STEREOCHEMISTRY OF SOME BICYCLIC COMPOUNDS

Thesis submitted for the
Degree of Doctor of Philosophy
in the University of London

by

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ABSTRACT

This thesis is presented in four parts.

Part I describes the synthesis of the hydrocarbon 3:4-5:6-dibenzo*cyclo*hepta-3:5-diene and the introduction of a carboxylic acid group into the diphenyl nucleus. On examination, no evidence of the existence of optical isomerism of the acid could be found. The ultraviolet absorption spectrum of the hydrocarbon, in ethanol solution, showed an inflection at 280 mμ, which had hitherto not been recorded.

The synthesis of 2:2'-bisbromoethyldiphenyl is described. Condensations of this compound with piperidine gave an unbridged product instead of the expected diphenyl, bridged across the 2:2'-positions with a chain of five atoms to form altogether a nine-membered bridging ring. Treatment of 2:2'-bisbromoethyldiphenyl with diethyl malonate in the presence of sodium ethoxide resulted in loss of the elements of hydrogen bromide and formation of 2:2'-divinyldiphenyl.

2-Carbomethoxy-2'-carbomethoxymethyldiphenyl was synthesized and treated with finely divided sodium in xylene. Instead of the expected acyloin-type condensation, a condensation of the Dieckmann type took place, resulting in a diphenyl containing a six-membered bridging ring.

Part II is devoted to the synthesis and reactions of 4:5-4':5'-tetramethyldiphenyl. This compound was prepared with the intention of introducing two chloromethyl groups in the 2:2'-positions, and forming a bridging ring by suitable condensations. Only one chloromethyl group could be introduced in the diphenyl nucleus.

Part III contains an account of the preparation of di-β-naphthol and the attempts to resolve it. Its dimenthoxyacetic ester was prepared but its dihydrogen succinate and dihydrogen phthalate could not be made.

Part IV describes the synthesis of N-benzoyl-2'-bromo-4':6'-dimethyldiphenylamine-3-carboxylic acid, although complete and final proof of its preparation was unobtainable.

The treatment of 2'-chloro-N-benzoyl-6-methyldiphenylamine-2-carboxylic acid with lithium aluminium hydride is also described.

The author wishes to express her sincere thanks to Professor E.E. Turner, F.R.S., for his supervision of her work and for his continued help and advice. She is also grateful to Dr. D.M. Hall for her interest and encouragement.

Notes

All melting points are uncorrected.

The analyses were carried out by Dr. Weiler and Dr. Strauss, Oxford, and by Alfred Bernhardt, Mulheim (Ruhr).

Stereochemistry of some bicyclic compounds

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PART I

STUDIES OF SOME 2:2'-BRIDGED DIPHENYLS

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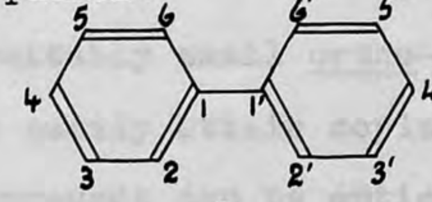
INTRODUCTION

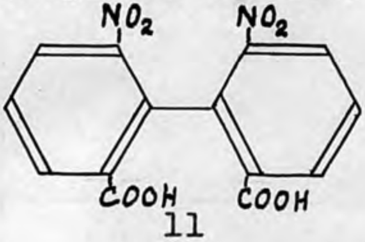
When the diphenyl molecule (1) rotates freely about the 1:1' single bond, the molecule must pass through a transition state in which the phenyl rings are not only collinear but also coplanar.



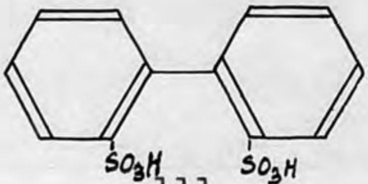
1

In the completely unsubstituted molecule of diphenyl itself, coplanarity is easily achieved. Dhar (Indian J. Physics, 1932,7,43) showed by x-ray crystal analysis that diphenyl in its crystalline state is planar, but electron diffraction investigations by Karle and Brockway (J.Amer.Chem. Soc.,1944,66,1974) showed that in liquid and vapour states the diphenyl molecule is non-planar.

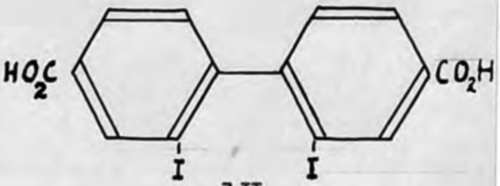
The benzene rings in a diphenyl molecule can be prevented from becoming coplanar by the introduction of suitable substituents in the ortho-positions of the diphenyl nucleus. The rotation about the 1:1'-bond is thereby restricted and the molecule is twisted and becomes dissymmetric. This has been demonstrated by the optical resolution of many compounds containing such substituents. Christie and Kenner (J.,1922, 121,614) resolved 6:6'-dinitrodiphenic acid (11) through its brucine salt; 2:2'-diphenyldisulphonic acid (111) was resolved through its strychnine hydrogen salt by Lesslie and Turner (J.,1932,2394); Searle and Adams (J.Amer.Chem.Soc., 1933,55,1649) resolved 2:2'-diiodo-4:4'-diphenic acid (IV) through its brucine salt.



ll



lll



lV

Compounds with suitably small <u>ortho</u>-substituents, or with none at all, can easily attain coplanarity. In intermediate cases compounds can be optically activated but are too optically labile to be resolved. They racemize easily and coplanarity is not prohibited. The activation energies for the configurational changes involved in racemization are of the order of 20-30 k.cals./g.mol.

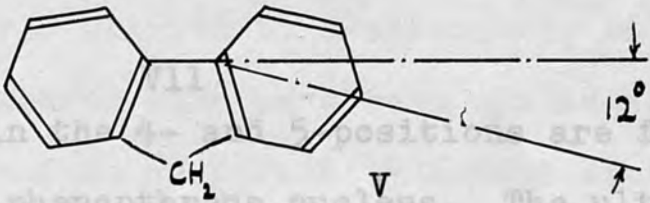
These optical studies give information about the ease with which the molecule can pass through the planar transition state, not about the preferred configuration of the molecule.

In some compounds the diphenyl skeleton can be forced to become non-coplanar by joining the 2:2'-positions to produce a strainless multiplanar bridge. The diphenyl skeleton itself remains collinear. Compounds having this bridged structure and containing also suitable substituents in the 6:6'-positions should be resolvable. Diphenyls which are bridged across the 2:2'-positions but which contain no other <u>ortho</u>-substituents, if not capable of resolution, should however be capable of showing unstable optical activity.

Bridged diphenyls can be conveniently classified according to the size of the bridging ring.

Bridge forming part of a five-membered ring.

The simplest bridged diphenyl is fluorene (V) in which the 2:2'-positions are linked by a single methylene group. Fluorene, however, is a strained molecule because, although its planar structure has been established, the benzene rings are not collinear but are bent at an angle of 12° with the 1:1'-bond. (Brown and Bortner, Acta Cryst.,1954,7,139; Burns and Iball, Nature,1954,173,635.)

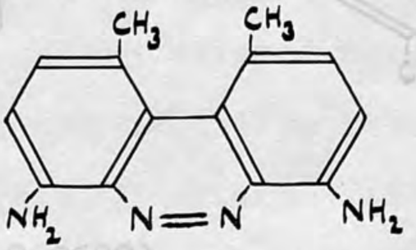


V

Bridge forming part of a six-membered ring.

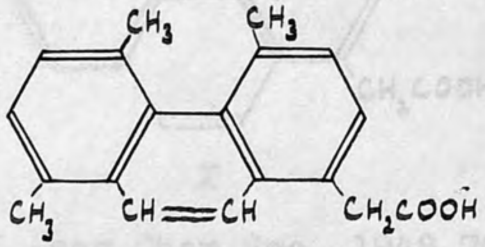
In some compounds the bridging ring is aromatic and lies in the same plane as the benzene rings. Substituents in the 6:6'-positions can only be accommodated if they are forced out of the plane of the benzene rings. The resulting deformation of the molecule, which has been called intramolecular overcrowding, gives rise to optical activity.

Theilacker and Baxmann (Annalen,1953,581,117) resolved (Vl) through its α-bromo-(+)-camphorsulphonate.



Vl

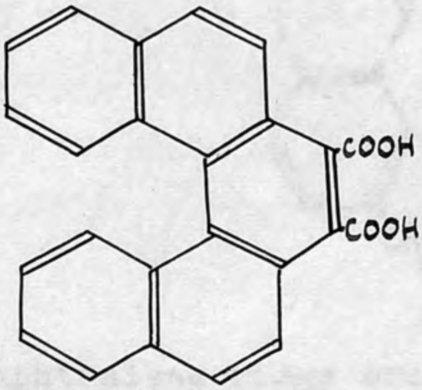
The optical activity is due to the deformation of the molecule, in which the methyl groups are forced out of the plane of the benzene rings. The optical activity is due to a similar cause in compound (Vll), the brucine salt of which underwent a second-order asymmetric transformation. (Newman and Hussey, J.Amer.Chem.Soc.,1947,69,978.)

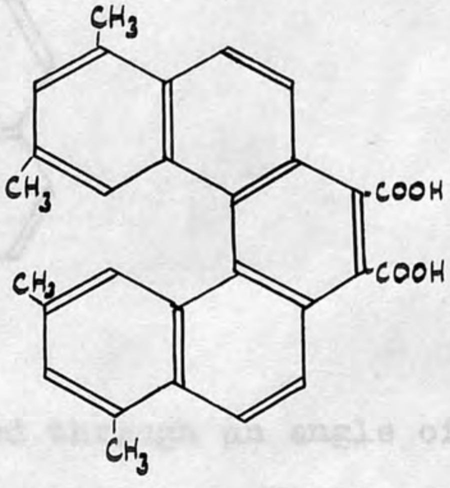


Vll

The methyl groups in the 4- and 5-positions are forced out of the plane of the phenanthrene nucleus. The ultra-violet absorption spectrum, studied by the same workers (ibid.,3023) has shown that the benzene rings are coplanar.

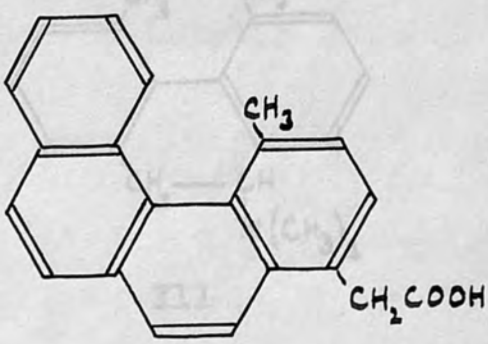
Other compounds which exhibit intramolecular overcrowding are





Vlll lX

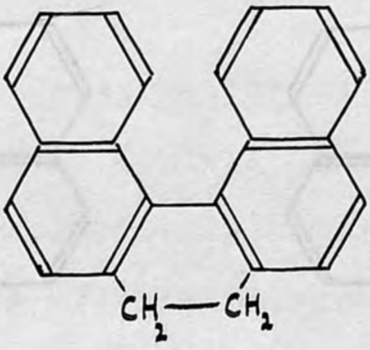
(Bell and Waring, J.,1949,2689)



X

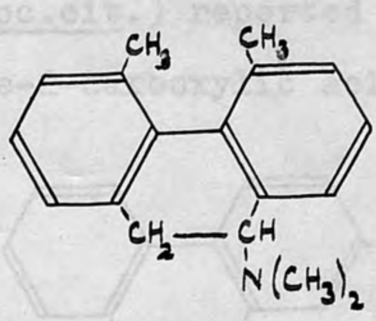
(Newman and Wheatley, J.Amer.Chem.Soc.,1948,70,1913)

A number of diphenyls bridged by a saturated, multiplanar bridge to form a six-membered ring have been synthesized in an optically active form from an optically active starting material. Hall and Turner (J.,1955,1242) obtained (X1) in an optically active form starting from resolved 1:1'-dinaphthyl-2:2'-dicarboxylic acid.



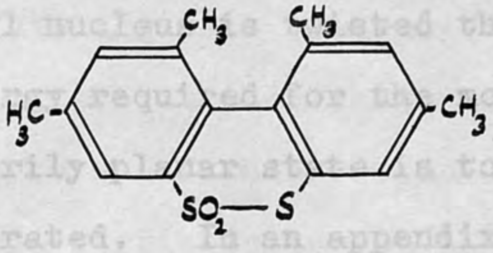
X1

The naphthalene rings are twisted through an angle of about 20° to accommodate the methylene bridge. Wittig and Zimmermann (Ber., 1953,86,629) obtained (X11) optically active from optically active 6:6'-dimethyl-2:2'-diphenic acid.

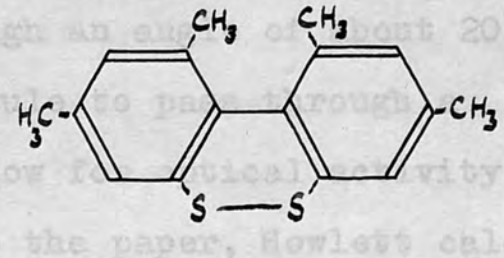


Xll

Armarego and Turner (J.,1956,3668) obtained optically active forms of (Xlll) and (XlV)

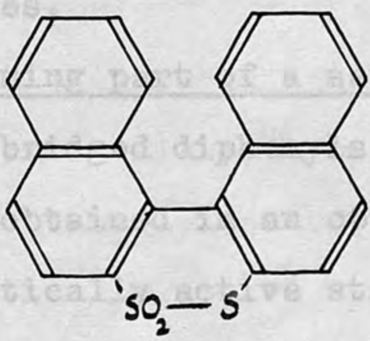


Xlll

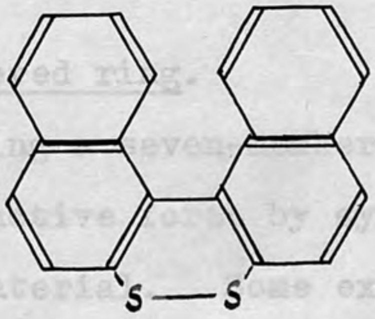


XlV

and of (XV) and (XVl)



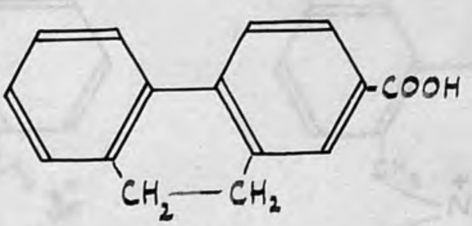
XV



XVl

by starting with the corresponding disulphonic acid in an optically active form. Models show that in these compounds the angle between the planes of the rings is about 35°. There is also a slight deformation of the molecule in order to accommodate the methyl groups in the 4- and 5-positions, or the benzene rings which act as substituents.

Hall and Turner (loc.cit.) reported attempts to activate 9-10-dihydrophenanthrene-2-carboxylic acid (XV11) which were unsuccessful.



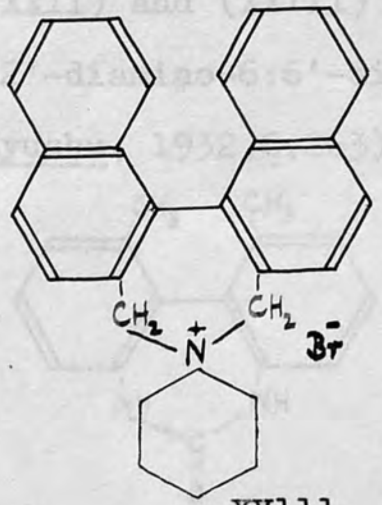
XV11

Models of 9-10-dihydrophenanthrene itself show that the diphenyl nucleus is twisted through an angle of about 20° and the energy required for the molecule to pass through a temporarily planar state is too low for optical activity to be demonstrated. In an appendix to the paper, Howlett calculated the energy of activation to be 1·4 k.cals./mol., and suggested that activity would only be detectable at very low temperatures.

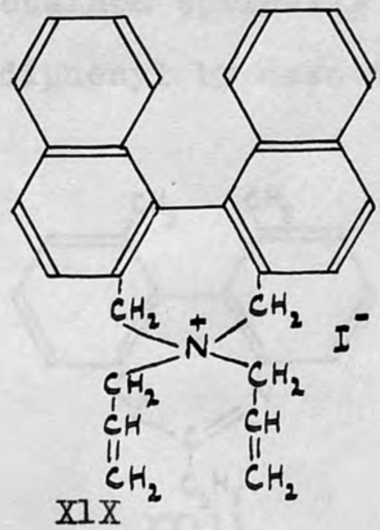
Bridge forming part of a seven-membered ring.

Many bridged diphenyls containing a seven-membered ring have been obtained in an optically active form by synthesis from an optically active starting material. Some examples are reviewed overleaf.

Hall and Turner (loc.cit.) have obtained (XV111) and (X1X) in optically active form by synthesis from optically active 1:1'-dinaphthyl-2:2'-dicarboxylic acid. The compounds had a large specific rotation.



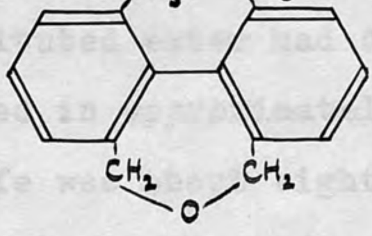
XVlll



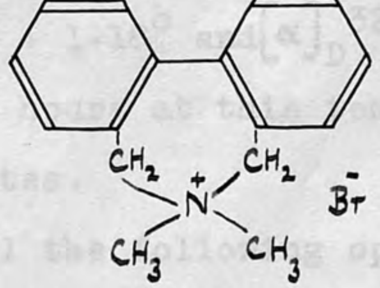
XlX

Compound (XVlll) with a seven-membered bridging ring is more optically stable than compound (Xl) which was studied by the same workers and which contains a six-membered bridging ring. Since the steric influence of the benzene rings which act as substituents should be the same in both compounds, the difference in optical stability must be due to the much greater distortion required for the seven-membered ring to pass through the planar configuration.

Wittig and Zimmermann (<u>loc.cit.</u>) obtained compounds (XX) and (XXl) optically active.

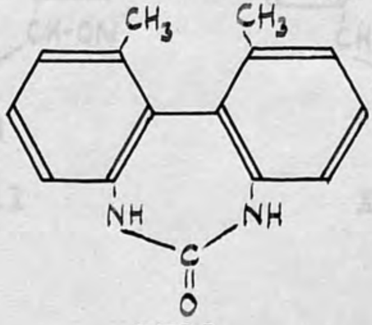


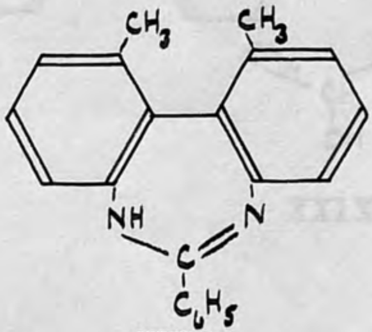
XX



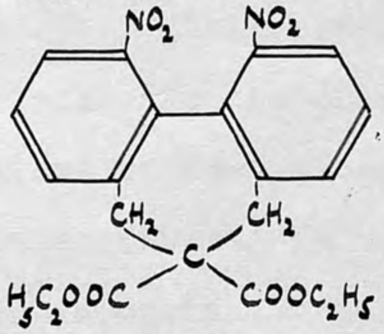
XXl

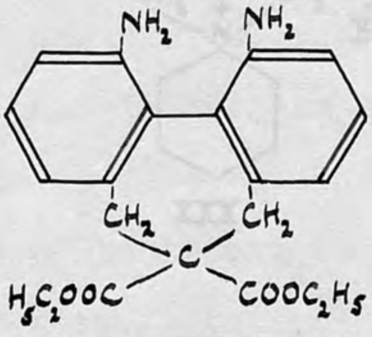
Compounds (XX11) and (XX111) were obtained optically active from (-)-2:2'-diamino-6:6'-dimethyldiphenyl by Sako (Mem. Coll.Eng. Kyushu, 1932,6,263).

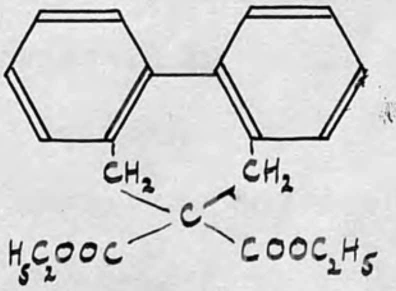

XX11


XX111

By starting from optically pure (+)-6:6'-dinitrodiphenic acid, Iffland and Siegel (J.Amer.Chem.Soc., 1958,80,1947) prepared (XX1V), (XXV) and (XXV1) as optically active compounds.

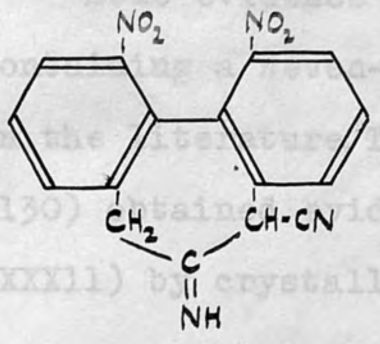

XX1V


XXV

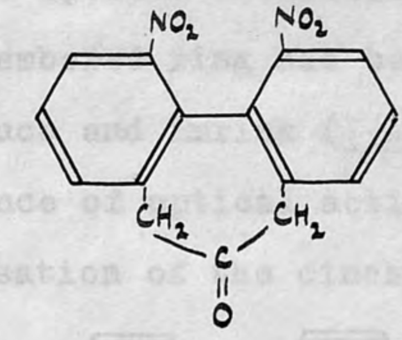

XXV1

The unsubstituted ester had $\alpha_D^{32\cdot5}$ + 1·18° and $[\alpha]_D^{32\cdot5}$ + 2·25°, and racemized in approximately five hours at this temperature. Its half life was about eighty minutes.

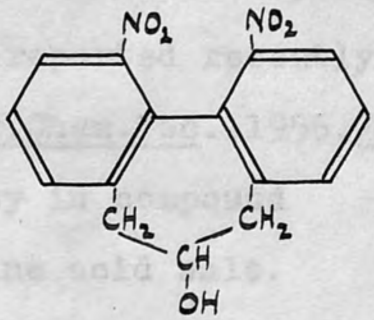
From the same starting material the following optically active compounds have been prepared:-



XXV11

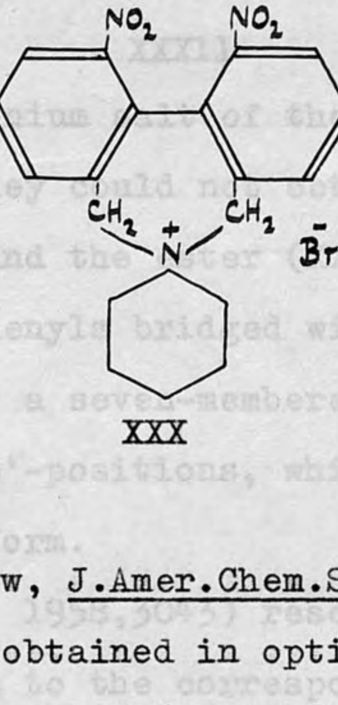


XXV111



XX1X

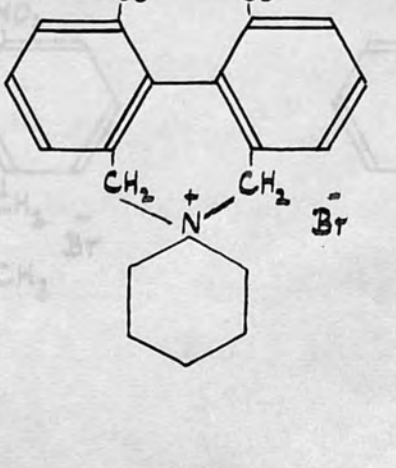
(Newman, Rutkin and Mislow, J.Amer.Chem.Soc.,1958,80,465)



XXX

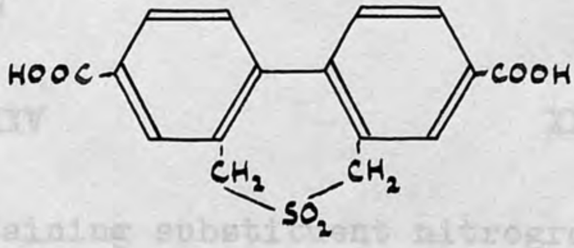
(Fitts, Siegel and Mislow, J.Amer.Chem.Soc.1958,80,480)

Compound (XXX1) has been obtained in optically active form from (+) 6:6'-dichlorodiphenic acid (idem.,ibid.).



XXX1

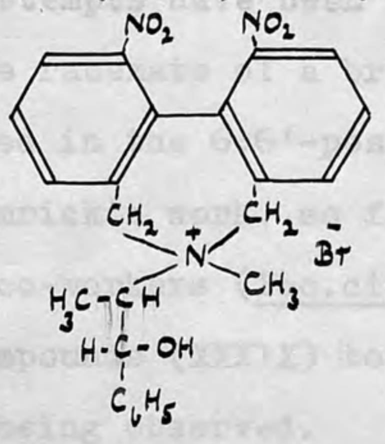
Some evidence of optical isomerism in a racemic diphenyl containing a seven-membered ring has been reported recently in the literature. Truce and Emrick (J.Amer.Chem.Soc.,1956,78, 6130) obtained evidence of optical activity in compound (XXX11) by crystallisation of the cinchonine acid salt.



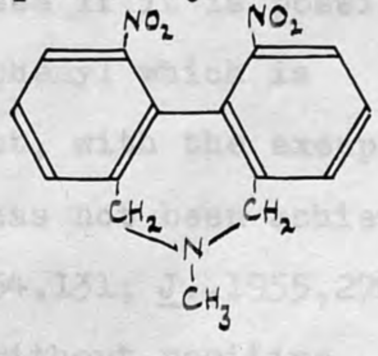
XXX11

They found that the ammonium salt of the free acid had $[\alpha]_D^{25}$ $+ 3{\cdot}1^{\circ}$ in solution. They could not obtain the lævoenantiomorph. This compound and the ester (XXV1) of Iffland and Siegel are the only diphenyls bridged with a chain of three atoms to form altogether a seven-membered ring, and unsubstituted in the 6:6'-positions, which have been obtained in an optically active form.

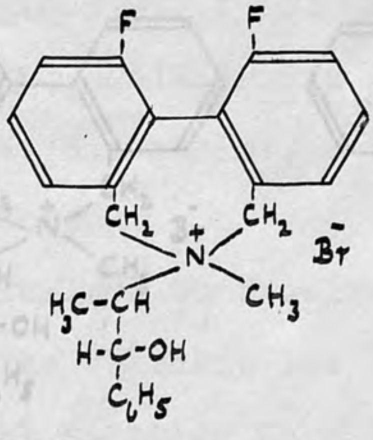
Ahmed and Hall (J., 1958,3043) resolved (XXX111) and (XXXV) and degraded them to the corresponding dihydrodibenzazepines (XXX1V) and (XXXV1) respectively.



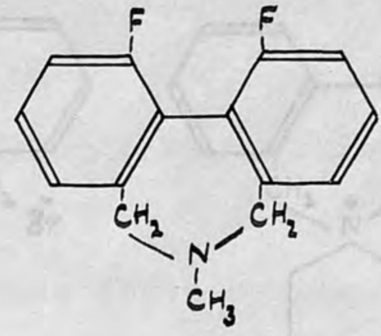
XXX111



XXX1V

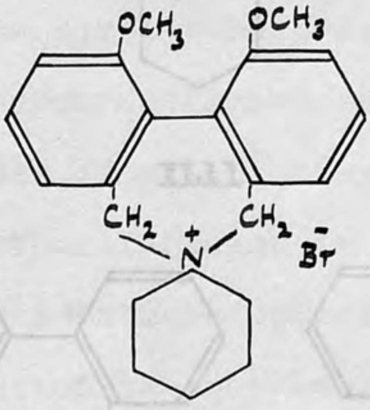


XXXV

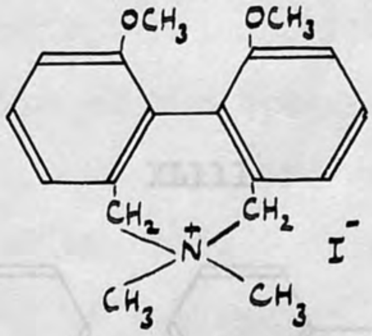


XXXV1

The compounds containing substituent nitrogroups had very high specific rotations and were optically stable. Turner and co-workers (J., 1952,854) resolved (XXXV11) through the camphorsulphonate but could not resolve (XXXV111).

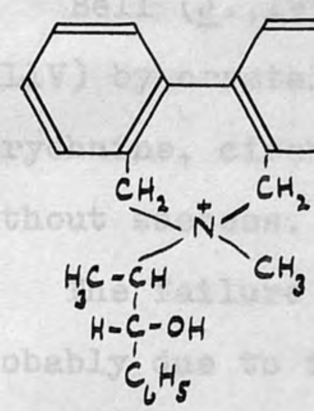


XXXV11

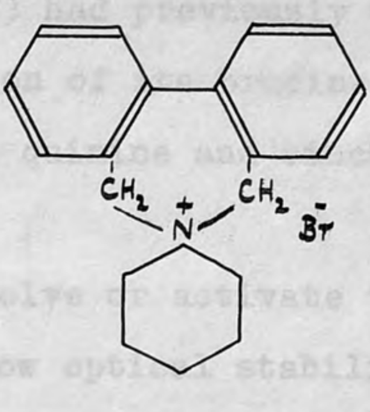


XXXV111

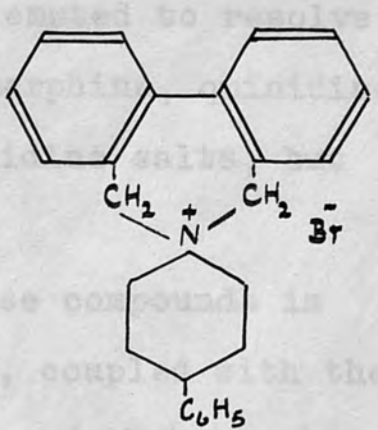
Many attempts have been made to see if it is possible to activate the racemate of a bridged diphenyl which is unsubstituted in the 6:6'-positions but, with the exception of Truce and Emrick's work, so far this has not been achieved. Turner and co-workers (loc.cit.; J.,1954,131; J.,1955,2708) examined compounds (XXX1X) to (XLV1) without positive activation being observed.



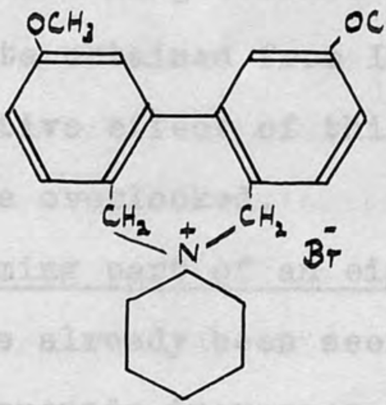
XXXlX



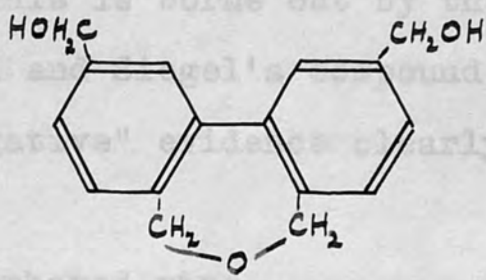
XL



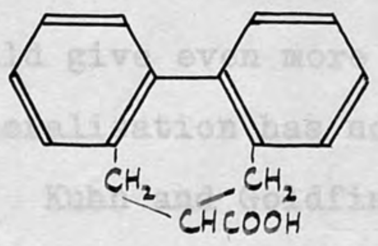
XLl



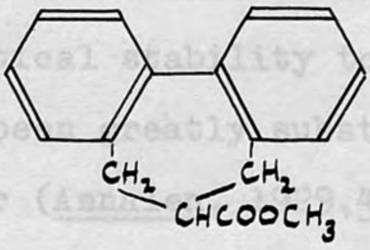
XLll



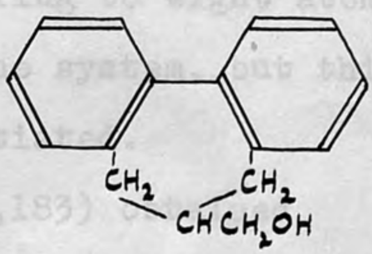
XLlll



XLlV



XLV



XLVl

Ahmed and Hall (<u>loc.cit.</u>) also re-examined (XXXlX) in chloroform solution over a temperature range from 0° to 50° but obtained no evidence of mutarotation.

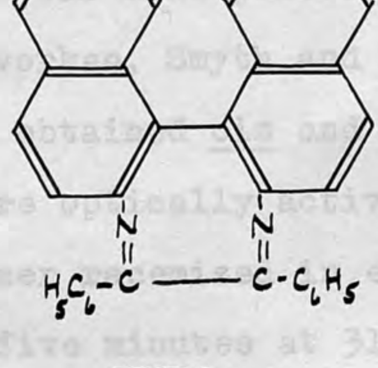
Bell (J.,1952,1527) had previously attempted to resolve (XL1V) by crystallisation of its brucine, morphine, quinidine, strychnine, cinchonine, quinine and cinchonidine salts, but without success.

The failure to resolve or activate these compounds is probably due to their low optical stability, coupled with the low optical rotation which is characteristic of the compact seven-membered ring structure. This is borne out by the optical data obtained from Iffland and Siegel's compound (XXV1). The cumulative effect of this "negative" evidence clearly must not be overlooked.

Bridge forming part of an eight-membered ring.

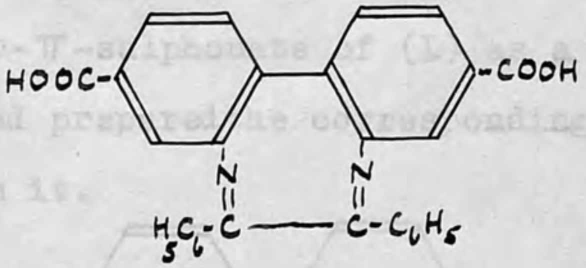
It has already been seen that the optical stability of bridged compounds increases as the size of the bridging ring is increased from six to seven atoms. It might be expected that a further increase in the size of the ring to eight atoms would give even more optical stability to the system, but this generalisation has not been greatly substantiated.

Kuhn and Goldfinger (Annalen, 1929,470,183) obtained (XLV11) in an optically active form by the interaction of (+)-2:2'-diamino-1:1'-dinaphthyl with benzil.



XLV11

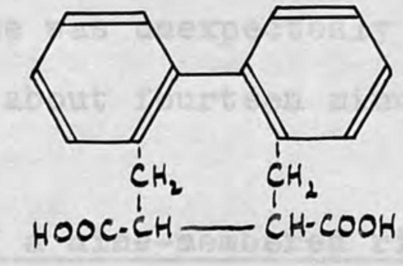
Other compounds have been studied which contain no 6:6'-substituents. Bell (*loc.cit.*) resolved (XLV111) through its brucine salt.



XLV111

The double bonds in the bridging ring of these last two compounds probably increase their optical stabilities by greatly reducing ring flexibility.

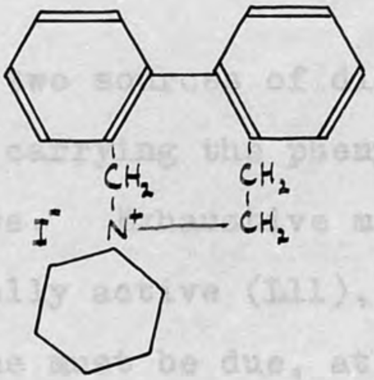
Turner and co-workers (*J.*,1955,2708) made compound (1L) and its corresponding esters.



1L

They obtained two forms of the acid which were probably *cis* and *trans* isomers but they also pointed out that additional diastereoisomerism due to the twisted ring system and to the asymmetric carbon atoms was also possible. In a later study of the same compound Dvorken, Smyth and Mislow (*J.Amer.Chem. Soc.*,1958,*80*,486) also obtained *cis* and *trans* forms of the acid, both of which were optically active and optically unstable. The *cis* isomer racemized in ethanol solution with a half life of eighty-five minutes at $31\cdot5^{\circ}$; the *trans* isomer was much less stable mutarotating with a half life of twelve minutes at the same temperature and in the same solvent.

Ahmed and Hall (<u>Chem.and Ind</u>., 1958,1329) obtained the (+)-α-bromocamphor-π-sulphonate of (L) as a single diastereoisomer, and preparedthe corresponding optically active picrate from it.

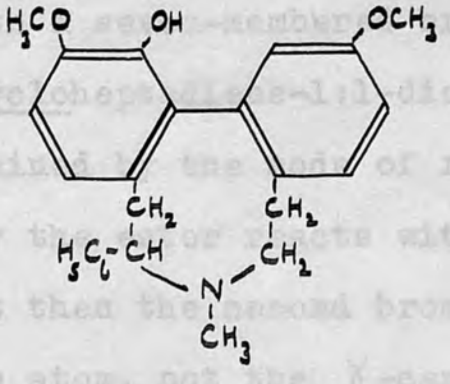


L

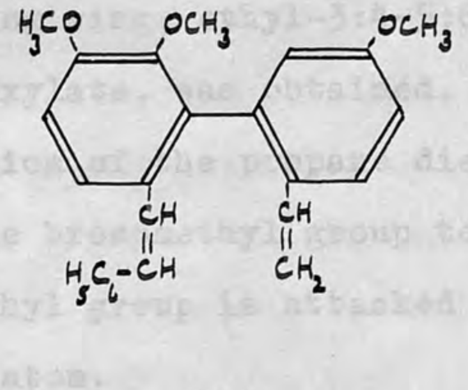
This dibenzazocine was unexpectedly optically labile. It had a half life of about fourteen minutes at 7° in ethanol solution.

<u>Bridge forming part of a nine-membered ring</u>.

It is well-known that nine-membered cyclic compounds are difficult to prepare and very few preparations have been described. Robinson (<u>Proc.Roy.Soc.A</u>.,1948,<u>192</u>,xiv) recorded the preparation of optically active phenyldihydrothebaine (L1) from the treatment of the natural product thebaine with phenyl magnesium bromide.



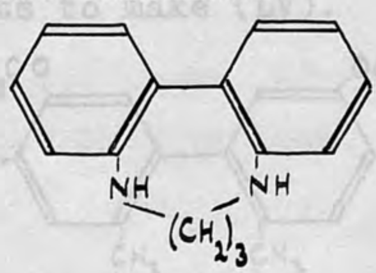
Ll



Lll

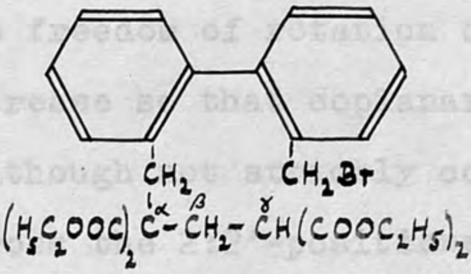
The compound possesses two sources of dissymmetry; the asymmetric carbon atom carrying the phenyl group, and the twisted diphenyl nucleus. Exhaustive methylation leads to the formation of optically active (Lll), hence the activity of phenyldihydrothebaine must be due, at least in part, to the presence of the diphenyl skeleton.

Stetter (<u>Ber</u>.,1953,<u>86</u>,380) described the preparation of (Llll) by the condensation of the di-<u>p</u>-toluenesulphonyl derivative of 2:2'-diaminodiphenyl with 1:3-dibromopropane in the presence of sodium butoxide.



Llll

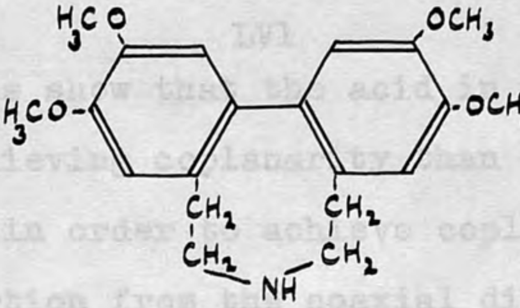
Other workers who have attempted to prepare a diphenyl compound containing a nine-membered ring have been less successful. Turner and co-workers (<u>J</u>.,1955,2708) studied the interaction of 2:2'-bisbromomethyldiphenyl with ethyl-propane -1:1-3:3-tetracarboxylate in the presence of sodium ethoxide. Instead of the expected compound the hydrocarbon ester with a seven-membered bridging ring, ethyl-3:4-5:6-dibenzo*cyclo*heptadiene-1:1-dicarboxylate, was obtained. This was explained by the mode of reaction of the propane diester. Initially the ester reacts with one bromomethyl group to give (L1V) but then the second bromomethyl group is attacked by the α-carbon atom, not the γ-carbon atom.



L1V

This two-stage attack by the α-carbon atom has been noted in other reactions involving this ester, but in this case steric hindrance would also tend to prevent attack by the γ-carbon atom.

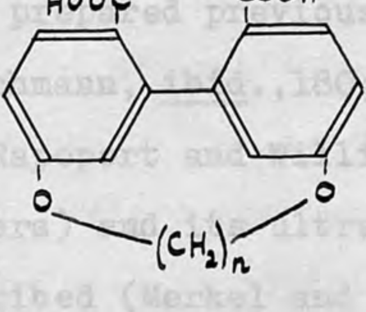
Cromartie, Harley-Mason and Wannigama (*J.*,1958,1982) failed in their attempts to make (LV).



LV

Bridge forming part of a higher-membered ring.

Little is known about diphenyls containing higher membered bridging rings. Stetter (loc.cit.) has prepared compounds similar to (Llll) with four and five methylene groups in the bridge, but no attempts at optical activation have been recorded. It is probable that as the bridging ring increases in size the freedom of rotation of the diphenyl nucleus will also increase so that coplanarity will again be easily achieved. Although not strictly comparable with diphenyls bridged across the 2:2'-positions, the 5:5'-(polymethylenedioxy)-diphenic acids (LVl) of Adams and Kornblum (J.Amer.Chem.Soc.,1941,63,188) are of interest.

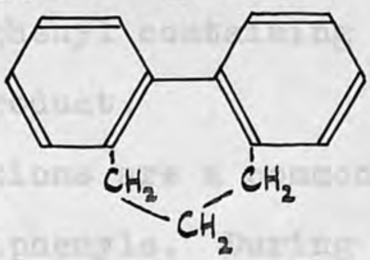


LVl

"Stuart" models show that the acid in which n = 10 has greater ease in achieving coplanarity than the compound in which n = 8, where in order to achieve coplanarity there has to be slight distortion from the coaxial diphenyl structure. The decamethylenedioxy acid is more optically labile than the octamethylenedioxy acid.

The present work has been concerned with 2:2'-bridged diphenyls which contain no other substituents in the diphenyl nucleus.

No diphenyl compound, bridged across the 2:2'-positions with a homocyclic bridging ring and containing no further substituents in the 6:6'-positions of the diphenyl nucleus, has been optically activated starting from the racemate, although, as has already been stated, many such activations have been attempted. Probably the simplest compounds of this type are the hydrocarbons which contain a bridging chain of methylene groups. An acid derivative of 9-10-dihydrophenanthrene, the simplest collinear diphenyl of this kind, has been examined for evidence of optical isomerism (Hall and Turner, J.,1955,1242). The hydrocarbon with three methylene groups in the bridging chain, 3:4-5:6-dibenzocyclohepta-3:5-diene (LVll), had been prepared previously (Lettré,Angew. Chem.,1947,59,218; Wichmann, ibid.,180; Cook, Dickson and Loudon, J.,1947,746; Rapoport and Williams, J.Amer.Chem.Soc., 1949,71,1774; and others) and its ultraviolet absorption spectrum was also described (Merkel and Wiegand,Annalen,1947, 557,242; z.Naturforsch.,1948,3,b,93).



LVll

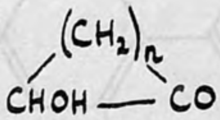
At the commencement of the present work it was considered of interest to attempt the optical activation of this bridged diphenyl containing a seven-membered homocyclic ring, and so the introduction of a salt-forming group into a non-blocking position of the diphenyl nucleus was accordingly effected.

A number of attempts to obtain the compound optically active were made. No evidence of optical isomerism was found. The ultraviolet absorption spectrum of the parent hydrocarbon was repeated.

It has already been seen that the difficulties of synthesizing a diphenyl containing a nine-membered bridging ring are considerable. Since the attempt of Turner and co-workers to condense 2:2'-bisbromomethyldiphenyl with ethyl propane-1:1-3:3-tetracarboxylate was unsuccessful because of the nature of the condensing ester, the possibility of introducing methylene groups into the bridging ring by elongating the groups in the 2:2'-positions of the parent diphenyl was considered. The possibility that the reactivity of bromine atoms at the end of such elongated groups would be diminished was not overlooked. The synthesis of 2:2'-bis-β-bromoethyldiphenyl was therefore carried out by the present worker, and condensations were attempted with ethyl malonate in the present of sodium ethoxide and with piperidine. Neither condensation gava a diphenyl containing a nine-membered bridging ring as the product.

Suitable condensations are a common means of synthesizing bridged diphenyls. During the synthesis of 3:4-5:6-dibenzo<u>cyclo</u>hepta-3:5-diene a Thorpe cyclisation of a dinitrile was carried out. Attention was given to the possibility of using other cyclisation methods for the preparation of cyclic derivatives of diphenyl. Some work carried out in 1947 (Prélog <u>et al</u>.,<u>Helv.Chim.Acta</u>,1947,<u>30</u>, 1741; Stoll and Hulstkamp,<u>ibid</u>.,1815; Stoll and

Rouvé,*ibid.*,1822) on the action of finely divided sodium on the esters of dicarboxylic acids led to the preparation of cyclic acyloins of the type (LV111) where n was seven or greater.

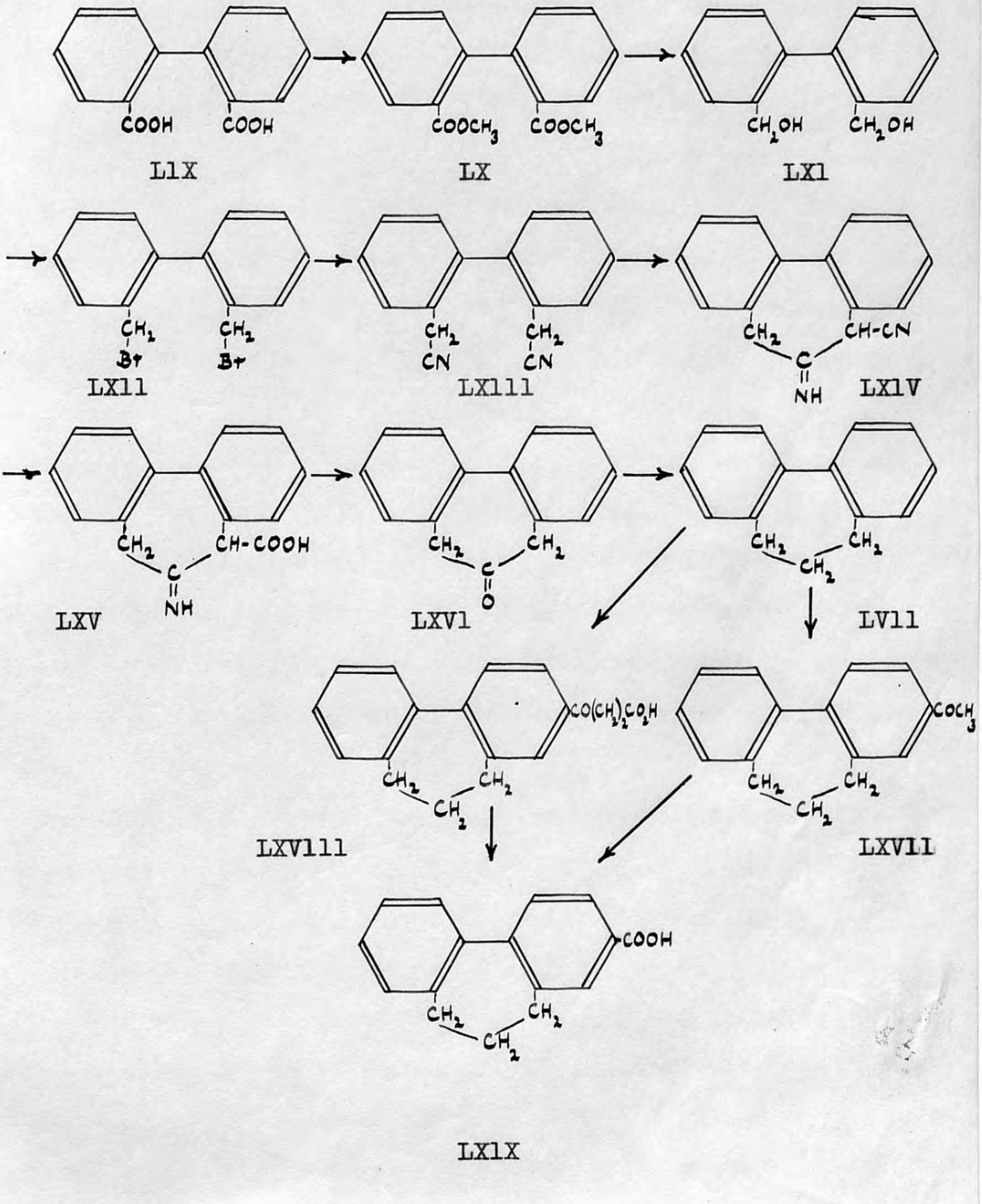


LV111

It seemed possible that a condensation of this type could be used for the preparation of bridged diphenyls. In the present work, the ester 2-carbomethoxy-2'-carbomethoxymethyl-diphenyl was treated with finely divided sodium using similar conditions to those of the above workers. It was hoped to prepare a diphenyl having a seven-membered acyloin bridging ring, and hence, by reduction, to obtain 3:4-5:6-dibenzo*cyclo*hepta-3:5-diene by a new method of synthesis. Instead of the expected acyloin-type condensation, however, the ester underwent a Dieckmann condensation and the product was a diphenyl containing a six-membered bridging ring.

EXPERIMENTAL

THE SYNTHESIS OF 3:4-5:6-DIBENZOCYCLOHEPTA-3:5-DIENE AND THE ACIDS DERIVED FROM IT.



Preparation of dimethyl-2:2'-diphenate LX

Diphenic acid supplied by Light and Co., was used. m.p. 228 - 230°.

Diphenic acid (100 g.) was dissolved in methanol (1000 g.). Concentrated sulphuric acid (100 g.) was added cautiously and the mixture was heated under reflux for six hours on a water bath. It was poured into approximately two litres of water and the ester came down as a white crystalline solid on stirring. It was filtered off and washed with sodium bicarbonate solution. It was crystallized from methanol and came down as prisms m.p. 73 - 74°. Yield 100 g. Percentage yield 89%.

In subsequent reactions the time of heating was reduced to four hours without decreasing the yield. It was also found unnecessary to crystallize the dimethyl diphenate. After drying, first at 60° in the air, and then over concentrated sulphuric acid in a vacuum desiccator, the crude ester melted at 73 - 74°. The crude yield was increased to 96%.

Preparation of 2:2'-bishydroxymethyldiphenyl LX1

The method of Hall, Lesslie and Turner, J.Chem.Soc.,1950,711 was used.

Lithium aluminium hydride (17 g.; 1·6 mol.,) in 600 ml. dry ether was placed in a flask fitted with a dropping funnel, double walled condenser and calcium chloride tube. A solution of dimethyl-2:2'-diphenate (76 g.; 1 mol.,) in 700 ml. dry ether was added at such a rate as to maintain a gentle refluxing of the ether. Anhydrous conditions were maintained throughout the addition. On completion of the addition the reaction mixture was allowed to stand for about fifteen minutes then the excess lithium aluminium hydride was decomposed by the cautious addition of water. Dilute sulphuric acid (1 volume bench dilute acid : 1 volume water) was added to break down the sludge of aluminates and complex salts. The reaction mixture formed two layers which were separated; the aqueous layer was washed with ether. The combined ethereal solutions were washed with water and the ether was distilled off. The diol remained as a solid. It crystallized from benzene in large needles, m.p. 111 - 113°. Yield 52.4 g. Percentage yield 87%. In a later reaction the yield was increased to 93%.

Preparation of 2:2'-bisbromomethyldiphenyl LX11

Hall, Lesslie and Turner, J.Chem.Soc.,1950,711.

48% $^{w}/w$ Hydrobromic acid (750 ml.) was heated under reflux until its temperature reached 90°. 2:2'-Bishydroxymethyl diphenyl (15 g.) was added gradually and the mixture was boiled for twenty minutes and allowed to cool. The pink oil which had separated out gradually solidified, and the solid was removed by filtration through a sintered glass funnel. It was dried in a vacuum over potassium hydroxide. Four reactions were carried out and the combined products were crystallized together from light petroleum (b.p. 60 - 80°), using decolorizing charcoal. The 2:2'-bisbromomethyldiphenyl crystallized in rhombs, m.p. 91 - 93°. Yield 83 g. Percentage yield 87%.

Preparation of 2:2'biscyanomethyldiphenyl LX111

Cope and Smith, J.Amer.Chem.Soc.,1956,78,1012.

Kenner and Turner, J.Chem.Soc.,1911,99,2101.

Potassium cyanide (29 g.; 2·2 mol.) was dissolved in water (200 ml.). Acetone (400 ml.) and 2:2'-bisbromomethyldiphenyl (68 g.; 1 mol.) were added. The mixture was heated under reflux to a temperature of 61° when an exothermic reaction set in which caused the mixture to boil for ten minutes without external heating. When the initial reaction had subsided the two-phase system was heated for an hour with frequent shaking, then was poured into two litres of cold water. An orange oil separated which gradually solidified. The solid was filtered off and crystallized from ethanol using charcoal to decolorize. The 2:2'-biscyanomethyldiphenyl came down in pale pink rectangular prisms, m.p. 77 - 79°. Yield 35 g. Percentage yield 74%.

Preparation of 1-imino-2-cyano-3:4-5:6-dibenzcyclohepta-3:5-diene LX1V

Kenner and Turner J.Chem.Soc.,1911,99,2101.

10% Sodium ethoxide was prepared by dissolving 0·46 g. sodium in 11·6 ml. of ethanol. 2:2'-Biscyanomethyldiphenyl (35 g.) was dissolved in ethanol (190 ml.) and 10% sodium ethoxide (10 ml.) was added. The mixture was boiled in a gentle current of hydrogen for one hour. Towards the end of the reaction the iminonitrile began to separate from the solution in clusters of pale beige needles. The solution was cooled and the solid filtered off and crystallized from ethanol.

m.p. 191 - 192° (Kenner and Turner gave m.p. 189°).

Yield 29 g. Percentage yield 84%.

<u>Preparation of 1-imino-3:4-5:6-dibenzcyclohepta-3:5-diene-2-carboxylic acid</u> LXV

Kenner and Turner, <u>J.Chem.Soc</u>.,1911,<u>99</u>,2101.

The 1-imino-2-cyano-3:4-5:6-dibenz*cyclo*hepta-3:5-diene (10 g.) was dissolved in 100 ml. concentrated sulphuric acid and left overnight. The solution was poured on to crushed ice and allowed to stand for two hours. The white solid which had separated out was filtered off and dried. A test portion was completely soluble in sodium hydroxide solution, showing that hydrolysis was complete. The 1-imino-3:4-5:6-dibenz*cyclo*hepta-3:5-diene-2-carboxylic acid crystallized from ethanol in fine needles, m.p. 179 - 180°. Yield 8·8 g. Percentage yield 82%.

<u>Preparation of 3:4-5:6-dibenzcyclohepta-3:5-dien-1-one</u> LXVl

Cope and Smith, <u>J.Amer.Chem.Soc</u>.1956,<u>78</u>,1012.

Sakan and Nakasaki <u>C.A</u>.,1952,<u>46</u>,5036.

A mixture of 1-imino-3:4-5:6-dibenz*cyclo*hepta-3:5-dien-2-carboxylic acid (3 g.), 88% syrupy phosphoric acid with specific gravity 1·75 (90 g.) and water (7·5 ml.) were boiled together under reflux for one and a half hours. A yellow oil separated and solidified on cooling. The strongly acidic mother liquor was diluted with distilled water and the solid was filtered off. The ketone crystallized from ethanol in large, pale yellow hexagonal prisms, m.p. 79 - 80o.

The products of four of the above reactions were collected and crystallized together.

Yield 8·5 g. Percentage yield 85%.

Preparation of 3:4-5:6-dibenzcyclohepta-3:5-diene LV11

Cope and Smith, J.Amer.Chem.Soc.,1956,78,1012.

The hydrocarbon was prepared by the Huang-Minlon modification of the Wolff-Kishner reduction (Huang-Minlon, J.Amer.Chem.Soc.,1946,68,2487).

Potassium hydroxide (4 g.) was dissolved in diethylene glycol (40 ml.) by gentle warming. 3:4-5:6-Dibenzcyclohepta-3:5-dien-1-one (2 g.) and 85% hydrazine hydrate (8 ml.) were added and the mixture was refluxed gently for two hours. The internal temperature was 132°. The formation of hydrazone was judged to be complete and water and excess hydrazine were distilled off until the temperature of the reaction mixture had reached 200°. The reaction mixture was refluxed for a further three hours, during which time the internal temperature rose to 214°. The mixture was cooled and diluted with 320 ml. water and then acidified with dilute hydrochloric acid. Meanwhile the distillate of hydrazine and water was extracted with ether and the ethereal washings were used to extract the acidified reaction mixture. The ethereal layer was washed successively with water, saturated sodium bicarbonate solution and saturated sodium chloride solution. The ether was distilled off and the residue solidified after being dried in a vacuum desiccator.

A portion of the hydrocarbon was crystallized from methanol, m.p. 38 - 40°.

A further portion was crystallized from aqueous ethanol, m.p. 55 - 56°. No difference in the crystalline structure of the two forms was apparent; both formed pale brown prisms. The melting points of both were depressed when mixed with 3:4-5:6-dibenz<u>cyclo</u>hepta-3:5-dien-1-one.

The total yield from this reaction was 0·8 g. Percentage yield 43%.

Subsequent reactions were carried out on 5 g. batches of the ketone and the yield of hydrocarbon was raised to 73%. The lower melting form of the hydrocarbon was not produced again; all further reactions yielded the more stable form which melted at 55 - 56° after crystallization from methanol.

The above synthesis was repeated until 39 g. of 3:4-5:6-dibenz<u>cyclo</u>hepta-3:5-diene had been synthesized.

<u>Acetylation of 3:4-5:6-dibenzo</u>cyclo<u>hepta-3:5-diene</u>.

Friedel Crafts reaction.

(a) Nitrobenzene was purified by steam distillation and dried over calcium chloride. 3:4-5:6-Dibenzo<u>cyclo</u>hepta-3:5-diene (1·9 g.; 1 mol.) and redistilled acetyl chloride (0·94 g.; 1·2 mol.) were dissolved in 36 ml. nitrobenzene. A cold solution of aluminium chloride (2·7 g.; 2 mol.) in 80 ml. nitrobenzene was added from a dropping funnel during forty-five minutes. During the addition the reaction flask was kept in an ice bath. It was allowed to come to room temperature and was kept at room temperature overnight. The reaction mixture was a dark brownish-green solution. It was poured on to ice and dilute hydrochloric acid was added. The mixture was steam distilled to remove the nitrobenzene. After most of the nitrobenzene had been removed a yellow gum began to separate in the distillate. The distillate was extracted with ether and the ether was distilled off. The residual gum was dried in a vacuum desiccator and was with difficulty induced to solidify after repeated triturations with light petroleum (b.p. 40 - 60°). The solid weighed 0·2 g., m.p. 67 - 70°. Evaporation of the light petroleum washings also yielded a further 0·1 g. of colourless needles, m.p. 68 - 70°. A mixed melting point of these two solids was 67 - 70°. Both solids gave a bright red precipitate when treated with Brady's reagent.

Yield 0·3 g. Percentage yield 13%.

A repetition of this reaction yielded 0·4 g. of acetyl derivative, m.p. 65 - 70°. Percentage yield 17%.

(b) 3:4-5:6-Dibenzo*cyclo*-hepta-3:5-diene (1·9 g.; 1 mol.) and acetyl chloride (0·86 g.; 1·1 mol.) were dissolved in 40 ml. carbon disulphide. The solution was added during twenty minutes to a rapidly stirred suspension of aluminium chloride (1·5 g.; 1·1 mol.) in 40 ml. carbon disulphide. A slight reaction was noticed at the surface of the aluminium chloride although no appreciable rise in temperature occurred. Stirring was continued for a further thirty minutes then the reaction mixture was refluxed on a water bath for four hours and left overnight. The carbon disulphide was distilled off and the residue poured into ice water. A pale yellow gum was formed, a little of which, when dissolved in ethanol, gave a bright red precipitate with Brady's reagent. The gum was taken up in chloroform. The chloroform solution was washed with water and dried over calcium chloride. The chloroform was removed by distillation and the residue was vacuum distilled. It distilled over a large range of temperature, 166 - 200° / 9 mm. The gum which distilled over could not be induced to solidify, nor would it form an oxime. On dissolving it in ethanol and leaving overnight in the cold a very small quantity of colourless needles was deposited, m.p. 66 - 68°.

(c) Aluminium chloride (8 g.; 3 mol.) was dissolved in 25 ml. nitrobenzene and redistilled acetic anhydride (2·6 g.;1·25 mol.) was added to the cold solution. A cold solution of 3:4-5:6-dibenzo*cyclo*hepta-3:5diene (3·9 g.; 1 mol.) in 15 ml. nitrobenzene was added gradually. A deep reddish-brown colour developed. The mixture was left in ice for three hours and then allowed to stand overnight at room temperature. It was poured on to ice and steam distilled. The distillation was not allowed to continue after nitrobenzene had come over and the residue in the distillation flask was extracted with ether. The ether was removed and the remaining gum was dried in a vacuum desiccator for some days. It did not solidify. It was dissolved in methanol. The acetyl derivative crystallized from the methanol in pale yellow needles, m.p. 68 - 71°. Yield 1·0 g. Percentage yield 21%.

The acetyl derivative was recrystallized from methanol with charcoal and then had melting point 69·5 - 72°.

The products from the previous acetylations were also treated in the same manner and the melting point rose to 70·5 - 72°. Mixed melting points gave no appreciable depression. The products were therefore combined and recrystallized from methanol, to constant melting point (70 - 72°).

(Found: C, 86·5; H, 6·8; $C_{17}H_{16}O$ requires C, 86·4; H, 6·8%).

Succinoylation of 3:4-5:6-dibenzocyclohepta-3:5-diene.

A cold solution of aluminium chloride (8 g.; 3 mol.) in 20 ml. nitrobenzene was added during thirty minutes to a solution of 3:4-5:6-dibenzocyclohepta-3:5-diene (3·9 g.; 1 mol.) and succinic anhydride (2·2 g.; 1·1 mol.) in 12 ml. nitrobenzene. The addition was made mainly at room temperature but vigorous evolution of hydrogen chloride took place towards the end of the addition, so the final portions of the solution were added at ice bath temperature. The reaction mixture stood in ice for two hours and then at room temperature overnight. After standing, the solution was a deep wine-red colour. It was poured on to a mixture of ice and dilute hydrochloric acid and was steam distilled. After the nitrobenzene had been removed the mixture in the distillation flask was made alkaline with saturated sodium carbonate solution. Steam distillation was continued for a further six hours, during which time all traces of nitrobenzene were removed and the keto acid went into solution as the sodium salt. The solution was filtered from a sludge of alumina while still warm and was acidified with concentrated hydrochloric acid. A white gum separated which became a brittle solid after standing overnight in the cold. The solid was removed from the acidic mother liquor and dried by crushing on a porcelain tile and then in a vacuum desiccator. It crystallized from glacial acetic acid in hexagonal prisms, m.p. 150·5 - 151·5°.

Yield 2·6 g. Percentage yield 44%.
(Found: C, 77·0; H, 6·3; $C_{19}H_{18}O_3$ requires C, 77·6, H, 6·2%.)

Oxidation of the acetyl derivative of 3:4-5:6-dibenzocyclohepta-3:5-diene LXV11

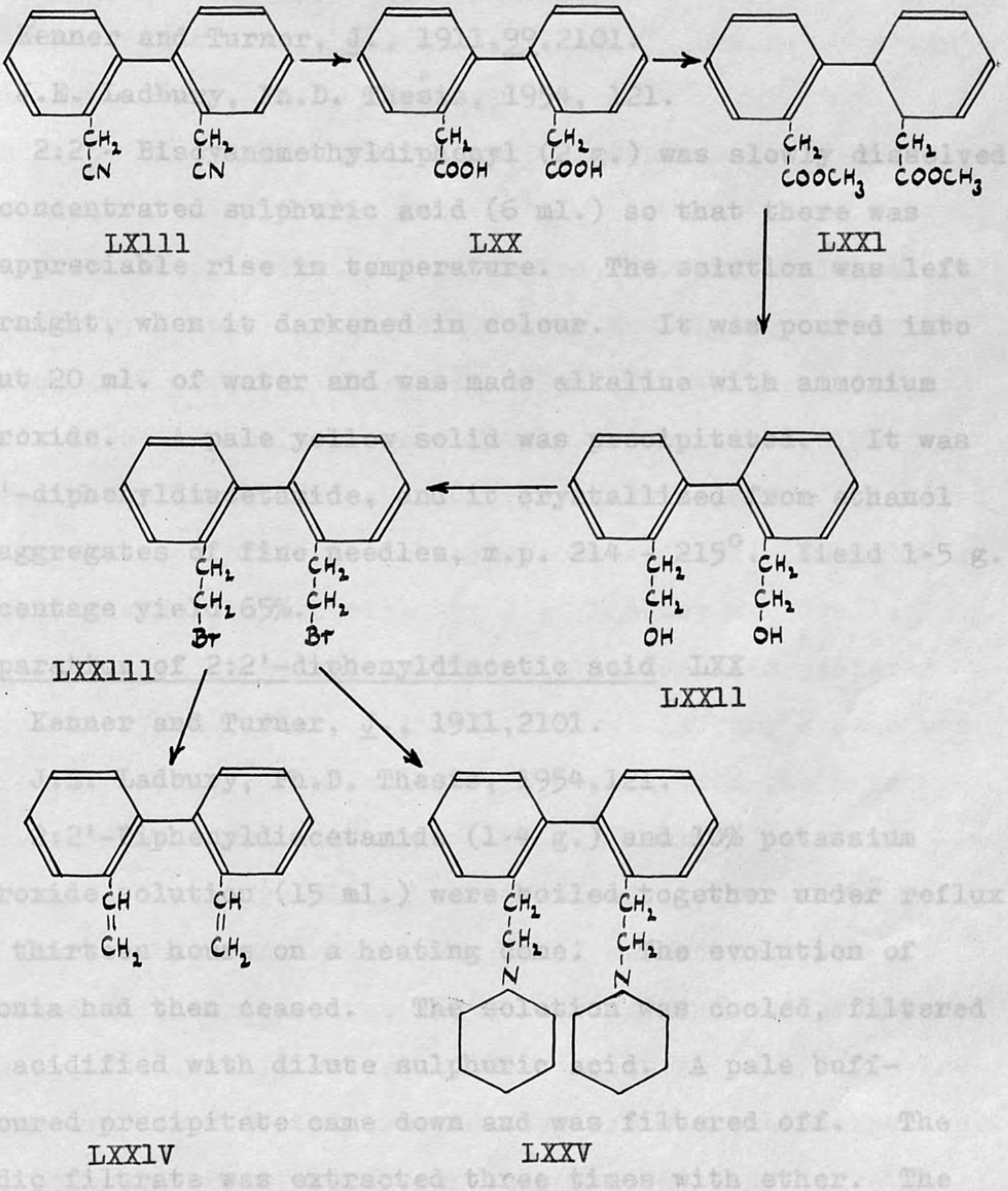
18% Sodium hypochlorite solution was made up by dissolving 16 g. sodium hydroxide in 100 ml. water, cooling the solution in ice, and passing in chlorine gas until 7·1 g. of chlorine had been absorbed. A further 326 ml. of water were added.

The acetyl derivative of the hydrocarbon (0·3 g.; 1 mol.) and 18% sodium hypochlorite solution (30 ml.; 5 mol.) were heated together under reflux for four hours. The reaction mixture was cooled and filtered, and sulphur dioxide was passed into the filtrate. A fine white precipitate came down, which was filtered off and crystallized from aqueous ethanol. The pure compound which crystallized in clusters of fine needles melted at 215°. Yield 0·24 g. Percentage yield 80%.
(Found: C, 80·54; H, 5·94; $C_{16}H_{14}O_2$ requires C, 80·63; H, 5·93%.)

Oxidation of the succinoyl derivative of 3:4-5:6-dibenzocyclohepta-3:5-diene LXV111

The succinoyl derivative of the hydrocarbon (1·1 g., 1 mol.) was heated with 18% sodium hypochlorite solution (7 mol.) as in the previous experiment. The product was purified as before, m.p. 214 - 215°. Yield 0·65 g. Percentage yield 73%.

SYNTHESIS AND REACTIONS OF 2:2'-BISBROMOETHYLDIPHENYL



LX111 LXX LXX1 LXX11 LXX111 LXX1V LXXV

Hydrolysis of 2:2'-biscyanomethyldiphenyl LX111

(a) Using concentrated sulphuric acid.

Kenner and Turner, J., 1911,99,2101.

J.E. Ladbury, Ph.D. Thesis, 1954, 121.

2:2'- Biscyanomethyldiphenyl (2 g.) was slowly dissolved in concentrated sulphuric acid (6 ml.) so that there was no appreciable rise in temperature. The solution was left overnight, when it darkened in colour. It was poured into about 20 ml. of water and was made alkaline with ammonium hydroxide. A pale yellow solid was precipitated. It was 2:2'-diphenyldiacetamide, and it crystallized from ethanol in aggregates of fine needles, m.p. 214 - 215°. Yield 1·5 g. Percentage yield 65%.

Preparation of 2:2'-diphenyldiacetic acid LXX

Kenner and Turner, J., 1911,2101.

J.E. Ladbury, Ph.D. Thesis, 1954,121.

2:2'-Diphenyldiacetamide (1·4 g.) and 10% potassium hydroxide solution (15 ml.) were boiled together under reflux for thirteen hours on a heating cone. The evolution of ammonia had then ceased. The solution was cooled, filtered and acidified with dilute sulphuric acid. A pale buff-coloured precipitate came down and was filtered off. The acidic filtrate was extracted three times with ether. The ether was removed by distillation and a small quantity of colourless solid was left. This was added to the main precipitate and the combined solids were crystallized from a comparatively large volume of water, with charcoal to decolorize. The compound crystallized as colourless irregular prisms, m.p. 173 - 175°. Yield 0·4 g. Percentage yield 28%.

Found: C, 70·99; H, 5·47. $C_{16}H_{14}O_4$ requires C, 71·08; H, 5·21%.

The melting point of 2:2'-diphenyldiacetic acid as recorded by Kenner and Turner, and by Mrs. Ladbury, was 153°. The compound prepared above was soluble in water giving an acidic solution. It was completely soluble in sodium hydroxide solution and ammonium hydroxide solution. A mixed melting point with 2:2'-diphenyldiacetamide was 163 - 170°. Some of the acid synthesized by J.E. Ladbury was available, m.p. 153°. A mixed melting point with the acid prepared above was 173 - 175°. A little of Mrs. Ladbury's acid was melted on a piece of porcelain and seeded with the acid prepared in the present work. Solidification occurred immediately. The resulting solid melted at 172 - 175°.

In a subsequent reaction a small second crop was obtained which softened at 153°, resolidified on further heating, and finally melted completely at 173 - 175°. The crystalline form of this second crop was short blunt needles.

It would therefore appear that 2:2'-diphenyldiacetic acid occurs in dimorphic forms, one which melts at 153° and another which melts at 173 - 175°. In this present work the higher melting form was always obtained, no matter which method was used for the preparation of the acid.

(b) Using a sulphuric acid-acetic acid mixture.

2:2'-Biscyanomethyldiphenyl (2 g.) was mixed with equal volumes (10 ml.) of concentrated sulphuric acid, glacial acetic acid and water. The mixture was heated under reflux and soon formed a homogeneous solution. It was boiled for two hours during which time it gradually darkened in colour. On cooling, the solution deposited crystals. The solid was filtered from the acidic mother liquor and was completely dissolved in ammonium hydroxide. When the alkaline solution was filtered and acidified with dilute sulphuric acid, the crystalline solid was reprecipitated. The solid was crystallized from water, m.p. 173 - 175°. Mixed melting point with 2:2'-diphenyldiacetic acid prepared previously by the present worker was also 173 - 175°. Yield of 2:2'-diphenyldiacetic acid was 2 g. Percentage yield 87%. Subsequent reactions were carried out on 10 gram batches of 2:2'-biscyanomethyldiphenyl. This method was the one used to prepare the acid in quantity.

(c) Using aqueous potassium hydroxide.

2:2'-Biscyanomethyldiphenyl (2 g.) and 10% aqueous potassium hydroxide (20 ml.) were boiled together under reflux for eight hours. Ammonia was given off, and after about one hour the oil floating in the alkaline solution was gradually converted into a pale yellow solid. The solid was crystallized from ethanol and came down as colourless needles, m.p. 190 - 192°. Mixed melting point with previously synthesized 1-imino-2-cyano-3:4-5:6-dibenzo*cyclo*hepta-3:5-diene was

190 - 192°. Yield 0·6 g. The alkaline mother liquor was acidified and deposited a small amount of solid, which, after crystallization from water, melted at 173 - 175°. Yield of 2:2'-diphenyldiacetic acid 0·2 g.

(d) Using alkaline hydrogen peroxide.

A mixture of 2:2'-biscyanomethyldiphenyl (5 g.; 1 mol.), 20 volume hydrogen peroxide (36 ml.; 3 mol.), 30% sodium hydroxide solution (30 ml.) and a little ethanol was warmed on a water bath held at 50° for three hours. Fine buff-coloured crystals appeared in the reaction mixture. The solid was filtered off and crystallized from ethanol, m.p. 190 - 191°. The compound contained nitrogen, and a mixed melting point with 1-imino-2-cyano-3:4-5:6-dibenzo*cyclo*hepta-3:5-diene was 190 - 192°. The compound was therefore the cyclic imino-nitrile. Yield 2.6 g. Percentage yield 52%.

(e) An attempt to hydrolyse 2:2'-biscyanomethyldiphenyl with syrupy phosphoric acid was unsuccessful.

Preparation of 2:2'-diphenoyldichloride.

(a) Using phosphorus pentachloride.

Underwood and Kochmann, J.Amer.Chem.Soc.,1924,46,2069.

J.E. Ladbury, Ph.D. Thesis, 1954,119.

F. Minhaj, Ph.D. Thesis, 1956, 114.

2:2'-Diphenic acid (15 g.; 1 mol.) and phosphorus pentachloride (27 g.; 2·1 mol.) were mixed together and heated under anhydrous conditions in an oil bath held at 190 - 195° for thirty minutes. The mixture became molten and reacted vigorously when the bath temperature was 187°. The temperature was allowed to fall to 150° and was maintained there for one hour. During this time air was drawn through the neck of the flask at frequent intervals to remove phosphorus oxychloride. The mixture was allowed to cool and was extracted with benzene. The dark-coloured benzene extract was slightly reduced in volume by evaporation. On cooling, it deposited a dark yellow-grey solid. Weight 5·5 g. The crude solid melted over a range from 180° to 210° but after crystallization from glacial acetic acid, with decolorizing charcoal, the melting point was 228 - 230°. A mixed melting point with 2:2'-diphenic acid was also 228 - 230°.

The reaction was repeated on half the above quantities. The reactants were ground together in a mortar and quickly transferred to the reaction flask. Reaction occurred in the cold with vigorous evolution of phosphorus oxychloride. When the initial reaction was complete the flask was fitted with a drying tube and warmed slightly on a water bath until all the solid had dissolved. Air was drawn through the neck of the flask to remove the phosphorus oxychloride. The reaction product was extracted with hot benzene. Dry light petroleum (b.p. 40 - 60°) precipitated a solid from the cool benzene solution. Weight 2 g., m.p. 94 - 97°. The melt was not clear. After standing overnight in a desiccator the solid melted at about 180° after preliminary softening at 97°. The diphenoyl dichloride was presumably being slowly hydrolysed to 2:2'-diphenic acid.

2:2'-Diphenic acid (5 g., 1 mol.) and phosphorus pentachloride (9 g., 2 mol.) were ground in a mortar and quickly transferred to a flask fitted with an air condenser and a drying tube. The reaction began in the cold and after the initial reaction had subsided the flask was heated in an oil bath held at 180 - 190° for twenty minutes. The temperature fell slightly and the phosphorus oxychloride was distilled off under reduced pressure produced by a water pump. The residue was allowed to solidify in a vacuum desiccator and was not extracted with benzene. The solid 2:2'-diphenoyldichloride melted at 94 - 97° but the melt was not clear.

(b) Using thionyl chloride.

Bell and Robinson, <u>J.</u>,1929,1695.

Nightingale, Heiner and French, <u>J.Amer,Chem.Soc</u>.,1950, <u>72</u>,1875.

2:2'-Diphenic acid (10 g.) and freshly distilled thionyl chloride, b.p. 76 - 78° (100 ml.) were mixed and warmed on a water bath held at 45 - 47° for ten hours. The mixture was left at room temperature overnight, by which time the diphenic acid had dissolved completely. The excess thionyl chloride was distilled off under slightly reduced pressure from a water pump. A few crystals were apparent in the residual solution which was extracted with hot dry benzene. The crystals were 2:2'-diphenic anhydride, m.p. 222°; mixed melting point with an authentic sample of anhydride was 220 - 222°. The benzene solution was diluted with dry light petroleum (b.p. 40 - 60°) and a further very small quantity of diphenic anhydride was obtained. The filtrate was evaporated to half its volume and on cooling it deposited crystals of 2:2'-diphenoyldichloride, m.p. 94 - 97°. Yield 9.9 g. Percentage yield 85%.

Attempts were made to shorten the time of the reaction by increasing the temperature of the water bath, but this was unsatisfactory as the yield of diphenic anhydride increased. If the reactants were boiled together under reflux the reaction product was wholly anhydride.

<u>Preparation of dimethyl-2:2'-diphenyldiacetate</u> LXXl

I <u>By an Arndt-Eistert synthesis</u>.

(a) <u>Preparation of diazomethane</u>.

For this reaction, diazomethane was prepared according to the method of de Boer and Backer, <u>Rec.Trav.chim</u>.,1954,<u>73</u>,229. The apparatus consisted of a round-bottomed flask fitted with a dropping funnel and a side arm leading to an efficient water condenser. The condenser was connected with two conical flasks in series. Both flasks were placed in freezing mixture and the second one contained about 100 ml. of ether. This trapped any diazomethane escaping from the first conical flask which was the main receiver. The flasks were connected with polythene tubing and all ground glass joints in the apparatus were fitted with protective sleeves of polytetrafluoroethylene. The preparation of diazomethane was carried out in a fume cupboard with the exhaust fan on.

Potassium hydroxide (20 g.) was dissolved in water (30 ml.) and the solution was transferred when cool to the round bottomed flask in a water bath. 96% Ethanol (100 ml.) was added. The temperature of the water bath was controlled at 60 - 65° throughout the preparation. N-Methyl-p-toluene sulphonylnitrosamide (86 g., 0·4 mol.) was dissolved in ether (500 ml.) and the solution was added from the dropping funnel to the aqueous alcoholic potassium hydroxide at the same rate as the ethereal diazomethane distilled over into the conical flask. When the addition was complete, ether was added from the dropping funnel until the distillate was clear and colourless. The ether in the second conical flask also contained diazomethane and was added to the main distillate. The total distillate should contain 11·8 - 12·2 g. of diazomethane, representing a 70 - 73% yield.

(b) Preparation of the diazodiketone.

J.E. Ladbury, Ph.D. Thesis, 1954.

2:2'-Diphenoyl dichloride (13·3 g., 1 mol.) was dissolved in ether and added gradually to the cold ethereal solution of diazomethane. Effervescence took place and continued for a short time after the addition was complete. The reaction mixture was allowed to stand overnight at room temperature in the fume cupboard with the exhaust fan on, to remove unreacted diazomethane. The ether was then removed by distillation under reduced pressure, from a water bath held at a temperature between 20 - 30°. The residue was a yellow oily liquid some of which solidified in rectangular prisms.

(c) Preparation of the ester.

The diazodiketone was not purified further but was treated at once with absolute methanol (200 ml.) and heated to an internal temperature of 50°. Silver oxide was made from 10% silver nitrate solution and dilute sodium hydroxide solution, and was washed well with water until free from alkali. A slurry of the freshly prepared silver oxide (43 g.) in methanol was added to the hot solution of the diazodiketone in portions, over a period of two and a half hours. The water bath was maintained at a temperature between 50° - 60°. On addition of the silver oxide effervescence took place but this gradually ceased. The reaction mixture was allowed to stand at room temperature overnight and was then treated with a further portion of freshly prepared silver oxide to ensure that the reaction was complete. A silver mirror had been deposited on the sides of the reaction flask. A test portion of the reaction mixture when treated with a drop of concentrated hydrochloric acid did not produce bubbles of nitrogen, showing that no unreacted diazodiketone was present.

The reaction mixture was boiled under reflux with decolorizing charcoal for three hours and then filtered. The methanol was removed by distillation under reduced pressure and the residual oil was dissolved in ether. The ethereal solution was washed well with sodium carbonate solution and with water and was dried over anhydrous sodium sulphate. Removal of the ether by distillation left a dark-coloured oil. The oil defied all attempts to solidify it, and attempted crystallisations from numerous solvents were unsuccessful. It was distilled three times under reduced pressure and finally gave a pale yellow oil distilling between 196 - 202° at 8 mm. pressure. n_D^{20} 1·559. Yield 3·5 g. This represents a yield of 20% of the theoretical calculated from the amount of diphenoyl dichloride used.

In an attempt to identify the oil, about 1 g. was boiled under reflux with equal quantities (25 ml.) of ethanol and 10% sodium hydroxide solution for seven hours until the reaction mixture was completely homogeneous. The mixture of alcohols was distilled off and the aqueous residue was acidified with dilute sulphuric acid. A pale yellow solid was precipitated which was filtered off, washed with water, and crystallized twice from water using charcoal to decolorize. Prismatic crystals came down. Melting point, and mixed melting point with 2:2'-diphenyldiacetic acid prepared previously, was 173 - 175°.

The remaining oil was dissolved in dry ether and was reduced with lithium aluminium hydride. The product was a small amount of colourless solid which crystallized from a mixture of benzene and light petroleum, and melted at 88 - 91°. This product was not identified, but a repetition of the Arndt-Eistert reaction on the same scale as above yielded 4·5 g. (32%) of oil boiling between 210 - 215° at 11 mm. pressure, the whole of which was reduced. The reduction product of this reaction was analysed. (See the subsequent preparation.)

Preparation of 2:2'-bis-β-hydroxyethyldiphenyl LXXll

Lithium aluminium hydride (1 g.; 1·6 mol.) was suspended in sodium-dried ether (60 ml.) in a dry round-bottomed flask fitted with a reflux condenser and calcium chloride tube and a dropping funnel. Dimethyl-2:2'-diphenyldiacetate (4·5 g., 1 mol.), prepared as an oil by the Arndt-Eistert reaction, was dissolved in dry ether (30 ml.) and was run into the reaction flask gradually to maintain a gentle refluxing of the ether. The reaction mixture was allowed to stand for half an hour then excess lithium aluminium hydride was decomposed cautiously with water. The mixture was acidified with dilute sulphuric acid (1 bench dilute acid : 1 water) until two clear layers were formed. The layers were separated and the aqueous layer was extracted with ether. The combined ethereal solutions were washed with water and the ether was distilled off. A colourless oil remained which readily solidified. The solid was crystallized from benzene/light petroleum (b.p. 40 - 60°), m.p. 89 - 91°. Yield 2·3 g. Percentage yield 62%.

The solid was recrystallized three times for analysis. It showed a tendency to crystallize with solvent of crystallization and so was dried carefully in a vacuum at 56°. The melting point was then 90 - 91°. Found: C, 79·3; H, 7·5. $C_{16}H_{18}O$ requires C, 79·3; H, 7·5%.

Preparation of dimethyl 2:2'-diphenyldiacetate.

II By esterification of 2:2'-diphenyldiacetic acid.

(a) 2:2'-Diphenyldiacetic acid (10 g.), methanol (100 ml.) and concentrated sulphuric acid (10 ml.) were mixed in a flask and boiled under reflux for six hours on a water bath. The mixture was poured into cold water. A pale yellow oil separated. The oil was taken up in ether and the ethereal solution was washed with sodium bicarbonate solution and with water, and was dried over anhydrous sodium sulphate. The dry ethereal solution was used directly for reduction with lithium aluminium hydride.

The reduction was carried out as described previously. The quantity of lithium aluminium hydride (1·6 mol.) needed for the reaction was calculated assuming a theoretical yield of ester. The yield of 2:2'-bis-β-hydroxyethyldiphenyl was 6·9 g. Percentage yield 77%, m.p. 89 - 91°.

The esterification and reduction were carried out a number of times. One preparation gave a yield of diol of 86%.

(b) Using diazomethane.

Diazomethane was prepared according to the method previously described. Half the previous quantities of reactants were used, and the ethereal solution finally collected was assumed to contain 6 g. of diazomethane. 2:2'-Diphenyldiacetic acid (10 g.) was added as a solid to the diazomethane solution, and nitrogen was evolved. The reaction mixture was left overnight in an exhaust chamber, then was filtered and the ether was removed by distillation under slightly reduced pressure. The residual ester was triturated with various solvents but did not solidify. It was dissolved in dry ether and reduced with lithium aluminium hydride, giving a 70% yield of 2:2'-bis-β-hydroxyethyldiphenyl, m.p. 90 - 91°.

A little of the 2:2'-diphenyldiacetic acid prepared by J.E. Ladbury, m.p. 153°, was esterified with methanol and concentrated sulphuric acid, and the ester was reduced. A small amount of 2:2'-bis-β-hydroxyethyldiphenyl was obtained, m.p. 89 - 91°. A mixed melting point with diol prepared previously was also 89 - 91°.

Preparation of 2:2'-bis-β-bromoethyldiphenyl LXX111

2:2'-Bis-β-hydroxyethyl diphenyl (8 g.) and 48% $^{W}/_{W}$ hydrobromic acid (400 ml.) were boiled together under reflux for one hour. The mixture was allowed to cool and about half the acid was removed by decantation. The volume was made up to approximately 400 ml. by the addition of fresh hydrobromic acid and the mixture was boiled under reflux for a further thirty minutes. The mixture was cooled and was extracted with benzene. The benzene extract was washed well with sodium bicarbonate solution and with water, and was dried over anhydrous sodium sulphate. The benzene was removed by distillation from a water bath and the residual oil was distilled under reduced pressure. Distillation began at 184°, then the temperature gradually rose to 194° and remained steady. The pressure was constant at 4 mm. Hg. The yield of 2:2'-bis-β-bromoethyldiphenyl was 9 g. Percentage yield 75%.

The pale yellow viscous liquid was redistilled and collected in two fractions

Fraction 1 2·7 g. b.p. 178 - 192° / 4 mm. n_D^{25}1·6150

Fraction 2 5 g. b.p. 192 - 198° / 4 mm. n_D^{25}1·6149.

The percentage of bromine present in the compound was estimated, first by a modification of Stepanow's method which gave unsatisfactory results, and finally by Carius' method. The bromine was weighed as silver bromide.

Found: Fraction 1, Br, 39·10;

Fraction 2, Br, 42·04. $C_{10}H_{16}Br_2$ requires Br, 43·43%.

The reaction was repeated on 10 g. of 2:2'-bis-β-hydroxyethyldiphenyl when the yield was increased to 87% of the theoretical.

Attempted condensation of 2:2'-bis-β-bromoethyldiphenyl with diethyl malonate.

Absolute ethanol was dried by heating 300 ml. under reflux with diethylphthalate (30 g.) and sodium (3 g.) for one hour. The dry alcohol was removed from the mixture by distillation.

About 50 ml. of dry ethanol was transferred to a carefully dried three-necked flask fitted with a stirrer, a dropping funnel and a reflux condenser with a calcium chloride drying tube. Sodium (2·3 g., 2 atoms) was added in small pieces and the mixture was stirred until the sodium had dissolved. Diethyl malonate (8 g., 1 mol.) was run into the flask and was washed in with a small volume of the dried alcohol. 2:2'-Bis-β-bromoethyldiphenyl (18·4 g., 1 mol.) in dry ether (30 ml.) was then run in from the dropping funnel and was washed in with a further small quantity of dry ether. There was no immediate reaction. The reaction mixture was heated in an oil bath, with stirring, and began to boil when the temperature of the oil bath was 50°. The reaction mixture became cloudy due to the separation of sodium bromide. Heating was continued for five hours, when a test portion of the mixture in distilled water was neutral to litmus and had a pH of 7-8. The mixture was allowed to cool and was left overnight. Water was then added and the mixture was extracted with ether. The ether solution was washed once with water and was dried over anhydrous sodium sulphate. The ether was removed by distillation and the residue was fractionally distilled under reduced pressure.

Fraction 1. b.p. 70 - 80° / 6 mm. Weight 0·8 g.
n_D^{25} 1·4200.

This was mainly unchanged diethyl malonate.

Fraction 2. b.p. 135 - 180° / 4 mm. Weight 3 g.

The temperature rose to 210° with very slow distillation.

Fraction 3. b.p. 210 - 225° / 4 mm. Weight 2·7 g.

The residue decomposed.

<u>Fraction 2</u>. This fraction rapidly deposited crystals on standing, in the form of clusters of colourless leaflets. These were removed from the oil by filtration. The yield was about 1 g. The solid was crystallized from absolute ethanol to constant melting point (79·5 - 80°). Analysis showed the solid to be 2:2'-divinyldiphenyl. Found: C, 92.9; H , 6.7.

$C_{16}H_{14}$ requires C, 93·2; H, 6·8%. A mixed melting point with an authentic sample of 2:2'-divinyldiphenyl was 79 - 80°.

The oil remaining when the solid was removed was found to contain bromine. A Carius estimation showed that the amount of bromine was only 9·67% of the molecule. The oil was left for some weeks in the hope that it might solidify. It set in a stiff jelly which was unchanged after being boiled with 10% alcoholic potassium hydroxide solution for three hours.

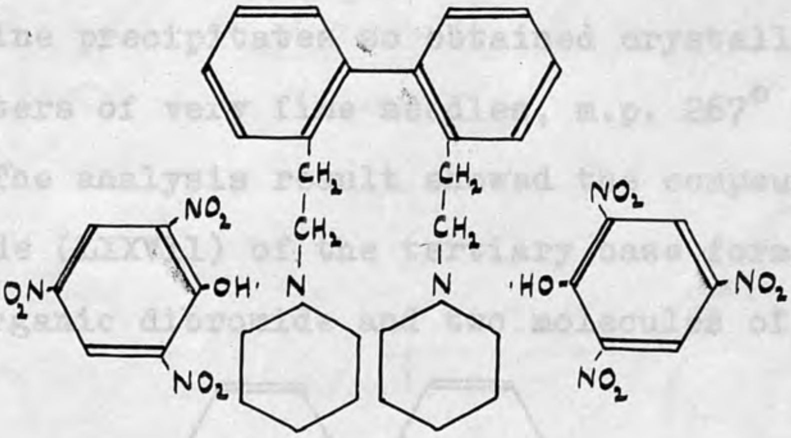
Fraction 3. A sodium fusion test carried out on a sample of this fraction showed that it too contained bromine. A Carius estimation showed that the amount present was 2·05% and so was probably only a trace. The oil was boiled under reflux for three hours with 10% alcoholic potassium hydroxide solution, then water was added and the solution was extracted with ether. The ethereal extract was slightly coloured but on evaporation of the ether only a trace of residue remained which was too small to be workable.

The aqueous alkaline solution was acidified with dilute hydrochloric acid. An oil was precipitated which was taken up in ether, and the ethereal solution was dried over anhydrous sodium sulphate. The ether was distilled off and the remaining oil was heated in a small flask in an oil bath held at 200 - 210° for about one hour. Bubbles of gas were given off but after cooling, the oil set in a hard glass, which was insoluble in sodium carbonate solution. The glass could not be worked further and was discarded.

Treatment of 2:2'-bis-β-bromoethyldiphenyl with piperidine.

1. 2:2'-Bis-β-bromoethyldiphenyl (3·7 g.; 1 mol.) before purification by vacuum distillation, was warmed on a water bath held between 50 - 60° for six hours with piperidine (1·7 g.; 2·2 mol.) in dry benzene (50 ml.) A crystalline solid separated out in fine needles and was filtered off and washed with warm dry benzene. The solid dissolved completely in water and no solid was precipitated when a concentrated aqueous solution of potassium iodide was added. The solid was therefore assumed to be entirely piperidine hydrobromide. The benzene reaction solution was warmed again for a further seven hours and a second crop of crystals was obtained. These were treated, and behaved, exactly like the first crop. Further warming of the benzene solution gave no more crystals and so the solution was evaporated down almost to dryness and the residual oil was washed thoroughly with dilute hydrochloric acid. Most of the oil dissolved in the acid; only a negligible amount of gum was left. The acidic solution was made alkaline with dilute sodium hydroxide solution. An oily suspension formed which was extracted with a mixture of light petroleum (b.p. 40 - 60°) and ether. The solvents were distilled off and the basic residue was treated with a saturated alcoholic solution of picric acid. A bright yellow precipitate was formed which was filtered off and crystallized to constant melting point (245° with decomposition) from glacial acetic acid. The picrate crystallized in short fine needles. It was dried over potassium hydroxide in a vacuum

desiccator and then heated for six hours at 160° in a drying pistol. Analysis showed this compound to be the picrate (LXXV1) of the tertiary base formed by the reaction of one molecule of dibromide with two molecules of piperidine.



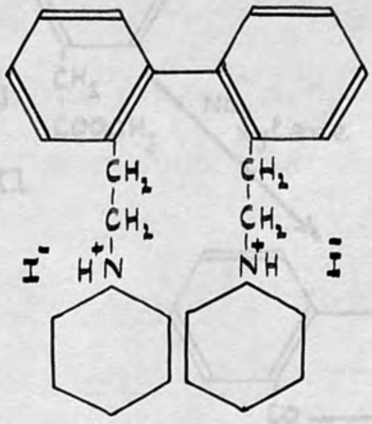
LXXV1

About 2 g. of picrate were formed. Found: C, 54·63, H, 4·78, N, 12·81. $C_{38}H_{42}N_8O_{14}$ requires C, 54·65; H, 5·07; N, 13·43%.

2. Pure distilled 2:2'-bis-β-bromoethyldiphenyl (3·7 g., 1 mol.) and piperidine (1·9 g., 1 mol.) were dissolved in dry benzene (50 ml.) and warmed on a water bath held between 50 - 60° for six hours. Piperidine hydrobromide came down in fine needles and was removed by filtration. Warming of the benzene solution was continued. After ten hours a more amorphous solid was apparent among the crystals of a further crop of piperidine hydrobromide. The combined solids were filtered off and dissolved in water. The piperidine hydrobromide dissolved instantaneously but the other solid required heat before it completely dissolved. A saturated aqueous solution of potassium iodide was added and a fine microcrystalline

solid came down when the solution was cooled in ice.

Meanwhile the warming of the benzene mother liquor continued and further portions of the solid were produced. All the solid was treated in the above manner. The combined microcrystalline precipitates so obtained crystallized from water in clusters of very fine needles, m.p. 267° with darkening. The analysis result showed the compound to be the hydroiodide (LXXVll) of the tertiary base formed from one molecule of organic dibromide and two molecules of piperidine.

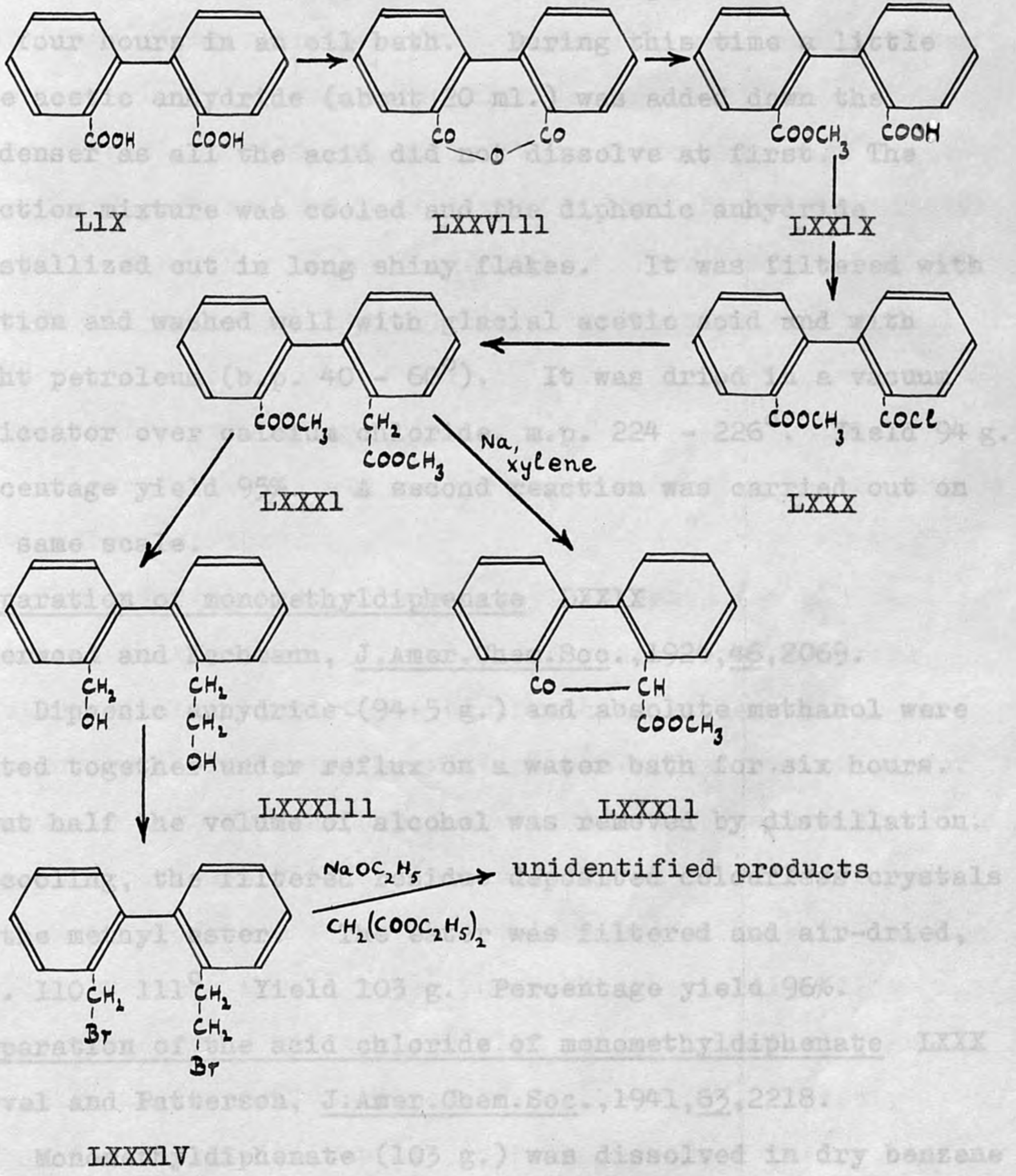


LXXVll

Found: C, 48·99; H, 5·92; I, 40·3; N, 4·0.

$C_{26}H_{38}N_2I_2$ requires C, 49·39; H, 6·06; I 40·14; N, 4·43%.

SYNTHESIS AND REACTIONS OF 2-CARBOMETHOXY-2'-CARBOMETHOXY-METHYLDIPHENYL.



Preparation of 2:2'-diphenic anhydride LXXVlll

Diphenic acid (107·5 g.) supplied by Light and Co., and acetic anhydride (300 ml.) were boiled together under reflux for four hours in an oil bath. During this time a little more acetic anhydride (about 20 ml.) was added down the condenser as all the acid did not dissolve at first. The reaction mixture was cooled and the diphenic anhydride crystallized out in long shiny flakes. It was filtered with suction and washed well with glacial acetic acid and with light petroleum (b.p. 40 - 60°). It was dried in a vacuum desiccator over calcium chloride, m.p. 224 - 226°. Yield 94 g. Percentage yield 95%. A second reaction was carried out on the same scale.

Preparation of monomethyldiphenate LXXlX

Underwood and Kochmann, J.Amer.Chem.Soc.,1924,46,2069.

Diphenic anhydride (94·5 g.) and absolute methanol were heated together under reflux on a water bath for six hours. About half the volume of alcohol was removed by distillation. On cooling, the filtered residue deposited colourless crystals of the methyl ester. The ester was filtered and air-dried, m.p. 110 - 111°. Yield 103 g. Percentage yield 96%.

Preparation of the acid chloride of monomethyldiphenate LXXX

Marvel and Patterson, J.Amer.Chem.Soc.,1941,63,2218.

Monomethyldiphenate (103 g.) was dissolved in dry benzene in a 1-litre flask fitted with a reflux condenser and a calcium chloride drying tube. Freshly distilled thionyl chloride (35·5 ml.) and pyridine (3 ml.) were added and the mixture was warmed on a water bath held at 45 - 50° for one hour. Most of the benzene was removed by distillation under reduced pressure at 60 - 70°. The residue was filtered and cooled and light petroleum (b.p. 40 - 60°) was added. After vigorous scratching the acid chloride crystallized. It was filtered with suction and washed very thoroughly with light petroleum. It was dried in a vacuum desiccator over calcium chloride, m.p. 59 - 61°. Yield 109 g. Percentage yield 99%.

Preparation of 2-carbomethoxy-2'-carbomethoxymethyldiphenyl LXXX1

Marvel and Patterson, loc.cit.

Diazomethane (12 g.) was prepared according to the method previously described.

The acid chloride of monomethyldiphenate (40 g.) was dissolved in dry ether (275 ml.) and added to an ethereal solution of freshly prepared diazomethane at ice-bath temperature. The reaction mixture was allowed to stand for an hour in ice and was then left at room temperature overnight, in a fume cupboard with the exhaust fan on. The ether was distilled off from a water bath maintained at 30 - 35°, using reduced pressure from a water pump. The residual yellow liquid diazoketone was treated with methanol (400 ml.) and warmed to an internal temperature of about 50°. Freshly prepared silver oxide, which had been made from 12·3 g. of silver nitrate and 2·9 g. of sodium hydroxide and washed free from alkali, was added in small portions over a period of forty-five minutes. At the first additions there was a brisk reaction with the evolution of nitrogen but this gradually died down. The reaction mixture was boiled under reflux with charcoal for five hours and was filtered. Most of the methanol was removed by distillation under reduced pressure. The residue was cooled and the 2-carbomethoxy-2'-carbomethoxymethyldiphenyl crystallized out. Two reactions were carried out on the same scale and the crude products were combined and recrystallized together from aqueous methanol, m.p. 66 - 67°. Yield 39 g. Percentage yield 47%. In all, 72 g. of this ester were synthesized in this way.

Condensation of 2-carbomethoxy-2'-carbomethoxymethyldiphenyl in the presence of sodium.

Commercial suphur-free xylene was purified by boiling under reflux with sodium for one hour. It was then distilled and dried over sodium wire before use.

The apparatus consisted of a one-litre three-necked round-bottomed flask supported in an electrically heated mantle. The first neck carried a thermometer and a double surfaced reflux condenser; the middle neck was fitted with a Hershberg stirrer; and the third neck was fitted with a dropping funnel and a gas inlet tube. All the apparatus was oven-dried.

Xylene (300 ml.) and small pieces of sodium (5·2 g., 2 atoms) were placed in the flask and oxygen-free nitrogen, which had bubbled through concentrated sulphuric acid, was passed in. The mixture was heated to an internal temperature of 105o when the stirrer was started. Stirring was continued as rapidly as possible and the molten sodium was dispersed in finely divided globules. 2-Carbomethoxy-2'-carbomethoxymethyldiphenyl (32 g., 1 mol.) was dissolved in xylene (150 ml.) and added dropwise to the reaction mixture over a period of two and a half hours. The temperature remained between 110° and 115° for a short time after the addition was begun then rose suddenly to 127°. It was maintained between 125° and 135° for the remainder of the addition.

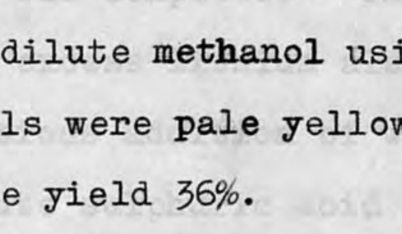
At the initial rise in temperature the reaction mixture began to go cloudy, and as the addition proceeded a brownish-yellow, finely divided precipitate began to separate as the sodium gradually disappeared. A slight green colouration was noticed at the inlets of the ester and the nitrogen.

After the addition was complete, stirring was continued for a further one hour, during which time the xylene was allowed to boil. The mixture was then allowed to cool, when the colour changed from the brownish-yellow to a dull, dark green. When the temperature had fallen to about 45° methanol was added to destroy any residual sodium. A little water was added, followed by dilute sulphuric acid. The colour of the reaction mixture changed to a reddish-brown. After acidification, the flow of nitrogen was stopped.

The reaction mixture was transferred to a separating funnel and the reddish-brown xylene layer was separated and washed with water, then with a 10% aqueous solution of sodium carbonate until the washings were colourless, and finally with more water until the aqueous washings were neutral to litmus.

The xylene was removed by steam distillation and the residual oil in the steam distillation flask was triturated well with light petroleum (b.p. 40 - 60°) until it solidified. The solid was crystallized from dilute methanol using decolorizing charcoal. The crystals were pale yellow prisms, mp. 87 - 89°. Yield 10 g. Percentage yield 36%.

Repeated crystallization from the same solvent, with charcoal, raised the melting point to a constant value of 90 - 92°. An analytical sample crystallized from undiluted methanol in colourless prisms, m.p. 91°. Analysis showed that a Dieckmann condensation had taken place, giving a product with a six-membered bridging ring (LXXX11).



LXXX11

Found: C, 76·14; H, 4·83; O, 18·92. $C_{16}H_{12}O_3$ requires C, 76·18; H, 4·80; O, 19·03%.

Preparation of 2-hydroxymethyl-2'-hydroxyethyldiphenyl LXXX111

S.R. Pal, Ph.D. Thesis, 1959.

A one-litre round-bottomed flask was fitted with a double surfaced condenser with a calcium chloride drying tube and a dropping funnel. A solution of 2-carbomethoxy-2'-carbomethoxymethyldiphenyl (40 g., 1 mol.) in dry ether (200 ml.) was added to a suspension of lithium aluminium hydride (8·5 g., 1·6 mol.) in dry ether (300 ml.) in the flask, at such a rate as to maintain a gentle refluxing of the ether. After the addition of the ester a little more hydride was added to ensure that reduction was complete. The reaction mixture was allowed to cool, then excess lithium aluminium hydride was decomposed by the cautious addition of water. The mixture was acidified with 5% dilute sulphuric acid and the ether layer was separated. The aqueous acidic layer was extracted twice with ether and the combined ethereal solutions were washed well with water and dried over anhydrous sodium sulphate. The ether was removed by distillation and the residue readily solidified. It crystallized from benzene in clusters of fine colourless needles, m.p. 102 - 103°. Yield 26 g. Percentage yield 81%.

<u>Preparation of 2-bromomethyl-2'-bromoethyldiphenyl</u> LXXXlV

S.R. Pal, <u>ibid</u>.

2-Hydroxymethyl-2'-hydroxyethyldiphenyl (12 g.) and 48% $^{w}/w$ hydrobromic acid were boiled together under reflux for half an hour. The mixture was cooled and as much hydrobromic acid as possible was decanted off. A further portion of acid (250 ml.) was added and the mixture was boiled for a further half-hour. When cold, the brown oil which had separated was extracted with benzene. The benzene solution was dried over anhydrous sodium sulphate and the benzene was then removed by distillation using slightly reduced pressure from a water pump. The residual dibromide was not purified further. The quantities of reactants for the following reaction were calculated based on a theoretical yield of dibromide (18·6 g.).

<u>Attempted condensation of 2-bromomethyl-2'-bromoethyldiphenyl with diethyl malonate.</u>

Absolute ethanol (300 ml.) was dried by boiling under reflux for one hour with sodium (3 g.) and diethyl phthalate (27 ml.). The alcohol was distilled directly into a dropping funnel previously marked at the required volume.

The apparatus, which was oven-dried, consisted of a 250 ml. three-necked round bottomed flask fitted with a double surfaced reflux condenser and a calcium chloride drying tube, a stirrer and a dropping funnel. The flask was supported in an electrically heated mantle.

Dried absolute ethanol (36 ml.) was run into the flask and sodium (2·4 g., 2 atoms) was added in small pieces. The mixture was stirred until all the sodium had dissolved. It was necessary to add about 20 ml. more ethanol to dissolve the last traces of sodium. Diethyl malonate (8 ml., 1 mol.) was added and was washed in with a little more alcohol. 2-Bromomethyl-2'-bromoethyldiphenyl was dissolved in sodium-dried ether (50 ml.) and run into the reaction mixture from the dropping funnel. The reaction mixture became cloudy as the dibromide was added. The mixture was heated under reflux with stirring for one hour, then the ether was distilled off. Heating and stirring were continued for a further three hours. A test portion of the mixture had then pH 7-8.

Water was added to the reaction mixture, when an oil was precipitated. The mixture was extracted with ether and the ethereal solution was washed once with water and dried over anhydrous sodium sulphate. The ether was distilled off and the viscous residue was distilled under reduced pressure. It distilled between 176 - 200°, but mainly between 196 - 200°. Some decomposition occurred. The distillate was a colourless viscous oil. Attempts to solidify it or to crystallize it were unsuccessful.

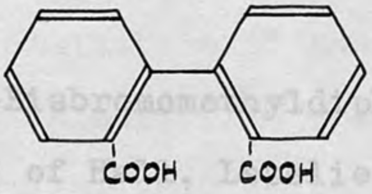
The oil was boiled under reflux with 10% ethanolic potassium hydroxide solution (40 ml.) for six hours. Water was added and a small quantity of oil which was precipitated was extracted with ether. The ethereal solution was dried over anhydrous sodium sulphate and the ether was distilled off. The residue was too small for further investigations and was therefore discarded.

The aqueous hydrolysis mixture was acidified with dilute hydrochloric acid and a yellow oil separated. The oil was extracted with ether and remained as a very viscous residue when the ether was distilled off. It could not be induced to solidify. A little of the oil in dilute sodium carbonate solution decolorized bromine water. Attempts to make the p-nitrobenzyl ester and the s-benzylthiouronium salt were unsuccessful.

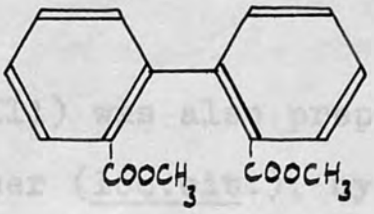
DISCUSSION OF RESULTS

The synthesis of 3:4-5:6-dibenzocyclohepta-3:5-diene and the acids derived from it.

The earlier stages of the synthesis of 3:4-5:6-dibenzo*cyclo*hepta-3:5-diene were quite straightforward and gave very good yields. Dimethyl-2:2'-diphenate (LX) was prepared from 2:2'-diphenic acid (L1X) by the standard method of esterification of an acid.



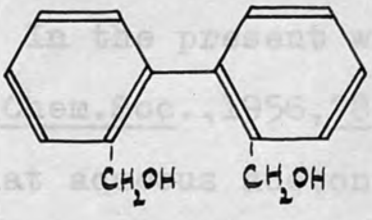
L1X



LX

It was found that the time of refluxing could be reduced from six hours to four without loss of yield. The crude yield of ester was almost quantitative and the ester could be used satisfactorily without further purification.

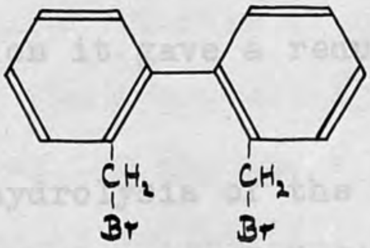
Dimethyl-2:2'-diphenate was reduced by an ethereal suspension of lithium aluminium hydride to give 2:2'-bis hydroxymethyldiphenyl (LX1) in high yields.



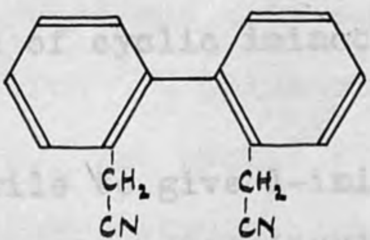
LX1

This method had been used by Hall, Lesslie and Turner (Nature,1949,163,537; J.,1950,711) in their synthesis of 9-10-dihydrophenanthrene. Water was used to decompose excess lithium aluminium hydride. Other workers recommend the use of ethyl acetate as being less dangerous (Brown, Org. Reactions,4,469), but in the present work it was found that the use of this reagent gave a product smelling strongly of ethyl acetate. The yield of diol was also reduced by as much as 20%.

2:2'-Bisbromomethyldiphenyl (LX11) was also prepared by the method of Hall, Lesslie and Turner (loc.cit.), by heating 2:2'-bishydroxymethyldiphenyl with a large excess of 48% hydrobromic acid.



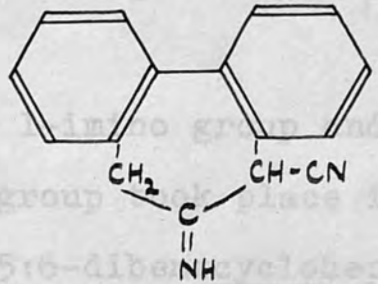
LX11



LX111

2:2'-Biscyanomethyldiphenyl (LX111) was first prepared by Kenner and Turner (J.,1911,99,2101), who used aqueous ethanol as a solvent. In the present work the method of Cope and Smith (J.Amer.Chem.Soc.,1956,78,1012) was used. The latter workers found that aqueous acetone was preferable as a solvent to aqueous ethanol, which caused partial hydrolysis of the dinitrile. The dinitrile could be crystallized satisfactorily from either absolute ethanol or methylated spirit.

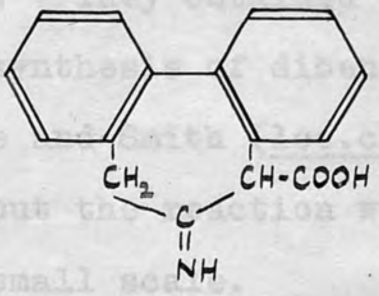
The method of Kenner and Turner (loc.cit.) was used to prepare 1-imino-2-cyano-3:4-5:6-dibenzocyclohepta-3:5-diene (LX1V) in 84% yield.



LX1V

Crystallization of the product from absolute ethanol gave the cyclic iminonitrile with a melting point of 191 - 192°, slightly higher than Kenner's recorded melting point of 189°. The crude iminonitrile was highly crystalline and had the correct melting point, but if hydrolysed without further purification it gave a reduced yield of cyclic iminocarboxylic acid.

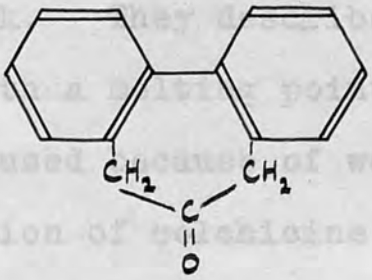
The hydrolysis of the iminonitrile to give 1-imino-3:4-5:6-dibenzcyclohepta-3:5-dien-2-carboxylic acid (LXV) was effected easily by concentrated sulphuric acid in the cold (Kenner and Turner, loc.cit.)



LXV

Only small-scale reactions could be carried out. An attempt to hydrolyse a 50 g. batch of the iminonitrile was unsuccessful. Much charring occurred and very little pure product was obtained.

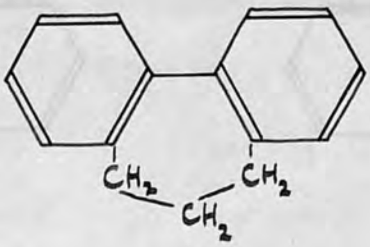
Hydrolysis of the 1-imino group and decarboxylation of the 2-carboxylic acid group took place in one stage to give the cyclic ketone 3:4-5:6-dibenz<u>cyclo</u>hepta-3:5-dien-1-one (LXV1).



LXV1

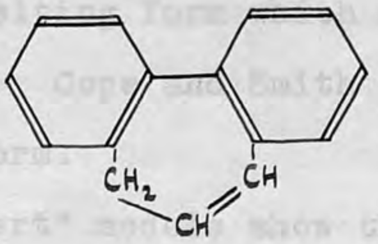
Kenner and Turner (<u>loc.cit.</u>) carried out this reaction by boiling the iminocarboxylic acid with 50% sulphuric acid under reflux for one and a half hours. The cyclic ketone was purified by steam distillation. In the present work a mixture of 88% syrupy phosphoric acid and water was used according to the method of Sakan and Nakasaki (<u>J.Inst.Polytech.Osaka City Univ.</u>,1950,1(<u>No.2</u>),23). They obtained the ketone as an intermediate in their synthesis of dibenztropolone. The same method was used by Cope and Smith (<u>loc.cit.</u>). The ketone was obtained in 85% yield but the reaction was only satisfactory when carried out on a small scale.

The hydrocarbon 3:4-5:6-dibenz<u>cyclo</u>hepta-3:5-diene (LV11) had been prepared by a number of workers.

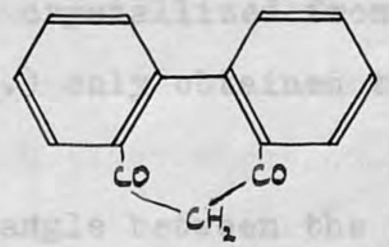


LV11

It was first synthesized by Lettré (*Angew.Chem.*,1947, *59*,218) and Wichmann (*ibid.*,180) using a synthesis similar to that of the present work. They described it as a beautiful crystalline compound with a melting point of 52°. Interest in the hydrocarbon was aroused because of work carried out to determine the constitution of colchicine (Lettré, *loc.cit.*), which has a mitosis-arresting effect on the growth of cells. 3:4-5:6-Dibenz*cyclo*hepta-3:5-diene is the parent hydrocarbon of certain degradation products of colchicine. It was synthesized by Rapoport and Williams (*J.Amer.Chem.Soc.*,1949, *71*,1774) who reported that the compound existed in dimorphic forms which had melting points of 40° and 55° respectively. The low melting form was only obtained on cooling the hydrocarbon. On standing, it was converted into the higher melting form which was also obtained by steam distillation of the hydrocarbon, or by crystallization from a solvent. Cook, Dickson and Loudon (*J.*,1947,746) obtained a small amount of the hydrocarbon as a side product in the reactions of 3:4-5:6-dibenz*cyclo*hepta-1:3:5-triene (LXXXV). It was also obtained by a Clemmensen reduction of 3:4-5:6-dibenz*cyclo*hepta-3:5-diene-2:7dione (LXXXV1) (Lucien and Taurins, *Canadian J.Chem.*,1952,*30*,208).



LXXXV



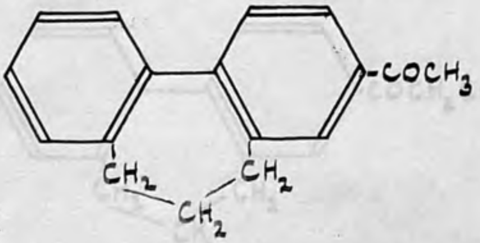
LXXXVl

Cope and Smith (*loc.cit.*) prepared the hydrocarbon by a Huang-Minlon modification of a Wolff-Kishner reduction of the ketone 3:4-5:6-dibenz*cyclo*hepta-3:5-dien-1-one (LXVl) (Page No.74) (Huang-Minlon, *J.Amer.Chem.Soc.*,1946,*68*,2487). This was the method adopted in the present work. The ketone was boiled under reflux with hydrazine hydrate and potassium hydroxide in diethylene glycol until the hydrazone was formed, then hydrazine and water were distilled off to raise the temperature of the reaction mixture. This obviates the necessity of using a large excess of sodium, which was used in the original Wolff-Kishner method to reduce the volume of water in order to enable the high reaction temperature to be reached.

In the present work the hydrocarbon was obtained as pale brown prisms in yields varying from 43% to 73%. The preparation was only carried out on a small scale. In the first experiment a portion of the product melted at $38 - 40^{\circ}$ after crystallization from methanol. The remainder melted at $55 - 56^{\circ}$ after being crystallized from ethanol. There was no apparent difference in crystalline structure. This was the only experiment in which the lower-melting form of the hydrocarbon was obtained. All other reactions gave the higher-melting form which was also crystallized from methanol. Cope and Smith (*loc.cit.*) only obtained the lower-melting form.

"Stuart" models show that the angle between the planes of the benzene rings in 3:4-5:6dibenzo*cyclo*hepta-3:5-diene is about 70°. (Merkel and Wiegand,*z*,*Naturforsch*.,1948,*3*,b,93). If a substituent salt-forming group were introduced into the diphenyl nucleus the resulting compound should be capable of showing optical activity. An acetyl group was introduced into one of the benzene rings and was then oxidised by sodium hypochlorite solution to a carboxylic acid group, which is a conveniently simple salt-forming group. By analogy with 9-10-dihydrophenanthrene the acetyl group would enter the diphenyl nucleus in the 2'-position, i.e., *para* to the diphenyl link.

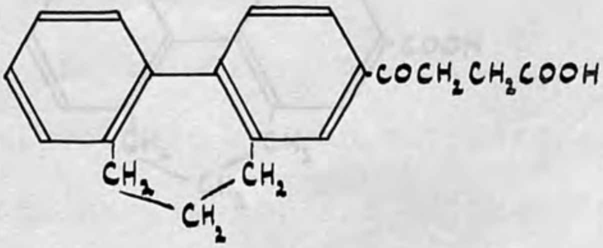
The introduction of the acetyl group into the diphenyl nucleus could only be effected in low yields. The addition of a cold solution of aluminium chloride in nitrobenzene to a cold solution of the hydrocarbon and acetyl chloride in the same solvent gave 2'-acetyl-3:4-5:6-dibenzo*cyclo*hepta-3:5-diene (LXV11) in 17% yield.



LXV11

It was difficult to remove final traces of nitrobenzene from the product, which was also steam volatile. Carbon disulphide was used as a solvent in a later reaction. The reaction mixture was boiled under reflux for four hours. The carbon disulphide could be distilled directly from the reaction mixture and so did not contaminate the product. An added advantage was the insolubility of the catalyst aluminium chloride in carbon disulphide. It dissolved in the more polar solvent nitrobenzene and its catalytic action may have been diminished. However, the use of carbon disulphide gave a reduced yield of acetyl derivative. In another reaction acetic anhydride was used instead of acetyl chloride as the acetylating agent. Nitrobenzene was again used as the solvent and a 21% yield of the required product was obtained.

Because of the poor yields obtained in the acetylation reactions of the hydrocarbon, a Friedel-Crafts reaction was carried out using succinic anhydride. The product of this reaction, 2'-(ω-carboxypropionyl)-3:4-5:6-dibenz<u>cyclo</u>hepta-3:5-diene (LXV111), contained a salt-forming group which could be combined directly with an alkaloid.

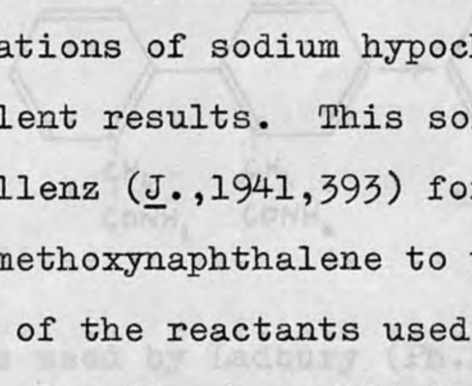


LXV111

The solvent used in the Friedel-Crafts reaction was nitrobenzene. In the working-up the bulk of the nitrobenzene was removed by steam distillation, then the mixture in the distillation flask was made alkaline, and the steam distillation was continued. The required product went into solution as the sodium salt and final traces of nitrobenzene could be removed. The yield of final product was 44%.

2'-Acetyl-3:4-5:6-dibenzocyclohepta-3:5-diene was oxidised to the carboxylic acid by an 18% solution of alkaline sodium hypochlorite. Hall (private communication) had found difficulty in oxidising 2-acetyl-9-10-dihydrophenanthrene with many different concentrations of sodium hypochlorite, but an 18% solution gave excellent results. This solution was also used by Robinson and Willenz (J.,1941,393) for the oxidation of 2-acetyl-5-chloro-7-methoxynaphthalene to the corresponding acid. The proportions of the reactants used were 1 molecule of ketone: 5 molecules of sodium hypochlorite.

The 2'-(ω-carboxypropionyl)-3:4-5:6-dibenzocyclohepta-3:5-diene was also oxidised by the same reagent under the same conditions, to give 2'-carboxy-3:4-5-6dibenzocyclohepta-3:5-diene (LX1X).



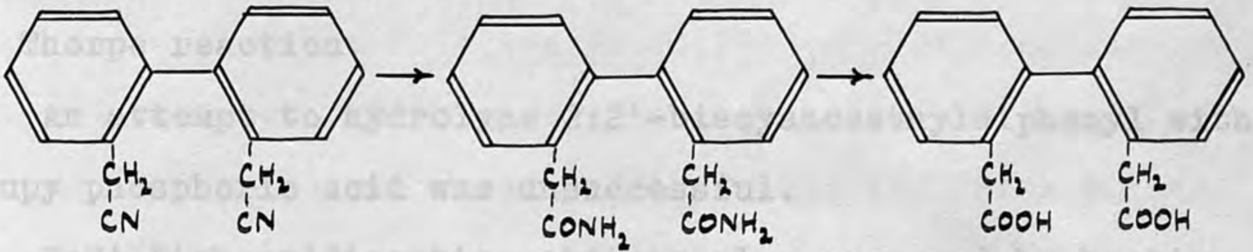
LX1X

The better method of preparing this acid from the hydrocarbon was through the succinoylation of the hydrocarbon, since this was a more convenient method, and gave higher yields, than the acetylation reaction.

Synthesis and reactions of 2:2'-bisbromoethyldiphenyl.

The purpose of this synthesis was to prepare a 2:2'-bridged diphenyl compound containing a nine-membered bridging ring.

Kenner and Turner (*J.*,1911,*99*,2101) prepared 2:2'-diphenyldiacetic acid (LXX) by a two-stage hydrolysis of 2:2'-biscyanomethyldiphenyl (LX111).



LX111 LXX

The same method was used by Ladbury (Ph.D. Thesis, 1954, 121) but in the present work it was found that hydrolysis with concentrated sulphuric acid to give 2:2'-diphenyldiacetamide, followed by an alkaline hydrolysis to give the acid, gave only a low overall yield of the final product. Different methods of hydrolysis were therefore tried.

When 2:2'-biscyanomethyldiphenyl was boiled under reflux for two hours with equal volumes of concentrated sulphuric acid, glacial acetic acid and water, 2:2'-diphenyldiacetic acid was obtained directly in one stage. Crystallization of the product from water gave an acid melting at 173 - 175°

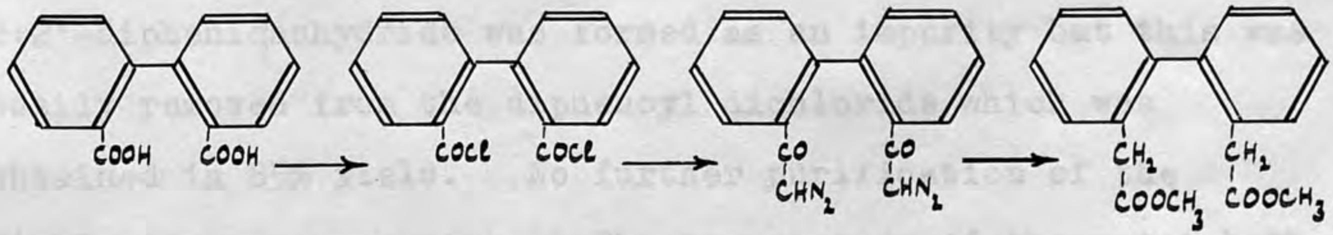
in an 87% yield. A small quantity of the acid was obtained when the dinitrile was boiled under reflux with 10% aqueous potassium hydroxide, but the major portion of the product was the cyclic iminonitrile, 1-imino-2-cyano-3:4-5:6-dibenz<u>cyclo</u>-hepta-3:5-diene (LXlV) (Page No.73). The same compound was obtained in 52% yield when the dinitrile was warmed with an alkaline solution of hydrogen peroxide. It is interesting to note that this diphenyl, bridged with a seven-membered bridging ring is formed so readily that cyclisation is effected in the presence of aqueous alkali as well as in the presence of sodium ethoxide, as in the original conditions of the Thorpe reaction.

An attempt to hydrolyse 2:2'-biscyanomethyldiphenyl with syrupy phosphoric acid was unsuccessful.

2:2'-Diphenyldiacetic acid was also prepared by heating 2:2'-diphenyldiacetamide with 10% potassium hydroxide solution until the evolution of ammonia ceased. This was the method used by Kenner and Turner (loc.cit.) but whereas their diphenyldiacetic acid melted at 151-152°, the acid obtained by the present worker melted at 173 - 175°. A little of Ladbury's acid, which also melted at the lower temperature, (loc.cit.) was available and a mixed melting point with the acid prepared in the present work was 173 - 175°. Ladbury's acid was melted and seeded with the higher melting form and the resulting solid melted at 172 - 175°. It would therefore appear that 2:2'-diphenyldiacetic acid exists in dimorphic forms. The higher melting form, which crystallized as irregular prisms, was always obtained in the present work. Only in one preparation a small second crop of acid softened at 153°, resolidified, and finally melted at 173 - 175°. The crystalline form was blunt needles.

Ladbury (loc.cit.) had attempted the preparation of the acid by Ullmann reactions on methyl-o-bromophenylacetate and on methyl-o-iodophenyl acetate but without success. The same worker obtained 2:2'-diphenyldiacetic acid by an Arndt-Eistert synthesis, in which the diazodiketone prepared from 2:2'-diphenoyldichloride in dioxane solution was treated with silver oxide in an aqueous solution of sodium thiosulphate. Smith and Muth (Proc.W.Va.Acad.Sci.,1953,25,42) recorded a 10 - 20% yield of 2:2'-diphenyldiacetic acid when they treated the diazodiketone of 2:2'-diphenic acid with silver benzoate in triethylamine solution.

In general, the Arndt-Eistert synthesis is more successful for the preparation of esters than for acids (Bachmann and Struve, Org.Reactions,1,38) and since the present synthesis of 2:2'-bisbromoethyldiphenyl required the preparation of an ester of 2:2'-diphenyldiacetic acid, an Arndt-Eistert reaction was carried out to prepare dimethyl 2:2'-diphenyldiacetate (LXX1).



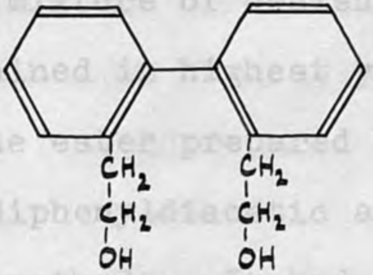
L1X

LXX1

Some difficulty was encountered in the preparation of 2:2'-diphenoyldichloride. Underwood and Kochmann (J.Amer. Chem.Soc.,1924,46,2069) prepared the dichloride in 81% yield by heating together a mixture of 2:2'-diphenic acid and phosphorus pentachloride at 190° and removing the phosphorus oxychloride by drawing air through the neck of the reaction flask. Ladbury (loc.cit.) reported a 61% yield of dichloride by the same method. Minhaj (Ph.D. Thesis, 1956, 116) had difficulty in preparing the dichloride by this method and the present worker could only obtain impure dichloride by using the above conditions. The product was discoloured and did not give a clear melt and was only obtained in low yields. The high temperature presumably caused some charring and the product appeared to be hydrolysed easily to 2:2'-diphenic acid. A better preparative method was one which used thionyl chloride instead of phosphorus pentachloride (Bell and Robinson, J.,1929,1695; Nightingale, Heiner and French, J.Amer.Chem.Soc.,1950,72,1875). A mixture of 2:2'-diphenic acid and thionyl chloride were warmed together on a water bath until the mixture was a clear liquid. This took ten hours or more and often required an additional length of time at room temperature. A little 2:2'-diphenic anhydride was formed as an impurity but this was easily removed from the diphenoyl dichloride which was obtained in 85% yield. No further purification of the dichloride was necessary. The temperature of the water bath in this preparation was critical; the best yield of diphenoyldichloride was obtained with a bath held at 45 - 47°. Heating at higher temperatures gave an increased yield of diphenic anhydride.

For the Arndt-Eistert reaction, diazomethane was prepared by the method of de Boer and Backer (Rec.Trav.chim., 1954,73,229). The starting material was N-methyl-p-toluene sulphonylnitrosamide which is chemically more stable at room temperature than other compounds used for the preparation of diazomethane, e.g. nitrosomethylurea. The nitrosamide in ethereal solution was added to aqueous alcoholic potassium hydroxide and the diazomethane was collected simultaneously in the ethereal distillate. Care was taken in handling the diazomethane. All ground glass joints of the apparatus were fitted with sleeves of polytetrafluoroethylene and all reactions were carried out in a fume cupboard with the exhaust fan on. The diazodiketone was made by adding an ethereal solution of 2:2'-diphenoyldichloride to an ice-cold ethereal solution of diazomethane. After excess diazomethane and ether had been removed the diazodiketone was left as a yellow oily liquid, part of which solidified. It was not purified further but was dissolved in excess warm methanol and treated immediately with silver oxide. The diazodiketone underwent rearrangement by a mechanism similar to the Curtius rearrangement of an acid azide (Bachmann and Struve, loc.cit.) and in the presence of methanol formed the ester dimethyl 2:2'-diphenyldiacetate. The ester was purified by repeated distillation under reduced pressure. It was obtained in yields ranging from 20 - 32%. It was a pale yellow oil which could not be solidified. This was rather surprising as dimethyl 2:2'-diphenyldiacetate would be expected to be solid. A portion of the oil, on hydrolysis with aqueous ethanolic sodium hydroxide, gave a crystalline sample of 2:2'-diphenyldiacetic acid, m.p. 173 - 175°.

As a further means of identification, and as the next stage in the synthesis, dimethyl 2:2'diphenyldiacetate was reduced by a suspension of lithium aluminium hydride in dry ether to give 2:2'-bis-β-hydroxyethyldiphenyl (LXXll) as colourless crystals, m.p. 89 - 91°.



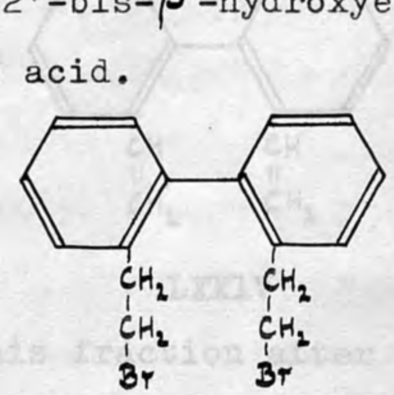
LXXll

Dimethyl 2:2'-diphenyldiacetate was also prepared by the direct esterification of 2:2'-diphenyldiacetic acid. The esterification was carried out in two ways. In the first method, the acid was added as a solid to an ethereal solution of diazomethane which had been prepared as previously described. After the reaction mixture had stood in an exhaust chamber overnight the ether was distilled off and the residual ester remained as a yellow oil. It resisted all attempts to solidify it. It was dissolved in dry ether and reduced to the corresponding diol. In the second method of esterification the acid was heated under reflux for six hours with methanol and concentrated sulphuric acid. The reaction mixture was poured into water and the ester was extracted with ether. The ethereal solution, after suitable washings, was dried over anhydrous sodium sulphate and was used directly in the reduction by lithium aluminium hydride.

A little of the 2:2'-diphenyldiacetic acid prepared by Ladbury, m.p. 153°, was esterified by methanol and concentrated sulphuric acid and the ester was reduced. The diol obtained melted at 89 - 91°. This was further proof of the dimorphism of 2:2'-diphenyldiacetic acid.

2:2'-Bis-β-hydroxyethyldiphenyl was obtained as colourless prisms from a mixture of benzene and light petroleum. It was obtained in highest yields (up to 86%) from the reduction of the ester prepared by the direct esterification of 2:2'-diphenyldiacetic acid using the methanol-sulphuric acid method. It had a tendency to crystallize with solvent of crystallization but careful drying in a vacuum at 56° removed the solvent satisfactorily.

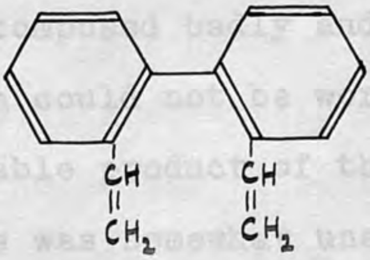
2:2'-Bis-β-bromoethyldiphenyl (LXX111) was easily prepared by heating 2:2'-bis-β-hydroxyethyldiphenyl with excess 48% hydrobromic acid.



LXX111

The yields were between 75% and 87%. The bromo compound was purified by fractional distillation under reduced pressure. No decomposition of the bromo compound was noticed. The percentage composition of bromine in the compound was estimated by a Carius estimation. A modification of a Stepanow estimation gave unsatisfactory results.

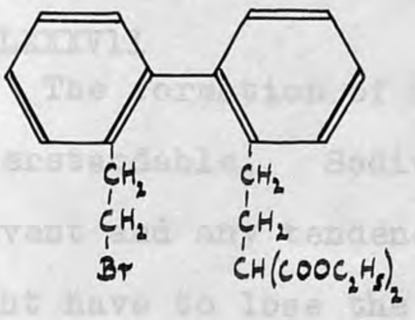
The attempted condensation of 2:2'-bis-β-bromoethyldiphenyl with diethyl malonate in the presence of sodium ethoxide, to give a diphenyl bridged to form a nine-membered ring, was unsuccessful. Sodium was dissolved in carefully dried ethanol and diethylmalonate was added to the solution. The dibromo compound was added and the mixture was heated under reflux until it was neutral to litmus. The reaction product was fractionally distilled under reduced pressure. The distillation was slow and the fractions were not well-defined. The first fraction was a small amount of unchanged diethyl malonate. The second and largest fraction deposited crystals which were proved by analysis and mixed melting point to be 2:2'-divinyldiphenyl (LXXlV).



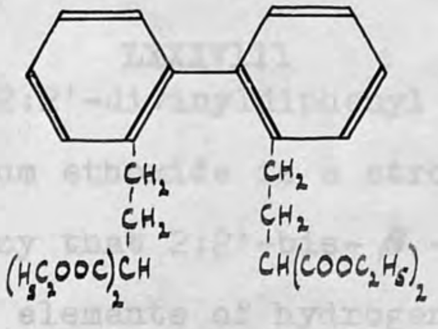
LXXlV

The residue of this fraction after the solid was removed contained 9·67% bromine. This figure did not correspond to either unchanged dibromo compound (requires

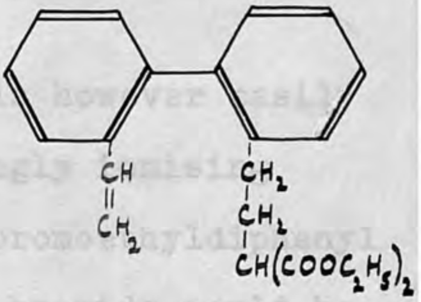
43·43% Br.) or to the product (a) of the reaction between one bromine atom and one molecule of diethyl malonate (requires 17·87% Br.).



a



b

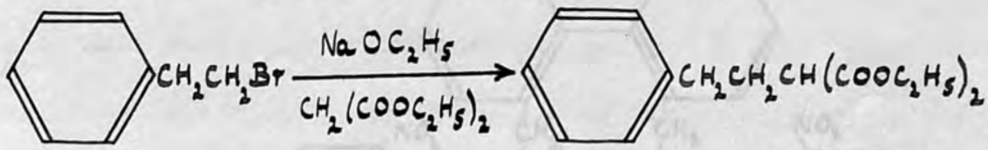


c

It was thought to be possibly a mixture of (a) and either (b) or (c), or possibly a mixture of all three. After it had been allowed to stand for some time to see if it would solidify it was found to be unaffected by boiling aqueous alcoholic potassium hydroxide.

The third fraction also contained a little bromine (2·05%). This was also presumably a mixture of the above compounds. The fraction was saponified with alcoholic potassium hydroxide solution and gave an oil. An attempt was made to dicarboxylate the oil by heating it in an oil bath at 200° but the oil decomposed badly and gave a hard intractable glass which could not be worked further.

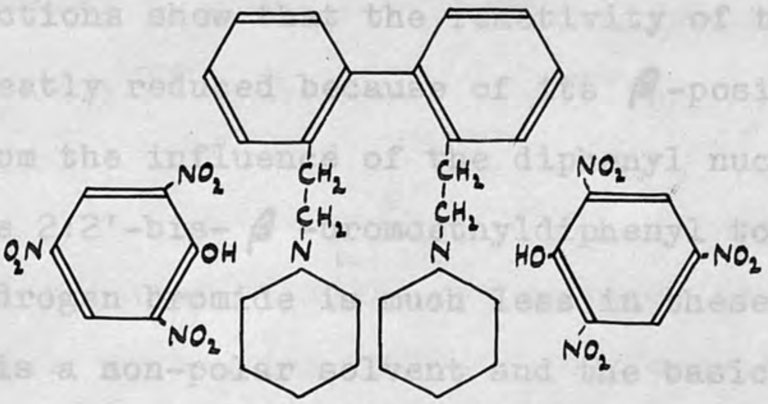
The only identifiable product of this reaction was 2:2'-divinyldiphenyl. This was somewhat unexpected as it was thought that if a cyclic product was not obtained the chief product would probably be (b). Fischer and Schmitz (<u>Ber</u>, 1906,<u>39</u>,2211) obtained β-phenylethylmalonic ester (LXXXV111) from the reaction between β-phenylethyl bromide (LXXXV11) and the sodio derivative of diethyl malonate.



LXXXV11 LXXXV111

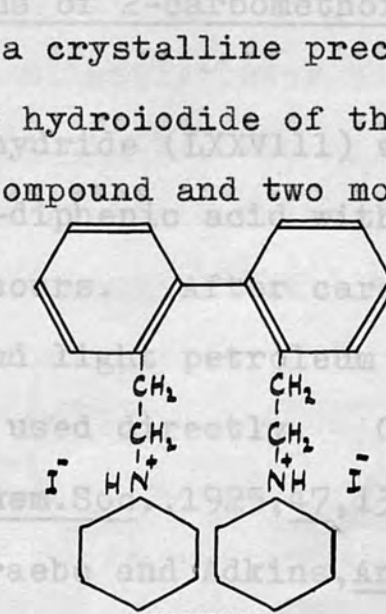
The formation of 2:2'-divinyldiphenyl is however easily understandable. Sodium ethoxide is a strongly ionising solvent and any tendency that 2:2'-bis-β-bromoethyldiphenyl might have to lose the elements of hydrogen bromide would be greatly increased under the conditions of the reaction. Some time after this work was carried out Mislow, in a private communication, reported that he had also obtained 2:2'-divinyldiphenyl as the only product in the reaction between 2:2'-bis-β-bromoethyldiphenyl and the sodio derivative of diethyl malonate.

The attempts to condense 2:2'-bis-β-bromoethyldiphenyl with piperidine to form a diphenyl containing a nine-membered heterocyclic bridging ring were also unsuccessful. In the first experiment the dibromocompound and piperidine were warmed together in dry benzene until no more piperidine hydrobromide was formed. The product, after suitable washings, was treated with a saturated alcoholic solution of picric acid. The bright yellow picrate so obtained analysed as the picrate of the base formed from the reaction between the dibromo compound and two molecules of piperidine (LXXV1).



LXXV1

The above reaction was carried out on impure 2:2'-bis-β-bromoethyldiphenyl since it was originally thought that the dibromo compound might decompose on distillation. After the dibromo compound had been distilled the reaction was repeated using the pure material. This time another solid appeared in the reaction mixture together with piperidine hydrobromide. The combined solids were filtered off and dissolved in water. The solution was treated with a saturated solution of potassium iodide and a crystalline precipitate was obtained. This analysed for the hydroiodide of the base formed from one molecule of dibromo compound and two molecules of piperidine (LXXV11).



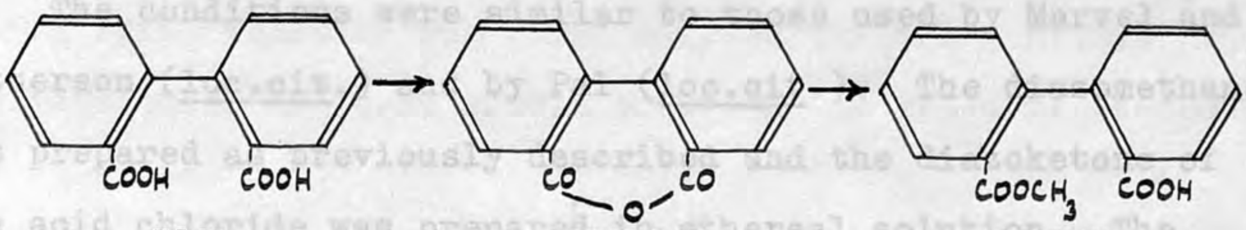
LXXV11

These reactions show that the reactivity of the bromine atom is not greatly reduced because of its β-position, so far removed from the influence of the diphenyl nucleus. The tendency of the 2:2'-bis-β-bromoethyldiphenyl to lose the elements of hydrogen bromide is much less in these reactions since benzene is a non-polar solvent and the basicity of the reaction medium is probably considerably reduced by the buffer action of the piperidine hydrobromide.

The failure to obtain the required condensation products with the nine-membered bridging ring is probably due to steric factors. It seems likely that the two bromine atoms never come close enough together for both to react with one molecule of diethyl malonate, or of piperidine. This work is further evidence of the difficulties of synthesizing diphenyl compounds bridged across the 2:2'-positions by a nine-membered bridging ring.

Synthesis and reactions of 2-carbomethoxy-2'-carbomethoxymethyldiphenyl

2:2'-Diphenic anhydride (LXXVlll) was prepared in 95% yield by heating 2:2'-diphenic acid with acetic anhydride in an oil bath for four hours. After careful washing with glacial acetic acid and light petroleum the diphenic anhydride was pure enough to be used directly. Other workers (Roberts and Johnson, J.Amer,Chem.Soc.,1925,47,1396; Oyster and Adkins, ibid.,1921,43,208; Graebe and Adkins,Annalen,1888,247 257) used less acetic anhydride and heated for only one hour.

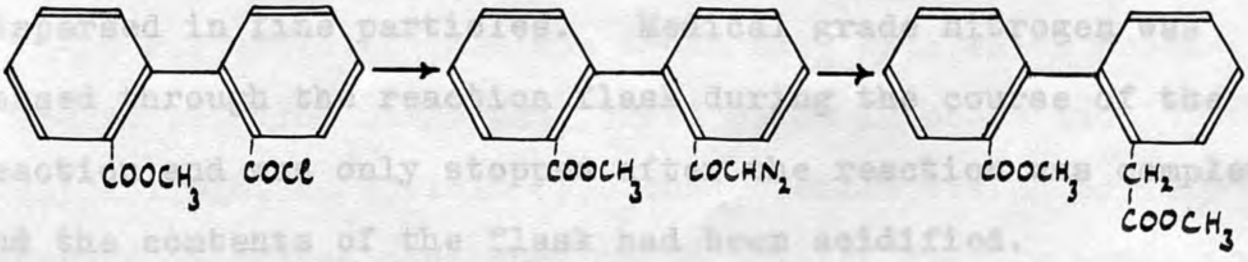


LlX LXXVlll LXXlX

Monomethyl diphenate (LXXlX) was prepared in almost quantitative yield by heating 2:2'-diphenic anhydride under reflux with methanol. Pal (Ph.D. Thesis, 1959,60) reported a yield of 84%, melting at 106 - 108°. Underwood and Kochmann (J. Amer.Chem.Soc.,1924,46,2069) also recorded this melting point but in the present work a slightly higher melting point, 110 - 111° was obtained.

Monomethyldiphenate was converted into its acid chloride (LXXX) when warmed with thionyl chloride and a little pyridine in dry benzene (Marvel and Patterson, J.Amer.Chem.Soc.,1941, 63,2218). The yield was almost quantitative. The acid chloride was dried over calcium chloride in a vacuum desiccator and was used without further purification although its melting point was slightly lower than that recorded by Marvel and Patterson (loc.cit.) and by Pal (loc.cit.)

The conversion of the acid chloride into 2-carbomethoxy-2'-carbomethoxymethyldiphenyl (LXXXl) by an Arndt-Eistert reaction was straightforward.



LXXX LXXXl

The conditions were similar to those used by Marvel and Patterson (loc.cit.) and by Pal (loc.cit.). The diazomethane was prepared as previously described and the diazoketone of the acid chloride was prepared in ethereal solution. The diazoketone rearranged in methanol in the presence of freshly prepared silver oxide to give the required ester in 47% yield with m.p. 66 - 67°. Marvel and Patterson, and Pal, obtained higher yields of the ester and a melting point of 71 - 72° after recrystallizing the ester from aqueous methanol. In the present work recrystallization did not raise the melting point. Pal reported the occurrence of dimorphic forms of 2-carbomethoxy-2'-carbomethoxymethyldiphenyl but no evidence of dimorphism was obtained in the present synthesis.

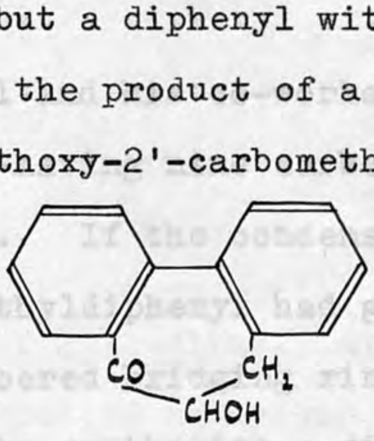
In the reaction between 2-carbomethoxy-2'-carbomethoxymethyldiphenyl and sodium care was taken to follow as closely as possible the conditions used in the condensations of esters of aliphatic dibasic acids to form cyclic acyloins (Prélog et al., Helv.chim.Act.,1947,30,1741; Stoll and Hulstkamp, ibid., 1815; Stoll and Rouvé, ibid., 1822). The solvent used was purified sulphur-free xylene and all apparatus was oven-dried. Rapid stirring of the reaction mixture was maintained so that the molten sodium was dispersed in fine particles. Medical grade nitrogen was passed through the reaction flask during the course of the reaction and was only stopped after the reaction was complete and the contents of the flask had been acidified.

A trial reaction was first carried out using methyl stearate under the same conditions. A 78% yield of stearoin was obtained.

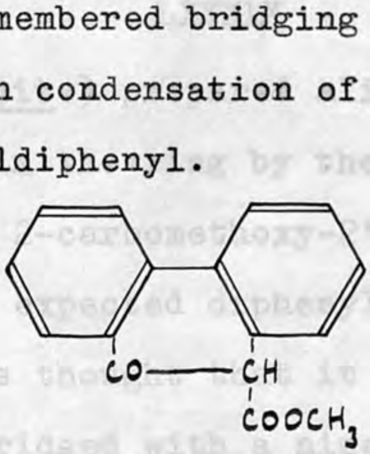
$$2\,CH_3(CH_2)_{16}COOCH_3 \xrightarrow{Na,\ xylene} CH_3(CH_2)_{16}CHOHCO(CH_2)_{16}CH_3$$

The product was identified by analysis and its infra red spectrum. This work is not recorded here as it had no true bearing on the problem under investigation.

A sharp rise in temperature was observed when 2-carbomethoxy-2'-carbomethoxymethyldiphenyl was added to the sodium in xylene. The product of the reaction was a beautifully crystalline compound having a melting point of 90 - 92°. It was obtained only in 36% yield but no other product could be isolated. On analysis, however, it was found to be not the expected diphenyl bridged with a seven-membered acyloin ring (LXXX1X) but a diphenyl with a six-membered bridging ring (LXXX11), the product of a Dieckmann condensation of 2-carbomethoxy-2'-carbomethoxymethyldiphenyl.

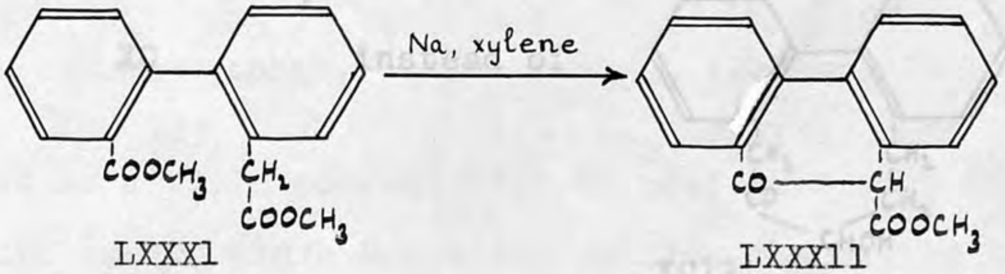


LXXX1X



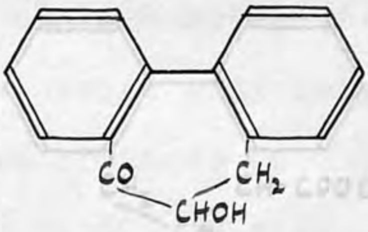
LXXX11

It was expected that the known ease with which seven-membered bridging rings are formed would increase the possibility of an acyloin-type condensation taking place. The observed Dieckmann condensation is however readily explained. 2-Carbomethoxy-2'-carbomethoxymethyldiphenyl contains a methylene group which is highly activated, both by reason of its proximity to the diphenyl nucleus and the effect of the adjacent carbonyl group of the ester group. On being treated with finely divided sodium, which is a characteristic Claisen condensation agent, a cyclisation of the Dieckmann type is the preferred reaction.



LXXXl LXXXll

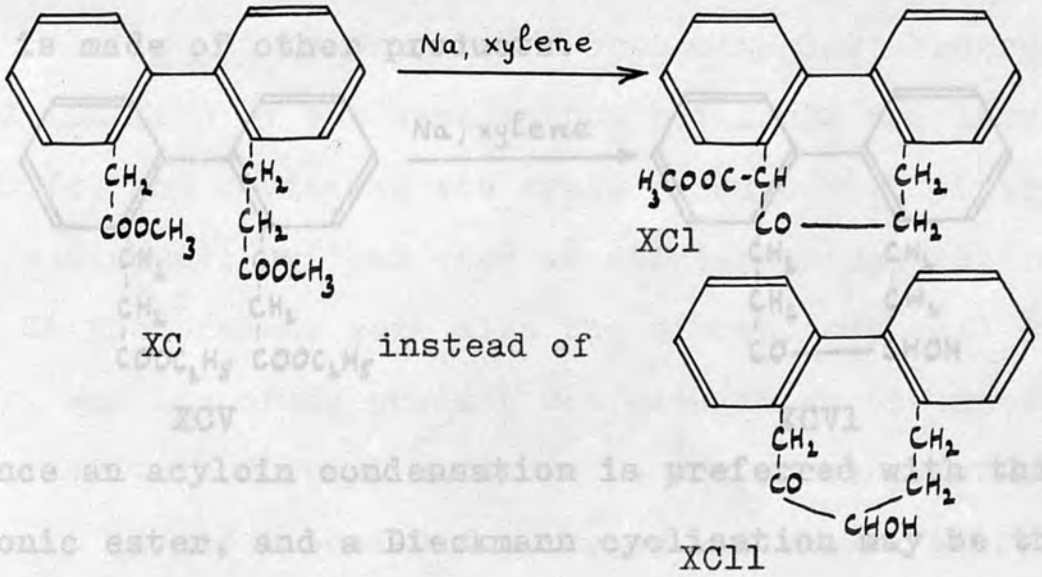
instead of

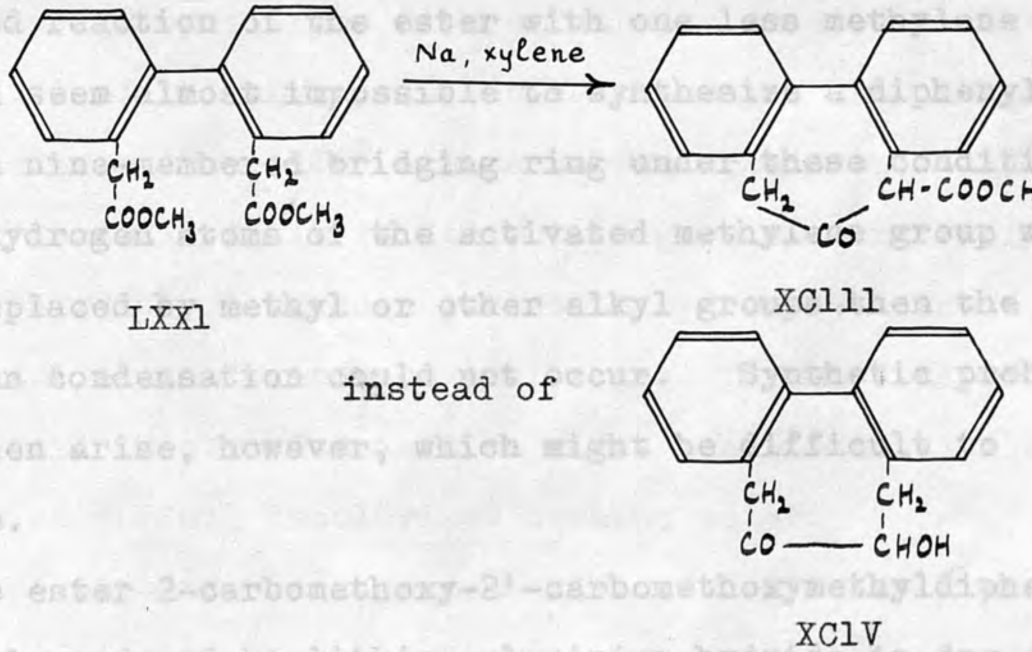


LXXXlX

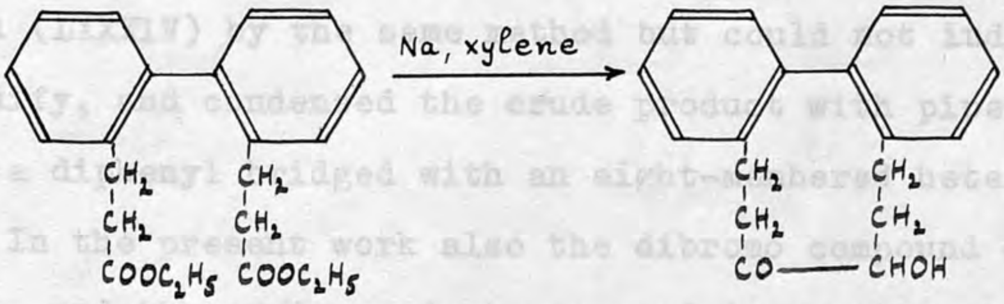
Stoll and his co-workers (<u>loc.cit</u>.) prepared alicyclic compounds having nine carbon atoms in the ring by the acyloin synthesis. If the condensation of 2-carbomethoxy-2'-carbomethoxymethyldiphenyl had given the expected diphenyl with a seven-membered bridging ring, it was thought that it would be possible to synthesize a diphenyl bridged with a nine-membered bridging ring by a similar condensation of 2-carbomethoxymethyl-2'-carbomethoxyethyldiphenyl (XC). This last ester, however, also contains an activated methylene group and under the conditions of an acyloin reaction would undergo a Dieckmann cyclisation to form a compound having an eight-membered bridging ring (XCl). Similarly dimethyl 2:2'-

diphenyldiacetate (LXXl) would form a compound containing a seven-membered bridging ring. (XClll)





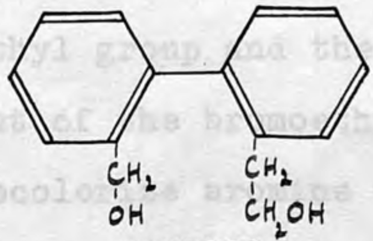
An ester of 2:2'-diphenyldipropionic acid does not contain a highly activated methylene group. This may mean that the tendency for a Dieckmann condensation to take place will be diminished and that the main reaction will be between the ester groups alone, that is, an acyloin-type condensation will take place. This has in fact been shown to occur. Mislow (private communication) has recently treated ethyl 2:2'-diphenyldipropionate (XCV) with sodium in xylene and has obtained a diphenyl bridged by a ten-membered acyloin-type ring (XCVl). The yield of this compound is low, but no mention is made of other products.



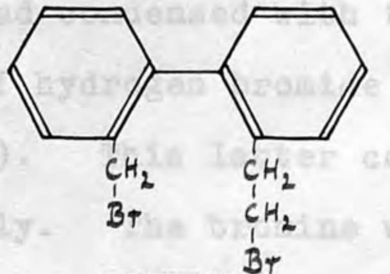
XCV XCVl

Since an acyloin condensation is preferred with this dipropionic ester, and a Dieckmann cyclisation may be the preferred reaction of the ester with one less methylene group, it would seem almost impossible to synthesize a diphenyl having a nine-membered bridging ring under these conditions. If the hydrogen atoms of the activated methylene group were to be replaced by methyl or other alkyl groups then the Dieckmann condensation could not occur. Synthetic problems would then arise, however, which might be difficult to overcome.

The ester 2-carbomethoxy-2'-carbomethoxymethyldiphenyl was easily reduced by lithium aluminium hydride in dry ether, using the usual technique. 2-Hydroxymethyl-2'-hydroxyethyldiphenyl (LXXXlll) was obtained in 81% yield, m.p. 102 - 103°. Pal, (Ph.D. Thesis, 1959,63) obtained a yield of 98%, m.p. 103 - 104°.



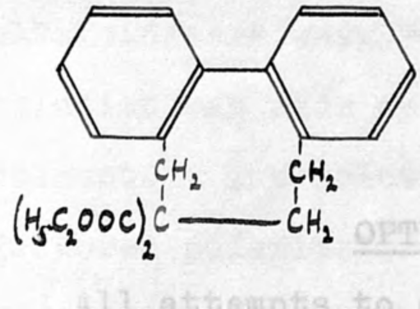
LXXXlll



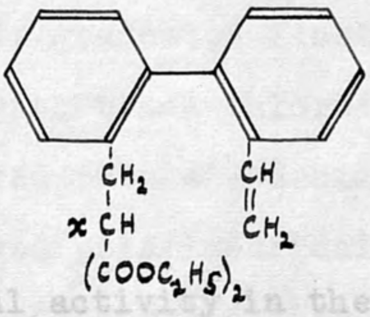
LXXXlV

The hydroxyl groups were replaced by bromine atoms when the diol was boiled under reflux with excess 48% hydrobromic acid. Pal (*loc.cit.*) prepared 2-bromomethyl-2'-bromoethyldiphenyl (LXXXlV) by the same method but could not induce it to solidify, and condensed the crude product with piperidine to form a diphenyl bridged with an eight-membered heterocyclic ring. In the present work also the dibromo compound did not solidify, and the crude product was used in an attempted condensation with diethyl malonate in the presence of sodium ethoxide. It was intended to prepare a diphenyl bridged across the 2:2'-positions with a four-carbon-atom bridge. The product of the attempted condensation was an oil boiling mainly between 196 - 200° with some decomposition. All attempts to solidify it failed but it gave an acidic oil on hydrolysis with 10% aqueous potassium hydroxide. The acidic oil did not solidify, nor could its *p*-nitrobenzyl ester or its *S*-benzyl thiouronium salt be made. A dilute alkaline solution of the oil decolorized bromine water.

Since the attempted condensation of 2:2'-bis-β-bromoethyldiphenyl with diethyl malonate under the same conditions had given 2:2'-divinyldiphenyl, it was thought that the product of the present reaction was a mixture of the required product with an eight-membered bridging ring (d) and the compound in which diethyl malonate had condensed with the bromomethyl group and the elements of hydrogen bromide had split out of the bromoethyl group (e). This latter compound would decolorize bromine water readily. The bromine would add on across the double bond and would also replace the hydrogen atom x.



d

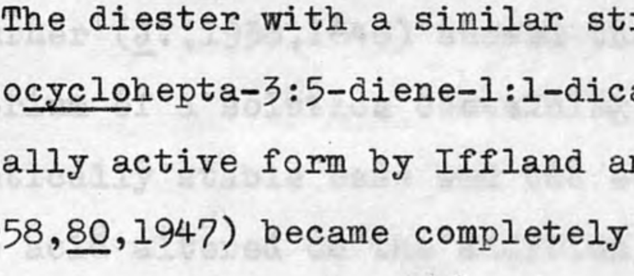


e

OPTICAL WORK

All attempts to observe optical activity in the acids derived from the hydrocarbon 3:4-5:6-dibenzo*cyclo*hepta-3:5-diene were unsuccessful. It seemed likely that any optical activity shown by this bridged diphenyl would be labile optical activity. The diester with a similar structure, ethyl-3:4-5:6-dibenzo*cyclo*hepta-3:5-diene-1:1-dicarboxylate, prepared in an optically active form by Iffland and Siegel (*J.Amer.Chem.Soc.*,1958,*80*,1947) became completely inactive after five hours at a temperature of 32·5°.

Two attempts to carry out a first-order asymmetric transformation were made with 2'-(ω-carboxypropionyl)-3:4-5:6-dibenzo*cyclo*hepta-3:5-diene (LXV111) and brucine at temperatures about 40° and 50°.



LXV111

A third experiment was carried out using cinchonidine as the alkaloid. Equivalent amounts of the acid and alkaloid were weighed into a 25 ml. graduated flask and the solution was made up to the mark with bench chloroform as the solvent. The solution was filtered into a 2-decimetre jacketed polarimeter tube and viewed polarimetrically. Water from a thermostatically controlled electric heater was circulated round the jacket of the tube and maintained it at a suitable required temperature. None of these experiments gave any indication that the acid had been activated.

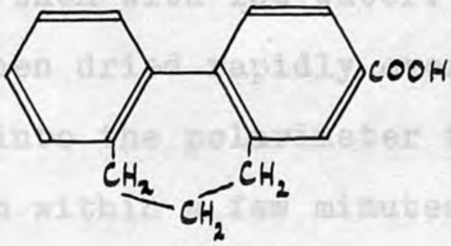
Jamison and Turner (J.,1938,1646) showed that the optical rotation at equilibrium of a solution containing one equivalent of an optically stable base and one equivalent of an optically labile acid altered on the addition of further quantities of the acid. The curve obtained by plotting the optical rotation as a function of the acid-base ratio is called an "addition curve". It was suggested that this phenomenon might be used to indicate potential optical activity in compounds which could not otherwise be optically activated.

The effect of adding excess acid (LXVlll) to a chloroform solution of quinidine was studied. An equivalent quantity of quinidine was dissolved in 25 ml. of chloroform in a graduated flask and the solution was transferred to the polarimeter tube. Successive equivalents of acid were added directly into the solution in the polarimeter tube and readings were taken as soon as all the acid had dissolved.

The results were not significant.

The ω-carboxypropionyl derivative of the hydrocarbon was not a very suitable compound for attempted optical activation. The salt-forming acid group was at the end of a long aliphatic sidechain and therefore remote from the source of potential optical activity, namely the twist about the diphenyl link. It was possible that any alkaloid would be unable to exert its maximum influence when combined with an acid group in such a position.

Attempted optical activations of 3:4-5:6-dibenzo<u>cyclo</u>hepta-3:5-diene-2'-carboxylic acid (LX1X) were carried out more thoroughly.



LX1X

First-order asymmetric transformations with brucine at different temperatures were attempted. The solvent used in most cases was "Solvent X". This was chloroform which had been washed well with water and dried carefully over calcium chloride followed by sodium sulphate and to which 2·5% by volume of absolute ethanol had been added. In each experiment the solvent was held in the thermostat for some time before it was used in order to acquire the temperature at which the experiment was carried out. One experiment was carried out at the low temperature of -10·5°. This temperature was obtained by using a specially constructed, well insulated thermostat in which solid carbon dioxide and methylated spirit were placed. An account of the construction and use of this thermostat is shortly to appear in print (Harris and Mitchell, Chem.and Ind.)

Although no actual mutarotations were observed in the above experiments, one or two of the acid-base salts were decomposed in solution and the solution of the free acid was viewed polarimetrically, in order to ensure that optical activity was completely absent. The decompositions were carried out as rapidly as possible in the cold. The solution of the alkaloid salt was washed with ice-cold concentrated hydrochloric acid, and then with ice water. The solution of the organic acid was then dried rapidly over anhydrous sodium sulphate and filtered into the polarimeter tube. Polarimetric readings could be taken within a few minutes of initial decomposition.

Harris (J.,1955,4152) observed the effect of temperature on the rotation at equilibrium of a solution of equivalent quantities of an optically stable base and an optically labile acid. The alkaloid quinidine and acids of the N-benzoyl-diphenylaminecarboxylic acid series were used. Solutions of the quinidine salts showed a wide variation of rotation with temperature, due to a change in the position of the equilibrium:-

(+) acid base $\rightleftharpoons$ (-) acid base, with temperature. It was concluded that if this phenomenon were general and capable of being distinguished from other temperature-dependent influences on rotation, it might be of use in the detection of optical activity in highly labile compounds. In the present work the effect of temperature on the rotation of a solution of the brucine salt of 3:4-5:6-dibenzo*cyclo*hepta-3:5-diene-2'-carboxylic acid was observed.

Attempts to make crystalline specimens of the alkaloid salts of the acid were made, using the alkaloids brucine, quinine, quinidine, cinchonine and cinchonidine in various solvents. In each case, equivalent quantities of the acid and alkaloid were weighed out and separately dissolved in the minimum volume of hot solvent. The solutions were mixed and filtered and a little of the solvent was removed by evaporation The solutions were corked and allowed to stand. Crystalline salts were obtained with the alkaloids quinine and cinchonidine in acetone solution. No mutarotation was observed with either salt when it was examined polarimetrically, nor did the free acids show any optical activity after the decomposition of the salts. Since no evidence of optical activity was obtained the salts were not analysed.

Failure to observe optical activity in the derivatives of 3:4-5:6-dibenzo*cyclo*hepta-3:5-diene is probably due to the optical instability of the bridged diphenyl system. The energy required for the molecule to pass through a temporarily planar state may be too low for optical activity to be demonstrated. Another factor is the low optical rotation which is characteristic of compounds having the compact bridged diphenyl structure. Success may be achieved when a technique is developed to study optically active compounds at very low temperatures, maybe as low as -50°. At this temperature, however, the optical rotation of bridged diphenyls may be very low indeed.

RESULTS

Optical work with 2'-(ω-carboxypropionyl)-3:4-5:6-dibenzo*cyclo*hepta-3:5-diene.

Examination of the acid under conditions in which a first-order asymmetric transformation might take place.

Experiment I

Brucine	0·7858 g.;	1 equivalent.
Acid	0·5880 g.;	1 equivalent

Solvent, bench chloroform.

$\alpha^{38\cdot8^\circ}_{5461}$ $-3\cdot39^\circ$

No change after five hours.

Experiment II

Brucine	0·3898 g.;	1 equivalent
Acid	0·2940 g.;	1 equivalent

Solvent, bench chloroform.

$\alpha^{48\cdot2^\circ}_{5461}$ $-2\cdot20^\circ$

No change after five hours thirty minutes.

Experiment III

Cinchonidine	0·2900 g.;	1 equivalent
Acid	0·2900 g.;	1 equivalent

Solvent, bench chloroform.

$\alpha^{24\cdot5^\circ}_{5461}$ $-3\cdot54^\circ$

No change after three hours twenty minutes.

The effect of adding excess acid to a solution containing equivalent amounts of acid and quinidine.

1. Quinidine 0·1620 g.; 1 equivalent.

   Solvent, bench chloroform.

   $\alpha_{5461}^{19\cdot7^{\circ}}$ $-3\cdot56^{\circ}$

2. 1 equivalent of base : 0·5 equivalent of acid.

   0·0735 g. acid was added.

   $\alpha_{5461}^{19\cdot7^{\circ}}$ $-3\cdot77^{\circ}$ three minutes after addition.

   No change after fifteen minutes.

3. 1 equivalent of base : 1 equivalent of acid.

   0·0735 g. acid added.

   $\alpha_{5461}^{19\cdot7^{\circ}}$ $-3\cdot74^{\circ}$ three minutes after addition.

   No change after one hour.

4. 1 equivalent of base : 1·5 equivalents of acid.

   0·0735 g. acid added.

   $\alpha_{5461}^{19\cdot7^{\circ}}$ $- 3\cdot71^{\circ}$ three minutes after addition.

   No change after fifteen minutes.

5. 1 equivalent of base : 2 equivalents of acid.

   0·0735 g. acid added.

   $\alpha_{5461}^{19\cdot7^{\circ}}$ $- 3\cdot63^{\circ}$ three minutes after addition.

   No change after fifteen minutes.

6. 1 equivalent of base : 2·5 equivalents of acid.

0·0735 g. acid added.

$\alpha^{19\cdot7^{\circ}}_{5461}$ $- 3\cdot56^{\circ}$

No change after twenty minutes.

7. 1 equivalent of base : 3 equivalents of acid.

0·0735 g. acid added.

$\alpha^{19\cdot7^{\circ}}_{5461}$ $- 3\cdot50^{\circ}$

Optical work with 3:4-5:6-dibenzo<u>cyclo</u>hepta-3:5-diene-2'-carboxylic acid.

<u>Examination of the acid under conditions in which a first-order asymmetric transformation might taken place</u>.

<u>Experiment I</u>

Brucine 0·7868 g.; 1 equivalent.

Acid 0·4720 g.; 1 equivalent.

Solvent, bench chloroform. Temperature controlled at 29·2°.

$\alpha^{29\cdot2^{\circ}}_{5461}$ $-1\cdot69^{\circ}$

No mutarotation was observed during five hours thirty minutes at 29·2°.

<u>Experiment II</u>

Brucine 0·3946 g.; 1 equivalent.

Acid 0·2375 g.; 1 equivalent.

Solvent, "Solvent X". Temperature controlled at 4·2°.

Time in minutes after wetting	$\alpha^{4\cdot2^{\circ}}_{5461}$
5·5	$-0\cdot69^{\circ}$
7·5	$-0\cdot69^{\circ}$
8·5	$-0\cdot68^{\circ}$
10	$-0\cdot69^{\circ}$
12·5	$-0\cdot69^{\circ}$

No mutarotation was observed during 121 minutes at 4·2°. The salt was decomposed in solution. The free acid was optically inactive.

Experiment III

Brucine 0·3942 g.; 1 equivalent.

Acid 0·2378 g.; 1 equivalent.

Solvent, "Solvent X". Temperature controlled at 24·0°.

$\alpha_{5461}^{24.0^\circ}$ - 0·93° three minutes after wetting.

No mutarotation was observed during ninety minutes at 24·0°.

Experiment IV

Brucine 0·3940 g.; 1 equivalent.

Acid 0·2380 g.; 1 equivalent.

Solvent, "Solvent X", Temperature controlled at -10·5°.

$\alpha_{5461}^{-10\cdot5^\circ}$ - 0·57° 2·5 minutes after wetting.

No mutarotation was observed during sixty minutes at -10·5°.

Experiment V

A similar low-temperature experiment was carried out using quinidine as the alkaloid but a solid separated in the polarimeter tube at about -6·0°. It redissolved at room temperature and could not be obtained again.

The effect of temperature on the rotation of a solution of equivalent quantities of acid and brucine.

Brucine 0·3939 g.; 1 equivalent.
Acid 0·2377 g.; 1 equivalent.
Solvent, "Solvent X".

Temperature	α_{5461}	
10·8°	-0·76°	three minutes after wetting.
25·2°	-0·93°	No mutarotation was observed during thirty minutes at 10·8°.
31·6°	-0·99°	
40·3°	-1·12°	
49·4°	-1·26°	

A graph of α against temperature was plotted. Figure 1, page 112.

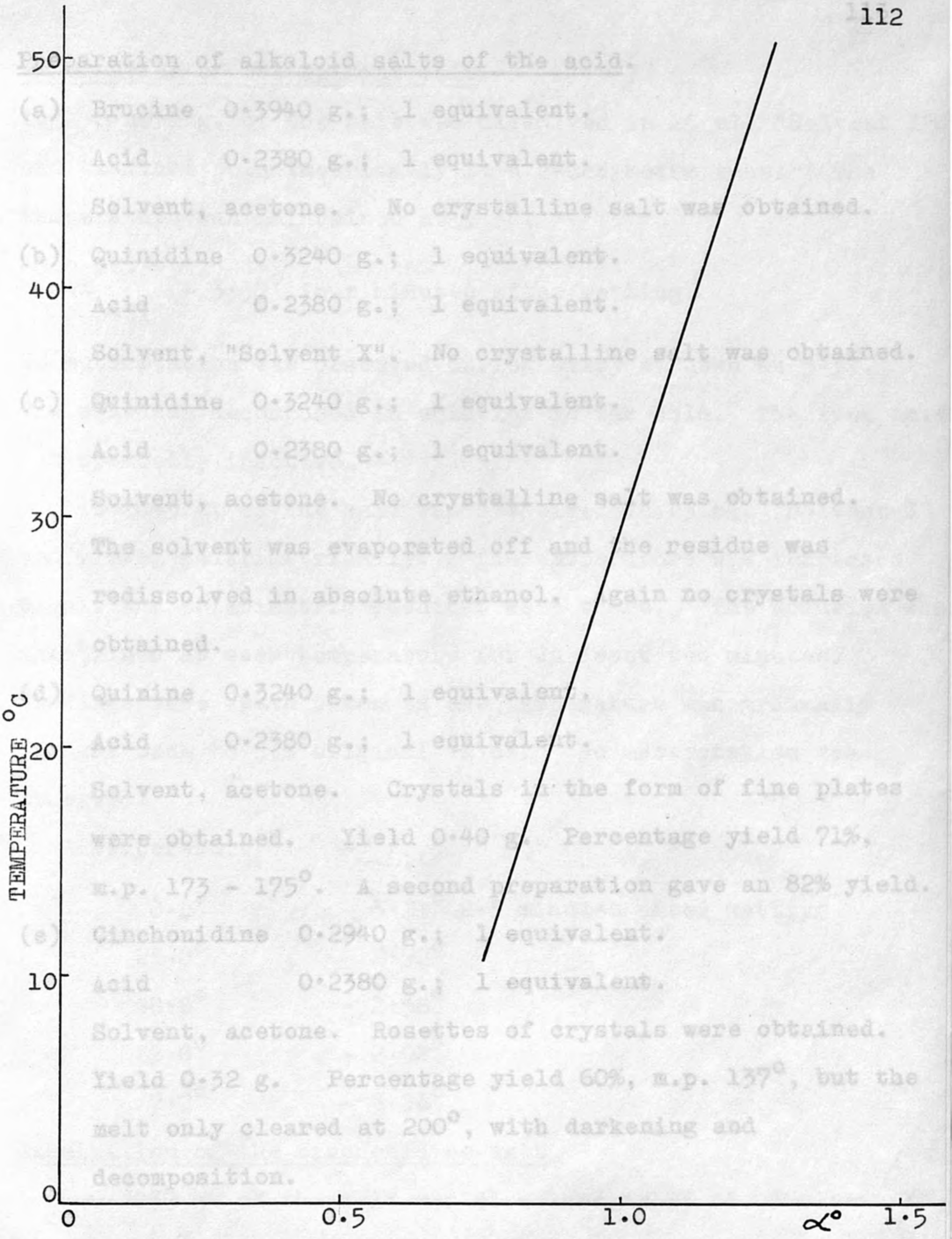
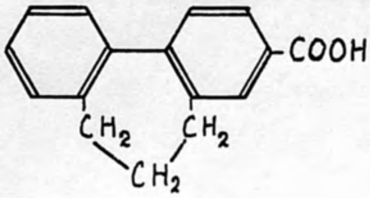


Fig. 1 Temperature curve of  and brucine

Preparation of alkaloid salts of the acid.

(a) Brucine 0·3940 g.; 1 equivalent.

Acid 0·2380 g.; 1 equivalent.

Solvent, acetone. No crystalline salt was obtained.

(b) Quinidine 0·3240 g.; 1 equivalent.

Acid 0·2380 g.; 1 equivalent.

Solvent, "Solvent X". No crystalline salt was obtained.

(c) Quinidine 0·3240 g.; 1 equivalent.

Acid 0·2380 g.; 1 equivalent.

Solvent, acetone. No crystalline salt was obtained. The solvent was evaporated off and the residue was redissolved in absolute ethanol. Again no crystals were obtained.

(d) Quinine 0·3240 g.; 1 equivalent.

Acid 0·2380 g.; 1 equivalent.

Solvent, acetone. Crystals in the form of fine plates were obtained. Yield 0·40 g. Percentage yield 71%, m.p. 173 - 175°. A second preparation gave an 82% yield.

(e) Cinchonidine 0·2940 g.; 1 equivalent.

Acid 0·2380 g.; 1 equivalent.

Solvent, acetone. Rosettes of crystals were obtained. Yield 0·32 g. Percentage yield 60%, m.p. 137°, but the melt only cleared at 200°, with darkening and decomposition.

Examination of the quinine salt.

1. 0·2051 g. of the salt was dissolved in 25 ml. "Solvent X" and examined polarimetrically in a 2-decimetre tube. The temperature was maintained at 3·3°.

$\alpha^{3\cdot3^{\circ}}_{5461}$ - 3·37° four minutes after wetting.

No mutarotation was observed during sixty minutes at 3·3°. The salt was decomposed in solution in the cold. The free acid was optically inactive.

2. 0·2045 g. of the salt was dissolved in 25 ml. "Solvent X" and viewed polarimetrically. The temperature was increased slowly and polarimetric readings were taken. The solution was maintained at each temperature for at least ten minutes. Readings were again taken as the temperature was gradually brought back to its original value. No mutarotation was observed.

Temperature	α_{5461}
8·2°	- 3·21° 2·5 minutes after wetting
25·8°	- 2·92°
48·6°	- 2·58°
25·8°	- 2·92°
7·2°	- 3·26°

Examination of the cinchonidine salt.

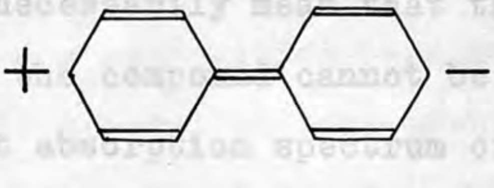
0·2239 g. of the salt was dissolved in 25 ml. "Solvent X" and examined polarimetrically. The temperature was controlled at 3·6°.

$\alpha^{3\cdot6^{\circ}}_{5461}$ $- 1\cdot72^{\circ}$ three minutes after wetting.

No mutarotation was observed during sixty minutes at $3\cdot6^{\circ}$. The salt was decomposed in solution in the cold. The free acid was optically inactive.

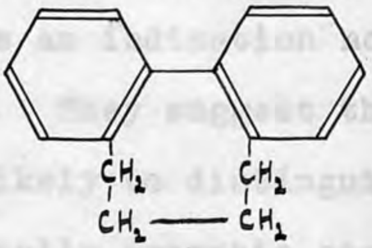
ULTRA-VIOLET ABSORPTION SPECTRA

The study of ultra-violet absorption spectra has been developed in recent years as a source of information about the configuration of compounds containing the basic collinear diphenyl skeleton. The spectrum of diphenyl itself shows a broad absorption band at a wavelength of 2490Å, which has an intensity of 18,000 in ethanol. (Beaven, Hall, Lesslie and Turner, J.,1952,854). This band is generally supposed to arise as a result of conjugation between the two benzene rings, when the 1:1'-bond acquires some double bond character, and is commonly known as the "conjugation band". Conjugation occurs by the overlapping of the orbitals of the π electrons of the benzene rings and it is thought to require the coplanarity of the rings. The presence of the high intensity band in the spectrum of diphenyl does not however indicate the preferred configuration of the molecule but indicates the ease with which coplanarity can be achieved. The double bond character of the 1:1'-link is only acquired by the molecule in its first excited state (XCVll), not in its ground state.

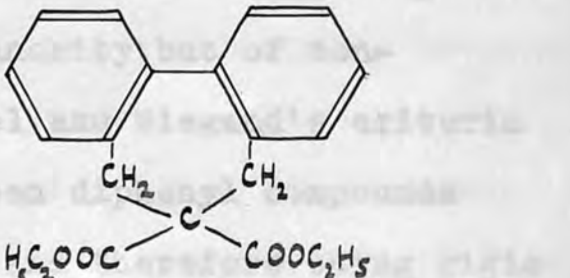


XCVll

Since the conjugation band in the spectrum of diphenyl shows that coplanarity is easily attained by the molecule, the occurrence of a similar conjugation band in the ultra-violet absorption spectrum of a 2:2'-bridged diphenyl has been generally assumed to indicate that evidence of optical isomerism of the compound will not be found. Cope and Smith (J.Amer.Chem.Soc.,1956,78,1012) report that the spectrum of 3:4-5:6-dibenzocyclohepta-3:5-diene (LVll) shows the diphenyl conjugation band, whereas that of 3:4-5:6-dibenzocyclo-octa-3:5-diene (XCVlll) does not. They say therefore that evidence of optical activity is being looked for in the latter compound but not in the former.



XCVlll



XXVl

Iffland and Siegel (ibid.,1958,80,1947) prepared 1:1-dicarbethoxy-3:4-5:6-dibenzocyclohepta-3:5-diene (XXVl) in optically active form and the conjugation band was still present in the ultra-violet absorption spectrum of the optically active compound. The conjugation band had a maximum at a wavelength of 249 mμ. It would therefore seem that the presence of the conjugation band in the spectrum of a compound does not necessarily mean that the existence of optical isomerism in the compound cannot be demonstrated.

The ultra-violet absorption spectrum of the hydrocarbon 3:4-5:6-dibenzocyclohepta-3:5-diene was of interest to the present worker. The spectrum was first studied by Merkel and Wiegand (z.Naturforsch.,1948,3b,93) who concluded that the diphenyl skeleton in the compound was non-coplanar since the spectrum showed a smooth curve without the appearance of any long-wave fine structure; the occurrence of well-resolved fine structure was thought to be indicative of coplanarity. Although this conclusion agrees with that obtained from a study of models of the compound, the evidence on which it is based is not wholly free from ambiguity. Beaven, Hall, Lesslie and Turner (loc.cit.) pointed out that in the spectra of 2:2'-6:6'-tetra substituted diphenyls fine structure arises from the absorption of the unconjugated partial benzenoid chromophores and is thus an indication not of planarity but of non-planarity. They suggest that Merkel and Wiegand's criteria are more likely to distinguish between diphenyl compounds having a wholly aromatic structure, and therefore being rigid and planar, and those containing a reduced bridging ring which forces the diphenyl skeleton to twist and therefore renders coplanarity less likely to be achieved.

Merkel and Wiegand's work showed that the spectrum of 3:4-5:6-dibenzo*cyclo*hepta-3:5-diene contains the characteristic broad diphenyl conjugation band. Cope and Smith (loc.cit.) report that the conjugation band had a maximum at a wavelength of 247 mμ with intensity $\mathcal{E}$ 15,700 in ethanol. In the present work, the spectrum had a conjugation band at a wavelength of 247 mμ , $\mathcal{E}$, 15,800 in ethanol and the spectrum also showed an inflection at a wavelength of 280 mμ , $\mathcal{E}$ *ca* 1050, which had hitherto not been reported. This long wave inflection may be similar to the more clearly-defined long wave band in the spectrum of 9-10-dihydrophenanthrene (λ_{max} 2995Å, $\mathcal{E}_{max}$ 4450 in ethanol). This is thought to arise from the absorption of the separate unconjugated phenyl chromophores, when the bridging methylene groups are acting simply as 2:2'-alkyl substituents. (Beaven _et.al._,_loc.cit._; Jones, _J.Amer.Chem.Soc._,1941,_63_,1658).

The spectrum of the compound obtained by the Dieckmann condensation of 2-carbomethoxy-2'-carbomethoxymethyldiphenyl was also taken by the present worker, but is of no special significance.

In the measurement of the ultra-violet absorption spectra a Unicam spectrophotometer (SP/500) was used. The solvent used was 95% ethanol and a stock solution of 20 ml. was made. (Concentration _Ca_ $1\cdot5 \times 10^{-3}$ g.mole/ℓ). Measurements of the optical density were first made over a range of wavelengths from 2200Å to 3200Å using the stock solution diluted fifty times, in a 10 mm. quartz cell. Subsequent measurements were taken as a check using 5 mm. and 2 mm. cells with suitable dilutions of the stock solution to give readings of the optical density in the most sensitive region of the instrument ($D = 0\cdot2 - 0\cdot5$). Especial care was taken in the regions of maxima and minima and points of inflection. The molar extinction coefficient ε was calculated from the formula $D = \varepsilon x c$ where D is the optical density, x is the width of the cell in cm., and c is the concentration of the solution in g. mol./litre. The curves were obtained by plotting ε against wavelength λ, on logarithmic paper. (pp. 121, 122.)

Ultra-violet absorption spectra.

Results

Diphenyl

Short-wave band: λ_{min} 2220Å ε_{min} 5100

λ_{max} 2490Å ε_{max} 18000

Solvent, ethanol.

(Beaven et.al.,J.,1952,854)

9-10-Dihydrophenanthrene

Short-wave band: λ_{min} 2370Å ε_{min} 2650

λ_{max} 2640Å ε_{max} 17000

Long-wave band: λ_{max} 2995 ε_{max} 4450

Solvent, ethanol.

(idem.,ibid.)

3:4-5:6-Dibenzo-cyclohepta-3:5-diene

Short-wave band: λ_{min} 2265Å ε_{min} 5400

λ_{max} 2470Å ε_{max} 15800

Inflection: λ 2800Å ε 1050

Solvent, ethanol.

Present work.

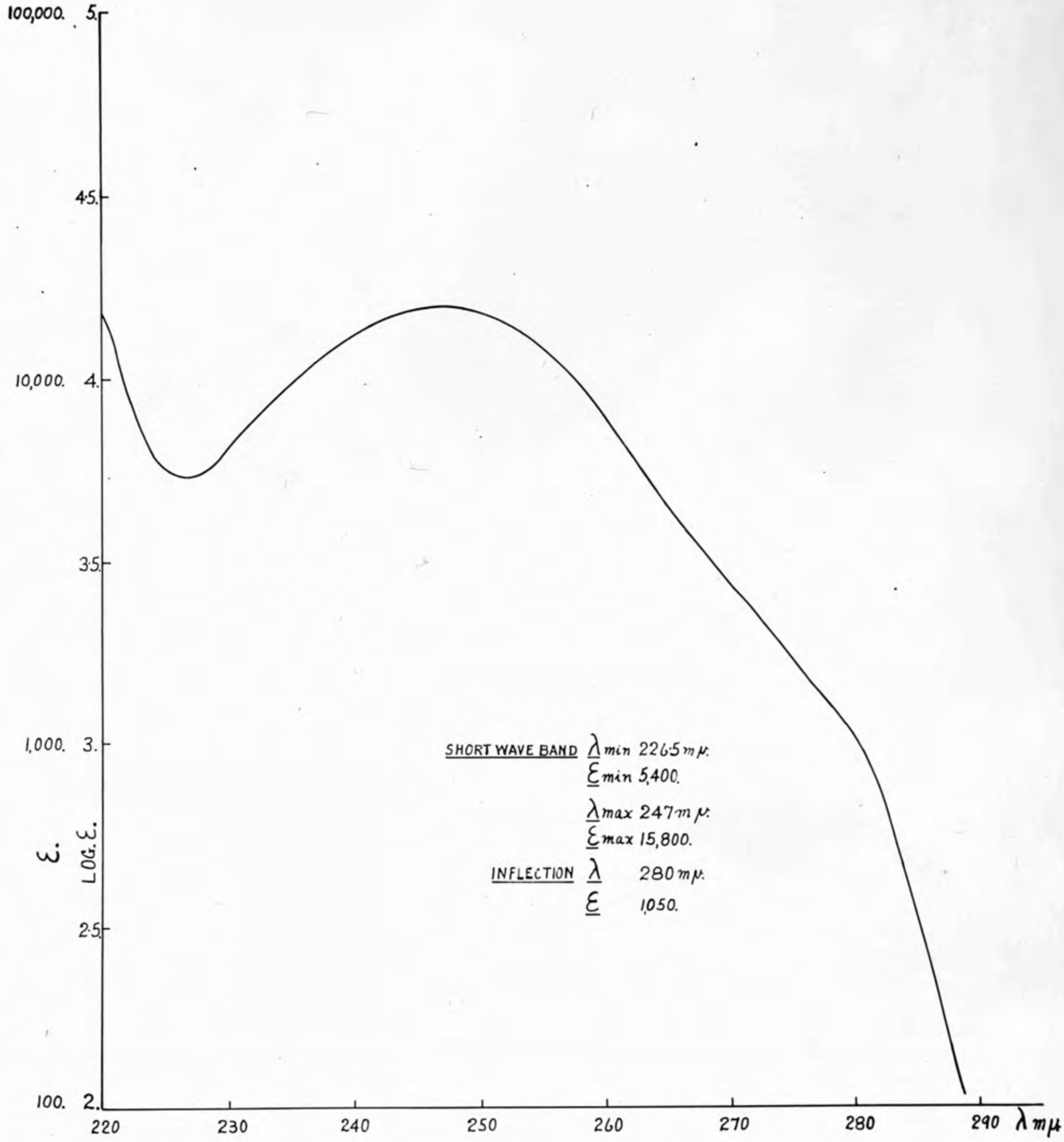
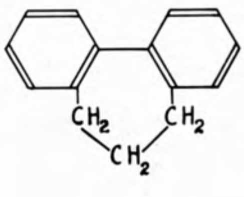
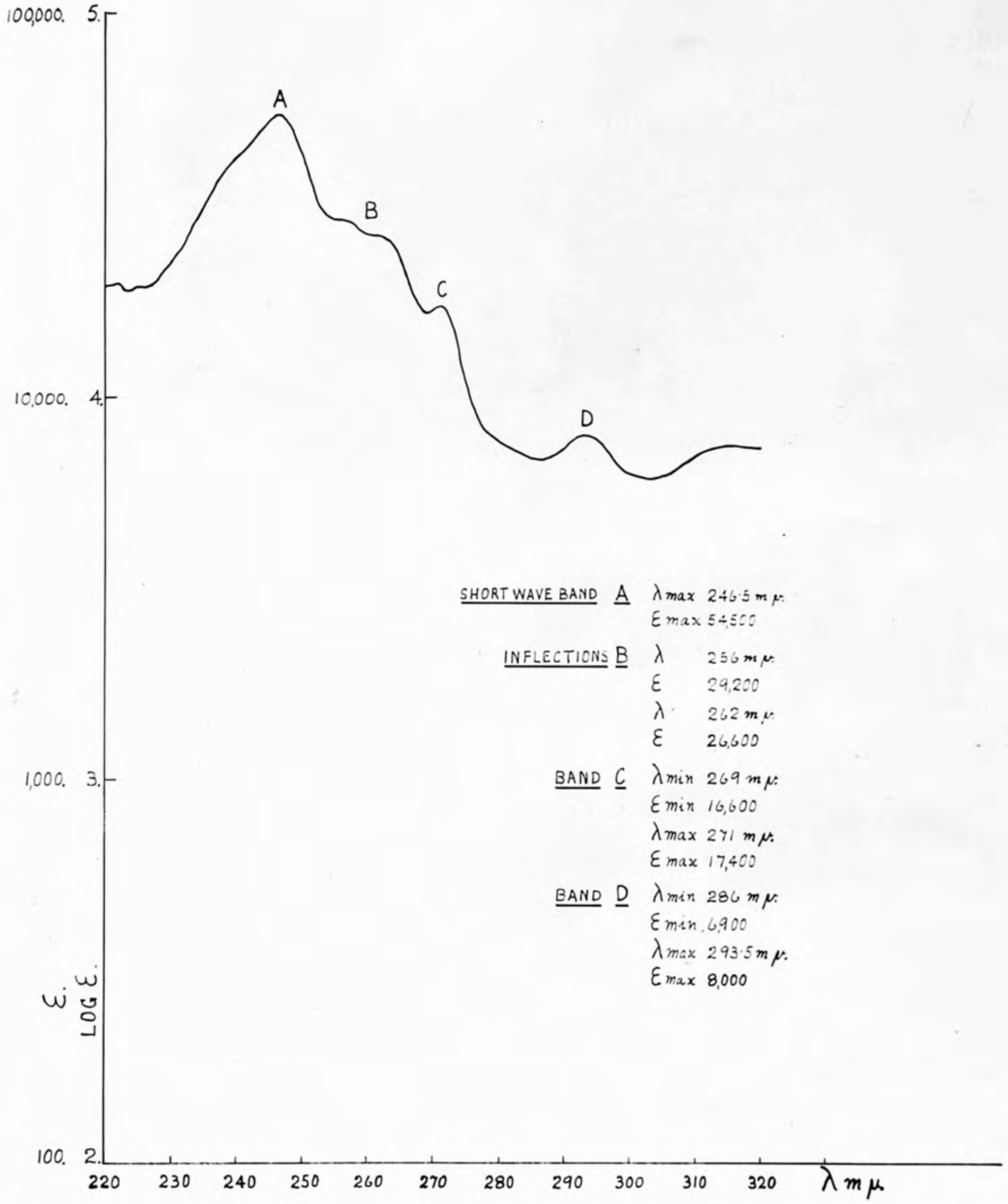
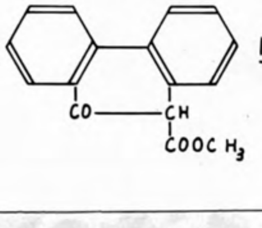


FIG. 2. ULTRAVIOLET ABSORPTION SPECTRUM OF  IN ETHANOL.



SHORT WAVE BAND	A	λmax	246·5 mμ.
		εmax	54,500
INFLECTIONS	B	λ	256 mμ.
		ε	29,200
		λ	262 mμ.
		ε	26,600
BAND	C	λmin	269 mμ.
		εmin	16,600
		λmax	271 mμ.
		εmax	17,400
BAND	D	λmin	286 mμ.
		εmin	6,900
		λmax	293·5 mμ.
		εmax	8,000

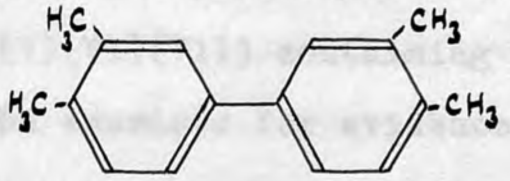
FIG 3. ULTRA VIOLET ABSORPTION SPECTRUM OF  IN ETHANOL.

PART II

SYNTHESES INVOLVING 4:5-4':5'-TETRAMETHYLDIPHENYL

INTRODUCTION

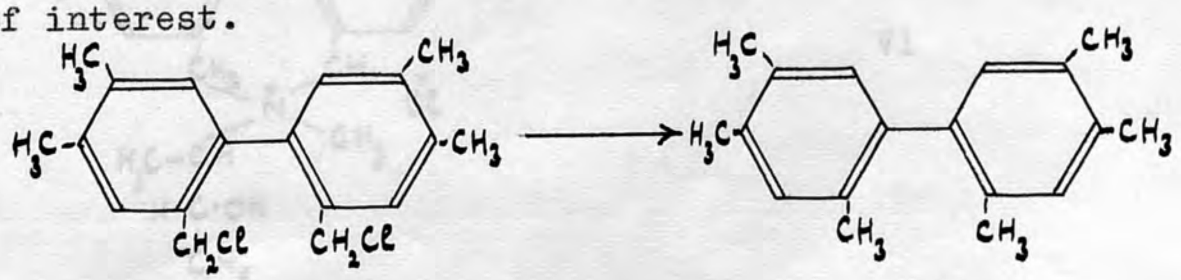
For some time 4:5-4':5'-tetramethyldiphenyl (1) had been looked upon as an interesting compound to be used as a starting material in synthetic work in the diphenyl series.



1

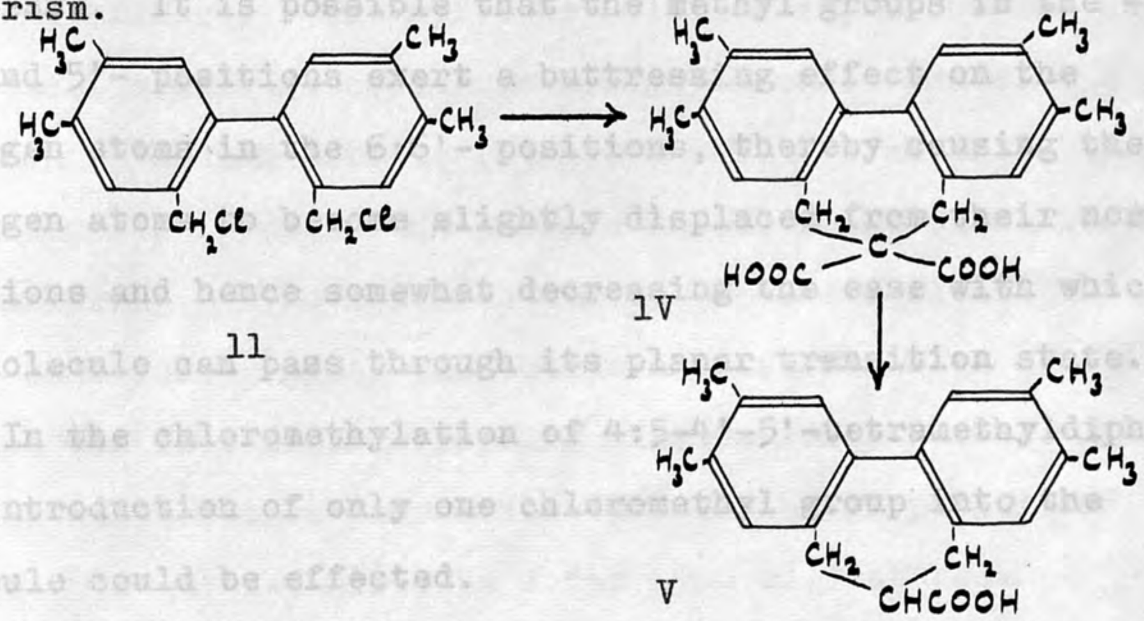
The compound is relatively easy to prepare by an Ullmann reaction on 4-iodo-o-xylene, which is itself prepared from 4-o-xylidine. It is very interesting to note that 4:5-4':5'-tetramethyldiphenyl is over one and a quarter million times as reactive as benzene in chlorination reactions in acetic acid, although the orientation of the entering groups is not known, (de la Mare, Hall, Harris and Hassan, <u>Chem.and Ind.</u>, 1958,1086).

It was hoped to introduce two chloromethyl groups in the 2:2'-positions of the diphenyl nucleus by the experimental technique of chloromethylation. Reduction of 2:2'-dichloromethyl-4:5-4':5'-tetramethyldiphenyl (11) by lithium aluminium hydride in a solvent such as tetrahydrofuran would be expected to give 2:4:5-2':4':5'-hexamethyldiphenyl (111). The ultra-violet absorption spectrum of this compound should be of interest.



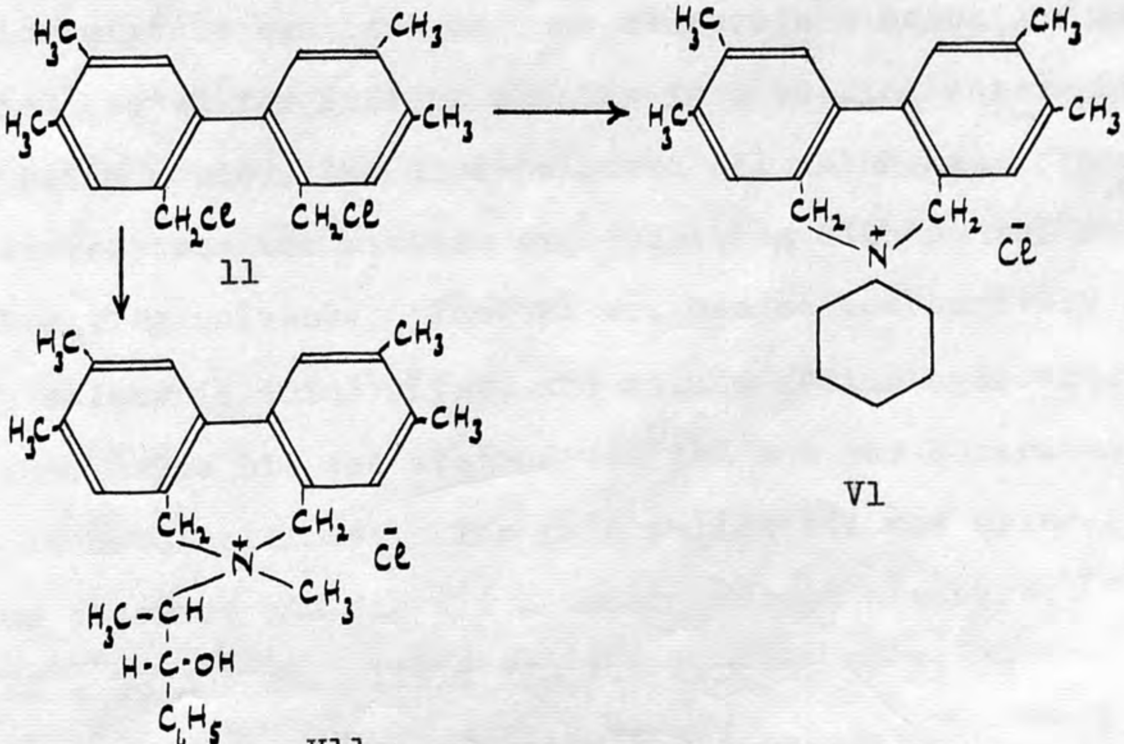
11 111

2:2'-Dichloromethyl-4:5-4':5'-tetramethyldiphenyl should be capable of undergoing condensations with suitable reagents such as ethyl malonate in the presence of sodium ethoxide, or secondary bases, for example piperidine or ephedrine. The resulting diphenyls (V)(Vl)(Vll) containing a seven-membered bridging ring could be examined for evidence of optical isomerism.


ll

lV

V


ll

Vl

Vll

Although no racemic diphenyl bridged across the 2:2'-positions with a chain of three atoms to form altogether a seven-membered ring, and containing no substituents in the 6:6'-positions, has been obtained in optically active forms, it was hoped that the substituent methyl groups in the diphenyl nucleus would in this case aid the detection of enantiomorphism. It is possible that the methyl groups in the 4-,5-4'- and 5'- positions exert a buttressing effect on the hydrogen atoms in the 6:6'- positions, thereby causing the hydrogen atoms to become slightly displaced from their normal positions and hence somewhat decreasing the ease with which the molecule can pass through its planar transition state.

In the chloromethylation of 4:5-4'-5'-tetramethyldiphenyl the introduction of only one chloromethyl group into the molecule could be effected.

EXPERIMENTAL

Preparation of 4-iodo-o-xylene.

Crossley and Hampshire, *J.*,1911,721.

4-*o*-Xylidine (121 g.; 1 mol.) was dissolved in a mixture of concentrated sulphuric acid (136 ml.; 2·5 mol.) and water (1 ℓ.) and the solution was cooled to -5°C in an ice-salt freezing mixture. The xylidine sulphate separated out and the reaction mixture became an orange-coloured paste. A solution of sodium nitrite (69 g.; 1 mol.) in water (150 ml.) was added slowly under the surface of the reaction mixture, with stirring. The reaction mixture became a clear, pale brown solution. After the sodium nitrite had been added the mixture was left in the freezing mixture for a further fifteen minutes and was then poured into a solution of potassium iodide (250 g.; 1·5 mol.) in water (500 ml.) at room temperature. There was a steady evolution of nitrogen. The reaction mixture was left at room temperature overnight and was then heated for fifteen minutes in a boiling water bath. After being cooled, the dark-coloured oil which had formed was removed from the mixture by separation without the use of an extracting solvent. The oil was washed successively with dilute sulphuric acid, water, and dilute sodium hydroxide solution. The oil was steam distilled and was separated from the aqueous distillate. The pale yellow oil was dried over calcium chloride and distilled under reduced pressure.

b.p. 86 - 96 / 4 mm. Yield 178 g. Percentage yield 77%.

The pure 4-iodo-*o*-xylene was almost colourless.

The experiment was repeated on the same scale. In all, 258 g. of 4-iodo-o-xylene were prepared.

Preparation of 4:5-4':5'-tetramethyldiphenyl.

Crossley and Hampshire, loc.cit.

4-Iodo-o-xylene (75 g.) was heated to a temperature of 220° in a metal bath and a small quantity of copper powder was added. The temperature of the reaction mixture at once rose above that of the metal bath. The addition of copper powder was continued until the reaction was complete. In all about 50 g of copper were used. The reaction mixture was maintained at about 240° for half an hour, then was extracted while still hot with boiling m-xylene.

The preparation was repeated using 103 g. of 4-iodo-o-xylene. The two m-xylene extracts were combined and the solvent was removed by distillation. The residue solidified and was crystallised from ethanol.

Yield 57 g., mp. 74 - 75°. Percentage yield 71%. In all 114 g. of 4:5-4':5'-tetramethyldiphenyl were synthesized by Ullmann reactions.

Chloromethylation of 4:5-4':5'-tetramethyldiphenyl.

1. The method was similar to that used for the chloromethylation of naphthalene (Org.Syn.,24,30).

A mixture of 4:5-4':5'-tetramethyldiphenyl (21 g., 1 mol.) trioxymethylene (11 g., 1·25 mol.), glacial acetic acid (26 ml.) syrupy phosphoric acid (16·5 ml.; 2·5 mol.) and concentrated hydrochloric acid (36·2 ml.; 4·2 mol.) was heated on a water bath at 80 - 85°C with stirring for six hours. The reaction mixture was cooled and ether (about 100 ml.) was added. The mixture was shaken and the ethereal layer was separated and washed successively with ice-water, ice-cold sodium bicarbonate solution and again with ice-water. The ethereal layer was then dried over anhydrous sodium sulphate and the ether was removed by distillation. The residual oil was distilled under reduced pressure. The pure product was a colourless, highly refractive liquid.

Yield 21 g. Percentage yield 80%. b.p. 158° / 2 mm.

n_D^{25} 1·5922

A Parr bomb analysis was carried out.

Found: Cl, 13·7. $C_{17}H_{19}Cl$ requires Cl, 13·5%.

After some time the oil set to a mass of fine crystals, the melting point of which, in bulk, was about 37°.

2. The above reaction was repeated using twice the quantity of trioxymethylene. During the heating hydrogen chloride, generated by the addition of concentrated sulphuric acid dropwise on to ammonium chloride, was passed into the reaction mixture. The product of the reaction, after purification, was again a colourless, highly refractive, viscous oil.

b.p. 184 - 204° / 3 mm. n_D^{25} 1·5917

Yield 18·5 g. Percentage yield 71%.

Again the oil became a mass of fine crystals after some weeks. The melting point of the crystals in bulk was again about 37°C.

3. The method used for the chloromethylation of 4:5-4':5'-tetramethoxydiphenyl (Quelet and Matarasso-Tchiroukhine, Compt.rend.,1956,242,918) was used.

4:5-4':5'-Tetramethyldiphenyl (10·5 g.; 1 mol.) was dissolved in the minimum volume of pure dioxane (75 ml.) and formaldehyde (37·5 ml. of a 40% solution; 7·5 mol.) was added. The homogeneous mixture was heated on a water bath held at 60 - 65° and hydrogen chloride was bubbled in to the reaction flask. After about fifteen minutes a dark-coloured oil began to separate in the reaction mixture. Heating and passage of hydrogen chloride was continued for six and a half hours. The reaction mixture was left overnight when it separated into two layers. The upper layer was removed and was washed with ice-water when a solid was precipitated. Ether was then added and the mixture was shaken. The ethereal solution was washed with ice-cold sodium bicarbonate solution and again with ice-water. The ethereal solution was dried over anhydrous sodium sulphate and the ether was removed by distillation. The residual solid was crystallized from ethanol.

m.p. 74°. Mixed m.p. with 4:5-4':5'-tetramethyldiphenyl 74 - 75°.

Formaldehyde was recovered from the lower layer of the reaction mixture, by extraction with ether. No other product was isolated.

4. A 250 ml. round-bottomed flask was fitted with a reflux condenser, stirrer and gas-inlet tube. A mixture of 4:5-4':5'-tetramethyldiphenyl (10·5 g.; 1 mol.), paraformaldehyde (9 g.; 2 mol.), glacial acetic acid (50 ml.), concentrated hydrochloric acid (18·1 ml.; 4·2 mol.) and zinc chloride (22 g.; 2·5 mol.) were heated on a boiling water bath for one hour with stirring. Hydrogen chloride was then passed into the reaction mixture. Heating, stirring and the passage of the gas were continued for a further six hours. A dark brown, viscous oil separated on the surface of the reaction mixture. Ether was added to dissolve the oil and the ethereal solution was filtered to remove inorganic matter. The solution was washed with ice-water, ice-cold sodium bicarbonate, and more ice-water, and was then dried over anhydrous sodium sulphate. The ether was distilled off.

The residual viscous oil contained chlorine but could not be distilled under reduced pressure. Attempts to crystallize the oil, using such solvents as chlorobenzene and dichlorobenzene as well as the more common solvents, were unsuccessful.

The experiment was repeated using twice the above quantities but again no solid product could be obtained.

In an attempt to prepare a crystalline derivative, a little of the oil (1·4 g.) was warmed with piperidine (2 ml.; 2·2 mol.) in dry benzene (50 ml.) in a water bath held at 60 - 70° for seven hours. The solid which separated in the reaction mixture was filtered off, washed with dry benzene and dissolved in water. The solution was washed once with a small quantity of ether and then was treated with a saturated aqueous solution of potassium iodide. A small amount of precipitate was formed but this could not be crystallized from any of the more common solvents. The quantity of precipitate was too small for further work to be carried out.

Reaction between 2-chloromethyl-4:5-4':5'-tetramethyldiphenyl and piperidine.

2-Chloromethyl-4:5-4':5'-tetramethyldiphenyl (2·6 g., 1 mol.) and piperidine (2·2 ml.; 2·2 mols.) were dissolved in dry benzene (50 ml.) and the solution was warmed under anhydrous conditions in a water bath held between 50 - 60° for about sixteen hours. The solution was cooled and sodium hydroxide solution was added. The crystals of piperidine hydrochloride which had formed during the reaction immediately dissolved in the aqueous medium. The benzene layer was separated and the aqueous layer was washed once with benzene. The combined benzene solutions were washed with water and dried over anhydrous sodium sulphate and the benzene and any residual piperidine were removed by distillation. A very viscous dark brown oil remained.

Yield 2 g. Percentage yield 66%.

The residual oil was warmed slightly with excess methyl iodide. A pale pink precipitate formed. Excess methyl iodide was volatilized off and the residue crystallized from ethanol in clusters of fine needles.

m.p. 201° with darkening. Yield 1·5 g. Percentage yield 50%.

Found: C, 61·65; H, 6·86; N, 3·35; I, 27·94.

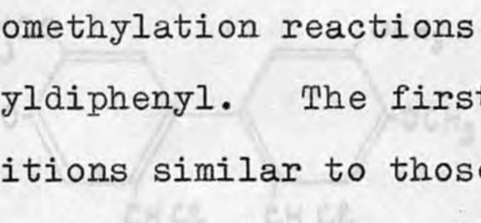
$C_{23}H_{32}NI$ requires C, 61·47; H, 7·17; N, 3·12; I, 28·24%.

DISCUSSION OF RESULTS

4-Iodo-o-xylene was conveniently prepared in 77% yield by diazotising 4-o-xylidine in sulphuric acid and pouring the solution of the diazonium salt into aqueous potassium iodide, according to the method of Crossley and Hampshire (J.,1911,721). The pure iodo-compound was an almost colourless oil.

An Ullmann reaction was carried out on 4-iodo-o-xylene at temperatures above 220°. The product was extracted by boiling m-xylene. 4:5-4':5'-Tetramethyldiphenyl was obtained in 71% yield. The hydrocarbon was a pale yellow crystalline solid of m.p. 74 - 75°. Crossley and Hampshire (loc.cit.) recorded a m.p. of 76°.

A number of chloromethylation reactions were carried out on 4:5-4':5'-tetramethyldiphenyl. The first reaction was carried out using conditions similar to those used for the chloromethylation of naphthalene (Org.syn.,24,30). A mixture of the hydrocarbon, trioxymethylene and concentrated hydrochloric acid was heated for six hours with glacial acetic acid as a solvent and syrupy phosphoric acid as a catalyst. The reaction mixture was extracted with ether and after suitable washings of the ethereal solution the monochloromethyl derivative of the hydrocarbon (V111) was isolated.

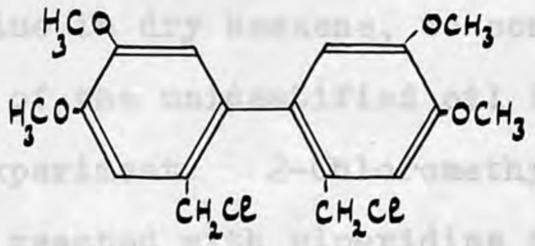


V111

2-Chloromethyl-4:5-4':5'-tetramethyldiphenyl was obtained as a high-boiling liquid which solidified after some time. The solid had a melting point of about 37° in bulk.

The reaction was repeated using a greater excess of trioxymethylene and hydrogen chloride gas was passed into the reaction mixture to maintain the concentration of hydrogen chloride in the reaction medium. Again the product was the monochloromethyl derivative.

The reaction was next carried out using the same conditions as those used for the preparation of 2:2'-dichloromethyl-4:5-4':5'-tetramethoxydiphenyl (1X) (Quelet and Matarasso-Tchiroukhine, <u>Compt.rend.</u>,1956,<u>242</u>,918).



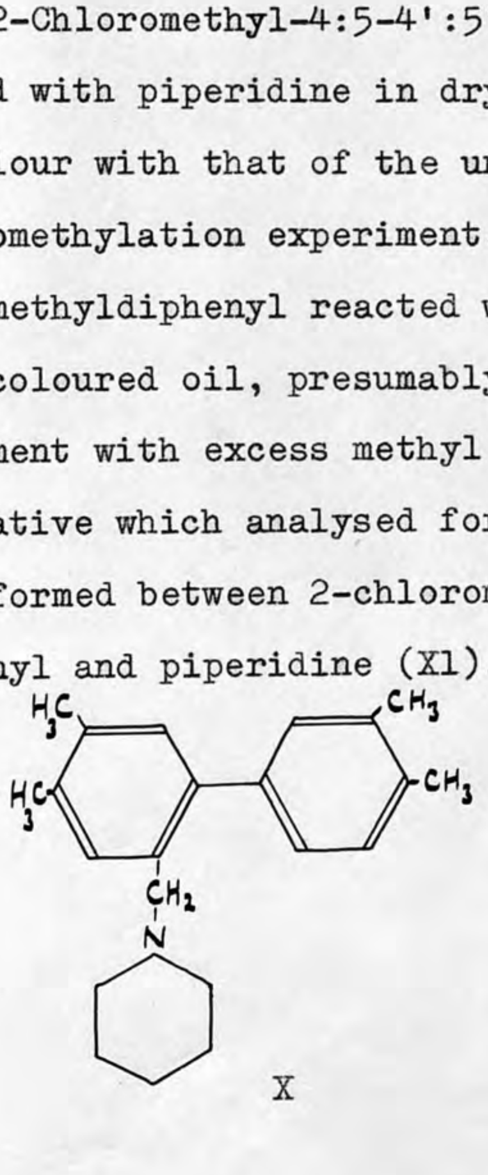
1X

Hydrogen chloride was passed into a solution of 4:5-4':5'-tetramethyldiphenyl and formaldehyde in pure dioxane at a temperature of 60 - 65°. There were no identifiable products of this reaction. Formaldehyde and 4:5-4':5'-tetramethyldiphenyl were recovered unchanged.

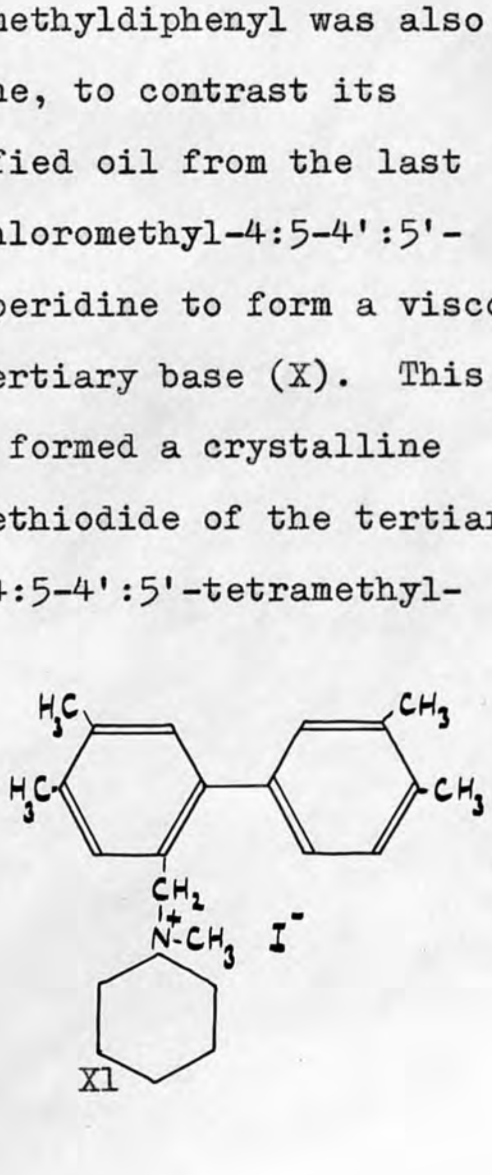
Finally a mixture of the tetramethyldiphenyl, paraformaldehyde, concentrated hydrochloric acid, glacial acetic acid as a solvent and zinc chloride as a catalyst was heated on a boiling water bath while hydrogen chloride was passed into the reaction mixture. Zinc chloride is usually a more effective catalyst than phosphoric acid in chloromethylation reactions.

The product of the reaction was a very viscous oil which could not be distilled, nor could it be induced to solidify. A sodium fusion showed it to contain chlorine. It was possibly the required 2:2'-dichloromethyl-4:5-4':5'-tetramethyldiphenyl and, in an attempt to form a crystalline derivative, the oil was warmed with piperidine in dry benzene. The solid which separated was dissolved in water and treated with a saturated solution of potassium iodide. A very small amount of precipitate was produced but this could not be crystallized from common solvents and was too small a quantity to be investigated further.

2-Chloromethyl-4:5-4':5'-tetramethyldiphenyl was also warmed with piperidine in dry benzene, to contrast its behaviour with that of the unidentified oil from the last chloromethylation experiment. 2-Chloromethyl-4:5-4':5'-tetramethyldiphenyl reacted with piperidine to form a viscous, dark-coloured oil, presumably the tertiary base (X). This on treatment with excess methyl iodide formed a crystalline derivative which analysed for the methiodide of the tertiary base formed between 2-chloromethyl-4:5-4':5'-tetramethyldiphenyl and piperidine (Xl).



X



Xl

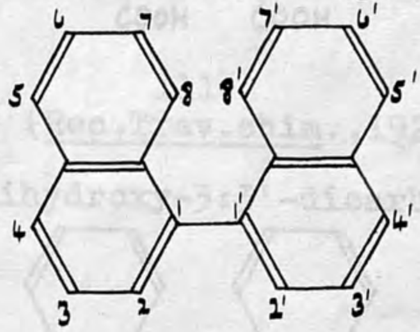
It seems likely that the difficulty of synthesizing 2:2'-dichloromethyl-4:5-4':5'-tetramethyldiphenyl is due to steric hindrance. The initial reaction is the entrance of one chloromethyl group in the 2-position of the diphenyl nucleus. The chloromethyl group is relatively large and would probably effectively hinder the substitution of a second chloromethyl group in the 2'-position. If this is so then the apparent ease with which 2:2'-dichloromethyl-4:5-4':5'-tetramethoxydiphenyl is synthesized (Quelet and Matarasso-Tchiroukhine, *loc.cit*) is remarkable.

PART III

THE STEREOCHEMISTRY OF DI-β-NAPHTHOL

INTRODUCTION

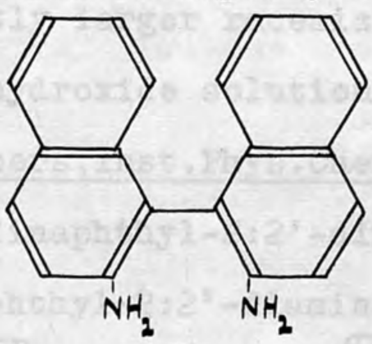
1:1'-Dinaphthyls may be considered as derivatives of diphenyl in which the extra benzene rings are acting as substituents (1).



1

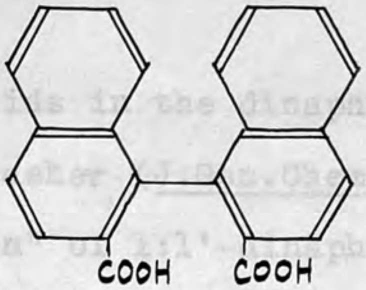
The free rotation about the 1:1'-bond may be restricted because of the presence of suitable substituents in the 2:2'-positions. Such suitably substituted dinaphthyls should be capable of existing in optically active forms.

Many suitable derivatives of 1:1'-dinaphthyl have been studied. 2:2'-Diamino-1:1'-dinaphthyl (11) was resolved through its α-π-bromocamphorsulphonate (Kuhn and Goldfinger, Annalen,1929,470,183; Wittig and Petri,ibid.,1933,505,25).



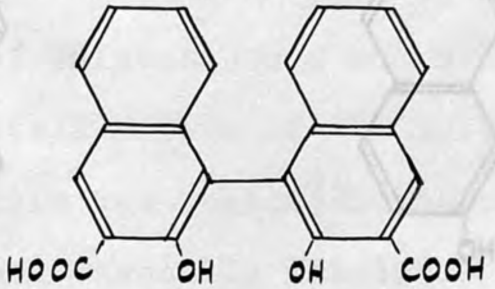
11

1:1'-Dinaphthyl-2:2'-dicarboxylic acid (111) was resolved through its quinine salt by Kuhn and Albrecht (ibid.,1928,465, 282) and was resolved later by Hall and Turner (J.,1955,1242).



111

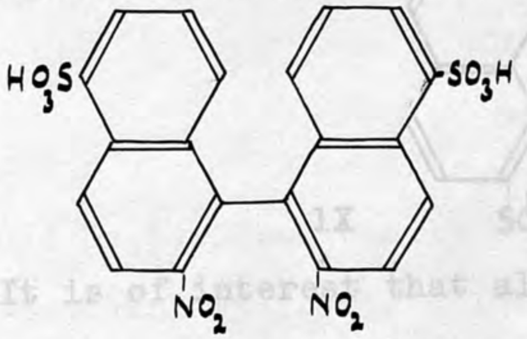
Stanley and Adams (Rec.Trav.chim.,1929,48,1035) resolved 1:1'-dinaphthyl-2:2'-dihydroxy-3:3'-dicarboxylic acid (1V)



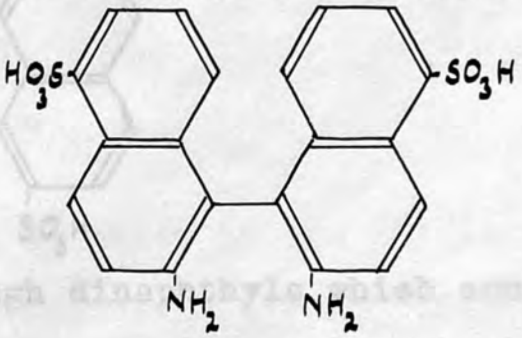
1V

through the dibrucine salt. The optically active acids showed high optical stability. No racemization occurred in boiling acetic acid solution, only slight racemization in a boiling solution of equal volumes of ethanol and hydrochloric acid, and only a slightly larger racemization occurred in boiling 10% potassium hydroxide solution.

Murahashi (Sci.Papers,Inst.Phys.Chem.Research,Tokyo,1932,17,297) resolved 1:1'-dinaphthyl-2:2'-dinitro-5:5'-disulphonic acid (V) and 1:1'-dinaphthyl-2:2'-diamino-5:5'-disulphonic acid (Vl).



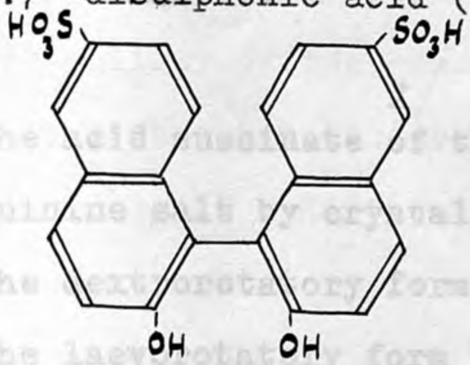
V



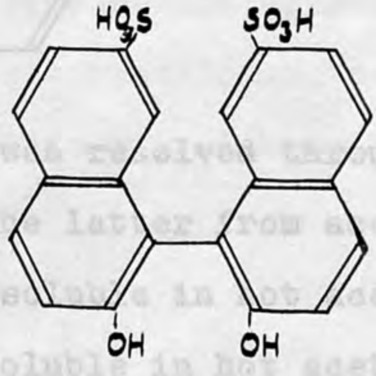
Vl

In both cases the barium salt of the disulphonic acid was resolved using either d or l α-phenylethylamine or d bornylamine.

Other sulphonic acids in the dinaphthyl series have been studied. Ioffe and Graehev (J.Gen.Chem.U.S.S.R.,1935,5,950) reported the "resolution" of 1:1'-dinaphthyl-2:2'-dihydroxy-6:6'-disulphonic acid (Vll) and 1:1'-dinaphthyl-2:2'-dihydroxy-7:7'-disulphonic acid (Vlll).



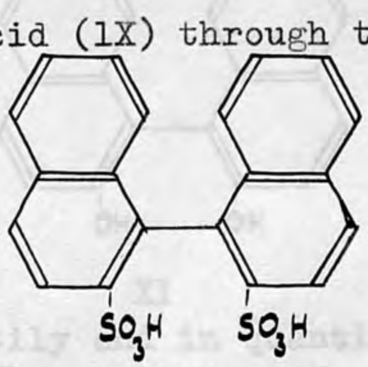
Vll



Vlll

The diastereoisomeric dibrucine salts were separated by fractional crystallisation but the acids themselves only showed optical activity as the sodium salts in alkaline solution. The acids in the free state or in acid solution were optically inactive. Recently Siegel (private communication) was unable to reproduce these results.

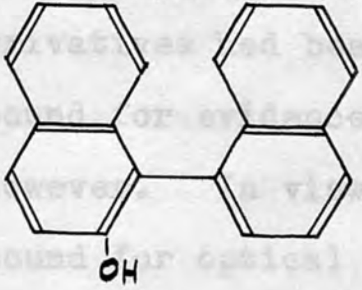
Armarego and Turner (J.,1956,3668) resolved 1:1'-dinaphthyl-2:2'-disulphonic acid (lX) through the dibrucine salt.



lX

It is of interest that although dinaphthyls which contain substituent hydroxyl groups have been studied, few optical resolutions have been attempted which involve the formation of a derivative of these groups. It is only recently that a hydroxy-1:1'-dinaphthyl containing no other substituent groups has been resolved.

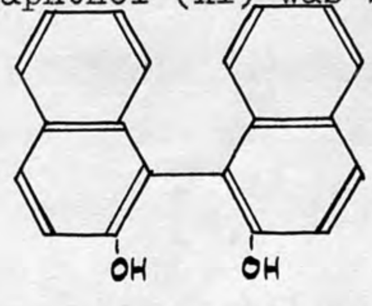
Berson and Greenbaum (J.Amer.Chem.Soc.,1958,80,653) reported the resolution of 2-hydroxy-1:1'-dinaphthyl (X).



X

The acid succinate of this compound was resolved through the quinine salt by crystallisation of the latter from acetone. The dextrorotatory form was readily soluble in hot acetone, the laevorotatory form virtually insoluble in hot acetone. The optically pure diastereoisomeric acid succinates were reduced with lithium aluminium hydride to give the optically active forms of 2-hydroxy-1:1'-dinaphthyl. The (+) form of this compound had a half-life of two days at 80°, in benzene solution.

In the present work the compound 2:2'-dihydroxy-1:1'-dinaphthyl, or di- β -naphthol (Xl) was studied.



Xl

It could be prepared easily and in quantity by the oxidation of β-naphthol by ferric chloride (Julius, Chemische Industrie, 10,98). It was hoped to effect a resolution of di- β -naphthol and to study its optical stability. It was expected that its optical enantiomorphs would show considerable optical stability.

Considerable work had already been carried out on di-β-naphthol. Its dimethyl ether, diethyl ether, diacetyl derivative and other derivatives had been prepared. No examination of the compound for evidence of optical isomerism had been carried out, however. In view of the apparent suitability of the compound for optical resolution, and the ease with which it can be prepared, this omission would seem to be highly significant.

EXPERIMENTAL

Preparation of di-β-naphthol

The method of Julius (Chemische Industrie,10,98) was used.

β-Naphthol (50 g.) was dissolved in a dilute solution of sodium hydroxide (15 g.) in water (2 l.). The solution was boiled and while still hot a solution of anhydrous ferric chloride (48 g.) and concentrated hydrochloric acid (50 ml.) in water (100 ml.) was added to it. A solid was precipitated. The mixture was boiled for a further twenty minutes until the solid had coagulated, and was then filtered while still hot. The solid was washed well with hot water. The preparation was carried out three times on the same scale and the combined products were crystallized from ethanol.

Yield 102 g. m.p. 216°. Percentage yield 78%.

The aqueous mother liquor from which the solid had been filtered yielded on cooling 20 g. of unchanged β-naphthol.

In all 161 g. of di-β-naphthol were prepared in this way.

Preparation of (-) menthoxyacetylchloride

(-) Menthoxyacetic acid was purified by distillation.

b.p. 136 - 140° / 3mm. $[\alpha]^{20}_{D}$ (-) 91·5°

Thionyl chloride was also distilled b.p. 74 - 80°.

(-) Menthoxyacetic acid (20 g.) and thionyl chloride (54 g.) were mixed in a flask fitted with a reflux condenser and calcium chloride tube, and warmed in a water bath at about 50°C for three hours. Excess thionyl chloride was distilled off, the last traces being removed by distillation under slightly reduced pressure from a water pump. The crude

(-) menthoxyacetyl chloride, which weighed 20 g., was not purified further.

Preparation of 1:1'-dinaphthyl-2:2'-dimenthoxyacetate

Di-β-naphthol (11·2 g.; 1 mol.) was dissolved in dry pyridine (100 ml.) and the solution was cooled in an ice bath. (-) Menthoxyacetyl chloride (20 g.; 2·2 mol.) was added gradually at the ice-bath temperature. The resulting pale brown solution was left at room temperature overnight. The solution was then poured on to a mixture of ice, slightly more than the calculated quantity of concentrated hydrochloric acid (120 ml.) and water (250 ml.). A solid separated which dissolved in ether. The ethereal layer was removed and the aqueous acidic layer was extracted repeatedly with ether until the extracts were colourless. The combined ethereal solutions were then washed repeatedly with dilute hydrochloric acid until the washings were colourless, and then with water. The ethereal layer was then washed with dilute sodium hydroxide solution and was again washed repeatedly with water. It was dried over anhydrous sodium sulphate and the ether was removed by distillation. The residual pale brown gum solidified on scratching. The solid was crystallized from ethanol using charcoal to decolorize. The crystals formed in clusters of fine leaflets.

Yield 23 g. m.p. 109°. Percentage yield 86·5%.

$[\alpha]_{5461}^{20^\circ}$ (-) 55·1°. Solvent, bench chloroform.

Found: C, 77·96; H, 8·21; O, 13·71. $C_{44}H_{54}O_6$ requires

C, 77·84; H, 8·02; O, 14.14%.

In all, 63 g. of the ester were prepared.

Reduction of 1:1'-dinaphthyl-2:2'-dimenthoxyacetate.

The reduction was carried out as rapidly as possible. 1:1'-Dinaphthyl-2:2'-dimenthoxyacetate (10 g.; 1 mol.), dissolved in anhydrous ether (100 ml.) was added gradually to a suspension of lithium aluminium hydride (1 g., 1·7 mol.) in anhydrous ether (50 ml.) at such a rate as to maintain gentle refluxing of the ether. After the reaction was complete water was added cautiously to decompose excess lithium aluminium hydride, then the mixture was acidified with dilute sulphuric acid until two clear layers were obtained. The layers were separated and the aqueous acidic layer was washed with ether. The combined ethereal solutions were washed once with water. The ether was distilled off as quickly as possible and the residual solid was washed rapidly with light petroleum (b.p. 40 - 60°) and dried. m.p. 216°.

A sample of the solid was viewed in chloroform solution in a polarimeter tube. It was optically inactive.

Treatment of di-β-naphthol with phthalic anhydride.

Di-β-naphthol (2·9 g.; 1 mol.) and phthalic anhydride (3 g.; 2 mol.) were dissolved in dry pyridine (50 ml.) and left overnight. The mixture was then heated on a boiling water bath for three hours under anhydrous conditions. It was cooled and poured into a mixture of water (120 ml.), concentrated hydrochloric acid (60 ml.) and ice. The organic layer was extracted with ether and the ethereal extract was washed successively with dilute hydrochloric acid, water, and sodium carbonate solution. The sodium carbonate solution removed a pale yellow solid from the ether. The solid was filtered off. It was insoluble in water but was soluble with difficulty in boiling sodium carbonate solution. This solution was filtered and acidified with dilute hydrochloric acid. A buff-coloured precipitate was formed which was removed by filtration and dried. The precipitate was recovered di-β-naphthol.

Weight 0·7 g. m.p. 210 - 215°.

The alkaline mother liquor from the sodium carbonate extraction of the ether was acidified with dilute hydrochloric acid. A very small amount of solid was obtained but this was too small to investigate further.

The ethereal layer was still coloured and the ether was distilled off. The residual solid was crystallized from aqueous ethanol.

Weight 1 g. m.p. 215 - 216°.

Mixed melting point with di-β-naphthol 215 - 216°.

The experiment was repeated on twice the above quantities using a mixture of triethylamine (50 ml.) and pyridine (20 ml.) as a solvent, and heating for a total of six hours. Again only recovered di-β-naphthol was isolated from the reaction mixture.

Treatment of di-β-naphthol with succinic anhydride.

Di-β-naphthol (2·9 g.; 1 mol.) and succinic anhydride (2 g.; 2 mol.) were dissolved in dry pyridine (50 ml.). The homogeneous dark brown solution was allowed to stand at room temperature overnight and then was heated on a boiling water bath for sixteen hours under anhydrous conditions. The reaction mixture was then poured into a mixture of water (120 ml.), concentrated hydrochloric acid (60 ml.) and ice. Ether was added, and the ethereal layer was separated and washed well with dilute hydrochloric acid, water, and finally 10% sodium carbonate until the washings were colourless. The pale brown sodium carbonate washings were acidified with dilute hydrochloric acid and a buff-coloured precipitate formed which was removed by filtration and washed well with cold water. It was crystallized from methanol.

m.p. 212 - 215°. Mixed melting point with di-β-naphthol 212 - 215°. After recrystallization from the same solvent the melting point was 214 - 215°.

The washed ethereal solution was still slightly coloured and so the ether was distilled off. The pale yellow residue was crystallized from aqueous ethanol. m.p. 213 - 215°.

All the solid recovered from the experiment was unchanged di-β-naphthol.

The experiment was repeated using succinic anhydride which had been freshly recrystallized from acetic anhydride, and heating for a longer period of time but again the experiment was unsuccessful.

Attempted preparation of 1:1'-dinaphthyl-2-hydroxy-2'-menthoxy acetate.

1. (-) Menthoxyacetyl chloride was prepared as previously described from (-) menthoxyacetic acid (11 g.) and thionyl chloride (20 g.)

Di-β-naphthol (14.2 g.; 1 mol.) was dissolved in dry pyridine (120 ml.) and the solution was cooled in ice. (-) Menthoxyacetyl chloride (11·5 g.; 1 mol.) was added. The homogeneous solution was left overnight and was then poured into a mixture of water, concentrated hydrochloric acid, and ice. Ether was added and the mixture was shaken. The ethereal layer was separated and was washed well with dilute hydrochloric acid, water and finally sodium hydroxide solution.

The alkaline washings were acidified. A solid was produced which was filtered, washed and dried. Weight 6 g. m.p. 210 - 213°. The solid was recovered di-β-naphthol.

The ethereal solution was evaporated and the solid residue was crystallized from ethanol. Weight 4·5 g. m.p.108°. This was 1:1'-dinaphthyl 2:2'-dimenthoxyacetate.

2. 1:1'-Dinaphthyl-2:2'-dimenthoxyacetate (10 g.) was dissolved in 95% ethanol (300 ml.) and the solution was mixed with 30 ml. of each of saturated aqueous solutions of sodium phosphate and disodium hydrogen phosphate. Both salts were used as the dodecahydrate and the solutions were made up at 15°C.

40% Formaldehyde solution (30 ml.) was added to the mixture which was then boiled under reflux for ten hours. It was cooled and filtered from inorganic material. The ethanol was removed by distillation and the residual liquid deposited a solid on cooling. The solid was filtered off and a further portion of solid was obtained when the mother liquor was diluted with distilled water (about 400 ml.). The combined solids were crystallized from ethanol. Weight 2·5 g. m.p. and mixed m.p. with di-β-naphthol 216 - 217°. No other product could be isolated.

Treatment of di-β-naphthol with β-camphorsulphonyl chloride

Preparation of β-camphorsulphonyl chloride.

β-Camphorsulphonic acid (10 g.; 1 mol.) and thionyl chloride (20 ml.) were warmed together on a water bath until all reaction had ceased. Excess thionyl chloride was distilled off under atmospheric pressure. The residual pale brown solid was washed well with light petroleum (b.p. 40 - 60°) Yield 5·7 g. m.p. 67 - 68°. Percentage yield 50%.

Di-β-naphthol (3·25 g.; 1 mol.) was dissolved in dry pyridine (50 ml.) and β-camphorsulphonyl chloride (5·7 g.; 2·2 mol.) was added. The solution was left overnight and then was poured into a mixture of ice and dilute hydrochloric acid. The mixture was extracted with ether and the ethereal solution was washed well with dilute hydrochloric acid and with water, and was then dried over anhydrous sodium sulphate. The ether was distilled off and the residual brown gum was dried in a vacuum desiccator. It did not solidify. It was dissolved in ethanol and the solution was kept at a temperature of about 4°C for some weeks but no crystals were deposited.

Attempted resolution of 1:1'-dinaphthyl-2:2'-dimenthoxyacetate

Many solvents were used in an attempt to find one which would separate 1:1'-dinaphthyl-2:2'-dimenthoxyacetate into the enantiomorphous forms. A small amount of the ester was dissolved in the hot solvent and the solution was filtered and allowed to cool. If crystals were deposited they were removed by filtration and their melting point was taken. In many instances a mixed melting point with racemic ester was also taken and the specific rotation in a solution of bench chloroform was also measured. The rotations were taken at room temperature (about 20°C) in a 2-decimetre polarimeter tube.

Results

Crystals were obtained from the solvents ethanol, methanol, 3:1 ethanol/water, n-propyl alcohol, n-butyl alcohol, isobutyl alcohol, cyclohexanol, acetone, ethylene glycol monoethylether, light petroleum, acetic acid, cyclohexane and acetonitrile.

The specific rotation of the crystals was $[\alpha]_{5461}$ - 55·7° ± 1·5°. The melting point of the crystals varied between 108° and 111°. Mixed melting points with racemic ester varied between 108° and 110°.

The ester was too insoluble in 1:1 mixtures of methanol and water, and of ethanol and water.

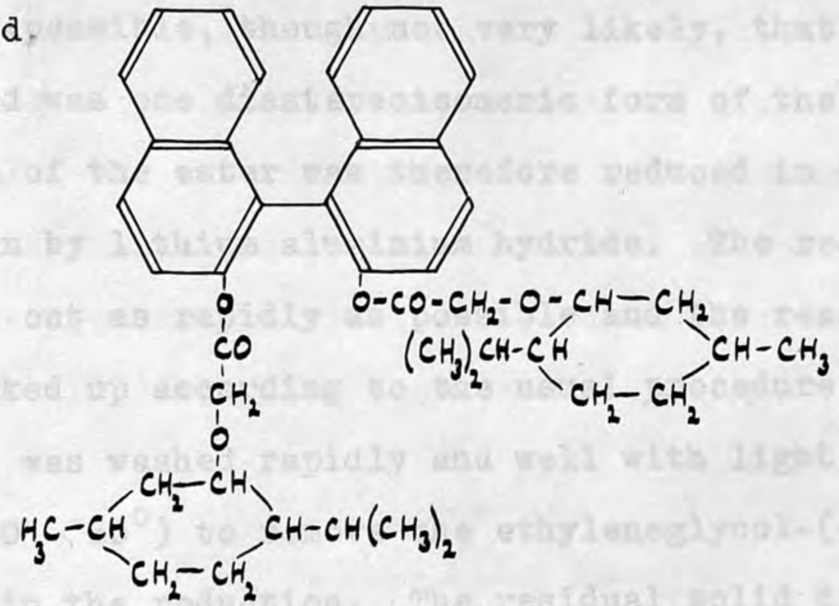
It was too soluble in the solvents cyclohexanone, ether, benzene, toluene, benzene/light petroleum (b.p. 60 - 80°), carbon tetrachloride and monochlorobenzene.

It may be concluded that no resolution of 1:1'-dinaphthyl-2:2'-dimenthoxyacetate had been achieved.

DISCUSSION OF RESULTS

Di-β-naphthol was easily prepared by the oxidation of β-naphthol using ferric chloride and concentrated hydrochloric acid (Julius, Chemische Industrie, 10,98). The yield of di-β-naphthol was about 80%. The crude di-β-naphthol could be crystallized from benzene but ethanol was a more satisfactory solvent. The melting point of recrystallized di-β-naphthol was 216°. Julius (loc.cit.) records the melting-point as varying between 212° and 218°.

1:1'-Dinaphthyl-2:2'-dimenthoxyacetate (X11) was prepared by the usual method of preparation of the ester of a phenol using the acid chloride. The reaction between di-β-naphthol and (-) menthoxyacetyl chloride was carried out in dry pyridine as a solvent. In the first experiment the pyridine was removed after the reaction was complete by distillation from an oil-bath at atmospheric pressure and the residual oil was poured into water and extracted with ether. It was difficult to remove the last traces of pyridine by this method

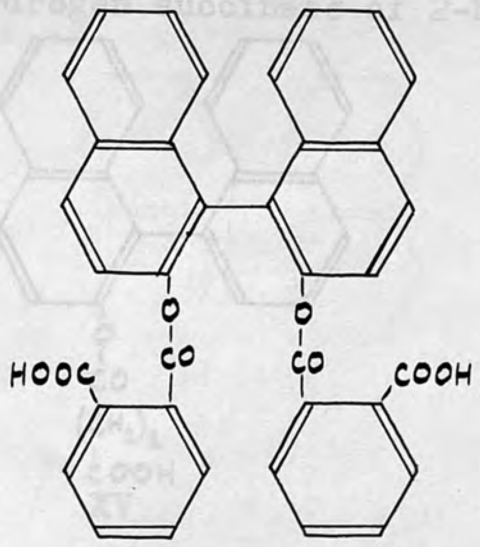


X11

and the yield of ester was low. A better method was to pour the reaction mixture into a mixture of ice and hydrochloric acid which removed the bulk of the pyridine. The ester was extracted with ether and suitable washings of the ethereal solution removed final traces of pyridine. The ester was a colourless solid crystallizing from ethanol in clusters of fine leaflets, m.p. 109°. It was obtained in yields of over 80%.

In the original preparation of 1:1'-dinaphthyl-2:2'-dimenthoxyacetate a low yield of ester was obtained. It was thought possible, though not very likely, that the product isolated was one diastereoisomeric form of the ester. A portion of the ester was therefore reduced in dry ethereal solution by lithium aluminium hydride. The reduction was carried out as rapidly as possible and the reaction mixture was worked up according to the usual procedure. The solid product was washed rapidly and well with light petroleum (b.p. 40 - 60°) to remove the ethyleneglycol-(-)-menthylether formed in the reduction. The residual solid di-β-naphthol had a melting point of 216° but was optically inactive when its chloroform solution was viewed polarimetrically.

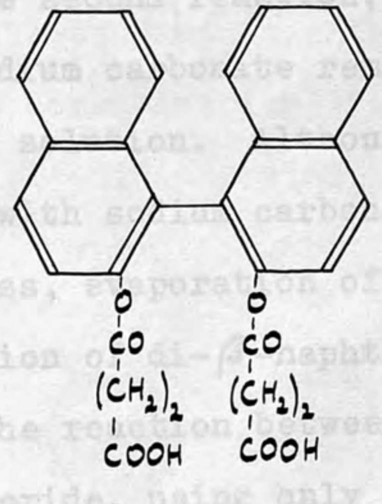
An attempt was made to prepare the dihydrogenphthalate of di-β-naphthol (X111).



X111

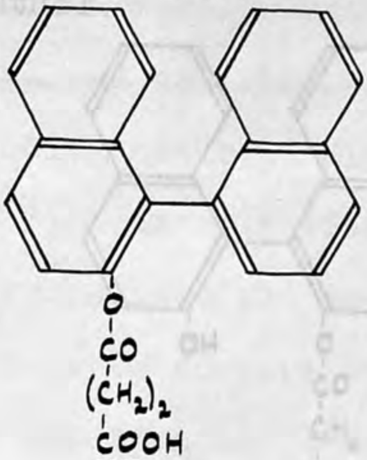
Di-β-naphthol was heated with phthalic anhydride in pyridine and the reaction mixture was worked up in the usual way. The only identifiable product was unchanged di-β-naphthol. The experiment was also unsuccessful when a mixture of triethylamine and pyridine was used as the solvent.

The preparation of the dihydrogen succinate of di-β-naphthol (X1V) was also unsuccessful.



X1V

Di-β-naphthol and succinic anhydride were heated together in anhydrous pyridine according to the method used by Berson and Greenbaum (J.Amer.Chem.Soc., 1958, 80, 653) for the preparation of the hydrogen succinate of 2-hydroxy-1:1'-dinaphthyl (XV).

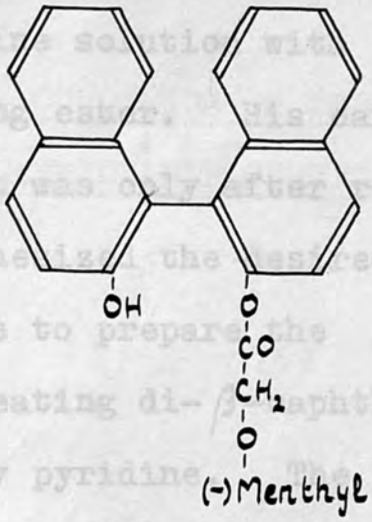


XV

Again the only identified product was unchanged di-β-naphthol.

The behaviour of di-β-naphthol in the various solvents used in these last two reactions is of interest. The unchanged di-β-naphthol was soluble in the ethereal extract of the reaction mixture. In the first reaction, using phthalic anhydride, sodium carbonate solution removed some of the di-β-naphthol from the ether as a solid, while evaporation of the ether solution yielded a further portion of di-β-naphthol. Again in the second reaction, in which succinic anhydride was used, sodium carbonate removed some of the di-β-naphthol, this time in solution. Although the ether solution was washed repeatedly with sodium carbonate solution until the washings were colourless, evaporation of the ether still yielded a further portion of di-β-naphthol.

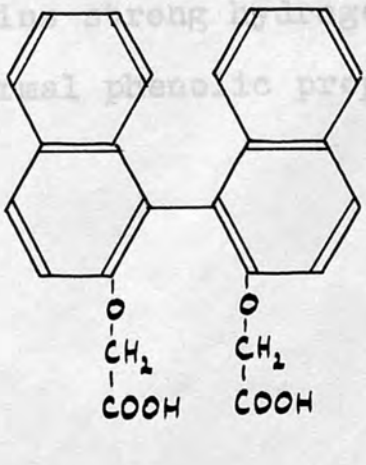
A repetition of the reaction between di-β-naphthol and (-) menthoxyacetyl chloride, using only one molecular proportion of the acid chloride in an attempt to prepare the monoester of di-β-naphthol (XVl), resulted only in the formation of the dimenthoxyacetate and the recovery of some unchanged di-β-naphthol.



XV1

A controlled hydrolysis of 1:1'-dinaphthyl-2:2'-dimenthoxyacetate using the buffered mixture of sodium phosphate Na_3PO_4 and disodium hydrogen phosphate Na_2HPO_4, according to the method of Benet (Bull.Soc.Chim.,1932,51,963) gave only the completely hydrolysed di-β-naphthol and not the expected monomenthoxyacetate.

In view of the failure to prepare the dihydrogen phthalate and dihydrogen succinate of di-β-naphthol, some work carried out by Siegel (private communication) is of interest. He attempted to prepare 1:1'-dinaphthyl-2:2'-dicarboxymethyl ether (XV11).



XV11

He finally prepared it in small quantities by condensing di-β-naphthol in alkaline solution with ethylbromoacetate and hydrolysing the resulting ester. His earlier experiments were unsuccessful and it was only after repeated failures that he eventually synthesized the desired compound.

An attempt was made to prepare the β-camphor sulphonate of di-β-naphthol by treating di-β-naphthol with β-camphorsulphonylchloride in dry pyridine. The product was isolated according to the usual method but it was a brittle gum which did not solidify; nor did it crystallize when its ethanolic solution was kept in the cold for some weeks.

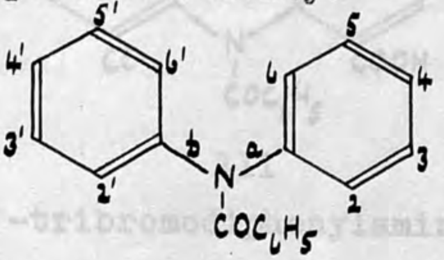
From this present work it can be seen that di-β-naphthol does not follow an expected pattern of behaviour. The ease with which the dimenthoxyacetate is formed is surprising in view of the difficulties of preparation of the dihydrogen succinate, dihydrogen phthalate and dicarboxymethyl ether (Siegel). The dimenthoxyacetate cannot be resolved easily. The solubilities of di-β-naphthol in various solvents do not follow a general rule. It seems likely that the molecule of di-β-naphthol contains strong hydrogen bonds, which are thus suppressing the normal phenolic properties of the hydroxyl groups.

PART IV

INVESTIGATIONS INVOLVING COMPOUNDS OF THE N-BENZOYLDIPHENYLAMINE CARBOXYLIC ACID SERIES

INTRODUCTION

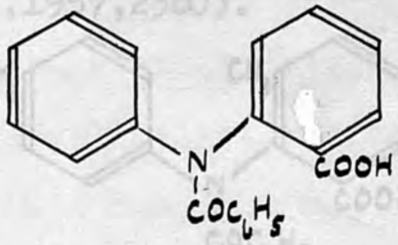
A large amount of research has been devoted in recent years to the study of the N-benzoyldiphenylamine carboxylic acids. These compounds, if suitably substituted, are capable of showing unstable optical activity.



1

Compounds of this type (1) which are suitably substituted in the 2-, 6-, 2'-, 6'- positions owe their optical activity to restriction of rotation about one, or perhaps two, carbon-nitrogen single bonds (a and b). The optical stabilities of these compounds depend largely on the size and positions of the substituent groups.

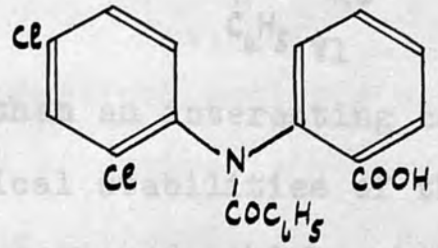
Of the many compounds in this series which have been studied, the following are examples:-



11

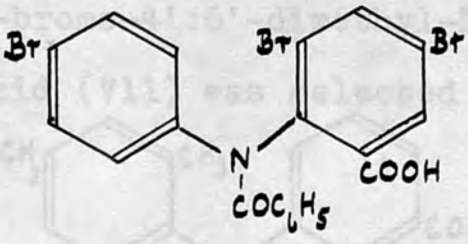
N-Benzoyldiphenylamine-2-carboxylic acid (11) was shown by an addition curve to be capable of undergoing asymmetric transformation, although no mutarotation was observed when the acid was dissolved in chloroform with cinchonidine or nor-d-ψ-ephedrine at -30°. (Jamison and Turner, J., 1938, 1646).

The same workers observed a rapid mutarotation when N-benzoyl-2':4'-dichlorodiphenylamine-2-carboxylic acid (111) was dissolved in chloroform with nor-d-ψ-ephedrine at -31°. (<u>idem.,ibid</u>.)



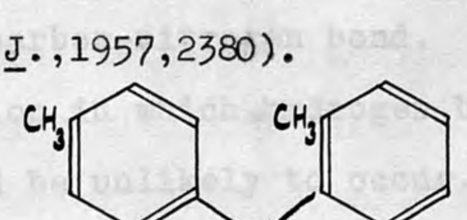
111

N-Benzoyl-4:6:4'-tribromodiphenylamine-2-carboxylic acid (lV) was resolved at -15° through its cinchonidine salt. (<u>idem.,ibid</u>.)



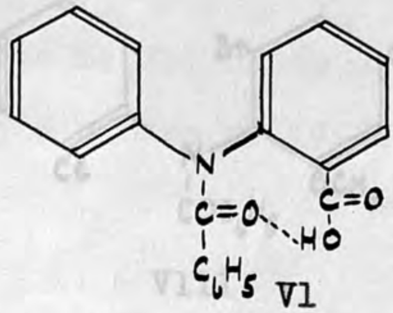
lV

N-Benzoyl-6:4'-dimethyldiphenylamine-2-carboxylic acid (V) underwent first-order asymmetric transformation in chloroform solution in the presence of cinchonidine (Brooks, Harris and Howlett, <u>J</u>.,1957,2380).



V

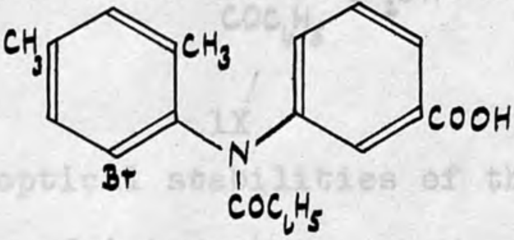
In all these compounds which have been optically activated the carboxylic acid group has been in position 2. It has been suggested that restriction of rotation about the nitrogen-carbon bond 'a' may be increased by hydrogen-bonding between the hydrogen atom of the carboxylic acid group and the oxygen atom of the carbonyl group attached to the nitrogen (Vl)



Vl

If this is so, **then** an interesting comparison may be made between the optical stabilities of the compounds already studied and those of compounds which, while still containing substituent groups in the blocking positions, have the carboxylic acid group elsewhere in the molecule.

The compound 2'-bromo-4':6'-dimethyl-N-benzoyldiphenylamine-3-carboxylic acid (Vll) was selected for study.

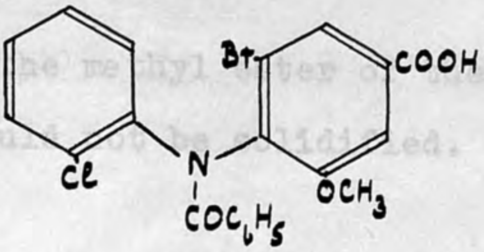


Vll

The compound has suitable substituents in the 2':6'-blocking positions which should effectively restrict the rotation about the carbon-nitrogen bond. The carboxylic acid group is in a position in which hydrogen bonding with the carbonyl group would be unlikely to occur.

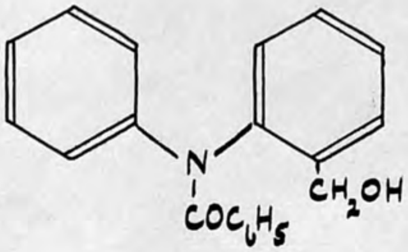
The synthesis of this compound was accordingly carried out by the present worker and the compound was examined for evidence of optical activity.

The synthesis of 2'-chloro-N-benzoyl-2-methoxy-6-bromodiphenylamine-4-carboxylic acid (Vlll), another suitably substituted acid, was attempted, but could not be carried out because of the insolubility of the ester methyl 5-bromovanillate in ether.



Vlll

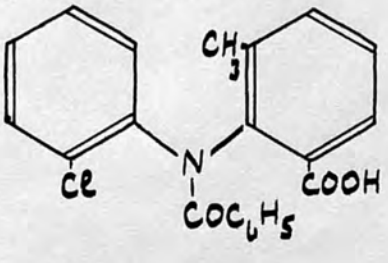
An interesting research problem would be the low-temperature reduction of optically active acids of the N-benzoyldiphenylamine carboxylic acid series, or of their esters, to obtain the corresponding optically active alcohols (lX).



lX

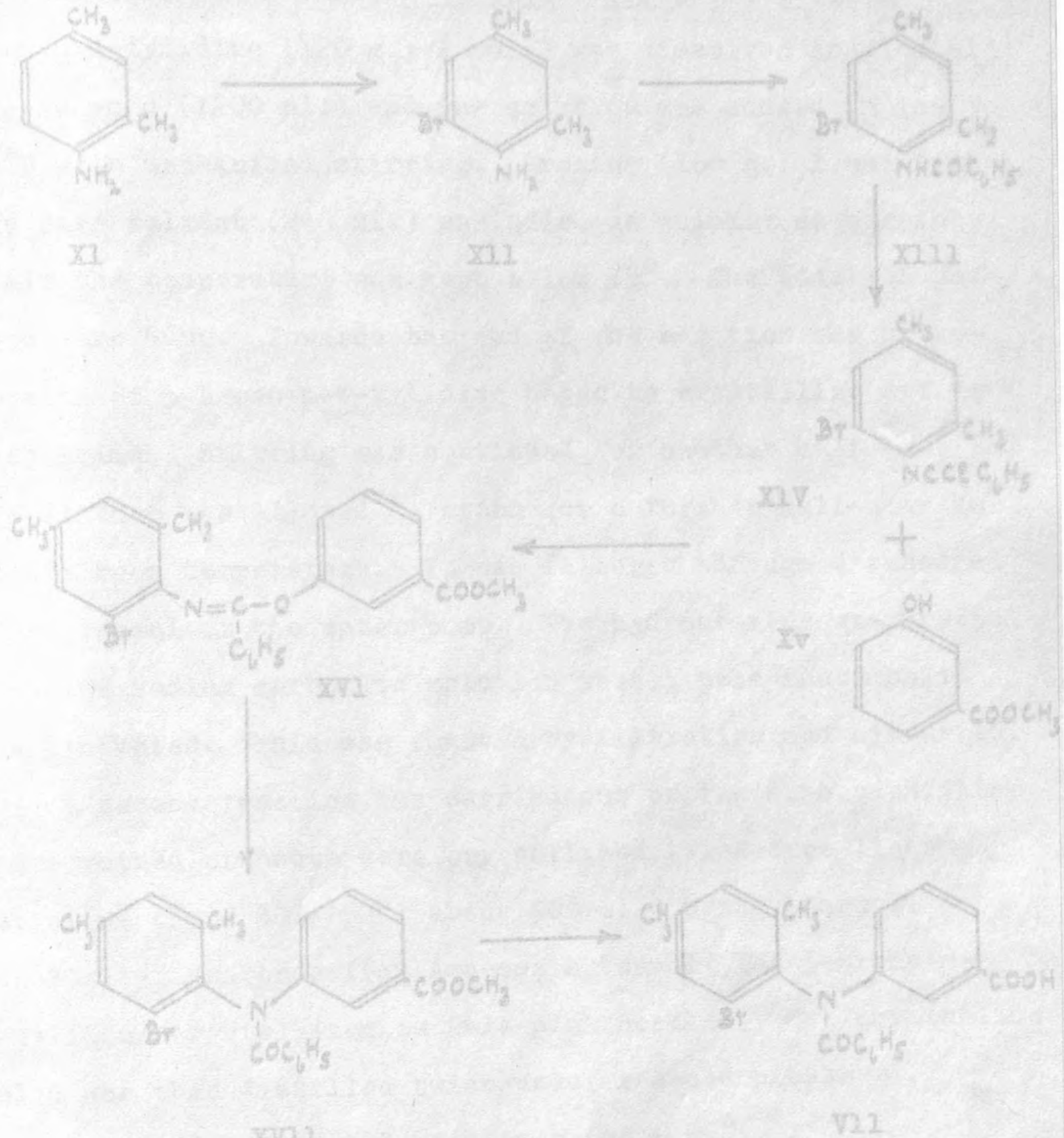
A comparison of the optical stabilities of the acids and alcohols should prove of interest.

It was with the intention of pursuing this problem that the present worker attempted to reduce the optically active acid d-N-benzoyl-4:6:4'-tribromodiphenylamine-2-carboxylic acid (lV) using lithium aluminium hydride at -30°. A highly coloured product rendered the experiment valueless. A similar reduction of N-benzoyl-2'-chloro-6-methyldiphenylamine-2-carboxylic acid (X) was made extremely difficult by the insolubility of the acid in ether.

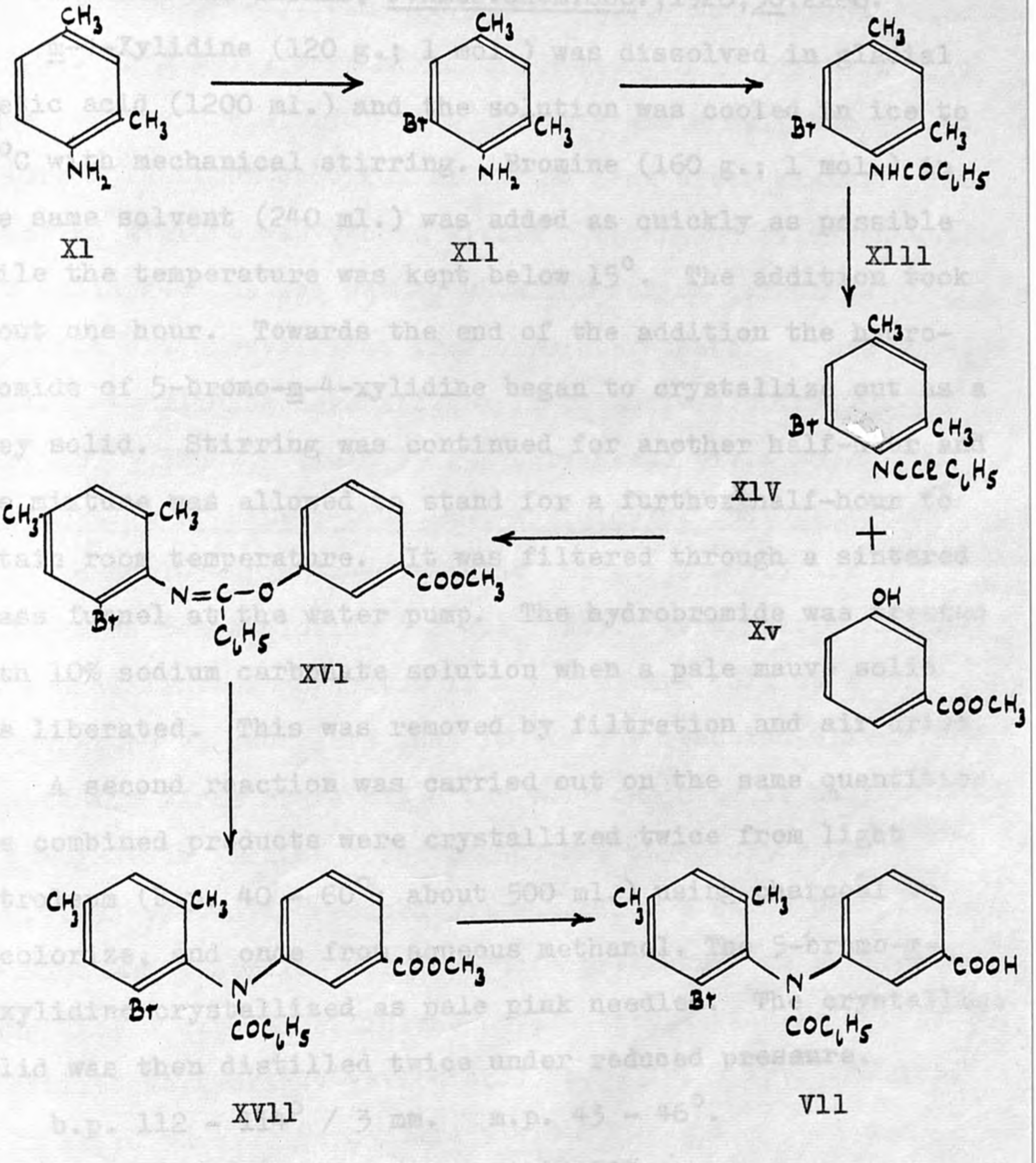


X

The reduction of the methyl ester of the acid gave a tarry product which could not be solidified.



THE SYNTHESIS OF 2'-BROMO-4':6'-DIMETHYL-N-BENZOYLDIPHENYLAMINE-3-CARBOXYLIC ACID



EXPERIMENTAL

Preparation of 5-bromo-m-4-xylidine (Xll)

Wheeler and Thomas, J.Amer.Chem.Soc.,1928,50,2286.

m-4-Xylidine (120 g.; 1 mol.) was dissolved in glacial acetic acid (1200 ml.) and the solution was cooled in ice to 10°C with mechanical stirring. Bromine (160 g.; 1 mol.) in the same solvent (240 ml.) was added as quickly as possible while the temperature was kept below 15°. The addition took about one hour. Towards the end of the addition the hydrobromide of 5-bromo-m-4-xylidine began to crystallize out as a grey solid. Stirring was continued for another half-hour and the mixture was allowed to stand for a further half-hour to attain room temperature. It was filtered through a sintered glass funnel at the water pump. The hydrobromide was treated with 10% sodium carbonate solution when a pale mauve solid was liberated. This was removed by filtration and air dried.

A second reaction was carried out on the same quantities. The combined products were crystallized twice from light petroleum (b.p. 40 - 60°; about 500 ml.) using charcoal to decolorize, and once from aqueous methanol. The 5-bromo-m-4-xylidine crystallized as pale pink needles. The crystalline solid was then distilled twice under reduced pressure.

b.p. 112 - 114° / 3 mm. m.p. 43 - 46°.

Yield 238 g. Percentage yield 60%.

Preparation of the benzoyl derivative of 5-bromo-m-4-xylidine Xlll.

5-Bromo-m-4-xylidine (100 g.; 1 mol.) and benzoyl chloride (71 ml.; 1·2 mol.) were mixed and heated in an oil bath held at a temperature of 130 - 140° for one and a half hours. A vigorous reaction occurred almost at once after mixing. The reaction mixture was ground with hot water and filtered hot. The solid residue was washed with 10% sodium carbonate solution and crystallized from absolute ethanol. Benzoyl-5-bromo-m-4-xylidine crystallized in colourless prisms, m.p. 187 - 188°. Yield 75 g. Percentage yield 50%.

Preparation of benz-5-bromo-m-4-xylidideiminochloride XlV

Benzoyl-5-bromo-m-4-xylidine (61 g.; 1 mol.) and phosphorus pentachloride (42 g.; 1 mol.) were heated together in a distillation apparatus in a water bath held at a temperature of just less than 100°. The reaction mixture was heated for three hours but after only one hour it had become a homogeneous liquid. The phosphorus oxychloride was distilled off using reduced pressure from a water pump and the residue was distilled using reduced pressure from a vacuum pump fitted with an efficient potash trap. The iminochloride distilled as a bright yellow oil. b.p. 192 - 195° / 2 mm.

Yield 52 g. Percentage yield 80%.

In all, 135 g. of iminochloride were prepared.

Preparation of N-2'-bromo-4':6'-dimethylphenylbenzimino-m-carboxymethylphenyl ether XVl

1. Sodium (3·1 g.; 1·3 atoms) was dissolved in absolute ethanol (100 ml.) and methyl m-hydroxybenzoate (20·3 g.; 1·3 mol.) was added. To the clear solution benz-5-bromo m-4-xylidideimino chloride (32·3 g.; 1 mol.), dissolved in dry ether (20 ml.) was added. A solid began to separate almost at once but the reaction mixture was allowed to stand at room temperature for two hours. Water was then added to dissolve the sodium chloride which had been precipitated during the reaction and the mixture was filtered. The colourless crystalline benziminoether was air dried and crystallized from ethanol to constant melting point (133 - 135°).

Yield 34·8 g. Percentage yield 79%.

Found: C, 63·21; H, 4·34; Br, 18·65. $C_{23}H_{20}N\ Br\ O_3$ requires C, 63·02; H, 4·60; Br, 18·23%.

A Carius estimation of bromine was carried out.

Found: Br, 18·60. $C_{23}H_{20}N\ Br\ O_3$ requires Br, 18·23%.

2. The reaction was repeated on a 52 g. batch of iminochloride. Yield 55 g. Percentage yield 71%.

After crystallization from ethanol the imino ether had m.p. 136 - 139° with preliminary softening. After two recrystallizations from acetone, and drying over concentrated sulphuric acid in a vacuum desiccator the melting point was 140 - 141° with no preliminary softening.

Found: C, 61·82; H, 4·62; N, 2·97; Br, 15·89, O, 10·60. $C_{23}H_{20}N\ Br\ O_3$ requires C, 63·02; H, 4·60; N, 3·20, Br, 18·23; O, 10·95%.

Preparation of methyl N-benzoyl-2'-bromo-4':6'-dimethyldiphenylamine-3-carboxylate XVll

1. The benzimino ether (17 g.) was heated in a hard glass boiling tube in a metal bath at an internal temperature of 270 - 280° for two hours. After cooling somewhat the product was extracted with boiling methanol and the solution was treated with decolorising charcoal and filtered. On cooling, a pale yellow solid crystallized out in rosettes of needles.

Yield 9 g. Percentage yield 53%.

The methyl-N-benzoyl-2'-bromo-4'-6'-dimethyldiphenylamine 3-carboxylate was repeatedly crystallized from ethanol, using charcoal to decolorize, to constant melting point. (167 - 169°, with preliminary softening.)

Found: C, 62·48; H, 4·77; Br, 16·93. $C_{23}H_{20}N\ Br\ O_3$ requires C, 63·02; H, 4·60; Br, 18·23%.

2. The reaction was repeated using the iminoether (28 g.) prepared in the second experiment of the previous preparation. Heating was discontinued **after** one and a quarter hours. The crude ester obtained from the methanolic extraction was recrystallized from ethanol using charcoal. Yield 15 g. Percentage yield 54%. m.p. 170 - 173° with slight preliminary softening.

After further recrystallizations from ethanol and careful drying over concentrated sulphuric acid in a vacuum desiccator the ester had a melting point of 173 - 174° with no preliminary softening.

Found: C, 62·56; H, 4·57; Br, 15·05. $C_{23}H_{20}N\ Br\ O_3$

requires C, 63·02; H, 4·60; Br, 18·23%.

Preparation of N-benzoyl-2'-bromo-4':6'-dimethyldiphenylamine-3-carboxylic acid VII

1. Ethanolic sodium hydroxide solution was prepared by dissolving sodium (2·3 g.) in absolute ethanol (100 ml.) and adding water (20 ml.).

Methyl-N-benzoyl-2'-bromo-4':6'-dimethyldiphenylamine-3-carboxylate (3 g.) was boiled under reflux with ethanolic sodium hydroxide solution (10 ml.) for one hour. The alcohol was removed by distillation and the residue was dissolved in water by warming. The aqueous solution was filtered and acidified with dilute hydrochloric acid. The colourless precipitate was removed by filtration and crystallized from aqueous ethanol. The acid crystallized as small prisms. m.p. 213 - 215°. Yield 1·7 g. Percentage yield 59%. After recrystallization for analysis the melting point rose to 216 - 217°.

Found: C, 63·34; H, 4·23; Br, 18·60. $C_{22}H_{18}N\,Br\,O_3$ requires C, 62·22; H, 4·28; Br, 18·84%.

2. The experiment was repeated using the ester of melting point 173 - 174° (13 g.). The crude acid obtained after acidifying the aqueous hydrolysis solution had a low melting point and so was dissolved in sodium bicarbonate solution to separate it from any unchanged ester. All the solid dissolved and was reprecipitated on the addition of dilute hydrochloric acid. The solid was filtered off and crystallized from ethanol. m.p. about 165°. Yield 9 g.

The acid obtained was boiled under reflux with more ethanolic sodium hydroxide for a further three hours. The acid was isolated by the usual procedure and was crystallized from ethanol. m.p. 177 - 178°. Mixed melting point with ester was 145 - 170°. The acid was then recrystallized from benzene, m.p. 178 - 179°.

A little was melted and seeded with the acid melting at 213 - 215°. The melt solidified and the solid had a melting point of 180 - 185° which fell to 178 - 179° after crystallization from benzene. The major portion of the acid was crystallized twice more from benzene and dried in a vacuum desiccator. The melting point was then 180°. Found: C, 56·78; H, 4·29: Br, 21·75. $C_{22}H_{18}N\,Br\,O_3$ requires C, 62·22; H, 4·28; Br, 18·84%.

The behaviour of N-benzoyl-2'-bromo-4':6'-dimethyldiphenylamine-3-carboxylic acid with alkaloids.

1. Attempts were made to prepare various alkaloid salts of the acid (m.p. 213 - 215°). In each case the acid (0·2122 g.; 1 equiv.) and alkaloid (1 equiv.) were separately dissolved in a suitable solvent. The solutions were mixed and filtered, a little solvent was evaporated off and the solution was corked and allowed to cool. The following alkaloids and solvents were used:-

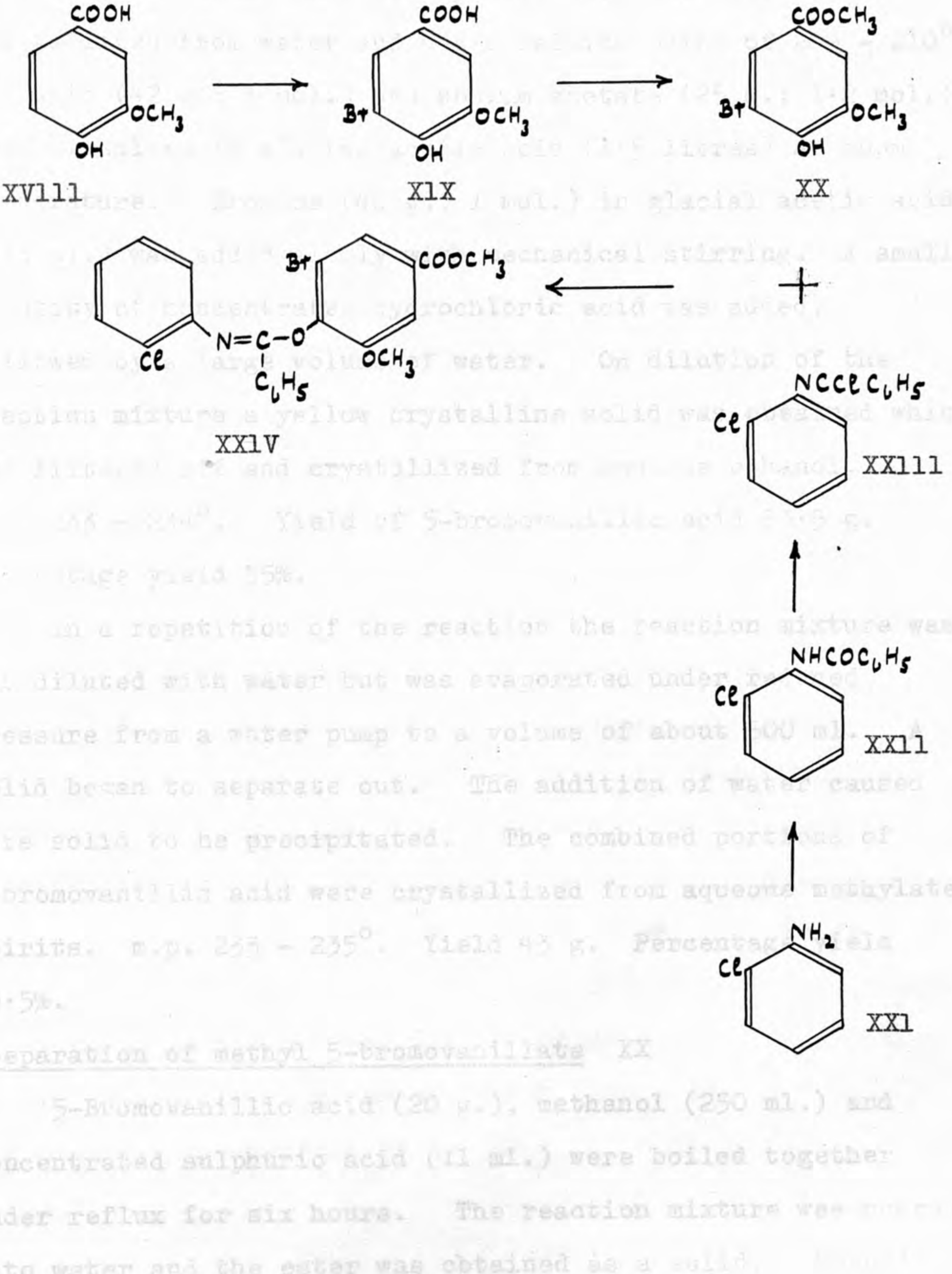
Brucine	(0·1970 g.) in acetone
Quinine	(0·1620 g.) in acetone
Quinidine	(0·1620 g.) in absolute ethanol
Cinchonidine	(0·1470 g.) in absolute ethanol.

In no case was a crystalline salt obtained.

2. N-Benzoyl-2'-bromo-4':6'-dimethyldiphenylamine-3-carboxylic acid (0·2122 g.; 1 equiv.) and cinchonidine (0·1470 g.; 1 equiv.) were dissolved in 25 ml. "solvent X" and examined polarimetrically. No mutarotation was observed during sixty-seven minutes at 2·6°C.

3. N-Benzoyl-2'-bromo-4':6'-dimethyldiphenylamine-3-carboxylic acid (0·2122 g.; 1 equiv.) and quinine (0·1620 g.; 1 equiv.) were dissolved in 25 ml. "solvent X" and examined polarimetrically. No mutarotation was observed during seventy-eight minutes at 3·6°C.

REACTIONS INVOLVED IN THE ATTEMPTED SYNTHESIS OF 2'-CHLORO-N-BENZOYL-2-METHOXY-6-BROMODIPHENYLAMINE-4-CARBOXYLIC ACID.



Preparation of 5-bromovanillic acid XlX

Robertson, J.,1908,798.

Vanillic acid, supplied by W.J. Bush and Co., was crystallized from water and had a melting point of 209 - 210°. The acid (42 g.; 1 mol.) and sodium acetate (25 g.; 1·2 mol.) were dissolved in glacial acetic acid (1·5 litres) at room temperature. Bromine (40 g.; 1 mol.) in glacial acetic acid (133 ml.) was added slowly with mechanical stirring. A small quantity of concentrated hydrochloric acid was added, followed by a large volume of water. On dilution of the reaction mixture a yellow crystalline solid was obtained which was filtered off and crystallized from aqueous ethanol. m.p. 233 - 234°. Yield of 5-bromovanillic acid 33·5 g. Percentage yield 55%.

In a repetition of the reaction the reaction mixture was not diluted with water but was evaporated under reduced pressure from a water pump to a volume of about 600 ml. A solid began to separate out. The addition of water caused more solid to be precipitated. The combined portions of 5-bromovanillic acid were crystallized from aqueous methylated spirits. m.p. 233 - 235°. Yield 43 g. Percentage yield 69·5%.

Preparation of methyl 5-bromovanillate XX

5-Bromovanillic acid (20 g.), methanol (250 ml.) and concentrated sulphuric acid (11 ml.) were boiled together under reflux for six hours. The reaction mixture was poured into water and the ester was obtained as a solid. Methyl

5-bromovanillate was crystallized from aqueous methanol. m.p. 154 - 156°.

Yield 19·3 g. Percentage yield 86%.

Preparation of o-chlorobenzanilide XX11

o-Chloroaniline (51·2 g.) and benzoyl chloride (47 ml.) were mixed cautiously in a round-bottomed flask. After the initial vigorous exothermic reaction the mixture was heated in an oil bath held at a temperature of 130 - 140° until it was a homogeneous liquid. It was then cooled and the solid obtained was ground well with hot water and filtered hot. The residue crystallized from aqueous methylated spirits in clusters of colourless needles. m.p. 103 - 105°.

Yield 67·5 g. Percentage yield 73%.

Preparation of benz-o-chloroanilideimino chloride XX111

o-Chlorobenzanilide (23 g.; 1 mol.) and phosphorus pentachloride (21 g.; 1 mol.) were mixed in a round-bottomed flask fitted with a distillation apparatus. The reaction began in the cold and was vigorous when the flask was heated in a water bath at a temperature of about 60°. The reaction was complete in about half an hour, after which phosphorus oxychloride was distilled off using reduced pressure from a water pump. The residue was distilled under reduced pressure using a vacuum pump fitted with a potash trap. The imino-chloride was a pale yellow oil. b.p. 170 - 173° / 4 mm.

Yield 18 g. Percentage yield 72%.

Attempted preparation of N-o-chlorophenylbenzimino-6-bromo-2-methoxy-4-carbomethoxyphenyl ether XXlV

Sodium (2·2 g.; 1·3 atoms) was dissolved in absolute alcohol (100 ml.) and methyl 5-bromovanillate (23 g.; 1·3 mol.) was added. The ester did not dissolve even when more alcohol was added. Benz-o-chloroanilideimino chloride (18 g.; 1 mol.) dissolved in dry ether (20 ml.) was added and the reaction mixture was left at room temperature for twenty-four hours. Water was then added. The solid was filtered off and crystallized from methanol. m.p. 154 - 156°. Mixed melting point with methyl 5-bromovanillate was 153 - 155°. Not all the starting material was recovered but no other product could be isolated.

Second-Order Asymmetric Transformation of N-benzoyl-4:6:4'-tribromodiphenylamine-2-carboxylic acid IV

Jamison and Turner, *J.*, 1938, 1646.

N-Benzoyl-4:6:4'-tribromodiphenylamine-2-carboxylic acid (3·9100 g.; 1 mol.) and cinchonidine (2·0717 g.; 1 mol.) were mixed and warmed with "AnalaR" acetone (110 ml.) An amorphous solid began to separate out almost at once from the solution. The mixture was at once chilled to -15° and was kept at this temperature for an hour. The solid was filtered off and air-dried.

Portion 1 Yield 2·3286 g.

After standing overnight the mother liquor deposited a further portion of solid. It was filtered and air-dried.

Portion 2 Yield 2·3641 g.

Total yield 4·6927 g.   Percentage yield 79%.

Each portion was separately decomposed by grinding with "AnalaR" pyridine at -15°. All apparatus was precooled in an ice-salt bath. The pyridine solution was filtered as quickly as possible, using suction, into a mixture of ice and concentrated hydrochloric acid. The precipitated acid was filtered, washed with dilute hydrochloric acid and water, and dried in a vacuum desiccator.

Portion 1 gave 1·4733 g. free acid.

Portion 2 gave 0·9515 g. free acid.

A little of each crop of free acid was examined polarimetrically.

<u>Portion 1</u>

A little of the free acid was dissolved in 25 ml. of bench chloroform and examined polarimetrically, using a 2-decimetre jacketed polarimeter tube.

Weight of acid   0·1660 g.   Temperature 23·3°

Zero 179·01

Time after wetting in minutes	Reading	α_D
1·75	179·41	+ 0·40
2·5	179·20	+ 0·19
3·0	179·13	+ 0·12
4·0	179·09	+ 0·08
5·0	179·03	+ 0·02
6·0	179·01	0

Portion 2

As before, a little of the free acid was dissolved in 25 ml. of bench chloroform and examined polarimetrically using a 2-decimetre jacketed polarimeter tube.

Weight of acid 0·1265 g. Temperature 23·2°C.

Zero 179·01

Time after wetting in minutes	Reading	α_D
3.0	179·23	+ 0·22
4·0	179·10	+ 0·09
4 mins.40 secs.	179·02	+ 0·01
5·5 mins.	179·01	0

Both portions of acid were dextrorotatory and racemized within six minutes at a temperature of 23·2°C. A second-order asymmetric transformation had taken place.

Treatment of d-N-benzoyl-4:6:4'-tribromodiphenylamine-2-carboxylic acid (lV) with lithium aluminium hydride.

Lithium aluminium hydride (0·1 g.; 1 mol.) was suspended in dry ether (50 ml.) in a round-bottomed flask placed in a bath of methylated spirits and solid carbon dioxide. d-N-Benzoyl-4:6:4'-tribromodiphenylamine-2-carboxylic acid (1 g.; 1 mol.) was added quickly as a solid. A reaction set in immediately. The temperature of the reaction mixture was kept below - 10°C. After the reaction had subsided, a little more lithium aluminium hydride was added to ensure that the reaction was complete. The cautious addition of ice-water caused a solid to separate out of the reaction mixture, which was a greenish-yellow colour. The solid did not dissolve when more ether was added. 5% Ice-cold sulphuric acid was added until the mixture separated into two layers. Most of the solid dissolved. The mixture was rapidly transferred to a separating funnel and the ether layer was run into a conical flask kept at a temperature of -20° to -30°. The experiment up to this point took ten minutes to perform. The ethereal solution was pale green in colour and was not clear. It was not improved by rapid filtration through glass wool. The ether was evaporated off as rapidly as possible by dropping the ethereal solution into an evaporating dish in an evacuated desiccator through a dropping funnel whose stem had been drawn out into a fine capillary thread. Some difficulty was experienced as the fine capillary tube was repeatedly blocked. The residue which was greenish-yellow in colour was kept over sulphuric acid in a vacuum desiccator overnight. It was then examined polarimetrically.

A portion of the residue (0·1327 g.), which was slightly gummy, was dissolved in bench chloroform (25 ml.) and filtered into a 2-decimetre polarimeter tube. The solution was too dark and too cloudy to be viewed. The solution was washed with dilute sulphuric acid and with water and was dried over anhydrous sodium sulphate and was re-examined polarimetrically. The solution was still slightly cloudy and was too darkly coloured to be viewed.

Treatment of 2'-chloro-N-benzoyl-6-methyldiphenylamine-2-carboxylic acid (X) with lithium aluminium hydride.

This experiment was carried out as quickly as possible. The technique was similar to that used in the above experiment.

1. Lithium aluminium hydride (0·38 g.; 1 mol.) was suspended in dry ether (150 ml.) in a reaction flask placed in a bath of methylated spirits and solid carbon dioxide. 2'-Chloro-N-benzoyl-6-methyldiphenylamine-2-carboxylic acid (3·7 g.; 1 mol.) was added as a solid. There was no apparent reaction. The temperature of the reaction mixture was -30°. After the addition of ice-water and ice-cold 5% sulphuric acid a white solid separated out which did not dissolve when more acid was added, nor when more ether was added. The ethereal layer was separated as usual and the solid was extracted with ether as much as possible. Ether was evaporated off as rapidly as possible using a vacuum distillation apparatus. The residue had a melting point of 197 - 199°. It was unchanged organic acid.

2. The experiment was repeated on the same scale. The reaction flask was immersed in a freezing mixture of ice and salt which maintained an internal temperature of -4° to -8°. The reaction mixture was kept at this temperature for three hours before excess lithium aluminium hydride was decomposed. The hydride was suspended in a larger volume of dry ether (250 ml.) and 10% sulphuric acid was used to acidify the reaction mixture. Any reaction product was isolated as in the previous experiment. The only solid obtained was

unchanged acid, m.p. 197 - 199°.

3. The reaction was carried out on the same scale but at room temperature. The acid was added as a suspension in dry ether to the suspension of lithium aluminium hydride. The reaction mixture was heated under reflux for two hours, cooled and worked up according to the usual procedure. The solid obtained after evaporation of the ether had a melting point of 194 - 199°. Mixed melting point with 2'-chloro-N-benzoyl-6-methyldiphenylamine-2-carboxylic acid was 197 - 203°.

4. Again the reaction was repeated using the same quantities of reactants. The acid was placed in the thimble of a Soxhlet extractor and the reaction mixture was boiled for twelve hours. The usual procedure for isolating the product was followed. The solid obtained after evaporation of the ether was again unchanged acid, m.p. 191 - 197°. Mixed melting point with acid 194 - 200°.

Preparation of methyl 2'-chloro-N-benzoyl-6-methyldiphenylamine-2-carboxylate XXV1

Diazomethane was prepared from N-methyl-*p*-toluene sulphonylnitrosamide according to the procedure previously described.

2'-Chloro-N-benzoyl-6-methyldiphenylamine-2-carboxylic acid (7·4 g.) was added as a solid to an ethereal solution of freshly prepared diazomethane (about 3 g.) Evolution of nitrogen occurred but the solid did not appear to dissolve. The reaction mixture was left overnight in an exhaust chamber and ether was distilled from the then colourless reaction

mixture. The residue was a very pale yellow solid. It was crystallized from methanol, m.p. 168 - 169°.
Yield 5 g. Percentage yield 66%.

Treatment of methyl 2'-chloro-N-benzoyl-6-methyldiphenylamine-2-carboxylate with lithium aluminium hydride.

The experiment was carried out at room temperature, using the usual procedure. The ester (5 g.; 1 mol.) suspended in dry ether (500 ml.) was added to a suspension of lithium aluminium hydride (0.8 g.; 1·6 mol.) in dry ether (50 ml.). After the addition the reaction mixture was boiled under reflux for two hours, when all the solid ester had dissolved. The reaction mixture was cooled, excess lithium aluminium hydride was decomposed and the mixture was acidified with dilute sulphuric acid. The ethereal layer was separated and the ether removed by distillation. The residue was a pale brown viscous oil which resisted all attempts to solidify it.

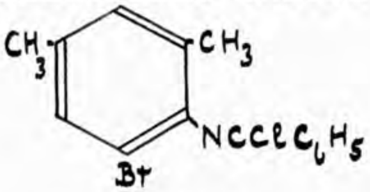
DISCUSSION OF RESULTS

The synthesis of 2'-bromo-4':6'-dimethyl-N-benzoyl-diphenylamine-3-carboxylic acid was accomplished without difficulty.

m-4-Xylidine was brominated using bromine in glacial acetic acid at a temperature of 10° to 15°C according to the method of Wheeler and Thomas, J.Amer.Chem.Soc.,1928,50,2286. The bromoxylidine separated out as the hydrobromide of the base. 5-Bromo-m-4-xylidine was liberated by treatment of the hydrobromide with 10% sodium carbonate solution. It was purified by repeated crystallization from light petroleum (b.p. 40 - 60°) and from aqueous methanol and finally by distillation under reduced pressure. Before distillation the bromoxylidine had a melting point of 41 - 45°. After distillation the melting point was 43 - 46°. Although still not sharp, the melting point was not improved by further treatment of the solid. Wheeler and Thomas (loc.cit.) give the melting point as 46°.

The benzoyl derivative of 5-bromo-m-4-xylidine was easily prepared by heating a mixture of the base and benzoyl chloride at a temperature of 130 - 140° for one and a half hours. The reaction mixture was extracted with hot water to remove any benzoic acid, and was filtered hot. After suitable washings benz-5-bromo-m-4-xylidine crystallized from absolute ethanol in colourless prisms, m.p. 187 - 188°.

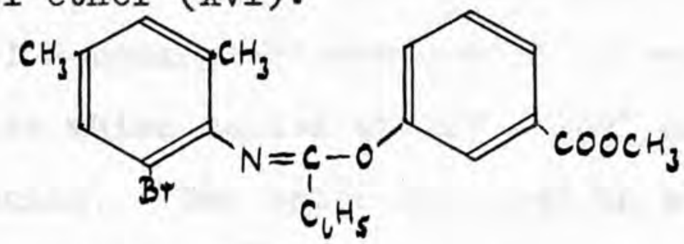
Benz-5-bromo-m-4-xylidideimino chloride (XlV) was



XlV

prepared by the usual method of heating benz-5-bromo-m-4-xylidide and phosphorus pentachloride at a temperature of just below 100°. After removal of phosphorus oxychloride, the reaction product was distilled under reduced pressure. Benz-5-bromo-m-4-xylidideimino chloride was a bright yellow oil, b.p. 192 - 195° / 2 mm.

To a solution of methyl m-hydroxybenzoate (XV), supplied by Light and Co., in ethanol containing sodium, was added benz-5-bromo-m-4-xylidideimino chloride dissolved in a little dry ether. The solid product was crystallized from ethanol to a constant melting point of 133 - 135°. The analysis result gave a slightly higher percentage of bromine than that required for N-2'-bromo-4':6'-dimethylphenylbenzimino-m-carbomethoxyphenyl ether (XVl).



XVl

A Carius estimation carried out by the present worker also gave a slightly high value for bromine.

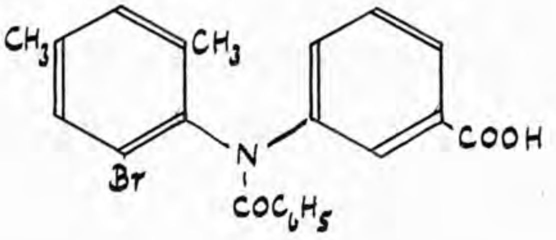
In a second preparation N-2'-bromo-4':6'-dimethylphenylbenzimino-m-carbomethoxyphenyl ether was obtained with a melting point of 140 - 141° after careful purification by crystallization from acetone. Although the higher melting point would seem to indicate that this substance was purer than the previous sample, the analysis results did not agree with the required percentage composition. The results for carbon and bromine were in this case lower than the required figures.

Methyl N-benzoyl-2'-bromo-4':6'-dimethyldiphenylamine-3-carboxylate (XVll) was prepared according to the general method involving the Chapman rearrangement of the above benzimino ether (Chapman, J.,1929,569).

XVll

The benzimino ether isomerised at a temperature of 270 - 280°, giving a product which was purified by repeated crystallizations from ethanol. The first preparation yielded a sample of methyl N-benzoyl-2'-bromo-4':6'-dimethyldiphenylamine-3-carboxylate which melted at 167 - 169° with slight preliminary softening. The ester prepared in a second reaction melted at 173 - 174° with no previous softening. The analysis results of both samples showed a low content of carbon and bromine.

N-Benzoyl-2'-bromo-4':6'-dimethyldiphenylamine-3-carboxylic acid (Vll) was prepared from the hydrolysis of the methyl ester using ethanolic sodium hydroxide solution.



Vll

The ester melting at 167 - 169° gave an acid which crystallized from ethanol in small colourless prisms and had a melting point of 213 - 215°. Analysis gave a high value of carbon.

The product from the hydrolysis of the ester melting at 173 - 174° was low-melting although it was completely soluble in sodium bicarbonate solution and was reprecipitated on the addition of dilute hydrochloric acid. It was boiled under reflux with ethanolic sodium hydroxide solution for a total time of four hours, but after purification by crystallization from ethanol the melting point was only 177 - 179°. The melting point was considerably lowered when the product was mixed with a sample of the methyl ester. After recrystallization from benzene the acid melted at 178 - 179°. A sample of the acid was melted and seeded with the acid melting at 213 - 215°, but the solid obtained did not show any significant change in melting point. The analysis result for this low-melting acid was very unsatisfactory.

In the preparation of the last three compounds the first reaction was carried out using as a starting material benz-5-bromo-m-4-xylidide which had been stored for some weeks.

The second preparation of each compound was carried out from freshly prepared starting material.

The results of analyses of compounds obtained in this synthesis were highly unsatisfactory. Solvation could not account for the results, nor could they be explained by loss of bromine from the benzene nucleus in which it is substituted by some side reaction. The values for bromine are not consistently low. Acridone formation under the conditions of the Chapman rearrangement would be unlikely to occur with the carboxylic acid group in the 3-position. In any case it could not account for the results of the imino ether analysis. It would appear that the cause of these irreproducible analyses results cannot be explained.

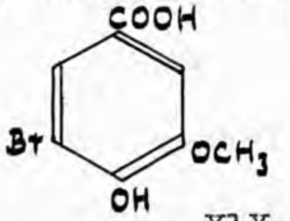
Professor E.E. Turner (private communication) also carried out the synthesis of N-benzoyl-2'-bromo-4':6'-dimethyldiphenylamine-3-carboxylic acid and obtained variable and inexplicable analyses results for the products of the three final stages.

An attempt was made to prepare crystalline salts of the acid with the alkaloids brucine, quinine, quinidine and cinchonidine but no crystalline salts were obtained. No mutarotation was observed with the acid and cinchonidine or quinine in solvent 'X'. Since complete proof that the acid had been obtained was not available, these negative results are not of great significance.

From the ease with which the synthesis could be carried out it would appear that N-benzoyl-2'-bromo-4':6'-dimethyldiphenylamine-3-carboxylic acid probably was synthesized, but in the absence of complete proof from the analyses results further work on this compound was abandoned.

Vanillic acid (XVlll) was brominated by the usual method using bromine in glacial acetic acid in the presence of sodium acetate (Robertson, J.,1908,798). The product was best isolated by the removal of most of the solvent by distillation under reduced pressure, followed by dilution of the residue with water.

5-Bromovanillic acid (XlX) was crystallized from aqueous methylated spirits and had a melting point of 233 - 235°. Raiford and Potter (J.Amer.Chem.Soc.,1933,55,1684) give the melting point as 231 - 232°.

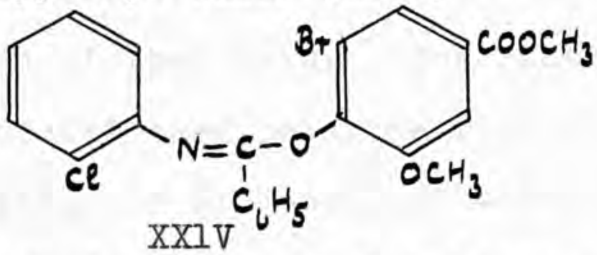


XlX

The methyl ester was prepared by heating the acid under reflux with methanol and concentrated sulphuric acid. The reaction mixture was poured into water when methyl 5-bromovanillate (XX) was obtained. After crystallization from aqueous methanol the pure ester melted at 154 - 156°.

o-Chlorobenzanilide (XXll) was prepared by heating o-chloroaniline and benzoyl chloride at a temperature of 130 - 140° until the mixture was homogeneous. On cooling, a solid was obtained which was well ground with hot water to remove benzoic acid, and filtered hot. The residual o-chlorobenzanilide had a melting point of 103 - 105° after crystallization from aqueous methylated spirits. It was easily converted into its imino chloride (XX111) when heated with phosphorus pentachloride for half an hour at 60°. After removal of phosphorus oxychloride the benz-o-chloroanilide-imino chloride was distilled under reduced pressure at a temperature of 170 - 173° / 4mm. It was a pale yellow oil.

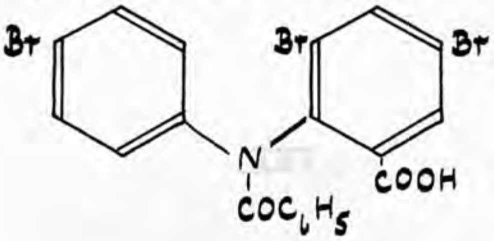
The preparation of N-o-chlorophenylbenzimino-6-bromo-2-methoxy-4-carbomethoxyphenyl ether (XX1V)



XX1V

could not be accomplished since methyl 5-bromo-vanillate was insoluble in the sodium ethoxide solution. It did not dissolve on the addition of excess ethanol. It appeared to change form and become more amorphous, but not even the finely divided compound would dissolve. After the reaction mixture had stood overnight, water was added. The only solid obtained was recovered methyl 5-bromovanillate.

d N-Benzoyl-4:6:4'-tribromodiphenylamine-2-carboxylic acid was prepared by second order asymmetric transformation of the racemic acid (1V) with cinchonidine.



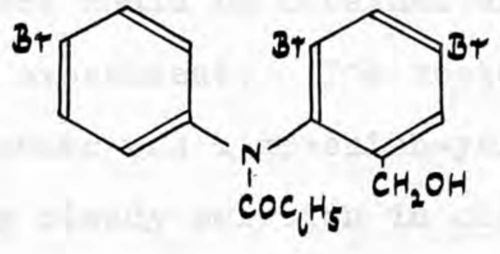
1V

The acid and cinchonidine were warmed in acetone until a solid began to separate out when the mixture was immediately chilled to -15°. After standing at this temperature for one hour the solid was filtered off. A further portion of solid was obtained from the mother liquor on standing.

The free acid was obtained by grinding the cinchonidine salt with pyridine at -15°. The acid was precipitated from the solution by means of hydrochloric acid.

Both crops of the cinchonidine salt of the acid gave dextrorotatory samples of free acid. The racemization of the free acid could be followed polarimetrically. This method of optical activation of N-benzoyl-4:6:4'-tribromodiphenylamine-2-carboxylic acid was similar to that originally used by Jamison and Turner (J.,1938,1646) but these workers effected a resolution of the acid, not a second-order asymmetric transformation.

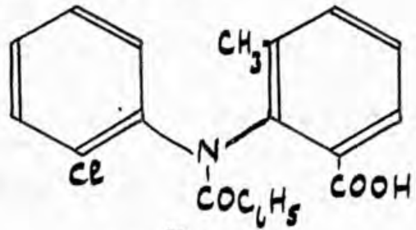
Optically active N-benzoyl-4:6:4'-tribromodiphenylamine-2-carboxylic acid was treated with lithium aluminium hydride in an attempt to form the corresponding alcohol (XXV).



XXV

The reduction was carried out as rapidly as possible at as low a temperature as possible in order to lose the minimum amount of optical activity. The reaction vessel was placed in a bath of methylated spirits and solid carbon dioxide, so that the internal temperature was kept well below -10°C. The acid was added as a solid in order to decrease the time in which it was in solution. An apparent reaction took place immediately. The product was isolated as rapidly as possible using the usual technique. All apparatus and solutions were kept cold. Operations which were impossible to carry out in a cold-bath were performed as quickly as was practicable. The ether layer containing the product was not washed but was stored at a temperature of -20° to -30° until all the ether had been evaporated off. Evaporation of the ether was achieved by allowing the solution to drop slowly through a dropping funnel, whose stem had been drawn into a fine capillary, into an evaporating basin held in an evacuated desiccator. Much time was lost at this stage because the fine capillary soon became blocked. The ethereal solution containing the product could be obtained within ten minutes of the start of the experiment. The residue after evaporation of the ether was a greenish-yellow gummy solid which gave a slightly cloudy solution in chloroform. Its chloroform solution was too dark to be examined polarimetrically.

Attention was then given to the finding of the optimum conditions for the reduction of an acid of the N-benzoyl-diphenylamine carboxylic acid series. The reduction of racemic 2'-chloro-N-benzoyl-6-methyldiphenylamine-2-carboxylic acid (X) was studied.



X

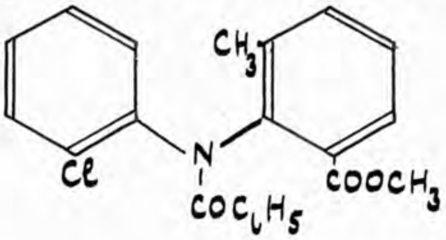
The acid was added as a solid to a suspension of lithium aluminium hydride in dry ether at a temperature of -30°. The experiment was again carried out in the shortest possible time, keeping all solutions and apparatus cold. The acid was insoluble in ether and reaction did not take place at this low temperature. Unchanged 2'-chloro-N-benzoyl-6-methyldiphenylamine-2-carboxylic acid was obtained from the reaction mixture. It had a melting point of 197 - 199°.

The experiment was repeated at a temperature just below 0°C and the reaction mixture was maintained at this temperature for three hours before being treated in the usual manner. Again no reduction of the acid occurred.

In a third experiment, carried out at room temperature, the acid was added as a suspension in dry ether to the lithium aluminium hydride. The reaction mixture was boiled under reflux for two hours, but again unchanged acid was obtained. In a final experiment the acid was placed in the thimble of a Soxhlet extractor and was extracted with ether for twelve hours, the ethereal solution falling into a suspension of lithium aluminium hydride. Although all the acid eventually dissolved, the solid isolated from the reaction mixture was again unchanged acid.

The acid isolated from these last two experiments which involved heating the reaction mixture, did not melt sharply at 197 - 199°, as did the other samples of recovered acid. The melting point of the acid recovered from the third experiment was 194 - 199°, that of the acid from the final experiment 191 - 197°. Mixed melting points with recrystallized 2'-chloro-N-benzoyl-6-methyldiphenylamine-2-carboxylic acid were 197 - 203° and 194 - 200° respectively. The melting point of the original acid was 201 - 203° although Jamison and Turner (J.,1940,264) recorded the melting point as being 197 - 198° and noted that the melting point varied with the rate of heating. This may account for the slight discrepancies in the melting points observed in the present work, although in the last two experiments partial reduction may have occurred.

It is obvious that direct reduction of 2'-chloro-N-benzoyl-6-methyldiphenylamine-2-carboxylic acid with lithium aluminium hydride was not satisfactory. It is well known that reductions with this hydride occur readily with the esters of carboxylic acids, and the methyl ester of the above N-benzoyldiphenylamine carboxylic acid was accordingly prepared. The acid was added to a freshly prepared ethereal solution of diazomethane. The solid did not apparently dissolve, although nitrogen was evolved. On removal of the ether, however, the residual solid was found to have a melting point of 168 - 169° after crystallization from methanol. Jamison and Turner (loc.cit.) obtained methyl 2'-chloro-N-benzoyl-6-methyldiphenylamine-2-carboxylate (XXVl)



XXVl

during the preparation of the acid, which had a melting point of 168 - 169°.

The ester was reduced by lithium aluminium hydride. The ester was insoluble in ether at room temperature, and was added to the suspension of hydride as a suspension itself in dry ether. The reaction mixture was boiled under reflux for two hours until all the ester had dissolved. The product was a viscous liquid which could not be induced to solidify. It was left in the cold for some weeks.

The insolubility of 2'-chloro-N-benzoyl-6-methyldiphenylamine-2-carboxylic acid in volumes of ether small enough to be of practical use makes the direct reduction method unsuitable for its optically active form. Although the formation of the methyl ester of an optically active form of the acid could probably be accomplished at low temperatures without great loss of optical activity, the relative insolubility of the ester itself in ether would prove a handicap. If the reduction mixture required to be heated under reflux any optically active product would most likely undergo racemization.