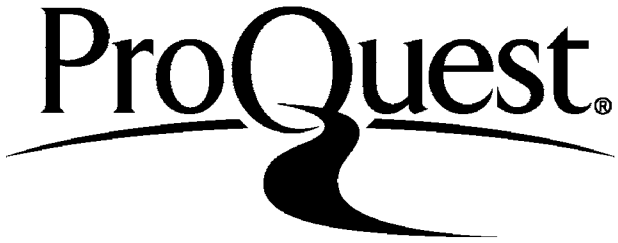
STUDIES IN 2:2'-BRIDGED DIPHENYLS

A thesis submitted to the University of London for the degree of Doctor of Philosophy.

by

SHAKTI RANI PAL

December 1958.



ABSTRACT

This thesis is divided into two sections.

Part I describes the syntheses and the optical properties of some 2:2'-bridged diphenyls. 4':1"-Dinitro- and 4':1"-difluoro-2:7-dihydro-3:4-5:6-dibenzazepines were obtained in optically active forms and their optical stabilities determined.

4':1"-Difluoro-, 4':1"-dibromo-, 4':1"-dichloro- and 4':1"-diiodo-2:7-dihydro-3:4-5:6-dibenzazepinium-1"'-spiro-piperidinium bromides and diethyl 4':1"-difluoro-3:4-5:6-dibenzcyclohepta-(3:5) diene-1:1-dicarboxylate were prepared. Attempts to obtain the mono-carboxylic acid from the diester in an optically active form were unsuccessful.

1:2:7:8-Tetrahydro-3:4-5:6-dibenzazocino-1-spiro-1'-piperidinium iodide was prepared. It was obtained in optically active forms and its optical stability studied.

Part II describes a study of the ultra-violet absorption spectra of 4':1"-dihalogeno-2:7-dihydro-3:4-5:6-dibenzazepinium-1"'-spiro-piperidinium bromides and diethyl 4':1"-difluoro-3:4-5:6-dibenzcyclohepta-(3:5)-diene-1:1-dicarboxylate and in particular the effect of ortho-substituents on the spectra of 2:2'-bridged diphenyls where the bridge forms part of a seven-membered ring.

Acknowledgements

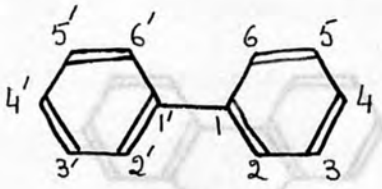
The author wishes to thank Dr. D.M. Hall for her continued help and advice, Professor E.E. Turner, F.R.S. for all the facilities provided and Aligarh University (India) for granting study-leave.

CONTENTS

PART I

INTRODUCTION

When suitable ortho-substituents are present in the collinear diphenyl molecule (I), the two benzene rings cannot become coplanar or rotate freely about the 1-1'-bond.



I

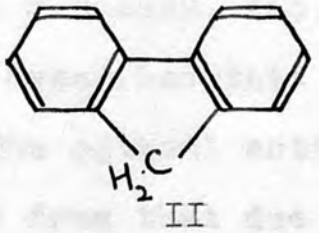
This can be demonstrated by the optical resolution of typical compounds. In some intermediate cases the compounds can be optically activated but cannot be resolved, whereas in compounds without ortho-substituents or with only small ortho-substituents which cannot even be activated, coplanarity is certainly not prohibited. But this is not so much a question of preferred configuration as of whether the molecule is able to pass through a flat coplanar transition state or not. Activation energies for configurational changes involved in racemisation are of the order of 20 - 30 k.cal.mol.$^{-1}$.

By suitably joining the 2-2'-positions of the diphenyl, molecules can be produced which combine the basic collinear diphenyl structure with a strainless multiplanar bridge, and should therefore exist in optically stable (isolable)

enantiomorphic forms, whether or not further substituents are present in the 6-6'-positions. Some of the o-o'-bridged diphenyls are discussed below:

(a) Bridge forming part of a five-membered ring:-

Fluorene (II) does not satisfy the above requirements because



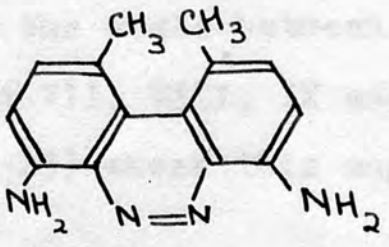
II

it is a strained planar structure in which the rings are no longer collinear (Brown & Bartner, Acta cryst., 1954, 7, 139; Burns & Iball, Nature, 1954, 173, 635).

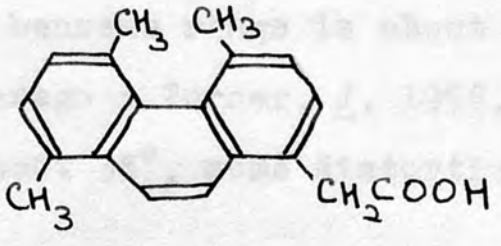
(b) Bridge forming part of a six-membered ring:-

Different situations may arise depending upon the nature of the bridging ring.

(i) In compounds like III, which was resolved through its (+)-camphorsulphonate (Theilacker & Baxmann, Naturwiss., 1951, 38, 156; Annalen, 1953, 581, 117), and IV, which was



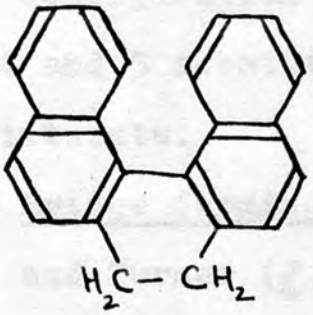
III



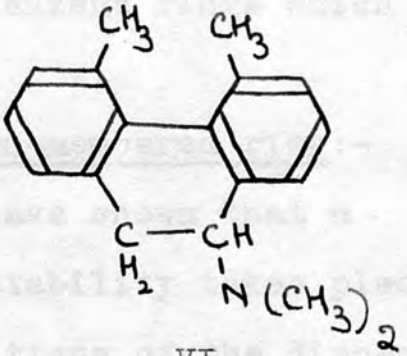
IV

obtained active by the second-order-transformation of its brucine salt (Newman & Hussey, J.Amer.Chem.Soc., 1947, 69, 978, 3023), the optical activity is due to the methyl groups being forced out of the plane of benzene rings, since the phenazine skeleton in III and phenanthrene skeleton in IV have been shown to be flat by ultra-violet absorption spectra of these compounds (Newman & Hussey, loc.cit.). Bell and Waring (J., 1949, 2689) described this phenomenon as intramolecular overcrowding. The optical activity resulting from this can be differentiated from that due to restriction of rotation round a single bond.

(ii) In compounds like V (Hall & Turner, J., 1955, 1242), VI (Wittig & Zimmermann, Chem.Ber., 1953, 86, 629)

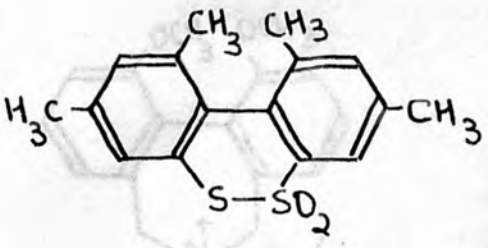


V

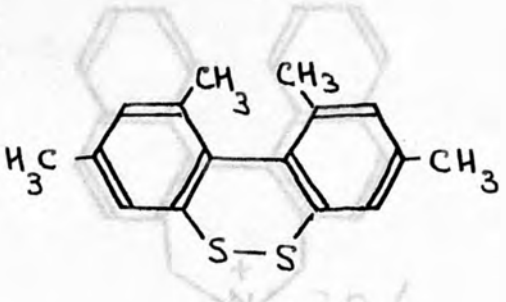


VI

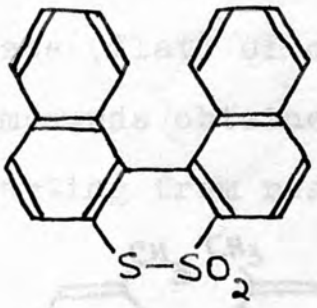
where the angle between the two benzene rings is about 20°, and in VII, VIII, IX and X (Armarego & Turner, J, 1956, 3668; 1957, 13) where this angle is about 35°, some distortion from



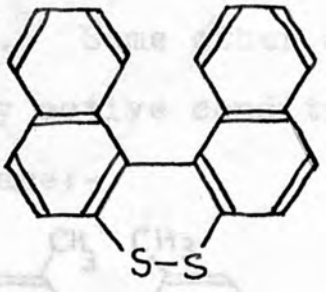
VII



VIII



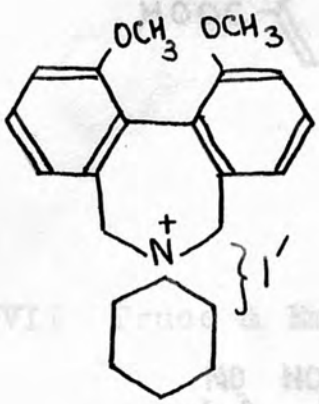
IX



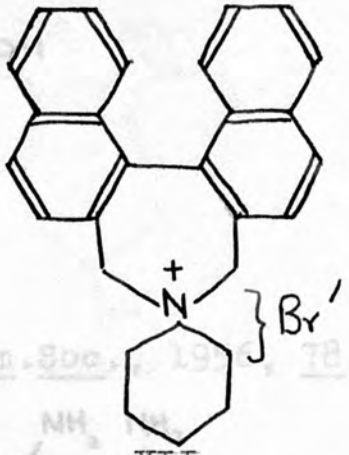
X

this configuration has still to take place to accommodate the 4 and 5 substituents, or the benzene rings which act as substituents.

(c) Bridge forming part of a seven-membered ring:- Hall and Turner (J., 1955, 1242) have shown that a considerable increase in optical stability takes place when the bridging ring in the 2:2'-positions of the diphenyl is enlarged from six to seven atoms. Thus XI and XII are much more optically stable than V. Since the steric interference in the two dinaphthyl compounds is the same, the difference in stability must be due to the greater distortion required for the seven-membered ring to pass through a transition

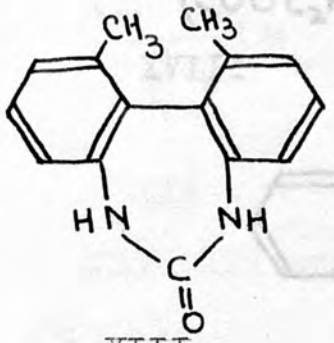


XI

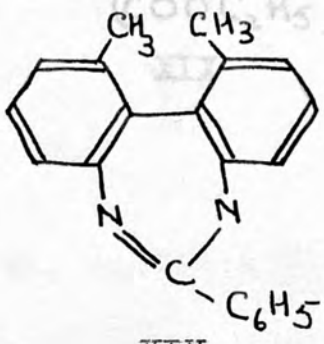


XII

state (flat) of optical inversion. Some other similar compounds obtained in an optically active condition by starting from resolved diphenyls are:-

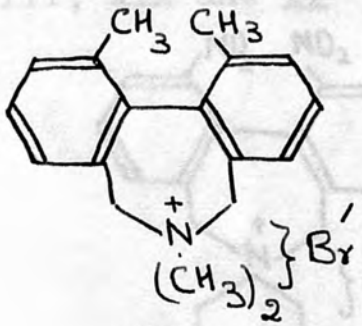


XIII

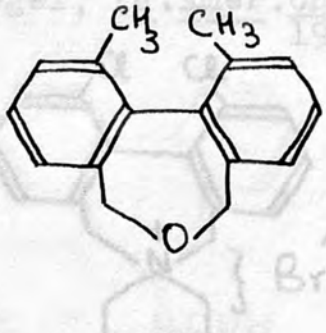


XIV

XIII and XIV Sako (Mem.Coll.Eng.Kyushu Imp.Univ., 1932, 6, 283)

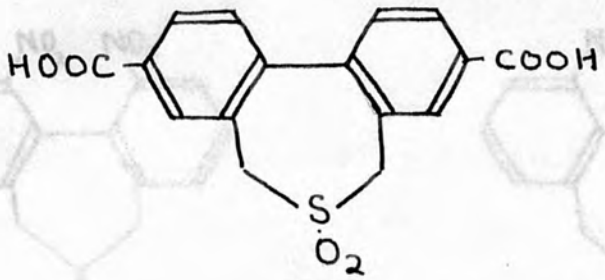


XV



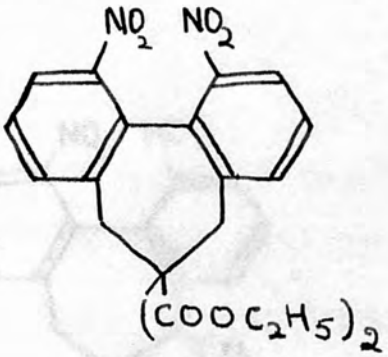
XVI

XV and XVI Wittig & Zimmermann (Chem.Ber., 1953, 86, 629)

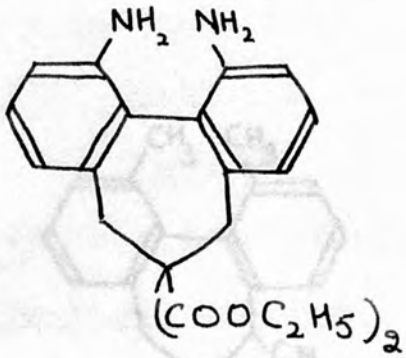


XVII

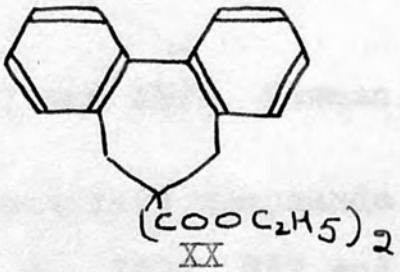
XVII Truce & Emrick (J.Amer.Chem.Soc., 1956, 78, 6130)



XVIII

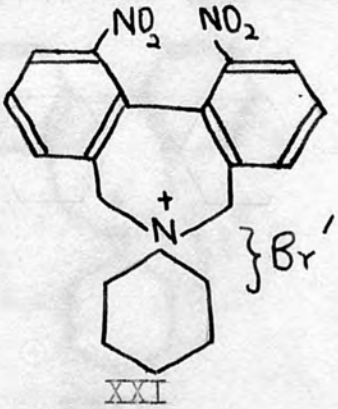


XIX

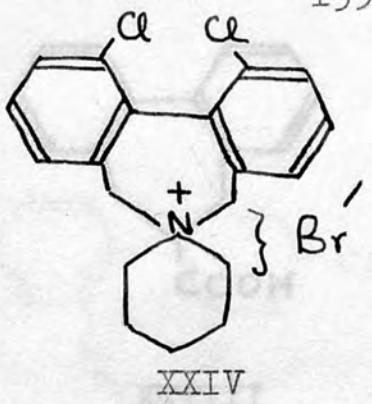


XX

XVIII, XIX and XX Iffland & Siegel, (J.Amer.Chem.Soc., 1958, 80, 1947)

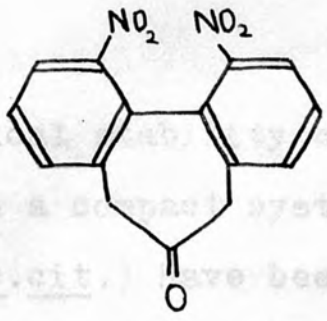


XXI

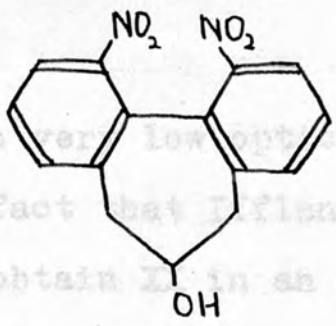


XXIV

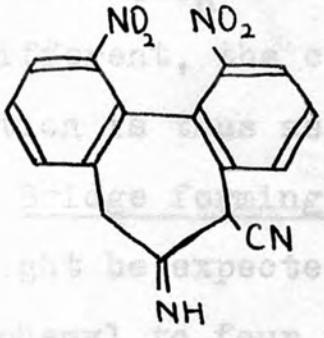
XXI and XXIV Fitts, Siegel & Mislow (ibid., 1958, 80, 480)



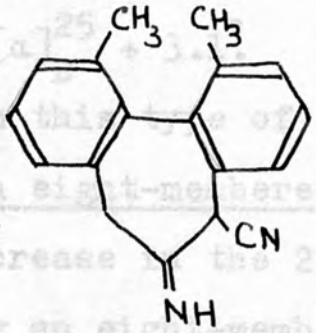
XXIII



XXIV



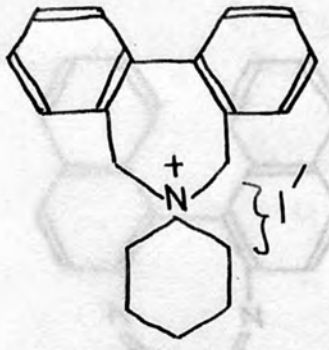
XXV



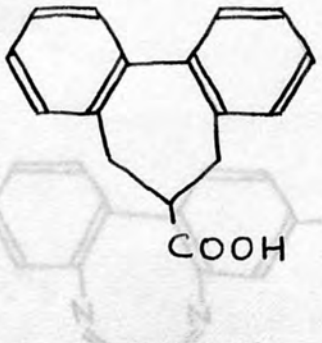
XXVI

XXIII, XXIV, XXV and XXVI Newman, Rutkin & Mislow, (ibid., 1958, 80, 465)

The failure to activate compounds like XXVII and XXVIII (Turner, et.al., J., 1952, 852 and 1950, 2708; Bell, ibid., 1952, 5042) is probably due to difficulties presented by low



XXVII

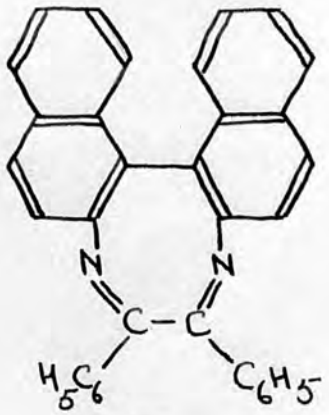


XXVIII

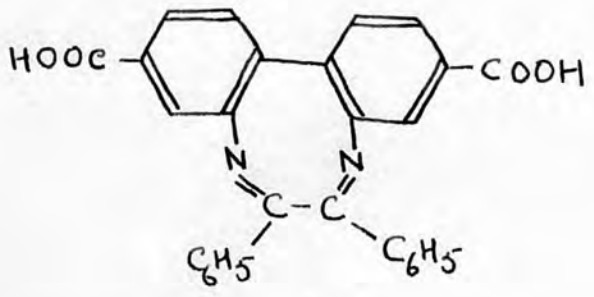
optical stability coupled with very low optical rotation of such a compact system. The fact that Iffland and Siegel (loc.cit.) have been able to obtain XX in an active form greatly substantiates this. However this compound is not very optically stable, loses activity in about 5 hr. at 31.5°, and possesses $[\alpha]_D^{32.5}$ + 2.25°. In XVII, although the bridging ring is different, the compound has $[\alpha]_D^{25}$ + 3.1°. Low optical rotation is thus associated with this type of structure.

(d) Bridge forming a part of an eight-membered ring:-

It might be expected that an increase in the 2:2'-bridge of a diphenyl to four atoms (giving an eight-membered ring) would make it harder for the molecule to achieve coplanarity, and thus lead to greater optical stability in compounds of this type. Kuhn and Goldfinger (Annalen, 1932, 470, 183) obtained XXIX starting from (-)- 2:2'-diamino-1:1'-dinaphthyl. Bell resolved XXX through its brucine salt.

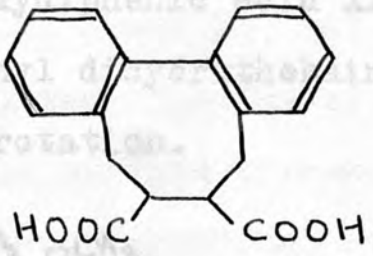


XXIX



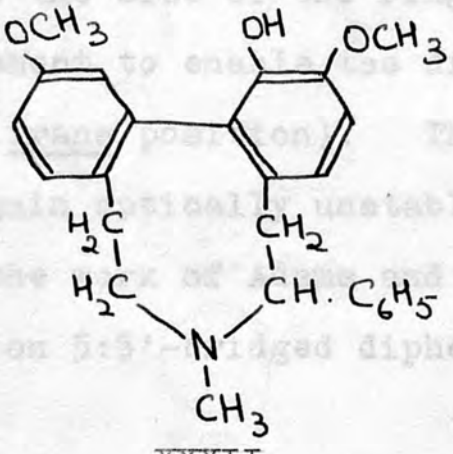
XXX

Additional double-bonds in the bridging rings probably confer considerable optical stability to these two compounds. Recently Dvorken, Smyth and Mislow (J.Amer.Chem.Soc., 1958, 80, 486) obtained cis and trans forms of XXXI in optically active but optically unstable forms.



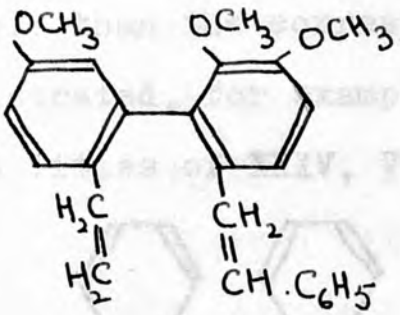
XXXI

(e) Bridge forming part of a nine-membered ring:-
Nine-membered alicyclic compounds are rather difficult to make, (Turner & Harris, Organic Chemistry, Longmans, Green & Co., p.288). Robinson (Proc.Roy.Soc.A, 1948, 192, 14) prepared XXXII in an optically active form starting from the natural product thebaine.

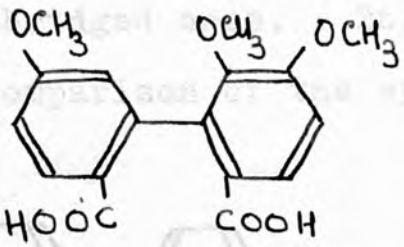


XXXII

This compound has two centres of asymmetry: one is the non-coplanar diphenyl configuration, the other is the carbon carrying the phenyl group. Its conversion into optically active 2:3:3'-trimethoxy-6-styryl-6'-vinyldiphenyl XXXIII by exhaustive methylation, and the oxidation of the latter to an active trimethoxydiphenic acid XXXIV shows that the original activity of phenyl dihydrothebaine XXXII was in part due to restriction of rotation.

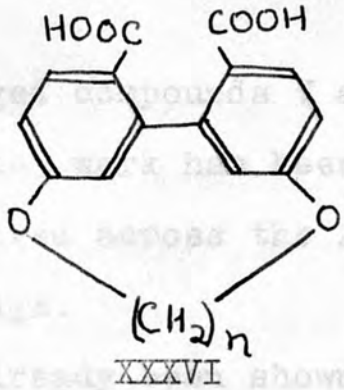


XXXIII



XXXIV

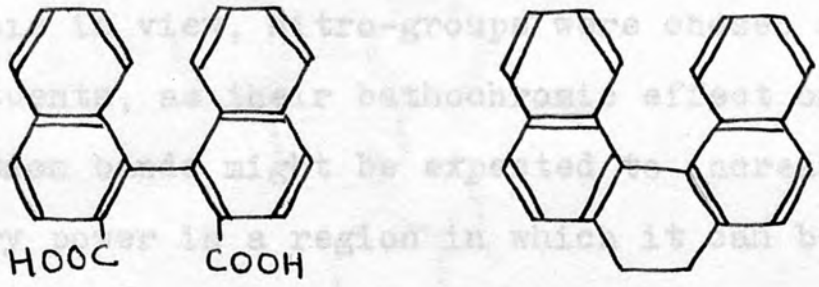
(f) Nothing much is known about the higher rings, but after a certain stage the size of the ring would give enough freedom of movement to enable the diphenyl rings to become coplanar (in a *trans* position). These compounds would therefore be again optically unstable. An interesting comparison is the work of Adams and Kornblum (*J.Amer.Chem.Soc.*, 1941, *63*, 188) on 5:5'-bridged diphenic acids XXXVI.



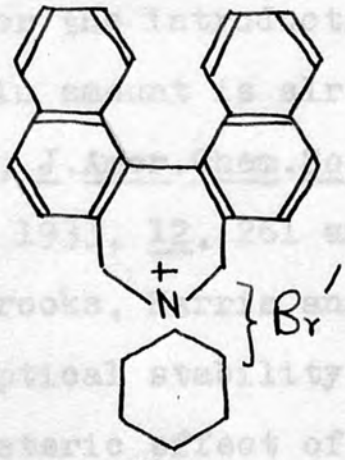
XXXVI

These authors successfully resolved two such compounds with value of n as 8 and 10, and found the former to be more optically stable than the latter.

On the whole bridged diphenyls are much less optically stable than the corresponding unbridged ones. This is illustrated, for example, by a comparison of the optical stabilities of XXXV, V and XII.



XXXV V



XII

The dicarboxylic acid XXXV is far more stable optically

than the bridged compounds V and XII.

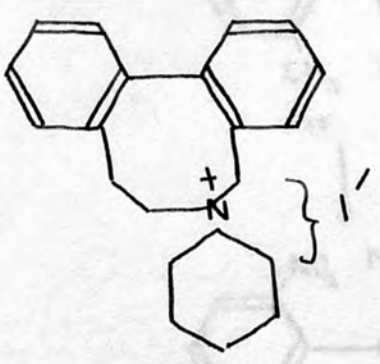
The present work has been confined to the study of diphenyls bridged across the 2:2'-positions with a three or four atom bridge.

It has already been shown that in the absence of any further substituents, a diphenyl bridged across the 2:2'-positions with a three-membered bridge has a very low specific rotation. In an attempt to study the effect of ortho-substituents on the optical stability of such compounds, it was thought desirable to facilitate the detection of optical resolution or asymmetric transformation, if either of them occured, by using compounds of higher specific rotation. With this in view, nitro-groups were chosen as suitable ortho-substituents, as their bathochromic effect on the electronic absorption bands might be expected to increase the optical rotatory power in a region in which it can be most easily detected. They have the further advantage of being a suitable starting point for the introduction of other groups and in addition a certain amount is already known about their steric (Stanley & Adams, J.Amer.Chem.Soc., 1930, 52, 1200; Adams & Yuan, Chem.Rev., 1933, 12, 261 and other papers) and other (idem, ibid.; Brooks, Harris and Howlett, J., 1957, 1934) effects on the optical stability of unbridged diphenyls.

The slight steric effect of fluorine compared with that of any other (necessarily larger) atom or group is apparent

from the studies of optical stabilities of unbridged hindered diphenyls (Kleiderer & Adams, J.Amer.Chem.Soc., 1931, 53, 1575; 1933, 55, 4219; Stanley, McMahon & Adams, ibid., p. 706; Stoughton & Adams, ibid., 1932, 54, 4426) and also from recent spectroscopic work (Beaven & Hall, J., 1956, 4637).

Since XXX and XXXI were the only two known examples of enantiomorphism in 2:2'-bridged diphenyls without other ortho-substituents, where the bridge formed a part of an eight-membered ring system, it was thought worthwhile to investigate the dibenzazocino compound XXXVII.

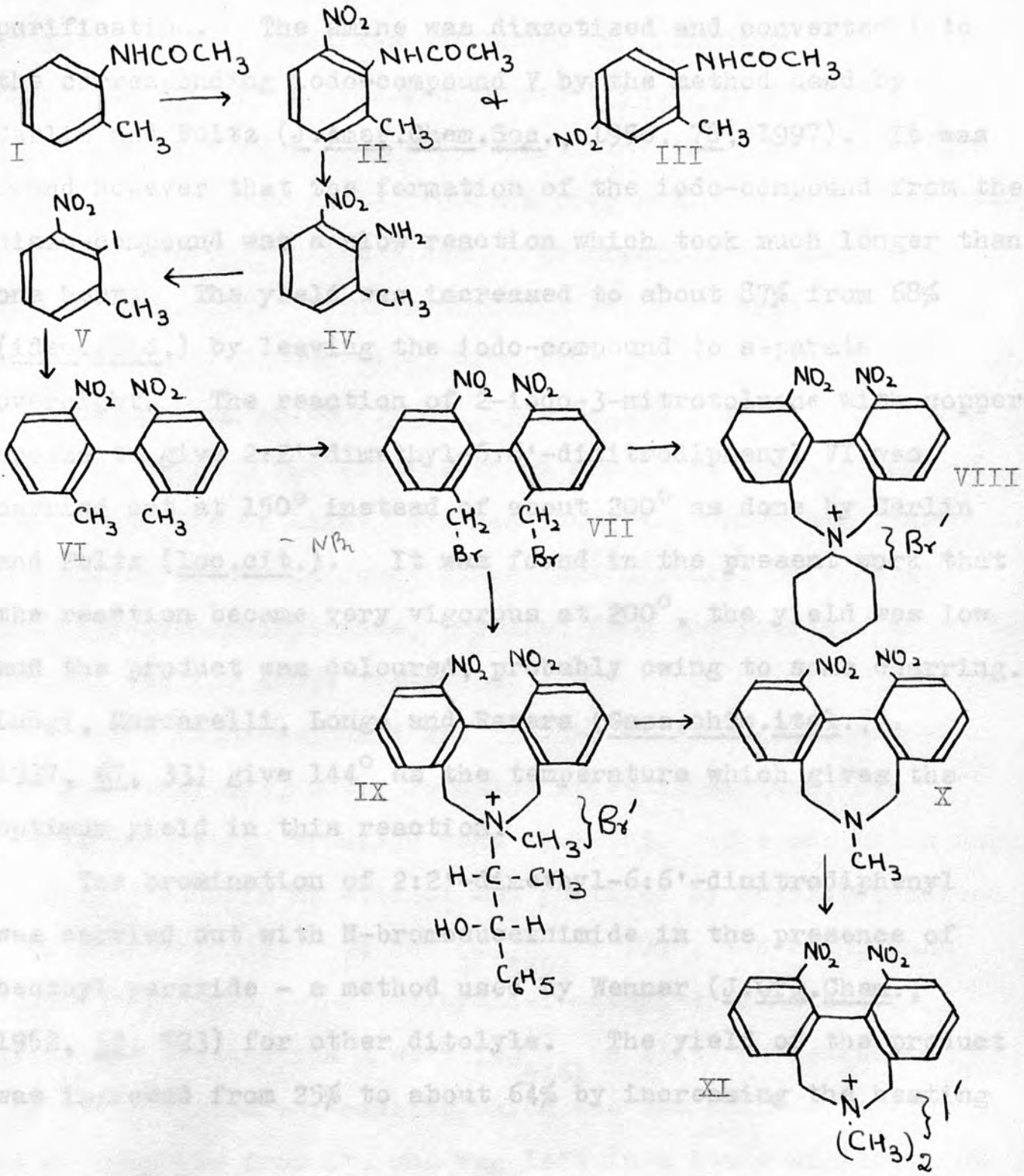


XXXVII

DISCUSSION

(a) Dinitrodibenzazepines:

The general scheme for synthesis was as follows:



2-Amino-3-nitrotoluene IV was prepared by the method of Cohen and Dakin (J., 1901, 79, 1111). The substance was quite pure after the steam-distillation and could be used without further purification. The amine was diazotised and converted into the corresponding iodo-compound V by the method used by Carlin and Foltz (J.Amer.Chem.Soc., 1956, 78, 1997). It was found however that the formation of the iodo-compound from the diazo-compound was a slow reaction which took much longer than one hour. The yield was increased to about 87% from 68% (idem.ibid.) by leaving the iodo-compound to separate overnight. The reaction of 2-iodo-3-nitrotoluene with copper-bronze to give 2:2'-dimethyl-6:6'-dinitrodiphenyl VI was carried out at 150° instead of about 200° as done by Carlin and Foltz (loc.cit.). It was found in the present work that the reaction became very vigorous at 200°, the yield was low and the product was coloured, probably owing to some charring. Lungi, Mascarelli, Longo and Ravera (Gazz.chim.ital., 1937, 67, 33) give 144° as the temperature which gives the optimum yield in this reaction.

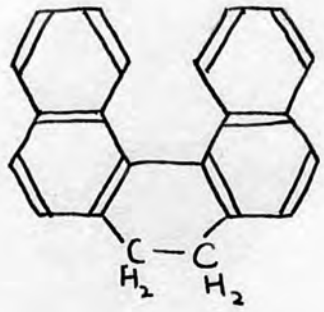
The bromination of 2:2'-dimethyl-6:6'-dinitrodiphenyl was carried out with N-bromosuccinimide in the presence of benzoyl peroxide - a method used by Wenner (J.Org.Chem., 1952, 17, 523) for other ditolyls. The yield of the product was improved from 25% to about 64% by increasing the heating

time and using absolutely pure dinitroditolyl, since it was found that impurities in the latter greatly reduced the yield. Shortly after we had first made this compound its preparation by a different method was announced by Iffland and Siegel (loc.cit.) and by Mislow and Newman (loc.cit.). Newman, Rutkin and Mislow (loc.cit.) report that they also tried the N-bromosuccinimide method for the preparation of the dibromide, but obtained only a 10% yield. Interaction of the 2:2'-bisbromomethyl-6:6'-dinitrodiphenyl VII with piperidine by a method used by Turner et.al. for the preparation of other dibenzazepinium salts (loc.cit.) gave the spiro-piperidinium compound VIII. The bromide which was first isolated seemed very sensitive to light, and was therefore converted into the iodide which was found to be less affected by light. The (+)-camphorsulphonate, prepared from the iodide, failed to crystallise for about two years.

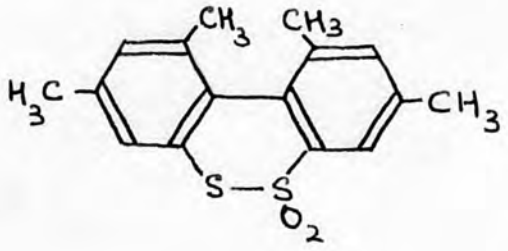
The dibromo-compound was in the meantime condensed with (-)-ephedrine and, after repeated crystallisations, two diastereoisomeric bromides were isolated. The one which was sparingly soluble in ethanol was purified by crystallisations from this solvent. It had $[\alpha]^{23}_{5461}$ - 709°, and by Hofmann degradation gave (-)-2:7-dihydro-1-methyl-4':1"-dinitro--3:4-5:6-dibenzazepine X with $[\alpha]^{19}_{5461}$ - 1343° in benzene. The other diastereoisomeride, which was too soluble in ethanol to crystallise from it, and was left in a state of about 70% purity after the solvent was removed, was purified by three crystallisations from acetonitrile.

It had $[\alpha]^{18}_{5461}$ + 689°, and in a similar way gave the (+)-azepine with $[\alpha]^{19}_{5461}$ + 1333°.

The azepine was optically stable in benzene solution up to about 100°. The yellow solution became very dark when heated at 110° in the air and so it was not possible to follow the racemisation by direct observation of a solution in a jacketed polarimeter tube at a suitable temperature. Therefore a solution of the azepine in benzene was heated in a number of sealed tubes in a thermostat-controlled oil-bath, the tubes were withdrawn at suitable intervals, chilled immediately, and the polarimetric readings taken at 18.5°. In this way the dinitroazepine in benzene solution was found to have a half-life of 16 hr. at 125°, and of 2.6 hr. at 145° and thus an activation energy E of 30 k.cal.mol.$^{-1}$, and a value of A (the non-exponential term in the Arrhenius equation $k = Ae^{-E/RT}$) of $10^{11.5}$ sec.$^{-1}$. This value of A is rather low for a bridged diphenyl. 9:10-Dihydro-3:4-5:6-dibenzophenanthrene and 1:3:8:10-tetramethyldibenzo-[ce]-dithiin-5:5-dioxide have

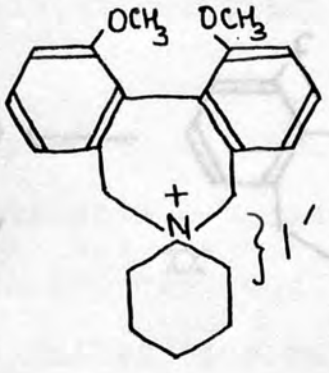


XII



XIII

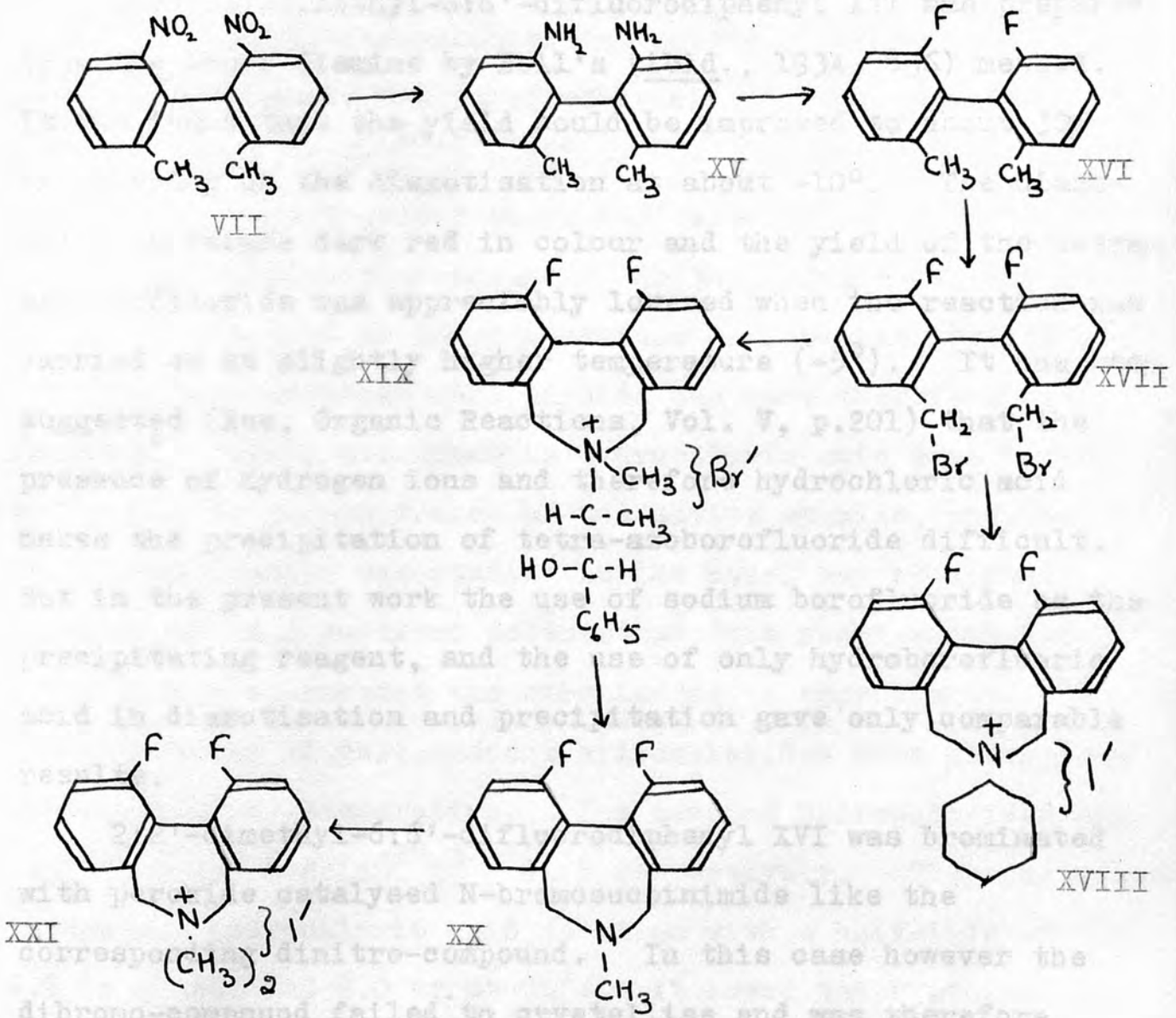
values of A of $10^{13.5}sec^{-1}$ and $10^{13.2}sec^{-1}$ respectively (Harris, Progress in Stereochemistry Vol. II. Ed. Klyne & de la Mare, Butterworths Scientific Publications, 1958, p.174). The lower value of A for the dinitro-compound may be due to the presence of the nitro-groups. Brooks, Harris and Howlett (loc.cit.) have shown that the introduction of nitro-groups into 6-nitrodiphenic acid lowers the value of A. The two cases are however not strictly comparable because the further nitro-groups introduced in their compounds are not in the ortho-position. Rather surprisingly, the dinitroazepine appeared to be much less stable (optically) than the dimethoxy-compound of Beaven, Hall, Lesslie and Turner (loc.cit.) which was only partly racemised after 8 hr. in boiling cyclo-hexanol solution (160°). However, the difference in the valency state of the nitrogen atom in the two compounds may well affect their relative optical stabilities, as may the alteration in the type of the solvent. To test this, the methiodide XI of the (-)-dinitroazepine



XIV

was made. It racemised in acetone solution (sealed tubes) at 145° with a half-life of 4.75 hr. It was thus found to be nearly twice as optically stable as the tertiary amine at that temperature but still not as stable as the quaternary dimethoxy-compound.

(b) Difluorodibenzazepines:-



2:2'-Dimethyl-6:6'-dinitrodiphenyl VII was reduced to give 2:2-dimethyl-6:6'-diaminodiphenyl XV. Various methods were tried for the reduction, such as catalytic reduction with platinum oxide in ethanol or acetic acid, and reduction with zinc and hydrochloric acid, but Kenner and Stubbings' method (J., 1921, 119, 593) of reducing with stannous chloride and hydrochloric acid was found to be best.

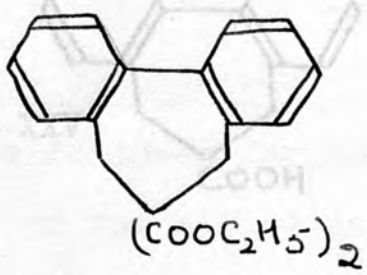
The 2:2'-dimethyl-6:6'-difluorodiphenyl XVI was prepared from the above diamine by Bell's (ibid., 1934, 836) method. It was found that the yield could be improved to about 30% by carrying on the diazotisation at about -10°. The diazo-solution became dark red in colour and the yield of the tetra-azoborofluoride was appreciably lowered when the reaction was carried on at slightly higher temperature (-5°). It has been suggested (Roe, Organic Reactions, Vol. V, p.201) that the presence of hydrogen ions and therefore hydrochloric acid makes the precipitation of tetra-azoborofluoride difficult. But in the present work the use of sodium borofluoride as the precipitating reagent, and the use of only hydroborofluoric acid in diazotisation and precipitation gave only comparable results.

2:2'-dimethyl-6:6'-difluorodiphenyl XVI was brominated with peroxide catalysed N-bromosuccinimide like the corresponding dinitro-compound. In this case however the dibromo-compound failed to crystallise and was therefore

condensed without isolation with piperidine and with (-)-ephedrine to give XVIII and XIX respectively.

The latter was crystallised from ethanol. The less soluble (+)-isomer crystallised out as fine needles, and was purified by further crystallisations from the same solvent to $[\alpha]_{5461}^{18.5}$ + 50°. Its diastereoisomer crystallised out as hydrated cubes on dilution of the mother-liquor after about 1/3 of the (+)-diastereoisomer had crystallised out. The (-)-diastereoisomer was purified by crystallisations from dilute ethanol to $[\alpha]_{5461}^{18.5}$ - 55°. The 4':1"-difluorodibenzazepines XX were expected to be far less stable than the corresponding dinitro-compound. So the Hofmann degradation was carried out at as low temperature as possible, ca. 70°. The resulting azepines were liquids and were therefore not isolated. Their solutions in hydrochloric acid were washed thoroughly to remove traces of the active epoxide, and then their racemisation was studied in the usual way by direct observation in a jacketed polarimeter tube round which hot water from a thermostat was circulating. Approximate concentrations of deliquescent hydrochlorides were determined subsequently by evaporation. The azepine hydrochlorides had $[\alpha]_{5461}^{18.5}$ + 45° and $[\alpha]_{5461}^{18.5}$ - 41.5° respectively. They racemised in aqueous hydrochloric acid solution with a half-life of 6.5 hr. at 80° and 2.0 hr. at 91°. At lower temperatures the

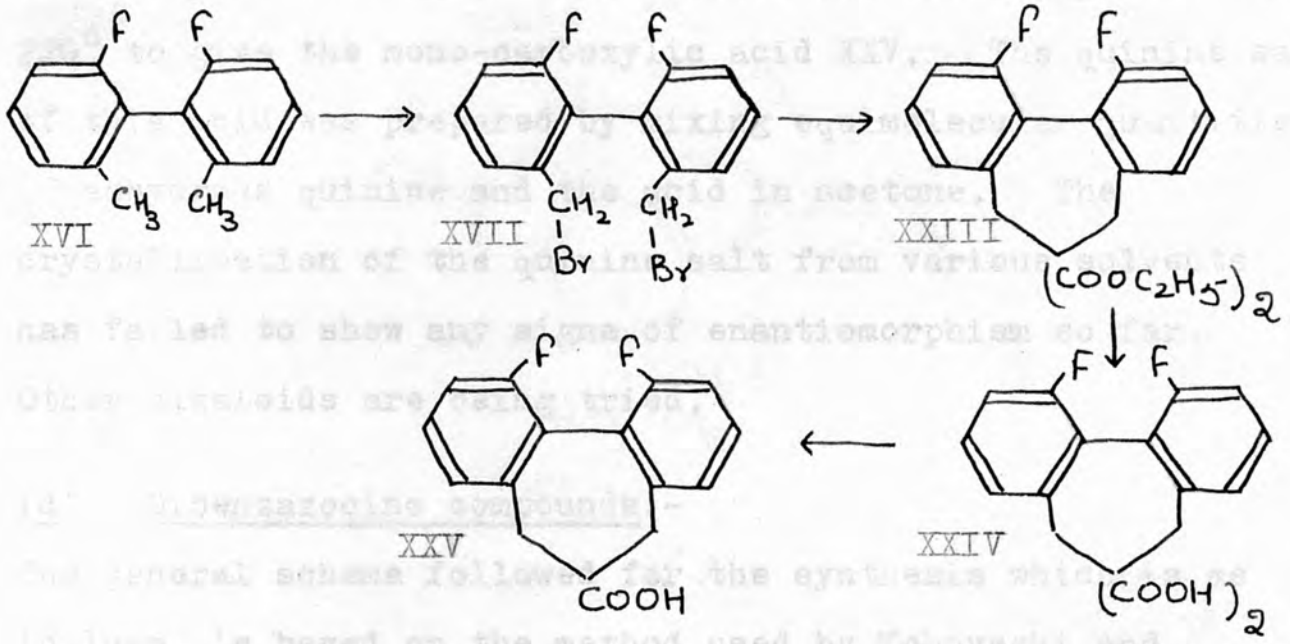
rate was too slow for convenient measurement; at higher temperatures the solvent was too near its boiling point. These rates give a value of about 28 k.cal.mol.$^{-1}$ for activation energy E, and $10^{12.7}$sec^{-1} for A, but the data are inadequate for accurate assessment. It is, however, clear that the compound is much more optically stable than the hydrocarbon ester XXII (Iffland & Siegel, loc.cit.)



XXII

which was inactive after 5 hours at 31.5°. Slight racemisation (perhaps a few units per-cent) probably occurred during the Hofmann degradation. The methiodide XXI was prepared from (±)-amine for analysis.

(c) 4':1"-Difluoro-3:4-5:6-dibenzcyclohepta-3:5-diene-1-carboxylic acid:-

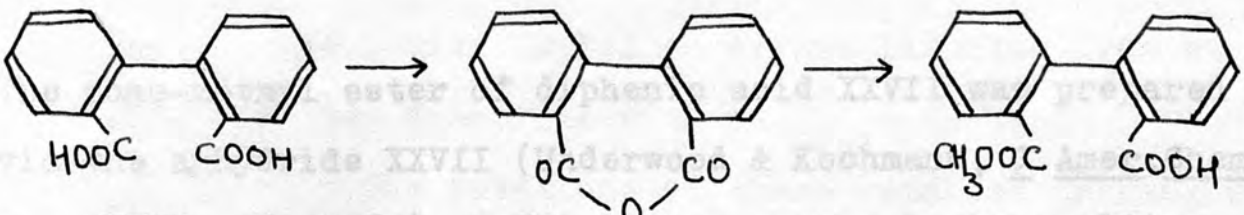


2:2'-Dimethyl-6:6'-difluorodiphenyl was brominated with peroxide-catalysed N-bromosuccinimide as before. The resulting dibromo-compound was condensed without isolation with sodio-malonic ester by a method used by Turner et.al. (J., 1955, 2708) and by Hall and Minhaj (ibid., 1957, 4584) for the condensation of other 2:2'-bisbromomethyldiphenyls with sodio-malonic ester. Dimethyl 4':1"-difluoro-3:4-5:6-dibenzcyclohepta-3:5-diene-1:1-dicarboxylate XXIII, which

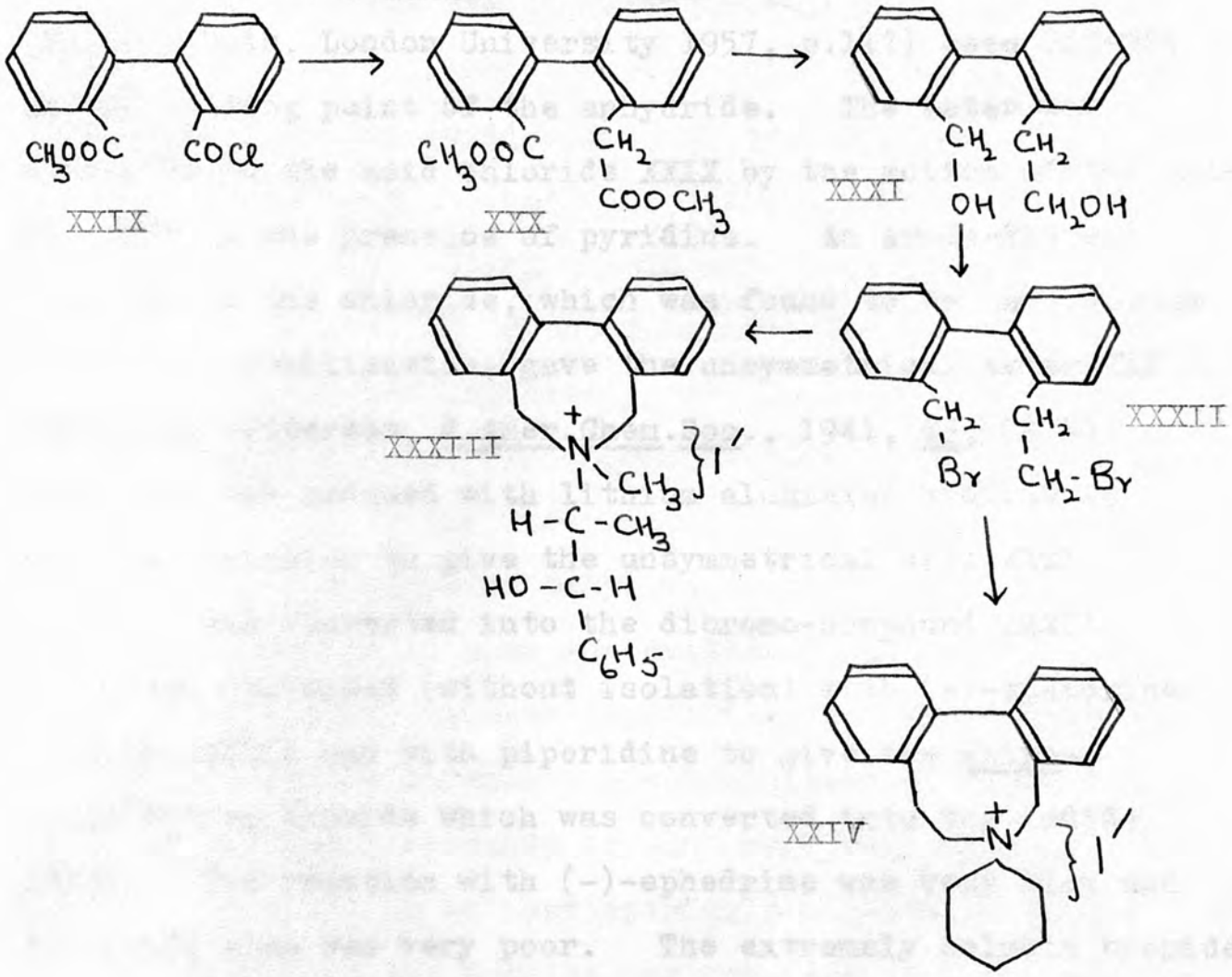
was obtained as a crystalline solid, was hydrolysed with 10% alcoholic potassium hydroxide to give the corresponding dicarboxylic acid XXIV. The latter was decarboxylated at 220° to give the mono-carboxylic acid XXV. The quinine salt of this acid was prepared by mixing equimolecular quantities of anhydrous quinine and the acid in acetone. The crystallisation of the quinine salt from various solvents has failed to show any signs of enantiomorphism so far. Other alkaloids are being tried.

(d) Dibenzazocino compounds:-

The general scheme followed for the synthesis which is as follows, is based on the method used by Kobayashi and Uyeo (J., 1957, 638) for the synthesis of OO-dimethylapogalanthamine:



XXVI XXVII XXVIII



The mono-methyl ester of diphenic acid XXVII was prepared via the anhydride XXVII (Underwood & Kochmann, J.Amer.Chem. Soc. 1924, 46, 2069). The latter gave a higher melting point (225-226°) than that recorded - i.e. 217-218° (Roberts & Johnson, J.Amer.Chem.Soc., 1925, 47, 1396;

Graebe & Aubin, Annalen, 1888, 247, 263). Everitt (Ph.D. Thesis, London University 1957, p.117) gave 223-224° as the melting point of the anhydride. The ester was converted to the acid chloride XXIX by the action of thionyl-chloride in the presence of pyridine. An Arndt-Eistert reaction on the chloride, which was found to be pure enough without crystallisation, gave the unsymmetrical ester XXX (Marvel & Patterson, J.Amer.Chem.Soc., 1941, 63, 2218). The ester was reduced with lithium aluminium hydride in ethereal solution to give the unsymmetrical diol XXXI. The diol was converted into the dibromo-compound XXXII, which was condensed (without isolation) with (-)-ephedrine to give XXXIII and with piperidine to give the spiro-piperidinium bromide which was converted into the iodide XXXIV. The reaction with (-)-ephedrine was very slow and the yield also was very poor. The extremely soluble bromide was converted into the more sparingly soluble iodide for isolation. The iodide XXXIII on crystallisation from ethanol separated into two fractions with $[\alpha]^{20}_{5461}$ - 60° and $[\alpha]^{20}_{5461}$ + 118°. The rotations of these remained unchanged on being heated in ethanol in sealed tubes at 100° for three hours. This showed that the enantiomorphism exhibited by this compound was due to the asymmetric quaternary N, and

not due to the non-coplanar diphenyl configuration.

In the meantime the (+) camphor-sulphonate of the spiro-piperidinium-azocine was prepared. This crystallised out from acetone, acetonitrile, benzene, or a mixture of ethyl acetate and ethanol and had $[\alpha]^{20}_{5461}$ + 26°. The iodide prepared from it by adding a cold saturated solution of potassium iodide at 0° to the solution of (+)-camphor-sulphonate at 0° was inactive. The iodide was therefore converted into (+)-α-bromocamphor-Π-sulphonate. The latter crystallised out as one diastereoisomer from acetonitrile as well as from a mixture of ethyl acetate - ethanol, and showed rapid mutarotation at room temperature in acetone solution. It was difficult to recover the iodide from the (+)-bromo-camphor-sulphonate because the solubilities of these two salts in different solvents at -10° were very similar. The picrate was found to be more sparingly soluble in ethanol at -10°. Therefore the picrate was prepared from (+)-α-bromo-camphor-Π-sulphonate by adding a cold saturated solution of picric acid (-10°) to a solution of the bromocamphor-sulphonate at -10°. The picrate, which separated out after slight trituration, was immediately filtered and dried in a vacuum-desiccator. It was found to be the (-)-isomer with $[\alpha]^{2}_{5461}$ - 54.4° in acetone five minutes after wetting the salt with solvent.

To get the other isomer ammonium-(-)-α-bromocamphor-π-sulphonate was prepared from (-)-camphor (Pope & Read, J., 1910, 97, 2199). The dibenzazocino-(-)-α-bromocamphor-π-sulphonate similarly crystallised out as one diastereoisomer from a mixture of ethyl acetate - ethanol, and showed rapid mutarotation at room temperature in acetone solution. The picrate prepared from it was the (+)-isomer, $[\alpha]^{2}_{5461}$ + 55.2° in acetone 5 minutes after wetting.

The mutarotation of the bromocamphor-sulphonates was studied at 7° (half-life 13.6 min.) and at 15.5° (half-life 3.2 min.). These two enantiomorphs, (-)-base (+)-α-bromocamphor-π-sulphonate and (+)-base (-)-α-bromocamphor-π-sulphonate, have nearly equal $[\alpha]_{initial}$ + 2.29°, and -4.00° respectively (obtained by extrapolation) and $[\alpha]_{final}$ + 64.6° and -65.1° at 15.5°.

The racemisation of the picrates was studied at 2°, 10°, 16° and 23° in acetone by direct observation through a polarimeter tube round which water at the suitable temperature was circulated. These experiments give an activation energy E = 22.0 k.cal.mol.$^{-1}$, and the value of A as $10^{14.05}$ sec^{-1}. This is the highest value of A so far found among the o-o'-bridged-diphenyls except for Mislow's (loc.cit.) cis acid (XXXI, p.9) which has A = $10^{14.6}$ sec^{-1} in 2.32N sodium hydroxide (E, 25.4 k.cal.mol.$^{-1}$), but only A = $10^{12.5}$ sec^{-1} in absolute ethanol (E, 22.8 k.cal.mol.$^{-1}$). It is possible

that a high value of A is associated with racemisation of a salt in an ionising solvent. Unfortunately it was not possible to test this by studying the picrate in a solvent of a different type, since it was very sparingly soluble in absolute ethanol at low temperatures and insoluble in solvents like benzene. In acetonitrile which has stronger ionising properties than acetone, the rate of racemisation at 2^{o} was found to be the same as in acetone. The value of 22 k.cal.mol.$^{-1}$ for E, and $10^{14.05}$ for A for the dibenzazocino-compound in acetone make it less stable than Mislow's acid (loc.cit.), for which the values of E and A in absolute alcohol and sodium hydroxide are given on the previous page.

EXPERIMENTAL

2-Amino-3-nitrotoluene.

Cohen and Dakin, J., 1901, 79, 1111.

Glacial acetic acid (144 g., 3 mols.) and fuming nitric acid (400 g., 8 mols.) were mixed and cooled to 10° in an ice-bath. Powdered o-acetotoluidide (120 g., 1 mol.) was added in small quantities keeping the temperature at 15°. The reaction mixture was kept stirred mechanically throughout the addition, and for 1½ hr. afterwards, when the temperature was allowed to rise to the room-temperature. The mixture was then poured into 2 litres of crushed ice, the precipitated nitro-acetotoluidines were filtered, washed with cold water and steam-distilled with 320 c.c. of concentrated hydrochloric acid without preheating. 2-Amino-3-nitrotoluene distilled over as orange yellow fine needles. Yield 45-48 g., m.p. 96-98°. After recrystallisation from dilute alcohol the m.p. was 97-98°. The preparation was repeated about 35 times and in all about 1600 g. of 2-amino-3-nitrotoluene were prepared. The compound as obtained by steam-distillation was used without further purification.

2-Iodo-3-nitrotoluene.

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

2-Amino-3-nitrotoluene (45 g., 1 mol.) was dissolved in hot

glacial acetic acid (360 g.) in a 2 litre beaker and the solution cooled to 15° in an ice-bath. Concentrated sulphuric acid (166 c.c.) was cooled to 0°C and sodium nitrite (29.7 g., 1.29 mols.) was added to it cautiously. The temperature rose to 40° during the addition, but the mixture was cooled to 0° again to give a thick sludge. This was added with mechanical stirring to the nitroamine solution, keeping the temperature below 25°. Addition took 0.75 hr., and the mixture was stirred at room-temperature for another ½ hr. The diazo-solution was then poured into 1 litre of crushed ice, and urea (29.7 g., 1.49 mols.) was added to it to destroy the excess of nitrous acid. This reaction took about 1 hr. Potassium iodide (71 g., 1.42 mols., in 360 c.c. of water) was then added to the diazo-solution. The reaction was very vigorous, and a brownish yellow solid started to separate. The reaction mixture was left for several hours, preferably overnight, till the iodo-compound separated out completely to give a clear mother-liquor again. The mixture was decolourised with sodium bisulphite. Solid iodo-compound was filtered off, washed with cold water, then with 10% sodium hydroxide, and then thoroughly with cold water. It was dried in air, and crystallised from aqueous alcohol. Pale yellow cubes, 1st crop, 64 g., m.p. 67.5-69°. Concentration of the mother-liquor gave an additional 4 g., m.p. 65-67°. Yield 81%. Carlin and Foltz (loc.cit.) give

m.p. 66-68° and yield 68%. The preparation was repeated about 30 times and in all about 2100 g. of 2-iodo-3-nitrotoluene were prepared.

2:2'-Dimethyl-6:6'-dinitrodiphenyl.

Carlin and Foltz, (loc.cit.).

2-Iodo-3-nitrotoluene (50 g., 1 mol.) was heated to 140° in a metal bath. Copper bronze (50 g., 4.1 atoms) was slowly added, keeping the temperature at about 150°. On each addition of copper, the temperature rose considerably. Throughout the addition, the mixture was kept well stirred by a stout thermometer which also recorded the reaction temperature. After all the copper had been added, the mixture was heated at 150° for ½ hr., and then at 190-200° for another 15 minutes. It was then cooled to 100°, and extracted with boiling benzene. Most of the benzene was distilled off, and the dinitroditolyl crystallised from benzene and light-petroleum (b.p. 40-60°). 1st crop 19 g., m.p. 110.5-112°, 2nd crop 2 g., m.p. 109-111°. Yield 81%. Carlin and Foltz (loc.cit.) give m.p. 109-110°, yield 79%. The preparation was carried out about 42 times, and in all 880 g. of 2:2'-dimethyl-6:6'-dinitrodiphenyl were prepared.

2:2'-Bisbromomethyl-6:6'-dinitrodiphenyl.

2:2'-Dimethyl-6:6'-dinitrodiphenyl (10.7 g., 1 mol.) was

dissolved in 64 c.c. of dry carbon tetrachloride. N-Bromo-succinimide (14.3 g., 2 mols.) and benzoyl peroxide (0.1 g.) were added. The mixture was heated under reflux in an oil-bath for 5 hr. 0.05 G. more of N-bromosuccinimide were added, washed down with 20 c.c. of dry carbon tetrachloride, and the reaction mixture heated under reflux for another 3 hr. It was then filtered hot through a preheated Buchner funnel, and washed with hot carbon tetrachloride. Some dibromo-compound separated out at this stage along with succinimide. The latter was removed by washing several times with ice-cold water. The filtrate and washings from the original reaction mixture were combined, and concentrated to about 75 c.c. On cooling in ice and scratching with a glass rod, 2:2'-bisbromomethyl-6:6'-dinitrodiphenyl came down as a yellow powder. It was filtered, washed with cold water, combined with the first fraction, and dried in a vacuum desiccator. The crude product weighed about 11 g., m.p, 168-178° with previous softening, (64%). It was crystallised from dry benzene. 1st crop 7 g., m.p. 183-185°. 2nd crop 3.5 g., m.p., 181-183°. After recrystallisation from dry benzene it had m.p. 184-185°. (Found: C, 39.3; H, 2.1; N, 6.2; Br, 37.4. $C_{14}H_{10}O_4N_2Br_2$ requires C, 39.1; H, 2.3; N, 6.5; Br, 37.2%). The preparation was carried out about eight times, and in all 88 g. of 2:2'-bisbromo-methyl-6:6'-dinitrodiphenyl were prepared.

2:7-Dihydro-4':1"-dinitro-3:4-5:6-dibenzazepinium-1-spiro-1"'-piperidinium Iodide.

2:2'-Bisbromomethyl-6:6'-dinitrodiphenyl (8.6 g., 1 mol.) was dissolved in hot dry benzene, the solution cooled to 50° and piperidine (3:3 g., 2.2 mols.) was added to it. The solution became cloudy and a sticky mass started separating immediately. The reaction mixture was kept at 50° for 3½ hr. (it had become clear again), cooled and the benzene poured off; the gummy solid was washed several times with warm benzene, and then triturated with cold water, and crystallised from water, giving 5.6 g. (65%), m.p. 302-303° decomp. The bromide was extremely light-sensitive, and was therefore converted into the iodide by adding saturated potassium iodide solution to the aqueous solution of the bromide, when sparingly soluble iodide separated out. The latter crystallised from water as fine yellow cubes, m.p. 306-308° decomp. (6 g.). (Found: C, 47.4; H, 3.9; N, 8.85; I; 26.8. $C_{19}H_{20}O_4N_3I$ requires C, 47.4; H, 4.2; N, 8.7; I, 26.3%).

2:7-Dihydro-4':1"-dinitro-3:4-5:6-dibenzazepinium-1-spiro-1"'-piperidinium (+)-camphorsulphonate.

The above quaternary iodide (6 g., 1 mol.) and silver (+)-camphorsulphonate (4.2 g., 1 mol.) were separately dissolved in 50% ethanol. The two solutions were mixed and boiled for ½ hr. Precipitated silver iodide was filtered off, and washed with warm alcohol. The filtrate and washing were

evaporated to dryness to give 7.1 g. of the spiro-camphor-sulphonate as a yellow sticky solid. It has failed to crystallise from ethanol, methanol, acetone, chloroform, water or acetonitrile during two years.

2:7-Dihydro-1-(2-hydroxy-1-methyl-2-phenylethyl)-1-methyl-4':1"-dinitro-3:4-5:6-dibenzazepinium Bromide.

(-)-Ephedrine hemihydrate (36 g., 2.3 mols.) was dissolved in benzene with warming and the solution dried overnight over anhydrous sodium sulphate. 2-2'-Bisbromomethyl-6:6'-dinitro-diphenyl (38.7 g., 1 mol.) was dissolved in hot dry benzene, the solution cooled to 50°, and the filtered ephedrine solution added to it. The mixture became cloudy and was warmed at 50° for several hours ($\sim$ 38 hr.). A gummy solid separated, which solidified on trituration with water. It was filtered, washed with warm benzene, then with cold water and dried in a desiccator (30.9 g., 66%). Repeated crystallisations of the quaternary bromide from absolute ethanol gave 12.5 g. of the pure less soluble (-)-diastereoisomer as fine yellow needles, m.p. 248-250° decomp. $[\alpha]^{23}_{5461}$ - 709 ±2°; $[\alpha]^{23}_{5893}$ - 544 ±2° in acetonitrile (C=0.994, l=1). It was not possible to use a two decimeter tube with this concentration because of deep yellow colour of the solution. (Found: C, 56.3; H, 4.6; N, 8.25; Br, 15.6: $C_{24}H_{24}O_5N_3Br$ requires C, 56.0; H, 4.7; N, 8.2; Br, 15.5%).

The more soluble diastereoisomer could not be crystallised from absolute ethanol, so the latter was distilled off under reduced pressure and the residual gum dried in a vacuum desiccator. Three crystallisations from acetonitrile gave the (+)-diastereoisomer as stout yellow needles, m.p. 227-228° (12.7 g.). $[\alpha]^{18}_{5461}$ + 689 ±5°, $[\alpha]^{18}_{5461}$ + 533 ±5° in acetonitrile (C=0.273, l=2). (Found: C, 55.6; H, 4.8; N, 8.1; Br, 15.2%). This diastereoisomer was very sparingly soluble in acetonitrile, so only a dilute solution could be observed polarimetrically.

(-)-2:7-Dihydro-1-methyl-4':1"-dinitro-3:4-5:6-dibenzazepine. (-)-Quaternary bromide (3.9 g., 1 mol.) was dissolved in ethanol and the solution kept hot on a steam-bath. Silver oxide prepared from silver nitrate (1.9 g., 1.5 mols.) and sodium hydroxide (0.39 g., 1.5 mols.) was added to it in small lots over a period of about one hour. The hot reaction mixture was then filtered and the filtrate transferred to a distillation flask. Ethanol, water and most of the β-methylstyrene oxide were removed under reduced pressure from a water-bath. A little more ethanol was then added to the residue and the last traces of the epoxide removed under reduced pressure at 120°. The residue in the flask was then dissolved in ether, and the (-)-amine extracted with dilute hydrochloric acid. The acidic solution was slightly warmed to remove the dissolved ether, cooled again, and the amine precipitated by the addition of

ammonia. It was filtered off, dried, and crystallised from benzene light petroleum (b.p. 60-80°) in yellow needles, (1.5 g., 66%) m.p. 169-170°, $[\alpha]^{19}_{5461}$ - 1343 ±5°, $[\alpha]^{19}_{D}$ - 1030 ±5°, (c=0.197 in benzene l=2) (Found: C, 60.4; H, 4.2; N, 13.8. $C_{15}H_{13}O_4N_3$ requires C, 60.2; H, 4.4; N, 14.05%).

(+)-2:7-Dihydro-1-methyl-4':1"-dinitro-3:4-5:6-dibenzazepine. Hofmann degradation on the (+)-quaternary bromide (2.2 g.) using silver oxide prepared from silver nitrate (1.1 g.) and sodium hydroxide (0.26 g.) gave the (+) tertiary amine (0.8 g., 81%). It crystallised from benzene light petroleum as fine yellow needles, m.p. 169-170°, $[\alpha]^{19}_{5461}$ + 1333 ±2°, $[\alpha]^{19}_{D}$ + 1024 ±2°. (c=0.454 in benzene). (Found: C, 59.8; H, 4.8; N, 14.1%).

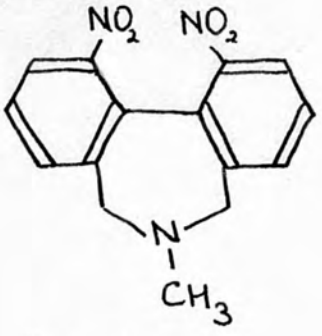
(-)-2:7-Dihydro-1:1-dimethyl-4':1"dinitro-3:4-5:6-dibenz-azepinium Iodide.

(-)-2:7-Dihydro-1-methyl-4':1"-dinitro-3:4-5:6-dibenzazepine (0.5 g.) was dissolved in dry ether. A few drops of methyl iodide were added, and the solution left to stand for a few hours. The yellow salt separated as a fine powder. It was filtered, washed with dry ether, and crystallised from ethanol (0.5 g.), m.p. 252-254° (decomp.).
$[\alpha]^{19}_{5461}$ - 813° in acetone (c 0.089). (Found: C, 43.1; H, 3.7; N, 9.5; I, 29.0: $C_{16}H_{16}O_4N_3I$ requires C, 43.5; H, 3.7; N, 9.5; I, 28.8%).

Racemisation of (+)- and (-)-2:7-dihydro-1-methyl-4':1"-dinitro-3:4-5:6-dibenzazepine.

The (+)-amine (0.198 g.) in benzene solution (100 c.c.) with $\alpha^{18.5}_{5461}$ + 2.64 was sealed in 8 tubes and heated in a thermostat at 125°. Tubes were removed at intervals, then chilled, and the rotations read at 18.5°. During 15.25 hr. the rotation fell to + 1.36°. Heating of the last tube was continued for a few days; the solution was then inactive. The experiment was repeated with (-)-amine at 125°. Similar experiments were done at 145°. Results of these experiments are given in tables I & II.

Table I

Racemisation of (+)  in Benzene.

t = 125°

c = 0.198 l = 1 Zero = 179.02

	Time in hours	Polarimetric Reading	Observed α_{5461}	$\log_{10}\alpha$
1.	0	181.66	2.64	0.4216
2.	0.5	181.60	2.58	0.4116
3.	1.75	181.52	2.50	0.3979
4.	2.75	181.41	2.39	0.3784
5.	4.75	181.21	2.19	0.3404
6.	7.75	180.93	1.91	0.2810
7.	11.25	180.66	1.64	0.2148
8.	15.25	180.38	1.36	0.1335

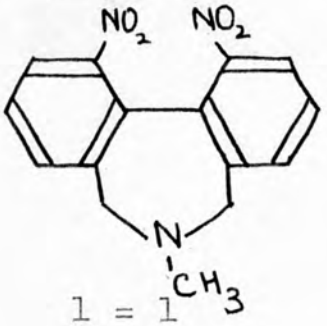
$k = 1.214 \times 10^{-5} sec^{-1}$.

Another similar experiment gave $k = 1.208 \times 10^{-5} sec^{-1}$.

Average value of $k = 1.2 \times 10^{-5} sec^{-1}$

$t_{\frac{1}{2}} = 15.85$ hr.

Table II

Racemisation of (-)  in benzene at 145°

c = 0.096 l = 1 Zero = 179.02

	Time in hours	Polarimetric Reading	Observed α_{5461}	$\log_{10}\alpha$
1.	0	177.70	1.32	0.1206
2.	0.5	177.86	1.16	0.0645
3.	1.0	178.00	1.02	0.0086
4.	1.75	178.18	0.84	$\bar{1}$.9243
5.	3.0	178.43	0.59	$\bar{1}$.7709
6.	4.0	178.57	0.45	$\bar{1}$.6532
7.	5.0	178.68	0.34	$\bar{1}$.5315
8.	6.5	178.79	0.23	$\bar{1}$.3617

$$k = 7.36 \times 10^{-5} sec^{-1}.$$

Another similar experiment gave $k = 7.46 \times 10^{-5} sec^{-1}$

Average value of $k = 7.4 \times 10^{-5} sec^{-1}$.

$$t_{\frac{1}{2}} = 2.6 \text{ hr.}$$

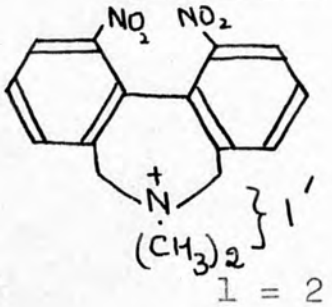
These values give E = 30 k.cal.mol.$^{-1}$ and

$$A = 10^{11.5} sec^{-1}$$

Graph I shows straight line plots of $\log_{10}\alpha$ against time.

Racemisation of (-)-2:7-Dihydro-1:1-dimethyl-4':1"-dinitro-3:4-5:6-dibenzazepinium Iodide was similarly carried out in acetone solution at 145°. The results are given in table III and Graph I.

Table III

Racemisation of  in acetone at 145°.

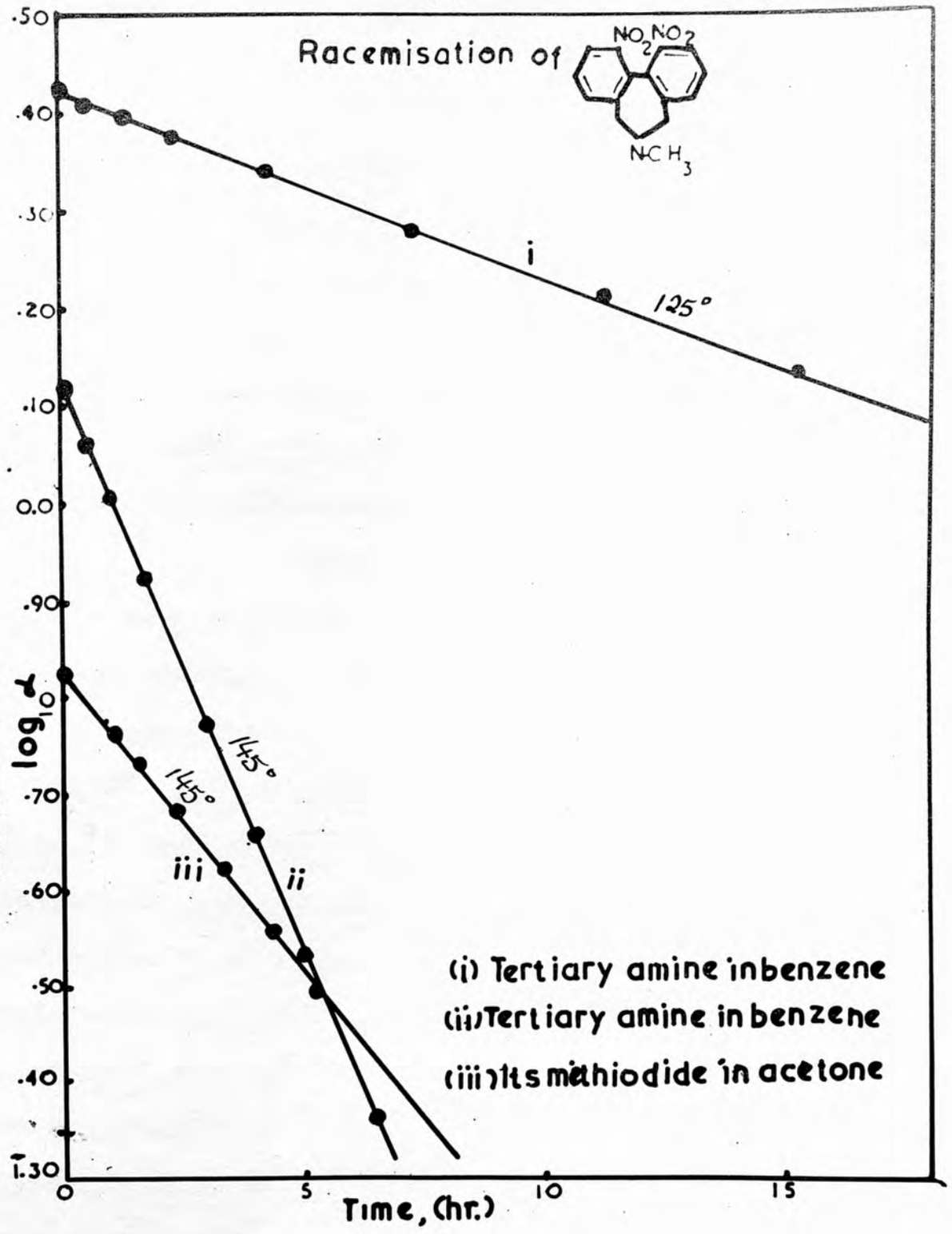
c = 0.0886 $\underline{l}$ = 2 Zero = 179.02

	Time in hours	Polarimetric Reading	Observed α_{5461}	$\log_{10}\alpha$
1.	0	178.35	0.67	$\bar{1}$.8261
2.	1	178.44	0.58	$\bar{1}$.7634
3.	1.5	178.48	0.54	$\bar{1}$.7324
4.	2.25	178.54	0.48	$\bar{1}$.6812
5.	3.25	178.60	0.42	$\bar{1}$.6232
6.	4.25	178.66	0.36	$\bar{1}$.5563
7.	5.25	178.71	0.31	$\bar{1}$.4914

$k = 4.05 \times 10^{-5} sec^{-1}$

$t_{\frac{1}{2}} = 4.75$ hr.

(L)


Racemisation of
NO2 NO2
N-CH3
.50
.40
.30
.20
.10
0.0
.90
.80
.70
.60
.50
.40
1.30
log10
i
125°
145°
145°
ii
iii
(i) Tertiary amine in benzene
(ii) Tertiary amine in benzene
(iii) Its methiodide in acetone
0
5
10
15
Time, (hr.)

2:2'-Dimethyl-6:6'-diaminodiphenyl.

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

2:2'-Dimethyl-6:6'-dinitrodiphenyl (27 g., 1 mol.) was dissolved in hot glacial acetic acid and slowly added to a boiling mixture of stannous chloride (150 g., 6.6 mols.) and concentrated hydrochloric acid (200 c.c., 18 mols.). The reaction was slow in the beginning but tended to be quite vigorous later. After all the dinitroditolyl solution had been added, the reaction mixture was kept slightly below its boiling temperature for 15 minutes. It was then cooled, and added to an excess of 30% sodium hydroxide solution. 2:2'-Dimethyl-6:6'-diaminodiphenyl separated out. It was filtered, washed with water, dried and was crystallised from light petroleum (b.p. 80-100°). 1st crop 16 g., m.p. 133-134°. Concentration of the mother-liquor gave another 2 g. of the amine, m.p. 131-133°. (85%). Kenner and Stubbings (loc.cit.) give the m.p. 136°.

Reduction with zinc and hydrochloric acid and catalytic reduction with platinum oxide in ethanol or glacial acetic acid were also tried but the yields were poorer. In about 40 experiments a total of 520 g. of 2:2'-dimethyl-6:6'-diaminodiphenyl were prepared.

2:2'-Dimethyl-6:6'-difluorodiphenyl.

F.Bell, J., 1934, 836.

2:2'-Dimethyl-6:6'-diaminodiphenyl (27 g., 1 mol.) was dissolved with slight warming in 108 c.c. of concentrated

hydrochloric acid and 270 c.c. of water. The solution was cooled to -10° in freezing mixture. A cooled solution of sodium nitrite (21.4 g., 2.3 mols., in 41 c.c. of water) was slowly added with mechanical stirring till the solution gave a faint test with starch iodide paper. During the addition the temperature was kept between -7° and -10°. The solution turned slightly red and was stirred for another ½ hr at the same temperature. Hydroborofluoric acid (88.5 c.c. of 40%, 3.4 mols.) which was pre-cooled to -10°, was then added to the diazo solution which was kept in the freezing mixture. After some scratching the tetrazoborofluoride crystallised out. It was filtered off, washed with cold alcohol and ether, and dried in a vacuum-desiccator. Yield 43 g., 86 %, decomposition temperature 103-105°. The tetrazoborofluoride was decomposed by introducing it in small lots into a bolt-head round-bottomed flask (2 litre) heated on a steam-bath. White fumed were evolved, and a red-brown residue was left in the flask. The latter was steam distilled. 2:2'-Dimethyl-6:6'-fluorodiphenyl distilled over and solidified in the receiver. It was filtered, dried and crystallised from methanol. Yield 8.5 g., 30%, (37% from tetrazoborofluoride) m.p. 44-45°. Bell (loc.cit.) gave m.p. 45°, yield 17%. In five such experiments a total of 42 g. of difluoroditolyl was prepared.

2:2'-Bisbromomethyl-6:6'-difluorodiphenyl.

Difluoroditolyl (20 g., 1 mol.) was dissolved in 64 c.c. of dry carbon tetrachloride. N-Bromosuccinimide (33 g.) and benzoyl peroxide (0.1 g.) were added to it. The mixture was heated under reflux in an oil-bath for 8 hr. It was filtered hot with suction and the precipitated succinimide was washed twice with warm dry carbon tetrachloride. The filtrate and washings were collected and concentrated to about 1/3 and cooled. Some more succinimide separated, which was filtered off. The filtrate was transferred to a flask and the rest of the solvent distilled off under reduced pressure. The residue was dried in a vacuum desiccator. It failed to solidify on trituration with different solvents and on cooling. It was therefore dissolved in dry benzene and used as such for further condensations. Wenner (J.Org.Chem., 1952, 17, 523) has used much larger amounts (1 - 2 g.) of benzoyl peroxide in the bromination of other halogenoditolyls. In the present work it was found that the use of larger amounts of catalyst with consequent liberation of bromine, did not improve the yield.

2:7-Dihydro-1-(2-hydroxy-1-methyl-2-phenylethyl)-1-methyl-4':1"-difluoro-3:4-5:6-dibenzazepinium Bromide.

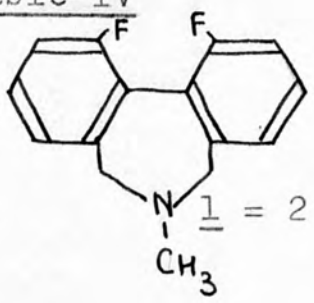
A solution of (-)-ephedrine hemihydrate (33 g. 2.2 mols. calculated on the basis of difluoroditolyl taken) in 350 c.c.

of benzene was dried over anhydrous sodium sulphate. The filtered solution was added to a warm solution of 2:2'-bisbromomethyl-6:6'-difluorodiphenyl in dry benzene. The mixture was kept warm ($\sim 50^{\circ}$) for 10 hr. White needles and a gum separated and the solution turned deep pink in colour. It was filtered hot, washed with warm benzene and then triturated with cold water. Needles (presumably ephedrine hydrobromide) dissolved in water; the gum solidified. The solid was filtered, washed and dried. Crude yield 21 g. (50%). Addition of potassium iodide solution to the filtrate gave 2 g. of the quaternary iodide.

The bromide was crystallised from methylated spirit. The less soluble diastereoisomer came out as fluffy white needles (7.2 g.) It was recrystallised from the same solvent thrice and then it had m.p. 233-234° (decomp). $[\alpha]_{5461}^{18.5}$ + 50.0 ±2.0°, $[\alpha]_{D}^{18.5}$ + 37.5 ±2°. (c = 0.439 in ethanol, l = 2). (Found: C, 62.6; H, 5.3; N, 3.5; Br, 17.2 $C_{24}H_{24}ONBrF_2$ requires C, 62.2; H, 5.25; N, 3.0; Br, 17.4%). The more soluble diastereoisomer was obtained as beautiful hydrated cubes on dilution of the mother liquor with water (6.6 g.). It was purified by crystallisation from the same solvent, m.p. 230-232°(decomp.). $[\alpha]_{5461}^{18.5}$ - 55 ±2°, $[\alpha]_{D}^{18.5}$ - 41 ±2° (c 0.509 in ethanol, l = 2). (Found: C, 60.6; H, 5.5; N, 2.9; Br, 16.6. $C_{24}H_{24}ONBrF_2 \cdot H_2O$ requires C, 60.3; H, 5.5; N, 2.9; Br, 16.7%)

(+)-4':1"-Difluoro-1-methyl-2:7-dihydro-3:4-5:6-dibenzazepin. (+) Quaternary bromide, $[\alpha]^{18.5}_{5461}$ + 50° (1g., 1 mol.) was dissolved in ethanol. Silver oxide (prepared from 0.5 g., 1.5 mol. of silver nitrate) was added in small lots in water to the bromide solution kept hot (~ 70°) on a water bath. Addition took fifteen minutes and the solution was kept hot for another ½ hr. It was then filtered through an ordinary funnel and the precipitate washed with a little warm alcohol. The filtrate and washings were immediately cooled in ice, and then transferred to a flask. Alcohol, water and most of the epoxide were removed at about 70° under reduced pressure. The residue in the flask was dissolved in 10% hydrochloric acid, and washed with ether, till the ether when examined in the polarimeter tube was inactive. Air was bubbled through the acidic solution to remove any dissolved ether and the solution was then examined in the polarimeter tube; it had $\alpha^{18.5}_{5461}$ + 0.79° (c, 0.877 as hydrochloride was determined by evaporating the solution after the readings were taken, l = 2), $[\alpha]^{18.5}_{5461}$ - 45 ±1°. The solution was then poured into a jacketed polarimeter tube round which water at 80° was circulated. The readings were taken at suitable intervals. The experiment was repeated at 80° and also at 91°. The results of these experiments are given in table IV and V and graph II.

Table IV

Racemisation of (-)  in 10% hydrochloric acid at 80°

Zero = 179.02 l = 2

	Time in hours	Polarimetric Reading	Observed α_{5461}	$\log_{10}\alpha$
1.	0	178.60	0.42	$\bar{1}.6232$
2.	1	178.64	0.38	$\bar{1}.5798$
3.	2	178.68	00.34	$\bar{1}.5315$
4.	3.5	178.73	0.29	$\bar{1}.4624$
5.	5.5	178.785	0.235	$\bar{1}.3711$

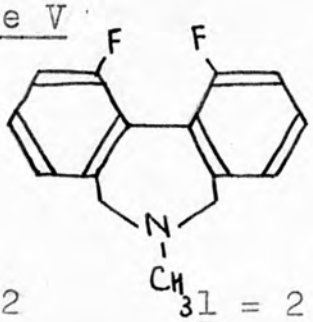
$$k = 2.95 \times 10^{-5} sec^{-1}$$

Another similar experiment gave $k = 2.945 \times 10^{-5} sec^{-1}$

Average value of $k = 2.95 \times 10^{-5} sec^{-1}$

$$t_{\frac{1}{2}} = 6.5 \text{ hr.}$$

Table V

Racemisation of (-)  in 10% hydrochloric acid at 91°

Zero = 179.02 1 = 2

	Time in hours	Polarimetric Reading	Observed α_{5461}	$\log_{10}\alpha$
1.	0	178.67	0.35	$\bar{1}.5441$
2.	0.5	178.72	0.30	$\bar{1}.4771$
3.	1	178.77	0.25	1.3979
4.	2	178.84	0.18	$\bar{1}.2553$
5.	3	178.89	0.13	$\bar{1}.1139$
6.	4	178.93	0.09	$\bar{2}.9542$
7.	5.5	178.97	0.05	$\bar{2}.6990$

$$k = 9.72 \times 10^{-5} sec^{-1}$$

Another experiment gave $k = 9.75 \times 10^{-5} sec^{-1}$.

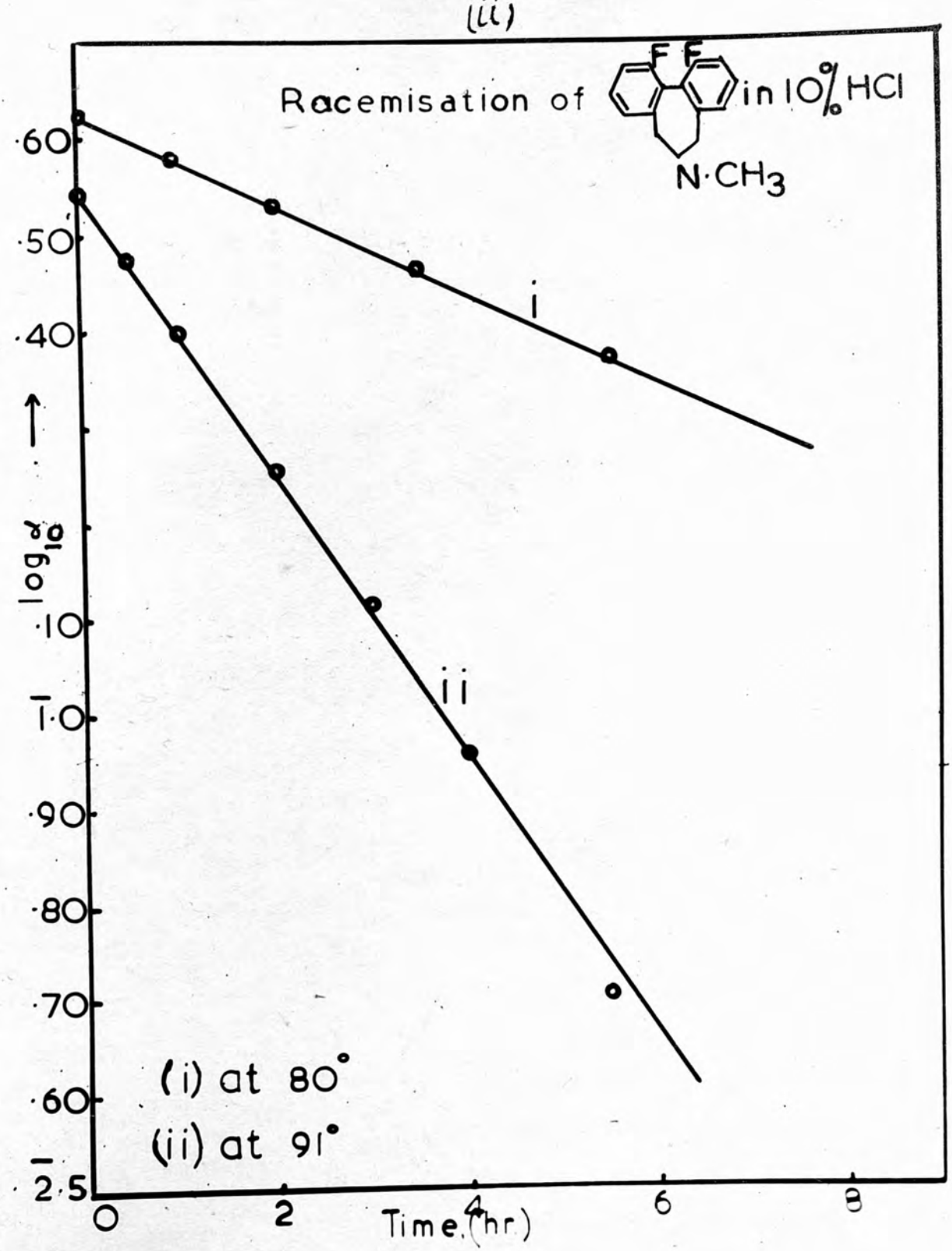
Average value of $k = 9.75 \times 10^{-5} sec^{-1}$.

$$t_{\frac{1}{2}} = 2.0 \text{ hr.}$$

From these values $E = 27.8$ k.cal.mol.$^{-1}$

and $A = 10^{12.7} sec^{-1}$.

(ii)


Racemisation of
F
F
in 10% HCl
N·CH3
·60
·50
·40
·10
1·0
·90
·80
·70
·60
2·5
log10 α
i
ii
(i) at 80°
(ii) at 91°
0
2
4
6
8
Time (hr)

(-)4':1"-Difluoro-2:7-dihydro-1-methyl-3:4-5:6-dibenzazepine.
This was similarly obtained by Hofmann degradation of the (-)-quaternary bromide (1 g.) using silver oxide prepared from silver nitrate (0.5 g.). When examined in the polarimeter it had $\alpha^{18.5}_{5461}$ - 0.47° (c = 0.566 as hydrochloride in 10% HCl) $[\alpha]^{18.5}_{5461}$ - 41.5 ±1°.

(±)-4':1"-Difluoro-2:7-dihydro-1:1-dimethyl-3:4-5:6-dibenzazepinium Iodide.
This was prepared by making the (±)-amine hydrochloride solution alkaline, extracting it with ether, drying the ethereal extract, and adding a few drops of methyl iodide to it. The methiodide which separated out, crystallised from absolute alcohol as fine prisms m.p. 253-254° decomp. (Found: ionic I, 32.7; $C_{16}H_{16}NIF_2$ requires, I, 32.8%).

2:7-Dihydro-4':1"-difluoro-3:4-5:6-dibenzazepinium-1-spiro-1"'-piperidinium Bromide.
2:2'-Dimethyl-6:6'-difluorodiphenyl (4.36 g., 1 mol.) was converted to the dibromo-compound as before, and the latter dissolved in 50 c.c. of hot dry benzene. Piperidine (4.5 c.c., 2.2 mols.) was added, and the mixture which became cloudy, was warmed on a water-bath for 3½ hr. A white solid separated and the solution became clear again. The solid was filtered off and washed several times with warm benzene. Since the quaternary bromide was found to be

extremely soluble in water it was converted into the iodide by adding saturated potassium iodide solution to its aqueous solution, when the less soluble quaternary iodide was precipitated. It was filtered, washed several times with cold water, and crystallised from water. White shining flakes. Yield 5.2 g. (60%) m.p. 268-270° decomp. (Found: C, 53.3; H, 4.3; N, 3.0; I, 29.35; $C_{19}H_{20}NIF_2$ requires C, 53.4; H, 4.7; N, 3.3; I, 29.7%).

The bromide was prepared again from the iodide by shaking a solution of the iodide in dilute alcohol with excess of freshly prepared silver bromide for ½ hr. The filtrate then did not give any test for iodine. Precipitated silver halides were then filtered off, the solution was evaporated to dryness under reduced pressure, and the residue dried in a vacuum-desiccator. It was then crystallised thrice from a mixture of ethylacetate-ethanol, m.p. 234-235° (Found: C, 55.2; H, 6.1; N, 3.4; Br, 19.8: $C_{19}H_{20}NBrF_2.2H_2O$ requires C, 54.8; H, 5.8; N, 3.4; Br, 19.2%). Mislow's (J.Amer.Chem.Soc., 1958, 80, 480) method of removing piperidine hydrobromide by the addition of concentrated solution of potassium hydroxide was also tried, but it was found also partly to convert the quaternary bromide into the hydroxide.

Note: Spectra of this & related compounds are discussed in Part II.

2:2'-Dimethyl-6:6'-dichlorodiphenyl.

2:2'-Dimethyl-6:6'-diaminodiphenyl (9 g., 1 mol.) was dissolved in 240 c.c. of 10% hydrochloric acid, and diazotised with sodium nitrite (6.2 g., 2 mols.) at -10° to -7°. The mixture was mechanically stirred during the addition of sodium nitrite which took about 1 hr., and the stirring was continued at this temperature for another ½ hr. The diazo solution gave a faint test with starch iodide paper then. It was then added to freshly prepared cuprous chloride (prepared from 21.2 g. of $CuSO_4.5H_2O$ and 10.1 g. of NaCl in 240 c.c. of water to give 2 mols. of CuCl) dissolved in 20 c.c. of concentrated hydrochloric acid in small quantities. The reaction mixture was left overnight at room temperature, warmed for ½ hr at 90° on a water bath, and then steam-distilled. The white solid which came over rather slowly was filtered, taken up in ether, washed with sodium hydroxide, then with water, and dried over anhydrous sodium sulphate. Ether was evaporated off, and the residue crystallised twice from dilute ethanol. White prisms, m.p. 119°, Yield 2.5 g. 25%. A.Angeletti (Att X.congr.inter.chim., 1939, 3, 26; CA., 1940, 34, 1008) obtained this compound from 6-chloro-6'-amino-2:2'-ditolyl, m.p. 119°. Mislow, et.al., (J.Amer. Chem.Soc., 1958, 80, 476) also prepared this compound from 2:2'-dimethyl-6:6'-diaminodiphenyl, m.p. 117-119°.

4'-1"-Dichloro-2:7-dihydro-3:4-5:6-dibenzazepinium-1-spiro-1"'-piperidinium Bromide.

2:2'-Dimethyl-6:6'-dichlorodiphenyl (2.5 g., 1 mol.) was dissolved in 32 c.c. of dry carbon tetrachloride, converted into the dibromo-compound by heating under reflux with N-bromosuccinimide (3.3 g., 2 mols.) and benzoyl peroxide (0.1 g.) for 9 hr. and worked up as in the case of the 2:2'-bisbromomethyl-6:6'-difluorodiphenyl. After the removal of carbon tetrachloride, the dibromo-compound was taken up in 50 c.c. of dry benzene, piperidine (2 c.c., ca. 2.2 mols.) was added, and the solution warmed for 4 hr. at 50°. The gum which separated was washed with warm benzene and triturated with water in which it proved to be too soluble. It was therefore converted into the iodide by the addition of a saturated solution of potassium iodide. The latter precipitated 2.5 g. (54%) of the quaternary iodide. Three crystallisations from very dilute alcohol gave stout needles m.p. 283-284° decomp. (Found: C, 49.3; H, 4.6; N, 3.25; Cl & I, 43.2; $C_{19}H_{20}NCl_2I$ requires C, 49.6; H, 4.4; N, 3.0; Cl & I, 43.0%). The bromide was prepared from the iodide as in the case of the difluoro-compound and crystallised thrice from ethyl acetate - ethanol mixture, m.p. 287-288° decomp. (Found: C, 50.5; H, 5.4; N, 3.5; Hal, 32.9; $C_{19}H_{20}NBrCl_2.2H_2O$ requires C, 50.8; H, 5·4; N, 3.1; Hal, 33.5%).

2:2'-Dimethyl-6:6'-dibromodiphenyl.

2:2'-Dimethyl-6:6'-diaminodiphenyl (9 g., 1 mol.) was dissolved in 240 c.c. of 10% hydrobromic acid, and diazotised with sodium nitrite (6 g., 2 mols., in 30 c.c. of water) as before. The diazo-solution was added to freshly prepared cuprous bromide ($CuSO_4.5H_2O$, 20.2 g., NaBr, 10.1 g., in 250 c.c. of water to give 2 mols. of CuBr) dissolved in 30 c.c. of concentrated (48%) hydrobromic acid in small amounts, and the mixture was left overnight at room temperature. It was then warmed at 90° for ½ hr on a water bath and steam-distilled. The white solid which came over slowly was filtered, dissolved in ether, and the ethereal solution washed with 10% sodium hydroxide solution, with water and then dried over anhydrous sodium sulphate. Ether was evaporated off and the residue crystallised twice from dilute alcohol, white needles, m.p. 109-110°, 3.5 g. (24%). F.Bell and Dinsmore (J. 1950, 3611) give m.p. 108-110°, yield 1%. Angeletti and Migliardi (Gazz.chim.ital., 1935, 65, 819) got this compound from 2:2'-dimethyl-6-amino-6'-bromodiphenyl in this and other papers, m.p. 108-110°.

4':1"-Dibromo-2:7-dihydro-3:4-5:6-dibenzazepinium-1-spiro-1"'-piperidinium Bromide.

2:2'-Dimethyl-6:6'-dibromodiphenyl (2.5 g., 1 mol.) was dissolved in 32 c.c. of dry carbon tetrachloride, converted

into the dibromo-compound by heating under reflux with N-bromosuccinimide (2.41 g., 2 mols.) and benzoyl peroxide (0.1 g.), and worked up as before. After removing carbon tetrachloride under reduced pressure, and drying the residue in a vacuum desiccator, the residue was dissolved in dry benzene. Piperidine (2.5 c.c., ca. 2.2 mols.) was added, and the solution warmed at 50° for 4 hr. The gum which separated out was washed with warm benzene and then triturated with water. It proved too soluble in water to be isolated and was therefore converted into the less soluble iodide, 2.3 g., (57%). The latter was crystallised four times from dilute alcohol, stout needles, m.p. 304-305° decomp. (Found: C, 42.1; H, 3.7; N, 2.3; Br & I, 51.85; $C_{19}H_{20}NBr_2I$ requires C, 41.5; H, 3.7; N, 2.55; Br & I, 52.25%). The bromide was prepared from the iodide as in the case of the difluoro-compound, and crystallised thrice from ethyl acetate - ethanol mixture, m.p. 272-273° decomp. (Found: C, 42.3; H, 4.8; Br, 44.5; $C_{19}H_{20}NBr_3.2H_2O$ requires C, 42.4; H, 4.5; Br, 44.55%).

2:2'-Dimethyl-6:6'-diiododiphenyl.

2:2'-Dimethyl-6:6'-diaminodiphenyl (10.6 g., 1 mol.) was dissolved in dilute sulphuric acid (25 c.c. in 250 c.c. of water) and diazotised with sodium nitrite (7.25 g., 2.1 mols. in 30 c.c. of water) as before. The diazo-solution was

added to a cold solution of potassium iodide (24.9 g., 3 mols. in 1 litre of water), stirred and kept at room temperature for 24 hr. It was then warmed on the water-bath for ½ hr. The brown solid which separated was filtered and extracted with ether. The ethereal solution was washed successively with dilute sodium hydroxide solution, water, dilute hydrochloric acid and with water again. Ether was distilled off and the residue steam-distilled using superheated steam. Diiododitolyl came over very slowly and solidified in the receiver. It was filtered and after two crystallisations from dilute alcohol gave pale needles, m.p. 92-93°, yield 2.2 g. (10%). Angeletti (Gazz.chim.ital. 1933, 63, 145; C.A. 1933, 27, 3467); Bell (J., 1934, 836); Lothrop (J.Amer.Chem.Soc., 1942, 68, 1698) also prepared this compound. Bell gives melting point 84°, yield 10% for the active compound.

2:7-Dihydro-4':1"-diiodo-3:4-5:6-dibenzazepinium-1-spiro-1"'-piperidinium Bromide.

2:2'-Dimethyl-6:6'-diiododiphenyl (1.82 g., 1 mol.) was dissolved in 25 c.c. of dry carbon tetrachloride, converted into the dibromo-compound by heating under reflux with N-bromosuccinimide (1.5 g., 2 mols.) and benzoyl peroxide (0.05 g.), and worked up as before. Carbon tetrachloride was then removed under reduced pressure; the residue was

dried in a vacuum desiccator and then triturated with dry light petroleum but it failed to solidify. It became hard when kept in dry ice but became gummy again on warming up. It was therefore taken up in dry benzene, 1 c.c. of piperidine was added, and the solution was warmed (ca. 50°) on a water bath for 4 hr. A gum separated out and was washed with warm benzene and then triturated with water. The quaternary bromide was found to be too soluble in water to be easily isolated. It was therefore converted into the iodide, 1.5 g. (55%). The quaternary iodide was crystallised four times from 50% ethanol, m.p. 315-317° decomp. (Found: C, 35.3; H, 3.1; N, 2.4; I, 59.2; $C_{19}H_{20}NI_3$ requires C, 35.5; H, 3.1; N, 2.2; I, 59.3%). The bromide was prepared as in previous cases. It was crystallised thrice from a mixture of ethyl acetate - ethanol, m.p. 300-301° decomp. (Found: C, 36.5; H, 3.7; Hal, 52.2; $C_{19}H_{20}NBrI_2 \cdot 2H_2O$ requires C, 36.1; H, 3.8; Hal, 52.8%).

Diethyl 4':1"-difluoro-3:4-5:6-dibenzocyclohepta-3:5-diene-1:1-dicarboxylate.

2:2'-Dimethyl-6:6'-difluorodiphenyl (8.72 g., 1 mol.) was dissolved in dry carbon tetrachloride and converted into the dibromo-compound by heating under reflux with N-bromosuccinimide (14.32 g., 1 mol.) and benzoyl peroxide (0.1 g.). After removal of carbon tetrachloride, the residue was dissolved

in ether, and the ethereal solution was washed five times with ice cold water to remove last traces of succinimide. It was then dried overnight over anhydrous sodium sulphate. Absolute alcohol was prepared by heating under reflux for 1 hr. ordinary absolute alcohol (300 c.c.) with diethyl phthalate (27 c.c.) and sodium (3 g.) which was added slowly to the cold alcohol, before refluxing was started. After one hour alcohol was distilled into a dry marked dropping funnel.

All apparatus (a three necked flask fitted with a stirrer, a double surface condenser with a $CaCl_2$ tube and dropping funnel) was dried thoroughly. Alcohol (25 c.c.) was run into the flask, stirring was started and sodium (1.84 g., 2 atoms) was added in small bits till it all dissolved. A little more alcohol was added (10 c.c.). Ethyl malonate (6.398 g., $\sim$6.1 c.c., 1 mol.) was added and washed in with a little more alcohol. The dibromide in ether was then slowly added and washed in with a little more dry ether. The solution started getting cloudy. It was heated under reflux at about 35° for 1 hour on a heating mantle, ether was mostly distilled off, and the mixture refluxed for another hour at 80°. The solution became neutral at this stage. Most of the alcohol was then distilled off, and water added to the residue to dissolve inorganic matter. A crystalline solid separated. It was

filtered off and crystallised from ethanol, 4.5 g., 21%. m.p. 140-144°. After two more crystallisations from the same solvent the m.p. was 146-147°. (Found: C, 67.5; H, 5.6; $C_{21}H_{20}O_4F_2$ requires: C, 67.3; H, 5.4%).

4':1"-Difluoro-3:4-5:6-dibenzocyclohepta-3:5-diene-1:1-dicarboxylic Acid.

The ester (3.5 g.) was heated under reflux with 10% alcoholic potassium hydroxide (100 c.c.) for 6 hr. On cooling a solid separated out, water was added and the solid dissolved completely. On acidifying with dilute hydrochloric acid, a crystalline solid separated. This was filtered and crystallised from aqueous alcohol, m.p. 204-206° decomp. On recrystallisation from the same solvent, the m.p. was 206-207°. (Found: C, 63.8; H, 4.0; $C_{17}H_{12}F_2O_4$ requires C, 64.15; H, 3.8%).

4':1"-Difluoro-3:4-5:6-dibenzocyclohepta-3:5-diene-1-carboxylic acid.

The dicarboxylic acid (2 g.) was heated in an oil bath kept at 220°, till the evolution of carbon dioxide stopped. The residue was then cooled and crystallised from aqueous alcohol in fine needles 1.5 g., m.p. 193°. The melting point remained unchanged on further crystallisation. (Found: C, 69.8; H, 4.7; $C_{16}H_{12}F_2O_2$ requires: C, 70.1; H, 4.4%).

Anhydrous Quinine.- was prepared by dissolving quinine (10 g.) in 200 c.c. of chloroform with slight warming, and drying the solution over anhydrous sodium sulphate. The solution was then filtered, most of the solvent distilled off, and the residue dried in a vacuum desiccator over paraffin wax. It had $[\alpha]_D^{15}$ - 158 in absolute alcohol (c=2.008, l=2); Rabe, (Annalen, 1910, 1373, 85).

Quinine Salt of 4':1"-Difluoro-3:4-5:6-dibenzocyclohepta-3:5-diene-1-carboxylic Acid.

Anhydrous quinine (0.9642 g., 1 mol.) and the acid (0.8156 g., 1 mol.) were dissolved in 75 c.c. of AR acetone. The solution was boiled and most of the solvent evaporated off, bringing the volume to about 25 c.c. Over a period of a few days fluffy needles of the salt separated out. (1.15 g.), m.p. 125°-130° with previous softening, $[\alpha]_{5461}^{24}$ - 104 ±4° in chloroform (c = 0.28, l = 2). On concentrating the mother liquor, and adding small amount of light petroleum to it another 0.5 g. of the salt separated out, m.p. 123-128°, $[\alpha]_{5461}^{24}$ - 103 ±4° in chloroform (c = 0.277, l = 2). The rotation of the quinine salt did not change on crystallisation from ethanol, methanol, a mixture of ethanol and ether or a mixture of acetone and petroleum ether. Acid prepared from it by addition of formic acid to the salt in cold was inactive. A sample of the quinine salt was crystallised twice from acetone, and dried in a pistol for analysis; it then had m.p.

128-130°. (Found: C, 70.7; H, 6.5; N, 5.0; $C_{36}H_{36}O_4N_2F_2 \cdot \frac{1}{2}H_2O$ requires C, 71.1; H, 6.1; N, 4.6%).

Diphenic anhydride.

Diphenic acid (107.5 g.) and acetic anhydride (300 c.c.) were heated under reflux for 4 hr. in an oil bath; a little more (10 c.c.) of acetic anhydride was added after 3 hr. because the whole of diphenic acid did not dissolve. The reaction mixture was cooled and diphenic anhydride separated out in shiny flakes; it was filtered with suction, washed with glacial acetic acid and then with light petroleum (b.p. 40-60°). It was dried in a vacuum desiccator m.p. 225-226°. Yield 94.5 g. (99.5%).
Other workers (Roberts & Johnson, J.Amer.Chem.Soc., 1925, 47, 1396; Oyster & Adkins, ibid., 1921, 43, 208; Graebe & Adkins, Annalen, 1888, 247, 263) have used a smaller proportion of acetic anhydride, and heated the reaction mixture only for 1 hr. The yield in their case was about 92% and m.p. 212°, 217-218°. Everitt, (Ph.D. Thesis, London University 1957) gives the melting point of the anhydride as 223-224°.

Monomethyl Ester of Diphenic acid.

Underwood and Kochmann (J.Amer.Chem.Soc., 1924, 46, 2069) Diphenic anhydride (94.5 g.) and absolute methyl alcohol (500 c.c.) were heated together on a water-bath for 6 hr. Excess of methyl alcohol was distilled off, and the residue crystallised from methyl alcohol, white crystals m.p.

106-108°. Yield 110.5 g., 84%.

Acid chloride of monomethyl diphenate.

Marvel and Patterson (J.Amer.Chem.Soc., 1941, 63, 2218). Monomethyl diphenate (110 g.) was dissolved in 460 c.c. of dry benzene in a 1 litre flask fitted with a condenser and a $CaCl_2$ tube. Thionyl chloride (38 c.c., redistilled) and pyridine (3 c.c.) were added. The flask was warmed on a water bath at 45-50° for 40 minutes. Benzene was removed under reduced pressure at 60-65°. An additional 15 c.c. of dry benzene was added to the residue and this also was removed under reduced pressure. The oily residue was dissolved in hot benzene, and filtered; the filtrate was concentrated to about 45 c.c. and cooled. Light petroleum (b.p. 40-60°) was then added precipitating an oily product, which crystallised on vigorous scratching for sometime. The white solid acid chloride was filtered, washed well with light petroleum, and dried in a vacuum desiccator. m.p. 63-64°, Yield 100 g., 85%. Marvel and Patterson (loc.cit.) give m.p. 63-64°, yield 93%.

2-Carbomethoxymethyl-2'-carbomethoxy Diphenyl

Marvel and Patterson (loc.cit.); (Diazomethane was prepared according to the method of de Boer and Backer, Rec.Trav.chim., 1954, 73, 229). Alcoholic potassium hydroxide (20 g. of

potassium hydroxide in 30 c.c. of water and 100 c.c. of 95% ethanol) was placed in a 500 c.c. round-bottomed flask fitted with two way adapter for a double surface condenser and a drop funnel. The condenser on the other side was connected to two 500 c.c. conical flasks cooled in ice and salt mixture, the second one containing about 50 c.c. of ether. All the ground glass joints were covered with polytetrafluoroethylene sleeves. The reaction flask was heated on a waterbath kept at 60-65°. N-Methyl-p-toluenesulphonylnitrosamide (84 g.) was dissolved in 500 c.c. of dry ether, and this ethereal solution slowly added to alcoholic potassium hydroxide in about 3 hr. Diazomethane in ether slowly distilled over. After the whole of nitrosamide was added residual diazomethane was distilled over by adding dry ether to the reaction flask through the dropping funnel, till the distillate was colourless, this gave between 11.6-12.2 g. of diazomethane. The acid chloride of monomethyl diphenate (40 g.) was dissolved in 275 c.c. of dry ether. This solution was added to the ethereal solution of diazomethane in a 3 litre conical flask kept in freezing mixture. Nitrogen was evolved and the solution became deep yellow in colour. It was kept in ice for 1 hr. and then at room-temperature overnight (in a fume cupboard with a fan on). Next morning ether was distilled off at 30-35° under reduced pressure using a water pump; the residual thick viscous liquid, the diazo-ketone, was dissolved in 400 c.c. of methanol and warmed to ca. 50° on a water bath in a 1 litre

round bottomed flask. A thermometer was kept in the flask. Silver oxide prepared from 12.3 g. of silver nitrate and 2.9 g. of sodium hydroxide, was added in small quantities over ½ hr. at 5 minute intervals. Evolution of nitrogen and the brisk reaction stopped after 2/3 of the silver oxide had been added. The reaction mixture was heated under reflux with charcoal for 5 hr. and filtered. Most of the methanol was distilled off and the residue was crystallised from methanol, m.p. 68-69°. After recrystallisation from aqueous methanol it had m.p. 71-72°. Yield 28 g. (66%). This substance crystallised from dilute methanol in two forms: thin slender needles, and stout hexagonal prisms; both had the same melting points when studied on Kopfler's heating stage and the same mixed melting point.

The experiment was repeated twice and in all 100 g of the acid chloride gave 70 g. of the unsymmetrical ester.

2'-Hydroxymethyl-2-β-hydroxyethyldiphenyl.

2-carbomethoxymethyl-2'-carbomethoxydiphenyl (40 g., 1 mol.) was dissolved in 200 c.c. of dry ether. Lithium aluminium hydride (8.5 g., 1.6 mols.) was suspended in 300 c.c. of dry ether in a 1 litre round bottomed flask, which was fitted with a double surface condenser with a $CaCl_2$ tube, and a dropping funnel. Ester solution was slowly dropped into the flask at such a rate to keep the ether gently refluxing. After the addition, a pinch of lithium aluminium hydride was added to ensure that all the ester had been reduced. Excess lithium

aluminium hydride was then decomposed by adding first wet ether and then water. A sludge of aluminates was formed. Dilute sulphuric acid (5%) was added until the reaction mixture was acidic. The upper ethereal layer was separated from the aqueous layer, the latter was extracted with ether, the ethereal layer and extracts were combined, washed with water, and dried over sodium sulphate. Ether was distilled off, and the diol crystallised from benzene m.p. 103.5-104°. Yield 31.5 g., 98%. (Found: C, 79.1; H, 7.0; $C_{15}H_{16}O_2$ requires C, 78.9, H, 7.1%). Another experiment was done with 29 g. of the ester. In all 50 g. of the diol were prepared.

1:2:7:8-Tetrahydro-3:4-5:6-dibenzazocino-1-spiro-1'-piperidinium Iodide.

2-Hydroxymethyl-2'-β-hydroxyethyldiphenyl (12 g.) was heated with hydrobromic acid (48%, 570 c.c.) for ½ hr. at 126°. Hydrobromic acid was then decanted off, and a fresh lot of 570 c.c. added. The mixture was heated for another ½ hr. It was poured into a beaker and allowed to cool. An oily substance separated which did not solidify. It was dissolved in benzene and the solution dried over anhydrous sodium sulphate. To the dried benzene solution of dibromo-compound, piperidine (13 c.c.) was added and the solution warmed at about 50° for 6½ hr. White needles separated and were filtered off and washed with warm benzene. The quaternary bromide was

found to be extremely soluble in cold water and the precipitate was therefore dissolved in cold water and a saturated solution of potassium iodide was added. A white solid precipitated. This was filtered and crystallised from water. Yield 7.5 g. (36%), m.p. 248° decomp. (Found: C, 59.3; H, 6.5; N, 3.05; I,31.5; $C_{20}H_{24}NI$ requires C, 59.1; H, 6.0; N, 3.45; I, 32.0%). Attempts to prepare the dibromo-compound by the reaction of the diol with phosphorostribromide at 0°, gave only a paste of organic matter with phosphates, from which it was found difficult to work up the dibromo-compound.

Silver (+)-camphorsulphonate.

Freshly prepared silver oxide (1.2 mols.) was added to an aqueous solution of (+)-camphorsulphonic acid (1 mol.) which was kept warm for ½ hr. The excess of silver oxide was then filtered off, and the filtrate evaporated to dryness on a water-bath. The residue was dissolved in minimum amount of hot distilled water and filtered to remove precipitated silver. The filtrate was evaporated to dryness again, the residue dried in a vacuum desiccator and used as such.

1:2:7:8-Tetrahydro-3:4-5:6-dibenzazocino-1-spiro-1'-piperidinium-(+)-camphorsulphonate.

The quaternary iodide (7 g., 1 mol.) and silver (+)-camphor sulphonate (5.86 g., 1 mol.) were dissolved separately in 50% alcohol; the solutions were mixed and heated for ½ hr.

Precipitated silver iodide was filtered off, and the filtrate was evaporated to dryness on a water bath. The residue was dried in a vacuum desiccator and crystallised from ethyl acetate-ethanol mixture giving the salt, with m.p. 225-226°, on recrystallisation, $[\alpha]^{20}_{5461}$ + 27.8 ±1.5° in ethanol (c = 0.718, l=2). (Found: C, 70.2; H, 7.7; N, 2.7; $C_{30}H_{39}NO_4S$ requires, C, 70.7; H, 7.7; N, 2.75%). Various solvents such as acetone, acetonitrile, benzene and chloroform were tried but the salt did not show any change in rotation. It was found to be too soluble in methanol, ethanol and water.

A solution of the(+)-camphorsulphonate was prepared in water at 0°, and a saturated solution of potassium iodide at 0° was added to it. Precipitated quaternary iodide was quickly filtered off in a precooled Buchner funnel and dried in a vacuum desiccator. It was dissolved in ethanol at 0°, and observed in a polarimeter tube. It was found to be optically inactive.

1:2:7:8-Tetrahydro-3:4-5:6-dibenzazocino-1-spiro-1'-piperidinium (+)-α-bromocamphor-Λ-sulphonate.

The quaternary iodide (2.975 g., 1 mol.) and silver α-bromo-camphor-Λ-sulphonate (3.07 g., 1 mol.) were dissolved separately in dilute alcohol; the solutions were mixed and warmed for ½ hr. Silver iodide separated and was filtered off with suction and washed with several portions of warm alcohol.

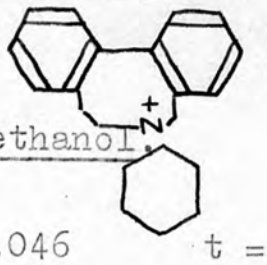
The filtrate and washings were collected and evaporated on a water bath to give a glassy residue (4.2 g.) of the bromo-camphorsulphonate, which was dried in a vacuum desiccator and then dissolved in a mixture of ethyl acetate and ethanol. It was too soluble in the latter alone. Over a period of a few weeks 3.5 g. crystallised out; the mother liquor was concentrated to give another 0.5 g. all as one isomer. A sample for analysis was crystallised twice again, and dried in a drying pistol for 1 hr. m.p. 201°, (Found: C, 60.55; H, 6.3; N, 2.5; S, 5.3; Br, 13.4; O, 11.0; $C_{30}H_{38}O_4NBrS$ requires C, 61.2; H, 6.5; N, 2.4; S, 5.4; Br, 13.6; O, 10.9%) The bromocamphorsulphonate was found to mutarotate in ethanol solution. Its mutarotation was studied at 7° in ethanol, and at 15.5° in acetonitrile. $[\alpha]^{15.5}_{\text{initial}}$ + 2.29° (by extrapolation)

$[\alpha]^{15.5}_{\text{final}}$ + 64.6°

(Table VI + VII
Graph III)

Another sample similarly prepared and crystallised from acetonitrile gave the same diastereoisomer.

Table VI

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

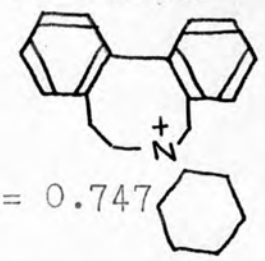
l = 2 c = 1.046 t = 7°

	Time in minutes	Polarimetric Reading	Observed α_{5461}	$\log_{10}\alpha$
1.	8	179.88	0.48	$\bar{1}.6812$
2.	9	179.91	0.45	$\bar{1}.6532$
3.	10	179.95	0.41	$\bar{1}.6128$
4.	12	179.99	0.37	$\bar{1}.5682$
5.	14	180.03	0.33	$\bar{1}.5185$
6.	16	180.07	0.29	$\bar{1}.4624$
7.	18	180.100	0.26	$\bar{1}.4150$
8.	20	180.125	0.235	$\bar{1}.3711$
9.	23	180.150	0.21	$\bar{1}.3222$
10.	26	180.185	0.175	$\bar{1}.2430$
11.	30	180.22	0.14	$\bar{1}.1461$
12.	37	180.26	0.10	$\bar{1}.0000$
13.	47	180.30	0.06	$\bar{2}.7782$
14.	60	180.33	0.03	$\bar{2}.4771$
15.	75	180.345	0.015	$\bar{2}.1761$
16.	∞	180.36		

$k = 8.52 \times 10^{-4} sec^{-1}$

$t_{\frac{1}{2}} = 13.56$ min.

Table VII

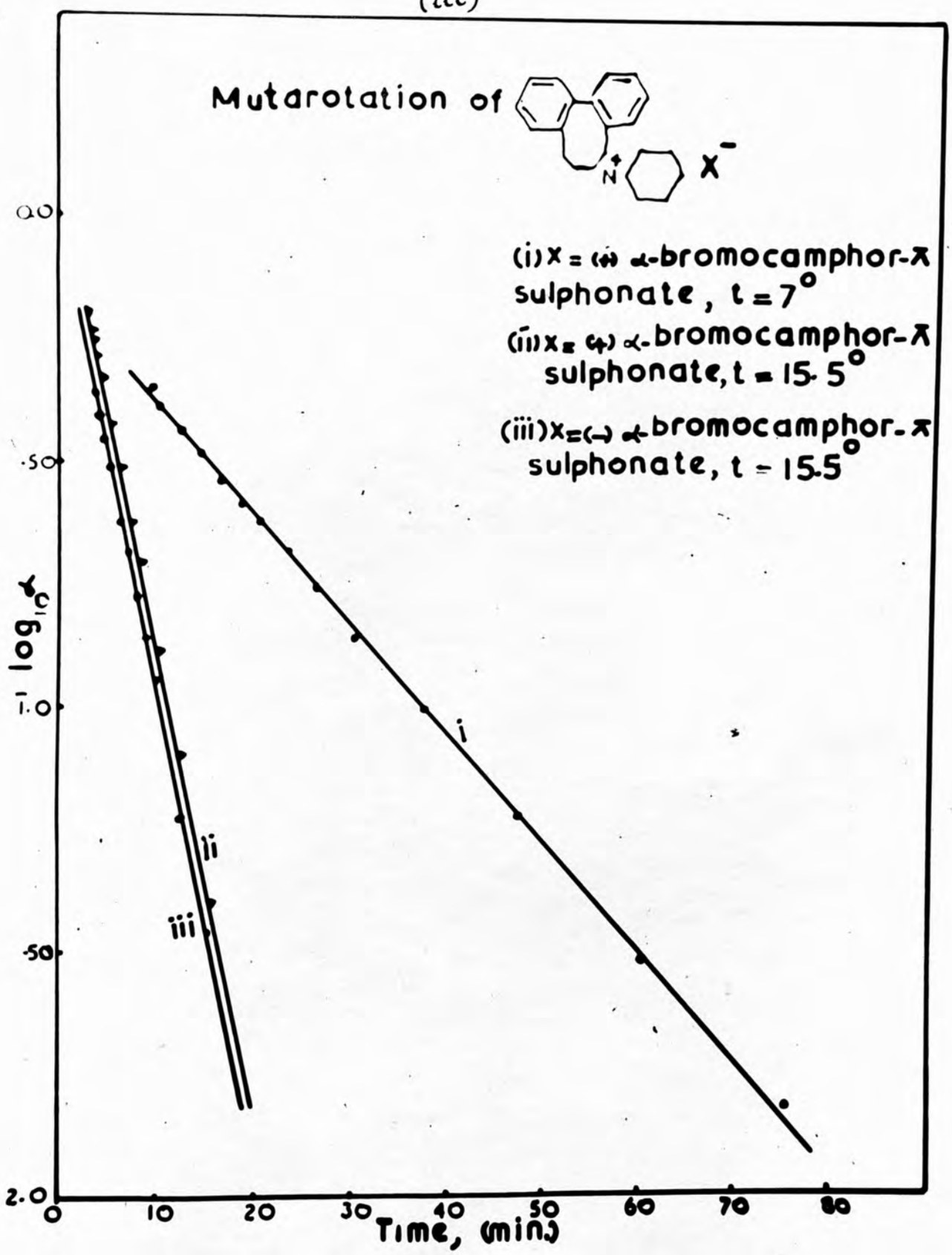
Mutarotation of  (+)-α-bromocamphor-π-sulphonate in acetonitrile.

l = 2 c = 0.747 t = 15.5°

	Time in minutes	Polarimetric Reading	Observed α_{5461}	$\log_{10}\alpha$
1	2.30	179.335	0.645	$\bar{1}.8096$
2	3	179.41	0.57	$\bar{1}.7559$
3	3.30	179.54	0.44	$\bar{1}.6435$
4	4	179.585	0.395	$\bar{1}.5966$
5	4.30	179.625	0.355	$\bar{1}.5502$
6	5	179.68	0.31	$\bar{1}.4914$
7	6	179.74	0.24	$\bar{1}.3802$
8	7	179.77	0.21	$\bar{1}.3222$
9	8	179.81	0.17	$\bar{1}.2304$
10	9	179.84	0.14	$\bar{1}.1461$
11	10	179.865	0.115	$\bar{1}.0607$
12	12	179.92	0.06	$\bar{2}.7782$
13	15	179.945	0.035	$\bar{2}.5441$
14	∞	179.98		

$k = 3.52 \times 10^{-3} sec^{-1}$

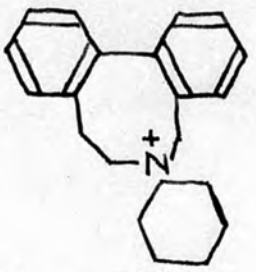
$t_{\frac{1}{2}} = 3.2$ min.


Mutarotation of
X⁻
(i) X = (+) α-bromocamphor-π sulphonate, t = 7°
(ii) X = (+) α-bromocamphor-π sulphonate, t = 15.5°
(iii) X = (−) α-bromocamphor-π sulphonate, t = 15.5°
log r
0.0
-.50
-1.0
-.50
-2.0
i
ii
iii
0
10
20
30
40
50
60
70
80
Time, (min.)

(-)-1:2:7:8-Tetrahydro-3:4-5:6-dibenzazocino-1-spiro-1'-piperidinium Picrate.

1:2:7:8-Tetrahydro-3:4-5:6-dibenzazocino-1-spiro-1'-piperidinium-(+)-α-bromocamphor-π-sulphonate was ground into a fine powder, and then dissolved in ethanol which had been precooled to about -10°. A solution of picric acid in ethanol saturated at -10°, was added to the above solution. With some scratching the yellow picrate started precipitating out. It was filtered in a cooled Buchner funnel and quickly dried in a vacuum desiccator. The whole process took about 15 minutes; during the dissolution and precipitation everything was kept cooled in ice and salt mixture. The picrate was found to be laevo-rotatory, and it racemised readily in solution. Its racemisation in acetone was studied at four different temperatures, 2°, 10°, 16°, 23°. (Tables VIII, IX, X and XI)- and also in acetonitrile at 2° (Table XII). $[\alpha]^2_{5461}$ - 54° in acetone 5 minutes after wetting and $[\alpha]^2_{5461}$ - 69° in acetonitrile 3 minutes after wetting. A sample for analysis was crystallised twice from ethanol m.p. 196-197°. (Found: C, 61.55; H, 5.1; N, 11.1; O, 22.05; $C_{26}H_{26}N_4O_7$ requires C, 61.6; H, 5.2; N, 11.0; O, 22.1%).

Table VIII

Racemisation of (-)  picrate in acetone.

c = 0.413 Zero = 179.01 $\underline{l}$ = 2 t = 2°

	Time in minutes	Polarimetric Reading	Observed α_{5461}	$\log \alpha_{10}$
1.	5	178.56	0.45	$\bar{1}.6532$
2.	7	178.60	0.41	$\bar{1}.6128$
3.	9	178.61	0.40	$\bar{1}.6021$
4.	15	178.67	0.34	$\bar{1}.5351$
5.	20	178.71	0.30	$\bar{1}.4771$
6.	25	178.745	0.265	$\bar{1}.4232$
7.	30	178.78	0.23	$\bar{1}.3617$
8.	40	178.83	0.18	$\bar{1}.2553$
9.	50	178.87	0.14	$\bar{1}.1461$
10.	60	178.91	0.105	$\bar{2}.0212$
11.	80	178.945	0.065	$\bar{2}.7782$

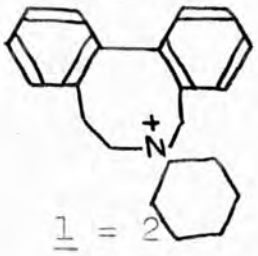
$$k = 4.417 \times 10^{-4} \text{sec}^{-1}$$

$$t_{\frac{1}{2}} = 26.6 \text{ min.}$$

Another similar experiment gave $k = 4.946 \times 10^{-4} \text{sec}^{-1}$

Average $k = 4.681 \times 10^{-4} . \text{sec}^{-1}$.

Table IX

Racemisation of (+)  picrate in acetone.

C = 0.747 $\underline{l}$ = 2 t = 10°

	Time in minutes	Polarimetric Reading	Observed α_{5461}	$\log_{10}\alpha$
1	2.30	179.78	0.77	$\bar{1}$.8865
2	3	179.745	0.735	$\bar{1}$.8663
3	3.30	179.71	0.70	$\bar{1}$.8451
4	4	179.69	0.68	$\bar{1}$.8325
5	5	179.635	0.625	$\bar{1}$.7959
6	6	179.59	0.58	$\bar{1}$.7634
7	7	179.54	0.53	$\bar{1}$.7243
8	8	179.485	0.475	$\bar{1}$.6767
9	10	179.41	0.41	$\bar{1}$.6128
10	12	179.34	0.33	$\bar{1}$.5185
11	15	179.25	0.24	$\bar{1}$.3802
12	20	179.185	0.175	$\bar{1}$.2430
13	25	179.15	0.14	$\bar{1}$.1461
14	30	179.085	0.075	$\bar{2}$.8751

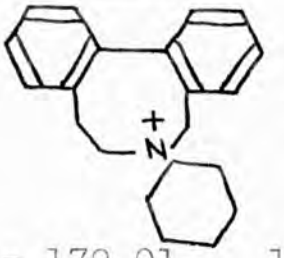
$$k = 1.384 \times 10^{-3} \text{sec}^{-1}$$

Another similar experiment gave $k = 1.275 \times 10^{-3} \text{sec}^{-1}$

Average $k = 1.33 \times 10^{-3} \text{sec}^{-1}$

$$t_{\frac{1}{2}} = 8.5 \text{ min.}$$

Table X

Racemisation of (−)  picrate in acetone.

C = 0.723 Zero = 179.01 $\underline{l}$ = 2 t = 16°

	Time in minutes	Polarimetric Reading	Observed α_{5461}	$\log_{10}\alpha$
1	2.30	178.31	0.71	$\bar{1}.8451$
2	3	178.39	0.62	$\bar{1}.7924$
3	4	178.50	0.51	$\bar{1}.7076$
4	5	178.60	0.41	$\bar{1}.6128$
5	6	178.67	0.34	$\bar{1}.5315$
6	7	178.73	0.28	$\bar{1}.4472$
7	8	178.78	0.23	$\bar{1}.3617$
8	9	178.825	0.185	$\bar{1}.2672$
9	10	178.86	0.15	$\bar{1}.1761$
10	11	178.89	0.12	$\bar{1}.0792$
11	12	178.91	0.10	$\bar{1}.0000$
12	14	178.945	0.065	$\bar{2}.8129$
13	16	178.965	0.045	$\bar{2}.6532$

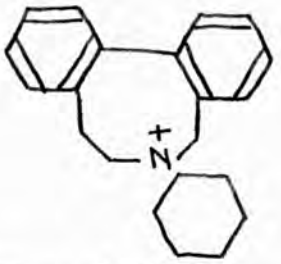
$k = 3.418 \times 10^{-3} sec^{-1}$

Another similar experiment gave $k = 3.161 \times 10^{-3} sec^{-1}$

Average $k = 3.29 \times 10^{-3} sec^{-1}$

$t_{\frac{1}{2}} = 3.4$ min.

Table XI

Racemisation of (-)  picrate in acetone.

C = 0.665 Zero = 179.01 $\underline{l}$ = 2 t = 23°

	Time in minutes	Polarimetric Reading	Observed α_{5461}	$\log_{10}\alpha$
1	2.5	178.60	0.41	$\bar{1}.6128$
2	2.75	178.65	0.36	$\bar{1}.5563$
3	3.00	178.685	0.325	$\bar{1}.5119$
4	3.25	178.74	0.27	$\bar{1}.4314$
5	3.5	178.76	0.25	$\bar{1}.3979$
6	4.5	178.86	0.15	$\bar{1}.1761$
7	5.5	178.91	0.10	$\bar{1}.0000$
8	7.5	178.975	0.035	$\bar{2}.5441$

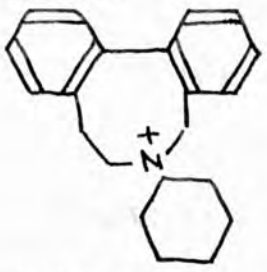
$k = 8.212 \times 10^{-3} sec^{-1}$

Another similar experiment gave $k = 8.696 \times 10^{-3} sec^{-1}$

Average $k = 8.45 \times 10^{-3} sec^{-1}$

$t_{\frac{1}{2}} = 1.35$ min.

Table XII

Racemisation of (-)  picrate in acetonitrile

C = 0.848 l = 2 Zero = 179.01 t = 2°

	Time in minutes	Polarimetric Reading	Observed α_{5461}	$\log_{10}\alpha$
1	3	177.845	1.165	0.0663
2	4	177.88	1.13	0.0531
3	5	177.91	1.10	0.0414
4	7	177.96	1.05	0.0212
5	9	178.01	1.00	0.0000
6	11	178.085	0.925	I.9661
7	13	178.125	0.885	I.9469
8	15	178.175	0.835	I.9217
9	17	178.23	0.78	I.8921
10	19	178.27	0.74	I.8692
11	21	178.305	0.705	I.8482
12	23	178.35	0.66	I.8195
13	25	178.38	0.63	I.7993
14	27	178.425	0.585	I.7672
15	31	178.485	0.525	I.7202
16	34	178.515	0.495	I.6946
17	37	178.58	0.43	I.6335
18	40	178.605	0.405	I.6075
19	44	178.655	0.355	I.5502
20	48	178.69	0.32	I.5051
21	53	178.725	0.285	I.4548
22	58	178.77	0.24	I.3802
23	70	178.83	0.18	I.2553

$k = 4.775 \times 10^{-4}\ sec^{-1}$

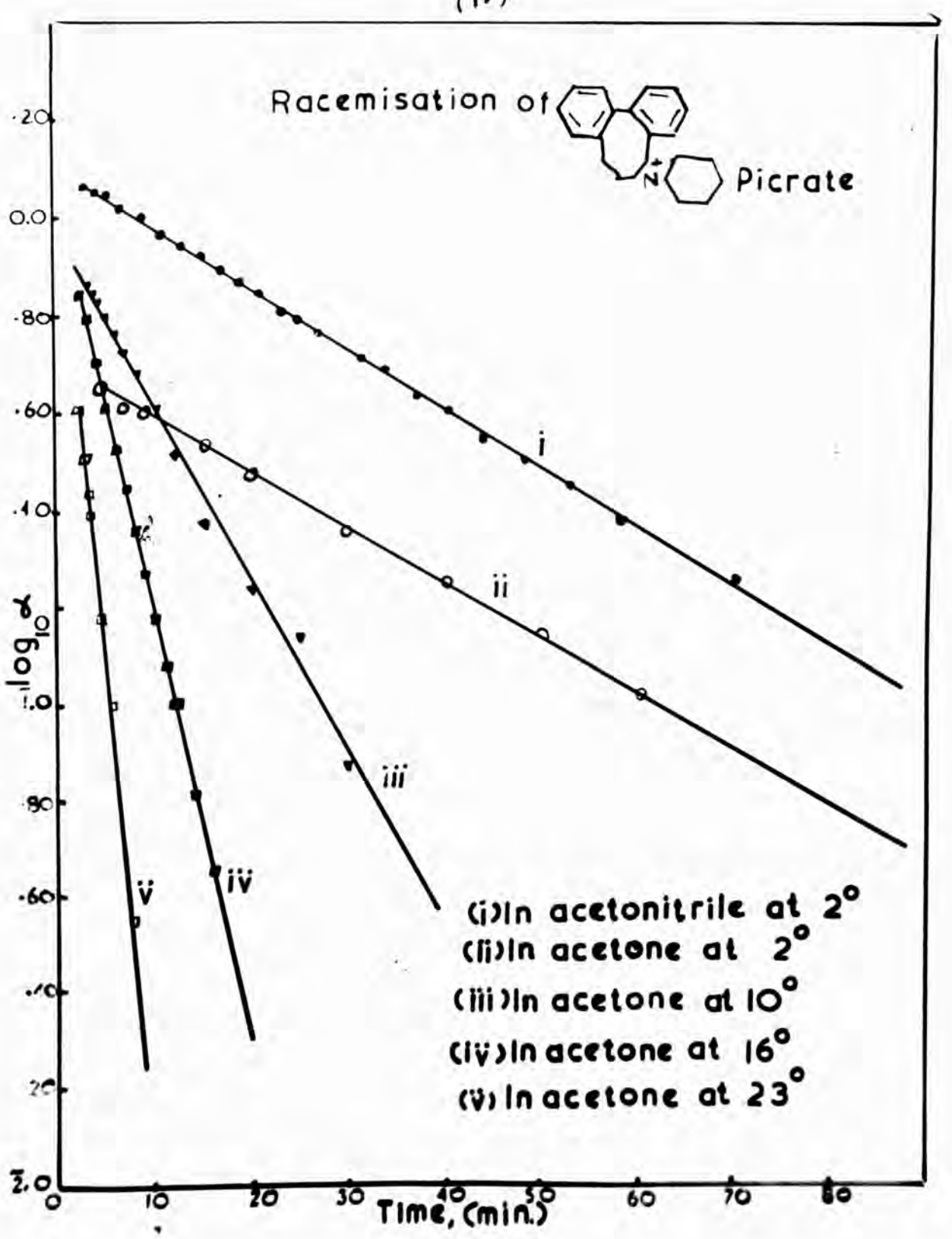

Racemisation of
Picrate
$\log_{10}\alpha$
Time, (min.)
i
ii
iii
iv
v
(i) In acetonitrile at 2°
(ii) In acetone at 2°
(iii) In acetone at 10°
(iv) In acetone at 16°
(v) In acetone at 23°

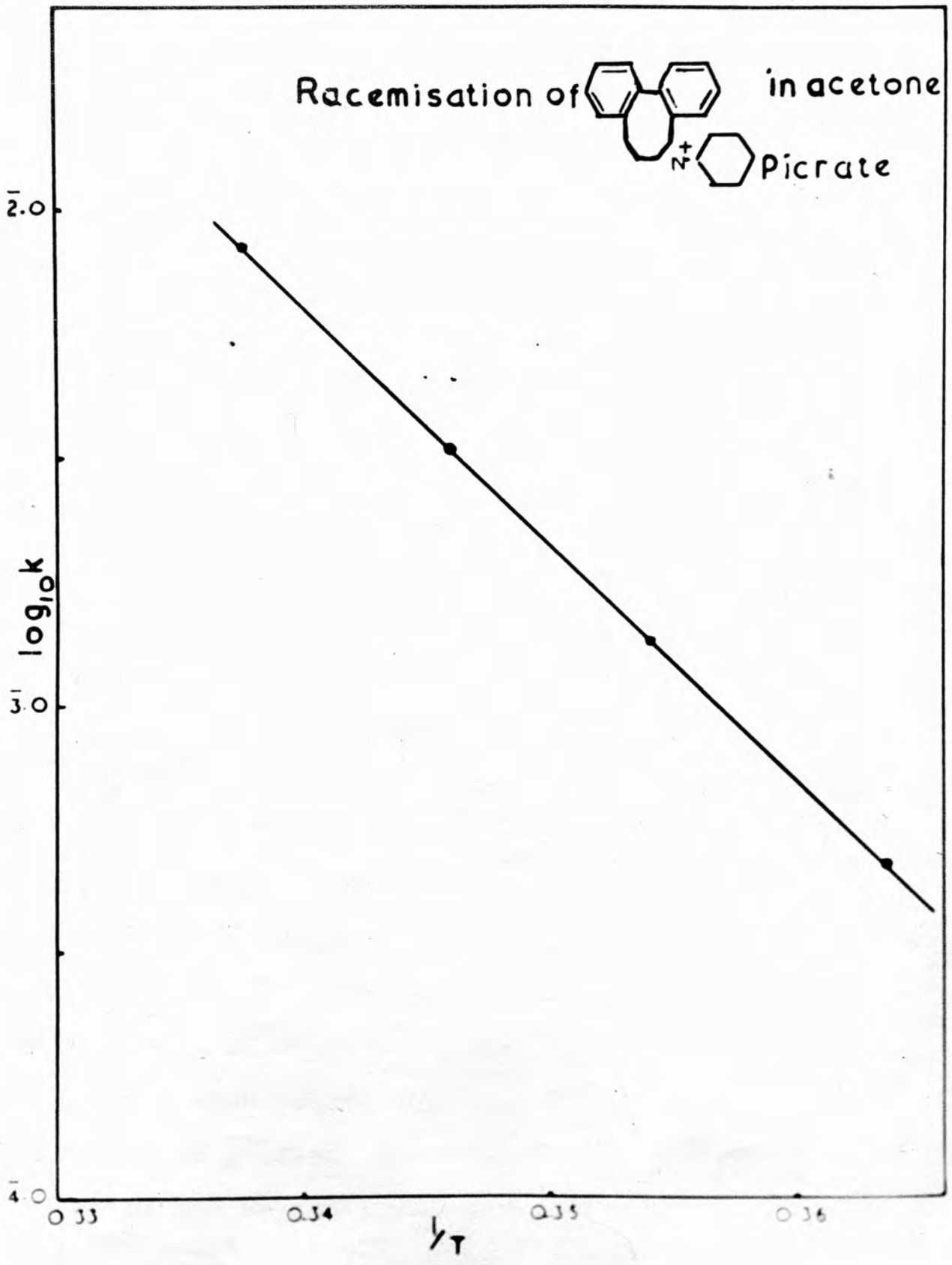
Table XIII

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

	$T(A^{\circ})$	$\frac{1}{T}$	k	log k
1	275	0.3623	$4.681 \times 10^{-4} sec^{-1}$	-4.6703
2	283	0.3534	$1.329 \times 10^{-3} sec^{-1}$	-3.1235
3	289	0.3460	$3.289 \times 10^{-3} sec^{-1}$	-3.5171
4	296	0.3378	$8.454 \times 10^{-3} sec^{-1}$	-3.9271

Staight line plot of log k against 1/T is given in graph V. The value of E comes to 22.0 $k.cal.mol^{-1}$ and that of A to $10^{14.05} sec^{-1}$.

(V)


Racemisation of
in acetone
Picrate
$\bar{2}.0$
$\bar{3}.0$
$\bar{4}.0$
$\log_{10} k$
0.33
0.34
0.35
0.36
1/T

Racemisation of (+) and (-) picrates and mutarotation of (+) and (-)-α-Bromocamphor- π -sulphonates of dibenzazocino piperidinium compound.

The solid was in each case ground into a fine powder. It was weighed and dissolved in the solvent which had been standing in water at a suitable temperature for at least ½ hr. The stop-clock was started from the time the solid was wetted with the solvent. The solution was rapidly filtered into a jacketted polarimeter tube round which water at a suitable temperature had been circulating for at least ½ hr. The rotations were read at suitable intervals by direct observation of the solution in the polarimeter tube.

(-) α-Bromocamphor

Pope and Harvey (J., 1901, 79, 74).

(-)-Camphor (150 g., 1 mol.) was powdered and heated on a water bath in a flask fitted with a reflux condenser and a dropping funnel. Bromine (160 g., 1 mol.) was added in small quantities, an occasional shaking being given to the reaction mixture which soon liquified. Heating was continued until the evolution of hydrogen bromide stopped. The reaction mixture was then poured into cold water with stirring, filtered with suction, and washed with cold water. It was then dried and crystallised from methanol. Yield 195 g., (85%), m.p. 76°. $[\alpha]_D^{23}$ - 116.8°, (C = 1.499, l = 2 in benzene)

Ammonium (-)-α-Bromocamphor-π-sulphonate.

Pope and Read (J., 1910, 97, 2199).

This is a modification of the method used by Kipping and Pope (ibid., 1893, 63, 577; 1895, 67, 356).

Oleum (290 c.c.) containing 20% of free sulphur trioxide (d. 1.92) was added to ordinary concentrated sulphuric acid (225 c.c.) to get a mixture of density 1.856 at 15°. 95 g. of (-)-α-bromocamphor was slowly added to 275 c.c. of this mixture, the temperature not being allowed to rise above 50°. The mixture became deep amber in colour as the bromocamphor went into solution. The mixture was agitated for a few minutes, and then carefully poured into two litres of crushed ice. A small amount of bromocamphor precipitated out, and it was filtered off with suction. The filtrate was almost neutralised with milk of lime, and neutralisation was completed with calcium carbonate. Precipitated calcium sulphate etc. was filtered off and washed several times with water. The filtrate and washings were combined and ammonium carbonate was added to precipitate calcium carbonate, which was filtered off again. The filtrate was evaporated in large pans and the residue crystallised from distilled water, 70 g. (40%) $[\alpha]^{22}_{5461}$ - 92.5°. After two crystallisations and air-drying the ammonium (-)-α-bromocamphor-π-sulphonate was pure and had $[\alpha]^{22}_{5461}$ - 105.4° (l = 2, c = 4.0325 in water).

Silver Salts of (+) and (-)-α-Bromocamphor- π -sulphonic acids

Methoden der Organischen Chemie, Houben and Weyl (Vol.4, p.515)

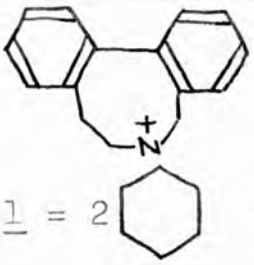
Concentrated solutions of equimolecular quantities of ammonium α-bromo-camphor-π-sulphonate and silver nitrate were mixed, warmed for about fifteen minutes and cooled in ice. Silver α-bromocamphor- π -sulphonate crystallised out. It was filtered, washed with cold water, and crystallised again from water. Colourless needles of the monohydrate ($Ag(C_{10}H_{14}O_4BrS).H_2O$) were used after drying in air.

1:2:7:8-Tetrahydro-3:4-5:6-dibenzazocino-1-spiro-1'-piperidinium-(-)-α-bromocamphor- π -sulphonate.

This was prepared just like the (+) isomer by mixing a solution of the quaternary iodide (0.9 g., 1 mol.) in ethanol with a solution of the silver salt of (-)-α-bromocamphor- π -sulphonic acid (0.94 g., 1 mol.) in dilute ethanol. The mixture was slightly warmed, and then filtered. The precipitated silver iodide was filtered and was washed with warm alcohol. The filtrate and washings were combined, evaporated on a water bath and the residue dried in a desiccator. 1.3 g. of the quaternary -(-)-α-bromocamphor- π -sulphonate thus obtained was crystallised from a mixture of ethyl acetate ethanol. 1.15 g crystallised out as one isomer. Its mutarotation was studied at 15.5° in acetonitrile (Table XIV) (Found: C, 60.9; H, 6.5. $C_{30}H_{38}O_4NBrS$ requires C, 61.2; H, 6.5%).

$[\alpha]^{15.5}_{final}$ - 65.09° $[\alpha]^{15.5}_{initial}$ 4.00° (by extrapolation)

Table XIV

Mutarotation of  (-)-α-bromocamphor-π-sulphonate in acetonitrile. (GRAPH iii)

C = 0.914 l = 2 t = 15.5°

	Time in minutes	Polarimetric Reading	Observed α_{5461}	$\log_{10} a$
1	2.30	178.48	0.66	$\bar{1}$.8195
2	3	178.41	0.59	$\bar{1}$.7709
3	3.30	178.34	0.52	$\bar{1}$.7160
4	4	178.29	0.47	$\bar{1}$.6721
5	5	178.20	0.38	$\bar{1}$.5798
6	6	178.13	0.31	$\bar{1}$.4914
7	7	178.06	0.24	$\bar{1}$.3802
8	8	178.02	0.20	$\bar{1}$.3010
9	10	177.95	0.13	$\bar{1}$.1139
10	12	177.90	0.08	$\bar{1}$.9031
11	15	177.86	0.04	$\bar{1}$.6021
12	∞	177.82		

$k = 3.68 \times 10^{-3} sec^{-1}$

$t_{\frac{1}{2}} = 3.1$ min.

Average k for (+) and (-)-bromocamphor-π-sulphonate in acetonitrile at 15.5° = $3.6 \times 10^{-3} sec^{-1}$.

$t_{\frac{1}{2}} = 3.2$ min.

Mutarotation of (+)-α-bromocamphor- -sulphonate can be represented as:

$$(-)B \underset{k_1}{(+)} A \rightleftharpoons (+)B \underset{k_2}{(+)} A$$

Similarly that of (-)-α-bromocamphor-π-sulphonate can be represented as:

$$(+)\ B\ (-)\ A \underset{k_1}{\rightleftharpoons} (-)\ B\ (-)\ A \underset{k_2}{}$$

k in the rate of mutarotation for (+) and (-)-α-bromocamphor-π-sulphonate is equal because in each case it is the sum of k_1 and k_2.

(+) 1:2:7:8-Tetrahydro-3:4-5:6-dibenzazocino-1-spiro-1'-piperidinium Picrate.

The spiro-piperidinium-(-)-α-bromocamphor-π-sulphonate was treated with a cooled solution of picric acid at -10°. The precipitated picrate was filtered quickly through a cooled buchner and dried in a desiccator. Its racemisation was studied at 10° in acetone. A sample for analysis was crystallised twice from ethanol and dried in a drying pistol m.p. 196-197°. (Found; C, 62.1; H, 5.0; N, 11.5; $C_{26}H_{20}N_4O_7$ requires C, 61,7; H, 5.2; N, 11.0%).

1:2:7:8-Tetrahydro-1-(2-hydroxy-1-methyl-2-phenylethyl)-1-methyl-3:4-5:6-dibenzazocinium Iodide.

The Dibromo-compound was prepared from the 2-hydroxymethyl-2'-β-hydroxyethyldiphenyl (15 g., 1 mol.) as before. It was extracted with benzene and the benzene extract dried over anhydrous sodium sulphate. A dried benzene solution of ephedrinehemihydrate (26 g., 2.3 mols.) was added to it. The mixture was warmed at 50-60° for about 40 hours. The

gum and fine needles that separated out were filtered, washed with warm benzene, and taken up in minimum amount of cold water. On addition of the saturated solution of potassium iodide, the quaternary iodide was precipitated. This was filtered and dried (4 g., 12%). It was crystallised from ethanol three times m.p. 224-225° decomp. (Found: C, 51.5; H, 6.15; ionic I 26.00, $C_{25}H_{28}NOI$ requires C, 51.8; H, 5.8; ionic I, 26.2%). On several controlled crystallisations from dilute alcohol it separated into two fractions: $[\alpha]^{18}_{5461}$ + 118° ± 2 (C = 0.2112 in ethanol, l = 2), $[\alpha]^{18}_{5461}$ - 60° ± 2 (C = 0.2264 in ethanol, l = 2). Neither of these showed any mutarotation at room temperature. Rotations of ethanolic solutions of these fractions after being heated in sealed tubes at 100° for three hr. after remained unchanged. In view of the complexity of the compound and the initial low yield of the quaternary iodide investigations were not carried on any further.

A Unicam spectrophotometer (SP/500) was used for the the measurement of the ultra-violet absorption spectra discussed in this section.

The solvent used was 95% ethanol; 20 c.c. of the stock solution was diluted to suitable dilutions, ranging between 2 - 5 x 10^{-5} g. mol./litre.

The optical density measurements were first determined using 10 mm. cells and subsequently checked by 5 mm. and 2 mm. cells, changing the dilution of the solution at the same time so as to get most of the measurements in the most sensitive region of the instrument (D = 0.4 - 0.5) especially the maxima and the minima. The formula $D = \varepsilon.x.c$ was used to calculate ε, the molar extinction coefficient, where D is the optical density, x the width of the cell in cm., and c the molar concentration of the solution.

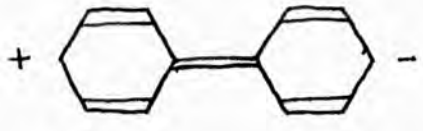
The prominent features of the spectra have been tabulated as well as some of the reference compounds. For curves ε has been plotted against the wavelength on logarithmic paper.

Study of the ultraviolet spectra is one of the methods for studying the configuration of molecules containing the collinear diphenyl structure. This method gives direct information only about the conjugation between the two phenyl rings, although conclusions involving relations

between resonance and coplanarity of the phenyl rings have been drawn. Diphenyl shows a high intensity band at 2490 Å with an intensity of 17,300 (in ethanol), which has been assumed to arise as a result of resonance between the two aromatic nuclei, the 1:1'-bond acquiring some double bond character. Such conjugation operates by overlapping of the π-orbitals of the two benzene rings and has generally been assumed to require coplanarity of these rings.

There is evidence from other sources, such as electron-diffraction study of diphenyl vapour (Karle & Brockway, J.Amer.Chem.Soc., 1944, 66, 1974; Bastiansen, Acta,chem. Scand., 1949, 3, 408) or a study of the dipole-moments of the substituted diphenyls (Littlejohn and Smith, J., 1953, 2456; 1954, 2552) which shows that diphenyl molecule is non-coplanar in the vapour state as well as in solution.

The presence of this band (often called the conjugation band) in the ultra-violet spectrum of diphenyl however, reflects the probability of the molecule becoming coplanar and not its preferred configuration; since I is the first excited state of diphenyl molecule and not its normal state.



I

Substituents in the diphenyl nucleus affect its spectrum depending upon their own nature as well as their position on the parent phenyl ring:

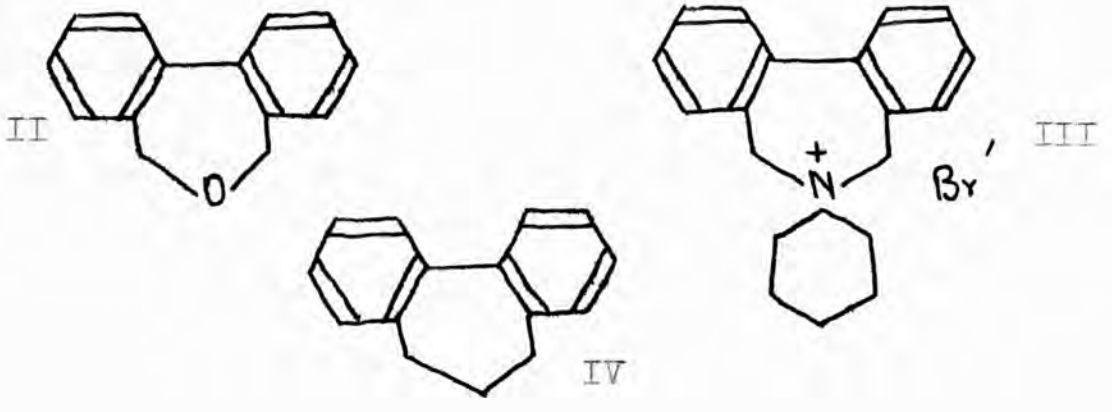
(a) Ortho-substituents: Substituents in the ortho-position have a very large steric effect. Beaven and Hall (J., 1956, 4637) have shown that the introduction of even a single fluorine substituent in one of the ortho-positions of the diphenyl results in a considerable short-wave shift to λ_{max} 2415 Å and reduction in intensity (ε_{max} 16500) of the conjugation band. With two chlorine atoms in the ortho-positions, the conjugation band is left only as an inflection at a much shorter wave-length (λ_{inf} 2300 Å) with a further reduction in intensity (ε_{inf} 6600). In addition to the steric effect, the ortho-substituents affect the spectrum owing to their electronic interaction with the parent phenyl ring.

(b) Para-substituents which do not have any steric effect at all, affect the spectrum mainly by their interaction with the phenyl ring; often their auxochromic effect increases the conjugation.

(c) Meta-substituents:- cannot have much steric effect, the electronic interaction (which is different from o and p-substituents because there can be no resonance between the diphenyl nucleus and substituents in the meta position) depends on the nature of the substituent. Ortho and para directing groups influence the spectrum differently from

meta directing ones, (Williamson & Rodebush, J.Amer.Chem.Soc., 1941, 63, 3018).

o-o'-Bridged diphenyls where the bridge forms a part of a seven-membered homocyclic or heterocyclic ring (hetero-atoms only O and N; S, Se, As etc. are not being considered because the participation of electrons of energy levels other than s and p make the spectra of their compounds much more complicated) show a high degree of conjugation. Calculation of θ (interplanar angle) with the use of normal covalent radii and bond angles gives the values of 43°, 47° and 49° for the unsubstituted oxepin, azepinium bromide and dibenzocycloheptadiene respectively (C - N^+ bond length is taken as 1.50 Å) Hall and Minhaj (J., 1957, 4584). The presence of the conjugation band (λ_{max} ca 2500 Å, 2480 Å, ε_{max} ca 16500-15500) in these compounds relects the configurational lability of these compounds and is quite consistent with their low optical stability.



All these compounds show an intense short waveband which is barely within the limit of study by the quartz spectrophotometer. In the oxepin, the conjugation band is shifted slightly to longer wave-length (λ_{max} 2505 Å) but it is decreased in intensity (ε_{max} 15500). In the azepinium bromide and methyl-dibenzocycloheptadiene-1-carboxylate the conjugation band is shifted to shorter wave-length (λ_{max} 2480 Å, λ_{max} 2485 Å) and is further reduced in intensity (ε_{max} 15000, ε_{max} 15500). Both oxepin and methyl dibenzocycloheptadiene-1-carboxylate have very low selective absorption in the long-wave region, (λ_{inf} 2770 Å, ε_{inf} 1600; λ_{inf} 2740 Å, ε_{inf} 1700 respectively). Azepinium bromide shows appreciable selective absorption in the long-wave region (λ_{inf} 2740 Å, ε_{inf} 4750; λ_{inf} 2810 Å, ε_{inf} 2250).

The effect of the various substituents on the spectra of these compounds has been studied only in the ones with heterocyclic bridging ring. The effect has been found to be qualitatively the same as in non-bridged compounds though it differs markedly in detail.

(a) Ortho-substituents: Only $-CH_3$ (Wittig and Zimmermann, Chem.Ber. 1953, 86, 629) and $-OCH_3$ (Beaven, Hall, Lesslie and Turner, J., 1952, 854) have been studied. In both cases the short-wave band is shifted to longer wave-length, the conjugation band which is definitely resolved in the case of $-CH_3$, but left as an inflection in the case of $-OCH_3$ is shifted to shorter wave length and is reduced in intensity in both the cases.

Selective absorption occurs at longer wave-length and is increased in intensity.

(b) Meta-substituents: Only $-OCH_3$ (Beaven, Bird, Hall, Lesslie, and Turner, J., 1954, 131) has been studied. A methoxy group in the meta-position has a similar effect on the short-wave and long-wave regions as it has when in the ortho-position, but it shifts the conjugation band to the longer wavelength though this band is reduced in intensity compared to that in the unsubstituted compounds.

(c) Para-substituents: Only $-OCH_3$ and Cl (Hall and Minhaj, loc.cit.) have been studied (though together with $-OCH_3$ or Cl in the two ortho-positions). These on the whole increase conjugation, shift the conjugation band to longer wavelength and increase its intensity. The effect in other regions is similar to that in the two cases given above ($-OCH_3$, in N-Acetylcolchinol methyl ether λ_{max} 2620 Å, ε_{max} 20,000, Huang, Tarbell and Arnstein, J.Amer.Chem.Soc., 1948, 70, 4181; Horowitz, Ullyot, E.C. Horning, N.G. Horning, Koo, Fish, Parker, Walker, ibid., 1950, 72, 4330; Rapoport, Williams and Cisney, ibid., 1951, 73, 1414).

Table I

Compound	Conjugation Band									
	λmax	εmax	λmin	εmin	λmax	εmax	λmin	εmin	λmax	ε max
1)2:7-Dihydro-3:4-5:6-dibenzoxepin	206.0	40,000	227.0	4,920	250.5	16,500			(ca.277)	1,600
* 2)2:7-Dihydro-4':1"-dimethoxy-3:4-5:6-dibenzoxepin					253.0 246.0	8,650 9,300	263.0	2,450	293.5 283.5	9,950 9,400
* 3)2:7-Dihydro-3':2"-dimethoxy-3:4-5:6-dibenzoxepin	222.0	51,000	246.0	9,450	255.0	11,000	271.0	3,200	(296.0) 286.0	4,800 5,600
4)2':4'-1":3"-tetrachloro-2:7-dihydro-3:4-5:6-dibenzoxepin.	217.0	42.500	239.0	9,500	257.0	19,000			(ca.290) (ca.280)	1,200 3,400
5)2:7-Dihydro-4':1"-dimethyl-3:4-5:6-dibenzoxepin					242.0	11,000				

1) Beaven & Johnson, J., 1957, 651. 2) Beaven, Hall, Lesslie & Turner, J., 1952,854. 3) idem,ibid, 1954, 131. 4) Hall & Minhaj, loc.cit. 5) Wittig & Zimmermann, Chem.Ber., 1953, 86, 629.

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

* Solvent Hexane.

Table II

Compound	Conjugation Band									
	λ_{max}	ε_{max}	λ_{min}	ε_{min}	λ_{max}	ε_{max}	λ_{min}	ε_{min}	λ_{max}	ε_{max}
1)Methyl-3:4-5:6-dibenzo-cyclohepta-3:5-diene-1-carboxylate	207.5	42,500	227.5	5,700	248.5	15,500			(ca.274)	1,700
2)3:4-5:6-Dibenzocyclo-hepta-3:5-diene-1-carbo-xylic acid	205.0	43,000	228.0	5,800	249.0	15,300			(ca.274)	1,700
3)Methyl-2':4':1":3"-tetra-chloro-3:4-5:6-dibenzocyclo-hepta-3:5-diene-1-carboxylate	215.5 (ca.223)	46,000 41,500	236.0	8,400	254.4	19,000			(ca.286)	810
4)1-Hydroxy-methyl3:4-5:6-dibenzocyclo-hepta-3:5-diene	205.5	43,000	227.5	5,400	248.5	15.500			(ca.269) (ca.277)	3,200 1,500
5)Dimethyl-3:4-5:6-dibenzocyclo hepta-3:5-diene-1-dicarboxylate			(ca.228)	(ca.6000)	249	16,980				
6)3:4-5:6-Di-benzcyclohepta-(3:5)-diene					247	15,700				

Nos. 1,2,4 Beaven, Bird, Hall, Johnson, Ladbury, Lesslie & Turner, J., 1955, 2708. No.3, Hall and Minhaj, J., 1957, 4584. No.5 Iffland & Siegel, J.Amer. Chem.Soc., 1958, 80, 1947; No.6. Cope & Smith, ibid, 1956, 78, 1012.

Table III

Compound	Conjugation Band									
	λ_{max}	ε_{max}	λ_{min}	ε_{min}	λ_{max}	ε_{max}	$\lambda_{min.}$	ε_{min}	λ_{max}	ε_{max}
1)2:7-Dihydro-3:4-5:6-dibenzazepinium-1-spiro-1"'-piperidinium Bromide *			224.0	4,500	248.0	15,000			(ca.281.5) (ca.272.0)	2,250 4,750
2)2:7-Dihydro-4':1"-dimethoxy-3:4-5:6-dibenzazepinium-1-spiro 1"'-piperidinium Bromide *			233.5	11,000	237.5	11,500	261.0	1.450	297.5	10,500
3)2:7-Dihydro-3':2"-dimethoxy-3:4-5:6-dibenzazepinium-1-spiro1"'-piperidinium Bromide *	226.0	54,500	250.0	9,900	257.0	10,500	277.0	3,650	297.0 284.5	3,000 4,200
4)2':4'-1":3"-Tetrachloro-2:7-dihydro-3:4-5:6-dibenzazepinium-1-spiro-1"'-piperidinium Bromide	222.0	41,500	242.5	9,600	259.5	18,100			(ca.293) 283.5	3,550 6,520
5)2:7-Dihydro-1:1':4':1"-tetramethyl-3:4-5:6-dibenzazepinium Bromide					242.0	9,000				

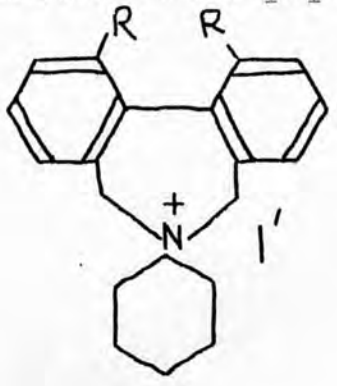
* Solvent, water

References for Table III

Nos. 1 & 2, Beaven, Hall, Lesslie & Turner, loc.cit.
" 3, Beaven, Hall, Lesslie & Turner, loc.cit.
" 4, Hall & Minhaj, loc.cit.
" 5, Wittig & Zimmermann, loc.cit.

Investigation of the effect of ortho-substituents in o-o'-bridged diphenyls in which the bridge forms a part of a homocyclic or heterocyclic seven-membered ring has been restricted to compounds mostly with heterocyclic bridging rings and substituents methoxyl and methyl. In the tetra chloro compounds studied by Hall and Minhaj (loc.cit.) the steric effect of o-chlorine atoms is over-ridden by the chlorine atoms in the para-position.

It therefore seemed desirable to extend this range by investigating the effect of different halogen atoms in the ortho-position on the ultra violet absorption spectra of such bridged compounds. Accordingly the four 2:2'-dimethyl-6:6'-dihalogenodiphenyls were prepared and converted into the 2:2'-bisbromomethyl-6:6'-dihalogenodiphenyls by the use of benzoyl peroxide catalysed N-bromosuccinimide. The resulting bromo-compounds could not be isolated and were converted directly into spiro-piperidinium iodides by condensation with piperidine.

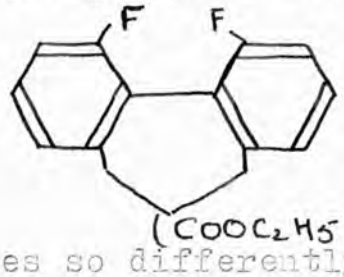


V

R = F
R = Cl
R = Br
R = I

The iodide ion was found to absorb very strongly in the region of 2100-2500 Å and thus completely mask the conjugation band. Therefore the iodides were converted into the bromides (the bromide ion does not absorb in this region).

Only in the case of the difluoro-compound was the dibromo-compound condensed with sodiomalonic ester to give diethyl 4':1"-difluoro-3:4-5:6-dibenzcyclohepta-3:5-diene-1-1-carboxylate, VI.



Fluorine behaves so differently from the other halogens that it is convenient to study the two fluoro-compounds (homocyclic and heterocyclic) separately before studying the other dihalogeno-compounds as a group, (Table IV, Graph 1).

There is evidence from studies in unbridged diphenyls (Beaven & Hall, loc.cit.; Hall & Minhaj, loc.cit.) and fluorobenzene (Cooper, J.Chem.Phys., 1953, 21, 403; Smith & Turton, J., 1951, 1701) of the striking contrast between fluorine substituents and those of chlorine, bromine and iodine in the same positions. Thus Beaven & Hall (loc.cit.) have shown that in 4:4'-difluorodiphenyl the conjugation band shifts to shorter wave-length and is reduced in intensity (λ_{max}2450 Å ε_{max}15000) compared with 4:4'-dichlorodiphenyl which shows a long-wave shift and increase in the intensity of the conjugation band (λ_{max}2590 Å ε_{max}25,200) Hall and Minhaj (loc.cit.).

Table IV.

Compound	Conjugation Band									
	λmax	εmax	λmin	εmin	λmax	εmax	λmin	εmin	λmax	εmax
1)Diethyl 4':1"-difluoro-3:4-5:6-dibenzocyclohepta-3:5-diene-1-1'-dicarboxylate	208.0	38,000	224.5	6,230	244.0	13,100	262.0	3,820	271.5	4,950
2)4':1"-Difluoro-2:7-dihydro-3:4-5:6-dibenzazepinium Bromide	ca.208.0	ca.42,000	229.0	8,250	243.5 241.0	12,600 12,600	257.0	2,900	275.0 (282.0) (280.5)	8,900 8,400 8,300

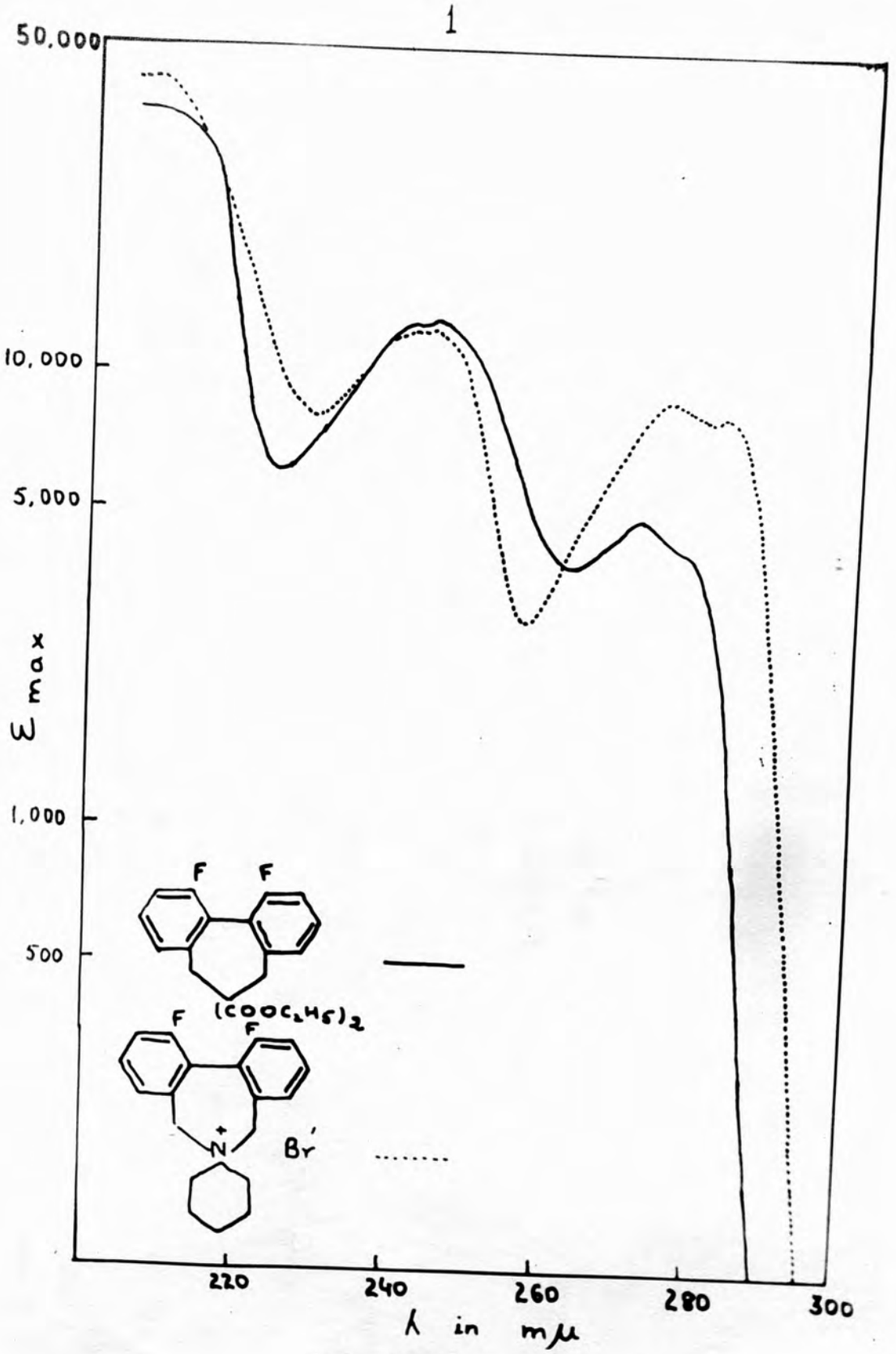
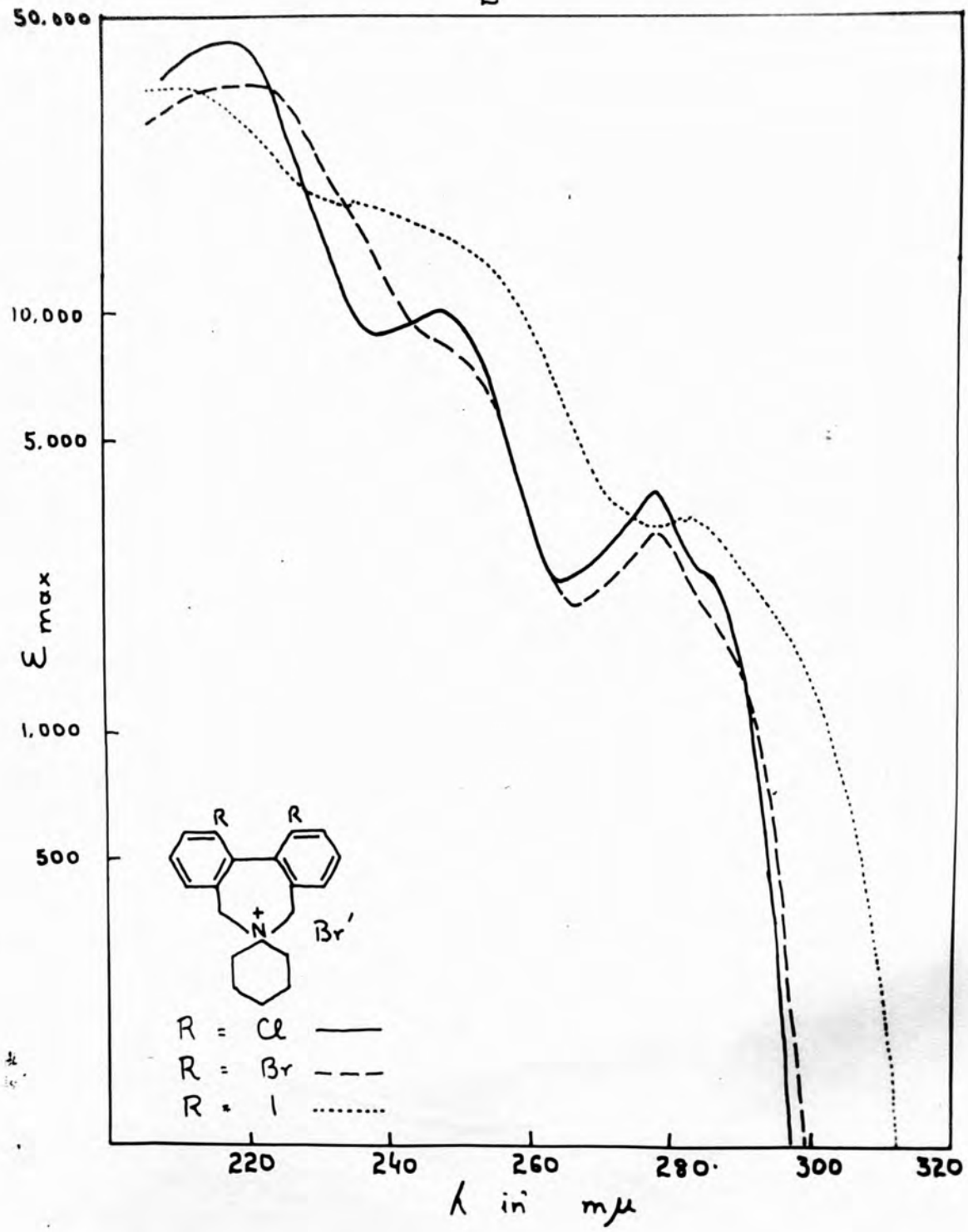

50,000
10,000
5,000
1,000
500
ε max
F F
(COOC2H5)2
F F
N+
Br'
220
240
260
280
300
λ in mμ

Table V

Compound	Conjugation Band									
	λ max	ε max	λ min	ε min	λ max	ε max	λ min	ε min	λ max	ε max
1)4':1"-Dichloro-2:7-dihydro-3:4-5:6-dibenzazepinium-1-spiro-1"'-piperidinium Bromide	219.0	43,000	238.0	9,000	247.0	10,000	264.5	2,340	277.0	3,750
2)4':1"-Dibromo-2:7-dihydro-3:4-5:6-dibenzazepinium-1-spiro-1"'-piperidinium Bromide	221.0	35,000			(246.0)	8,850	266.5	2,050	277.5 (286.0)	2,950 1,900
New set of readings - no conjugation band										
3)2:7-Dihydro-4':1"-diiodo-3:4-5:6-dibenzazepinium-1-spiro-1"'-piperidinium Bromide	212.0	33,000	234.0	18,000	(235.0)	18,200	277.5	3,100	282 fs	3,250


50.000
10,000
5,000
1,000
500
ε max
220
240
260
280
300
320
λ in mμ
R
R
N
Br'
R = Cl
R = Br
R = I

In the difluorodibenzazepinium bromide, the conjugation band is quite well resolved but it is considerably shifted to the shorter wave-length (λ_{max} 2435°, ε_{max} 12600) and reduced in intensity compared to the unsubstituted compound. The short wave band has moved slightly to the longer wave-length (λ_{max} 2080 Å, ε_{max} ca 42000). These two factors together have increased the intensity (ε_{min} 8250) at the short wave minimum which occurs at 2290 Å by making the long wave side of the very intense short wave band overlap the short wave side of the conjugation band. The long wave region shows considerable increase in absorption; there are two resolved bands; λ_{max} 2750 Å, ε_{max} 8900, λ_{max} 2820 Å, ε_{max} 8400, reflecting the absorption due to fluorodiphenyl chromophores and the original longwave absorption of the unsubstituted azepinium bromide in this region.

In the difluorodibenzocycloheptadiene compound also, the well resolved conjugation band has been considerably shifted to the short wave length (λ_{max} 2440 Å, ε_{max} 13100). The short wave band is lower in intensity than in the unsubstituted compound (λ_{max} 2080 Å, ε_{max} 38000), but the short wave minimum which occurs at a shorter wavelength in this case has a higher intensity (λ_{min} 2245 Å, ε_{min} 6230). In the long wave region there is only one well resolved band (λ_{max} 2715 Å, ε_{max} 4950), with an inflection at (λ_{inf} 2770 Å, ε_{inf} ca 4250).

Thus broadly speaking, fluorine substituents in the ortho-positions of both the dibenzazepinium bromide and the dibenzocycloheptadiene compound have similar effect on the spectra of these compounds, except in the long wave region. The presence of two resolved bands in the heterocyclic compound compared with only one band and an inflection in the homocyclic one reflects the fact that in this region the unsubstituted heterocyclic compound shows higher absorption than the unsubstituted homocyclic one.

The other dihalogenodibenzazepinium bromides can now be studied as a group. (Table V, Graph 2).

The conjugation band is quite resolved in the dichloro-compound; though its intensity is considerably lower than that of the unsubstituted azepiniumbromide, it has not suffered a very considerable short wave shift (λ_{max} 2470 Å, ε_{max} 10,000). In the dibromo-compound the conjugation band is left only as an inflection (λ_{inf} 2460 Å, ε_{inf} 8850). The spectrum of the diiododibenzazepinium bromide is that of a highly hindered compound. The broad band with λ_{max} 2350 Å (ε_{max} 18200) is not a conjugation band, but is due to the absorption of iodophenyl chromophores.

The dichloro-compound has a high intensity band at 2190 Å (ε_{max} 43000) which makes the short wave minimum at

2380 Å of much higher intensity than in the unsubstituted compound. In the dibromo-compound, this band is of lower intensity than in the dichloro-compound (λ_{max} 35000), but because it has shifted still more to the longwave side (λ_{max} 2210 Å) and become much broader, it has completely masked the short wave minimum. With no conjugation band in the diiodo-compound this minima is not expected, but the short wave band is however present (λ_{max} 2120 Å, ε_{max} 33000).

In the longwave region the dichloro-compound shows a well resolved band at 2770 Å, (ε_{max} 3750), and a marked inflection at 2860 Å (ε_{inf} 2300). In the dibromo-compound this band has shifted slighly to the longer wave-length ($_{max}$ 2775 Å, $_{max}$ 2950), the inflection as a result being less marked (λ_{inf} 2860 Å, ε_{inf} 1900). In the diiodo-compound the long wave band is not so well resolved as in the other cases, but it shows some fine structure.

On the whole it can be concluded that in the o-o'-bridged diphenyls where the bridge is the main factor in determining the configuration of the molecule, the ortho-substituents can approach one another more closely than in non-bridged diphenyls where the interaction between such ortho-substituents is the dominant factor in determining preferred configuration. This can probably explain why for instance the bridged dichloro-compound shows a fairly well resolved conjugation band, and even in the bridged dibromo-compound there is a suggestion of it as an inflection, whereas 2:2'-dichloro-

diphenyl shows only an inflection, and the 2:2'-dibromo-diphenyl not even that.

STERIC EFFECTS IN 2 : 2′-BRIDGED DIPHENYLS WITH A HETEROCYCLIC BRIDGING RING. PART I. OPTICALLY ACTIVE DIHYDRODIBENZAZEPINES

BY
SHAKTI R. AHMED
AND
D. MURIEL HALL

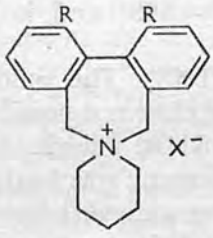
Preprinted from the
Journal of the Chemical Society, September, 1958, pages 3043—3047.

618. *Steric Effects in 2 : 2′-Bridged Diphenyls with a Heterocyclic Bridging Ring. Part I. Optically Active Dihydrodibenzazepines.*

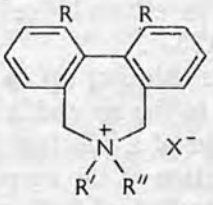
By Shakti R. Ahmed and D. Muriel Hall.

2 : 2′-Bisbromomethyl-6 : 6′-dinitrodiphenyl has been condensed with (−)-ephedrine and the resulting quaternary bromide separated into two diastereoisomers. Hofmann degradation of the two bromides gave (−)- and (+)-2 : 7-dihydro-1-methyl-4′ : 1″-dinitro-3 : 4-5 : 6-dibenzazepine with $[\alpha]_{5461}^{19}$ −1343° and +1333° respectively. The cyclic amines are optically stable in benzene solution up to about 100° and racemise slowly at 125°. Similar condensation of 2 : 2′-bisbromomethyl-6 : 6′-difluorodiphenyl with (−)-ephedrine, followed by Hofmann degradation of the diastereoisomeric bromides, gave optically active (but probably not optically pure) (−)- and (+)-4′ : 1″-difluoro-2 : 7-dihydro-1-methyl-3 : 4-5 : 6-dibenzazepine. The hydrochlorides of the fluoro-amines racemise in aqueous acid at 80° with a half-life of 6·5 hr.

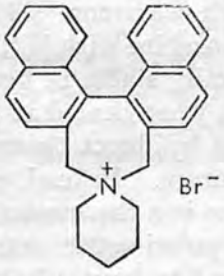
Optical activity has been demonstrated in compounds of the types (I) and (II) only when *ortho*-substituents [or fused benzene rings as in (III) and (IV)] are present.[1,2] In view of the high optical stability and very low specific rotation of the dimethoxy-compound (I*a*) ($[\alpha]_{5461}^{22}$ +4·0° and −3·8°), this failure to resolve compounds of types (I*b*) and (II), in which R = H, was originally attributed to experimental difficulties rather than to lability of configuration. Support for this view came from the greatly increased specific rotations (presumably associated with their different light-absorbing properties) of the dinaphthyl compounds (III) and (IV) which have $[\alpha]_{5461}^{20}$ +306·5° and +205·3° respectively.



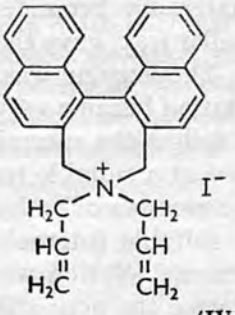
(I*a*) : R = OMe, X = I.
(I*b*) : R = H, X = I.
(I*c*) : R = NO_2, X = I.
(I*d*) : R = F, X = I.



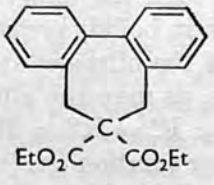
(II)



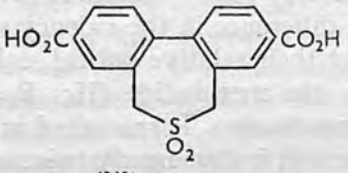
(III)



(IV)



(V)



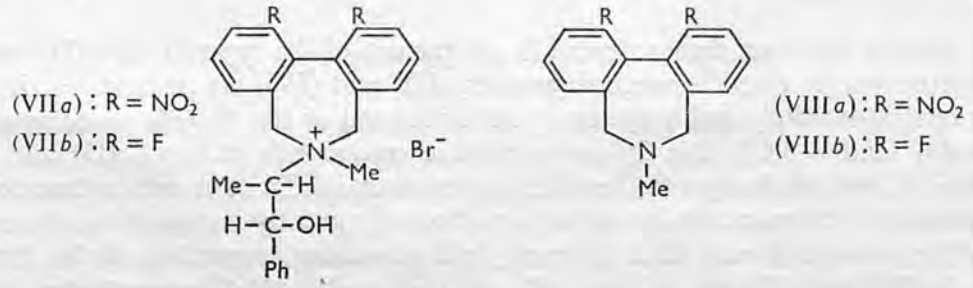
(VI)

However, more recent work on diphenyls with other types of bridging rings suggests that in the absence of other *ortho*-substituents compounds with a bridge of three or four atoms possess only low optical stability.[3,4,5] At the same time further evidence of the low optical rotation associated with this type of structure has been obtained. Thus compound (V) [3] had $[\alpha]_D^{32\cdot5}$ +2·25° and compound (VI) [4] had $[\alpha]_D^{25}$ +3·1°.

In order to extend our knowledge of the configurational stability of 2 : 2′-bridged diphenyls we have therefore begun a study of the effects of various *ortho*-substituents on

the optical stability of compounds of the types (I) and (II). At the same time it seemed desirable to facilitate the detection of optical resolution or asymmetric transformation, if either of them occurred, by using compounds of higher specific rotation. With this in view we selected nitro-groups as suitable *ortho*-substituents for preliminary study, as their bathochromic effect on the electronic absorption bands might be expected to increase the optical rotatory power in the region in which it can most easily be measured. They have the further advantage of being a suitable starting point for the introduction of other groups and, in addition, a certain amount is already known about their steric [6] and other [6,7] effects on the optical stability of *unbridged* diphenyls.

Accordingly 2 : 2′-dimethyl-6 : 6′-dinitrodiphenyl was prepared and was brominated by *N*-bromosuccinimide in the presence of benzoyl peroxide, a method used by Wenner [8] for other ditolyls. Interaction of the resulting 2 : 2′-bisbromomethyl-6 : 6′-dinitrodiphenyl * with piperidine gave the *spiro*-piperidinium compound (I*c*) which was isolated as the iodide. However, the camphorsulphonate failed to crystallise for nearly a year. The dibromo-compound was meanwhile condensed with (−)-ephedrine and, after repeated crystallisation, two diastereoisomeric bromides (VII*a*) were isolated. The one which was less soluble in ethanol had $[\alpha]_{5461}^{23}$ −709° and by a Hofmann degradation gave (−)-2 : 7-dihydro-1-methyl-4′ : 1″-dinitro-3 : 4-5 : 6-dibenzazepine (VIII*a*), with $[\alpha]_{5461}^{19}$ −1343°. The



quaternary bromide which was more soluble in ethanol, had $[\alpha]_{5461}^{18}$ +689° and, in a similar way, gave the (+)-azepine with $[\alpha]_{5461}^{19}$ +1333°.

The azepine was optically stable in benzene solution up to about 100°. The yellow solution became very dark when heated at 110° in the air and it was therefore not possible to follow the racemisation by direct observation of a solution in a jacketed polarimeter tube at a suitable temperature. Instead, a solution of the azepine in benzene was heated in a number of sealed tubes in a thermostat-controlled oil-bath, and tubes were withdrawn at suitable intervals for polarimetric examination. In this way the dinitroazepine in benzene solution was found to have a half-life of 16 hr. at 125° and of 2·6 hr. at 145°, whence the activation energy is 30 kcal. mole^{-1}. Rather surprisingly the dinitroazepine appears to be much less optically stable than the dimethoxyazepinium compound (I*a*), which was only partly racemised after 8 hr. in boiling *cyclo*hexanol solution (160°).[1] However, the difference in the valency state of the nitrogen atom in the two compounds may well affect their relative optical stabilities, as may the alteration in type of solvent. To test this, the methiodide (II; R = NO_2, R′ = R″ = Me, X = I) of the (−)-dinitroazepine was made. It racemised in acetone solution (sealed tubes) at 145° with a half-life of 4·75 hr. It is thus nearly twice as optically stable as the tertiary amine at that temperature, but still not as stable as the quaternary dimethoxy-compound.

The slight steric effect of fluorine, compared with that of any other (necessarily larger) atom or group, is apparent from extensive studies [10] of optical stabilities in non-bridged hindered diphenyls and also from recent spectroscopic work.[11] We therefore prepared 2 : 2′-difluoro-6 : 6′-dimethyldiphenyl [12] and brominated it with peroxide-catalysed *N*-bromosuccinimide. In this case the dibromo-compound failed to crystallise and was

* Shortly after we had first made this compound its preparation by a different method was announced by Iffland and Siegel [3] and by Mislow and Newman.[9]

condensed without isolation with piperidine, giving the salt (I*d*), and with (−)-ephedrine, giving the salt (VII*b*). The latter was crystallised from ethanol and the less soluble bromide obtained as needles with $[\alpha]_{5461}^{18\cdot5}$ +50°. Its diastereoisomer crystallised from aqueous ethanol in hydrated cubes with $[\alpha]_{5461}^{18\cdot5}$ −55°. In view of the expected optical instability of these compounds, Hofmann degradation was carried out at the lowest temperature practicable, *viz.*, about 70°. The resulting azepines (VIII*b*) were liquid and were therefore examined in dilute hydrochloric acid solution without isolation. Approximate concentrations of the deliquescent hydrochlorides were determined subsequently by evaporation. The azepine hydrochlorides had $[\alpha]_{5461}^{18\cdot5}$ +45° and $[\alpha]_{5461}^{18\cdot5}$ −41·5° respectively. They racemised in aqueous hydrochloric acid solution with a half-life of 6·5 hr. at 80° and of 2·0 hr. at 91°. At lower temperatures the rate was too slow for convenient measurement; at higher temperatures the solvent was too near its boiling point. These rates give a value of about 28 kcal. mole^{-1} for the activation energy but the data are inadequate for accurate assessment of E. It is, however, clear that the compound is much more optically stable than the hydrocarbon ester (V), which was inactive after 5 hr. at 32·5°.[3] Slight racemisation (perhaps a few units per cent.) probably occurred during the Hofmann degradation.

The quaternary ephedrinium iodide[1] without *ortho*-substituents (VII; R = H) was also re-examined. It showed no mutarotation in chloroform solution at temperatures in the range 0—50°.

Experimental

(In all polarimetric readings, unless otherwise stated, l = 2.)

2 : 2′-*Bisbromomethyl*-6 : 6′-*dinitrodiphenyl*.—2 : 2′-Dimethyl-6 : 6′-dinitrodiphenyl was prepared by the method of Carlin and Foltz,[13] except that it was found preferable to carry out the Ullmann reaction at 150° instead of 200°. The dinitroditolyl, m. p. 110·5—112° (10·7 g.), was heated under reflux in dry carbon tetrachloride (64 c.c.) with *N*-bromosuccinimide (14·3 g.) and benzoyl peroxide (0·1 g.) for 5 hr. A little more (0·05 g.) catalyst was washed in with carbon tetrachloride (20 c.c.) and heating continued for another 3 hr. The hot solution was filtered and concentrated; crude dibromide separated on cooling. Some of it had also crystallised with the succinimide and was isolated by washing out the latter with much cold water. The product was crystallised from dry benzene (yield, 9·5 g., 64%).* Recrystallisation gave pure 2 : 2′-bisbromomethyl-6 : 6′-dinitrodiphenyl as pale yellow pointed prisms, m. p. 184—185° (Found: C, 39·3; H, 2·1; N, 6·2; Br, 37·4. Calc. for $C_{14}H_{10}O_4N_2Br_2$: C, 39·1; H, 2·3; N, 6·5; Br, 37·2%). The use of slightly impure dinitroditolyl greatly reduced the yield of brominated product.

2 : 7-*Dihydro*-4′ : 1″-*dinitro*-3 : 4-5 : 6-*dibenzazepinium*-1-spiro-1‴-*piperidinium Iodide*.—Piperidine (3·74 g., 2·2 mols.) was added to a solution of the dinitro-dibromide (8·6 g., 1 mol.) in benzene at 50° and the mixture kept at this temperature for 3½ hr. The solution was then decanted from the gum, which was washed with warm benzene and triturated with cold water. The bromide crystallised from water as a pale cream solid, m. p. 302—303° (decomp.) (5·6 g., 65%). It darkened rapidly in light and was therefore converted into the *iodide*, which crystallised from water in deep yellow prisms, m. p. 306—308° (decomp.) (Found: C, 47·4; H, 3·9; N, 8·85; I, 26·8. $C_{19}H_{20}O_4N_3I$ requires C, 47·4; H, 4·2; N, 8·7; I, 26·4%).

(−)-2 : 7-*Dihydro*-1-(2-*hydroxy*-1-*methyl*-2-*phenylethyl*)-1-*methyl*-4′ : 1″-*dinitro*-3 : 4-5 : 6-*dibenzazepinium Bromide*.—A solution of (−)-ephedrine hemihydrate (12 g., 2·3 mols.) in benzene was dried (Na_2SO_4) and added to a solution of 2 : 2′-bisbromomethyl-6 : 6′-dinitrodiphenyl (12·9 g., 1 mol.) in dry benzene at 50°. The mixture became cloudy; it was kept at *ca.* 50° for 35 hr., during which a gum gradually separated. The gum solidified on treatment with water; it was washed with warm benzene and then with cold water (crude yield, 10·3 g.) and crystallised repeatedly from absolute ethanol. The less soluble quaternary (−)-*bromide* (2·5 g.) was obtained as yellow needles, m. p. 248° (decomp.), $[\alpha]_{5461}^{23}$ −709°, $[\alpha]_{D}^{23}$ −544° (*c* 0·994 in MeCN, l = 1) (Found: C, 56·3; H, 4·6; N, 8·25; Br, 15·6. $C_{24}H_{24}O_5N_3Br$ requires C, 56·0; H, 4·7; N, 8·2; Br, 15·5%).

(+)-2 : 7-*Dihydro*-1-(2-*hydroxy*-1-*methyl*-2-*phenylethyl*)-1-*methyl*-4′ : 1″-*dinitro*-3 : 4-5 : 6-*di*-

* Newman, Rutkin, and Mislow[14] report that they also tried this method of preparation of the dibromide (cf. ref. 9) but only obtained a 10% yield.

SOCIETY OF CHEMICAL INDUSTRY

Founded 1881. Incorporated by Royal Charter, 1907

President: SIR ROBERT ROBINSON, O.M., F.R.S.

OPTICAL ACTIVITY IN A 2:2′-BRIDGED DIPHENYL WHERE THE BRIDGE FORMS PART OF A HETEROCYCLIC EIGHT-MEMBERED RING

By Shakti R. Ahmed and D. Muriel Hall

Bedford College, Regent's Park, London, N.W.1

Reprinted from Chemistry and Industry,
October 11, 1958

LONDON: 14 BELGRAVE SQUARE, S.W.1

REPRINTED FROM CHEMISTRY AND INDUSTRY, 1958, p. 1329

OPTICAL ACTIVITY IN A 2 : 2′-BRIDGED DIPHENYL WHERE THE BRIDGE FORMS PART OF A HETEROCYCLIC EIGHT-MEMBERED RING

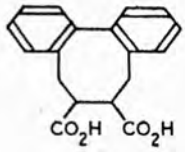
By Shakti R. Ahmed and D. Muriel Hall

*Bedford College, Regent's Park, London, N.W.*1

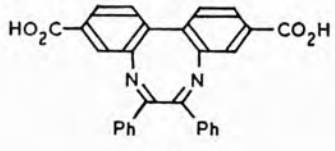
Recently Dvorken, Smyth and Mislow[1] obtained the *cis* and *trans* acids (I) in optically active, optically unstable forms. Earlier, Bell[2] had resolved the acid (II). These are the only examples of enantiomorphism in 2 : 2′-bridged diphenyls without other *ortho* substituents, where the bridge forms part of an eight-membered ring. In the case of Bell's compound the additional double bonds in the ring apparently confer very considerable additional optical stability.

We have now prepared 1 : 2 : 7 : 8-tetrahydro-3 : 4–5 : 6–dibenzazocino-l-*spiro*-l′-piperidinium iodide (III) by a method based on that used by Kobayashi and Uyeo[3] for the synthesis of *0 : 0*-dimethyl*apo*-galanthamine. The (+)-α-bromocamphor-π-sulphonate was obtained as a single diastereoisomeride, m.p. 201° (Found: C, 60·55; H, 6·3; O, 11·0; N, 2·5; Br, 13·4; S, 5·3. $C_{30}H_{38}O_4NBrS$ requires C, 61·2; H, 6·5; O, 10·9; N, 2·4; Br, 13·6; S, 5·4%) which in ethanol solution underwent very rapid mutarotation at 20° and had a half-life of about 14 minutes at 7° (α_{5461} changing from +0·87° to +1·35°; $l = 2$, *c.*, 1·05).

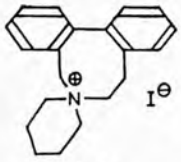
By dissolving some of the salt in ethanol at –10° and treating the solution at –10° with cold ethanolic picric acid the (–) -picrate was obtained with m.p. 196–197°, $[\alpha]^2_{5461}$–54° ($l = 2$, *c.*, 0·413) in acetone (5 minutes after wetting the salt with solvent) (Found: C, 61·55; H, 5·1; O, 22·05; N, 11·1. $C_{26}H_{26}O_7N_4$ requires C, 61·5; H, 5·4; O, 22·1; N, 11·0%). The picrate racemised in acetone solution with a half-life of about 27 minutes at 2°, α_{5461} changing from –0·45° to 0°.



(I)



(II)



(III)

The heterocyclic compound is thus less optically stable than Mislow's acids, which had half lives of 85 and 12 minutes at 31·5° for racemisation (the *cis*) and mutarotation (the *trans*).

Received August 12, 1958

References

[1] Dvorken, L. V., Smyth, R. B. & Mislow, K., *J. Amer. chem. Soc.*, 1958, **80**, 486
[2] Bell, F., *J. chem. Soc.*, 1952, 1527
[3] Shigeru Kobayashi & Shojiro Uyeo, *ibid.*, 1957, 638

PRINTED BY RICHARD MADLEY LTD., 54 GRAFTON WAY, LONDON, W.1, ENGLAND