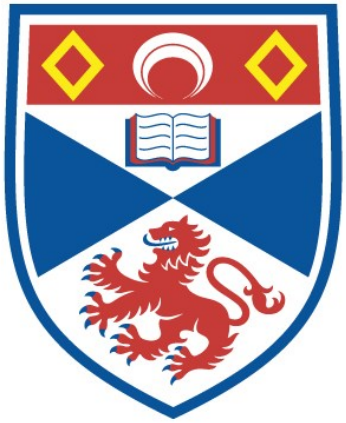
# STEREOCHEMICAL RESEARCHES OF REDUCED QUINOLINES

**Walter Lamb Davidson**

**A Thesis Submitted for the Degree of PhD**
**at the**
**University of St Andrews**



**1949**

"STEREOCHEMICAL RESEARCHES ON REDUCED QUINOLINES"

being a Thesis

presented by

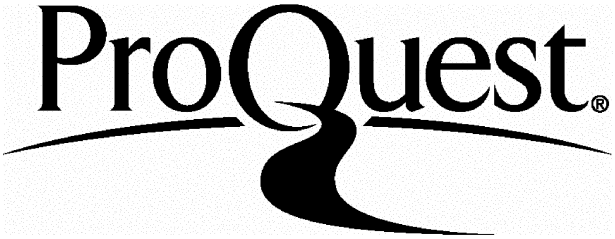
WALTER LAMB DAVIDSON, B.Sc.,

to the

UNIVERSITY OF SAINT ANDREWS

in application for the

DEGREE OF DOCTOR OF PHILOSOPHY



## DECLARATION

I hereby declare the following Thesis to be a record of results of experiments carried out by me, and furthermore that the Thesis is my own composition, and has not been previously presented for a Higher Degree.

The investigation was conducted in the Chemical Research Laboratory of the United College, under the direction of Professor John Read, M.A., Ph.D., Sc.D., F.R.S.

Signed.

Date.

## CERTIFICATE

I hereby certify that Mr. W.L. Davidson, B.Sc., has spent nine terms at Research Work under my supervision in the Chemical Research Laboratory of the University of St. Andrews, that he has fulfilled the conditions of Ordinance No. 16 (St. Andrews), and that he is qualified to submit the accompanying Thesis in application for the Degree of Doctor of Philosophy.

Director of Research

## UNIVERSITY CAREER AND RESEARCH EXPERIENCE

I entered the United College, University of St.Andrews, in October 1942, and pursued the recognised course for graduation in Science, and graduated B.Sc. in Chemistry and Natural Philosophy in June 1945. In June 1946 I was awarded Post-graduate Honours of the Second Class in Chemistry.

I was admitted as a Research Student in October 1946, having obtained a Grant from the Department of Scientific and Industrial Research. This Grant was held by me until September 1948, thereafter I held a Post-graduate Scholar-:ship awarded by the University of St. Andrews until the termination of my studies in St. Andrews in December 1948.

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EXPERIMENTAL

# PART I.

# A CONTRIBUTION TO THE STEREOCHEMISTRY OF

# TERVALENT NITROGEN

# INTRODUCTION

The chapter of stereochemistry which deals with the attempted resolution of saturated tervalent nitrogen compounds is a long and interesting one, but is as yet incomplete. The problem has been attacked in many ways; but despite the great amount of work which has been carried out the failure to achieve the resolution of such compounds has been complete.

The problem is essentially a simple one. If the nitrogen atom has a tetrahedral configuration then an unsymmetrically substituted amine $NR_1R_2R_3$ should be capable of existing in optically isomeric forms. This can be expressed diagramatically either by representing the nitrogen atom by a tetrahedron with three of the apices occupied by the radicals and the fourth by the remaining unshared pair of electrons (figs. 1a, 1b.), or the unshared pair of electrons can be ignored and the compounds represented by a pyramid (figs. 1c, 1d.). Both have been used in the literature but represent identical viewpoints.

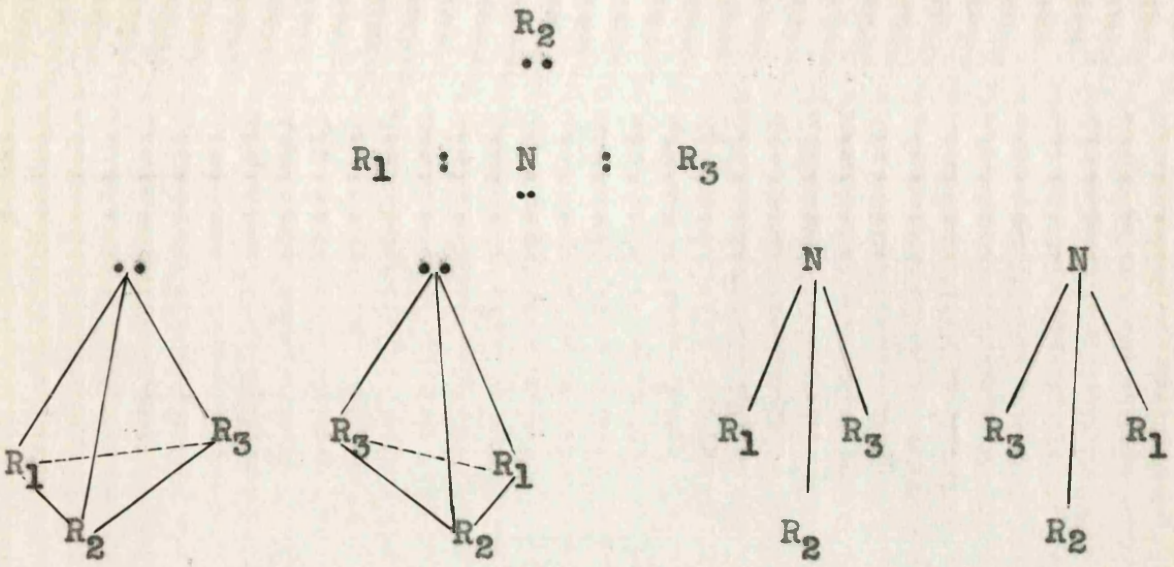



fig.1a. fig. 1b. fig. 1c. fig. 1d.

The alternative to this type of configuration is a planar one in which the valencies are disposed at an angle of 120° to each other. There exists, however, a consider-:able amount of evidence to show that the tervalent nitrogen atom has a non-planar configuration and that a planar configuration is impossible. The first part of the evidence comes from the examination of the structure, ease of formation and stability of certain organic compounds. This can be called the chemical evidence and is of compara-:tive long standing. Secondly, the determination of a number of physical properties of ammonia and simple amines has eliminated the possibility of a planar configuration for these compounds/

compounds/. This can be called the physical evidence and dates from about 1926. Thirdly and lastly, the modern theory of directed valence developed from 1930 onwards: based on the wave theory of the electron, this requires a non-planar configuration for the tervalent nitrogen atom.

The Chemical Evidence.

The ease of formation and stability of the nitriles and diazonium salts makes it clear that the three nitrogen valencies cannot be distributed in the same plane. In the former (fig. 2), three carbon valencies, known to be tetrahedrally directed are joined to three nitrogen valencies giving rise to a stable structure. It is reasonable, therefore, to assume that the nitrogen has a like distribution of its valencies rather than a planar one. Likewise a study of models of the diazonium salts (fig. 3) shows that a non-planar configuration is necessary for the ease of formation and stability which they possess.

$R-C\equiv N$ $(Ar-N\equiv N)^{+}\ X^{-}$

fig. 2 fig. 3

There is an intimate connection, this time in cyclic systems, between the tetrahedral carbon atom and the tervalent nitrogen atom. The nitrogen atom can replace the tetrahedral group — CH—, as for example in pyridine and benzene, without any loss in stability, just as the group —NH— can be substituted for the tetrahedral group —CH— , as in tetrahydroquinoline and tetra-:hydronaphthalene, with no loss in stability. The nitrogen-containing rings may even show an increased stability over the corresponding /

corresponding carbocyclic compounds. The conception of the planar configuration of the three nitrogen valencies is, therefore, incompatible with the properties of these ring systems, and the nitrogen valency angles must at least almost equal those of the carbon atom.

The nitrogen-rich ring system tetrazole[1] exhibits a stability wholly comparable to other aromatic cyclic systems, and this observation, together with the extreme ease of formation of tetrazole and its derivatives, can only be accounted for by assuming that the nitrogen atoms assume non-planar configurations. Similarly, the quinuclidine ring system (fig. 5) merits attention because of its great ease of formation and chemical resistance. This is indicative of a strainless structure, which, in the case of the quinuclidine ring, can only arise if the nitrogen atom is tetrahedral.

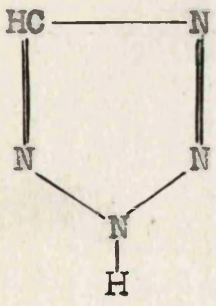



fig. 4

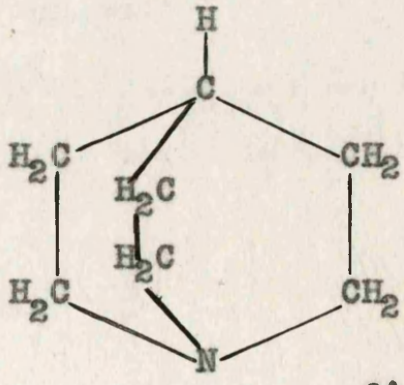



fig. 5

Finally comes a consideration of the stereochemistry of the oximes and related compounds. It is well known that oximes exist in stable <u>syn</u>- and <u>anti</u>-forms. Hantzsch and Werner[2] explained/

explained this fact by extending the theories of van't Hoff on geometrical isomerism to cover the case of the oximes. They postulated that there was no free rotation about the C-to-N double bond and that the hydroxyl group was not symmetrically placed with respect to the carbon and nitrogen atoms, as would be the case if the valencies of the latter were planar. This hypothesis has been completely substantiated. A direct demonstration of its truth was afforded by the investigation of the oxime of cyclohexanone-4-carboxylic acid which, according to the theory of Hantzsch and Werner[2], should exist in enantiomorphic forms. Mills and Bain[3] in 1910 showed this to be the case by achieving a complete resolution of this compound. This work was extended by Mills and his collaborators to cover the benzoylphenylhydrazone and semicarbazone (fig. 6) of cyclohexanone-4-carboxylic[4] acid and later the pyridylhydrazone of cyclohexylene dithiocarbonate[5] and the carboxyphenylhydrazone of β-methyltrimethylene dithiocarbonate[6] (fig. 7)

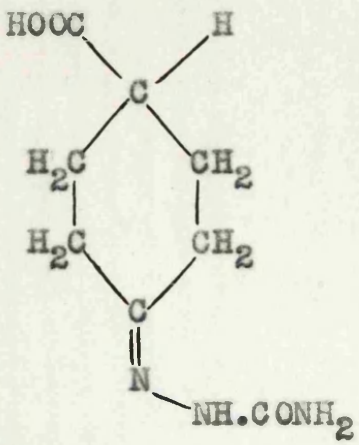



fig. 6

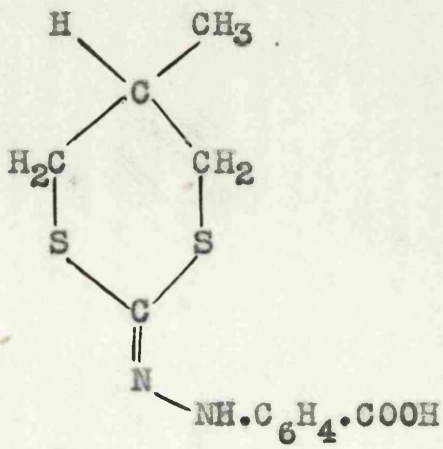



fig. 7

None of these compounds could exist in optically isomeric forms/

forms if the valencies of the doubly-bound nitrogen atom lie in one plane.

The Physical Evidence

The chemical evidence has been obtained from a study of compounds containing a doubly or trebly linked nitrogen atom or in which the nitrogen atom is contained in a simple or complex ring-system. The physical evidence, however, has been derived from measurements carried out on simple amines and in particular on the parent substance ammonia.

Ammonia has been found to have a considerable dipole moment[7], which is most readily explained on a tetrahedral or pyramidal basis. The evaluation of the principal moments of inertia of the ammonia molecule by different methods[8] also shows the molecule to be pyramidal. The height of the ammonia pyramid[9], the H-H and N-H distances[10] and the intervalency angles have been determined with a high degree of accuracy from the infra-red absorption spectrum of ammonia. This work is excellently reviewed up to 1940 by D.M. Dennison[10] in an article on the "Infra-Red Spectra of Polyatomic Molecules".

Electron diffraction measurements on the vapour of trimethylamine[11] and the infra-red absorption spectrum of methylamine[12] both indicate a pyramidal configuration for the nitrogen atom. A study of the infra-red and Raman spectra[13] and the measurement of the dipole moment[14] of hydrazine also uphold/

uphold this configuration.

X-ray measurements carried out on hexamethylenetetramine (urotropin) by various investigators[15],[16],[17] enable a clear picture of its crystal structure to be drawn. The carbon atoms are octahedrally arranged with respect to each other and the nitrogen atoms tetrahedrally; with respect to the carbon atoms the nitrogen atoms lie at the apices of regular pyramids, the other apices of which are occupied by carbon atoms. This structure has been confirmed by electron diffraction measure-:ments carried out by G.C. Hampson and A.J. Stosick[18] on the vapour of hexamethylenetetramine. The study of the crystal structure of ammonia by X-rays[19] also shows the nitrogen atom to be pyramidal. Recently Robertson and his co-workers[20] have obtained excellent electron-density maps for hexamethylene diamine which confirms further a pyramidal structure for the nitrogen atom.

Directed Valency and the Tervalent Nitrogen Atom.

A consideration of the electronic structure of the nitrogen atom in the light of modern developments in the theory of valency is of value in elucidating its stereochemistry. Since the introduction of quantum mechanics in 1926 and the conse-:quent development of the wave theory of the electron, the relationships existing between atomic structure and valency configurations have been greatly clarified. The calculation of the relations between electronic structures and covalency directions has been approached along two lines of attack: namely, the method of localized electron pairs developed by Heitler, London, Pauling and Slater[21], and that of molecular orbitals developed/

developed mainly by Hund and Mulliken[21]. J.H. Van Vleck and A. Sherman[21] in an article on "Directed Valence" outline the development of these theories and show how they are only two initial approximations leading to the same final solution. These calculations involve a great deal of advanced mathematics, but a consideration of some of the results which have arisen from them allows the stereochemistry of the nitrogen atom (among others) to be related to the number of shared and unshared electrons in its valency shell and the electronic sub-groups which they occupy.

It has been established that valency directions are determined by the characteristics of the s and p electrons in the atom. The L shell of an atom, which in the case of nitrogen is the valency shell, is made up of one s-orbital and 3 p-orbitals; the p-orbitals have their axes of symmetry at right angles to each other and are not so stable as the s-orbital. Each orbital, by the Pauli Exclusion Principle, can be occupied by only two electrons which have paired spins. An s-electron acting as a valency electron can form a bond equally well in any direction as it has a centro-symmetric charge cloud. A p-electron on the other hand is strongly directional when it forms a covalent bond. This result arises from the concentration of the charge cloud of the p-electron along its axis of symmetry, in which direction pure p-bonds are formed. By applying these consideration alone to the nitrogen atom a preliminary configuration for the ammonia molecule can be inferred.

The/

The valency shell of nitrogen has the principal quantum number n = 2, and so consists of one 2s orbital and three 2p orbitals. These orbitals are occupied by five electrons. Two of the electrons are s-electrons with paired spins, and completely occupy the 2s orbital (Pauli Exclusion Principle). The remaining three electrons are distributed equally between the three 2 p-orbitals, and in the tervalent state have unpaired spins. When the nitrogen atom in this state combines with hydrogen to form ammonia the three unpaired p-electrons function as valency electrons and the hydrogen atoms are most strongly attracted in the directions of the mutually perpendicular axes of symmetry of these p-electrons. Thus, if pure s- and p-bonds are formed the ammonia molecule would be pyramidal with intervalency angles of $90^{\circ}$ and with the N-H bonds making an angle of $54.7^{\circ}$ with the axis of the ammonia pyramid. The experimental values for these angles are $108^{\circ}$ and $69^{\circ}$ [10]. The discrepancy could be attributed to the repulsion of the resultant positive charges on the hydrogen atoms which arise from the partial ionic character of the N-H bonds, (cf. the well established dipole moment of ammonia). This occurrence would cause a flattening of the pyramid and a corresponding increase in the bond angles.

However, if the quadrivalent carbon atom which has four electrons in the L shell is treated in the same way, the conclusion is that the carbon atom forms three p-bonds at right angles to each other and a fourth weaker bond, using the s-orbital, in an arbitrary direction. This, of course, is completely contrary to/

to what is known of the carbon atom from organic chemical data, which shows the carbon atom to have a fixed tetrahedral configur-:ation with the bonds equivalent in all respects. The solution to this problem in the Heitler-London-Pauling-Slater theory is found in the idea of hybridization as first introduced by Pauling[22] in 1928. In the carbon atom the strongest bonds which can be formed are not those yielded by electrons in pure 2s or 2p orbitals but by electrons which are in intermediate states occupying hybrid orbitals caused by the hybridization of the s and p wave functions. These hybrid orbitals are tetrahedrally directed, thus giving rise to the well known configuration of the carbon atom.

This theory applies to all elements of the first short period of the periodic table. Thus when these elements form four covalent bonds they have a tetrahedral configuration. If, however, only three bonds are formed as in the tervalent nitrogen atom, two opposing effects appear to be operative. An unshared pair of electrons will tend to occupy the stable s-orbital, leaving the 3 p-orbitals free for the formation of mutually perpendicular bonds, as already discussed. Alternatively, as first suggested by J.H. Van Vleck[23], the five electrons in the valency shell tend to be in four tetrahedral hybrid orbitals, one of the orbitals being doubly occupied by an unshared pair of electrons and the remaining three singly occupied by valency electrons. This disposition gives rise to an intermediate state as indicated by the experi-:mental intervalency angle of 108°.

However/

However, it is abundantly clear from quantum mechanical treatment that the ammonia molecule is non-planar. The config-:uration is normally considered to be that of a regular pyramid.

The combination of the chemical, physical and theoretical evidence for the non-planar distribution of the valencies of the tervalent nitrogen atom has led to the continued search for the theoretically possible optical isomerides, when otherwise the problem might have been abandoned in the face of repeated failures to resolve the compounds of the type $NR_1R_2R_3$. One other factor which has influenced many investigators is what appears to be the anomalous existence of stable optically active forms of the sulphonium salts, sulphinic esters and sulphoxides which have similar electronic configurations to tervalent nitrogen compounds.

Sulphonium Salts, Sulphinic Esters and Sulphoxides.

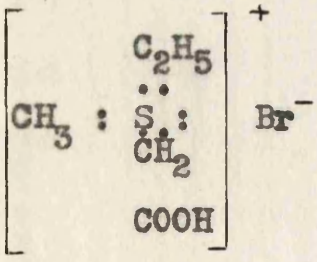


fig. 8

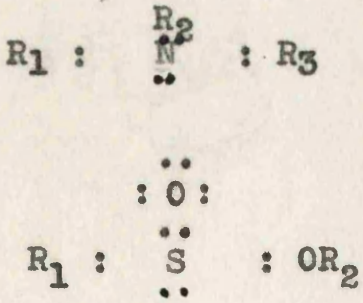


fig. 9

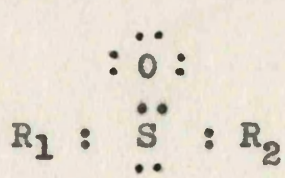


fig. 10

Pope and Peachey[24] in 1900 successfully achieved the resolution of the sulphonium salt (fig. 8), alomost simultaneously with a similar resolution carried out by Smiles[25]. Kenyon[26], Smiles[27] and Wedekind[28] accomplished further resolutions of these salts.

The/

The sulphinic esters (fig. 9) were investigated initially by Phillips[29] who effected a resolution in 1925, obtaining the optically active ethyl ester of p-toluenesulphinic acid and later the optically active n-butyl ester. Phillips[30], Maclean and Adams[31] and Bell and Bennet[32], have effected the resolution of various sulphoxides (fig. 10).

To account for the asymmetry of the sulphinic esters and sulphoxides, the oxygen atom is normally shown as linked to the sulphur atom by a semi-polar bond rather than a double-bond as shown above. However, Sutton[33] and his collaborators no longer consider the non-planar configurations of the sulphoxides and related compounds as decisive evidence against the sulphur-oxygen bond being double. They propose that the stereochemistry of sulphur with a decet of electrons in the valency group is probably based not on the regular tetrahedron but on the trigonal bipyramid like that of quinquecovalent phosphorus[34]. The new configuration does not vary greatly from the old one and still bears a close resemblance to that of the tertiary amines.

## HISTORICAL

The earliest attempts to resolve tervalent nitrogen compounds were unsuccessful for the simple reason that they were concerned with secondary amines of the type $NR_1R_2H$ such as ethyl benzylamine[35], benzylhydroxylamine[36] N-methylaniline[37], tetrahydroquinoline[37], and tetrahydropyridine, which give symmetric cations $(NR_1R_2HH)^+$ on salt formation with optically active acids. When the error was realised attention was turned to amines of the tertiary type $NR_1R_2R_3$. However, completely negative results were obtained by different investigators in attempted resolutions of methylethyl-β- napthylamine[38], methyl-n-propylamine, benzyl-p-nitrobenzyl-hydroxylamine, methylethylaniline and kairoline[39], with d-camphor-10-sulphonic acid and d-α-bromocamphor-π-sulphonic acid.

In the above compounds salt formation with the optically active acids was invariably carried out on the nitrogen atom whose configuration was being investigated. This was considered to be undesirable by certain workers who consequently studied compounds with a group capable of salt formation, remote from the nitrogen atom under observation. Among the compounds of this type to be investigated were methyl-ethylaniline sulphonic acid[40] (fig. 11), N-phenyl-N- naphthylanthranilic acid, and N-phenyl-N-p-tolylanthranilic acid[39] (fig. 12).

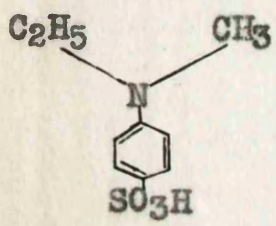



fig. 11

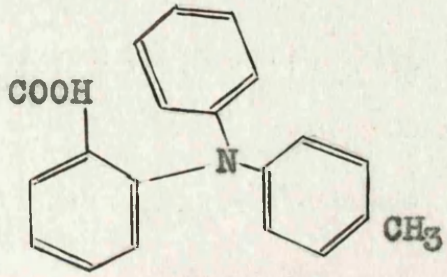



fig. 12

They all contain an acid group and were crystallised with strychnine, quinine and brucine; but fractional crystallisation of these salts gave negative results. Negative results were also obtained from the study of the substituted hydrazines, p-tolyl-:hydrazine[41] (fig. 13), and benzylphenylhydrazine[42] (fig. 14) whose d-tartrates, and, in the case of the latter, the d-camphor-10-sulphonate were found to be optically homogeneous.

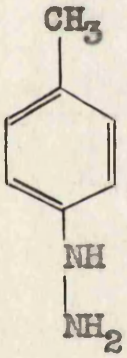



fig. 13

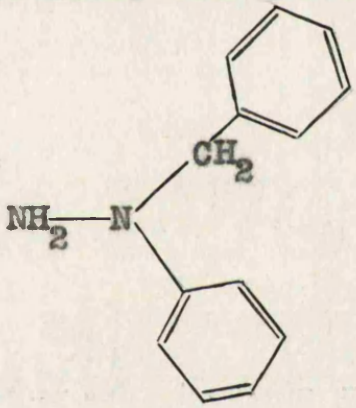



fig. 14

Schreiber and Shriner[43] in their investigations in this field, also carried out salt formation on a group remote from the nitrogen atom whose configuration was being studied. They studied substituted p-phenylenediamines in which the substituent groups were acyl- or sulphonyl-groups (figs. 15, 16). They considered that these groups were likely to be less mobile than alkyl or aryl groups, and therefore more likely to stabilise the configuration of the nitrogen atom. The d-camphor-10-sulphonates of these compounds exhibited anomalous mutarotation; but this was shown by the investigators to arise from the reaction of the primary amino-group with the keto-group of the acid, forming ketimines. Caution, they concluded, must therefore be used in deducing from mutarotation/

mutarotation data alone that resolution of a racemic compound by means of this acid, is taking place.

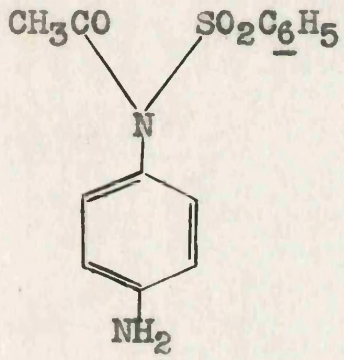


fig. 15

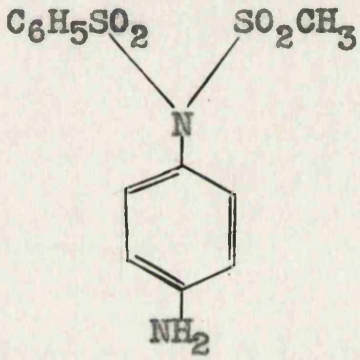


fig. 16

Wedekind and Klatte[44] obtained variations in the rotatory powers of the fractions during the fractional crystallisation of the salts of substituted pyrazolones (figs. 17, 18) with d-camphor-10-sulphonic acid and d-$\alpha$-bromocamphor-$\pi$-sulphonic acid. However, decomposition of the salts gave inactive bases.

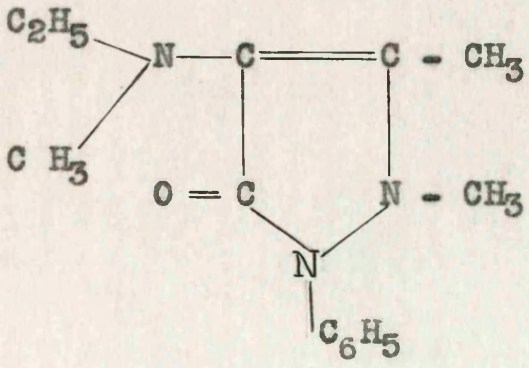


fig. 17

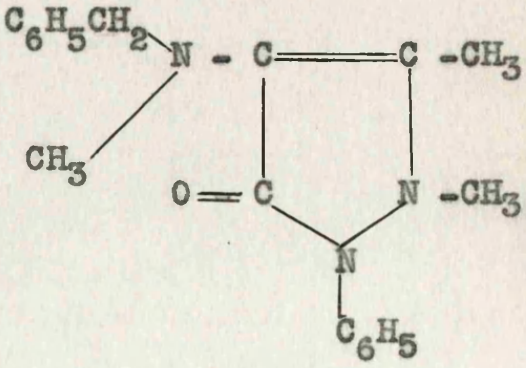


fig. 18

Attention has been drawn above (p.11) to the sulphonium salts, sulphoxides and sulphinic esters, which have been shown to exist in stable optically active forms and which have similar electronic structures to tervalent nitrogen compounds. Meisenheimer and his collaborators[39] noticed that all the sulphonium salts which had been resolved contained the grouping $-CH_2CO-$ and so prepared, and attempted to resolve, certain amines of the type $R_1R_2NCH_2COR$, such as N-methyl-N-ethylacetonylamine and N-phenacyltetrahydroquin-:oline; but no sign of asymmetry was detected. Menon and Peacock[45], noting similarities to the sulphoxides and sulphinic esters, attempted the resolution of certain substituted aniline derivatives without success.

Denner[46] on the other hand, in the belief that the hydroxyl group of the oxime played some part in the production of stable stereoisomeric oximes, regarded certain unsymmetri-:cal hydroxylamines as likely compounds to be resolvable. However, both methylethylhydroxylamine (fig. 19) and methylbenzylhydroxylamine (fig. 20) gave negative results.

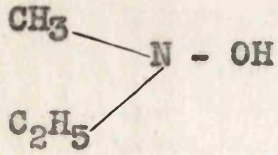


fig. 19

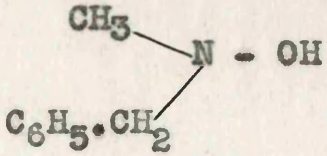


fig. 20

As these hydroxylamines are unsubstituted on the oxygen atom they tend to tautomerize to the aminoxide form and so racemise rapidly. Denner eliminated this possibility in/

in methylbenzyloxy-p-aniline sulphonic acid (fig. 21) but its salts with d-phenylethylamine showed no tendency to separate into isomerides.

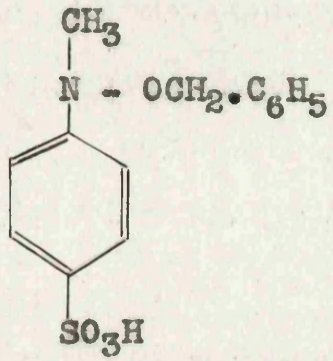


fig. 21

Kipping and Solway[47] tackled the problem from a different angle. They argued that if the nitrogen valencies were not in one plane a primary or secondary amine, when condensed with a dl-acid chloride would give two different dl-substituted amides separable by fractional crystallis-:ation. With the amides obtained by condensing dl-benzyl-:methylacetyl chloride with methylaniline, p-toluidine, phenylhydrazine and benzylaniline, there was no indication of the formation of such isomerides. A possible reason for failure was the formation of a doubly racemic salt $\begin{pmatrix} \underline{d}B\underline{d}A, & \underline{d}B\underline{l}A \\ \underline{l}B\underline{l}A, & \underline{l}B\underline{d}A \end{pmatrix}$. In order to eliminate this possibility, they examined the behaviour of p-toluidine and benzylaniline towards d-benzylmethylacetyl chloride, but obtained no evidence for the formation of the diastereoisomers lB.dA and dB.dA. This work was followed by the examination of the/

the optically active bases d-hydrindamine, l-methylhydrind-:amine, l-menthylamine and l-phenylethylamine with the d-acid chloride, in the hope that the nitrogen atom acting as a centre of asymmetry in a compound already containing two asymmetric centres (fig. 22) would greatly enhance the difference in solubility between the two isomerides and facilitate separation by fractional crystallisation.

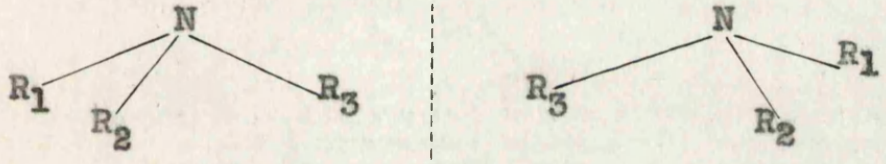



fig. 22

The amides were again found to be optically homogeneous. Similar results were obtained by Frerejacque[47a] using d-camphor-3-sulphonyl chloride with ethylaniline and o- and p-toluidine.

Several investigations, which had as their primary consideration the resolution of bases containing an asymmetric carbon atom, have at the same time yielded negative evidence regarding the resolution of compounds containing an "asymmetric" nitrogen atom. The bases α-methyldihydro-:indole[48] (fig. 23), tetrahydroquinaldine[49] (fig. 24), and p-tolutetrahydroquinaldine[50] contain both an asymmetric carbon atom and an "asymmetric" nitrogen atom; but in the resolution/

resolution and subsequent examination of the active modifi-:cations of these bases, no activity due to the nitrogen atom was found.

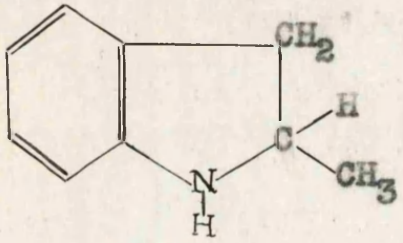



fig. 23

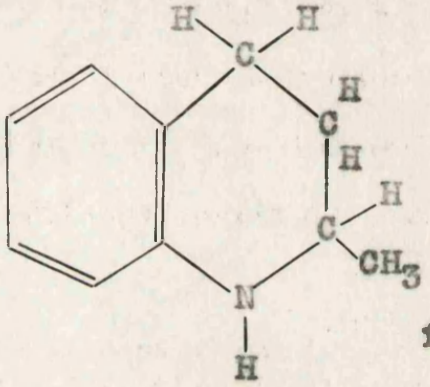



fig. 24

Several investigators have studied compounds in which all of the valencies of the tervalent nitrogen atom are contained in a complex ring system. Jackson and Kenner[51] sought to prepare systems containing a benzene ring and two five-membered rings fused as shown in fig. 25, in order to prove that the nitrogen valencies were coplanar, since they contended that "two five-membered rings associated with a benzene nucleus in the manner contemplated must be coplanar". They failed, however, to form such compounds.

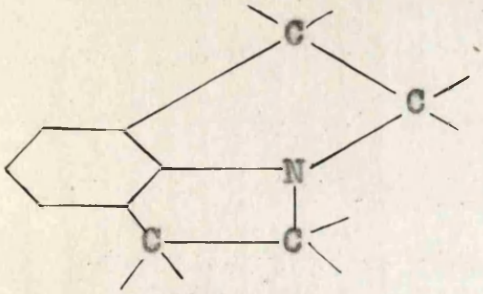



fig. 25

Horwood and Tucker[52], on the other hand, did succeed in preparing analogous compounds, 1:9-phenylene-:carbazole and its derivatives. Contrary to the contention of Jackson and Kenner, however, they considered the strain imposed on the nitrogen valencies by a coplanar configuration of the three/

three central rings to result in a permanent tetrahedral configuration of the nitrogen atom in order to relieve this strain (fig. 26). Consequently, an unsymmetrically substit-:uted compound of this type should be capable of resolution. Attempted resolution of such compounds, e.g. 1:9-phenylene-carbazole-3:6-dicarboxylic acid (fig. 27) failed prematurely as their salts with the alkaloid bases were unstable in solvents.

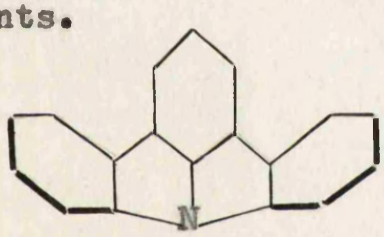



fig. 26

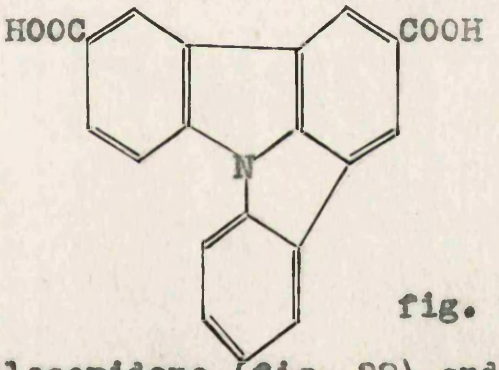



fig. 27

Hayashi[53] examined carbazoleacridone (fig. 28) and its several monosubstituted products, but found no indication of the existence of any optical isomers due to the nitrogen atom.

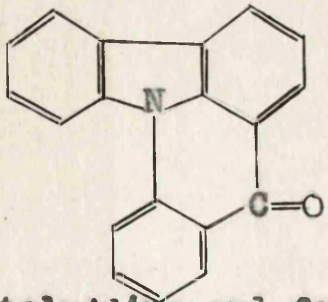



fig. 28

When p-toluidine and formaldehyde are condensed, a complex ring system known as Troeger's base [54], is formed. Prelog and Wieland[55] succeeded in 1945 in resolving this compound/

compound by a chromatographic method using a column of activated d-lactose hydrate as the resolving medium. The asymmetry of this molecule is conditioned by the non-planar orientation of the tervalent nitrogen atoms giving rise to the mirror images (fig29). However, as the structure is a very rigid one, the resolution must be attributed to molecular asymmetry. E. Havinga[56] also reports the resol-:ution of this base by an identical method and obtaining precisely the same results as Prelog and Wieland.

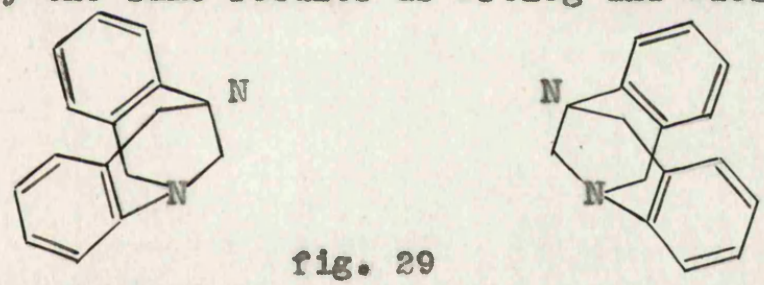



fig. 29

In general it can be said of the study of nitrogen ring-systems in which all the three nitrogen valencies are contained in rings, that no conclusions regarding the valency directions of the nitrogen can be drawn merely from the existence of optical isomers but only from the ease of formation and stability of the compounds.

The most recent work to be undertaken on the problem of the stereochemistry of tervalent nitrogen has been concerned with unsymmetrically substituted ethyleneimines. Meisenheimer and Chou[57] investigated the ethyleneimine (fig. 20), but used optically active acids in their attempted resolution/

resolution thereby destroying any possible asymmetry due to the nitrogen atom by formation of a symmetrical ion $(NR_1R_2H_2)^+$. To avoid the formation of a symmetrical ion Adams and Cairns[58] attempted the preparation of the compound fig. 31, but only oils were obtained. Mole and Turner[59] have also examined ethyleneimines, but like the other investigators encountered a great deal of difficulty in synthesising suitable compounds. Work on these compounds is presumably still in progress.

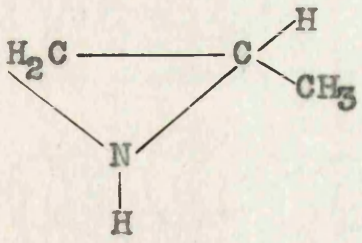
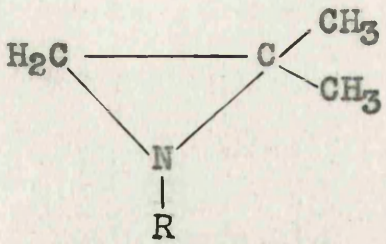


fig. 30



R=d-camphor-10-sulphonyl

fig. 31

This historical survey of the attempted resolutions of tervalent nitrogen compounds is by no means an exhaustive one. It shows, however, the many types of approach which have been made to the problem, and how they have all failed. The reason for many of these failures will be discussed later. Ludwig Orthner[60], Groth and Holmberg[61], Lions and Ritchie[62], Kenner and Stratham[63], Ludwig and Mumm[64], and many others have contributed to the stereochemistry of tervalent nitrogen and there is no doubt that many unsuccessful attempts to resolve these compounds remain unpublished.

## THEORETICAL

By utilising two of the three valencies of the nitrogen atom in the formation of a double bond, Mills and Bain[4] were successful in 1910 in demonstrating optical activity for the oxime of cyclo-:hexanone-4-carboxylic acid (see p.5).


fig. 32.

It is noteworthy, however, that the resolution was achieved as a result of optical activation. The activity of the morphine and quinine salts of the acid was evanescent in character and the rate of racemisation of the salts increased with the weakness of the base from which they were derived. Consequently, during the resolution of the acid, the removal of the morphine d-acid salt or the quinine l-acid salt from the solution left no corresponding amount of the diastereoisomeric salt in the mother liquors; and subsequent separation of the morphine or quinine salts in every instance yielded dextro or laevorotatory ammonium salts/

salts respectively after treatment with dilute ammonia. The optical activity of this compound is, therefore, not of the most stable type (cf. the d-camphorsulphonate of methyl ethyl-n-propyl tin[65], 2:2-diiodo-4:4-dicarboxylicbiphenyl[66], chlorobromomethane sulphonic acid[67]). However, the fact remains that in this compound the nitrogen atom exerts an optically perceptible non-planar configuration.

Since a nitrogen atom participating in a double bond is thus able to exert a 'tetrahedral' configuration, it appears possible that it still might be able to do so when the nitrogen forms part of a larger ring-system (the double bond being virtually a two-membered ring). Before examin-:ing this possibility further, an explanation of the apparent ease of racemisation of compounds of the type $NR_1R_2R_3$ must be considered.

Meisenheimer[39] in 1925 was the first to offer an explanation of the racemisation. He postulated that the non-resolvability of tervalent nitrogen compounds could be explained by assuming that, although the three valencies of the amine Nabc were probably not at an angle of 120° to each other, and hence form two mirror image tetrahedrons, yet they continuously vibrate through a middle position in which/

which they are at 120° to each other in the same plane. This plane becomes a plane of symmetry, so that racemisation continuously goes on and resolution becomes possible only when the isomeric forms are stabilized. This interconversion of the enantiomorphs can be expressed diagrammatically (fig. 33) and was considered to require the application of a relatively small amount of energy to the system.

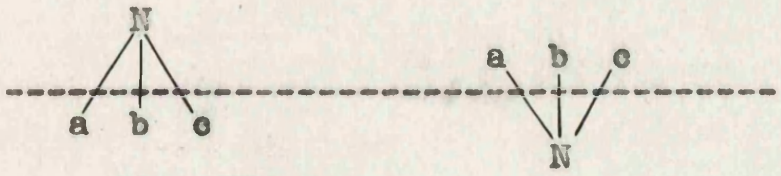



fig. 33

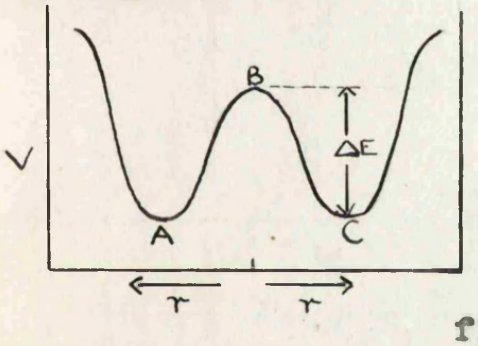
Meisenheimer, however, could produce no experimental or theoretical evidence in support of this mechanism. It was only with the development of infra-red absorption techniques and the examination of the infra-red absorption spectrum of ammonia that such evidence was forthcoming.

The ammonia molecule belongs to the class of symmetric rotators and has a permanent electric moment. It exhibits, therefore, absorption in the far infra-red consisting primarily of a uniformly spaced set of lines. These were first observed by Badger and Cartwright[68], Barker[69], and Wright and Randall[70]. Certain of these lines were observed to have a doublet structure which could have been produced by a vibration in the molecule similar to that postulated

by/

by Meisenheimer.

Dennison and Uhlenbeck[71] represented the energy of the ammonia molecule by a potential curve of the general form fig. 34, showing the relation of the potential energy to the distance of the nitrogen atom from the plane of the hydrogen atoms.




V = potential energy
r = distance of the nitrogen atom from the base of the pyramid.

fig, 34

The two minima are symmetrical and represent the positions of equilibrium of the nitrogen atom on either side of the plane of the hydrogen atoms. The potential function used by these investigators gave a satisfactory explanation of many of the novel features of the infra-red spectrum of ammonia. The vibrational energy levels which fall below the peak B of the potential hill ABC are double and give rise to a doublet structure. Dennison and Uhlenbeck showed that the magnitude of the splitting of each energy level (which gives rise to the doubling) depends only on the dimensions of the molecule and on the magnitude of the vibration frequency involved, while later authors[72] have made more detailed calculations on how the exact height of the potential barrier is related to the observed splitting. The height of the potential barrier gives a value for the energy required/

required for the passage of the nitrogen atom through the plane of the hydrogen atoms which, if small in the case of the compound $NR_1R_2R_3$, would preclude the existence of active modifications of such compounds.

Manning[72a] found the activation energy, that is, the energy necessary to pass over the potential barrier, to be 6kg.-cals./mole. This was lower than the value of Dennison and Uhlenbeck; but Wall and Glockler[72b] and Morse and Rosen[72c] obtained higher values (9.5kg.-cals./mole).

Cleeton and Williams[73] in 1933 observed a broad absorption band in ammonia at atmospheric pressure in the region of 1cm. wavelength, which they correctly attributed to the inversion of the pyramidal ammonia molecule. Bleaney and Penrose[74] have continued work on the spectrum in this region. More accurate methods of resolution have shown that many fine structure lines in the infra-red to be multiplets produced by the double minima potential of ammonia[75]. The exact nature of the potential curve has not been determined according to Bleaney and Penrose who suggest that the expressions used by Manning[72a] and Dennison[75] require modification.

Kincaid and Henriques[76] have evaluated the activation energies for several compounds of the type $R_3N$. They base their/

their computations on the fact, used by the investigators mentioned above, that one of the normal modes of vibration, $\nu_3$, of the molecule brings about a planar configuration. In this vibration the group $R_1R_2R_3$ treated as a rigid equilateral triangle, and the nitrogen atom oscillate with respect to each other, the plane of the triangle always remaining parallel to itself (fig. 35). They use the expression

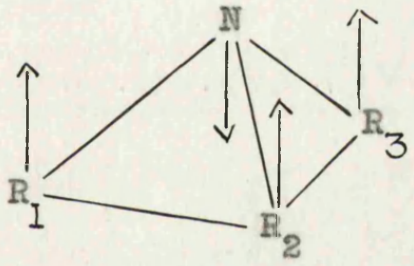



fig. 35

of Wall and Glockler to work out the necessary values for the compounds examined.

For the resolution of a dl-modification of a compound to be detectable at room temperature by the ordinary methods, the intra-molecular first order rate constant for racemis-:ation must be less than $10^{-15}$ sec.$^{-1}$. Thence, from the Arrhenius equation (fig. 36) it is found that E, the activ-:ation energy, must be greater than 25kg.-cals/mole, if resolution at room temperature is to be possible.

$$k = Z.e^{\left(\frac{-\Delta E}{RT}\right)} \approx 10^{13}.\ e^{\left(\frac{-\Delta E}{R.T}\right)}$$

fig. 36.

Their values are inclined to be too high, 11kg.-cals/

mole/

mole. for ammonia, as the expression used gives a pointed rather than a rounded potential hill, leading to inflated results. The relative values of the activation energies of the compounds examined are significant. Trimethylamine, 15kg.-cals./mole., has a value considerably below the limiting value for resolution. Kincaid and Henriques discuss in general compounds of the type $NR_1R_2R_3$, where $R_1$, $R_2$ or $R_3$ is a hydrogen atom or where they are all large saturated aliphatic groups, aromatic groups,.or electro-:negative groups,to show that the activation energy of inversion will certainly not be more than 15kg.-cals./mole. for such compounds. The resolution of these compounds is, therefore, impossible at room temperature. (Similar arguments are elaborated by W.H. Mills[77]).

The value of 15kg.-cals./mole. indicates, however, that resolution should be possible at -80°. Stewart and Allen[78] developed techniques for the attempted resolution of tertiary amines at such a temperature, but these were completely unsuccessful. This result indicates perhaps that the value of 15kg.-cals./mole. for trimethylamine is too great.

N-Methyl-ethyleneimine has a much higher activation energy ,38kg.-cals./mole. Even if this value is too great it is in excess of 25kg.-cals/mole. by a sufficient amount to/

to suggest, that an ethyleneimine, substituted so that the nitrogen atom is the only possible source of asymmetry, should be capable of existing in stable optically active modifications. Such compounds are being investigated (see p.22) but considerable chemical difficulties have been encountered.

The work of Kincaid and Henriques offers an explanation for the stable optical activity exhibited by the sulphonium salts. The activation energy obtained for $(CH_3)_3S^+$ was 100kg.-cals./mole. and so the possibility of the inversion of the molecule taking place under normal conditions is excluded. Jamison, Lesslie and Turner[79] suggest that the difference in optical stability between the sulphoxides and the amines may be due (a) to the larger size of the sulphur atom, (b) to the presence of the strong Sulphur-to-oxygen double bond, and possibly (c) to stabilising resonance between the electrons of the double bond and the pair of unshared electrons which 'occupy' the lower half of the trigonal bipyramid.

The activation energies for compounds of the reduced quinoline type in which the nitrogen atom is contained in a six-membered ring have not been computed. The strain in these compounds is small compared with that in the three-membered/

membered ring of the ethyleneimines and the activation energy is likely to be near the limiting value of 25kg.-cals./mole. If the value for the activation energy of the oxime of cyclohexanone-4-carboxylic acid were known, then it would be clear how far analogies between this compound and such compounds as the reduced quinolines could be taken. However, this is not the case and a study of certain reduced quinolines was undertaken to find if any optical activity attributable to the tervalent nitrogen atom could be detected.

Tetrahedral nitrogen in an ac. - reduced quinoline should give rise to two stereoisomeric derivatives when the H of the -NH- group is replaced by a radical R which stabilises the configuration of the molecule. If R were a symmetric radical the stereoisomers should differ in physical properties, including solubility and melting point, much in the same way as syn- and anti- forms of oximes. If R were asymmetric and optically active, as in the d-oxymethylenecamphor radical the stereoisomers would differ also in optical rotatory power. Such stereoisomers may be denoted as below (fig. 37), the thick and dotted lines indicating positions of R above and below the plane of the paper respectively.

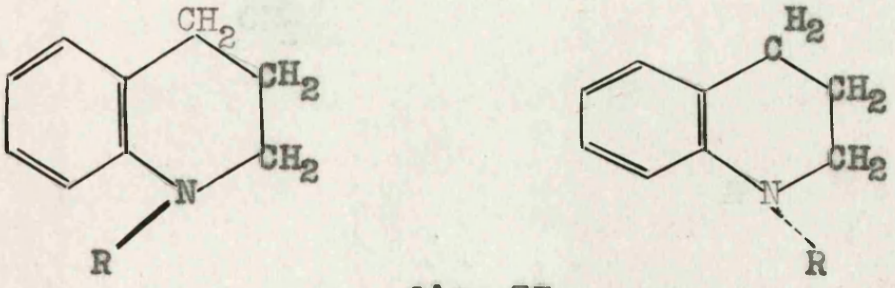



fig. 37.

(1) A beginning was made by examining the condensation product of ac.- tetrahydroquinoline with d-oxymethylene camphor.

Many years ago Pope and Read[80] prepared the condensation products of ac.-tetrahydroquinoline with d- and dl-oxymethylenecamphor. The condensation proceeded readily/

readily under the conditions used and the product from the condensation with d-oxymethylenecamphor crystallised from light petroleum in large, pale yellow prisms, melting at 110°, and having a specific rotatory power of +505° in alcohol. However, these investigators made no attempt to examine the homogeneity of the mother liquors to find if there was any evidence of the existence of a stereo-isomeride due to the spatial distribution about the tervalent nitrogen atom. It appeared possible that the product might contain two distinct substances represented by fig. 37 above.

Consequently, it was decided to condense ac.-tetrahydroquinoline with d-oxymethylenecamphor and to examine the products to find if it was possible to isolate these two forms, or at least to get an indication of the existence of such forms.

Several such condensations were carried out and the crude crystalline condensation product had a specific rotation of +360° in alcohol, this value being 145° below that of the recrystallised material of Pope and Read[80]. Two distinct types of crystals were noticed during the fractional crystallisation, but did not appear to be easily separable by this method. They were, therefore, separated mechanically and had specific rotations of +375.2° and +114° respectively./

respectively. However, on carrying out a repeated fractional crystallisation of part of the crude product the value of Pope and Read, $(\alpha)_D = +505^\circ$ (alcohol) could not be nearly attained, the maximum value being $(\alpha)_D = +390^\circ$.

It was found that the d-oxymethylenecamphor was optically impure. The camphor stock from which it was prepared had been shown by an intial determination of its rotatory power to be pure d-camphor. However, on closer investigation it was found to consist of a mixture of d- and dl- camphor.

A fresh series of preparations of d-oxymethylenecamphor was carried out using pure d-camphor. All the preparations had specific rotations of +198-200° in alcohol, after 30 mins. in agreement with the value of Pope and Read[81]. Four condensations were then carried out with ac.- tetra-:hydroquinoline. The crude products had specific rotations of +492° to 498° in alcohol. At various stages in the isolation of the condensation product small quantities of crystalline material separated out. These were always collected and their optical properties examined but the values of their rotations were never outside the range, from +492 to+498°. The value of the specific rotation of the 24.39 g. of crude product from the condensations was +496.5°/.

496.5°. Although this was only some 9° lower than the maximum value of Pope and Read, the material was subjected to a repeated fractional crystallisation; but even in the lower fractions there was no evidence of a separation into two forms. On both sides of the table of fractionation the specific rotation of the various fractions rose to +509°. The highest value for any fraction was +511°.

It would appear, then, that d-oxymethylenecamphor in condensing with ac.- tetrahydroquinoline does not give rise to the two postulated diastereoisomers, or if they are formed that they are easily interconvertible by the inversion of the molecule, as already discussed (p.25). The possib-:ility that the configuration of the molecule had been stabilised completely in one of the two possible positions was eliminated by fusing some of the condensation product in a crucible; the optical rotatory power of the compound remained unchanged during this process. This would not have been the case if the compound had been the d-oxymethy-:lenecamphor derivative of one of the two postulated active modifications, as racemisation would have undoubtedly occurred. It seemed possible that some other optically active reagent, such as an optically active acid chloride, might yield a more favourable result.

(2)/

(2) Investigations were thus begun on the condensation product of ac.-tetrahydroquinoline and d-camphor-10-sulphonyl chloride. This condensation was carried out in dry pyridine. A dark red solution was obtained on pouring into an excess of acid, and the red crystalline compound obtained therefrom was obtained colourless only after repeated treatment with norit in boiling alcohol. It was not considered advisable to carry out this repeated treatment with a compound which might show a rather delicate type of optical activity and further, the process was too lengthy. Other methods of carrying out the condensation were, therefore, considered.

A Schotten-Baumann reaction was carried out with little success. This was followed by a condensation utilising excess of the ac.-tetrahydroquinoline itself to remove the hydrochloric acid produced in the reaction. This method proved successful, and good yields of colourless condensation products were obtained.

A fractional crystallisation of the d-camphor-10-sulphonyl-ac.-tetrahydroquinoline was then carried out. The optical rotations were taken in chloroform. The results showed a decrease from $+26^{\circ}$, the specific rotation of the crude material, to $+24^{\circ}$ on both sides of the fraction table. It was observed that there was an apparent mutarotation taking place. The apparent falling away of the angle of rotation/

rotation was attributed, after investigation, to the time taken for the chloroform solution to reach a stable state. The angle of rotation was small and the results of the fractional crystallisation were interpreted as showing that the d-camphor-10-sulphonyl-tetrahydroquinoline was optically homogeneous.

(3). A further condensation was attempted with l-methoxy-:acetyl chloride but the product was a dark brown oil which would not crystallise.

(4). Since the methods already described of carrying out condensations of ac.- tetrahydroquinoline with equivalent amounts of d-oxymethylenecamphor or an optically active acid chloride did not yield positive results, it was decided to introduce the idea of reaction velocities. Pope and Read[80] found that dl-ac.-tetrahydroquinaldine could be resolved with oxymethylenecamphor only by taking advantage of the different reaction velocities of the d- and l- forms of the base with active oxymethylenecamphors. Conceivably there might be a similar inhibition with ac.-tetrahydro-:quinoline. However, when ac.-tetrahydroquinoline (2.5 mols.) was treated with d-oxymethylenecamphor (1 mol.) in the usual way the residual base was optically inactive and the condensation product gave specific rotations practically identical with those obtained previously.

(5)/

(5). At this stage it was decided to leave the examination of unsubstituted ac.-tetrahydroquinoline, as the results showed no promise of providing evidence of any optical activity due to the saturated tervalent nitrogen atom. Certain substituted tetrahydroquinolines have already been examined by different investigators. As mentioned (p. 16 ) Meisenheimer and his collaborators examined certain N-substituted tetrahydroquinolines. They found in every case that the d-$\alpha$-bromocamphor-$\pi$-sulphonates of the compounds investigated showed no tendency to separate into isomerides. The $\alpha$-substituted tetrahydroquinoline, tetrahydroquinaldine, was investigated by Pope and Read[49]. They were principally concerned with the investigation of the optical activity arising from the asymmetric $\alpha$-carbon atom; but during their work they found no trace of optical activity which could be attributed to the "asymmetric" nitrogen atom rather than to the asymmetric carbon atom.

(6). Attention was, therefore, turned to the stereochemical aspects of more highly substituted ac.-reduced quinolines, in particular to 2:2:4-trimethyl-1:2-dihydroquinoline (fig. 38)

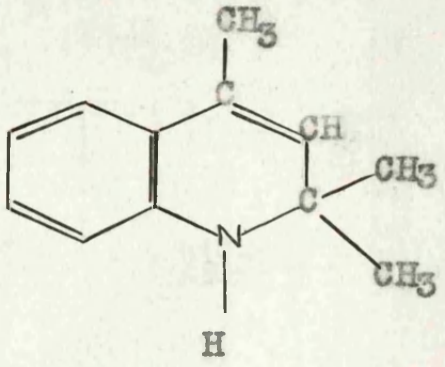



fig. 38

It seemed likely that the presence of the two methyl groups in the 2- position might introduce a mechanical blocking effect, leading to a spatial stabilisation of the third group attached to the neighbouring tervalent nitrogen atom. If, as will be discussed later, there is resonance between the unshared pair of electrons of the nitrogen atom and the aromatic ring of the quinoline, this would lead to a flattening of the nitrogen valencies and an aid to inversion. The presence of two methyl groups in the 2-position might in a suitably N - substituted quinoline inhibit this resonance by steric interaction.

(a) Condensation with d-oxymethylenecamphor was first of all carried out. Test-tube experiments in the absence of solvents showed that pure 2:2:4-trimethyl-1:2-dihydro-:quinoline did condense with d-oxymethylenecamphor at the temperature of the boiling water-bath. Moreover, condensations carried out under precisely the same conditions as for tetrahydroquinoline in varying concentrations of acetic acid, yielded only small amounts of a yellow gum. The yield was greatly increased by concentrating the reaction mixture for some 45 minutes on the water-bath.

Two condensation products were isolated. The first, a yellow powder, exhibited a specific rotatory power in 0.5% alcoholic solution, $(\alpha)_D^{18} = +99.6^\circ$. By a careful fractional crystallisation this compound was shown to be optically homogeneous. The second product was a thick/

thick mobile resin with a specific rotatory power $(\alpha)_D^{18}$ = + 211.6°.

Both compounds gave analysis figures in agreement with those calculated for the d-oxymethylenecamphor derivative of 2:2:4-trimethyl-1:2-dihydroquinoline. These two compounds were not, however, the diastereoisomers dA.lB and dA.dB. Molecular weight determinations of the gum proved it to be the d-oxymethylenecamphor derivative of the dimer of the base, or of a mixture of the dimer and higher polymers. Under the acid conditions of the reaction, part of the 2:2:4-trimethyl-1:2-dihydroquinoline had reacted directly with the d-oxymethylenecamphor, but the remainder had undergone polymerisation before reacting. No attempt was made to carry out the condensation under conditions which would exclude polymerisation as sufficient of the derivative of the monomer was obtained to ascertain of its optical homogeneity.

(b). The 2:2:4-trimethyl-1:2-dihydroquinoline was condensed next with d-camphor-10-sulphonyl chloride, As brilliantly coloured solutions were obtained in pyridine, the condensation was carried out in excess of the base; no condensation product was isolated. The condensation was then attempted by refluxing the base and the acid chloride in light petroleum for 4 hours, but again there appeared to/

to be no reaction. There was also no condensation in quinoline at 150-170°.

When the condensation was attempted in excess of the base at temperatures from 120-170° methane was lost and some of the base assumed a totally aromatic structure. Long yellowish crystals of the hydrochloride of the result-:ing 2:4-dimethylquinoline separated above the reaction mixture. No condensation product could be isolated from the deeply coloured reaction mixture, but a certain amount of condensation must have occurred as evidenced by the formation of hydrochloride. There may also have been further decomposition as an extremely evil odour developed, which could not be explained by the occurrence of condens-:ation or the elimination of methane.

d-Camphor-10-sulphonyl chloride condenses readily with tetrahydroquinoline; the reaction also proceeds with tetra-:hydroquinoline. However, the introduction of a second methyl group into the 2-position seems effectively to hinder the entrance of the bulky sulphonyl group into the molecule. The deep colours produced during the attempted condensations would probably have rendered the polarimetric examination of the amide impracticable had it been formed and isolated.

(c). The condensation product of 2:2:4-trimethyl-1:2-dihydroquinoline and l-menthoxyacetyl chloride was obtained as/

as a dark green oil which would not crystallise. No accurate determination of its optical rotatory power could be made because of the deep colour.

(7). It did not seem probable that 2:2:4-trimethyl-1:2-dihydroquinoline would give rise to suitable N-substit-:uted derivatives with other optically active reagents, and attention was now turned to its dihydro-derivative 2:2:4-trimethyl-1:2:3:4-tetrahydroquinoline (fig. 39).

This compound was obtained by the catalytic hydrogen-:ation of 2:2:4-trimethyl-1:2-dihydroquinoline using a palladised strontium carbonate/catalyst. The reduction product was obtained as a colourless crystalline compound, m.p.40-41.5°.

It is an externally compensated base with an asymmetric carbon atom in the 4-position. As the pyridine ring is fully reduced it cannot undergo polymerisation.

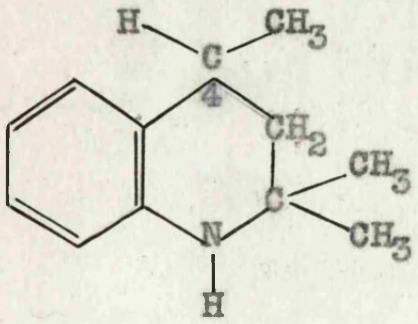



fig. 39

When this compound is condensed with an optically active reagent such as an optically active acid chloride, two/

two pairs of diastereoisomeric compounds should be formed. One pair would arise from the asymmetric carbon atom and the other pair from the "asymmetric" nitrogen atom.

(a). The d-oxymethylenecamphor derivative was investigated first of all. The product of the condensation was a thick yellow gum. This gum would not crystallise completely; from certain solvents it separated along with a number of well-developed crystals. It was found impossible to separate the two materials.

It seemed probable that the two compounds were the diastereoisomers dA.lB and dA.dB. due to the assymetric carbon atom. Pope and Read[80] succeeded in separating the corresponding diastereoisomers of tetrahydroquinaldine by taking advantage of the different reaction velocities of the d- and l-forms of the base with d-oxymethylenecamphor. Similar experiments to those of Pope and Read were carried out with 2:2:4-trimethyl-1:2:3:4-tetrahydroquinoline but no separation was achieved. The condensation product was a homogeneous gum with a specific rotatory power identical with that of the condensation product of equivalent quantities of the base and d-oxymethylenecamphor. No conclusions regarding the stereochemistry of the tervalent nitrogen atom or of the molecule as a whole could be drawn from this reaction.

(b). It did not seem likely that 2:2:4-trimethyl-1:2:3:4-tetrahydroquinoline/

1:2:3:4-tetrahydroquinoline would condense with d-camphor-10-sulphonyl chloride because of the blocking effect of the methyl groups in the 2-position. This was shown to be the case. During a number of condensations carried out under fairly vigorous conditions no trace of the amide was detected. An almost complete range of spectral colours was obtained during the reaction and the attempted isolation of a product.

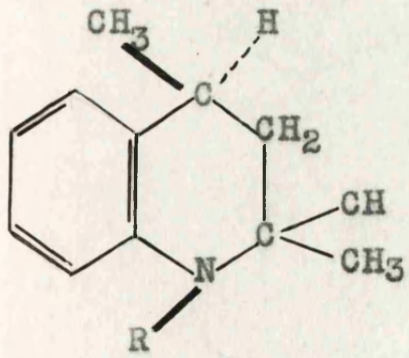
(c). The third optically active reagent to be condensed with 2:2:4-trimethyl-1:2:3:4-tetrahydroquinoline was l-menthoxyacetyl chloride. The condensation proceeded readily in pyridine on the water-bath and the amide separated on pouring into an excess of dilute hydrochloric acid as a yellow gum.

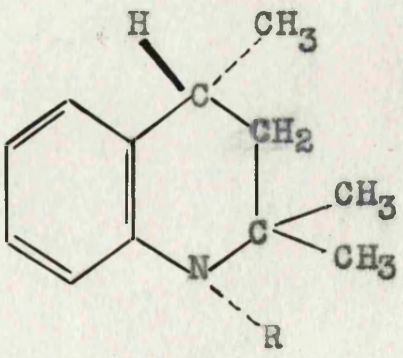
The gum would not crystallise and it was purified by distillation at greatly reduced pressures, of the order of 0.07 mm. It appeared to distil on to the finger of a sublimation apparatus in separate fractions. These fractions had specific rotations of $-80^{\circ}$, $-79^{\circ}$, $-59^{\circ}$ and $-30^{\circ}$, respectively, as compared with $-60^{\circ}$ for the crude material. The lowest fraction was shown by analysis to be impure; and the possibility that a partial separation of the diastereoisomers due to the carbon atom was taking place was removed on the subsequent preparation of l-menthoxyacetyl-l-2:2:4-trimethyl-1:2:3:4-tetrahydroquinoline. During the preparation of the latter compound optical

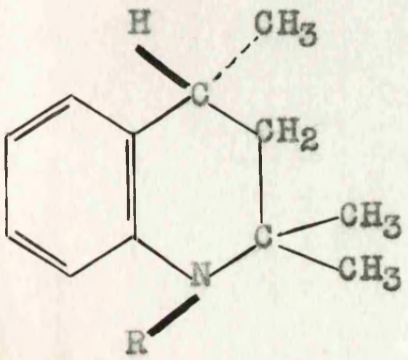
inversion/

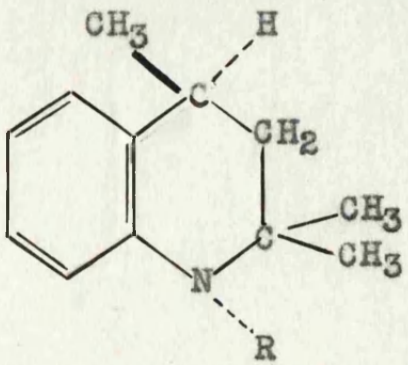
inversion occurs and it is dextrorotatory with a specific rotatory power in alcohol $(\alpha)_D = +97.3^\circ$. The condensation of the racemic base with l-menthoxyacetyl chloride was repeated, but as the product was never obtained crystalline it was of little use for stereochemical work and it was not investigated further.

(d). In an effort to obtain crystalline derivatives of 2:2:4-trimethyl-1:2:3:4-tetrahydroquinoline attention was turned to N-substitution with symmetric reagents. The stabilisation of the configuration of the molecule of the base by N-substitution with a symmetric radical R would result in the formation of 2 racemic compounds (fig. 40) separable by fractional crystallisation.



(i) Acetyl-2:2:4-trimethyl-1:2:3:4-tetrahydroquinoline.

The acetyl derivative of the base was a beautifully crystalline compound, m.p.83°. It remained completely unchanged during a fractional crystallisation from ligroin and was considered to be a single compound.

(ii) Benzoyl-2:2:4-trimethyl-1:2:3:4-tetrahydroquinoline.

Benzoylation of the base was not easily achieved. A Schotten-Baumann reaction yielded a small amount of a highly fragrant oil. When the benzoylation was carried out in pyridine a very viscous yellow oil was obtained, and gums were obtained when the base was refluxed with benzoyl chloride and pyridine in sodium dried benzene. The gums were purified by distillation and certain of them were seen to contain small amounts of crystalline material.

Reddelien and Thurm[81] found that the benzoylation of 2:2:4-trimethyl-1:2:-dihydroquinoline with benzoyl chloride yielded greasy products, but that if benzoic anhydride was used a crystalline derivative was obtained. Consequently, 2:2:4-trimethyl-1:2:3:4-tetrahydroquinoline was heated with benzoic anhydride for several hours. Two products were isolated from the reaction mixture. The first consisted of very fine white crystalline needles, m.p. 175-177°, but did not analyse as the benzoyl derivative of the base.

The/

The second was a thick gum which was purified by distillation. It yielded analysis figures in agreement with those calculated for the benzoyl derivative of the base, and was eventually obtained as crystalline tablets which were very soluble in organic solvents.

As far as could be determined, the benzoyl-2:2:4-trimethyl-1:2:3:4-tetrahydroquinoline was a homogeneous colourless crystalline compound, m.p. 70-72°.

(iii) p-Nitrobenzoyl-2:2:4-trimethyl-tetrahydroquinoline.

The p-nitrobenzoyl derivative was readily formed when 2:2:4-trimethyl-1:2:3:4-tetrahydroquinoline was refluxed with p-nitrobenzoyl chloride and pyridine in sodium-dried benzene. Two compounds crystallised from the concentrated benzene solution. Only one of these, however, was the p-nitrobenzoyl derivative. The other compound was p-nitrobenzoic anhydride which had presumably been formed during the removal of excess p-nitrobenzoyl chloride from the reaction mixture.

The p-nitrobenzoyl derivative was shown to be a homogeneous yellow crystalline compound which crystallised from benzene in hard yellow uniterminal prisms, m.p. 131-132°. There was no trace of the two postulated racemic compounds.

(8)/

(8). No further derivatives of the racemic base were investigated as there seemed no liklihood of obtaining any positive information from them regarding the stereochemistry of the tervalent nitrogen atom. Instead attention was transferred to similar derivatives of the active modific-:ations of the base, l-2:2:4-trimethyl-1:2:3:4-tetrahydro-:quinoline.

(a). The d-oxymethylenecamphor derivative of the l-base was a thick yellow syrup which was purified by distillation. The higher fractions distilling at circa. $4.5 \times 10^{-5}$ mm. and consisting of the pure derivative exhibited a specific rotatory power $(\alpha)_D$ = +300 to 304°. When the pure gum was treated with a trace of ether overnight in the refrigerator there was a decrease in the angle of rotation; but no consistency could be obtained in the results and no conclusions were drawn from them.

A specimen of the gum crystallised after distillation, when scratched in contact with a little ligroin. A further condensation was carried out using carefully purified oxymethylenecamphor and a small amount of crystalline material was obtained by seeding the solution of the condensation product in light petroleum, with the crystalline material. The d-oxymethylenecamphor-2:2:4-trimethyl-1:2:3:4-tetrahydroquinoline was very soluble in all organic solvents/

solvents and an efficient fractional crystallisation was impossible. The derivative was examined as fully as possible and appeared within the limits of the experiment to be optically homogeneous.

(b). The l-base was then condensed with l-menthoxy-:acetyl chloride. Optical inversion occurred during the condensation, as the amide, a clear yellow gum, exhibited an optical rotatory power in alcoholic solution $(\alpha)_D^{18}$ = + 97.3. It could not be induced to crystallise.

(c). In contrast to the beautiful crystalline nature of the acetyl derivative of the racemic base, the acetyl derivative of the l-base was obtained as a very viscous syrup. In alcoholic solution it had a very high dextro-rotation $(\alpha)_D$ = + 477°. Its behaviour in this respect was similar to that of the acyl derivatives of l-tetra-:hydroquinaldine and l-p-tolutetrahydroquinaldine which show high dextro-rotations. No conclusions about its optical homogeneity could be drawn as it remained non-crystalline during its investigation.

(d). The l-base was then benzoylated by heating for 7-8 hours with benzoic anhydride. As with the racemic base there were two products of this reaction. The first, very fine needles, was optically inactive and so was not a derivative/

derivative of the l-base. It was identical with the similar compound obtained during the benzoylation of the racemic base. The second product, a green gum, crystallised when scratched in contact with aqueous alcohol. This crystalline material was then used to seed an alcoholic solution of the gum and the benzoyl-l-base separated in small colourless rectangular plates.

When this derivative was subjected to a fractional crystallisation from alcohol its optical rotatory power showed little variation and there was no indication of the separation into isomerides. The diastereoisomers lB.dA. and lB.lA would have existed if the configuration of the nitrogen atom had been stabilised.

Optical inversion again occurred as the specific rotatory power of benzoyl-l-2:2:4-trimethyl-1:2:3:4-tetra-:hydroquinoline was $(\alpha)_D$ = +386° in benzene. This value is similar to the recorded values for the benzoyl derivatives of l-tetrahydroquinaldine[49] and l-p-tolutetrahydroquinaldine[50].

(e). The p-nitrobenzoyl derivative of the l-base was next examined. It was prepared by refluxing equivalent quantities of the l-base and p-nitrobenzoyl chloride in the presence of pyridine in sodium-dried benzene. Like the other acyl derivatives it showed a high dextrorotation in organic solvents. The rotatory power varied slightly during

a/

a fractional crystallisation from acetone but the variation was not considered to be significant. It was accordingly considered to be a single compound, the optical activity of which owed its existence purely to the presence of the asymmetric carbon atom.

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## Summary and Discussion of Results

The following compounds were prepared and found to be crystalline:-

1. Tetrahydroquinoline-d-oxymethylenecamphor.
2. d-Camphor-10-sulphonyl-tetrahydroquinoline.
3. d-Oxymethylenecamphor-2:2:4:-trimethyl-1:2-dihydroquinoline
4. Acetyl-dl-2:2:4-trimethyl-1:2:3:4-tetrahydroquinoline.
5. Benzoyl-dl-2:2:4-trimethyl-1:2:3:4-tetrahydroquinoline.
6. p-Nitrobenzoyl-dl-2:2:4-trimethyl-1:2:3:4-tetrahydro-:quinoline.
7. d-Oxymethylenecamphor-l-2:2:4-trimethyl-1:2:3:4-tetra-:hydroquinoline.
8. Benzoyl-l-2:2:4-trimethyl-1:2:3:4-tetrahydroquinoline.
9. p-Nitrobenzoyl-l-2:2:4-trimethyl-1:2:3:4-tetrahydro-:quinoline.

The following compounds were found to be non-crystalline:-

10. l-Menthoxyacetyl-tetrahydroquinoline
11. l-Menthoxyacetyl-2:2:4-trimethyl-1:2-dihydroquinoline.
12. d-Oxymethylenecamphor-2:2:4-trimethyl-1:2:3:4-tetra-:hydroquinoline.
13. l-Menthoxyacetyl-2:2:4-trimethyl-1:2:3:4-tetrahydro-:quinoline.
14. Acetyl-l-2:2:4-trimethyl-1:2:3:4-tetrahydroquinoline.
15. l-Menthoxyacetyl-l-2:2:4-trimethyl-1:2:3:4-tetrahydro-:quinoline.

The/

The d-camphor-10-sulphonyl derivatives of 2:2:4-trimethyl-quinolines could not be prepared because of the screening of the -NH- group by the methyl groups in the 2-position.

The crystalline compounds were subjected to fractional crystallisation and were found in the case of the optically active compounds 1-3 and 7-9 to be optically homogeneous, and in the case of the racemic compounds 4-6 to be single substances. In no case was a trace of optical activity detected which could not be explained by the presence of asymmetric carbon atoms.

The absence of any optical activity due to the "asymmetric" nitrogen atom indicates that the activation energies of inversion for the compounds investigated must be very close to or less than the limiting value of 25kg.-cals./mol. required for resolution.

The inversion of the compounds investigated , by the "dropping through" of the nitrogen nucleus, is likely to have been assisted by two resonance effects.

1. Resonance between the unshared electron-pair of the nitrogen atom and the benzene ring of the quinoline.

2. Resonance between the unshared electron-pair of the nitrogen atom and the N-substituting group R.

It is known that the aniline molecule resonates among the/

the three structures, fig. 41.

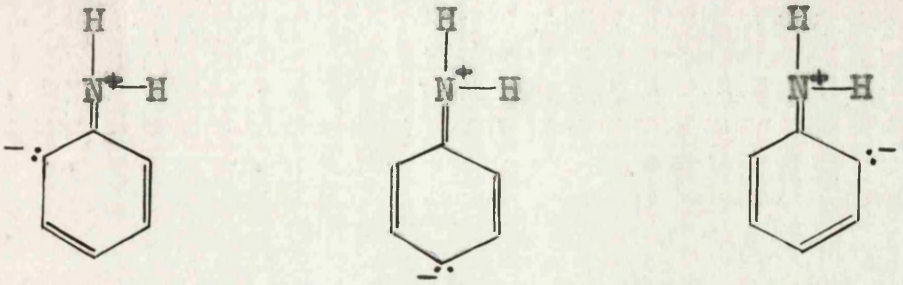
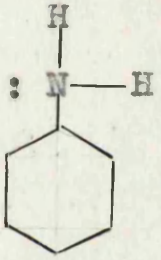


fig. 41.

as well as the normal structures.



The resonance energy attributed to the canonical forms shown in fig. 41 is 8.4kg.-gals./mol.[82]

Therefore, in a tetrahydroquinoline similar forms such as shown in fig. 42 will exist.

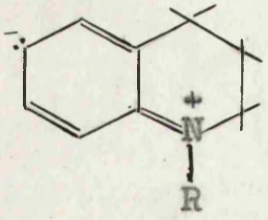


fig. 42.

Where R = d-oxymethylenecamphor there will also be resonance between the forms in fig. 43;

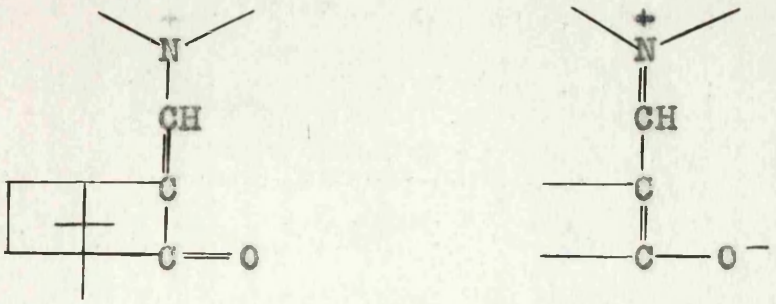


fig. 43.

and if R is an acyl group other than sulphonyl resonance will also occur (fig. 44)

fig.44.

In the case of the sulphonyl group there is no resonance and only the one structure exists (fig. 45).

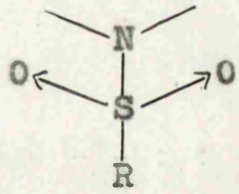


fig. 45.

In order that resonance of the above types may occur, giving partial double-bond character to the bonds connecting the nitrogen atom to the benzene ring and the group R, the molecule must approximate to the coplanar configuration requisite for double-bond character. This adjustment must lead to a flattening of the equilibrium configuration of the nitrogen valencies and so increase the ease with which inversion may occur. This adjustment is, of course, counter-:balanced to a certain extent by the additional strength of the nitrogen-carbon bonds resulting from the resonance; but the over-all effect is likely to decrease the resistance of the molecule to inversion.

Hampson/

Hampson and Birtles[83] showed, by dipole measurements, that the presence of two ortho-substituents in aromatic nitro-compounds (fig. 46) largely inhibited resonance of the type considered, by keeping the plane of the nitro-group out of the plane of the ring.

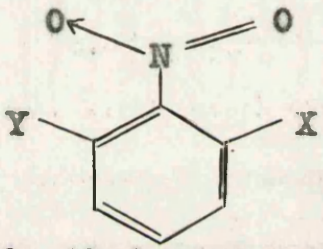



fig. 46.

It is conceivable that some such steric interaction occurred in the 2:2:4-trimethyl quinolines investigated, although the effect was likely to have been small. If, instead of reducing the 3:4-double-bond of the dihydro-:quinoline, the compound had been brominated, giving the 3:4:6:8-tetrabromo derivative, the combined effect of the 8-bromo group and the two methyl groups in the 2-position might have been sufficient to inhibit the resonance to a large extent but would have rendered N-substitution more difficult.

In the d-camphor-10-sulphonyl derivative of tetrahydro-:isoquinoline the nitrogen valencies would have no partial double-bond character as resonance with the unshared electron pair of the nitrogen atom cannot occur and inversion of the molecule would be due purely to the mutual oscillation of the nitrogen nucleus and the attached groups. However, time did not allow of the investigation of this compound.

The/

The initial analogy to the oxime of cyclohexanone-4-carboxylic acid was perhaps not particularly pronounced, in that the nitrogen-to-carbon double bond in the oxime is extremely strong, and stability is also obtained by resonance between the structures (fig. 47), and probably from the attraction of the opposite charges on the carbon and oxygen atoms arising from the different polarities of the nitrogen-carbon and nitrogen-oxygen bonds, ref. (Fig. 48).

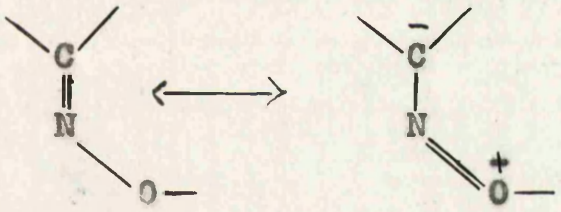


fig. 47.

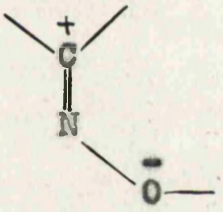


fig. 48

The completely negative results obtained give additional confirmation to the arguments set forth on the non-resolva-:bility of saturated tervalent nitrogen compounds, by W.H. Mills[77] in his Presidential Address to the Chemical Society in 1943, They also furnish further evidence in favour of his opinion that some really new method of attack must be devised if this problem is to be solved without, as he considers, an expenditure of effort out of proportion to the value of the result.

## EXPERIMENTAL

## PREPARATION OF STARTING MATERIALS

### Reduction of Quinoline to ac.-tetrahydroquinoline.

The quinoline was reduced to the 1:2:3:4-tetrahydro derivative by the method of Hofmann and Koenigs[84] using tin and concentrated hydrochloric acid. It was found that the reaction mixture had to be heated on the water-bath for 4-5 hours before the tin had completely reacted. During the purification of the reduced product through the hydro-:chloride, if more than the merest excess of concentrated hydrochloric acid was added a viscid brown mass was obtained on concentrating. The most satisfactory method was to add the concentrated hydrochloric acid with continual stirring until the oil had just dissolved; the hydrochloride then came out immediately as fine white crystalline needles. If allowed to crystallise more slowly beautiful large crystall-:ine needles were obtained, but as the only method of drying these was by powdering them on a porous plate, it was preferable to use the first method of separating the hydro-:chlorides. The yield of hydrochloride in this reduction was only about 50-60% of the calculated amount. The reduced quinoline was stored as the hydrochloride until required.

### Crystalline 1:2:3:4-tetrahydroquinoline.

Tetrahydroquinoline is normally a colourless oil b.p. 249-50°/755 mm./

249-50°/755 mm. When it was subjected to temperatures in the region of 0° for some time, long transparent square-ended prismatic needles formed in the oil. The crystals were large, well defined and had highly plane faces.

The melting point of the crystals was determined in the normal manner with a standard thermometer, m.p.15.3-15.4°. The crystalline mass was then melted, cooled to 10° and innoculated with the crystalline base; a standard thermometer immersed in the crystallising substance showed a temperature rise to 15.36°. The melting point of 1:2:3:4-tetrahydroquinoline was, therefore, taken to be 15.35°. Traces of quinoline completely inhibited the crystallisation.

Preparation of d-Oxymethylenecamphor.

This compound was prepared by the method of Bishop, Claisen and Sinclair[85] (Annalen, 1894, 281, 331) by the condensation of d-camphor and amyl formate in the presence of sodium wire in sodium-dried ether. From 200g. d-camphor about 85g. (33% theoretical) of d-oxymethylenecamphor was obtained, m.p. 69-73°. Four similar preparations were carried out.

These preparations exhibited specific rotatory powers in alcohol at 18°:-

$(\alpha)_D = +114^\circ$ (c=0.94, t = 30 mins.)

$(\alpha)_D = +139^\circ$ (c=0.85, t = 30 mins,)

$(\alpha)_D = +145^\circ$ (c=0.80, t = 25 mins.)

This showed the material to be optically impure; Pope and Read recorded the value $(\alpha)_D = +198^\circ$ (c=0.7, alcohol, t = 30 mins.). The impurity was traced to the camphor stock. It was initially shown to have $(\alpha)_D = +42.5^\circ$ (c=20, alcohol, 2dcm. tube), but closer inspection proved it to consist of a mixture of slabs of d- and dl-camphor. Subsequent preparations, using pure d-camphor, exhibited specific rotatory powers in agreement with the value of Pope and Read.

A later preparation carried out under similar conditions yielded a product with a slightly lower rotatory power. The mutarotation proceeded from $+193^\circ$ after 15 mins. to $+177^\circ$ after 3 days, as compared to the equilibrium value or $+185^\circ$ of Pope and Read. The rotatory power remained unchanged after treatment of the product with ether in alkaline solution, followed by reprecipitation with 30% acetic acid. Steam-distillation also had little effect in increasing the value.

Oxymethylenecamphor becomes deep yellow on preservation and eventually deteriorates to a sticky yellow mass. It was found that after four months preservation in ground-glass stoppered bottles the d-oxymethylenecamphor could be regenerated/

regenerated in an optically pure condition by steam-distillation; thereafter the products yielded had specific rotations in alcohol, after completion of the mutarotation, of +130-160°. Purification is best carried out immediately a decided stickiness appears. Preservation in sealed tubes was effective in avoiding this deterioration.

Preparation of d-Camphor-10-sulphonyl chloride.

This was prepared by treating d-camphor-10-sulphonic acid with excess thionyl chloride.under reflux on the water bath. After removal of the excess thionyl chloride light petroleum (b.p. 60-80°) plus a little sodium dried ether, was added and the sulphonyl chloride crystallised from the ether-light petroleum solution.

m.p. 70°. Yield 75% theoretical. $(\alpha)_D$ = +32° (chloroform)

d-Camphor-10-sulphonic acid is recovered from its salts with bases as its ammonium salt. A preparation was, therefore, carried out using the ammonium salt of the acid. The salt, however, did not appear to go into complete solution with the thionyl chloride and only a poor yield of rather impure sulphonyl derivative was obtained.

Reduction of Quinaldine to dl-ac.-Tetrahydroquinaldine

The reduction was carried out as for quinoline with tin and concentrated hydrochloric acid. When the reduction was complete a slight excess of soda was added and the mixture subjected/

subjected to prolonged distillation in a current of steam. The tetrahydroquinaldine was extracted from the distillate with ether, the ethereal solution dried over calcium chloride, and the ether removed by distillation.

Purification of reduced product.

1. By condensation with oxymethylenecamphor.

The condensation was carried out as described (p.64). The yellow crystalline compound from the ether was refluxed with dilute hydrochloric acid for 2 hours. The oxymethylenecamphor as it was formed during the hydrolysis was deposited as a fine yellow powder on the worm of the condenser. The solution was basified with dilute sodium hydroxide, the base extracted with ether, and the ether removed by distillation. Yield of pure secondary base from 10 c.c. reduction product was 3 c.c.

2. By acetylation with acetic anhydride.

10 c.c. reduction product was refluxed for 1 hour with 20 c.c. acetic anhydride. The mixture was poured into water when the acetyl derivative separated as a brown oil. The oil was extracted with ether and shaken several times with dilute hydrochloric acid to remove the unreduced quinaldine. The ether was removed and the acetyl derivative refluxed with conc. hydrochloric acid for 2-2½ hours. The solution was basified with dilute sodium hydroxide, the liberated/

liberated base extracted with light petroleum, and the extract dried over sodium sulphate. The removal of the light petroleum by distillation gave a brown oil which was distilled at 20 mm. giving 7 c.c. of light yellow secondary base. The remainder of the reduction product was purified in this way.

3. Other methods of purification are:-

(a) Conversion to the benzoyl derivative and hydro-:lysis with concentrated hydrochloric acid for several days.

(b) Fractional distillation

These were not utilised as the method (2) was regarded to be the easiest and most efficient method.

Preparation of l-Menthoxyacetyl Chloride.

8.6g. l-Menthoxyacetic acid was heated with 14 c.c. thionyl chloride for an hour on the water-bath. Excess of thionyl chloride was then removed by distillation in vacuo, eventually with the addition of a little benzene. The residual acid chloride was then purified by distillation at reduced pressure; the fraction distilling at 124-130°/8.5 mm. was collected and was a colourless fuming liquid, $(\alpha)_D^{16}$ = -84.1° (c = 2, chloroform).

1a. Condensation of ac.-Tetrahydroquinoline with d-Oxymethylenecamphor.

Hot solution of 2.85g. d-oxymethylenecamphor in 3 c.c. absolute alcohol and 2 c.c. ac.-tetrahydroquinoline in 7 c.c. 50% acetic acid were mixed. After a short time the mixture was poured into cold water. An oil, which became viscid, separated, and was extracted with light petroleum. The extract was shaken several times with dilute hydrochloric acid to remove ac.-tetrahydroquinoline, and with dilute sodium hydroxide to remove d-oxymethylene-:camphor. Concentration of the light petroleum gave a yield of pale yellow crystals, which had m.p. 110°, $(\alpha)_D$ + 312° (c = 0.5, alcohol).

During subsequent condensations crystalline materials separated

(a) on pouring reaction mixture into cold water,

(b) on shaking with dilute acid and alkali,

and two distinct types of crystals (c) and (d) were mechan-:ically separated from the light petroleum solutions. The following rotations of these solids were taken in 0.5% alcoholic solutions:-

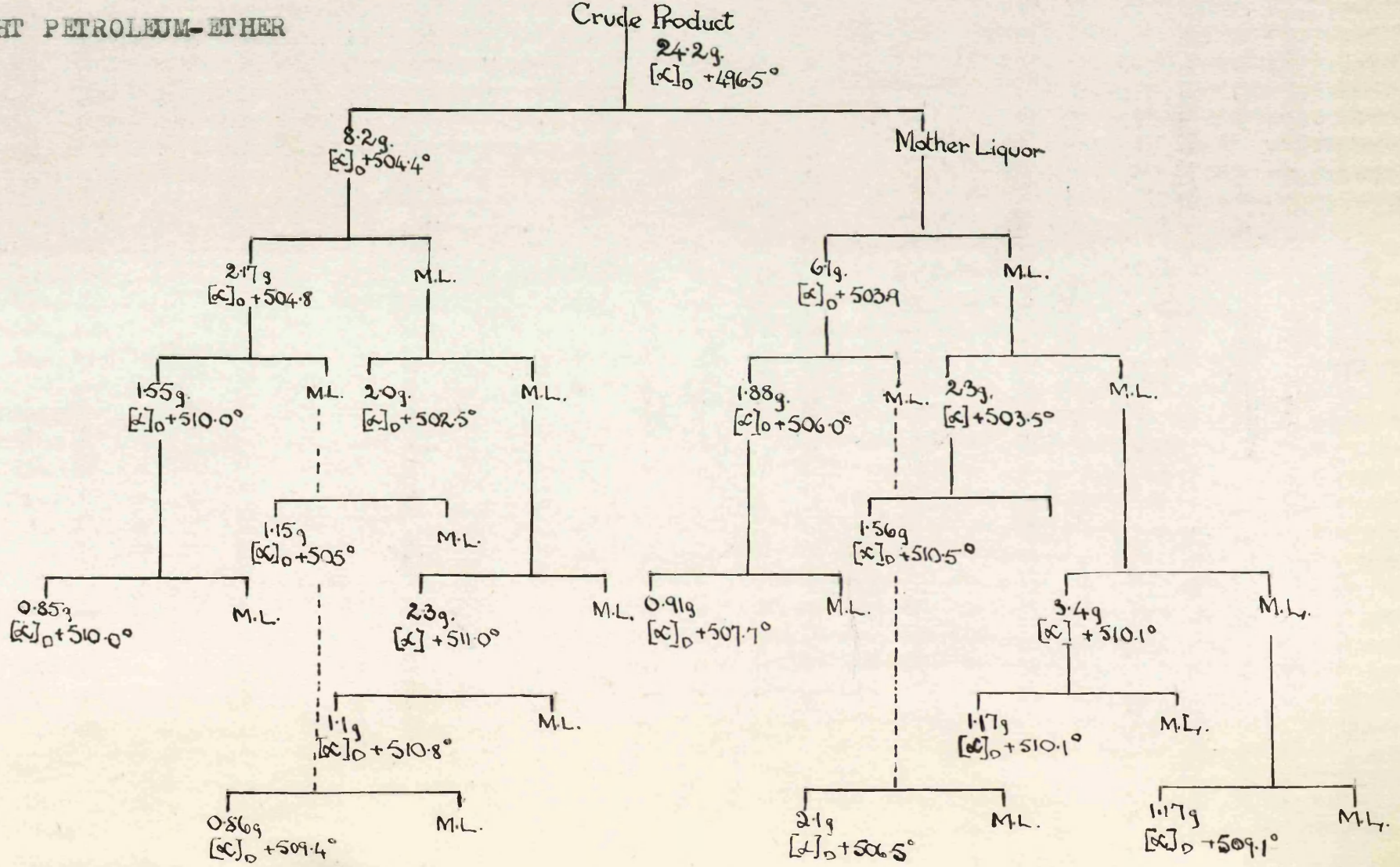
(a) pale yellow crystals: m.p. 111°, $(\alpha)_D$ = +305.0°
(b) crystalline powder: m.p. 112°, $(\alpha)_D$ = +302.0°
(c) large prismatic crystals: m.p. 111-113° $(\alpha)_D$ = +375.2°
(d) crystalline needles: m.p. 112-113°, $(\alpha)_D$ = +114.0°

20.5g/

# FRACTIONAL CRYSTALLISATION OF ac.-TETRAHYDROQUINOLINE-d-OXYMETHYLENE CAMPHOR.

SOLVENT:-

LIGHT PETROLEUM-ETHER



20.5g. of the ac-tetrahydroquinoline-d-oxymethylene-: Camphor was prepared, $(\alpha)_D$ +312°. After repeated fractional crystallisation the maximum specific rotation was +385.3° (c = 0.5, alcohol).

This product was not optically homogeneous because of the optical impurity of the d-oxymethylenecamphor from which it was prepared.

(b). Further condensation of ac-tetrahydroquinoline with d-oxymethylenecamphor were carried using a freshly prepared supply of d-oxymethylenecamphor, $(\alpha)_D$ +198° (c = 0.5, alcohol, t = 30 mins). Crystalline materials separating at different stages in the isolation of the condensation product had specific rotations varying from +492° to +498° in 0.5% alcoholic solution. The 24.3g. of crude product had a specific rotation of +496.5°.

Fractional Crystallisation.

24.3g. of the crude condensation product was subjected to a repeated fractional crystallisation from an ether light petroleum mixture. The ac-tetrahydroquinoline-d-oxymethylene camphor crystallised in extremely fine pale yellow crystals, m.p. 112-113°. The table of the fraction-:ation is shown opposite.

When a little of the product $(\alpha)_D$ = +509° was care-:fully fused in a crucible and its optical rotatory power determined on solidifying, it was found to be unchanged

$(\alpha)_D$ /

$(\alpha)_D = +507^\circ$.

The compound gave a purple colouration with chromic acid.

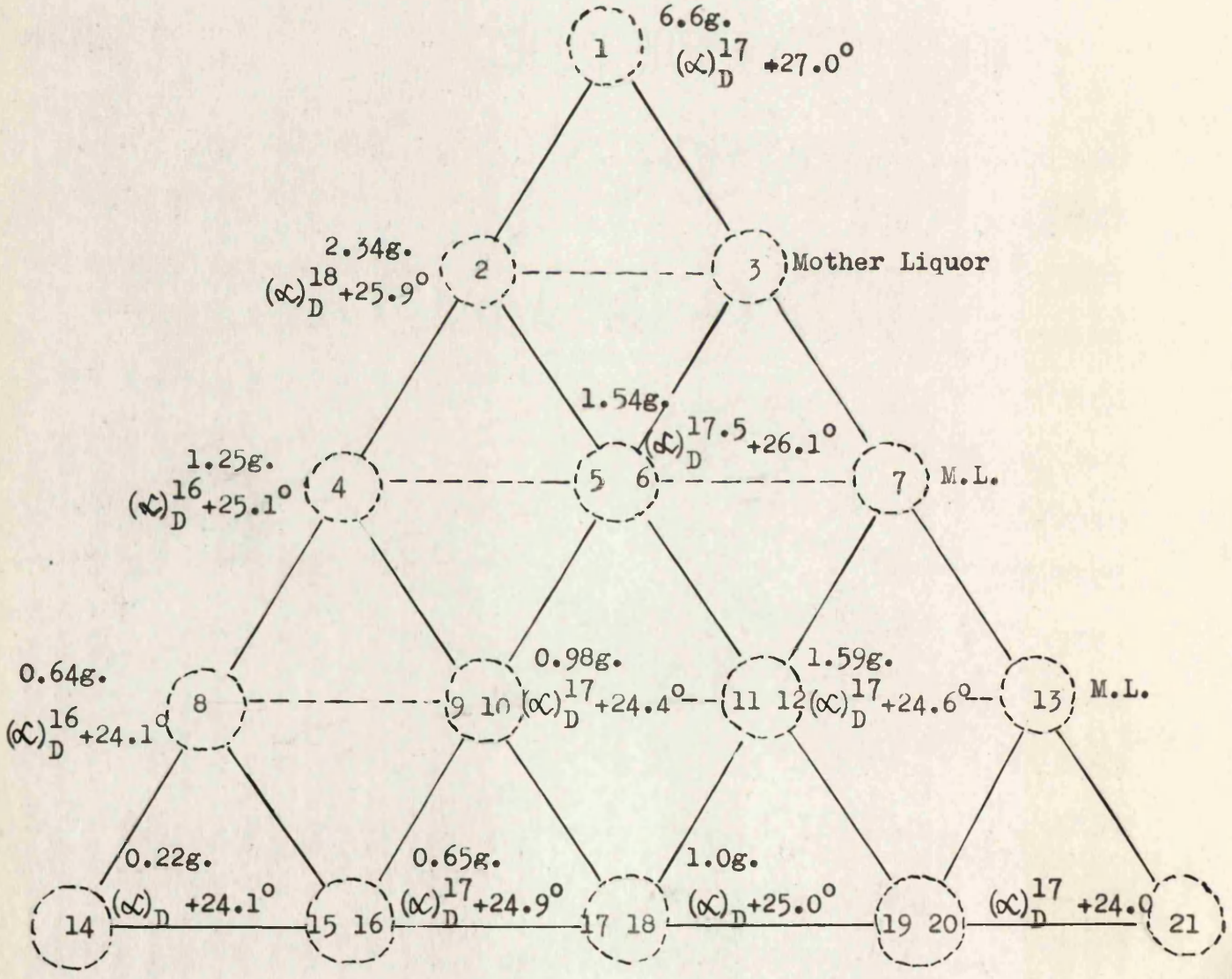
2. Condensation of ac-Tetrahydroquinoline with d-Camphor-10-Sulphonyl Chloride.

(i). 5g. (30% excess) d-camphor-10-sulphonyl chloride was dissolved in 9 c.c. dry pyridine in a small conical flask and 2 c.c. ac-tetrahydroquinoline added. The flask, well stoppered, was allowed to stand over-night at room temperature. The mixture was poured into excess dilute hydrochloric acid, resulting in the production of a dark red solution with the separation of a solid condensation product. The dark red amorphous material obtained on filtration was obtained as red crystalline needles from ethyl acetate; but the crystals when examined under the microscope appeared to be stained rather than intrinsically red. Following the treatment of Read and Galloway[87] who obtained crimson solutions when condensing d-camphor-10-sulphonyl chloride with p-aminoacetanilide and mono-d-camphor-10-sulphonyl-p-phenylenediamine in dry pyridine, the red crystals were repeatedly treated with norit in boiling alcohol. After 5 such treatments a colourless crystalline specimen was obtained.

That the red colouration is due to the presence of pyridine/

**FRACTIONAL CRYSTALLISATION OF d-CAMPHOR-10-SULPHONYL-ac.-TETRAHYDROQUINOLINE.**

**SOLVENT:- ALCOHOL-ACETONE.**




**Rotations taken in 2dm. tubes in chloroform (c = 0.5).**

pyridine/ is seen from the fact that d-camphor-10-sulphonyl chloride gives crimson solutions with aniline, monomethyl-:aniline and β-naphthylamine in the presence of pyridine but not in its absence.

(ii) A.Schotten-Baumann reaction was carried out but no crystalline product was obtained.

(iii) 69g.d-camphor-10-sulphonyl chloride and 6 c.c. (50% excess) ac.-tetrahydroquinoline were mixed with gentle heating in a small conical flask. After standing over-night at room temperature 5.1g. of light orange condensation product was obtained on pouring the mixture into excess of dilute acid. After a single treatment with norit in boil-:ing alcohol a colourless crystalline powder was obtained and had m.p. 100°, $(\alpha)_D$ = +27.1° (c = 0.5, chloroform).
Analysis:-

Found: C = 65.7%, H = 7.3%

$C_{19}H_{25}O_3NS$ requires: C = 65.4%, H = 7.2%

Fractional Crystallisation of d-Camphor-10-sulphonyl-ac-tetrahydroquinoline.

This was carried out as shown in the table opposite. The solvent used was an alcohol-acetone mixture. The rotations were taken in chloroform in 2 dcm. polarimeter tubes.

A/

A little of the amide was carefully fused in a crucible, gently heated for a short time after fusion, and then allowed to solidify. There was no significant change in the optical rotatory power as a result of this process.

Before fusion:- $(\alpha)_D^{18} = +24.0 \pm 1.2^\circ$ (c = 0.72 chloroform 4 dcm.)

After fusion:- $(\alpha)_D^{18} = +22.9 \pm 2.6^\circ$ (c = 0.51 chloroform 4 dcm.)

The specific rotations were calculated from a series of 25 readings of the angle of rotation and 10 readings of the zero point, by a method discussed on page . They show the limits within which the true specific rotation will lie 99 times out of 100. The limits within which it will lie 9 times out of 10 are $+24.0 \pm 0.7^\circ$ and $22.9 \pm 1.3^\circ$. In both cases the ranges overlap appreciably and no significant change can be claimed.

4. Condensation of ac-Tetrahydroquinoline with d-oxymethylene-:camphor introducing reaction velocities.

5 c.c. (2.5 mols.) base and 2.85g. (1 mol.) d-oxymethylene-:camphor were condensed as previously described. The light petroleum extract was shaken well with dilute hydrochloric acid to remove the unreacted ac-tetrahydroquinoline. The acid washings were basified with dilute sodium hydroxide and/

and the ac-tetrahydroquinoline extracted with light petroleum. After removal of the solvent by distillation, the unchanged base was examined polarimetrically in a micro-tube but gave no perceptible optical rotation.

The crude condensation product had $(\alpha)_D$ +494°; the first few fractions of a fractional crystallisation had $(\alpha)_D$ +504°, +506.5° and +508.0° respectively.

5. (a) Condensation of 2:2:4-Trimethyl-1:2-dihydroquinoline with d-Oxymethylenecamphor.

(i) 2.0g. base was dissolved in 15 c.c. 50% acetic acid plus a trace of glacial acetic acid. 2.08g. d-oxy-:methylenecamphor was added at room temperature and the mixture poured into an excess of cold water. There was no separation of an oily product. The aqueous solution was extracted with light petroleum and the extract shaken with dilute sodium hydroxide to remove d-oxymethylenecamphor and with dilute hydrochloric acid to remove unchanged base. The light petroleum solution was concentrated yielding a small amount of a yellow crystalline compound, m.p. 149 - 151°.

(ii). The condensation was repeated using hot solutions. Yield of yellow crystalline compound was 0.35g, (18% of theoretical amount) and had m.p. 148° - 60°; $(\alpha)_D$ +356° (c = 0.5 alcohol)./

(c = 0.5 alcohol). This was impure anilino-d-oxymethylene-:camphor.

(iii) Test-tube experiments in absence of solvents at 100°, 120°, 130° and 140° showed condensation had taken place by the condensation of water on the sides of the test-tubes; in no case was a crystalline end product obtained.

(iv) 1.01g. purified base was condensed with 1.04g. d-oxymethylenecamphor as in (ii) above. The end product was a yellow syrup which would not crystallise. No trace of the anilino-d-oxymethylenecamphor derivative was now found.

(v) 1 c.c. base in 18 c.c. 60% acetic acid condensed with 1.04g. d-oxymethylenecamphor in 5 c.c. alcohol yielded a yellow syrup. A like result was obtained using 10 c.c. 80% acetic acid as solvent.

(vi) 2g. base were added to a convenient amount (12 c.c.) of 50% acetic acid and glacial acetic acid on the water-bath until the base just went into solution. A hot solution of 2g. d-oxymethylenecamphor in the minimum of alcohol was then added; there was no apparent reaction. The yellow solution was allowed to concentrate on the water-bath for 45 minutes. When the dark green solution was then poured into cold water a thick resinous mass separated. This was extracted with a mixture of ether and light petrol-:eum and the extract treated with acid and alkali. The solution/

solution was dried over anhydrous sodium sulphate and appreciably concentrated on the water-bath. After repeated scratching a yellow crystalline powder separated and was filtered off, washed with ether and dried in vacuo.

0.1007g. in 20 c.c. alcohol in a 2dcm. tube had a specific rotation $(\alpha)_D^{17.5} = +155.0^\circ$.

The mother liquors were concentrated and a further yield of crystalline material was obtained. On continued concentration the mother liquors took on a sticky appearance and a thick yellow gum was left when they were taken to dryness. This gum would not crystallise when taken up in various solvents and seeded with the crystalline material.

0.1013g. of the gum in 20 c.c. alcohol in a 2 dcm. tube had a specific rotation $(\alpha)_D = +211.6^\circ$.

The crystalline material was recrystallised from alcohol and separated in small yellow prismatic needles.
0.1007g. in 20 c.c. alcohol : 2dcm. tube : $(\alpha)_D^{18} = +99.5^\circ$.
After a further 2 recrystallisations:-
0.1011g. in 20 c.c. alcohol : 2 dcm. tube : $(\alpha)_D^{19} = +100.1^\circ$
0.2210g. in 34.8 c.c. alcohol: 4dcm. tube : $(\alpha)_D^{19} = +99.8^\circ$

A further condensation was carried out using 10g. base. The solution of the condensation product in light petroleum was not concentrated to as small a bulk as previously, and the/

the solution was seeded with the crystalline derivative. 7.5g. of a yellow crystalline powder were obtained. 0.1001g. in 20 c.c. alcohol : 2dcm. tube: $(\alpha)_D^{17.5}$ = +100.2°.

Recrystallisation from absolute alcohol gave products with the following specific rotations in 1% alcoholic solutions in 2 dcm. tubes.

6.4g., $(\alpha)_D$ = +99.7° ; 5.2g., $(\alpha)_D$ = +100.1° ; 4.7g., $(\alpha)_D$ = +99.8° ; 3.5g., $(\alpha)_D$ = +99.4° ; 2.8g., $(\alpha)_D$ = +99.5° ; 1.1g., $(\alpha)_D$ = +99.2° ; 0.4g., $(\alpha)_D$ = +99.9°.

A further specimen of this compound was recrystallised from a large amount of alcohol and a very small initial fraction removed. 0.1004g. in 20 c.c. alcohol : 2dcm. tube ; $(\alpha)_D$ = +99.8°.

The mean specific rotation was considered to be $(\alpha)_D$ = 99.8±1.1°.

Analysis:

Crystalline compound:-

| | | |
|---|---|---|
| Found: | C = 82.25%, | H = 8.9% |
| Gum: | | |
| Found: | C = 82.71%, | H = 9.1% |
| $C_{23}H_{29}NO$ requires | C = 82.40%, | H = 8.7% |

Molecular weight determinations of the gum :- 712,648,412.

$C_{23}$/

$C_{23}H_{29}NO$ = 335.

The gum was the d-oxymethylenecamphor derivative of the polymerised base.

(5b), Condensation of 2:2:4-trimethyl-1:2-dihydroquinoline with d-Camphor-10-sulphonyl chloride.

(i) 3 c.c. base (66% excess) and 1.44g. d-camphor-10-sulphonyl chloride were heated gently in a small conical flask till solution was complete, and the flask allowed to stand overnight at room temperature. The mixture was poured into an excess of dilute hydrochloric acid with vigorous stirring. A solid white crystalline compound separated. This material was filtered off, washed with water, and dried in vacuo. It had zero rotatory power in alcohol and m.p.180-186°. Further investigation showed it to be almost entirely the hydrochloride of the base; unchanged acid chloride was also detected.

When the reaction was repeated using a greater excess of dilute acid there was no crystalline separation and no condensation product was isolated.

(ii) 1.5g. base and 0.72g. d-camphor-10-sulphonyl chloride, were refluxed in light petroleum for 4 hours. After washing the reaction mixture thoroughly with dilute acid, water and alkali, the light petroleum was removed by distill-:ation leaving no trace of a condensation product.

(iii)/

(iii). 0.5g base and 0.72g. acid chloride were dissolved in quinoline and heated in an oil bath for 1 hour at 130° and for 2½ hrs. at 150-170°. The dark red reaction mixture dissolved in dilute hydrochloric acid to an intense red solution which was extracted with light petroleum: it proved to contain no condensation product.

(iv). 1.5g. base (100% excess) and 0.72g. acid chloride were heated gently over a small flame for 3 hrs. The solution darkened rapidly and long yellow needles began to form above the liquid; an extremely evil odour was detected. After 20 minutes a yellowish crust with long needles radiating from it had formed above the reaction mixture and was mechanically removed. This material was very soluble in water and gave a white precipitate insoluble in nitric acid, with silver nitrate. It sublimed above 212°.

The reaction mixture, a thick tar, was treated with hot dilute hydrochloric acid and the acid solution extracted with ether. The ethereal extract, after treatment with acid and alkali, was found to contain no condensation product.

The acid solution was basified and a gummy material with a strong quinoline odour separated. This gum did not yield a crystalline acetyl derivative but a small amount of picrate m.p. 182°/

m.p. 182° decomp. was obtained.

The reaction was repeated under known temperature conditions. At 130° the solution became dark green, viscous, and an offensive odour was obvious; reaction occurred as evidenced by a gentle bubbling. At 155-160° needles of hydrochloride began to separate and the bubbling continued. The temperature was then raised to 190° for a short time. No condensation product was isolated from the resultant tar. Analysis of the hydrochloride:-

Found: C = 68.5%, H = 6.4%

$C_{11}H_{11}N.HCl$. requires: C = 68.3%, H = 6.20%

$C_{12}H_{15}N.HCl$ requires: C = 68.7%, H = 7.60%

The hydrochloride was considered to be that of 2:4-dimethyl-:quinoline.

2:4-Dimethylquinoline is produced during the acid decom-:position of 2:2:4-trimethyl-1:2-dihydroquinoline[92], and methane is readily split off from the latter by heating with metallic amides[93], such as sodium or magnesium anilides, giving a quantitative yield of 2:4-dimethylquinoline. In the present case it appeared that during the heating with d-camphor-10-sulphonyl chloride at least part of the base lost methane (cf. the bubbling of the reaction mixture) and went over to the dimethylquinoline structure.

(5c). 1-Menthoxyacetyl-2:2:4-trimethyl-1:2-dihydroquinoline.

Equivalent quantities of the acid chloride and base were dissolved in pyridine and heated gently on the water-bath for a/

a short time and then allowed to stand overnight in the stoppered flask. The amide was obtained as dark green gum which would not crystallise. The deep colour of the gum rendered its polarimetric examination impossible.

Catalytic Reduction of 2:2:4-Trimethyl-1:2-dihydroquinoline, to 2:2:4-Trimethyl-1:2:3:4-tetrahydroquinoline.

See page 109.

(6) Condensation of 2:2:4-Trimethyl-1:2:3:4-tetrahydroquinoline with d-Oxymethylenecamphor.

The condensation was carried out as for the dihydro com-:pound. The product of the reaction was a thick yellow gum. This gum was taken up in a little light petroleum, well scratched, without effect, and allowed to evaporate spontan-:eously; crystals formed in the gum from which they could not be separated.

Attempts to find a solvent from which the crystalline material would be deposited prior to the separation of the gum were unsuccessful. From acetone, methyl alcohol, ethyl alcohol and glacial acetic acid a homogeneous yellow gum was obtained. From benzene, toluene, ethyl acetate, toluene-acetone, ethyl acetate-alcohol an inseparable mixture of gum and crystals was obtained. The crystals in the gum from benzene solution were large and well developed but were apparently too soluble to separate/

separate alone.

$(\alpha)_D = + 207^\circ$ (c = 0.55, alcohol, 2dcm. tube)

$(\alpha)_D = + 202^\circ$ (c = 0.7, alcohol, 4dcm. tube).

Attempted separation utilising reaction velocities (cf. Pope and Read[80]).

2.5g. base (2.5 equivalents) and 1g. d-oxymethylenecamphor (1 equivalent) were condensed as above. A thick yellow gum was again obtained.

$(\alpha)_D^{18} = + 199^\circ$ (c = 0.50, alcohol, 2dcm. tube)

$(\alpha)_D^{18} = + 197.5^\circ$ (c = 0.9, alcohol, 4dcm. tube)

Little or no separation had occurred. Crystals were again formed in the gum when it was taken up in benzene.

Condensation with d-Camphor-10-sulphonyl Chloride.

1.5g. crystalline 2:2:4-trimethyl-1:2:3:4-tetrahydroquin-:oline and 0.72g. d-acid chloride were heated in an oil-bath to 130°; the solution became light green. The temperature was raised to 155°; the solution became dark green and very viscous. The temperature was kept at 160-185° for 3½ hours but there was no separation of hydrochloride; a rather offensive odour developed. The deep blue reaction mixture was poured into excess dilute hydrochloric acid but no sulphonyl derivative separated. A little of the dark blue tar seemed to be insoluble in acid, and after treatment with acid and alkali was taken up in acetone in which it gave a deep blue solution rapidly changing through mauve and purple to a deep wine-red.

After/

After several treatments in norit the colour was still too dark to allow of polarimetric examination.

An ethereal extract of the acid solution was shown to contain no condensation product. A wide range of colours was obtained during this process.

(6c.) Condensation with l-Menthoxyacetyl Chloride.

0.55g. l-Menthoxyacetyl chloride and 0.5g. 2:2:4-trimethyl-1:2:3:4-tetrahydroquinoline were dissolved in pyridine (5 c.c.) and allowed to stand overnight in a stoppered flask. The pyridine hydrochloride which separated went into solution when the mixture was poured into excess dilute hydrochloric acid; the amide separated as a yellow oil and was extracted with ether: 0.62g. of the amide, a thick oil, was obtained but would not crystallise from any of the usual organic solvents. The gum was purified by distillation on to the finger of a sublimation apparatus. The distillation proceeded as follows:-

| Fraction | Pressure. mm. | Oil-bath. | Weight g. | $\alpha_D$, 2dcm. chloroform | $(\alpha)_D^{18}$ | Description |
|---|---|---|---|---|---|---|
| 1. | $7.868\times10^{-2}$ | 100-130° | 0.0514 | -0.412 | -80° | mobile yellow oil |
| 2. | $7.868\times10^{-2}$ | 100-130° | 0.0248 | -0.200 | -79.9° | " " |
| 3. | $2.42\times10^{-5}$ | 170-180° | 0.0370 | -0.200 | -54.0° | thick " |
| 4. | $2.42\times10^{-5}$ | 230-240° | 0.0091 | -0.035 | -39° | orange resin |
| RESIDUE | | | 0.0345 | -0.064 | -18.6° | |

Analysis.

Fraction 1.

Found: C = 77.11%, H = 9.99%

$C_{24}H_{37}NO_2$ requires: C = 77.21%, H = 9.92%

Fraction 4.

Found: C = 70.14%, H = 8.2%

(6d,i). Acetyl-dl-2:2:4-trimethyl-1:2:3:4-tetrahydroquinoline.

1g. Crystalline base and 0.8 c.c. (50% excess) acetic anhydride were refluxed for 45 mins. The solution darkened noticeably and a brown crystalline powder separated on pouring into water. The acetyl derivative, a brown powder m.p.80°, recrystallised from ligroin in well-developed rhombic crystals, m.p.81°. They gave a blood red colouration with chromic acid. The melting point remained unchanged on repeated recrystallis-:ation.

(ii). Benzoyl-dl-2:2:4-trimethyl-1:2:3:4-tetrahydroquinoline.

Using Benzoyl Chloride.

(a) Schotten-Baumann Reaction.

1g. Crystalline base in 35 c.c. 2N-sodium hydroxide was shaken for 35 mins. with 1.5 c.c. benzoyl chloride. The excess acid chloride was hydrolysed and the solution extracted with ether, the extract shaken with dilute acid, dried over anhydrous sodium sulphate and the ether removed by distillation. A small amount of a fragrant yellow oil was obtained.

(b). In benzene

1g./

1g. Base was refluxed in 35 c.c. sodium-dried benzene for 1 hour with 1 c.c. pyridine and 1.6 c.c. benzoyl chloride. The benzene solution was then well shaken with dilute acid and alkali, dried over anhydrous sodium sulphate, and the benzene distilled. The residue, a brown oil, smelled of acid chloride and was treated with warm alkali. The oil became dark red on contact with alkali, green on heating, and extracted with ether to a brilliant green solution. A green limpid oil with a fragrant smell was obtained from the ethereal solution. The oil distilled on to the finger of a sublimation apparatus in an oil-bath at 80-100°, at a pressure of 0.13 mm. as a thick yellow oil. When kept for a number of weeks the oil became light green and a number of crystals formed in it.

(ii). The experiment (b,i) was repeated using only 25% excess benzoyl chloride and the purple oil which was obtained was free from acid chloride. The ethereal solution of the oil was green but yielded a purple oil on evaporation. The oil was distilled and obtained as a thick yellow oil which turned dark blue and crystallised partially.

(c). <u>In pyridine</u>.

Benzoylation in pyridine yielded a deep red solution from which a viscous brown oil was obtained. The oil distilled as follows:-

| | | |
|---|---|---|
| 80-100° (oil-bath) | 0.15 m.m. | a mobile oil. |
| 80-125° " | 0.15 m.m. | yellow gum |
| 80-140° | $1.4\times10^{-4}$ m.m. | a little thick resin. |

These materials could not be induced to crystallise.

Using Benzoic Anhydride.

(i). 0.5g. base and 0.75g. benzoic anhydride were heated gently for 6 hrs. A soft dark green mass was obtained and was extracted with ether; the ether solution well treated with acid and alkali, (the green ethereal solution turned red with alkali but the green colour was regenerated on shaking with acid). A small amount of a green crystalline powder separated from the ethereal solution and was filtered with some difficulty from the sticky solution. The mother liquors yielded a green gum. The green crystals, m.p. 170-175° crystallised from alcohol as fine white crystalline needles m.p. 175-177°.

The experiment was repeated on the water-bath. The heating was continued for 8 hrs. but the starting materials were recovered unchanged.

(ii). Experiment (i) was repeated using larger quantities. The reaction mixture was heated for 5 hrs. at 115-130°, and then for 1 hr. at 140-150°. The blue green oily mass was treated as in (i). The ether solution, acid and alkali washings were all highly coloured; the latter underwent brilliant colour changes on neutralisation. Two products were again obtained, very light blue needles m.p. 175-178° and a green gum. The gum was purified by distillation and gave a deep red colour with chromic acid, whereas the crystalline material gave no colouration.

After keeping for some time the gum crystallised when rubbed in contact with aqueous alcohol. The gum was dissolved in the minimum amount of 80% ethyl alcohol and seeded with the crystalline/

crystalline material. A yield of colourless tabular crystals was obtained, m.p. 68-70°: the mother liquors contained a small amount of material m.p.66-69°. The tabular crystals were very soluble in most organic solvents. When recrystallised from alcohol the melting point rose and remained steady at 71-72°.

Analysis.

Tabular crystals, m.p. 71-72°: (analysed as gum) -

Found: C = 81.8%, H = 7.53%

$C_{19}H_{21}NO$ requires: C = 81.7%, H = 7.53%

Crystalline needles, m.p. 175-178° -

Found: C = 75.0%, H = 4.3%

The identity of this compound was not discovered.

(6d,iii). p-Nitrobenzoyl-dl-2:2:4-trimethyl-1:2:3:4-tetrahydro-:quinoline.

a. lg. p-Nitrobenzoyl chloride and lg. base were dissolved in pyridine and allowed to stand overnight in a stoppered flask. The product of the reaction was isolated in the normal way. A small amount of a deep orange crystalline powder, m.p.125-127° was obtained. It was sparingly soluble in light petroleum but easily soluble in acetone from which it crystallised in yellow prisms, m.p. 131-133°. The yield of the derivative was 20%.

The experiment was repeated and the reaction mixture heated on the water-bath for 30 mins. The green solution was poured into excess dilute hydrochloric acid; no satisfactory product was isolated from the blue solution.

b./

b. 1.5g crystalline base and 2g. p-nitrobenzoyl chloride were refluxed with 1 c.c. pyridine for 45 mins. in 35 c.c. sodium dried benzene. The hot benzene solution was poured into dilute hydrochloric acid and well shaken, followed by shaking with alkali. The benzene solution was dried over anhydrous sodium sulphate and the solution concentrated by distillation. 0.7g. of soft white sparkling plates separated, m.p. 185-187°. These were recrystallised from acetone and then had m.p. 187-189°. This product gave no colouration with chromic acid and so was almost certainly not a derivative of the base. Further concen-:tration of the benzene solution yielded two crops of hard yellow prisms m.p. 128-130°. This product gave a cherry red colour with chromic acid; on repeated crystallisation from acetone the m.p. was unchanged at 131-132°.

Analysis.

Yellow prisms, m.p. 131-132°

| | | | |
|---|---|---|---|
| Found: | C = 70.5%, | H = 5.9%, | N = 8.9% |
| $C_{19}H_{20}N_2O_3$ requires | C = 70.4%, | H = 6.2%, | N = 8.6% |

White crystalline plates, m.p.187-189°.

| | | | |
|---|---|---|---|
| Found: | C = 53.7%, | H = 2.4%, | N = 8.8% |
| $C_{14}H_8O_7N_2$ requires | C = 53.2%, | H = 2.2%, | N = 8.8% |

The analysis showed this compound to have the empirical formula $C_7H_4NO_3$ and therefore to be p-nitrobenzoic anhydride, $C_4H_8O_7N_2$, m.p. 189-190°; agreement is also shown with the analysis/

analysis figures (above). Mixed melting points and hydrolysis to p-nitrobenzoic acid confirmed it to be this compound.

The derivatives of dl-2:2:4-trimethyl-1:2:3:4-tetrahydro-:quinoline were prepared using small quantities of reactants with a view to the subsequent preparation of the corresponding derivatives of the l-base which was not available in large quantities.

Resolution of dl-2:2:4-Trimethyl-1:2:3:4-tetrahydroquinoline.

See Part IIA.

(7,a). d-Oxymethylenecamphor-l:2:2:4-trimethyl-1:2:3:4-tetrahydroquinoline.

1.06g. l-Base and 1.1g. d-oxymethylenecamphor were condensed in the normal manner (cf. 6a). The product was a mobile gum which did not crystallise from alcohol, acetone, benzene or toluene. The crystalline material formed by the condensation of the dl-base and d-oxymethylenecamphor was therefore not the derivative of the l-base, lB.dA.

0.1042g. gum in 20 c.c. alcohol in a 2dcm. tube at 20° gave:-

$(\alpha)_D^{20} = +248^\circ$, $(\alpha)_{5643} = +315^\circ$, $(\alpha)_{6563} = +186.7^\circ$, $(\alpha)_{4861} = +480^\circ$.

Rotatory Dispersion $Hg_{5463}/Na_D = 1.267$.

The gum was purified by distillation in a standard sublimation apparatus. Two fractions distilled at 0.2 mm., oil-bath 85° and 105°, and had $(\alpha)_D = +256^\circ$, $(\alpha)_{5643} = +300^\circ$

R.D./

R.D. 1.17 (c = 0.41, alcohol).

$(\alpha)_D$ = +230°, $(\alpha)_{5643}$ = +281 R.D. = 1.26 (c = 0.3, alcohol).

The next three fractions distilled at $2.026 \times 10^{-3}$mm., $4.56 \times 10^{-5}$mm., $2.02 \times 10^{-5}$mm., oil-bath 90°, 100°, 124°, and had

$(\alpha)_D$ = +304.8°, $(\alpha)_{5643}$ = +392.8°, R.D.= 1.28 (c = 0.4 alcohol).

$(\alpha)_D$ = +296.1°, $(\alpha)_{5643}$ = +375°.0°, R.D.= 1.27 (c = 0.4 alcohol).

$(\alpha)_D$ = + 306.2°, $(\alpha)_{5643}$ = +390.1°, R.D.= 1.28 (c = 0.3 alcohol).

The first two fractions probably contained unchanged d-oxymethy-:lenecamphor despite previous treatment with alkali; but no mutarotation was detected.

Another condensation was carried out and a 55% yield of a yellow gum was obtained; more thorough treatment with alkali was carried out.

$(\alpha)_D^{17}$ = + 292.2°, $(\alpha)_{5463}$ = +380°, R.D.= 1.30 (c = 0.4 alcohol).

The gum was purified as above. There was no distillation at 0.2 mm. the gum began to distil at $7.56 \times 10^{-2}$ mm. and the first fraction which, for some reason unexplained, had a rose-pink alcoholic solution when viewed through a 2dcm polarimeter tube, had an approximate specific rotatory power $(\alpha)_D$ = +286.6°. The oil bath temperature was raised from 85° to 100° and more gum distilled, $(\alpha)_D^{17.5}$ = +301.8°, $(\alpha)_{5463}$ = +380.4° (c= 0.4) alcohol).

The remainder of the gum distilled at lower pressures, $5.066 \times 10^{-4}$mm. and $2.026 \times 10^{-5}$mm. and had similar rotatory powers.

$(\alpha)_D$ = + 304.7°, $(\alpha)_{5643}$ = +383.3°, R.D. 1.26 (c = 0.5 alcohol)

$(\alpha)_D$ = + 302.6°, $(\alpha)_{5463}$ = +381.9, R.D. 1.26 (c = 0.9 alcohol)

A/

A portion of the yellow gum was dissolved in ether and the ethereal solution divided between two 20 c.c. standard flasks A and B. The ether was then removed and the flask A placed in a highly evacuated desiccator. The flask B was placed in the refrigerator overnight with a trace of ether; then after gentle warming was allowed to stand in a highly evacuated desiccator for some time. The specific rotatory powers of the two specimens were then determined.

A. $(\alpha)_D^{19.5} = + 306.6^\circ$ (c = 0.5, alcohol)

B. $(\alpha)_D^{19.5} = + 282^\circ$, $(\alpha)_{5463} = + 370.5^\circ$ R.D. 1.31 (c = 0.5, alcohol).

The gum above $(\alpha)_D = + 304.7^\circ$ was transferred to a 20 c.c. flask and treated with ether in the refrigerator. The specific rotatory power fell to $(\alpha)_D^{18} = +291.4^\circ$, $(\alpha)_{5463} = +375.3^\circ$ (c = 0.45 alcohol). However, a further sample $(\alpha)_D = +301.1^\circ$ showed practically no change in optical rotatory power on similar treatment with ether; and yet another showed a decrease of $5.5^\circ$. Further investigation showed various apparently unrelated changes in the optical rotatory powers on similar treatment. This indicated that the changes were probably due to experimental procedure and may have resulted from ether retained in the gum.

The matter was not investigated further as part of the purified derivative crystallised and was used to seed a fresh preparation of the compound, carried out with carefully purified d-oxymethylenecamphor. A small amount of crystalline derivative so obtained was very soluble in all organic solvents, m.p. 77 - 79°.

(α)/

$(\alpha)_D^{16} = +308.5^\circ$ (c = 0.45, alcohol).

It was recrystallised from ethyl alcohol containing a trace of ethyl acetate.

$(\alpha)_D = +304.0^\circ$ (c = 0.40, alcohol).

In a subsequent crystallisation when very small initial and final fractions were removed, the specific rotatory power varied only a few degrees, 306-310°. It was difficult to carry out an efficient fractional crystallisation because of the high solubility of the compound.

(7,b). 1-Menthoxyacetyl-1,2:2:4-trimethyl-1:2:3:4-tetrahydro-:quinoline.

The condensation was carried out in the same manner as for the racemic base (p. 78). The amide was a clear yellow gum.

$(\alpha)_D = + 98.0 \pm 4.2^\circ$ (c = 0.31, alcohol, 4dcm.)

(7,c). Acetyl-1-2:2:4-trimethyl-1:2:3:4-tetrahydroquinoline.

This derivative was prepared by refluxing the base with 50% excess acetic anhydride for 30 mins. It was a pleasant smelling viscous oil which did not crystallise at liquid air or solid $CO_2$ temperatures when scratched in contact with various solvents.

$(\alpha)_D^{18} = +477.6^\circ$, $(\alpha)_{5463} = +593.0^\circ$, $(\alpha)_{4861} = +825.8^\circ$ (c = 0.5, alcohol, 2dcm.).

Rotatory Dispersion $Hg_{5463}/Na_D = 1.243$.

$(\alpha)_D^{18} = + 514.8^\circ$, $(\alpha)_{5463} = +622.1^\circ$ (c = 0.4, benzene, 2dcm).

Rotatory/

Rotatory Dispersion $Hg_{5463}/Na_D$ = 1.21; $(M)_D$ = 1490.

Analysis:

Found: C = 77.7%, H = 8.74%

$C_4H_{19}NO$ requires C = 77.4%, H = 8.76%

( 7d) Benzoyl-l-2:2:4-trimethyl-l:2:3:4-tetrahydroquinoline.

0.5g. l-Base was mechanically shaken with 1g. benzoyl chloride in alkaline solution for 30 mins. Under these conditions no benzoylation occurred; unchanged base.( $)_D$ = -47.4° (c = 0.4 , benzene) was recovered.

1.2g. l-base was heated with 1.6g. benzoic anhydride for 2 hrs. at 130° and 5 hrs. at 180°. The reaction mixture was treated as in the similar reaction with the racemic base (p.81). A green gum was isolated which exhibited a specific rotatory power in 0.5% benzene solution $(\alpha)_D^{17.5}$ = + 316.6°. This gum was scratched in contact with a little sodium dried ether and fine crystalline needles separated in the gum. Just sufficient ethyl alcohol was added to dissolve the gum leaving the needles, which were then filtered off and dried in vacuo. The needles, m.p. 180-181°, in 16 c.c. alcohol and 4 c.c. acetone showed no optical rotatory power; this compound was not, therefore, a derivative of the l-base.

The residual green gum then crystallised and was dissolved in the minimum of ethyl alcohol from which it separated in small colourless/

colourless rectangular plates, m.p. 95-6°.

$(\alpha)_D^{16.5}$ = +383.6°, $(\alpha)_{5463}$ =+462.2° (c = 0.18, benzene)

A fractional crystallisation of 2.6g. of this benzoyl derivative yielded fractions with the following rotatory powers ($Na_D$ line).

2.3g. +386.1°; 1.8g., +384.4°; 1.1g., +386.5°; 0.7g. +383.5°; 0.1g., +387.3°. (c = circa. 0.25, benzene).

(7,e). p-Nitrobenzoyl-l-2:2:4-trimethyl-1:2:3:4-tetrahydro-:quinoline.

The l-base was p-nitrobenzoylated by the same method used for the racemic base (p.83). The derivative was obtained in 40% yield as short yellow prisms, m.p. 137-138°.

$(\alpha)_D^{20}$ = +475.0° (c = 0.1, acetone, 2dcm.)

The compound was recrystallised from acetone, m.p. 137-38°

1. $(\alpha)_D^{19}$ = + 462.1° (c = 0.35, acetone, 4dcm).
2. $(\alpha)_D^{20}$ = + 468.2°, $(\alpha)_{5463}^{17}$ = +631.7° (c = 0.1, acetone, 2dcm.)
3. $(\alpha)_D^{18}$ = + 469.5°, $(\alpha)_{5463}^{18}$ = +634.4° (c = 0.33, acetone, 2dcm.)

Analysis

Found: C = 70.4, H = 6.00, N = 8.42 %

$C_{19}H_{20}N_2O_3$ requires: C = 70.4, H = 6.20, N = 8.64 %

The derivatives of the l-base containing the grouping $N - \overset{O}{\overset{\|}{C}} - R$ all showed optical inversion and a marked inflation of the optical rotatory power.

# PART II A

## THE OPTICAL RESOLUTION OF

## dl-2:2:4-TRIMETHYL-1:2:3:4-TETRAHYDROQUINOLINE

## INTRODUCTION

The active bases used in the stereochemical field for the resolution of externally compensated acids are, for the most part, naturally occurring bases of the alkaloid type such as strychnine, quinine and brucine. These bases are obtainable in only one of their active modifications.

This means that, in the majority of cases, the use of such a base provides access to only one of the enantiomeric forms of the acid. The other form is then obtained by using another base which gives a pair of diastereoisomeric salts with reverse solubility relationships; if with the first base the salt l̲B.d̲A. is the less soluble salt, then, with the second, the salt l̲A.d̲B. must be the less soluble.

If both forms of the resolving base are available a comparatively simple method of obtaining both forms of the optically active acid can be employed. This method depends on the fact that the salts d̲A.l̲B. and l̲A.d̲B., as well as the salts l̲A.l̲B. and d̲A.d̲B. are enantiomorphic and possess the same solubility.

If in the resolution of a racemic acid dl̲.A with an active base l̲B, the salt d̲A.l̲B. is less soluble than its diastereo-:isomer, it is removed from the solution; after repeated recrystallisation the d̲A liberated from it is optically pure.

$$\left.\begin{matrix} \underline{d}A \\ \underline{l}A \end{matrix}\right) + 2\ \underline{l}B \longrightarrow \underline{d}A.\underline{l}B + \underline{l}A.\underline{l}B.$$

The/

The more soluble salt l-A.l-B. is left in the mother liquor along with a little of the salt d-A.l-B. Optically pure l-acid can then be obtained by decomposing the impure salt l-A.l-B. and combining the partially resolved, but impure, l-A with the optical antipode of the original active base. The enantiomorphic salt l-A.d-B. is less soluble than the salt d-A.d-B. and crystallises first from the solution. Repeated recrystallisation and subsequent decomposition of this salt yields the optically pure l-acid.

α-Phenylethylamine, hydroxyhydrindamine, tetrahydroquinaldine and p-tolutetrahydroquinaldine are examples of bases available in both active modifications. The first two mentioned have been used extensively in stereochemical work.

There are, however, relatively few active bases readily obtainable in their racemic and active modifications. It was decided, therefore, to investigate the base 2:2:4-trimethyl-1:2:3:4-tetrahydroquinoline (fig. 1) to find if the compound itself was readily obtainable, and if so, if its complete resolution could be easily achieved.

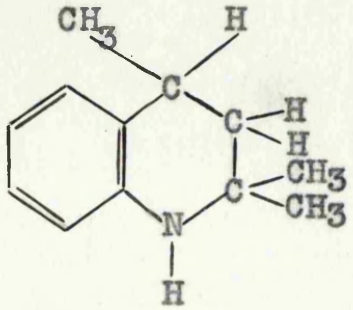



fig. 1.

## THEORETICAL

When equimolecular quantities of aniline and acetone are condensed in the presence of traces of iodine or concentrated hydrochloric acid as catalyst, the product is 2:2:4-trimethyl-1:2-dihydroquinoline.

Knoevenagel[88] and his collaborators were the earliest investigators of this reaction, but they considered the product to be merely the anil of acetone. Reddelien and Thurm[89] on the other hand were of the opinion that it was 2:2:4-trimethyl-1:2-dihydroquinoline and Kalnin[90] called it 3-methyl-2-iso-:propenyl-indoline. Cliffe[91] and other workers[92] supported the contention of Reddelien and Thurm and the work of Craig[93] finally established the dihydroquinoline formulation as correct.

By varying the conditions of the reaction an interesting series of by-products is obtained; but if carried out at 100° in the absence of water and with a trace of hydrochloric acid as catalyst the main product is 2:2:4-trimethyl-1:2-dihydro-:quinoline along with a percentage of its dimer and higher polymers. The polymerisation takes place across the 3:4 double-bond and is greatly enhanced by the presence of higher concentr-:ations of hydrochloric acid (fig. 2).

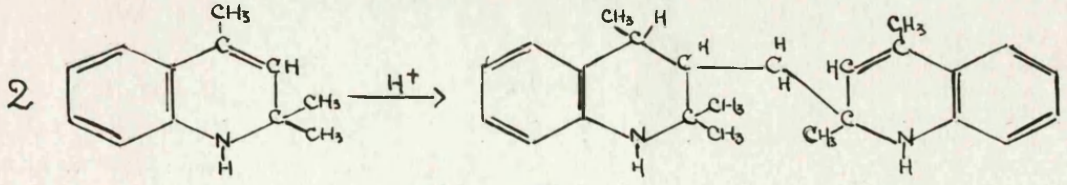


fig. 2

1:2-Dihydroquinolines with a methyl and alkyl group in the 2-position, an alkyl group in the 4-position and variously substituted in the 6-position are used as antioxidants for rubber compositions. In this respect the 6-phenyl[95], 6-butyl[96], 6-ethoxy and 6-phenoxy[97] derivatives of 2:2:4-trimethyl-1:2-dihydroquinoline are used in the rubber industry. 2:2:4-Trimethyl-1:2-dihydroquinoline is, therefore, obtainable commercially in large quantities.

The technical material is a yellow oil containing unchanged aniline. It can be purified by fractional distillation or by conversion to its hydrochloride. The base obtained from the hydrochloride distils 135°/20 mm. as an almost colourless oil which crystallises on standing, m.p. 26-27°. The suppliers state that spontaneous dimerisation tends to occur but this was never encountered when the base was stored in the crystalline state.

2:2:4-Trimethyl-1:2-dihydroquinoline contains no centre of assymetry other than the "asymmetric" nitrogen atom. When it is converted to its dihydro derivative, 2:2:4-trimethyl-1:2:3:4-tetrahydroquinoline, by the reduction of the 3:4 double bond, the carbon atom in the 4-position becomes asymmetric and the base is now externally compensated (fig. 3).

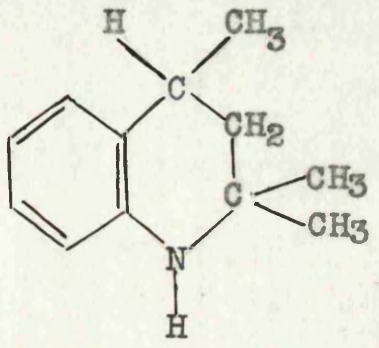



fig. 3.

Knoevenagel[97] achieved the reduction of the 3:4 double-bond with sodium and alcohol but called the reduction product 2:2:3:3-tetramethylindoline. Reddelien and Thurm[99] obtained an identical product by carrying out the reduction in a tube autoclave with hydrogen under 10 atmospheres pressure at 100°, with a nickel-silica catalyst. Craig[92] found that a mixture of the monomer and polymers was completely depolymerised and reduced to the dihydro derivative by shaking with hydrogen in presence of the Raney nickel catalyst under a pressure of 10 atmospheres at 250-280°.

In the present research the reduction of Knoevenagel with Na and alcohol was repeated and the expected product obtained. The reduction was also achieved by the method of Skita-Paal using colloidal palladium. It was found, however, that the most satisfactory method of carrying out the reduction was to use a palladised strontium carbonate catalyst with hydrogen under a pressure of seven atmospheres at room temperature. Using these conditions the reduction was rapid and quantitative. The reduction product, 2:2:4-trimethyl-1:2:3:4-tetrahydro-:quinoline, distilled at 125-27°/10 mm. as a colourless oil which crystallised in the collecting flask as a colourless transparent mass, m.p. 40-41°.

Optical Resolution of dl-2:2:4-Trimethyl-1:2:3:4-tetrahydro-:quinoline.

A number of preliminary experiments were carried out in which/

which the base was crystallised with various optically active acids. The acids used were d-camphor-10-sulphonic acid, tartaric acid, d-$\alpha$-bromocamphor-$\pi$-sulphonic acid and its ammonium salt. The object of these experiments was to find a suitable optically active acid with which to carry out the resolution.

The Tartrate and Bitartrate

Both of these salts were clear yellow glasses which crystallised partially after six months. They had previously failed to crystallise when thoroughly scratched with various organic solvents.

The d-Camphor-10-sulphonate

This salt was not readily obtainable in a crystalline state. It did crystallise, however, in slender needles which could be recrystallised from ethyl acetate. The mother liquors darkened rapidly on standing and tended to deposit sticky or gelatinous materials on concentration. The recrystallised salt had a specific rotation in 0.5% aqueous solution of $+10.8^{\circ}$, whence $(\alpha)_D = +43.9^{\circ}$. This indicated that the salt lB.dA was less soluble than its diastereoisomer as the molecular rotation of the acid in aqueous solution is $+52^{\circ}$.

The d - $\alpha$ - Bromocamphor-$\pi$-sulphonate

Equivalent quantities of crystalline base and aqueous d-d-bromocamphor- -sulphonic acid were mixed on the water-bath and alcohol added to complete the solution. The solution

was/

was evaporated to a yellow syrup which readily crystallised on scratching in contact with ether. This material did not crystallise from the minimum of hot absolute alcohol, but separated in long crystalline needles from aqueous alcoholic solution. 0.1000g. exhibited a rotation $\alpha_D^{17}$ =+0.473 in 0.5% aqueous solution in a 2dm. tube whence $(\alpha)_D^{17}$ = + 47.3, $(M)_D$ = +230°. Further investigation of this salt-formation showed that an initial fraction could be deposited with a specific rotation in 0.5% aqueous solution of +45.7° to 46.7°. The specific rotation fell to a minimum of +43.0 ± 0.9° on repeated crystallisation from aqueous alcohol.

Ammonium Salt Method

In certain cases the resolution of an externally compensated base is effected by the addition of rather less than an equivalent of the ammonium salt of an optically active acid to a hot solution of 2 equivalents of the hydrochloride of the base.

$$2\left.\begin{matrix}\underline{d}B\\ \underline{l}B\end{matrix}\right\} + \underline{d}A.NH_3 + 2HCl. \qquad \underline{d}A.\underline{l}B + \underline{d}A.dB.HCl. + NH_4Cl.$$

The salt $\underline{d}A.\underline{l}B$ is the least soluble of all the possible salts formed and crystallises from the solution.

Pope and Read[49] found in the case of the closely related base tetrahydroquinaldine that this method using ammonium $\underline{d}$-$\alpha$-bromocamphor-$\pi$-sulphonate yielded an initial separation of the pure salt $\underline{d}A.\underline{l}B$.

The application of this method to $\underline{dl}$-2:2:4-trimethyl-1:2:3:4-tetrahydroquinoline gave a yellow oil which crystallised quite/

quite readily and had a specific rotation $(\alpha)_D^{18} = +46.6^\circ$. The conditions of the experiment were varied and the oil and milky supernatant liquor examined separately; but in each case the initial separation of salt had a specific rotation in water + 46.3 to 47.1°.

The fractional crystallisation of the d-$\alpha$-bromocamphor-$\pi$-sulphonate seemed likely to provide a satisfactory means of access to one of the active modifications of the base. The two methods of forming this salt - using the free acid and base or the ammonium salt of the acid and hydrochloride of the base - yielded initial deposits of salt with similar specific rotations and in similar yield. Further experiments, however, using the free acid, showed that after the removal of the bulk of the salt lB.dA. from the solution, concentration of the mother liquors yielded a salt rich in the diastereoisomeric salt dB.dA. Also, by suitably regulating the proportion of alcohol present in the crystallising solution, two salts of quite distinct crystalline habit crystallised almost simultaneously and could be separated mechanically. It was decided, therefore, to carry out the resolution of the base using d-$\alpha$-bromocamphor-$\pi$-sulphonic acid as being the method likely to give the most interesting results.

The Optical Resolution

After mixing the externally compensated base and the calculated quantity of d-$\alpha$-bromocamphor-$\pi$-sulphonic acid, just/

just sufficient 40% alcohol was added to keep the salt in solution just below the boiling temperature. On cooling, there was a copious separation of the salt in hard compact lustrous prisms which in 1% aqueous solution had $(\alpha)_D = +44.8^{\circ}$. This salt was systematically crystallised from varying dilutions of ethyl alcohol until repeated crystallisation failed to lower the specific rotation. It was difficult to ascertain when this state of affairs had been reached as the salt crystallised with a varying number of molecules of water of crystallisation; this caused significant variations in the specific rotatory power. The value for the pure anhydrous salt dA.lB was considered to be $(\alpha)_D^{18} = +44.4 \pm 1.1^{\circ}$.

The base liberated from this salt had a rotation of $\alpha_D^{17} = -40.25^{\circ}$ when examined in 0.5dcm. micro-tube in the homogeneous state. This showed the salt from which it was regenerated to be the salt lB.dA. as assumed.

The aqueous alcoholic mother liquors were not easily worked up. When they were concentrated a brown oil came out of solution and tended to contaminate any crystalline deposit. When sufficient alcohol was added to keep this oil in solution, the crystallisation of the salt was almost inhibited. The constitution of this oil was not determined as it could not be easily isolated; even if this had been possible its dark colour would probably have rendered its polarimetric examination impracticable.

The/

The initial mother liquors containing the bulk of the more soluble salt dA.dB, were concentrated on the water bath. Two fractions of fine soft crystalline needles rich in the salt dA.dB were obtained; the second had a specific rotation $(\alpha)_D = +65.9^\circ$ approximately $2^\circ$ lower than that expected for the optically pure salt dA.dB. Subsequent fractions were mostly contaminated with the dark brown oil, despite attempts to keep it in solution. Consequently the mother liquors were evaporated to dryness leaving a sticky brown mass which could not be induced to crystallise. An attempt was made to render the concentration of the mother liquors more even by using alcoholic ethyl acetate for the fractional crystallisation. In this way it was hoped to eliminate the separation of an oil. The salt was not very soluble in ethyl acetate but crystallised from it in well formed prismatic needles with an accompanying fall in the specific rotation. However, when a little of the salt $(\alpha)_D = +46.6^\circ$, was recrystallised from 30% alcoholic ethyl acetate small white needles separated which had a specific rotation of $(\alpha)_D = +52.9^\circ$. In this solvent the salt dA.dB was apparently less soluble than the diastereoisomeric salt dA.lB. Therefore, the fractions of d-$\alpha$-bromocamphor-$\pi$-sulphonate with molecular rotations greater than $+285^\circ$ (i.e. containing an excess of the salt dA.dB) were recrystallised from 30% alcoholic ethyl acetate. This process, however, proved only partially successful in isolating the pure salt dA.dB. The fraction/

fraction $(\alpha)_D^{18}$ = +65.9° recrystallised from alcoholic ethyl acetate in pure white hemispheres of soft crystalline needles $(\alpha)_D^{18}$ = +67.9°; and concentration of the dark mother liquors yielded a further fraction of this material. The soft crystalline needles were found to be the pure salt dA.dB. However, continued investigation of this crystallisation showed that the diastereoisomeric salts were normally mutually soluble over the range $(M)_D$ + 300 to + 323° giving salts with varying crystalline habits. These salts were not separable by fractional crystallisation from alcoholic ethyl acetate, although this goal was achieved on the one occasion mentioned above.

The various residues with high rotations were treated with alkali and the liberated base extracted and distilled under reduced pressure. The light yellow oil so obtained had a rotatory power in the homogeneous state of $\alpha_D^{17}$ = +26.5 in a 0.5 dcm. micro-tube; this showed the presence of 83% of the enantiomeric d-base.

A portion of this oil in the presence of an equivalent of hydrochloric acid was crystallised with 8% less than the calculated amount of ammonium - l -α-bromocamphor-π-sulphonate, the ammonium salt of the optical antipode of the resolving acid. The enantiomorphic salt lA.dB. separated and was fractionally crystallised from aqueous alcohol. The behaviour of this salt varied from that of its enantiomer only in its manner of crystallisation. Its crystalline habit was distinct from that of/

of the salt dA.lB. which can be explained by the salts being dimorphic. The base liberated from this salt had $\alpha_D^{18}$ = +40.50° and was the optically pure d-base.

Alternative methods of obtaining the d-base, obviating the use of the l-acid, were examined. The first method depended on the crystalline nature of the racemic base as compared with the oily nature of the active modifications. The latter have melting points well below 0°C and were never obtained crystalline. When, therefore, the partially resolved dextro-base was seeded with a little of the racemic base the l-base present crystall-:ised with an equivalent amount of d-base; crystallisation and filtration carried out at low temperatures gave d-base of 96.5% purity.

The second method consisted in converting the crude base from the residues into the acetyl derivative: the racemic acetyl derivative crystallised from the solution in light petroleum, leaving the acetyl derivative of the active modific-:ation in solution. The latter is a clear yellow gum with a high specific rotation; but it was only obtained with 93% purity by this method.

Summary and Discussion of Results.

dl-2:2:4-Trimethyl-1:2:3:4-tetrahydroquinoline was obtained by the reduction of 2:2:4-trimethyl-1:2-dihydroquinoline with a palladised strontium carbonate catalyst under a pressure of 7 atmospheres of hydrogen at room temperature. The dihydro compound was available in quantity from commercial sources.

The complete resolution of dl-2:2:4-trimethyl-1:2:3:4-tetrahydroquinoline was achieved using d- and l-$\alpha$-bromocamphor-$\pi$-sulphonic acid. The enantiomorphic salts lB.dA. and dB.lA were beautifully crystalline but tended to separate with an indefinite number of molecules of water of crystallisation. This behaviour made it difficult to ascertain of the optical purity of the salts without determining the water of crystall-:isation or liberating the base from them. Both active modifi-:cations of the base were obtained in a state of optical purity from these salts.

The active modifications of the base were colourless oils; the racemic base was crystalline. d-Base of 96.5% purity was obtained from the partially resolved d-base regenerated from the residues of the resolution after the removal of the l-base, by crystallisation of the racemic base from the crude oily d-base. The acyl derivatives of the active modifications (l-base examined, PartI) all showed optical inversion and an inflation of the optical rotatory power.

This base might be of use in the resolution of externally compensated/

compensated acids, although it did not show a pronounced tendency to form crystalline salts - the tartrate and d-camphor-10-sulphonate were poorly crystalline. Reactions, other than salt formation, involving the nitrogen atom tended to be sterically hindered by the two methyl groups in the 2-position. A considerable amount of colour was associated with the reactions of this base, but the aqueous solutions of the $\alpha$-bromocamphor-$\pi$-sulphonates became purple in colour only after a considerable time. In the majority of cases clear colourless polarimetric solutions were obtained.

## EXPERIMENTAL

### Note on Presentation of Results and Experimental Error

An optically active salt can normally be considered to have attained a state of optical purity when its specific rotatory power remains unchanged during successive crystall-:isations. The possible sources of error in determining this rotatory power are -

(a) in the preparation of the polarimetric solution

(b) in the length of the polarimetric tube

(c) in the observation of the angle of rotation

as seen from the equation

$$(\alpha) = \frac{100 \times \alpha}{l \times c}$$

$(\alpha)$ = specific rotation

$\alpha$ = angle of rotation

C = weight of substance in 100 c.c. solvent

l = length of polari-:meter tube

Consider the case 0.1000g. salt in 20 c.c. water giving $\alpha = 0.43$ in a 2dm. tube. and $(\alpha)_D = 43.0^\circ$.

(a) The weighing of the specimens of salt were carried out to an accuracy of $\pm$ 0.0001g. An error of this order results in an error of $\pm 0.1^\circ$ on a specific rotation of $43^\circ$ (this is the order of the rotation in question). The volume of the solution was measured from the same burette involving an error of $\pm$ 0.05 c.c. and a resultant error of $\pm 0.01^\circ$ on a specific rotation of $43^\circ$.

(b) The length of the polarimeter tubes used was correct to $\pm$ 0.05 mm. and no error resulted in the specific rotation.

(c)/

(c) The probable error in the observation of the rotation and of the zero reading was obtained by a statistical analysis of various series of readings. It was found that the actual rotation could be obtained to an accuracy of $\pm$ 0.01° to $\pm$0.025, for a series of 10 readings of the angle of rotation and the zero point provided the solutions were perfectly clear. This results in an appreciable error, $\pm$ 1° to $\pm$ 2.5° on the specific rotation under consideration.

In the present case the salt dA.lB. was not very soluble in water and the highest practicable rotation in 2 dcm. tube was of the order $\alpha_D$ = +0.48° and $\alpha_{5463}$ = 0.70°. The writer obtained more regular series of readings using the $Na_D$ than the Hg green line and the majority of readings were taken using the former. As the error arising from (c) was likely to be appreciable, certain of the specific rotations were calculated showing $\pm$ limits of uncertainty of the observed average to assist in deciding if any significant change had occurred in the specific rotatory power. The method of calculation was that of the American Society for Testing Materials in their Manual of Presentation of Data, p.39.

Example.

0.1014g. salt in 20 c.c. water in a 2dm. tube  $\bar{V}$ = standard deviation.

Angle of rotation/

| Angle of rotation | | | Zero Reading | | |
|---|---|---|---|---|---|
| R | | | R | | |
| 0.47 | 0 | 0 | +0.03 | 0 | 0 |
| 0.50 | +3 | 9 | +0.05 | +2 | 4 |
| 0.47 | 0 | 0 | +0.01 | -2 | 4 |
| 0.45 | -2 | 4 | +0.03 | 0 | 0 |
| | +1 | | +0.03 | 0 | 0 |
| 0.48 | | 1 | +0.03 | 0 | 0 |
| 0.48 | +1 | 1 | +0.03 | 0 | 0 |
| 0.47 | 0 | 0 | +0.04 | +1 | 1 |
| 0.47 | 0 | 0 | +0.02 | -1 | 1 |
| 0.47 | 0 | 0 | +0.03 | 0 | 0 |
| 0.47 | 0 | 0 | | | |
| 0.473 | +3 | 15 | +0.03 | 0 | 1.0 |

Zero.

$r = \sqrt{1.5 - (0.3)^2}$

$= 1.18$

$\pm (1.083 \times 1.18) = 1.28$

Zero = $+0.03 \pm 0.0128$

Angle of Rotation: $r = \sqrt{1.0 - (0)^2} = 1$

$(1 \times 1.083) = 1.083$

$= +0.473 \pm 0.01083$

Zero = $+0.03 \pm 0.0128$

---

$= 0.443 \pm 0.0236$

$$(\alpha)_D = \frac{100 \times 0.443}{2 \times 5 \times 1014} = 43.7 \pm 2.3$$

$$\frac{100 \times 0.0236}{2 \times 5 \times 1014}$$

This result means that for this series of 10 readings the true specific rotation lies within the range $43.7 \pm 2.2^{\circ}$, 99 times out of 100. The figure 1.083 is obtained from a table given in the Manual and depends on the number of readings and the limits used, in this case 99 in 100. The range within which the true specific rotation will lie 9 times out of 10 is $43.7 \pm 1.3$; the value 0.611 is used instead of 1.083.

In/

In this research when specific rotations are presented in this manner they were calculated from two series of 10 readings, as shown, and the limits used were 99 in 100, unless otherwise stated.

Purification of Technical 2:2:4-Trimethyl-1:2-dihydroquinoline.

Distillation of the technical material at 20 mm. gave the following fractions:-

(i) 79-100° aniline

(ii) 100-135° aniline plus 2:2:4-trimethyl-1:2-dihydro-:quinoline.

(iii) 135° 2:2:4-trimethyl-1:2-dihydro-:quinoline.

Distillation using an 18" point-column at a pressure of 30 mm. gave an almost quantitative separation of the two oils, and the bulk of the base was purified by this means. An alternative method of purification was also used. This entailed the addition of concentrated hydrochloric acid to an ethereal solution of the base causing an almost immediate precipitation of the hydrochloride of the base. This was filtered off, recrystallised from dilute hydrochloric acid, decomposed with alkali, and the regenerated base extracted and distilled under reduced pressure. A pure specimen of the base was thus obtained, m.p. 26-27°.

Reduction of 2:2:4-Trimethyl-1:2-dihydroquinoline to its Dihydro-derivative 2:2:4-Trimethyl-1:2:3:4-tetrahydroquinoline

Reduction with Sodium and Alcohol.

30g. of 2:2:4-trimethyl-1:2-dihydroquinoline were dissolved in 150 cc. alcohol and refluxed with 30g. of sodium, added gradually, until all the sodium had gone into solution. A further 170 c.c. of alcohol was added during the reaction to avoid the separation of crystalline sodium ethoxide. The solution/

solution was then rendered more strongly alkaline with sodium hydroxide and the base steam-distilled. This proved a rather lengthy process as the base distilled in very fine droplets.

When the distillation was complete the distillate was exactly neutralised with dilute hydrochloric acid and concentrated on the water-bath. The reduced base crystallised as the hydrochloride in small, highly developed, lustrous crystals, m.p. 210°, which were collected and dried under reduced pressure.

Reduction by the Skita-Paal Method.

15g. of 2:2:4-trimethyl-1:2-dihydroquinoline in 75 cc. of ether were hydrogenated using 0.5g. of gum arabic and 0.3g. of palladium chloride as catalyst, under a pressure of 7 atmospheres of hydrogen at room temperature. The absorption of hydrogen proceeded quite rapidly, the calculated amount was taken up in 20 minutes.

The catalyst was removed on filtercel and the ether by distillation, leaving a dark yellow oil. This oil distilled at 125-127°/10 mm. as a colourless oil which crystallised in the receiver. The melting point of this compound, 39-41°, and the melting point of its acetyl derivative, 83°, agreed with the values given by Reddelien and Thurm[89] for 2:2:4-trimethyl-1:2:3:4-tetrahydroquinoline. The catalyst was not easily removed by filtration through filtercel, but the alternative method of isolating the reduction product by steam-distillation and extraction with ether gave much poorer yields.

Reduction with a Palladised Strontium Carbonate Catalyst.

Preparation of the Catalyst.

25g. of finely powdered Analar strontium carbonate were suspended in 300 cc. of water at 60° while a solution of 0.5g. of palladium chloride in 20 cc. water and 1 cc. of 2N-hydrochloric acid was stirred in the suspension. The light brown solid was allowed to settle and the clear supernatant liquor was siphoned off. The solid was again warmed with some 300 cc. water to 60° and the supernatant liquor siphoned off as before. This process was repeated 5-6 times and the solid then filtered off and washed on the filter until completely free from chloride ion. The light brown catalyst was then dried in a vacuum desiccator and preserved in a well-stoppered bottle.

Use of this Catalyst

(i) 20g. of 2:2:4-trimethyl-1:2-dihydroquinoline in 85 cc. of sodium dried ether were shaken at room temperature with 3g. palladised strontium carbonate under a pressure of 7 atmospheres of hydrogen. The requisite fall in pressure from 96 lbs./sq. ins. to 91 lbs./sq. ins. occurred in 25 minutes. The reduction product was isolated as in the Skita-Paal method; the catalyst was easily removed on filtercel. The bulk of the base was reduced in this way.

Analysis

Found: C = 82.3%, H = 9.62%

$C_{12}H_{17}N$ requires: C = 82.3%, H = 9.71%

Reductions/

Reductions using Adams platinum catalyst and Raney Nickel catalyst were also attempted but were unsuccessful due to the poisoning of the catalysts by mercaptan arising from a carbo-:hydrate research. The power hydrogenator itself became poisoned with mercaptan and remained so following thorough treatment with solvents and mercury.

Externally Compensated 2:2:4-Trimethyl-1:2:3:4-tetrahydro-:quinoline.

Externally compensated 2:2:4-trimethyl-1:2:3:4-tetra-:hydroquinoline was a colourless crystalline solid, m.p. 41-41.5°. It distilled at 125-126°/10 mm. as a colourless oil which crystallised in the receiver to a colourless crystalline mass which occasionally contained large, well developed tabular crystals. It had a pleasant smell and in high dilution had a fragrant flower-like odour. It showed purple fluorescence in alcohol and ether and on prolonged exposure to the air developed a brilliant purple surface colouration; the pure colourless base was regenerated by crystallisation from light petroleum. It did not form a carbonate but very readily took up hydrochloric acid from the air. Although there was no unusual source of hydrochloric acid in the laboratory, feathery crystals of hydrochloride invariably formed near the base if exposed for any length of time.

The base crystallised as follows:-

(a)

(a) It separated from its solution in light petroleum in six-sided tabular crystals, distinctly zoned and with the appearance of hollowness towards the centre. Occasionally large highly developed tabular crystals with sharply defined plane faces were obtained; the largest of these weighed 3g. and measured approximately 3.0 x 2.0 x 0.4 cm.

(b) Microscopic examination of a drop of liquid base inoculated with a little of the crystalline base showed it to crystallise in long flattened twinned needles with 90° re-entrant angles.

(c) When the base was melted in a crystallising basin, cooled slowly and the oil poured off before crystallisation was complete, masses of lustrous prismatic needles were obtained. As far as could be ascertained these showed the development of a pinacoid and three well defined domes. Goniometric examination of the base was rendered impracticable both by its low melting point and by poor reflection from the faces. It showed high double refraction and straight extinction in all sections.

Resolution of dl-2:2:4-Trimethyl-1:2:3:4-tetrahydroquinoline.

Preliminary Experiments.

(a) The Tartrate.

0.5g. of dl-2:2:4-trimethyl-1:2:3:4-tetrahydroquinoline in a little alcohol was added to a hot concentrated aqueous solution of 0.43g. d-tartaric acid, and alcohol added to clear the solution. The solution was evaporated to a yellow glass which/

which would not crystallise. Crystallisation was initiated after several months.

(b). The Hydrogen Tartrate

This salt was prepared using 0.5g. base and 0.86g. acid, and like the tartrate was a clear yellow glass which started to crystallise after remaining for several months.

(c). The d-Camphor-10-sulphonate.

(i). 0.35g. of the racemic base was added to a hot concentrated solution of 0.5g. d-camphor-10-sulphonic acid and the solution evaporated to a clear yellow gum. The gum crystallised when rubbed on a watch glass in contact with a little dry ether. The remainder of the gum was seeded with the crystalline salt. The rotation of the microcrystalline powder so obtained could not be determined as the solution in water was too cloudy to permit of accurate polarimetric examination. The salt would not crystallise from various dilutions of ethyl and methyl alcohols.

(ii) 2g. d-Camphor-10-sulphonic acid in 8 cc. water were added to 1.4g. crystalline base in a little alcohol on the water-bath. The solution was allowed to evaporate spontaneously and was seeded from time to time with crystalline salt from (i). This treatment yielded only a partially crystalline syrup. The syrup was taken up in the minimum of hot absolute alcohol and allowed to evaporate very slowly. In this way a separation of slender crystalline needles was obtained. The crystals were filtered with difficulty from the bluish mother liquors, washed

with/

with a little very dilute alcohol and dried in vacuo.

0.1001g. in 20 cc. water had a rotation $\alpha_D^{16.5} = 0.13^\circ$ in a 2 dm. polarimeter tube, whence $(\alpha)_D^{16.5} = +12.9^\circ$ and $(M)_D = +52.5^\circ$.

The salt was very soluble in most organic solvents but crystallised from ethyl acetate in dense clusters of needles. The solution in ethyl acetate darkened rapidly and tended to deposit sticky or gelatinous materials.

0.2810g. in 35 cc. water exhibited a rotation $\alpha_D^{17} = +0.23^\circ$ in a 4dm. tube, whence $(\alpha)_D^{17} = +11.1$ and $(M)_D = +45.1^\circ$.

Found: C = 64.33%, H = 8.40%

$C_{22}H_{33}O_4NS$ requires: C = 64.62%, H = 8.10%

(d). The d-$\alpha$-Bromocamphor-$\pi$-sulphonate.

(i) 0.5g. crystalline dl-2:2:4-trimethyl-1:2:3:4-tetra-:hydroquinoline was added to a hot aqueous solution of 0.9g. d-$\alpha$-bromocamphor-$\pi$-sulphonic acid and alcohol added to effect complete solution. The solution was evaporated to a clear yellow syrup which crystallised readily on scratching in contact with a little dry ether. The crystalline material sintered at 160° and melted at 168-176°. 0.1002g. in 20 cc. water had a rotation $\alpha_D^{17.5} = +0.529^\circ$ in a 2dm. tube whence $(\alpha)_D^{17.5} = +52.7^\circ$. (The anhydrous salt with $(\alpha)_D = +57.2^\circ$ would have $(M)_D = +278^\circ$ which is the value of the molecular rotation of ammonium d-$\alpha$-bromocamphor-$\pi$-sulphonate determined under the same conditions).

The/

The salt did not crystallise from ethyl alcohol; but when the solution was diluted with water and allowed to evaporate spontaneously the salt separated in prismatic needles, m.p. 170-176°.

0.1012g. in 19.8 cc. water exhibited a rotation $\alpha_D^{18} = +0.47^\circ$ in a 2dcm. tube whence $(\alpha)_D^{18} = +46.5^\circ$.

(ii) 2.6g. base and 15 cc. N-acid were mixed on the water-bath and alcohol added to complete the solution. Microscopic examination of a drop of this solution showed the formation of rosettes of short crystalline needles followed by the deposition of aggregates of long slender needles. The solution was allowed to cool when 2.16g. crisp crystalline salt came out of solution and was filtered off and dried in vacuuo, m.p. 170-176°.

$(\alpha)_D^{19} = +46.1^\circ$ (c = 0.51, water).

The salt was recrystallised from 25% ethyl alcohol and a yield of 1.64g. prismatic needles obtained.

$(\alpha)_D^{18} = +44.2^\circ$ (c = 0.65, water). m.p. 120-126°.

Further crystallisation from 20 cc. 30% ethyl alcohol yielded 1.3g. long flattened needles.

$(\alpha)_D^{18} = +43.4^\circ$ (c = 0.54, water). m.p. 120-126°.

After a further three crystallisations the specific rotation remained steady at +42.8°.

(iii) Experiment (ii) was repeated without the addition of ethyl alcohol. The salt which separated had $(\alpha)_D^{17.5} = +50.0^\circ$. Recrystallisation of this salt from 47 cc. 19% alcohol yielded 3.1g./

3.1g. prismatic needles with $(\alpha)_D^{18} = +44.9^\circ$.

A drop of the initial mother liquors was seen under the microscope to contain on evaporation two distinct types of crystals; prismatic needles rich in the salt l-A.d-B. and aggregates of long slender needles rich in the salt d-A.d-B. The mother liquors were concetrated and a brown oil which separated was redissolved in alcohol; a fraction of greyish crystalline salt separated with $(\alpha)_D^{18} = +62.0^\circ$.

(iv). Experiment (ii) repeated with the addition of 10 cc. water and 7 cc. alcohol; the crystallisation was allowed to proceed overnight. Two types of crystals were deposited.

1. 3.9g. hard prismatic needles forming a bottom layer. $(\alpha)_D^{18} = +47.3^\circ$ (c= 0.6, water). Impure salt l-B.d-A.
2. A number of dense white hemispheres of soft crystall-:ine needles which were mechanically removed. $(\alpha)_D^{18} = +62.1^\circ$ (c= 0.5, water). Impure salt d-B.d-A.

These and similar experiments indicated that the pure salt d-A.l-B. could be obtained and that it might also be possible to obtain the diastereoisomeric salt d-B.d-A.

(e) Ammonium Salt Method.

(i) An almost boiling concentrated solution of 1g. of dl-2:2:4-trimethyl-1:2:3:4-tetrahydroquinoline hydrochloride was added to a hot aqueous solution of 6.72g. ammonium d-$\alpha$-bromo-:camphor-$\pi$-sulphonate. The solution immediately became intensely milky and a yellow oil separated. The oil crystallised on seeding with the salt l-B.d-A.

0.1008g. in 20 cc. water had a rotation $\alpha_D^{18} = +0.477^\circ$ in a 2dm. tube whence $(\alpha)_D^{18} = +47.3^\circ$.

(ii). Experiment (i) was repeated using more concentrated solutions. The oil crystallised immediately on scratching and 13.g. salt was filtered off, washed and dried in vacuo .

$(\alpha)_D^{17.5} = +47.6^\circ$ (c = 0.54, water).

(iii) Experiment (i) was repeated with the addition of 17 cc. water. There was no immediate separation of an oil, but on cooling small droplets of oil separated and crystallised almost immediately. Yield 1.2g.

$(\alpha)_D^{17.5} = +46.9^\circ$ (c = 0.53, water, 2dcm. tube).

Further experiments gave similar results. The salt 1B.dA. was never obtained with a specific rotatory power less than $+46.5^\circ$.

Optical Resolution of dl-2:2:4-Trimethyl-1:2:3:4-tetrahydro-:quinoline.

The resolution was carried out using d- and l- α-bromo-:camphor-π-sulphonic acids as the resolving acids. This was considered to be the best method available and approximately 50% yields of the l-base were obtained. No quantitative figure can be given for the yields of the d-base, but they were considerably less that 50%. A typical case was:-

40g. of crystalline racemic base and 240 cc. of 0.96N-d-α-bromocamphor-π-sulphonic acid were mixed on the water-bath and 140 cc. water plus 90 cc. alcohol added. On cooling, there was a/

a copious separation of the optically impure salt lB.dA. in colourless, compact, lustrous prisms: 58g., $(\alpha)_D$ = +46.6°, (c = 0.5, water). After six crystallisations from 30% ethyl alcohol the salt lB.dA (30g.) was considered to be optically pure.

1-2:2:4-Trimethyl-1:2:3:4-tetrahydroquinoline-d-$\alpha$-bromocamphor-$\pi$-sulphonic acid.

This salt crystallised in prismatic needles showing hexagonal development and well defined domes; it occasionally separated in long flattened needles. The salt crystallised with a varying number of molecules of water: m.p. 120-126° sinters 115°.

$(\alpha)_D^{18}$ = + 42.8 ± 1.1° (c = 0.62, water).

Found (anhydrous salt): C = 54.0, H = 6.71%.

$C_{22}H_{32}O_4BrS$ requires: C = 54.3, H = 6.59%.

4.170mg. lost 0.267mg. at 110° showing the presence of 1.8 molecules of water of crystallisation.

The salt $(\alpha)_D$ = 42.8 ± 1.1° therefore had $(M)_D$ = +221.9 ± 5.7°.

The pure salt lA.dB. was also obtained with 1.6, 1.9 and 2.3 molecules of water of crystallisation, and the salts had respectively $(M)_D$ = +223.4 ± 7.6°; 222.1 ± 4.4°, 221.7 ± 8.5° as calculated from their specific rotations.

The specific rotatory power of the pure anhydrous salt dA.lB. was considered to be $(\ )_D$ = +44.4 ± 1.1° (water), m.p. 179-80°.

1-2:2:4-Trimethyl-1:2:3:4-tetrahydroquinoline.

The salt lB.dA. was treated with alkali and the liberated base extracted with ether. The ethereal solution was dried over anhydrous sodium sulphate and the ether removed by distillation. 7.2g. of a pleasant smelling brownish oil were obtained from 20g. salt.

0.1336g. in 20 cc. alcohol at 22° gave:-

| | $Na_D$ | $Hg_{5463}$ | 4861 | 4358 |
|---|---|---|---|---|
| $\alpha$ | -0.63 | -0.79 | -1.22 | -1.57 |
| $(\alpha)$ | -47.5 | -59.1 | -91.6 | -117.0 |

The l-base distilled at 92°/1.4mm., 88°/1.1mm., 76°/0.3mm. as a colourless oil.

$\alpha_D^{17} = -40.25°$, $\alpha_{5463}^{17} = -51.36$ (homogeneous, 0.5dcm.).

$(\alpha)_D^{15} = -68.7°$, $(\alpha)_{5463}^{15} = -87.6$ (c = 1.3, benzene).

The l-base did not crystallise at 0°, but in a bath of liquid air, alone or in a little light petroleum, crystallisation appeared to occur; the crystalline material so obtained melted at a temperature which could not be established. The l-base, therefore, appeared to crystallise at a temperature far below the ordinary one, whereas the racemic form was normally crystalline at room temperature and melted at 40.41.5°. A somewhat similar case is shown by the active and inactive tetrahydroquinaldines.

$n_D^{17°}$ 1.5551 $d_4^{20°}$ 0.9865.

The above constants of the l-base were determined.

1-2:2:4/

1-2:2:4-Trimethyl-1:2:3:4-tetrahydroquinoline Hydrochloride.

The hydrochloride was prepared by dissolving the active base in just sufficient 1.1N-hydrochloric acid on the water-bath. Small, compact, lustrous, very highly-developed crystals of the hydrochloride separated on cooling, m.p. 206-209°.

0.1025g. in 20 cc. water in a 2dm. tube had $(\alpha)_D$ = -28.1 ± 2.2° (n = 20). The mean value for a series of determin-:ations was -27.9 ±1.8°.

Found: Cl = 17.0%

$C_{12}H_{17}N.HCl$ requires: Cl = 16.8%

The water of crystallisation could not be determined because of the volatile nature of the salt, but the analysis indicated that there was none. The molecular rotation was thus $(M)_D$ = -59.0 ± 3.8°.

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The acetyl, benzoyl and p-nitrobenzoyl derivatives of l-2:2:4-trimethyl-1:2:3:4-tetrahydroquinoline are described in Part I (7, c.d. ande). As compared with the parent base they all showed optical inversion, with high dextrorotations.

1-2:2:4-Trimethyl-1:2:3:4-tetrahydroquinoline-l-α-bromocamphor-π-sulphonate

0.38g. l-base was dissolved in 2 c.c. 1.1N-hydrochloric acid on the water-bath and a hot aqueous solution of 0.7g. of the ammonium salt of the l-acid added. The salt lB.lA separated immediately as an oil which crystallised to a hard white crystalline mass. The salt was collected, washed with a little water, and dried in vacuo: m.p. 170-76°.

$(\alpha)_D$/

$(\alpha)_D^{17} = -67.9 \pm 2.6^\circ$ (c = 0.52, water).

$(\alpha)_{5463}^{17} = -84.8 \pm 1.8^\circ$.

This salt contained 0.36 molecules of water of crystallisation:

$(M)_D = -334.9 \pm 12.6^\circ$.

The Enantiomeric d-Base

d-2:2:4-Trimethyl-1:2:3:4-tetrahydroquinoline--l-$\alpha$-bromocamphor-$\pi$-sulphonate.

The enantiomeric d-base was obtained as the salt dB.lA.

The residues from the resolution were treated with alkali and the liberated base extracted with ether, the ether removed by distillation and the base distilled under reduced pressure. The yellow oils obtained distilled at $80^\circ$/0.65mm. and exhibited rotatory powers in 0.5 dcm. tubes in the homogeneous state.

$\alpha_D^{16} = +26.5^\circ$ 82.9% d-base.

$\alpha_D^{16} = +28.0^\circ$ 84.8% d-base.

The salt dB.lA. was then prepared by crystallising these oils in the presence of an equivalent of hydrochloric acid with 8% less than the calculated amount of ammonium-l-$\alpha$-bromocamphor-$\pi$-sulphonate. The salt dB.lA separated as an oil which crystallised on scratching: m.p. 118-126°.

$(\alpha)_D^{17} = -43.9^\circ$ (c = 0.52, water).

After/

After 3 crystallisations from 30% ethyl alcohol the salt lA.dB. was obtained in an optically pure state.

$(\alpha)_D = -42.7^\circ \pm 1.3^\circ$ ($c = 0.6$ / $n = 20$). water

The combination of the possible error in the observation of the angle of rotation and the variation in the number of molecules of water of crystallisation made it difficult to decide when the salt was optically pure.

Found: C = 54.0, H = 6.93%

$C_{22}H_{32}O_4NBrS$ requires: C = 54.3, H = 6.59%

3.905mg. lost 0.235mg. at 110° showing the presence of 1.7 molecules of water of crystallisation:

$(M)_D = -222.6 \pm 8.3^\circ$.

d-2:2:4-Trimethyl-1:2:3:4-tetrahydroquinoline.

The d-base was obtained from the salt dB.lA in the same way as the l-base from the enantiomorphic salt lB.dA. It distilled at 95°/1.6mm. as a colourless oil and had

$(\alpha)_D^{15} = +40.51^\circ$ (homogeneous, 0.5dcm.)

$\alpha_{5463} = +51.88^\circ$, $-\alpha_{4686} = +77.85^\circ$, $\alpha_{6503} = +29.42^\circ$

Rotatory Dispersion $Hg_{5463}/Na_D = 1.28$, $n_D^{17^\circ} = 1.556$

$(\alpha)_D^{14} = +68.2^\circ$, $(\alpha)_{5463}^{14} = +87.9^\circ$ (benzene, c = 1.5)

d-2:2:4-Trimethyl-1:2:3:4-tetrahydroquinoline Hydrochloride.

This salt was prepared by dissolving the d-base in the minimum amount of 1.1N-hydrochloric acid on the water-bath. The/

The salt which separated on cooling was recrystallised from dilute hydrochloric acid; the crystals were very lustrous and well-developed. Attempts to grow crystals sufficiently large for a full goniometric examination were unsuccessful: m.p. 207-09°.

$(\alpha)_D^{18}$ = +27.8 ± 1.0° (c = 0.8, water, n = 20).

$(M)_D$ = 58.8 ± 2.1°.

Found: Cl = 16.62%

$C_{12}H_{17}N.HCl$ requires: Cl = 16.79%.

d-2:2:4-Trimethyl-1:2:3:4-tetrahydroquinoline d-α-bromocamphor-π-sulphonic acid.

This salt was obtained by concentrating the mother liquors after the removal of the salt lB.dA. The separation of a brown oil hindered this process; it was kept in solution by the addition of alcohol to the solution. A stage was reached in the concentration when the oil persisted in separating and the mother liquors were taken to dryness. Immediately prior to this a fraction of dense hemispheres of pure white needles were obtained.

$(\alpha)_D$ = +65.9° (water, 2dcm.)

When recrystallised from 30% alcoholic ethyl acetate, the optically pure salt dA.dB. was obtained, m.p. 170-176°.

$(\alpha)_D$ = 67.7 ± 1.2° (c = 0.61, water).

Found: C = 54.3, H = 6.73%

$C_{22}H_{32}O_4NBrS$ requires: C = 54.3, H = 6.59%

There/

There were 0.5 molecules of water of crystallisation present and thus $(M)_D = +335.0 \pm 5.9^\circ$.
The base liberated from this salt had $(\alpha)_D^{15} = +68.3^\circ$ (c = 1.0, benzene).

The separation of the pure salt dA.dB. in this manner was the exception rather than the rule. In subsequent resolutions the purest salt obtained in this way had $(\alpha)_D = +65.6^\circ$. The alcoholic ethyl acetate solution tended to deposit sticky or gelatinous materials.

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From the values of the molecular rotatory powers of the various salts recorded above, the molecular rotatory powers of the optically active basic and acidic ions can be calculated and compared with those found for the 2:2:4-trimethyl-1:2:3:4-tetrahydroquinoline hydrochlroides and the ammonium α-bromo-:camphor-π-sulphonates by means of the formulae:

(M) of dB.dA. + (M) of lB.dA = 2(M) of dA ion.

(M) of dB.dA. - (M) of lB.dA. = 2(M) of dB ion.

The following table gives the values of $(M)_D$ of the ions found in these ways.

| | lB | dB | lA | dA |
|---|---|---|---|---|
| Calculated | $-56.2 \pm 10.4^\circ$ | $+56.6 \pm 5.8$ | $-278.8 \pm 10.4$ | $+278.5 \pm 5.8$ |
| Found | $-59.0 \pm 3.8$ | $+58.8 \pm 2.1$ | $-278.1 \pm 4.0$ | $+277.5 \pm 4.4$ |

The following table shows the values of the molecular rotations of the salts calculated from their specific rotations found, as compared with the algebraic sum of the molecular rotations/

rotations of the active basic and acidions (calculated);-

| | dA.lB | lA.dB | dA.dB | lA.lB |
|---|---|---|---|---|
| Calculated | +218.5 ± 8.2 | -219.3 ± 6.1 | +336.3± 6.5 | -336.5± 7.8 |
| Found | +221.9 ± 5.7 | -222.6 ± 8.3 | +335.0± 5.9 | -334.9±12.6 |

The values of the molecular rotatory powers of the ions and salts calculated in the two different ways differ somewhat, but such differences are not unusual.[49a]

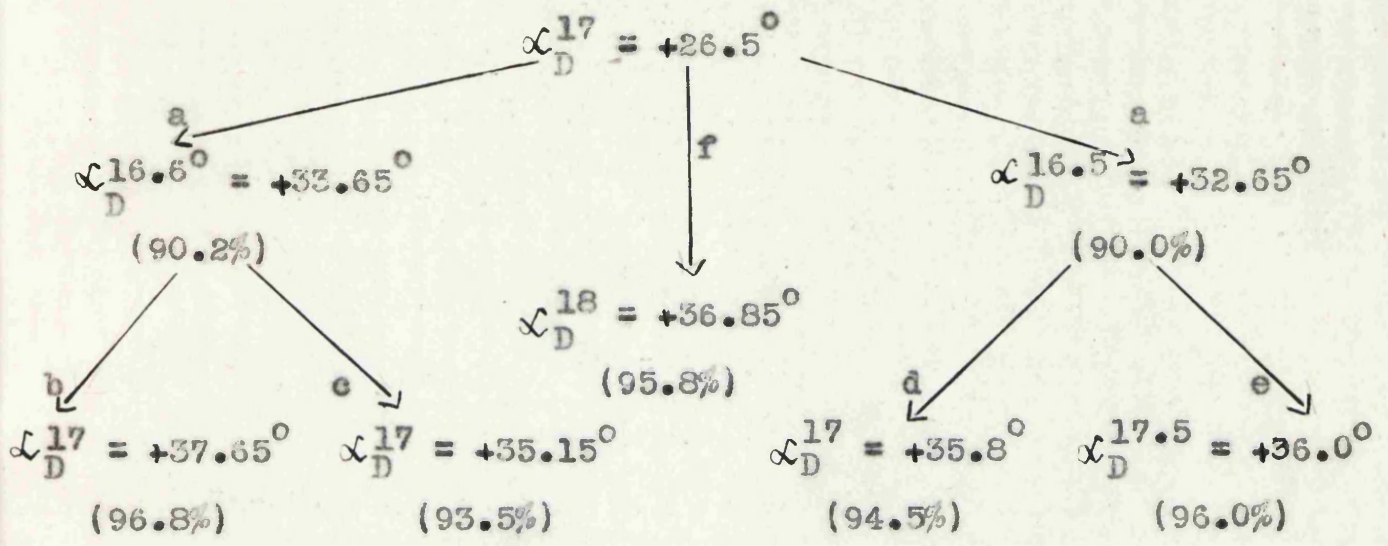
The following alternative methods for obtaining the enantiomeric d-base were investigated but were found to be only partially successful. These methods did not involve the use of l-$\alpha$-bromocamphor-$\pi$-sulphonic acid, the optical antipode of the resolving acid.

1. The first method consisted in inoculating, with the crystalline racemic base, the optically crude oily base containing 82% d-base. The crystalline racemic base which separated was filtered off. The most satisfactory procedure was found to be to inoculate the oil, place in the refrigerator at -10° for 2 days, remove and stir the apparently completely crystalline material until the temperature rose to +4°, replace in the refrigerator for a day and pipette off the supernatant oil. In this way d-base of 96.8% purity was obtained.

$\alpha_D^{17}$ = +37.65° (homogeneous, 0.5dm.)

The accompanying table gives an indication of this investigation.

Partially resolved d-base (82.9%)




The percentages refer to amount of d-base present.

a = seeded with racemic base and filtered at room temperature.

b = placed in refrigerator for 2 days, stirred (see text) and oil removed by pipette.

c = oil filtered from crystals after removal of bulk of oil by pipette.

d = placed in refrigerator at $-10^\circ$ for two days and filtered in the refrigerator without stirring.

e = as d but filtered after stirring.

f = placed in refrigerator for 3 days at $-10^\circ$, and filtered in refrigerator after stirring.

All rotations were taken in 0.5dm. tubes (homogeneous)

When no stirring (as described in text) was carried out the material appeared completely crystalline with no supernatant oil. Stirring produced this oil, and in the subsequent filtration/

filtration after a further period in the refrigerator the minimum of the oil filtered through the crystalline racemic base.

The rotatory powers were determined in the homogeneous state in 0.5dm. tubes.

2. The second method entailed the acetylation of the crude oil (82% d-base) with acetic anhydride and inoculation of the resulting gum, in ligroin, with the acetyl derivative of the racemic base. The l-base present was thus removed as the crystalline acetyl-dl-base and the acetyl d-base, a gum, left in solution. However, the purest specimen of d-acetyl derivative obtained in this way in a series of experiments had

$$(\alpha)_D^{17.5} = -443.7^\circ \quad (c = 0.55, \text{alcohol})$$

This showed the presence of only 93% d-base as calculated from the specific rotatory power of the pure acetyl-l-base, $(\alpha)_D^{18} = +477.0^\circ$.

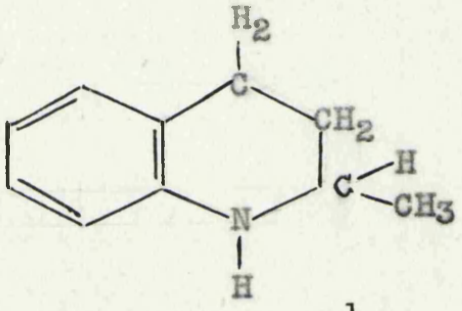
# PART II B

## EXPERIMENTS ON THE OPTICAL RESOLUTION

## OF dl-TETRAHYDROQUINALDINE

## THEORETICAL

As shown originally by Pope and Peachey[100] dl-ac. tetrahydroquinaldine (fig. 1 ) is readily resolved by means of d-$\alpha$-bromocamphor-$\pi$-sulphonic acid, according to the so-called "salt-formation" method of Pasteur.



1.

The process of resolution depends upon the fact that the salt dA.lB is less soluble than the diastereoisomeric salt dA.dB:

$$2dA + dl\,B = dA.lB + dA.dB.$$

In examples of this kind the less soluble salt has a higher melting-point than its diastereoisomer, which often tends to be deposited in an amorphous or gummy condition. This particular optical resolution has been investigated very fully. Moreover, the same base has been resolved by taking advantage of the different speeds with which its d- and l- forms react with d-oxymethylenecamphor. A considersation of these two methods led to an examination of further possible ways of applying an optically active acid in resolving this base, and the experiments outlined below were carried out with this object in view.

(1) It seemed possible that the idea of preferential combination

combination (or different reaction-velocity) might apply to the "salt-formation" method of optical resolution. Accordingly, 2 equivalents of the dl-base were dissolved in light petroleum and 1 equivalent of the d-acid in water. These solutions were shaken together in a mechanical shaker and water added from time to time to prevent crystallisation taking place. After 2 hours the layers were separated and the petroleum layer dried over calcium chloride. After the removal of the solvent the residual base was examined in a 0.5dm. micro-tube in the polar-:imeter and found to be optically inactive.

The aqueous layer was shaken with a little light petroleum to remove mechanically retained base and then evaporated to dryness on the water-bath in a weighed dish. The salt was obtained as a viscid mass, so dark in colour that its rotation in water could not be found. If there had been no preferential combination the specific rotation of this mixture would have been the mean of the values of the salts dA.lB and dA.dB, viz. $+32.22^{\circ}$ and $+87.49^{\circ}$ respectively, with $(M)_D$ of about $+273^{\circ}$.

To overcome this difficulty, the base was liberated from the viscid mixture by the addition of baryta, extracted with light petroleum and examined in a micro-tube as above. Again there was no perceptible optical rotation. The experiment was repeated several times; but in no case could a perceptible optical rotation be established in either the residual or liberated base.

(2)/

(2) A method of partial neutralisation was next examined.

Equivalent amounts of dl-base and d-acid were dissolved in hot water to give an equimolecular mixture of the salts dA.lB and dA.dB. Powdered baryta, $BaOH_2.8H_2O$, was then added in portions and the liberated base steam-distilled off each time, the distillates being collected separately so as to obtain a fractional neutralisation. Each fraction of the base was extracted with light petroleum and dried over calcium chloride; after the removal of the solvent the base was examined in the polarimeter. In no case, however, was a perceptible optical rotation observed.

These results indicate that the resolution of dl-ac.-tetrahydroquinaldine with d-$\alpha$-bromocamphor-$\pi$-sulphonic acid is a direct consequence of the difference in the solubility between the diastereoisomeric salts dA.lB and dA.dB., and that it cannot be achieved by the methods outlined above.

## EXPERIMENTAL

Investigation of possible new methods of resolving dl - ac. - Tetrahydroquinaldine.

1. 2 equivalents (4 c.c.) of pure dl-ac.-tetrahydroquinaldine in light petroleum (40 c.c.) and 1 equivalent of d-α-bromo-camphor-π-sulphonic acid in water (100 c.c.) were placed in a bottle and shaken vigorously in a mechanical shaker. Water was added from time to time to prevent crystallisation taking place; the volume of the aqueous layer at the end of the experiment was 580 c.c. After two hours the layers were separated.

The light petroleum layer was shaken with a little water to remove any trace of salt and dried over calcium chloride. After removal of the solvent the unchanged base, a brown oil, was distilled at 20mm. and the resulting light yellow oil was examined polarimetrically in a 0.5 dm. micro-tube; there was no appreciable optical rotation.

The aqueous layer was shaken with a little light petrol-eum to remove any mechanically retained base and evaporated to dryness on the water-bath in a weighed porcelain dish. The resulting viscid brown salt was treated with a known weight of freshly powdered baryta and the liberated base extracted with light petroleum. After drying over calcium chloride the light petroleum was removed by distillation and the/

the base obtained as a brown oil. It was too discoloured to allow of accurate polarimetric determination; after distill-:ation at 10-15mm. the small amount of pale yellow base showed no perceptible optical rotation in a 0.5dm. micro-tube.

Extremely careful evaporation of the aqueous layer always yielded the salt as a viscid brown mass ; and in no case did the residual or liberated bases show any perceptible optical rotation.

2. 1 Equivalent (60.4 c.c.) of N-d-$\alpha$-bromocamphor-$\pi$-sulphonic acid was mixed with one equivalent (8g.) dl-tetrahydroquinaldine in a 500 c.c. round-bottomed flask. 1.74g. freshly powdered baryta ($\frac{1}{2}$ theoretical amount to liberate the total base) was added and the mixture steam-distilled. There was no visible trace of the base in the distillate and a further gram of baryta was added and the distillation continued. The distillate was extracted with light petroleum. The reaction mixture was diluted with a view to extracting it with light petroleum to remove any undistilled base; but the salt separated as a lower oily layer and crystallised. When sufficient water was added to keep the salt in solution, it still tended to separate when shaken with light petroleum; this procedure was not pursued. The extract was dried over anhydrous sodium sulphate and the solvent removed by distillation. The residual base had no perceptible optical rotation when examined in a 0.5dm. tube.

1.5g. baryta was then added but again the base obtained by steam/

steam distillation was optically inactive. The remaining fractions examined in the same way had no apparent optical rotation. In most cases the fractions were distilled at 15mm. so that the base could be examined with some degree of accuracy in the polarimeter. Further experiments gave identical results; never was a trace of optical activity detected.

The active tetrahydroquinaldines have an optical rotation in the homogeneous state in a 0.5dm. tube $\alpha_D = \pm 30.6^{\circ}$ so that even the smallest excess of one of the active modifications in the liberated base would have been detectable on polarimetric examination.

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