, 27.8.
**Calc. for $C_{21}H_{26}NO_2I$:** C, 55.9; H, 5.8; N, 3.1; O, 7.1; I, 28.1%.

Racemisation of impure (+)- and (-)-2,7-dihydro-4',1"-dimethoxy-3,4:5,6-dibenzazepinium-1-spiro-1'"-piperidinium iodide.

The impure (-)-azepinium iodide (~0.2 g.) in dimethyl formamide solution (16 c.c.) was sealed, under vacuum, in eight tubes and was heated in cyclohexanol at 160.0°. The method and apparatus were the same as those described on p. 45. The tubes were removed at intervals and were chilled by plunging them first into hot water and then into cold water. Polarimetric readings were taken at room temperature. The rotation of the solution fell from -0.35° to -0.14° in 5½ hours. Similar experiments were carried out at 140.3° (using xylene), 156.2° (using cyclohexanone), 162.5° (using cyclohexanol) and 172.2° (using phenetole). The results of these experiments are given in Tables I - V and in graphs 1, 2 and 3.

In the experiment at 162.5°, a tube was left at this temperature for more than thirty hours. At the end of this time, the solution in the tube was found to be optically inactive.

TABLE I.

Racemisation of (impure) (-)-  in dimethyl formamide at 140.3° (± 0.5°).

l = 1 Zero = 180.08°

λ = 5461 Å initial $[\alpha]^{22}_{5461}$ -22.9° in $CH_3CN$

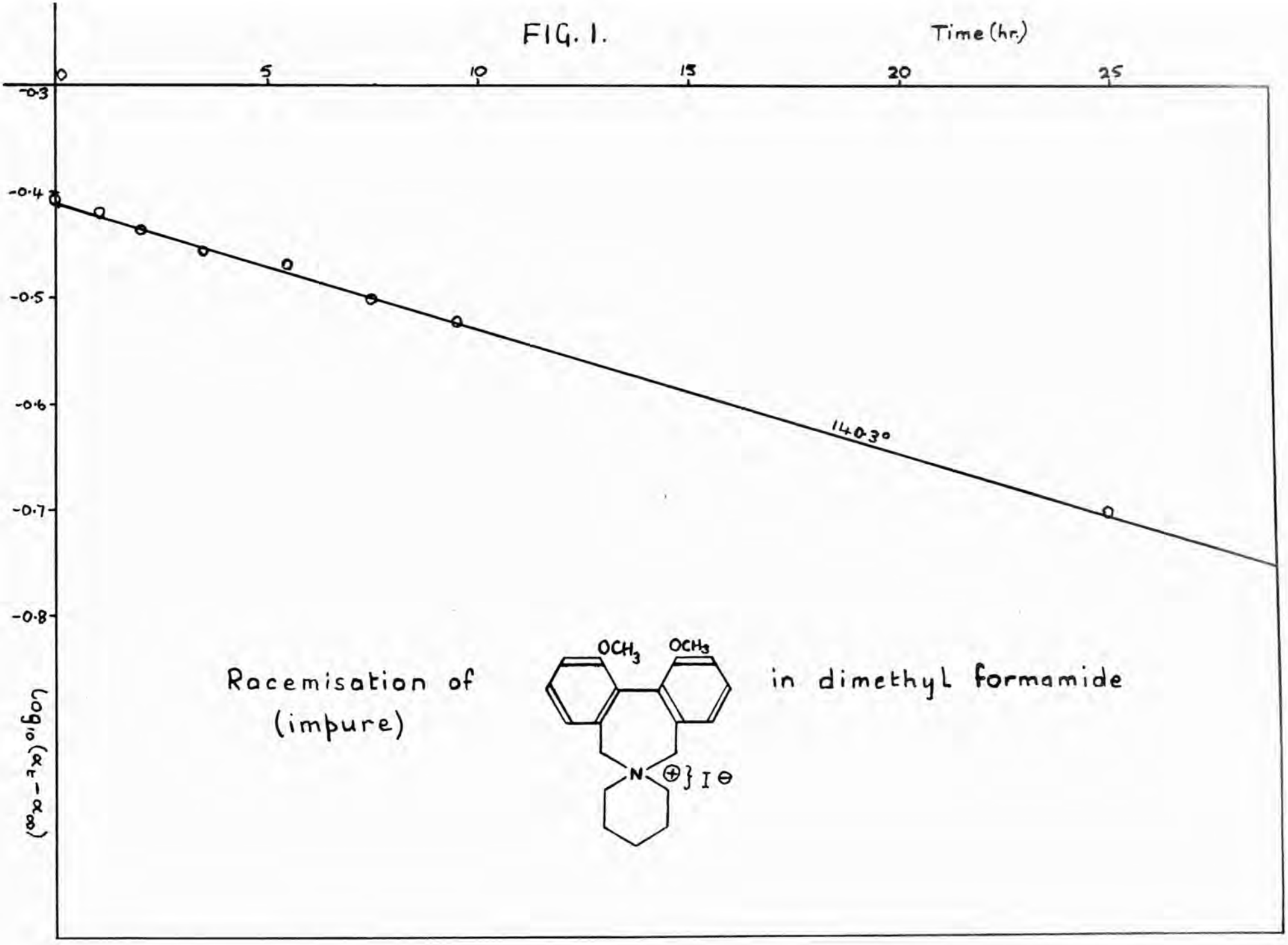
| | Time in hours | Polarimetric reading | $(\alpha_t - \alpha_\infty)$ | $\log_{10}(\alpha_t - \alpha_\infty)$ |
|---|---|---|---|---|
| 1 | 0 | 179.69° | 0.39° | $\bar{1}$.5911 |
| 2 | 1.0 | 179.70° | 0.38° | $\bar{1}$.5798 |
| 3 | 2.0 | 179.715° | 0.365° | $\bar{1}$.5623 |
| 4 | 3.5 | 179.73° | 0.35° | $\bar{1}$.5441 |
| 5 | 5.5 | 179.74° | 0.34° | $\bar{1}$.5315 |
| 6 | 7.5 | 179.765° | 0.315° | $\bar{1}$.4983 |
| 7 | 9.5 | 179.78° | 0.30 | $\bar{1}$.4771 |
| 8 | 25.0 | 179.88° | 0.20 | $\bar{1}$.3010 |

$k = 2.68 \times 10^{-2}$ hr.$^{-1}$

$t_{\frac{1}{2}} = 25.9$ hr.

Constant boiling liquid, xylene.

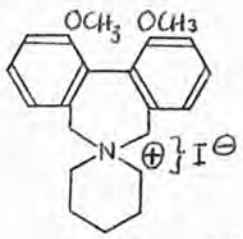
FIG. 1.




Racemisation of  in dimethyl formamide

(impure)

TABLE II.

Racemisation of (impure) (+)-  in dimethyl formamide at 156.2° (± 0.5°)

l = 1 Zero = 180.08°

λ = 5461Å initial $[\alpha]^{21}_{5461}$ +11.0° in $CH_3CN$

| | Time in hours | Polarimetric reading | $(\alpha_t - \alpha_\infty)$ | $\log_{10}(\alpha_t - \alpha_\infty)$ |
|---|---|---|---|---|
| 1. | 0 | 180.43° | 0.35° | $\bar{1}$.5441 |
| 2. | 0.75 | 180.39° | 0.31° | $\bar{1}$.4914 |
| 3. | 1.5 | 180.365° | 0.285° | $\bar{1}$.4548 |
| 4. | 2.25 | 180.335° | 0.255° | $\bar{1}$.4065 |
| 5. | 3.0 | 180.31° | 0.23° | $\bar{1}$.3617 |
| 6. | 3.75 | 180.29° | 0.21° | $\bar{1}$.3222 |
| 7. | 4.5 | 180.27° | 0.19° | $\bar{1}$.2788 |
| 8. | 5.5 | 180.245° | 0.165° | $\bar{1}$.2175 |

$k = 1.36 \times 10^{-1}$ hr.$^{-1}$

$t_{\frac{1}{2}} = 5.1$ hr.

Constant boiling liquid, cyclohexanone.

TABLE III.

Racemisation of (impure) (-)-  in dimethyl formamide at 160.0° (± 0.5°)

$\underline{l}$ = 1 Zero = 180.08°

$\lambda$ = 5461 Å initial $[\alpha]^{22}_{5461}$ -22.9° in $CH_3CN$

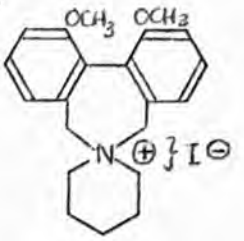
| | Time in hours | Polarimetric reading | $(\alpha_t - \alpha_\infty)$ | $\log_{10}(\alpha_t - \alpha_\infty)$ |
|---|---|---|---|---|
| 1. | 0 | 179.73° | 0.35° | $\bar{1}$.5441 |
| 2. | 0.5 | 179.755° | 0.325° | $\bar{1}$.5119 |
| 3. | 1.0 | 179.78° | 0.30° | $\bar{1}$.4771 |
| 4. | 1.75 | 179.82° | 0.26° | $\bar{1}$.4150 |
| 5. | 2.5 | 179.85° | 0.23° | $\bar{1}$.3617 |
| 6. | 3.5 | 179.885° | 0.195° | $\bar{1}$.2900 |
| 7. | 4.5 | 179.915° | 0.165° | $\bar{1}$.2175 |
| 8. | 5.5 | 179.94° | 0.14° | $\bar{1}$.1461 |

$k = 1.70 \times 10^{-1}$ hr.$^{-1}$

$t_{\frac{1}{2}} = 4.1$ hr.

Constant boiling liquid, cyclohexanol.

TABLE IV.

Racemisation of (impure) (+)-  in dimethyl formamide at 162.5° (±0.5°)

l = 1 Zero = 180.08°

λ = 5461 Å initial $[\alpha]^{21}_{5461}$ +11.0° in $CH_3CN$

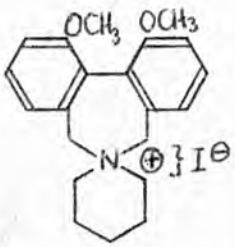
| | Time in hours | Polarimetric reading | $(\alpha_t - \alpha_\infty)$ | $\log_{10}(\alpha_t - \alpha_\infty)$ |
|---|---|---|---|---|
| 1. | 0 | 180.55° | 0.47° | $\bar{1}$.6721 |
| 2. | 0.5 | 180.51° | 0.43° | $\bar{1}$.6335 |
| 3. | 1.0 | 180.47° | 0.39° | $\bar{1}$.5911 |
| 4. | 1.75 | 180.41° | 0.33° | $\bar{1}$.5185 |
| 5. | 2.5 | 180.36° | 0.28° | $\bar{1}$.4472 |
| 6. | 3.5 | 180.31° | 0.23° | $\bar{1}$.3617 |
| 7. | 4.5 | 180.28° | 0.20° | $\bar{1}$.3010 |
| 8. | 5.5 | 180.23° | 0.15° | $\bar{1}$.1761 |

$k = 2.07 \times 10^{-1}$ hr.$^{-1}$

$t_{\frac{1}{2}} = 3.35$ hr.

Constant boiling liquid, cyclohexanol.

TABLE V.

Racemisation of (impure) (-)-  in dimethyl formamide at 172.2° (±0.5°)

l = 1 Zero = 180.07°

λ = 5461 Å initial $[\alpha]^{22}_{5461}$ -7.9° in $CH_3CN$

| | Time in hours | Polarimetric reading | $(\alpha_t - \alpha_\infty)$ | $\log_{10}(\alpha_t - \alpha_\infty)$ |
|---|---|---|---|---|
| 1. | 0 | 179.83° | 0.24° | $\bar{1}$.3802 |
| 2. | 0.25 | 179.85° | 0.22° | $\bar{1}$.3424 |
| 3. | 0.5 | 179.875° | 0.195° | $\bar{1}$.2900 |
| 4. | 0.75 | 179.90° | 0.17° | $\bar{1}$.2304 |
| 5. | 1.0 | 179.925° | 0.145° | $\bar{1}$.1614 |
| 6. | 1.5 | 179.96° | 0.11° | $\bar{1}$.0414 |
| 7. | 2.0 | 179.985° | 0.085° | $\bar{2}$.9294 |
| 8. | 2.5 | 179.005° | 0.065° | $\bar{2}$.8129 |

$k = 5.55 \times 10^{-1}$ hr.$^{-1}$

$t_{\frac{1}{2}} = 1.25$ hr.

Constant boiling liquid, phenetole.

FIG. 2

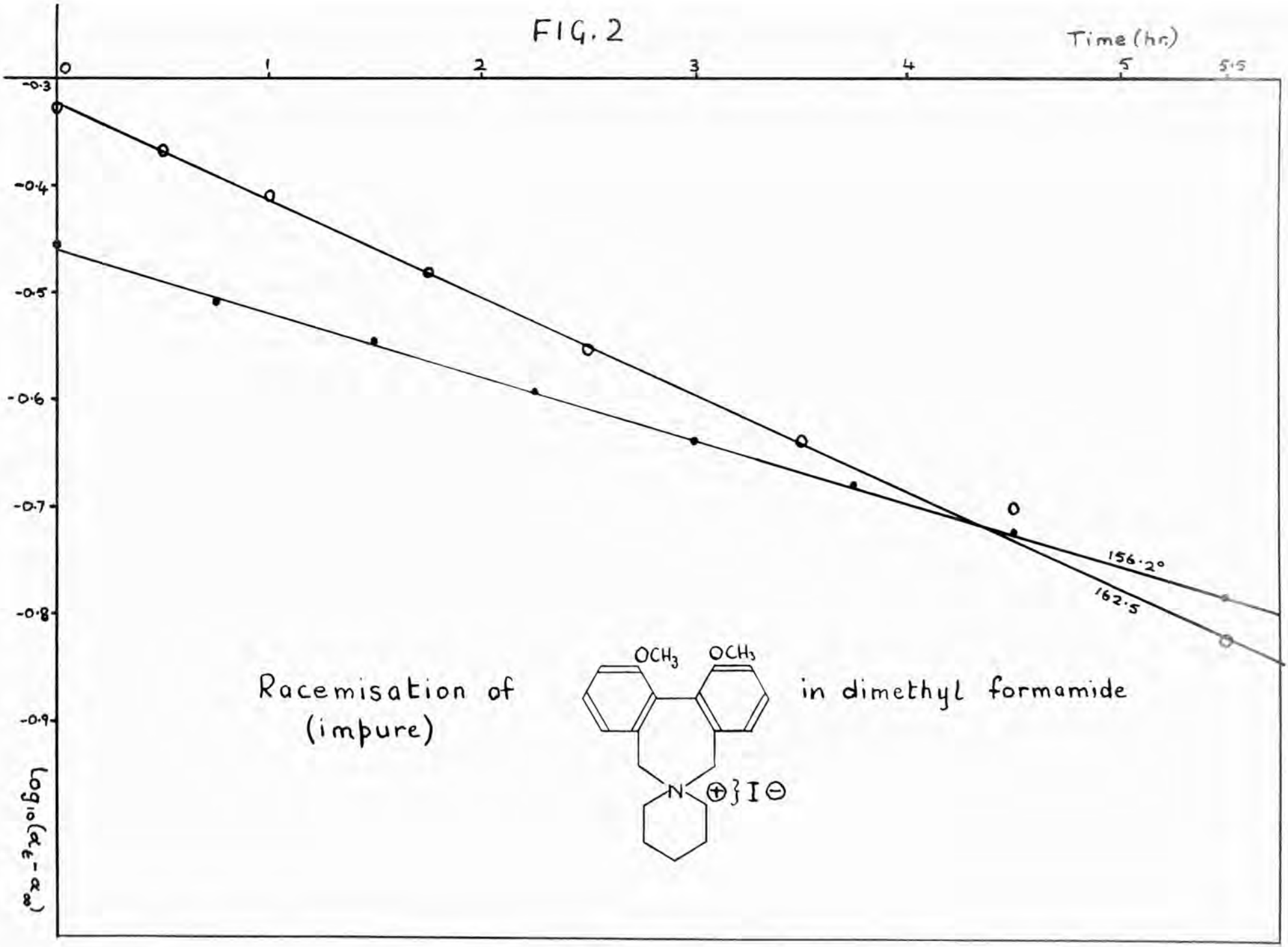

Time (hr)
0
1
2
3
4
5
5·5
-0·3
-0·4
-0·5
-0·6
-0·7
-0·8
-0·9
$\log_{10}(\alpha_t - \alpha_\infty)$
156·2°
162·5
Racemisation of
(impure)
$OCH_3$
$OCH_3$
N
⊕
I⊖
in dimethyl formamide

FIG. 3

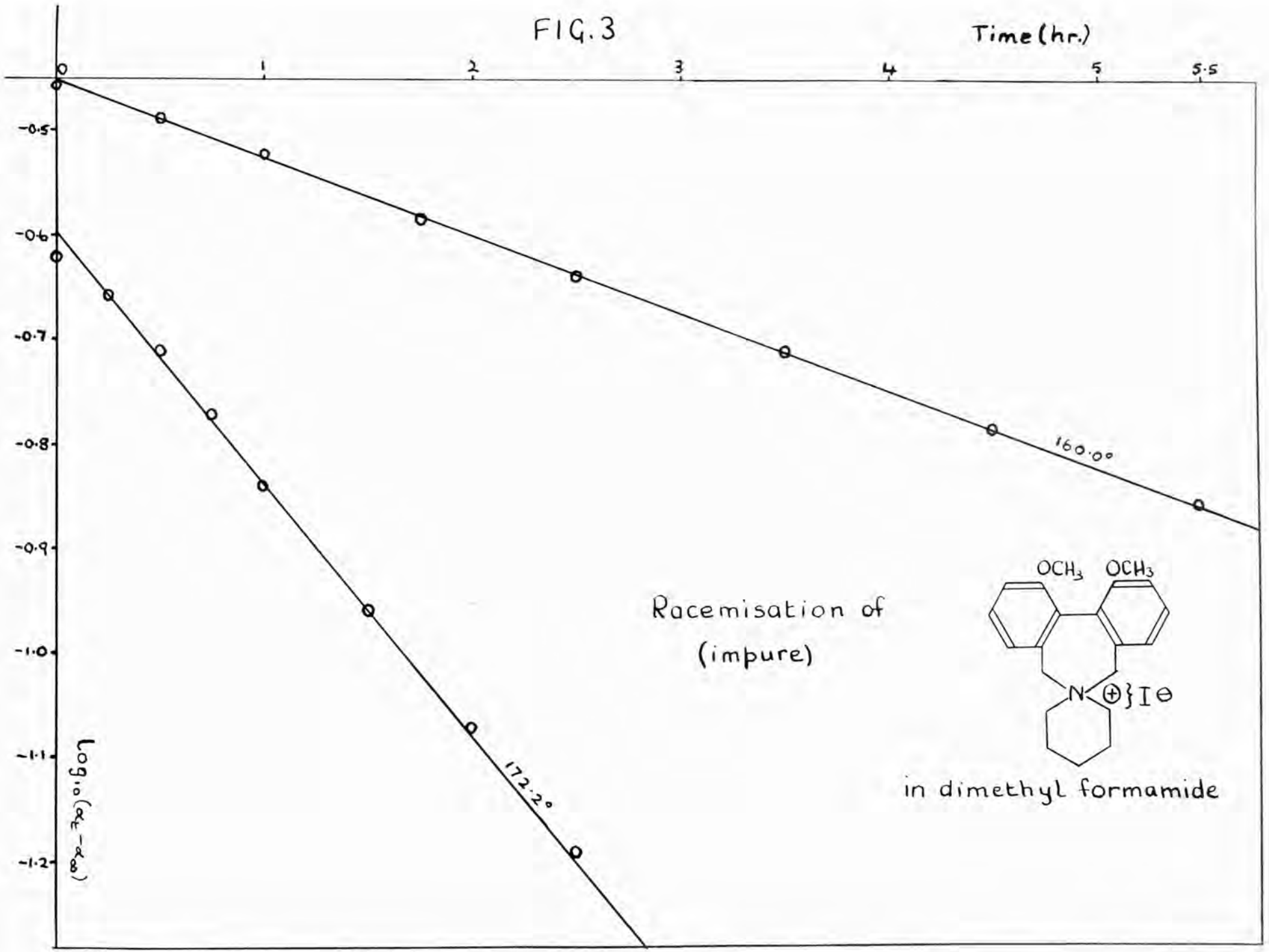
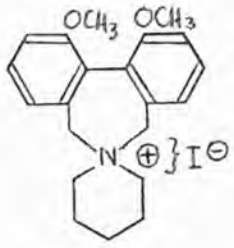

Time (hr.)
0
1
2
3
4
5
5·5
-0·5
-0·6
-0·7
-0·8
-0·9
-1·0
-1·1
-1·2
$\log_{10}(\alpha_t - \alpha_\infty)$
160·0°
172·2°
Racemisation of
(impure)
$OCH_3$ $OCH_3$
N ⊕ } I ⊖
in dimethyl formamide

TABLE VI.

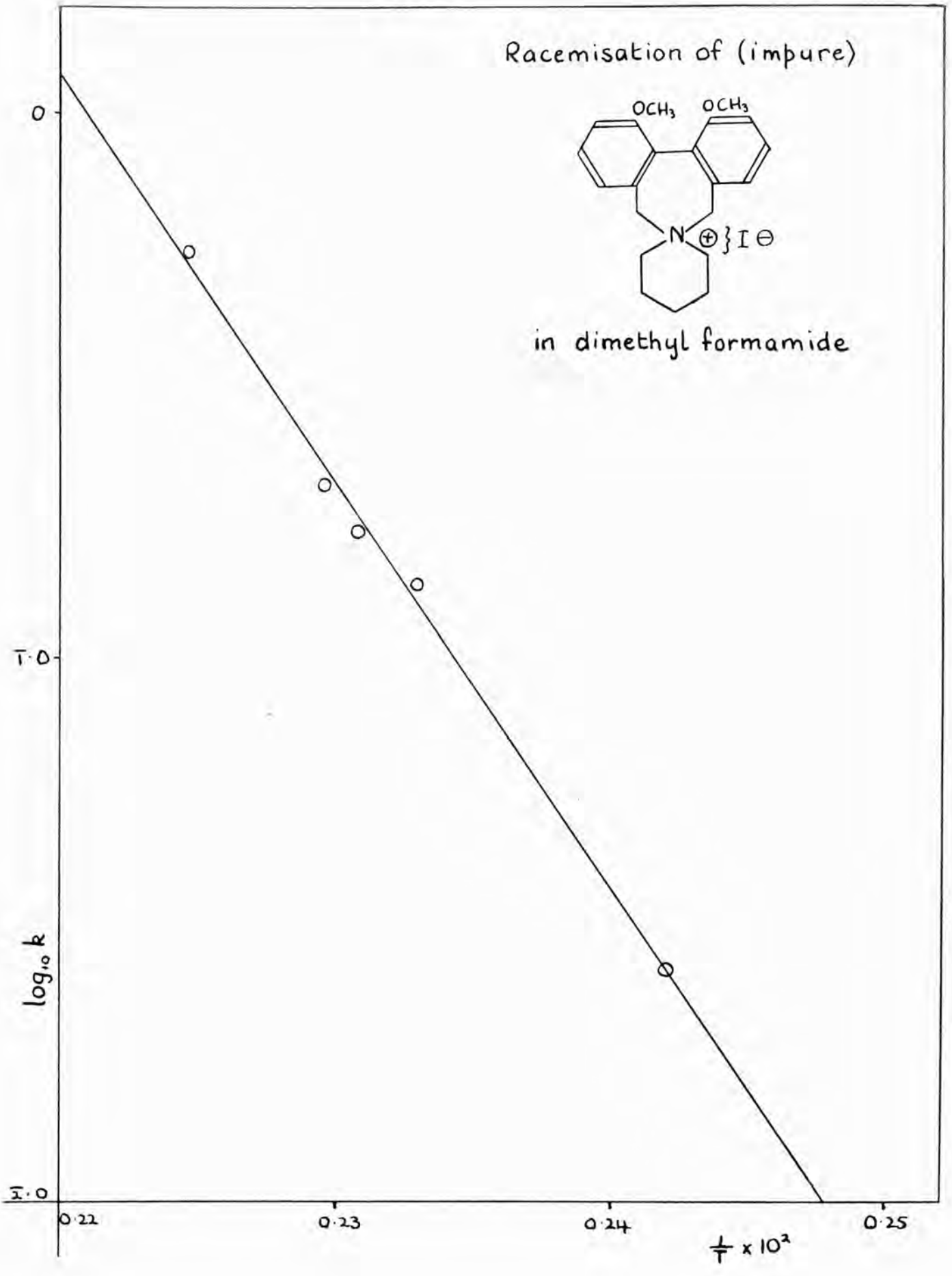
Racemisation of (impure)  in dimethyl formamide.

$\log_{10} k/\frac{1}{T}$

| | T (°C) | T (°K) | $\frac{1}{T} \times 10^2$ | k in hr.$^{-1}$ | $\log_{10} k$ |
|---|---|---|---|---|---|
| 1. | 140.3° | 413.3° | 0.2419 | 0.0268 | $\bar{2}.4281$ |
| 2. | 156.2° | 429.2° | 0.2330 | 0.1363 | $\bar{1}.1345$ |
| 3. | 160.0° | 433.0° | 0.2309 | 0.1702 | $\bar{1}.2309$ |
| 4. | 162.5° | 435.5° | 0.2296 | 0.2069 | $\bar{1}.3158$ |
| 5. | 172.2° | 445.2° | 0.2246 | 0.5554 | $\bar{1}.7446$ |

The straight line plot of $\log_{10} k$ against $\frac{1}{T}$ is given in Fig.4. The value of E comes to 34.1 kcal./mole, and that of A to $10^{12.9}$ sec.$^{-1}$

FIG. 4.


Racemisation of (impure)
OCH3
OCH3
N ⊕ } I ⊖
in dimethyl formamide
0
1̄·0
2̄·0
log10 k
0·22
0·23
0·24
0·25
1/T x 10²

(b) Diazocines.

2-Iodo-3-nitrotoluene.

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

Sodium nitrite (29.6 g.; 1.3 mol.) was dissolved in concentrated sulphuric acid (166 c.c.), keeping the temperature below 40°. After cooling this solution to 0°, it was added to a solution of 2-amino-3-nitrotoluene (45 g.; 1 mol.) in glacial acetic acid (360 g.), keeping the temperature of this mixture between 15° and 25°. The mixture was stirred mechanically throughout. The addition took 45 minutes, after which the diazo solution was stirred for 30 minutes at room temperature. Then it was poured on to a litre of crushed ice in a four-litre beaker. Urea (29.7 g.; 1.5 mol.) was added gradually, with stirring, and, after leaving for an hour, a solution of potassium iodide (71 g.; 1.4 mol.) in water (360 c.c.) was added. A yellow precipitate was obtained, and the mixture was left to stand overnight. A little sodium metabisulphite was then added to decolourise the solution, and the precipitate was filtered off. It was washed with a little water, then with 10% sodium hydroxide solution, and finally with more water. It was recrystallised from aqueous alcohol. The yield of 2-iodo-3-nitrotoluene, m.p. 65-67°, was 73%.

2,2'-Dimethyl-6,6'-dinitrobiphenyl.

(Carlin and Foltz, J.Amer.Chem.Soc., 1956, 78, 1997; Adapted by Ahmed and Hall, J., 1958, 3043).

Copper bronze (50 g.) was added gradually to 2-iodo-3-nitrotoluene (50 g.) in a boiling tube, which was being heated at 140° in a metal bath. The copper bronze was added at such a rate that the temperature of the mixture in the boiling tube did not rise above 170°. When the addition of copper bronze was complete, the mixture was heated at 150° for 30 minutes and then at 190-200° for 15 minutes. On cooling to ~100°, the mixture was extracted with boiling benzene and the solution was filtered. The filtrate was evaporated to dryness and the residue was recrystallised from ethanol. A yellow, crystalline solid, which was 2,2'-dimethyl-6,6'-dinitrobiphenyl, was obtained. The yield of 2,2'-dimethyl-6,6'-dinitrobiphenyl, m.p. 108-110°, was 21 g. (81%).

2,2'-diamino-6,6'-dimethylbiphenyl.

(Kenner and Stubbings, J., 1921, 119, 593).

A hot solution of 2,2'-dimethyl-6,6'-dinitrobiphenyl (27 g.; 1 mol.) in glacial acetic acid was added gradually to a boiling solution of stannous chloride (150 g.; 6.6 mol.) in concentrated hydrochloric acid (200 c.c.; 18 mol.) over a period of twenty minutes. The mixture was kept just below boiling for a further fifteen minutes. On cooling, it was poured into an excess of 30% sodium hydroxide solution. The alkaline solution was extracted with ether and the ethereal solution was dried over sodium sulphate. The ether was distilled off and the residue was recrystallised from ethanol. A yellow, crystalline solid, which was 2,2'-diamino-6,6'-dimethylbiphenyl was obtained. The yield of 2,2'-diamino-6,6'-dimethylbiphenyl, m.p. 132-134°, was 11 g. (52%).

Resolution of 2,2'-diamino-6,6'-dimethylbiphenyl.
(Meisenheimer and Horing, Ber., 1927, 60, 1429).

A boiling solution of 2,2'-diamino-6,6'-dimethylbiphenyl (20 g.; 1 mol.) in absolute ethanol (100 c.c.) was added to a boiling solution of (+)-tartaric acid (14 g.; 1 mol.) in absolute ethanol (70 c.c.). The tartrate, which crystallised out on cooling, was filtered off and was repeatedly recrystallised from absolute alcohol until constant optical rotation was obtained. This was achieved after three recrystallisations. The yield of tartrate, m.p. 164-165°, was 7.6 g.
$[\alpha]^{19}_{5461} = +24.5^{\circ}$ (c, 1.0015, in absolute alcohol).

The salt was dissolved in a mixture of dilute hydrochloric acid and water and the free amine was precipitated on the addition of dilute ammonia solution. The amine (4.6 g.) was recrystallised repeatedly from absolute alcohol until constant optical rotation was obtained. This was achieved after three recrystallisations. The yield of optically pure (+)-2,2'-diamino-6,6'-dimethylbiphenyl, m.p, 156-158°, was 2.1 g.
$[\alpha]^{20}_{5461} = +63.7^{\circ}$ (c, 0.6905, in chloroform).

The mother liquor, in which the tartrate had been prepared and which contained 11.4 g. of tartrate, was evaporated down to dryness. The residue was dissolved in a mixture of dilute hydrochloric acid and water and the free amine was precipitated on the addition

of dilute ammonia solution. The amine was recrystallised three times from absolute alcohol until constant optical rotation was obtained. The yield of (-)-2,2'-diamino-6,6'-dimethylbiphenyl, m.p. 155-157°, was 2.0 g. $[\alpha]^{19}_{5461}$ =-63.8° (c, 0.5255, in chloroform).

4',1"-Dimethyl-2,3-diphenyl-5,6:7,8-dibenzo-1,4-diazocine.

2,2'-Diamino-6,6'-dimethylbiphenyl (0.5 g.; 1 mol.) and benzil (0.5 g.; 1 mol.) were dissolved in hot propionic acid (10 c.c.) and the solution was boiled under reflux for three hours. Most of the solvent was distilled off and the residue was dissolved in hot ethanol. The yellow, needle-like crystals, which came down on cooling, were filtered off and recrystallised from ethanol. The yield of 4',1"-dimethyl-2,3-diphenyl-5,6:7,8-dibenzo-1,4-diazocine, m.p. 209-210°, was 0.2 g. (20%).

(-)-4',1"-Dimethyl-2,3-diphenyl-5,6:7,8-dibenzo-1,4-diazocine.

A solution of (+)-2,2'-diamino-6,6'-dimethylbiphenyl (0.5 g.; 1 mol.) and benzil (0.5g.; 1 mol.) in propionic acid (10 c.c.) was boiled under reflux for five hours. The propionic acid was then distilled off and the residue was dissolved up in boiling ethanol. On cooling, some yellow needles of benzil, m.p. 94-95°, crystallised out. These were filtered off and the mother liquor was evaporated down to dryness. The crystalline residue was ground up twice with small volumes of cold light petroleum (b.p. 60-80°) to remove some soluble impurities, such as small traces of benzil. The residue was recrystallised from light petroleum (b.p.60-80°). Yellow prisms crystallised out of a concentrated solution. The yield of (-)-4',1"-dimethyl-2,3-diphenyl—5,6:7,8-dibenzo-1,4-diazocine, m.p. 179-180°, was 0.1 g. (10%).
$[\alpha]^{22}_{5461}$ = -2,080° (c, 0.4450, in chloroform).
(Found: C, 86.7; H, 5.7; N, 7.5. $C_{28}H_{22}N_2$ requires C, 87.0; H, 5.7; N, 7.25%).

(+)-4',1"-Dimethyl-2,3-diphenyl-5,6:7,8-dibenzo-1,4-diazocine.

(+)-4',1"-Dimethyl-2,3-diphenyl-5,6:7,8-dibenzo-1,4-diazocine, prepared in the same way from (-)-2,2'-diamino-6,6'-dimethylbiphenyl, had a m.p. of 179-180°.
$[\alpha]^{19}_{5461}$ = +2,060° (c, 0.6300, in chloroform).
(Found: C, 87.0; H, 5.7; N, 7.2. $C_{28}H_{22}N_2$ requires C, 87.0; H, 5.7; N, 7.25%).

4',1"-Dimethyl-2,3-dimethyl-5,6:7,8-dibenzo-1,4-diazocine.

A solution of 2,2'-diamino-6,6'-dimethylbiphenyl (1 g.; 1 mol.) and diacetyl (0.4 g.; 1 mol.) in ethylene glycol (25 c.c.) was heated in an oil bath at 160-170° for one hour. The solution was allowed to cool and was then poured into cold water. The mixture was extracted with ether and the ethereal extracts were dried over sodium sulphate. Ether was distilled off and the residue was dissolved in the least volume of dry benzene. This solution was passed through an alumina column, eluting with more dry benzene. A pale yellow solid was obtained when one of the fractions from the column was evaporated to dryness. It was recrystallised from light petroleum (b.p. 80-100°) to give a white, crystalline solid. The yield of 4',1"-dimethyl-2-3-dimethyl-5,6:7,8-dibenzo-1,4-diazocine, m.p. 138-140°, was ~ 0.1 g. (7%).
(Found: C, 82.1; H, 6.8. $C_{18}H_{18}N_2$ requires C, 82.4; H, 6.9%).

Methyl p-aminobenzoate.

(Riegel and Buchwald, J.Amer.Chem.Soc., 1929, 51, 484).

p-Aminobenzoic acid (200 g.) was dissolved in methanol (2,000 c.c.) in a 5 litre, round-bottomed flask. The flask was fitted with a reflux condenser and concentrated sulphuric acid (100 c.c.) was added cautiously to the flask down the condenser. The solution was then boiled under reflux for thirteen hours. Most of the methanol was distilled off and the residue was poured into ~ 2.5 litres of cold water. The solution was neutralised by adding solid sodium bicarbonate. The solid ester was filtered off, washed with water and recrystallised from ethanol. The yield of methyl p-aminobenzoate, m.p. 111-113°, was 190 g. (86%).

Methyl p-iodobenzoate.

(Method of Cheung King Ling, unpublished).

Powdered methyl p-aminobenzoate (67 g., 1 mol.) was made into a paste with a small amount of water in a 3-litre beaker. 6 N Hydrochloric acid (670 c.c.) was added and the mixture was cooled, with stirring, to below $0^{\circ}$ in an ice-salt mixture. A solution of sodium nitrite (33 g.; 1.06 mol.) in 100 c.c. of water was added gradually, keeping the temperature below $0^{\circ}$. The diazo solution was stirred for a further 30 minutes, and was then poured slowly, with stirring, into a 3-litre beaker containing a solution of potassium iodide (74 g.; 1 mol.) in 100 c.c. of water. The mixture was warmed on a water bath until the evolution of nitrogen had almost ceased. The solid iodo-ester was filtered off, washed twice with acidified sodium metabisulphite solution to remove any free iodine, and then several times with cold water. It was recrystallised from methyl alcohol. The yield of methyl p-iodobenzoate, m.p. 112-114$^{\circ}$, was 83 g. (71%).

Methyl 4-iodo-3-nitrobenzoate.

(Method of Cheung King Ling, unpublished).

A solution of methyl 4-iodobenzoate (29 g.) in concentrated sulphuric acid (37.5 c.c.) was cooled to below 0° in an ice-salt mixture. A mixture of concentrated nitric acid (15 c.c.) and concentrated sulphuric acid (15 c.c.) was added, with stirring, keeping the temperature between 0° and 5°. The mixture was stirred for 2½ hours at 0° and was then poured onto ice. The solid product was filtered off. It was extracted with boiling water to remove a large quantity of an unknown by-product. The insoluble residue, which was methyl 4-iodo-3-nitrobenzoate, was recrystallised from methyl alcohol. The yield of methyl 4-iodo-3-nitrobenzoate, m.p. 103-104°, was 20.9 g. (62%).

Dimethyl 2,2'-dinitrobiphenyl-4,4'-dicarboxylate.

(Method of Cheung King Ling, unpublished).

Methyl 4-iodo-3-nitrobenzoate (50 g.), in a boiling tube, was heated to 180° in a metal bath. Copper bronze (35 g.) was added gradually, keeping the temperature of the mixture between 180° and 190°. When all the copper bronze had been added, the mixture was kept at 180-190° for ten minutes. It was then extracted with boiling chloroform and the solution was filtered. The chloroform was distilled

off and the solid residue was recrystallised from aqueous acetone. The yield of dimethyl 2,2'-dinitrobiphenyl-4,4'-dicarboxylate, m.p. 160-161.5°, was 24.5 g. (84%).

Dimethyl 2,2'-diaminobiphenyl-4,4'-dicarboxylate.
(Method of Cheung King Ling, unpublished).

Dimethyl 2,2'-dinitrobiphenyl-4,4'-dicarboxylate (18 g.) was dissolved in a mixture of 96% ethanol (1,000 c.c.) and toluene (160 c.c.) in a 2-litre, 3-necked, round-bottomed flask, fitted with a reflux condenser, a dropping funnel and a thermometer. The thermometer was fitted so that its bulb was immersed in the solution. The solution was heated on a water bath to $\sim 70^{\circ}$. The flask was then removed from the water bath and two teaspoonsful of W-2 Raney nickel were added to the solution. Hydrazine hydrate (100%; 55 c.c.) was added slowly from the dropping funnel at such a rate that the temperature of the reaction mixture remained constant. There was vigorous effervescence during the addition of the hydrazine hydrate, and the colour of the solution changed from bright yellow, through dark brown, to very pale yellow. The reaction mixture was boiled on the water bath for 15 minutes and was then filtered hot, taking care to keep the Raney nickel damp with alcohol. The filtrate was concentrated to a small

bulk by distilling under reduced pressure. When the concentrated solution had cooled, the amine crystallised out as a white solid. It was filtered off and dried. The yield of dimethyl 2,2'-diaminobiphenyl-4,4'-dicarboxylate, m.p. 174-175°, was 12.4 g. (83%).

2,2'-Diaminobiphenyl-4,4'-dicarboxylic acid.

Dimethyl 2,2'-diaminobiphenyl-4,4'-dicarboxylate (9 g.; 1 mol.) was heated under reflux with a solution of potassium hydroxide (7.8 g.; 4 mol.) in water (20 c.c.) and ethanol (125 c.c.) for three hours. Then most of the ethanol was distilled off and the residue was poured into cold water. Glacial acetic acid was added until the solution had a pH value of 5. The pale yellow precipitate was filtered off, washed with water and redissolved in sodium carbonate solution. The solution was filtered and the acid was reprecipitated with glacial acetic acid. It was filtered off, washed with water and dried. The yield of 2,2'-diaminobiphenyl-4,4'-dicarboxylic acid, m.p. 323° (with decomposition), was 8.0 g. (98%).

2,3-Dimethyl-5,6:7,8-dibenzo-1,4-diazocine-2',3"-dicarboxylic acid.

2,2'-Diaminobiphenyl-4,4'-dicarboxylic acid (2 g.; 1 mol.) was heated with a solution of diacetyl (0.7 g.; 1 mol.) in ethylene glycol (20 c.c.) at 130-140°. The mixture was shaken frequently while being heated. The solid amino-acid gradually dissolved in the hot solution and another, highly-crystalline solid appeared on the sides of the flask. The solution was filtered hot after heating for one hour, and the bright yellow, crystalline solid remaining on the filter paper was washed with ethanol to remove the last traces of the ethylene glycol solution. The product was recrystallied from ethylene glycol to give small, pale yellow plates. The yield of 2,3-dimethyl-5,6:7,8-dibenzo-1,4-diazocine-2',3" -dicarboxylic acid, m.p. > 360°, was 1.4 g. (59%). (Found: C, 66.8; H, 4.3; N, 8.6. $C_{18}H_{14}O_4N_2$ requires C, 67.1; H, 4.4; N, 8.7%).

2,3-Diphenyl-5,6:7,8-dibenzo-1,4-diazocine-2',3"-dicarboxylic acid

2,2'-Diaminobiphenyl-4,4'-dicarboxylic acid (1 g.; 1 mol.) was heated, under reflux, with a boiling solution of benzil (0.78 g.; 1 mol.) in glacial acetic acid (70 c.c.) for 25 hours. The hot solution was then filtered and evaporated down to ~ a third of its original volume. Hot water was added to the hot solution until a yellow solid started to crystallise out. The solution was cooled to room

temperature and the crystalline product was filtered off. It was dissolved in sodium bicarbonate solution. The solution was filtered to remove any unchanged benzil, and was then acidified with dilute hydrochloric acid to reprecipitate the acid. This was filtered off and recrystallised from aqueous acetic acid. The yield of 2,3-diphenyl-5,6:7,8-dibenzo-1,4-diazocine-2',3"-dicarboxylic acid, m.p. $> 360^{\circ}$, was 0.4 g. (22.5%).

Resolution of 2,3-diphenyl-5,6:7,8-dibenzo-1,4-diazocine-2'3"-dicarboxylic acid.

(Bell, J., 1952, 1527).

2,3-Diphenyl-5,6:7,8-dibenzo-1,4-diazocine-2',3"-dicarboxylic acid (2.0 g.; 1 mol.) and anhydrous brucine (3.54 g.; 2 mol.) were dissolved in boiling ethanol (95%; 400 c.c.) and the hot solution was filtered. The bright yellow, needle-like crystals, which came down on cooling, were filtered off. The crystals were heated up with boiling ethanol ( $\sim$ 75 c.c.) and, on cooling, the undissolved crystals were filtered off. This was repeated three times more until constant optical rotation was obtained. $[\alpha]^{22}_{5461} = -750^{\circ}$ (c, 0.4580, in chloroform).

The brucine salt (2.0 g.) was dissolved in chloroform and the chloroform solution was extracted three times with 10% sodium hydroxide solution. The aqueous

extracts were shaken twice with fresh chloroform and then once with ether. Nitrogen was blown through the aqueous solution to drive off the ether dissolved in it. Dilute hydrochloric acid was then added to precipitate the pale yellow acid, which was filtered off, washed with water and dried. Recrystallisation from aqueous acetic acid did not change the optical rotation. The yield of (-)-2,3-diphenyl-5,6:7,8-dibenzo-1,4-diazocine-2',3"-dicarboxylic acid, m.p. 274-276°, was 0.7 g.

$[\alpha]^{24}_{5461}$ =-1,850° (c, 0.3050 in dimethylformamide).

The original mother liquor, in which the brucine salt had been made, was evaporated down to dryness. The residue was dissolved in chloroform and the decomposition of the brucine salt to give the (+)-dicarboxylic acid was carried out as before. Once again, recrystallisation of the acid from aqueous acetic acid did not change the optical rotation. The yield of (+)-2,3-diphenyl-5,6:7,8-dibenzo-1,4-diazocine-2',3"-dicarboxylic acid, m.p. 275-277°, was 0.75 g.

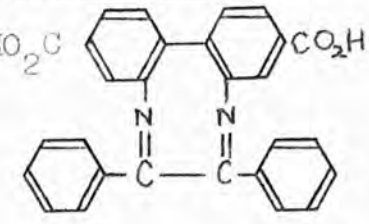
$[\alpha]^{18.5}_{5461}$ =+1,750° (c, 0.1490, in dimethylformamide).

Racemisation of (+)- and (-)-2,3-diphenyl-5,6:7,8-dibenzo-1,4-diazocine-2',3"-dicarboxylic acid.

The (-)-diazocine-dicarboxylic acid (~ 0.03 g.) in ethyl benzoate solution (20 c.c.) was sealed, under vacuum, in ten tubes and was heated in diphenyl ether at 261.5°. The method and apparatus are described on page 45. The tubes were removed at intervals and chilled by plunging first into hot water and then into cold water. Polarimetric readings were taken at room temperature. During nine hours, the rotation fell from -2.69° to -2.01°. Similar experiments were carried out at 247.0° (using 1-methyl-naphthalene), 268.5° (using diphenylmethane), 274.0° (using ethyl cinnamate), and 288.0° (using dimethyl phthalate). The results of these experiments are given in Tables VII - XI, and in graphs 5, 6 and 7.

In an experiment in which the (-)-diazocine-dicarboxylic acid was dissolvedin N,N'-dimethyl-formamide, the solution was heated at ~ 330° for five hours. At the end of this time, the solution was found to be optically inactive.

TABLE VII.

Racemisation of (+) -  in ethyl benzoate at 247.0° (±0.5°)

$\underline{l} = 1$ Zero = 180.08°

$\lambda = 5461$ Å

| | Time in hours | Polarimetric reading | $(\alpha_t - \alpha_\infty)$ | $\log_{10}(\alpha_t - \alpha_\infty)$ |
|---|---|---|---|---|
| 1. | 0 | 182.93° | 2.85° | 0.4548 |
| 2. | 2.0 | 182.91° | 2.83° | 0.4518 |
| 3. | 4.0 | 182.82° | 2.74° | 0.4378 |
| 4. | 6.0 | 182.78° | 2.70° | 0.4314 |
| 5. | 8.0 | 182.70° | 2.62° | 0.4183 |
| 6. | 23.5 | 182.21° | 2.13° | 0.3284 |
| 7. | 25.5 | 182.13° | 2.05° | 0.3118 |
| 8. | 27.5 | 182.10° | 2.02° | 0.3054 |
| 9. | 29.5 | 182.05° | 1.97° | 0.2945 |
| 10. | 31.5 | 182.00° | 1.92° | 0.2833 |
| 11. | 47.5 | 181.65° | 1.57° | 0.1959 |
| 12. | 51.5 | 181.60° | 1.52° | 0.1818 |
| 13. | 55.5 | 181.54° | 1.46° | 0.1644 |

$k = 1.32 \times 10^{-2}$ hr.$^{-1}$

$t_{\frac{1}{2}} = 52.6$ hr.

Constant boiling liquid, 1-methylnaphthalene.

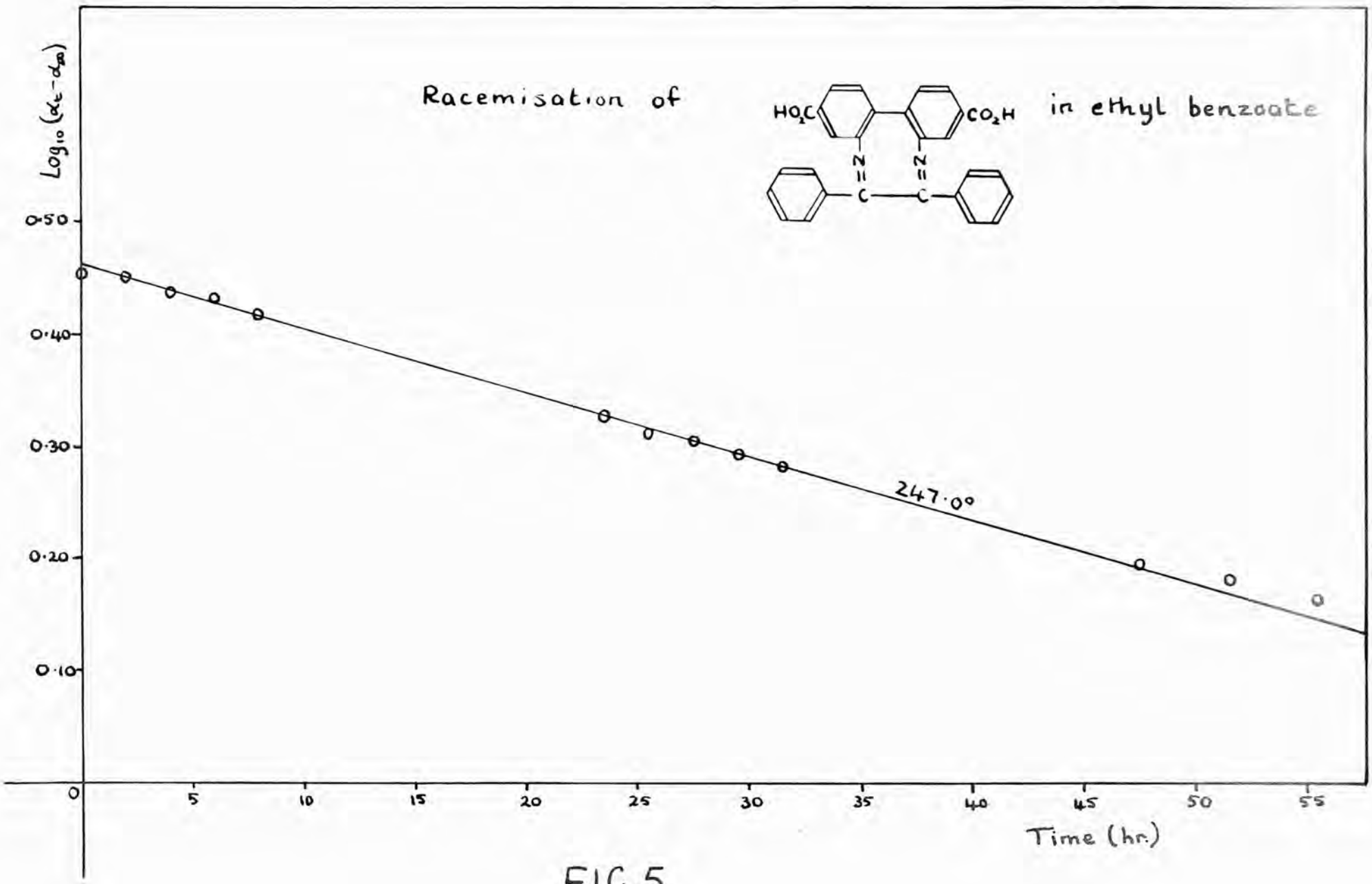
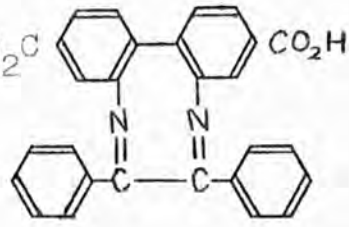

Racemisation of
HO2C
CO2H
in ethyl benzoate
N
N
C
C
Log10 (αt − α∞)
0·50
0·40
0·30
0·20
0·10
0
247·0°
0
5
10
15
20
25
30
35
40
45
50
55
Time (hr.)

FIG. 5

TABLE VIII.

Racemisation of (-)  in ethyl benzoate at 261.5° (±0.5°)

$\underline{l}$ = 1 Zero = 180.07°

$\lambda$ = 5461 Å

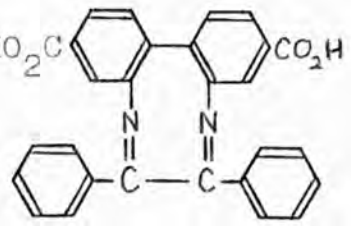
| | Time in hours | Polarimetric reading | $(\alpha_t - \alpha_\infty)$ | $\log_{10}(\alpha_t - \alpha_\infty)$ |
|---|---|---|---|---|
| 1. | 0 | 177.38° | 2.69° | 0.4298 |
| 2. | 1.0 | 177.46° | 2.61° | 0.4166 |
| 3. | 2.0 | 177.51° | 2.56° | 0.4082 |
| 4. | 3.0 | 177.58° | 2.49° | 0.3962 |
| 5. | 4.0 | 177.70° | 2.37° | 0.3747 |
| 6. | 5.0 | 177.76° | 2.31° | 0.3636 |
| 7. | 6.0 | 177.85° | 2.22° | 0.3464 |
| 8. | 7.0 | 177.91° | 2.16° | 0.3345 |
| 9. | 8.0 | 177.96° | 2.11° | 0.3243 |
| 10. | 9.0 | 178.06° | 2.01° | 0.3032 |

$k = 3.29 \times 10^{-2}$ hr.$^{-1}$

$t_{\frac{1}{2}} = 21.1$ hr.

Constant boiling liquid, diphenyl ether.

TABLE IX.

Racemisation of (-)  in ethylbenzoate at 268.5° (±0.5°)

$\underline{1} = 1$ Zero = 180.08°

$\lambda = 5461$ Å

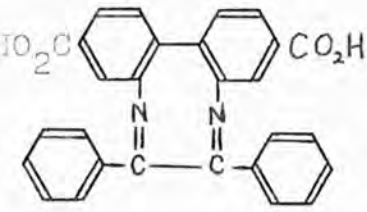
| | Time in hours | Polarimetric reading | $(a_t - a_\infty)$ | $\log_{10}(a_t - a_\infty)$ |
|---|---|---|---|---|
| 1. | 0 | 177.31° | 2.77° | 0.4425 |
| 2. | 1.0 | 177.42° | 2.66° | 0.4249 |
| 3. | 2.0 | 177.55° | 2.53° | 0.4031 |
| 4. | 3.0 | 177.71° | 2.37° | 0.3747 |
| 5. | 4.0 | 177.84° | 2.24° | 0.3502 |
| 6. | 5.0 | 177.89° | 2.19° | 0.3404 |
| 7. | 6.0 | 178.09° | 1.99° | 0.2989 |
| 8. | 7.0 | 178.19° | 1.89° | 0.2765 |
| 9. | 8.0 | 178.26° | 1.82° | 0.2601 |
| 10. | 9.0 | 178.35° | 1.73° | 0.2380 |

$k = 5.53 \times 10^{-2}$ hr.$^{-1}$

$t_{\frac{1}{2}} = 12.5$ hr.

Constant boiling liquid, diphenylmethane.

TABLE X.

Racemisation of (-)  in ethyl benzoate at 274.0° (±1.0°).

$\underline{l}$ = 1 Zero = 180.08°

$\lambda$ = 5461 Å

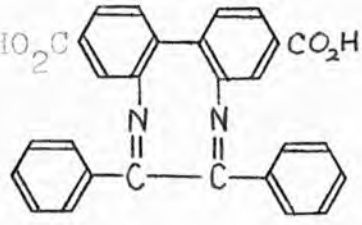
| | Time in hours | Polarimetric reading | $(a_t - a_\infty)$ | $\log_{10}(a_t - a_\infty)$ |
|---|---|---|---|---|
| 1. | 0 | 177.44° | 2.64° | 0.4216 |
| 2. | 1.0 | 177.60° | 2.48° | 0.3945 |
| 3. | 2.0 | 177.76° | 2.32° | 0.3655 |
| 4. | 3.0 | 177.95° | 2.13° | 0.3284 |
| 5. | 4.0 | 178.08° | 2.00° | 0.3010 |
| 6. | 5.0 | 178.26° | 1.82° | 0.2601 |
| 7. | 6.5 | 178.46° | 1.62° | 0.2095 |
| 8. | 8.0 | 178.60 | 1.48° | 0.1703 |

$k = 7.91 \times 10^{-2}$ hr.$^{-1}$

$t_{\frac{1}{2}} = 8.8$ hr.

Constant boiling liquid, ethyl cinnamate.

TABLE XI.

Racemisation of (-)  in ethyl benzoate at 288.0° (±0.5°)

$\underline{l}$ = 1 Zero = 180.07°

$\lambda$ = 5461 Å

| | Time in hours | Polarimetric reading | $(a_t - a_\infty)$ | $\log_{10}(a_t - a_\infty)$ |
|---|---|---|---|---|
| 1. | 0 | 177.37° | 2.70° | 0.4314 |
| 2. | 0.33 | 177.51° | 2.56° | 0.4082 |
| 3. | 0.66 | 177.60° | 2.47° | 0.3927 |
| 4. | 1.0 | 177.81° | 2.26° | 0.3541 |
| 5. | 1.33 | 177.92° | 2.15° | 0.3324 |
| 6. | 1.66 | 178.04° | 2.03° | 0.3075 |
| 7. | 2.0 | 178.11° | 1.96° | 0.2923 |
| 8. | 2.5 | 178.26° | 1.81° | 0.2577 |
| 9. | 3.0 | 178.44° | 1.63° | 0.2122 |
| 10. | 3.5 | 178.56° | 1.51° | 0.1790 |

$k = 16.8 \times 10^{-2}$ hr.$^{-1}$

$t_{\frac{1}{2}} = 4.13$ hr.

Constant boiling liquid, dimethyl phthalate.

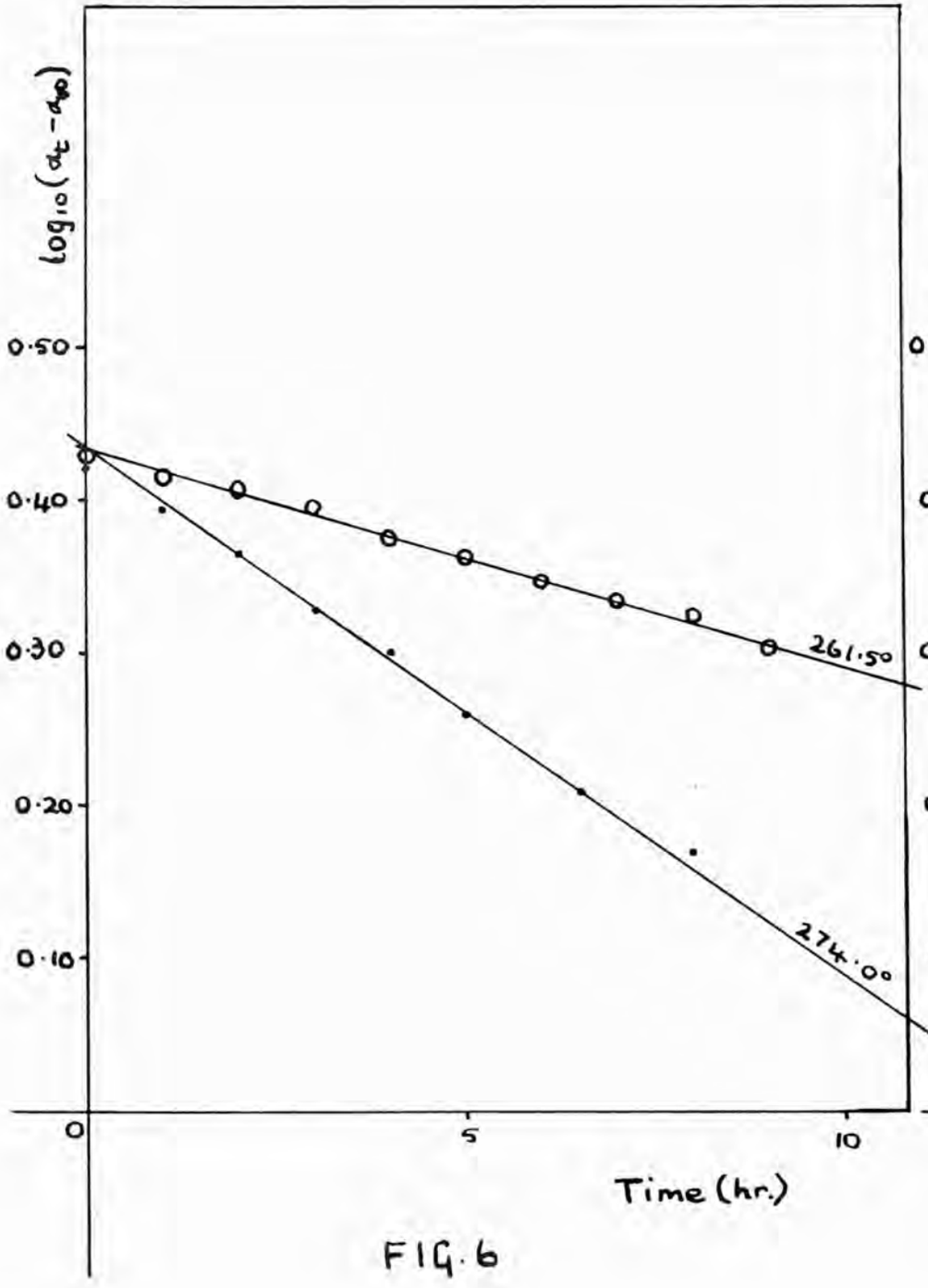

$\log_{10}(\alpha_t - \alpha_\infty)$
0·50
0·40
0·30
0·20
0·10
0
5
10
Time (hr.)
261·5°
274·0°

FIG. 6

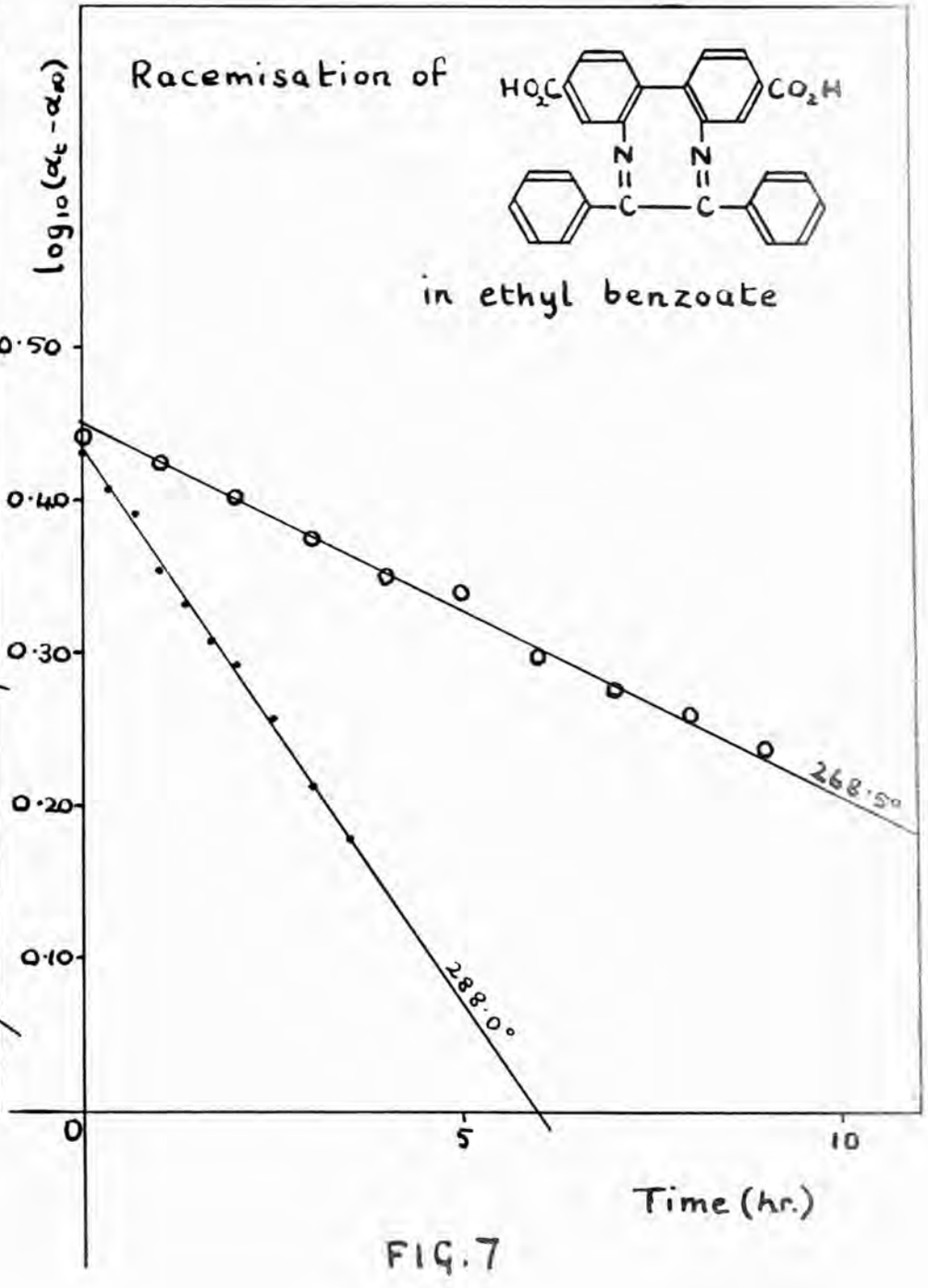
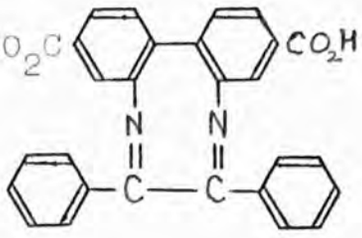

Racemisation of
$HO_2C$
$CO_2H$
N
N
C
C
in ethyl benzoate
$\log_{10}(\alpha_t - \alpha_\infty)$
0·50
0·40
0·30
0·20
0·10
0
5
10
Time (hr.)
268·5°
288·0°

FIG. 7

TABLE XII.

Racemisation of  in ethyl benzoate.

$\log_{10}k/\frac{1}{T}$

| | T (°C) | T (°A) | $\frac{1}{T} \times 10^2$ | k in hr.$^{-1}$ | $\log_{10}k$ |
|---|---|---|---|---|---|
| 1. | 247.0° | 520.0° | 0.1923 | 0.01317 | $\bar{2}$.1196 |
| 2. | 261.5° | 534.5° | 0.1871 | 0.03292 | $\bar{2}$.5175 |
| 3. | 268.5° | 541.5° | 0.1847 | 0.05532 | $\bar{2}$.7429 |
| 4. | 274.0° | 547.0° | 0.1828 | 0.07907 | $\bar{2}$.8980 |
| 5. | 288.0° | 561.0° | 0.1783 | 0.1679 | $\bar{1}$.2251 |

The straight line plot of $\log_{10}k$ against $\frac{1}{T}$ is given in Fig.8. The value of E comes to 36.5 kcal/mole, and that of A to $10^{10.0}$ sec.$^{-1}$.

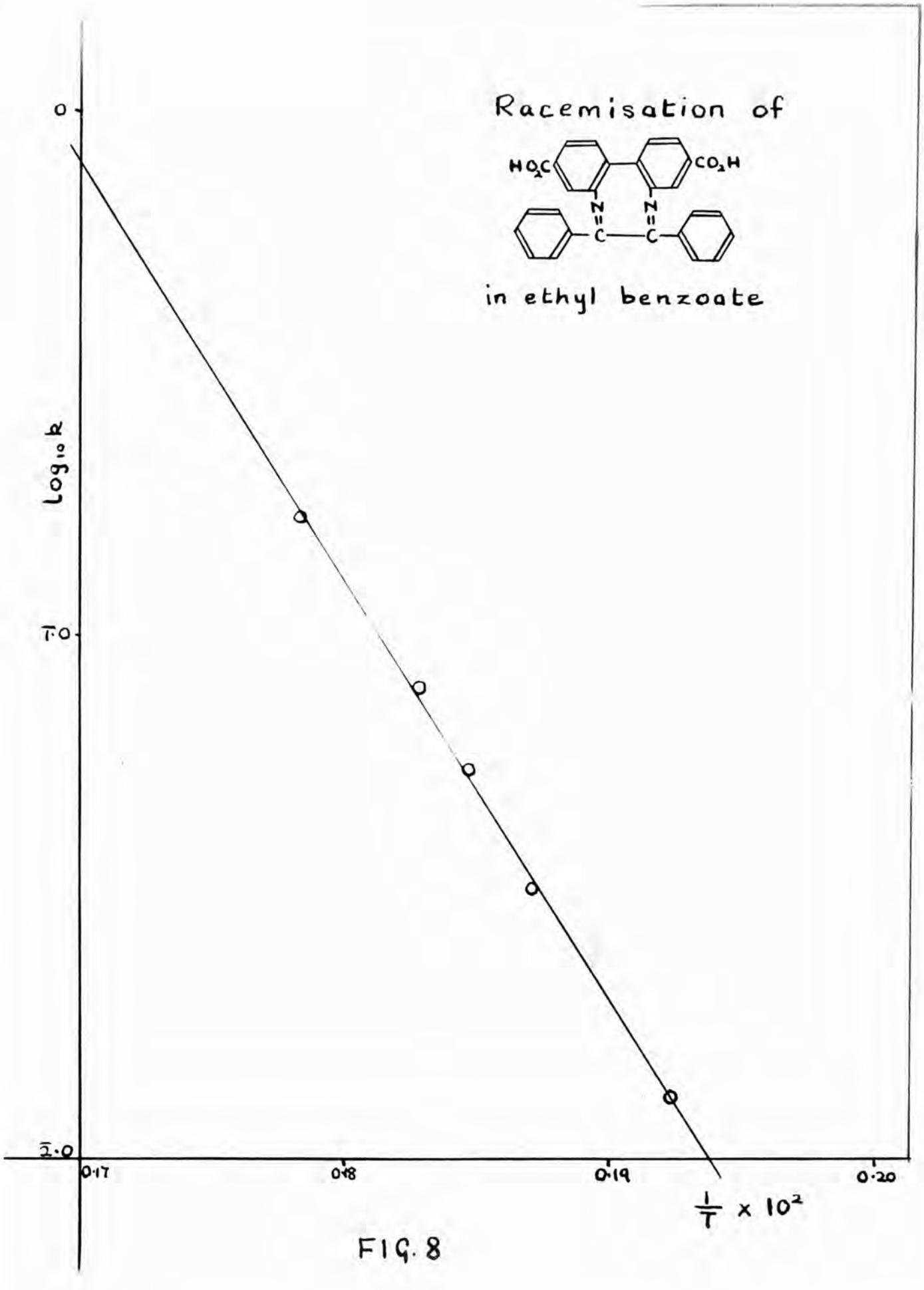

Racemisation of
HO2C
CO2H
N
C
C
N
in ethyl benzoate
0
1·0
2·0
Log10 k
0·17
0·18
0·19
0·20
1/T x 10²

FIG. 8

2,2'-Dinitrobiphenyl.

(Shaw and Turner, J., 1933, 135).

Copper bronze (80g.) was added in 4 lots over a period of 20 minutes to a boiling tube containing o-chloronitrobenzene (120 g.). The boiling tube was being heated in a metal bath kept at 250-260°. After being heated for another ten minutes, the mixture was allowed to cool and was extracted with hot o-dichlorobenzene. The solution was filtered and petroleum ether (40°-60°) was added until the solution went cloudy. 2,2'-Dinitrobiphenyl crystallised out. The dark brown crystals were filtered off and dried. The yield of 2,2'-dinitrobiphenyl, m.p. 120-122°, was 54%.

2,2'-Diaminobiphenyl.

2,2'-Dinitrobiphenyl (40 g.; 1 mol.) was added, with stirring, over a period of 15 minutes to a boiling solution of stannous chloride (245 g.; 6.6 mol.) in concentrated hydrochloric acid (296c.c.; 18 mol.) After being heated for a further 15 minutes, the solution was cooled and poured into a large excess of sodium hydroxide solution. The solution was extracted with ether and the ethereal solution was dried over sodium sulphate. The ether was distilled off, and the residue was distilled under reduced pressure at 167-168°/3 mm. The yield was 70%. 2,2'-Diaminobiphenyl was recrystallised from ethanol to give pale yellow crystals, m.p. 77°.

2,3-Dimethyl-5,6:7,8-dibenzo-1,4-diazocine.

A solution of 2,2'-diaminobiphenyl (1 g.; 1 mol.) and diacetyl (0.5 g.; 1 mol.) in ethylene glycol (13 c.c.) was heated in an oil bath at 130-135° for one hour. The solution was cooled and was poured into cold water. The mixture was extracted with ether and the ethereal extracts were dried over sodium sulphate. Ether was distilled off and the residue was dissolved in the least volume of dry benzene. This solution was passed through an alumina column, eluting with more dry benzene. A pale yellow solid was obtained when one of the fractions from the column was evaporated down to dryness. It was recrystallised from light petroleum (b.p. 60-80°) to give a white, crystalline solid. The yield of 2,3-dimethyl-5,6:7,8-dibenzo-1,4-diazocine, m.p. 129-130°, was 0.5 g. (33%). (Found: C, 82.2; H, 6.15. $C_{16}H_{14}N_2$ requires C, 82.0; H, 6.0%).