THESIS

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DEGREE OF DOCTOR OF PHILOSOPHY

by

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SUMMARY

Approaches to Azatropones

Previous work towards the synthesis of azatropones has been reviewed.

Various routes to benz[f]azatropones and benz[f]azatropolones have been investigated.

The acyloin reaction on methyl-N-[2-methoxycarbonylethyl]-anthranilate led to a variety of products, in which the presence of the desired seven membered ring ketol could only be inferred.

Claisen condensation of diethyl oxalate with ethyl-N-[o-ethoxycarbonylmethylphenyl]-N-toluene-p-sulphonylglycine led unexpectedly to a known substituted oxindole as well as to other products. The possible mechanism is discussed.

Claisen condensation of diethyl malonate with methyl-N-ethoxycarbonylmethyl-N-toluene-p-sulphonyl anthranilate, under two different sets of reaction conditions, led to two different but related indolone derivatives of unusual structure, the evidence for which is discussed: a mechanism for their formation is proposed.

Some brominated derivatives of 2,3,4,5-tetrahydrobenz[f] azepin-5-one have been synthesised, together with sundry oxidation, dehydrobromination, and dehydrogenation products.

An attempt to synthesise benz[f]azepin-3-one gave a known dimeric product containing the quinoline nucleus: presumably by a mechanism involving an unusual type of benzoin reaction.

Attempts to prepare dibenz[b,e]azepin-4-one are described.

Suggestions for further work in this field are made.

ACKNOWLEDGEMENTS

The author would like to express his sincere gratitude to Dr. G.R. Proctor, under whose guidance this work was performed, for much invaluable advice and encouragement, to Professor P.L. Pauson for the use of the facilities of his department during this study, to the analytical department and Dr. P. Bladon, for micro-analysis, and infrared and n.m.r. spectra, to Mrs. L. Rees and Miss C. McWhinnie for technical assistance and also to the Science Research Council for the award of a research studentship.

APPROACHES TO AZATROPONES

CONTENTS

INTRODUCTION

Aromaticity

The theory of aromaticity of chemical compounds has undergone, in the past century, a progressive change, from the qualitative observations of the late nineteenth century, to the quantitative calculations of the present day.

From the earliest attempts to explain the structure of benzene, 'the marsh-gas of the aromatic series'[1]; by Armstrong and Baeyer[2], Claus[2], Ladenberg (I)[2], Dewar (II)[2], and Kekule (III)[2], whose theories have become familiar,

I

II

a b

III

modern chemists have developed the ability to synthesise compounds which in fact contain the structures (I)[3], (II)[3,4], and (III a or b)[5].

Kekule's[6] resonance structures (III) for benzene have been described by Baker[2], as, 'perhaps the most fruitful single suggestion in the history of organic chemistry'. This accolade may not be undeserved, in the light of the fact that Kekule's theory was proposed almost fifty years before the advent of the electronic theory of valency.

The revolutionary nature of Kekule's description of the benzene nucleus, was in his recognition that the 'second half' of a double bond, unlike a single bond, could not be assigned a fixed position in the molecule.

In the ensuing years, the characteristic properties of benzenoid aromatic molecules became recognised. The stability of the system was shown, by its ease of formation and the difficulty of effecting addition reactions at the double bonds; whereas the ring hydrogen atoms were readily replaced by other groups in electrophilic substitution reactions, e.g. sulphonation, nitration, halogenation, acylation, etc. The aromatic nucleus was also noted to confer unusual properties on substituents, e.g. acidity of phenols, the lowered basicity of aromatic amines and their ability to undergo azo coupling.

A major advance in the understanding of these reactions came in 1925, when Armit and Robinson[7] proposed the theory of the 'aromatic sextet', as a group of mobile electrons responsible for the unique character of the system. With no mathematical foundation, but a wealth of empirical information, this theory served to interpret and predict the aromaticity, not only of carbocyclic, but also that of heterocyclic compounds such as pyridine and pyrrole.

A few years later (about 1930), saw the birth of the wave mechanical treatment of aromaticity. Two methods were evolved; the resonance theory[8] developed by Pauling and others, and the molecular orbital theory due mainly to Huckel[9,10].

The resonance theory allowed mathematical calculation of resonance energies, which are experimentally measurable, and striking agreement with theory was frequently obtained. Consequently the concept continued to find favour among chemists, with its use of classical 'structures' which were already well establishe

The Huckel theory, on the other hand, had a less immediate appeal, since its molecular orbitals had no obvious counterpart in classical chemistry. However, the results provided by this method resolved many of the ambiguities of the other theory.

The molecular orbital approach imagines that in an isolated aromatic system, such as benzene, each pair of adjacent atoms has between them a localised two electron band, called a σ-bond, and that the remaining six valency electrons, called π-electrons, are not localised in particular bonds, but occupy orbits which extend over all six carbon atoms. The number of these orbits, or molecular orbitals, is equal to the number of atoms in the system, and each molecular orbital is a function of the atomic orbitals of the atoms concerned.

It is therefore possible to construct a set of n simultaneous equations for the n atoms in the molecule: solution of these equations will define the energies of the molecular orbitals.

Three types of molecular orbital are possible. These are:-

a) Bonding orbitals, whose energy is less than the sum of the individual energies of the atomic orbitals concerned, and hence their occurrence favours the stability of the system.

b) Non-bonding orbitals whose energy is equal to the sum of the individual energies of the atomic orbitals.

c) Anti-bonding orbitals whose electrons have energy in excess of the energies of the atomic orbitals. The occurrence of electrons in these orbitals is energetically disadvantageous.

The numbers of each of the three types of orbital and their energies, are determined by solution of the wave equation. In accordance with the Pauli exclusion principle, not more than two electrons can be allocated to each orbital.

Solution of the wave equation for benzene determines that there are three bonding, and three antibonding orbitals. In the ground state the π-electrons occupy the orbitals of lowest energy, i.e. the bonding orbitals.

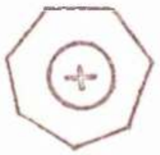
The energy of the $3 \times 2\pi$-electron system in benzene is found to be about 39 k. cal. mole less than that of three isolated double bonds, and is therefore a measure of the stabilisation conferred on it by electron delocalisation.

The pattern of molecular orbital energies in benzene turns out to be typical of cyclic systems generally, and it is found that a stable closed electron shell is formed when n (the number of π-electrons) is 2,6,10,14, etc. This conclusion is embodied in the Huckel rule in which he states that, 'monocyclic conjugated polyolefins having the symmetry of a regular polygon possess a closed electron shell, and consequently aromatic stability, if the number of π-electrons is $4n + 2$ (where n is any integer)'. The concept of the closed electron shell can be likened to the stable configuration of the inert gases, in that addition or removal of an electron requires the expenditure of energy.

The empirically derived theory of the 'aromatic sextet' was thus seen to have a mathematically defined basis, and was in fact the particular case of $n = 1$ in the $4n + 2$ Huckel rule. Similarly the probable non-aromaticity of cyclobutadiene and cyclooctatetraene was explained, and has since been adequately demonstrated. No earlier theory had rigorous grounds for this contention.

Huckel was also able to explain the stability of the cyclopentadienyl anion (IV), and foresee the possibility of obtaining a stable cycloheptatrienyl cation (V). The latter conclusion

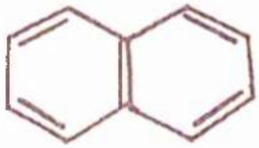
IV



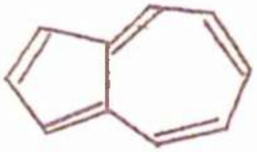
V

was only confirmed twenty-three years later in 1954 when Doering and Knox[11] synthesised tropylium bromide.

The criterion of a closed electron shell as a necessary condition for aromatic behaviour is applicable to any cyclic system. The rule however, was only derived for monocyclic molecules, but numerous experimental results show it to be applicable to bicyclic fused systems. Consequently if the bridging bond is neglected, naphthalene (VI) and azulene (VII), are derivatives of a ten-membered cyclic hydrocarbon, cyclodecapentaene, containing 10π-electrons, (i.e. n = 2 in the formula



VI



VII

$4n + 2$), and therefore aromatic. The rule can also be extended to a number of polycyclic systems. Thus anthracene and phenanthrene have 14π-electrons and as derivatives of a fourteen membered ring should be, and are found to be, aromatic.

Vol'pin[12] generalises the rule as, 'any plane (or nearly plane) fused system containing no atoms common to more than two rings will be aromatic if the number of π-electrons in it is equal to $4n + 2$ (where n is a whole number)'.

Definitions of aromaticity have changed over the years[13], due to the difference between, 'like benzene in chemical properties', which is the classical definition, and, 'having a low ground state enthalpy', which is the modern theoretical meaning, as stated by Wheland[14].

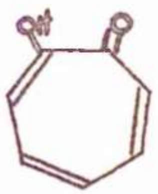
An attempt has been made, by Elvidge and Jackman[15], to measure aromaticity, using nuclear magnetic resonance spectroscopy, by estimating the extent of the π-electron delocalisation in terms of the induced ring current. They have concluded, 'we can define an aromatic compound, therefore, as a compound which will sustain an induced ring current. The magnitude of the ring current will be a function of the delocalisation of the π-electrons around the ring and therefore a measure of aromaticity'.

Hafner[16] has summarised the position by stating that, 'a high degree of electron delocalisation, i.e. a strong ring current of the π-electrons does not always guarantee benzene-like reactivity and stability. It therefore appears justified to distinguish between 'aromatic character' of the ground state, and 'aromatic' reactivity and stability.'

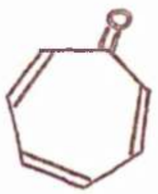
Tropones and Tropolones

In 1945, Dewar[17] proposed that the 2-hydroxy-cyclohepta-2,4,6-trien-1-one (VIII) skeleton would satisfactorily account for the chemistry of the mould product stipitatic acid, and the alkaloid colchicine. His suggestion formed the basis for the subsequent studies on this novel aromatic system, giving rise to several hundred papers.

VIII



VIIIa



IX

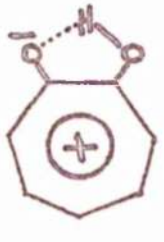
Independently, Nozoe[18a] and others, working on the essential oil of Formosan cedar, had isolated a substance which they called 'Hinokitiol'. By 1940 they had determined that it contains an α-enolone structure in an unsaturated seven membered ring[18b], and possesses aromatic properties[18c].

The parent compound (VIII), named 'Tropolone', by Dewar, was finally synthesised in 1950, independently by Cook[19] and Nozoe[20] and their respective collaborators.

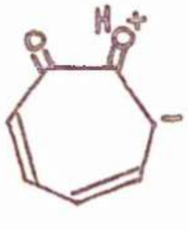
The synthesis of tropone (IX) was reported in 1951 by Doering[21] and Dauben[21].

Tropolone was originally thought to be a resonance hybrid of (VIII) and (VIIIa), but later physicochemical studies have shown it to be a mobile tautomeric system involving these structures.

The physical and chemical properties of tropolone can be attributed to the number of tautomeric and resonance structures possible, including the 'aromatic' resonance forms (X) and (Xa) etc. Similarly, the properties of tropone, i.e. a high dipole



X



Xa

XI

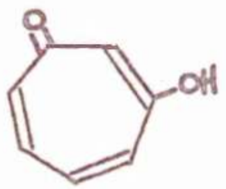
moment, show some degree of ionic contribution as in (XI), and the 'aromaticity' is due to 6π-electrons resonating in

7 p-orbitals.

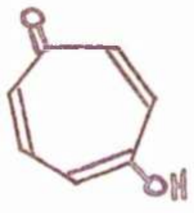
Tropolones undergo nearly all the common aromatic electrophilic substitution reactions, e.g. nitration, sulphonation, halogenation, hydroxymethylation etc., but do not undergo Friedel-Crafts acylation or alkylation, due to the formation of conjugate acids, or complex metal salts, in the presence of strong acids, or metal salts, respectively.

Tropones do not undergo electrophilic halogenation reactions in the normal fashion, but tend to form addition compounds initially, which then eliminate to form the requisite 'substitution' product.

β-Tropolones (XIa) and γ-tropolones (XIb) are not internally hydrogen bonded as are the α-isomers, and their physical properties reflect this, i.e. decreased volatility, increased melting point, etc. Their **preparation** and relative properties have been reviewed by Coffey and Johnson[22].



XIa



XIb

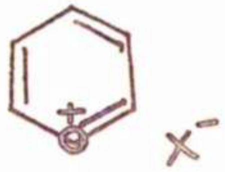
Tropones and Tropolones have been reviewed by Pauson[23] and Nozoe[24].

Aromatic Heterocycles

The aromatic character of certain five and six membered rings containing hetero atoms is well established by theory and practice. Baker[2] has pointed out that aromatic systems can be derived, in principle, from benzene by replacing the group =CH- by =N-, to give pyridine (XII), or by $=\overset{+}{N}-R$ to give pyridinium derivatives (XIII), and by $=\overset{+}{O}-$ to give pyrilium derivatives (XIV).

XII

XIII



XIV

Similarly five membered aromatic systems can be obtained by replacing the group -CH=CH- in benzene, [or =CH- in the cyclopentadienyl anion (IV)] by, -NH- to give pyrrole (XV), -O- to give furan (XVI) and -S- to give thiophen (XVII).

XV

XVI

XVII

In the series (XII - XIV), the hetero atom is contributing one $p\pi$-electron to complete the 'shell' of 6π-electrons. In the second series (XV - XVII), the hetero atom is contributing a 'lone pair' of electrons in order to make up the 'aromatic sextet'.

Pyridine consequently has almost the same geometry as benzene, with only very slight distortion of the ring at the nitrogen atom. The electron density of the π-cloud is, however, very slightly greater at the nitrogen atom than at the carbon atoms, due to the greater electronegativity of nitrogen. Thus the pyridine nucleus has a greater tendency than benzene to undergo nucleophilic attack, and conversely a greater reluctance to undergo electrophilic attack.

Physically pyridine has a measured resonance energy which has been quoted variously from 23 - 35 k. cal. mole[14,25].

Chemically it is considered to be as aromatic as benzene in its chemical reactions.

Pyrrole is not as chemically stable as pyridine since in the presence of strong acids the lone pair of electrons of the nitrogen atom can be shared with a proton, thereby disrupting the 'aromatic sextet', and polymerisation usually occurs. The nitrogen atom of pyridine can, however, donate its lone pair to electron acceptors without disrupting the closed electron shell, and in doing so gives rise to the pyridinium ion (XIII).

The foregoing comments serve to illustrate the two different modes of bonding of the nitrogen atom in nitrogen heterocyclic compounds.

Seven Membered Nitrogen Heterocyclic Compounds

The manifold possibilities for the preparation of seven membered nitrogen heterocyclic systems of aromatic character or otherwise, have been largely unexplored prior to about 1960. However, recent years have seen a quickening interest in the study of these systems.

By application of Baker's[2] suggestions, it can be seen that substitution of the group =N- for =CH-, in a seven membered carbocyclic system should maintain the number of electrons involved in ring formation at its previous value. It is usually assumed[9] that this substitution would cause only a slight 'perturbation' of the system, and has no effect on whether or not the electron shell is closed.

Another possibility, of less interest in this context, is to substitute the group -NH- for the =CH- moiety, with the result that there is a one electron increase in the ring-forming electrons. Of compounds of this type, i.e. in the seven membered ring series, the parent azepine (XVIII) has

XVIII

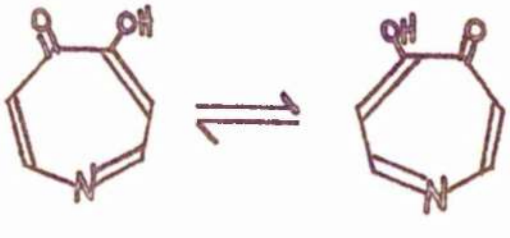
XIX

not yet been prepared, but several mono-and di-benzo derivatives have been synthesised, as well as various polysubstituted, and dihydro derivatives[26,27,28,29]. These compounds are iso-electronic with the cycloheptatriene anion (XIX), detected recently by Dauben[30], and its heptaphenyl derivative by Breslow and Chang[31]. Both carbocyclic systems of 8π-electrons have proved to be thermally unstable.

Hafner[16] attributes the stability of the substituted azepines to the stability of the benzenoid nucleus in the benzazepines or to the resonance possibilities of the substituted azepines.

Seven membered nitrogen heterocyclic compounds whose electron systems should obey the Huckel 4n + 2 rule, have been investigated by only a handful of workers. The compounds of interest are theoretically derived from tropone and tropolone.

There are nine possible isomeric dioxy- mono-azepines, if as in tropolone chemistry, the oxygen functions are considered to be equivalent[32,33]. Each of the nine isomers can presumably exist in the tautomeric forms shown (XX), by analogy with the tropolones.

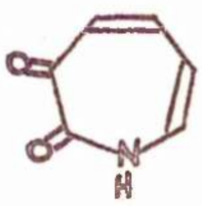


a b

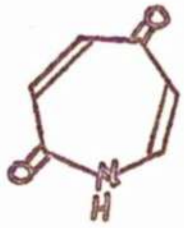
XX

XXI

Also, four of these nine isomers theoretically have an additional tautomeric possibility, i.e. that of the lactam, or vinylogous lactam, (structures XXI - XXIV).



XXII

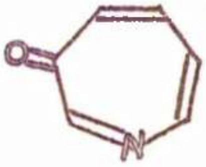


XXIII

XXIV

In the 'azatropone' series there are only three theoretical possibilities (XXVa- XXVIIa).

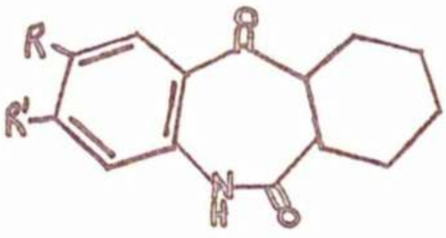
XXVa



XXVIa

XXVIIa

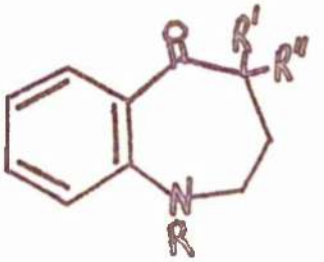
Probably the earliest reported derivative of the system is the lactam (XXIVa), described by Kranzlein[34].



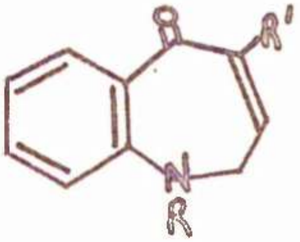
XXIVa

XXV

Later workers[35,36,37,38] have reported the ketones (XXV; R = H and CH_2Ph) and (XXVI; R = Me and pMe.C_6H_4.SO_2.



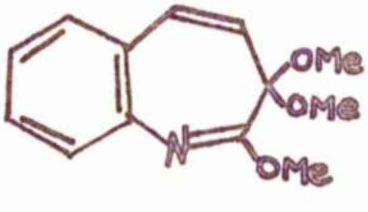
XXVI



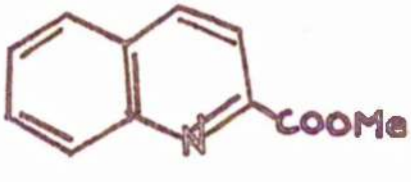
XXVII

R' = R'' = H) without describing any dehydrogenation procedures on them. However, Proctor[39,40] has since described the preparation of the diketone (XXVI; R = pC$_6$H$_4$MeSO$_2$, R' R'' = O) and the dihydroazepinone (XXVII; R = H, R' = OEt).

Look[41] has prepared the derivative (XXVIII), but attempted demethylation led to the formation of methyl quinaldate (XXVIIIa).



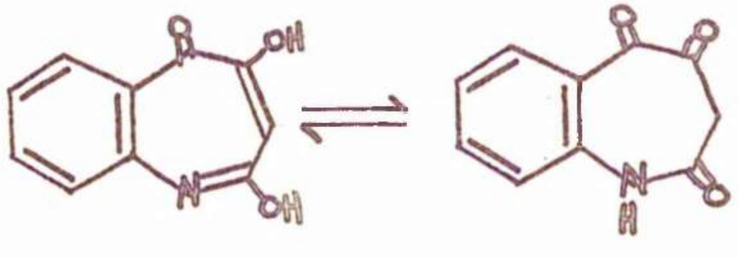
XXVIII



XXVIIIa

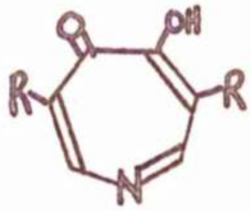
Another interesting lactam derivative (XXIX) has been described by Rees[42], who does not describe any rigorous proof of the existence of the lactim tautomer (XXIXb). In the same paper, Rees has reported the preparation of the lactam (XXX), but concludes that it shows no heterotropolone behaviour.

XXIX

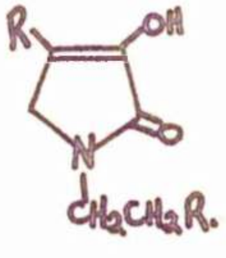


XXX

A claim, by Treibs[43], to have prepared various derivatives of the parent azatropolone (XXXI), has very recently been disproved by Rees[44], who has shown the compounds to be



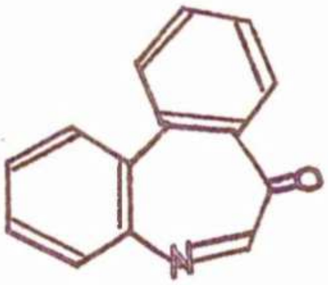
XXXI



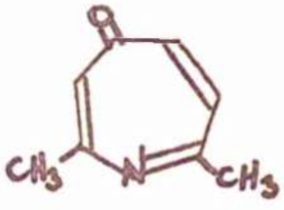
XXXII

of the type (XXXII).

The first reported azatropone derivative (XXXIII) was described in 1960 by Proctor[45]. The deep purple compound



XXXIII

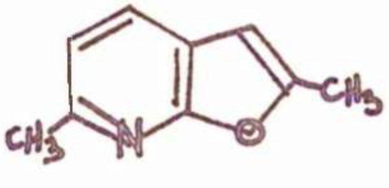


XXXIV

shows C=0 absorption at 1613 cm.$^{-1}$, reminiscent of tropolones[23], but lower than previously recorded tropones[23,46] and it appears to undergo some interesting reactions[47].

Of more interest would have been the parent azatropone

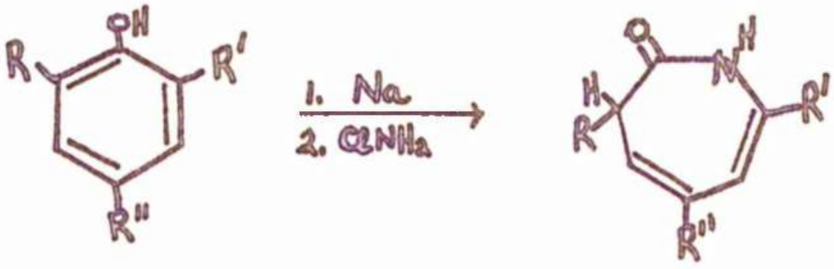
(XXXIV), reported by Johnson[48] and co-workers in 1962, but which, unfortunately, proved to be the furopyridine (XXXV), as they have shown in a later paper[49].



XXXV

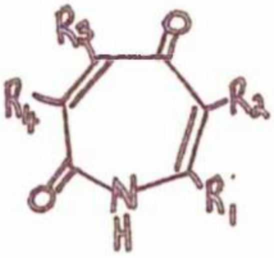
XXXVI

Sundry dihydroazepinones have been described, such as (XXXVI) prepared by Erb and Vogel[50] via a lengthy series of reactions. However, Paquette[51] has developed a simple route to compounds of this type (XXXVIII) by a one-step ring expansion of tri-substituted phenols (XXXVII)

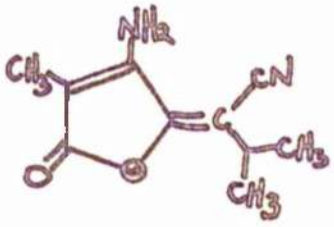


XXXVII XXXVIII

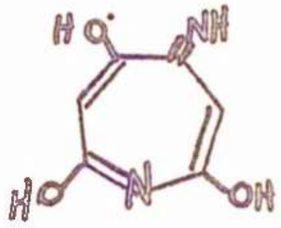
Folkers[52] and his co-workers have made a series of azepindiones of the type (XXXIX), by ring-expansion of



XXXIX



XL

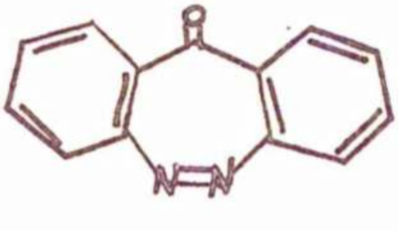


XLI

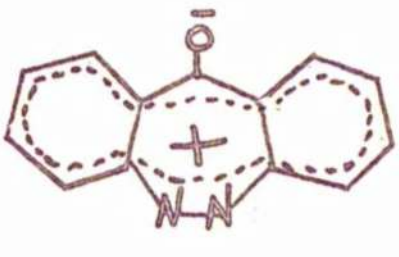
suitably substituted p-quinones, using a variation of the Schmidt reaction[53]. An attempt at a similar type of reaction on thymoquinone, by Rees[54,55], led initially to the unusual compound (XL), which on further treatment gave the azepine derivative (XLI). The latter compound decomposed on attempted hydrolysis to the azatropolone.

Diazepinones

One diazatropone derivative (XLII) has been prepared by Johns and Markham[56].



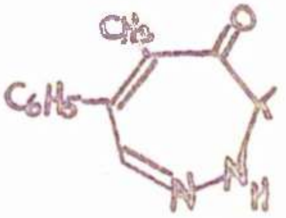
XLII



XLIII

The compound appears to be very stable, and it is suggested that the ionic 'tropylium' structure (XLIII) plays some part in its formulation, and hence that it is a true heterotropone. However, the chemistry of the parent system is obviously modified by the presence of the fused benzene rings.

The dihydrodiazepinone (XLIV) described by Moore[57] does



XLIV

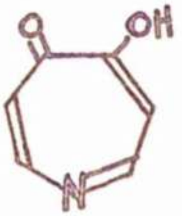
not appear to lend itself to dehydrogenation, and these workers have tended to concentrate on the interesting rearrangements of the system[58,59,60].

The foregoing survey shows that, to the author's knowledge, only one 'azatropone' and one 'diazatropone' (both dibenzo-derivatives), and no 'azatropolones' incapable of lactam formulation, have been prepared to date.

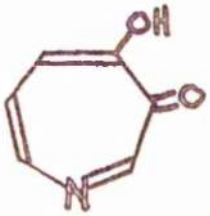
DISCUSSION

In the introduction to this work, it has been seen that most of the azatropolones or azatropones prepared to date, have been lactams, with the consequent modifications to their chemical and physical properties to be expected of this formulation[42]. Therefore, in proposing desirable compounds for attempted synthesis, lactam structures were avoided. In addition, it was considered that a tropolone structure (α preferably), with its attendant tautomeric possibilities, would be more stable than a tropone one.

With the above precepts in mind, it can be seen that the 'ideal' structures would be (XLV) or (XLVI).

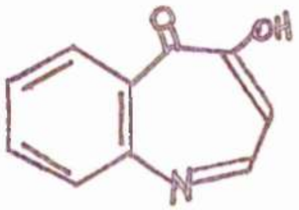


XLV

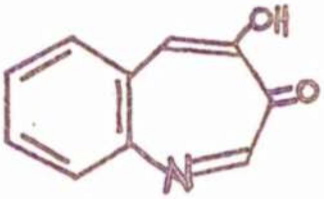


XLVI

An enhanced stability might be expected of the benzo derivatives of these systems, and hence the initial goal of this project became that of preparing compounds of the type (XLVII) and (XLVIII).

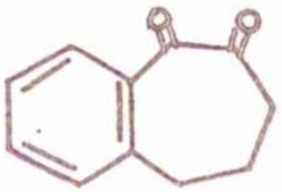


XLVII

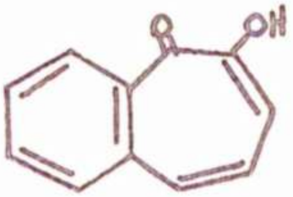


XLVIII

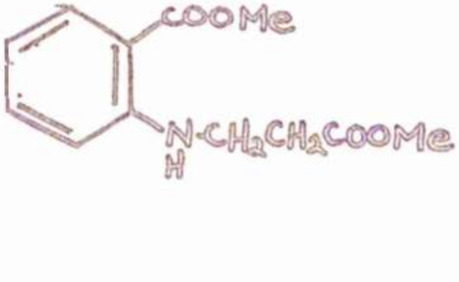
The ready conversion of benzocycloheptanedione (XLIX) to the benzotropolone (L)[61], prompted an investigation of the acyloin reaction on the diester (LI) as a means of obtaining



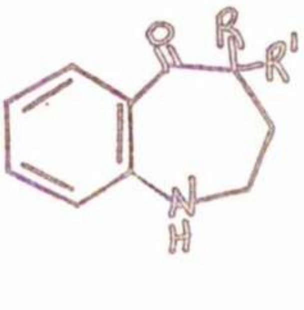
XLIX



L



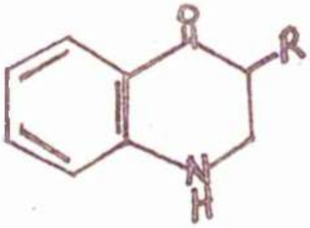
LI



LII

the hydroxy ketone (LII; R = H, R' = OH) and thence the diketone (LII; R,R' = O).

Earlier studies[37] had shown that conventional acyloin procedures, on diester (LI), gave rise to dihydroquinolones (LIII; R = H and COOMe), but that when carefully purified toluene



LIII

$$R-N\begin{matrix}\diagup CH_2CH_2COOEt\\ \diagdown CH_2CH_2COOEt\end{matrix}$$

LIV

was used as solvent, no reaction occurred.

Leonard[62] and co-workers have prepared a series of cyclic aza-acyloins and have found that aza-keto-esters were frequently forme at the same time.

The use of liquid ammonia as solvent in the acyloin reaction has been recommended[63] and thus all the reactions were performed i carefully dried and redistilled liquid ammonia.

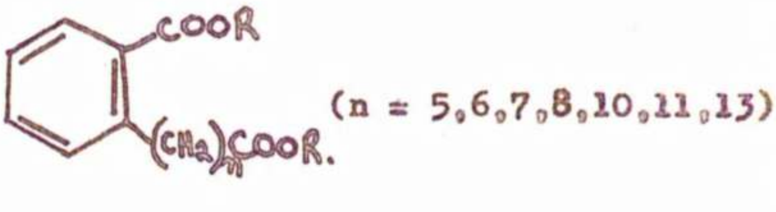
A preliminary reaction of the diester (LIV; R = H) i.e. an attempted preparation of the parent system (LV; R = H), gave only colourless unidentifiable oils, which were not further investigate

Similar reactions of the aryl diester (LI) with sodium in liquid ammonia gave, on working up, tarry mixtures containing polymeric material. Thin layer chromatography[64] of the mixture, revealed the presence of starting diester, and the dihydroquinolone (LIII; R = COOMe), along with very polar materials. Chromatography of these mixtures, on neutral deactivated alumina or silica gel, gave, after separation of the above products, dark gums which on distillation, rechromatography, or benzoylation, failed to yield analytically identifiable compounds. The infrared spectra of the polar materials indicated the presence of hydroxy ketones, which could have been of the required structure. However, oxidation of these compounds with Bismuth oxide[65] led to non crystalline solids which were probably mainly polymeric, although their infrared spectra displayed two absorptions in the C=O region.

These results, complement earlier studies in these laboratories[40] which showed that this reaction at best gave very poor yields of material difficultly separable from the polymeric by products.

Leonard[62] and his collaborators were unable to isolate the parent cyclic acyloin (LV; R = Et) but did isolate the

LV



LVI

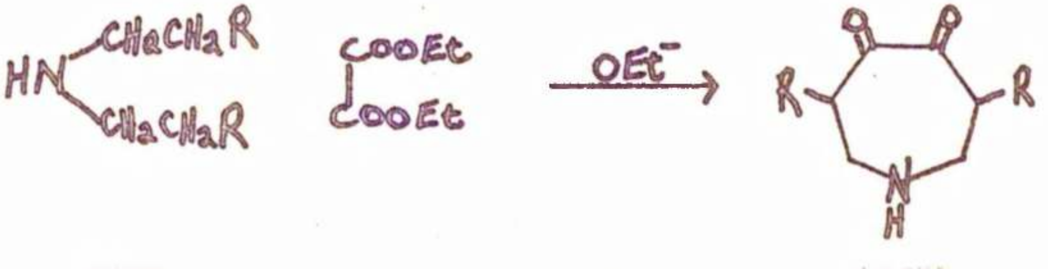
N-phenyl derivative in 10% yield.

Finlay[66] in his recent review of the acyloin reaction, has remarked on the scarcity of examples of seven-membered carbocyclic acyloins, and Huisgen[67] has reported that aryl alkyl diesters of the type (LVI; R = Me and Ph) did not yield 'definite' acyloins, either in xylene or refluxing ammonia as solvent.

Ester Condensation Reactions

The possibility of synthesising a benzazatropolone, via Claisen condensation of the appropriate aliphatic and aromatic diesters, appeared promising.

It had been reported[43] that condensation of the disubstituted amine (LVII; R = CN and COOEt) with diethyl oxalate gave



LVII

LVIII

(LVIII; R = CN and COOEt) which was subsequently dehydrogenated, with sulphur and quinoline, to various azatropolone derivatives. As has been said in the introduction, this claim has since been disproved[44], but the route is a reasonable one in the light of previous reports, which have described analogous syntheses of cycloheptanediones by condensation of ethyl oxalate with diethyl pimelate[68], and with diethyl-γ,γ-ethylenedioxopimelate[69].

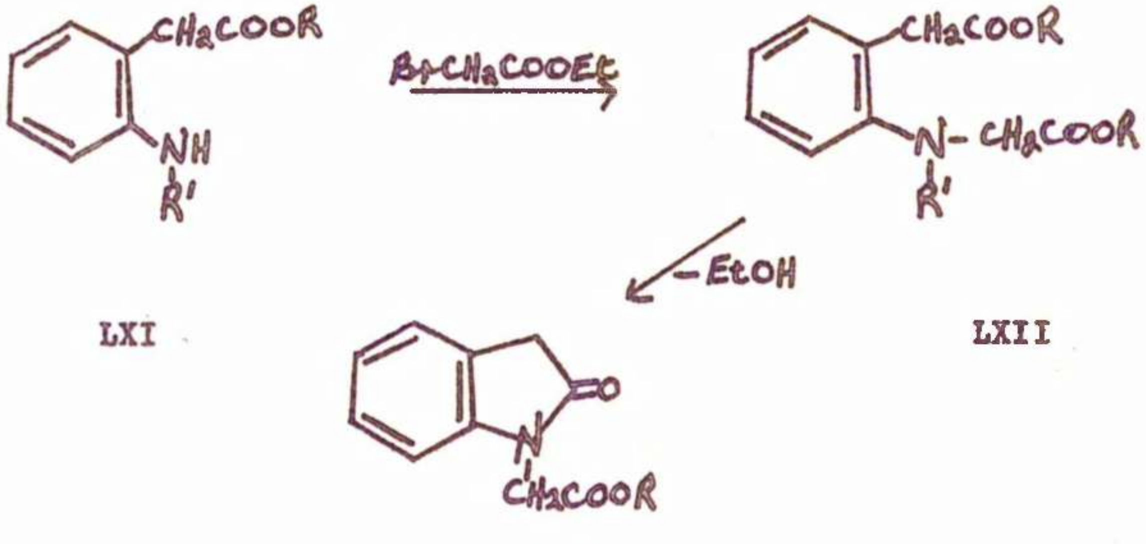
Benzotropolones and benzotropones have been prepared by condensation of phthalaldehyde with substituted acetones[70,71,72,73,74].

It therefore appeared possible that condensation of diethyl oxalate with a compound such as (LIX; R = Et) could lead to the dihydroazatropolone (LX; R = Et). In both of these compounds, R' would be a suitable protecting group, i.e. readily removable.

LIX LX

Preliminary attempts to prepare the amino-diester (LXII; R = Et, R' = H), by reaction of ethyl-bromoacetate with (LXI; R = Et, R' = H) led to an oxindole derivative (LXIII), whose structure was established by analysis and nuclear magnetic resonance spectroscopy.

The sulphonamide (LXI; R = Et, R' = pMe$C_6H_4SO_2$)



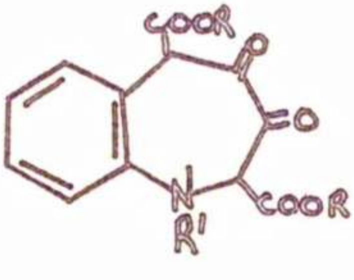
LXI

LXII

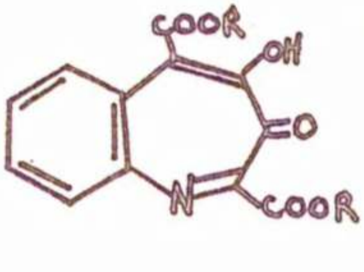
LXIII

was prepared and readily yielded the desired diester (LXII; R = Et, R' = $pMeC_6H_4SO_2$) on treatment of its potassium salt with ethyl bromoacetate.

The choice of the sulphonyl group, for protection of the nitrogen atom allowed ready formation of the diester. However, in addition, it seemed possible that, in the event of the desired condensation taking place to form the diketone (LX; R = Et, R' = $pMeC_6H_4SO_2$) subsequent or simultaneous elimination[75] of the sulphonyl group would occur to form the azatropolone (LXIV; R = Et).

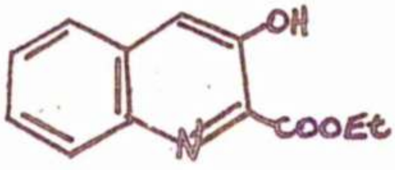


LX

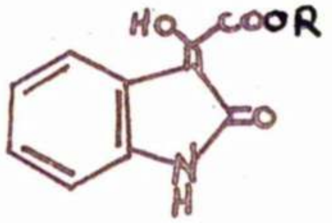


LXIV

In practice, the reaction gave a complex mixture of products, from which the main identifiable components were always a hydroxy quinoline ester, for which the structure (LXV) is proposed, and the acidic oxindole derivative (LXVI; R = Et).

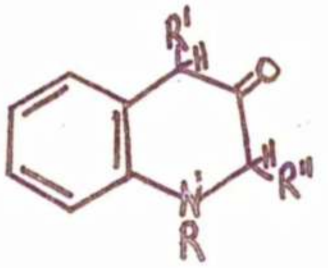


LXV

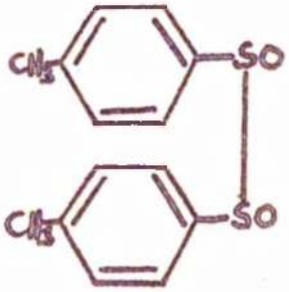


LXVI

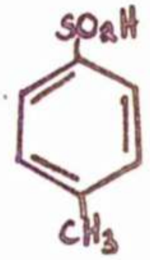
Also isolated were the Dieckman condensation product (LXVII;



LXVII



LXVIII



LXIX

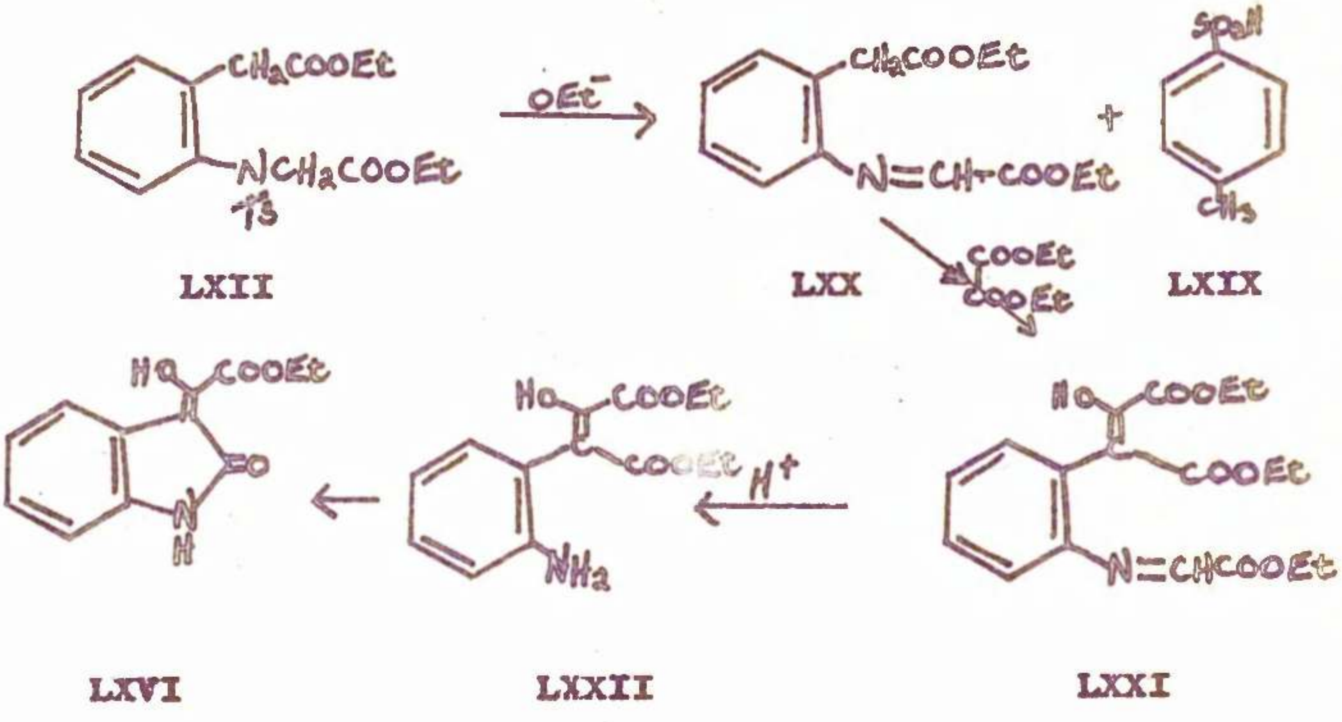
R = $p\mathrm{MeC_6H_4SO_2}$, R' = H or COOEt, R'' = COOEt or H), the disulphoxide (LXVIII) and toluene-p-sulphinic acid (LXIX) and in one work-up procedure the acid (LXVI; R = H).

A 'blank' reaction, i.e. on the diester (LIX) alone in the absence of diethyl oxalate, and performed under similar conditions, gave all of these products except the oxindole derivatives (LXVI; R = Et and H)

The oxindole derivative (LXVI; R = Et) formed, a methyl ester on reaction with diazomethane, an acid (LXVI; R = H) on hydrolysis; and a quinoxaline derivative on reaction with o phenylene diamine. These reactions proved its identity with the compound m.p. 187° prepared by Wislicenus[76], by the reaction of ethyl oxalate with oxindole in the presence of sodium ethoxide.

The formation of the oxindole (LXVI; R = Et) could be explained by assuming that elimination of the sulphonyl group is the initial reaction to, form the anil (LXX). Subsequent

Scheme I



or concurrent nucleophilic attack of the aryl-methylene anion on diethyl oxalate would give (LXXI). At this stage it could be possible that the acidic work-up conditions would hydrolyse the anil to (LXXII) which could cyclise to (LXVI; R = t).

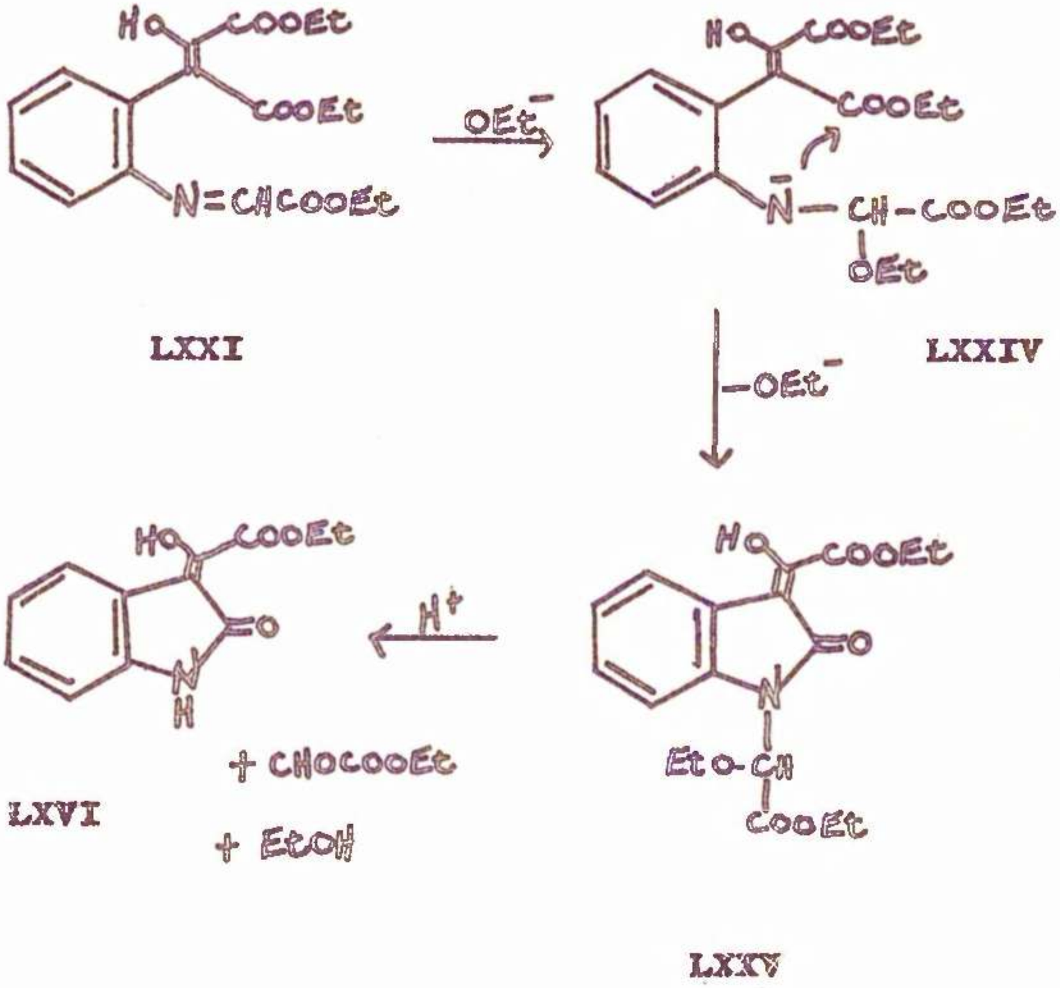
Formation of the oxindole derivative (LXVI; R = Et) under similar conditions by the action of ethyl oxalate on oxindole has been reported[76], but reaction of these components under the conditions used for the diester reaction gave a lower yield (8%) of (LXVI; R = Et), than that from the diester reaction (ca 13%), due possibly to the greater acidity of the aryl methylene group in the diester (LIX; R = Et, R' = $pMeC_6H_4SO_2$) than the same group in oxindole. These findings tend to substantiate the mechanism of formation of (LXXI). However, if, as has been suggested, the subsequent course of the reaction proceeds via hydrolysis during the acidic working-up of the reaction then there should have been a substantial yield of ethyl-2,3-dioxycinchoninate (LXXIII) from the cyclisation below.

LXXII LXXIII

Wislicenus[76] has prepared the ester (LXXIII) in high yield (94%) by the reaction of ethyl oxalate with ethyl-*o*-aminophenylacetate in the presence of base, giving only a trace of the by-product (LXVI; R = Et).

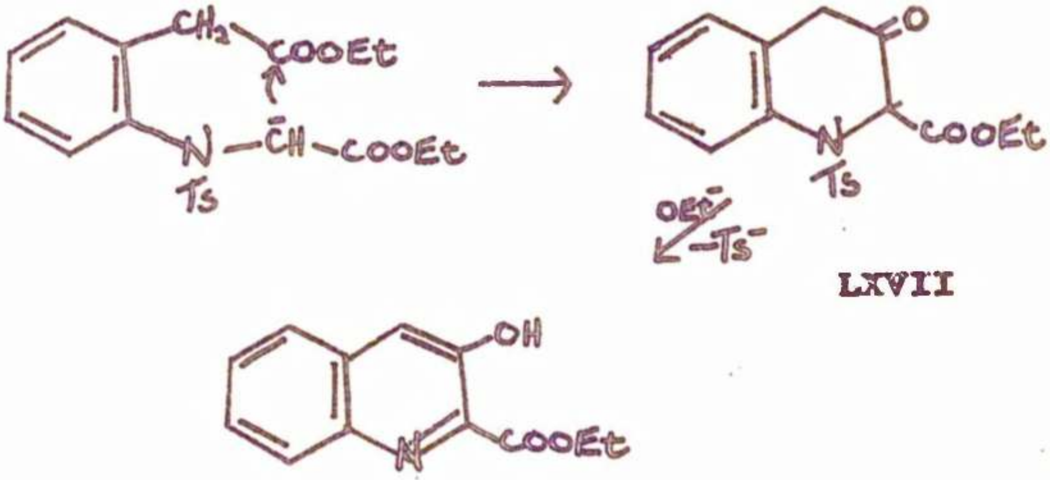
It would therefore seem that an intramolecular rearrangement of the anil (LXXI) must take place to form the oxindole compound (LXVI; R = Et), as shown in Scheme II.

Scheme II



It is tentatively proposed that ethoxide ion can add across the anil double bond, due to electron deficiency at the carbon atom, forming the anion (LXXIV) which can cyclise to the carbinolamine derivative (LXXV). The last step, i.e. elimination of ethylglyoxalate, could possibly take place during the acidic working-up conditions.

The two quinoline derivatives (LXV) and (LXVII) are to be expected from the reaction competing with anil formation i.e. as shown below.



LXVII

LXV

It is to be expected that the dihydroquinoline ester (LXVII) should be found in trace quantities and the quinoline ester (LXV) in much higher yield, due to the reactivity of (LXVII). The formulation of (LXV) as 2-ethoxycarbonyl-3-hydroxyquinoline followed from elemental analysis of the compound and its toluene-p-sulphonyl derivative.

The ultraviolet spectrum of compound (LXV) was virtually identical to that of quinoline-2-aldehyde. Infrared and nuclear magnetic resonance spectra were consistent with its being a hydrogen bonded quinoline ester. Finally the reported m.p. 69-71°[77] of the other possible isomer, 4-carboethoxy-3-hydroxyquinoline precluded this formulation for (LXV) which had m.p. 112-113°.

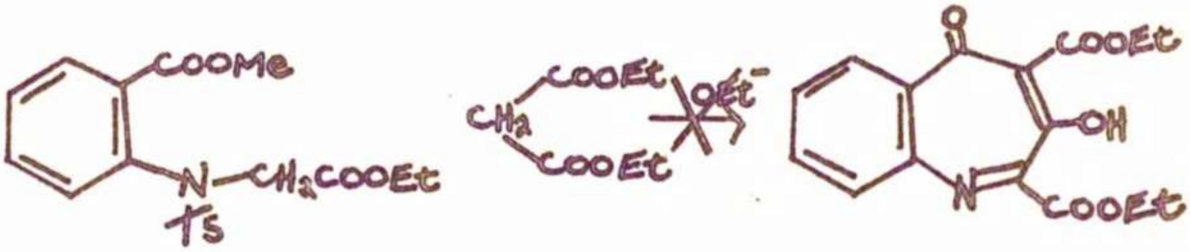
It is not known whether the other quinoline derivative (LXVII) has the ester group in the 2, or the 4 position.

The presence of toluene-p-sulphinic acid (LXIX) is usual in reactions of this type[78], and the acid was identified by its infrared spectrum, m.p., 80-81°[79], and observed deliquescence. Di-p-toluene disulphoxide (LXVIII) is thought to have arisen from the decomposition of toluene-p-sulphinic acid, a transformation reported in the literature[80], and was identified by elemental analysis and by its m.p. 74-76°[81].

The other unidentified portion of the reaction mixture was a gum, which, from its infrared spectrum appeared to contain starting material.

The detailed investigation of this reaction was carried out mainly to obtain additional information about the oxindole compound (LXVI; R = Et) as it was initially thought to have a seven membered ring structure of the type required.

Another condensation reaction, which was investigated, was that between the diester (LXXVI) and diethyl malonate. It was hoped that the reaction shown could be performed in one



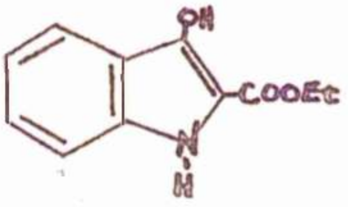
LXXVI LXXVII

or more steps, with the object of obtaining the β-azatropolone (LXXVII).

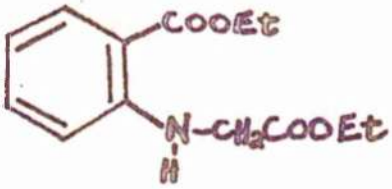
In practice, the reaction, when carried out in ethanolic sodium ethoxide, gave two main products which were separated by chromatography of the neutral portion of the reaction mixture. Toluene-p-sulphinic acid and di-p-toluene-disulphoxide were also identified in the acidic portion of the reaction mixture.

The first of the two neutral products obtained by chromatography, was a pale yellow crystalline solid m.p. 115°, which formed an acetate, and toluene-p-sulphonate.

Analysis of the compound and its derivatives identified it as ethylindoxylate (LXXVIII), which has been prepared[82]



LXXVIII



LXXIX

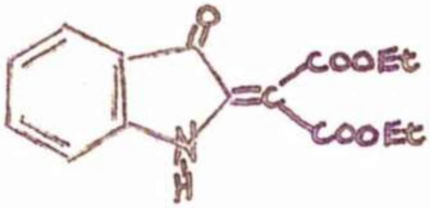
from the diester (LXXIX) by treatment with base.

The second compound isolated was an orange crystalline solid, ($C_{15}H_{15}NO_5$)m.p. 112° which formed a dinitrophenylhydrazone ($C_{21}H_{19}N_5O_8$). The infrared spectrum of the material showed absorptions corresponding to secondary amine, and ketonic and ester carbonyl.

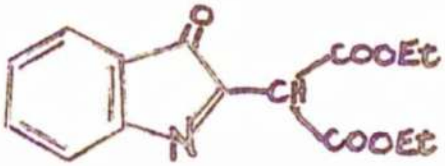
Nuclear magnetic resonance measurements showed the presence of two ethyl esters, i.e. two triplets centred at 8.7 and 8.63 τ equivalent to 6 protons (2 x CH_3), a multiplet centred at 5.6 τ equivalent to 4 protons (2 x $-CH_2-$), an aryl multiplet at 2.2-3.2 τ (4 protons), and a broad singlet at 0.8 τ, 1 proton (NH).

Further evidence was gathered from mass spectral analysis which showed major peaks at m/e 289, 243, 215, 171, 143, 115, 89, 76.

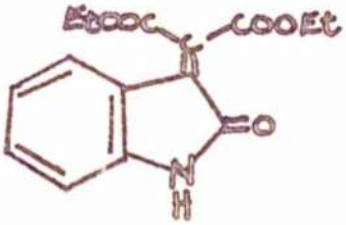
From all the evidence shown, the compound has been formulated as diethyl-(3-oxo-2-indolinylidene)-malonate (LXXX). It was considered that the isomeric indolone (LXXXI)



LXXX



LXXXI



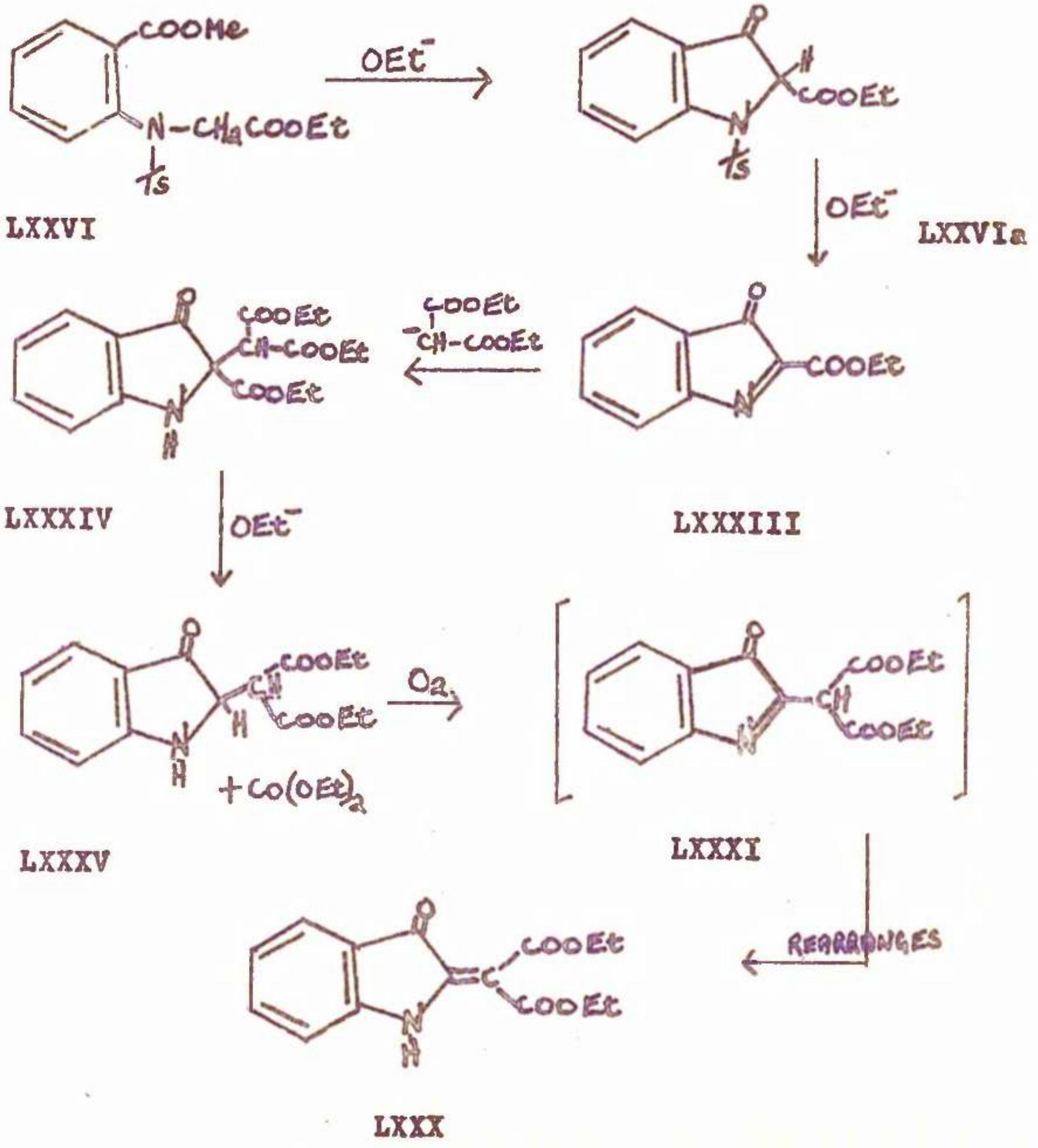
LXXXII

may have been a contributing structure, but the ultraviolet spectrum of compound (LXXX) bore a greater resemblance to the published spectrum of isatin[83], than to that of 2-phenyl indolone[84]. The separation of the ethyl ester peaks in the n.m.r. spectrum is also consistent with their being held rigidly in slightly different magnetic environments.

The isomeric diethyl-(2-oxo-3-indolinylidene)-malonate (LXXXII) m.p. 149°[85] is known, and could therefore be ruled out as a structural possibility.

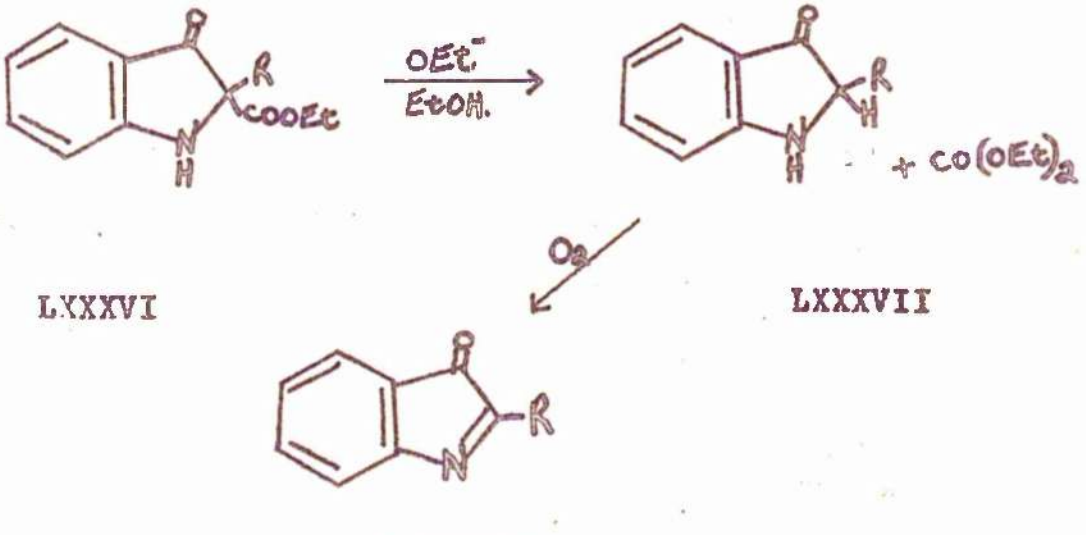
A suggested mechanism for the production of the diester (LXXX), under these reaction conditions, is shown in Scheme III.

Scheme III



The indolone ester (LXXXIII) is considered to be the first product, by cyclisation, then elimination of the sulphonyl group. Addition of anionic fragments to the reactive C=N-double bond of schiff bases[86], as well as similar additions to indolone derivatives[87] are known. Therefore, the next step could well be addition of malonic ester to form the triester (LXXXIV).

Neunhoeffer[88] has described the displacement of ester groups from 2-indoxyl esters such as (LXXXVI; R = Me, Et, Ph and COOEt) in the presence of alcoholic sodium ethoxide, to form indoxyl derivatives like (LXXXVII; R = Me, Et, Ph, and COOR) and diethyl carbonate. The resultant indoxyls can autoxidise, or be oxidised by hydrogen peroxide, to indolone derivatives



LXXXVI

LXXXVII

LXXXVIII

(LXXXVIII; R = Me, Et, and Ph). Autoxidation does not take place when R = COOR in (LXXXVII).

Therefore, in Scheme III, the triester (LXXXIV) could lose the group COOEt to form diethylcarbonate, and the diester (LXXXV), which should readily autoxidise to the indolone (LXXXI) followed by rearrangement to (LXXX).

The hydrogen from (LXXXV) could alternatively be transferred to the indolone ester (LXXXIII) to form ethyl indoxylate (LXXVIII) and since this would not autoxidise, this reaction would account for its presence in the mixture.

When the condensation was carried out in anhydrous benzene, only a trace of the orange product (LXXX) was obtained but this time a yellow (blue fluorescent) compound ($C_{18}H_{21}NO_7$) m.p. 108°, was obtained in about 20-30% yield. This compound was initially thought to be the intermediate triester (LXXXIV) postulated in the previous reaction, but its nuclear magnetic resonance spectrum was more consistent with the formulation (LXXXIX), since it contained three separate methyl triplets

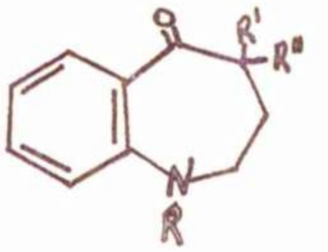
LXXXIX XC

centred at 8.66, 8.79 and 9.2τ respectively, equivalent to a total of 9 protons, a multiplet from 5.4 - 6.3τ equivalent to 6 protons (3 x -CH$_2$-), a sharp singlet at 5.3τ (one proton), a broad singlet at 4.2τ (NH) and 4 aryl protons as a multiplet at 2.2-3.2τ. These measurements preclude its formulation as (LXXXIV) since in that molecule, the diethyl malonyl residue should give rise to only one methyl triplet (equivalent to six protons) due to the equivalence of the ester groups, and the tertiary ester group should have produced a separate methyl triplet signal equivalent to three protons.

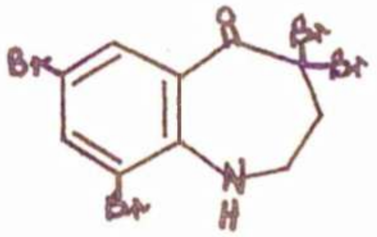
The production of this compound appears to demonstrate that in aprotic conditions, the reaction proceeds by a different route. It is suggested that in this case the reaction involves the intermediate (XC), i.e. that anil formation precedes ring closure, and not vice versa as was postulated for the previous reaction.

Reactions of 2,3,4,5-Tetrahydro-1-toluene-p-sulphonyl benz[f]azepin-5-one

Having failed to synthesise the required seven membered ring containing two oxygen functions, attention was directed to the known tetrahydro-azepinone (XCI; $R = pMeC_6H_4SO_2$, $R' = R'' = H$)[37].



XCI

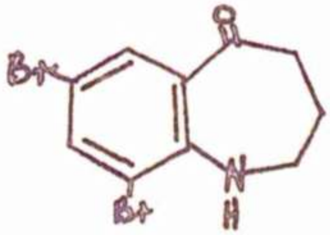


XCII

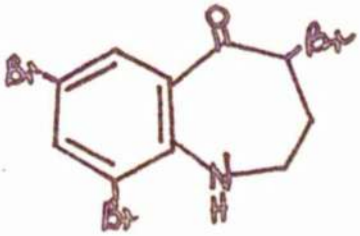
Although the mono and dibromo derivatives of this compound i.e. (XCI; $R = pMeC_6H_4SO_2$, $R' = Br$, $R'' = H$) and (XCI; $R = pMeC_6H_4SO_2$, $R' = R'' = Br$) respectively, and the diketone (XCI; $R = pMeC_6H_4SO_2$, $R' = R'' = O$) have been prepared[39], the toluene-p-sulphonyl group could not be removed by the usual reagents.

During some investigations on the bromination of the ketone (XCI; $R = pMeC_6H_4SO_2$, $R' = R'' = H$), it was found that excess bromine converted it in high yield to the tetrabromo compound (XCII), the tosyl group having been smoothly cleaved at room temperatures.

Very mild hydrolysis procedures, i.e. prolonged refluxing with aqueous acetone, on the tetrabromide (XCII), were without appreciable effect. However, more vigorous conditions i.e. refluxing aqueous alcoholic potassium carbonate, barium hydroxide, sodium hydroxide etc., all converted it mainly to complex mixtures which were found to contain the dibromide (XCIII) and the tribromide (XCIV) as well as quantities of polar materials which could not be identified. It was felt that conditions vigorous enough to bring about the desired hydrolysis were also probably sufficient to destroy the reactive dicarbonyl system (XCV) produced, causing possibly, benzilic acid rearrangement to the hydroxy acid (XCVI) although no evidence for this

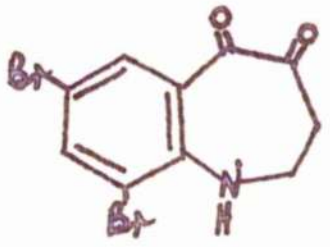


XCIII

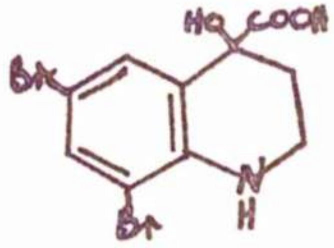


XCIV

was found. The presence of trace quantities of the desired



XCV



XCVI

diketone (XCV), was shown by the formation of a quinoxaline derivative from the crude reaction product. The diketone (XCV) was eventually prepared in better yield by selenium dioxide oxidation of the dibromo ketone (XCIII): again it could not be purified, but was isolated as the quinoxaline derivative.

The dibromo ketone (XCIII) was prepared by zinc and methanol reduction of the tetrabromide (XCII), or the tribromide (XCIV), which in turn were synthesised by bromination of the dibromide (XCIII). These transformations served to identify the various products of the hydrolysis reaction.

It was noted that a considerable amount of starting material was usually recovered in the hydrolysis of the tetrabromide (XCII) suggesting that the decomposition of the products proceeds at a greater rate than the initial hydrolysis.

The debromination, noted in this reaction, which must be a reductive process, has been previously reported to occur in a similar system (XCI; R = $pMeC_6H_4SO_2$, R' = R'' = Br), during dehydrogenation[39] and hydrolysis[40] experiments.

It would appear that these products could arise from a disproportionation process taking place between the tetrabromide (XCII) and the products of hydrolysis.

Garbisch[89] has reported the replacement of bromine by hydrogen, as a minor process occurring during the dehydrobromination of cyclic α-bromo ketones.

It was found that the tetrabromide (XCII) was fairly stable to dehydrobrominating reagents, and could be recovered in about 70% yield after refluxing for 4 hours in collidine, or on refluxing with lithium chloride in dimethylformamide. The other products of these reactions were intractable tars.

Treatment of the tetrabromide with anhydrous potassium tert butoxide in dimethylsulphoxide for 24 hours at room temperature gave a 50% recovery of starting material, along with a low yield of a yellow substance (m.p. 220°) which appeared to be somewhat unstable, turning red slowly in the presence of air. Elemental analysis of this compound corresponded approximately to the loss of two bromine atoms from the original molecule. Nuclear magnetic resonance measurements could not be made on this material because of its insolubility, and it is consequently thought to be dimeric. The tetrabromide (XCII) was recovered unchanged after 24 hours solution in oleum at 0° followed by pouring on ice, a process which has been used[90] to convert geminal dibromides to ketones.

The difficulty of effecting hydrolysis of the α-dibromo ketones (XCI; R = $pMeC_6H_4SO_2$, R' = R'' = Br) or (XCII), must be, in part, due to the steric crowding which has to prevail during the intermediate stage of the Sn_2 process.

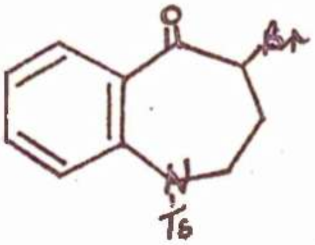
The similar reluctance of these molecules to undergo dehydrobromination, is thought to be associated with the internal strain imposed on the molecule in assuming the geometry required for the eliminating atoms to lie in the trans planar configuration necessary[91] for elimination. The very facile elimination of hydrogen bromide from the bromo ketone (XCVII)

XCVII

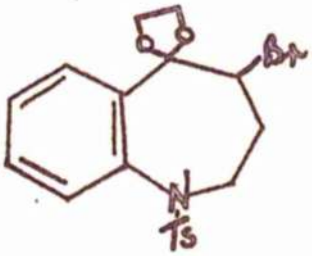
XCVIII

to form the diketone (XCVIII), which is described by Rees[42], can be explained by the activating effect of the amide carbonyl on the β-hydrogen atom, thus facilitating nucleophilic attack, and hence elimination.

The preferred conformations of seven membered rings have not yet been very fully investigated, and no information appears to be available on heterocyclic seven membered rings, but an examination of molecular models of compound (XCVII), suggests that a trans planar configuration (to hydrogen) would be readily available to the bromine atom for elimination. In a compound of type (XCIX), however, although it appears to have a greater degree of freedom than the compound (XCVII) some configurations are liable to be hindered by interactions of the bulky sulphonyl group, or bromine atom, and this may account for the observed disinclination towards dehydrobromination.



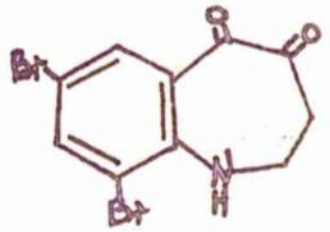
XCIX



C

An examination of the model of compound (C), suggested that the extra freedom conferred on the seven membered ring by the transformation of the trigonally hybridised carbonyl-carbon atom in (XCIX) to the tetrahedral hybridisation of the ketal form, should facilitate elimination of the α-bromine atom. In practice, the compound (C) was recovered virtually unchanged after 4 hours refluxing in collidine, and therefore it would appear that some other factor is contributing to its stability.

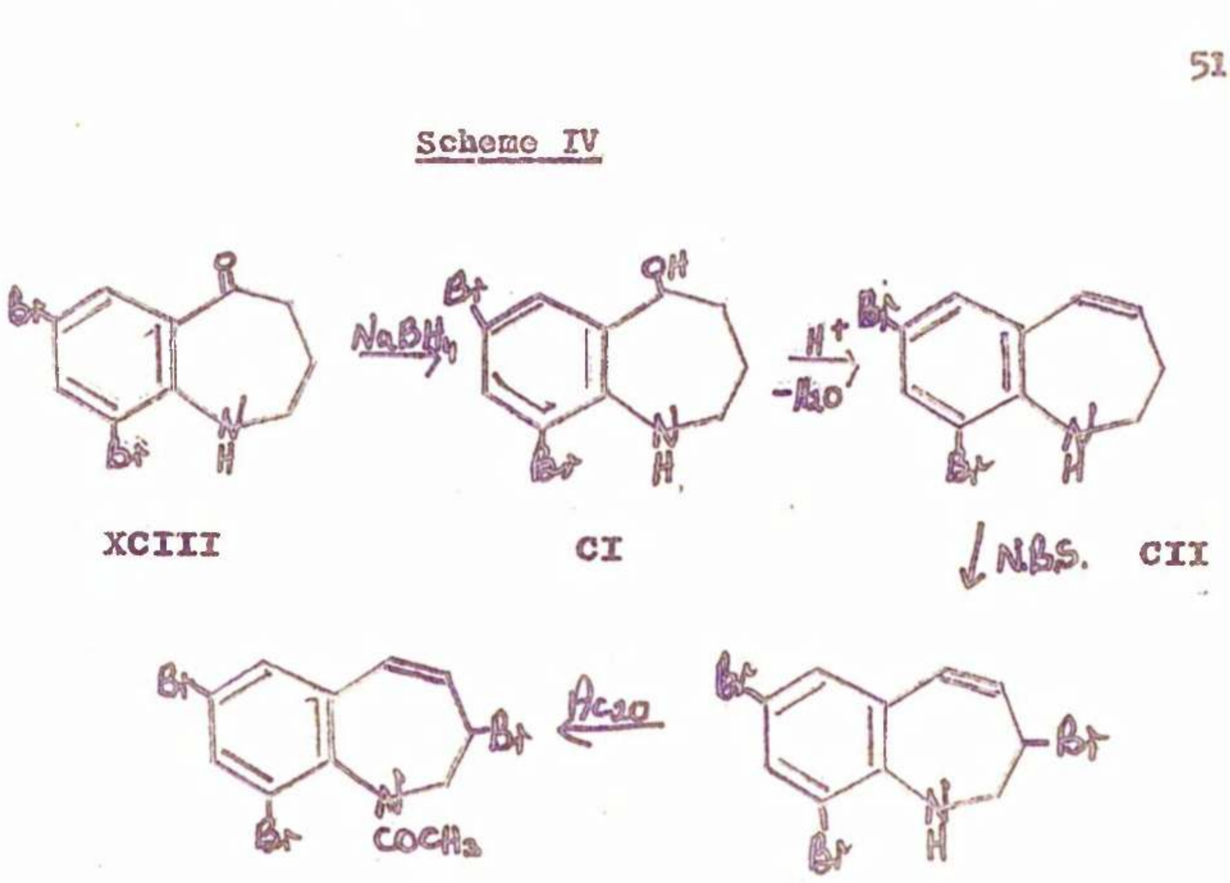
The crude mixture containing the dibromo diketone (XCV) which was obtained by selenium dioxide oxidation of the dibromo ketone (XCIII) could not be dehydrogenated with dichloro-dicyanoquinone (D.D.Q.) to give any recognisable products. Similar attempts to dehydrogenate the ketone (XCIII) with D.D.Q. merely led to a quantitative recovery of the starting material.



XCV

Various transformations of the system were carried out, and these are shown in Scheme IV.

Scheme IV

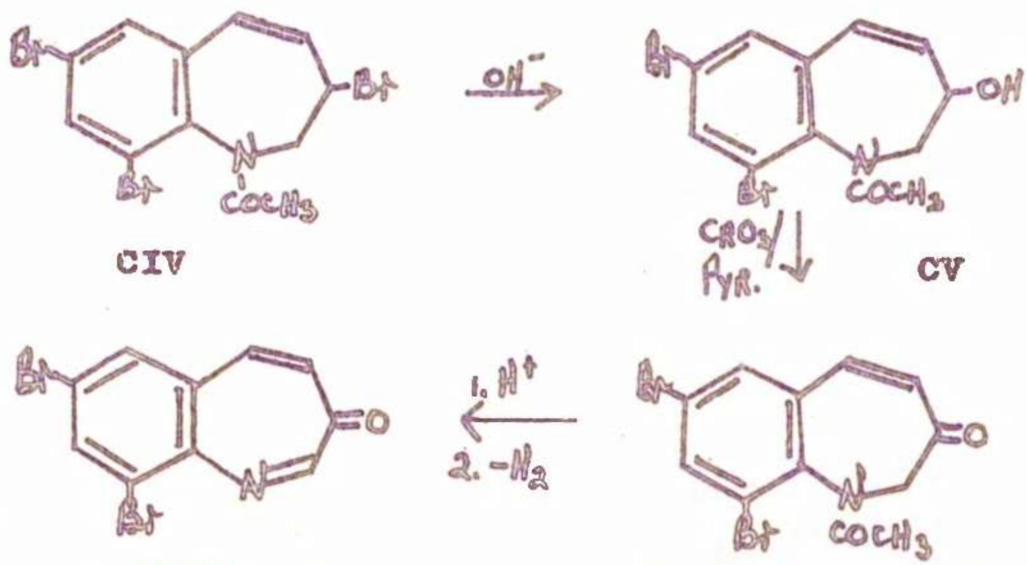


XCIII CI CII

CIV CIII

The final steps of the proposed transformations should have been as shown below in Scheme V, to prepare the azatropone

Scheme V

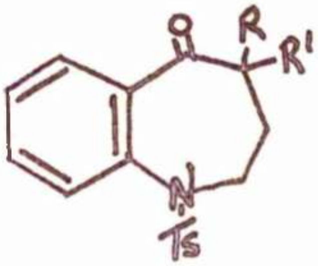


CIV CV

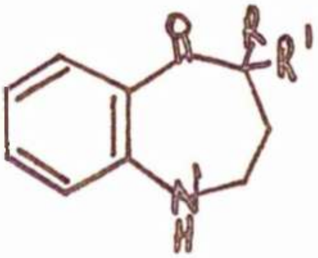
CVII CVI

(CVII), but were not carried out due to the lack of material.

The difficulty encountered[39] in cleaving the N-S bond of the diketone (CVIII; R, R' = O) prompted attempts to form

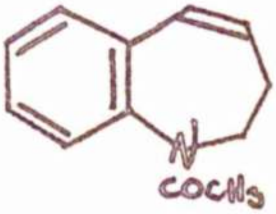


CVIII

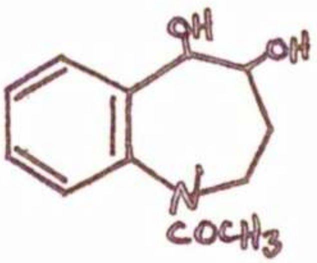


CIX

the diketone (CIX; R, R' = O) after removal of the sulphonyl group in the ketone (CVIII; R = R' = H). A route to the dihydroazepine (CX) was readily available by sodium and liquid ammonia cleavage[92] of the sulphonyl group in the ketone (CVIII; R = R' = H) to give the amino ketone



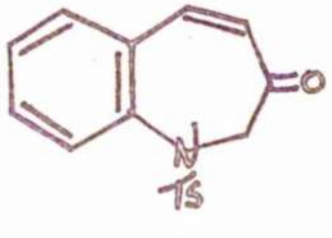
CX



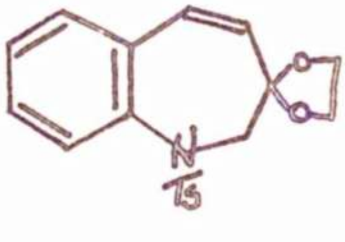
CXI

(CIX; R = R' = H), followed by reduction of the ketone, dehydration of the secondary alcohol formed, and finally acetylation to give the compound (CX). At this stage an attempt to form the diol (CXI) by hydroxylation of the double bond with neutral potassium permanganate solution[93] led to a high recovery of the unchanged olefin.

A similar lack of reactivity of this double bond towards hydroxylating agents, was observed in another two compounds (CXII) and (CXIII). In the case of (CXII), neutral potassium permanganate solution caused some loss of material, probably due to ring opening of the dihydroxy ketone formed, but the starting material was recovered in 70% yield.



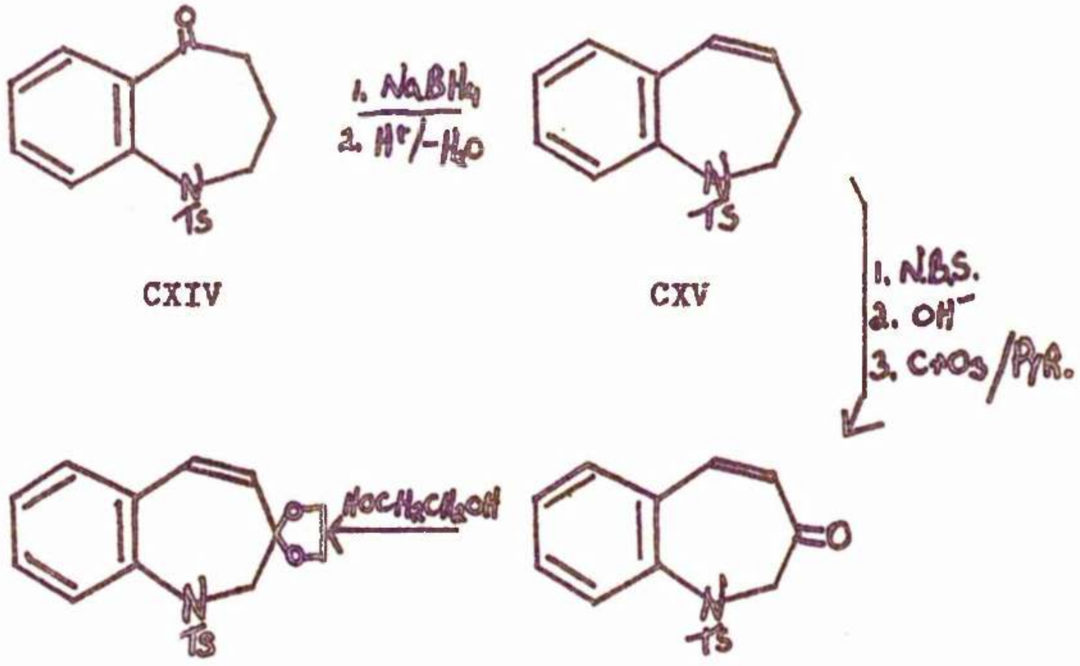
CXII



CXIII

Similarly, prolonged treatment of both compounds (CXII) and (CXIII) with osmium tetroxide, led to an 86% recovery of (CXII), although the ketol (CXIII) did in fact oxidise somewhat after eleven days reaction time, yielding only a small amount of hydroxylated material which could not be obtained in a pure state, the remainder being recovered in greater than 55% yield.

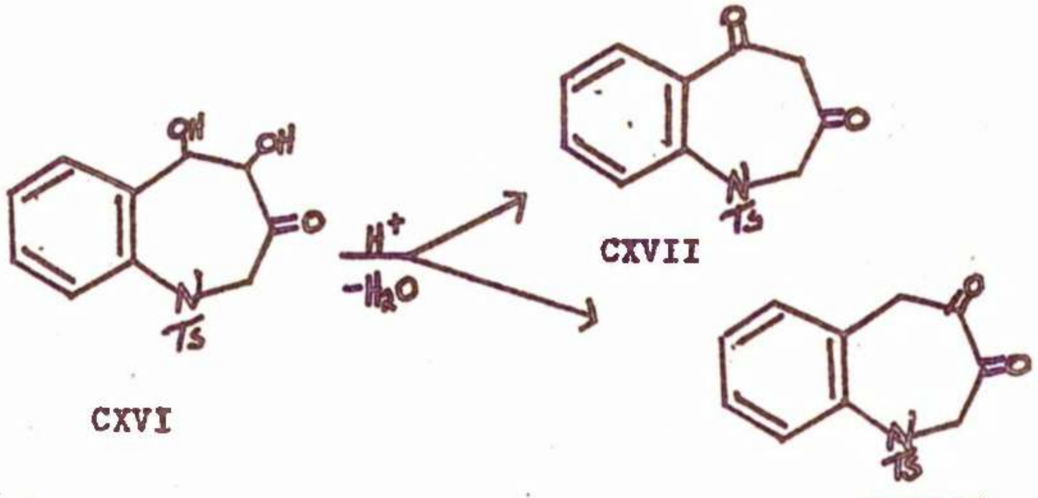
The foregoing compounds were prepared by standard procedures from the ketone (CXIV) as shown below. It



CXIV CXV

CXIII CXII

was hoped that hydroxylation of the ketone (CXII) would give the dihydroxy ketone (CXVI), which in turn could dehydrate to a mixture of two diketones (CXVII) and (CXVIII).

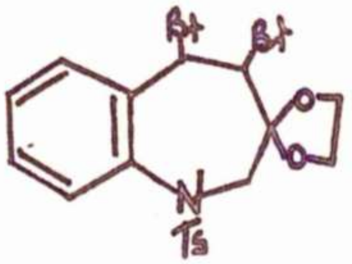


CXVI

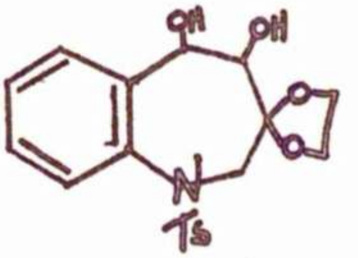
CXVII

CXVIII

The failure of osmium tetroxide in ether, to react with α-β unsaturated ketones has been noted before[94], but alternativ procedures involving alkaline potassium permanganate, or epoxidation with alkaline hydrogen peroxide[95], were liable to cause elimination of the sulphonamide, and consequently protection of the carbonyl group seemed necessary. The long reaction time necessary for hydroxylation of the ketol (CXIII) with osmium tetroxide, and the difficulty of isolating the products, impelled a search for a better route to the dihydroxy ketone (CXVI). Bromination of the ketal (CXIII) readily gave the dibromide (CXIX) as a crystalline material. However, hydrolysis of the dibromide in aqueous acetone, followed by dehydration and acidic hydrolysis of the ketal group, (without purification of the intermediate



CXIX



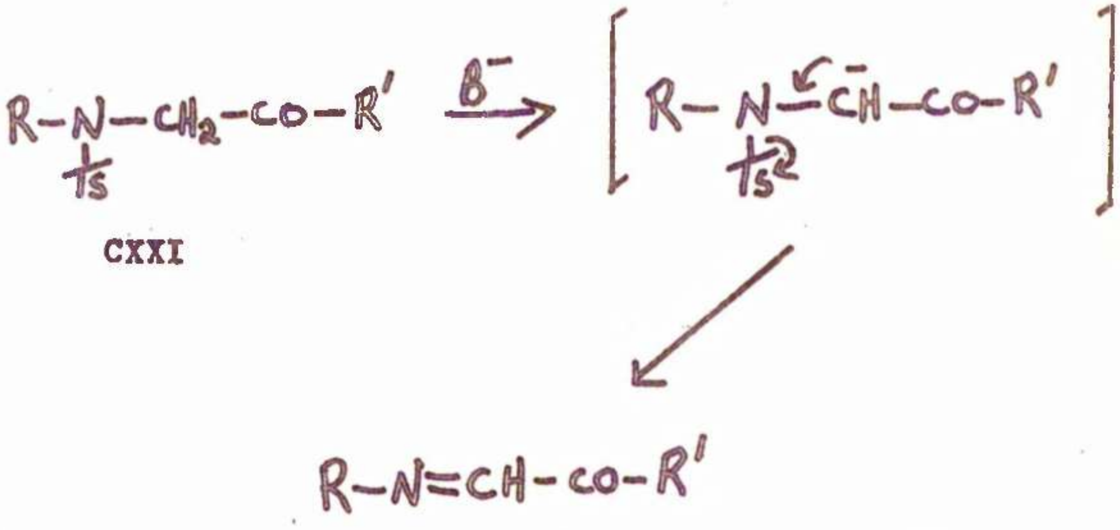
CXX

diol (CXX)) led only to a low yield of diketone which was not identified, but which showed infrared absorptions at 1755 and 1682 cm.$^{-1}$, the former absorption being larger than the latter. The material was therefore probably a mixture of the desired compounds (CXVII) and (CXVIII).

The Base-catalysed Elimination of Sulphonamides

In the preparation of many of the compounds described in this work, the intended final preparative step was envisaged as a base catalysed elimination of the toluene-p-sulphonamide group as shown in Scheme VI. The groups R and R' would have been, in this case, part of a seven membered ring.

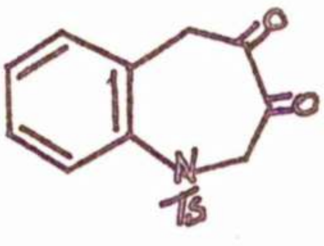
Scheme VI



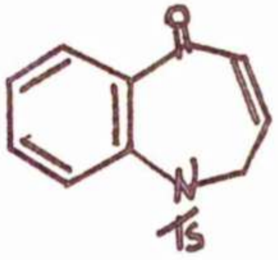
CXXI

CXXII

Thus the only requirement was seen to be that the hydrogen atoms on the carbon atom adjacent to the nitrogen atom, be activated directly by an electron withdrawing group as in the diketone (CXVIII), or vinylogously as in the

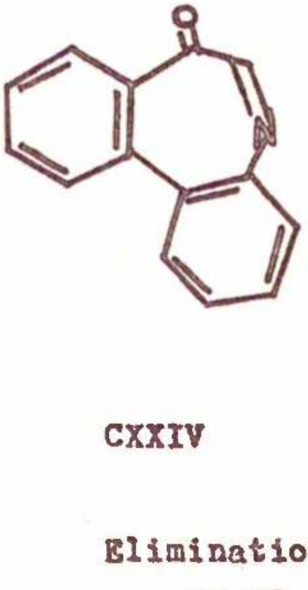


CXVIII

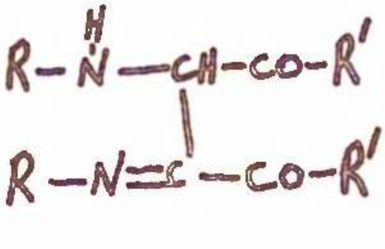


CXXIII

unsaturated ketone (CXXIII). Proctor[45] has used this reaction as the final synthetic step of an azadibenzotropone (CXXIV).



CXXIV



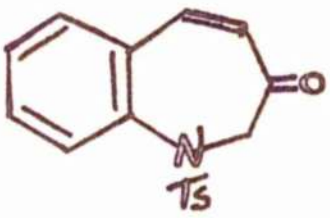
CXXV

CXXVI

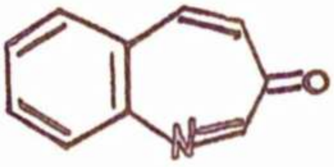
Eliminations of the type shown in Scheme VI have been described[75,78,96], but Negishi and Day[97] have recently shown that when using Proctor's[75] reaction on the compound (CXXI; R = R' = Ph), the product was not the anil (CXXII), but an exact dimer, although they were unable to propound a structure for the dimer. However, Proctor and co-workers[98] have shown that the dimer is a compound of the type (CXXV; R= R' = Ph), and that monomers like (CXXVI; R = R' = R'' = Ph) can be obtained if the starting material has only one hydrogen atom available for elimination, the other being substituted by a suitable group such as Me or Ph.

The latter result has been implicitly demonstrated by a number of workers[99,100,101,102], who have used the reaction satisfactorily in synthetic work.

The successful preparation of the azadibenzotropone (CXXIV) by the elimination reaction, suggested that the compound (CXII) should lend itself to a similar process



CXII

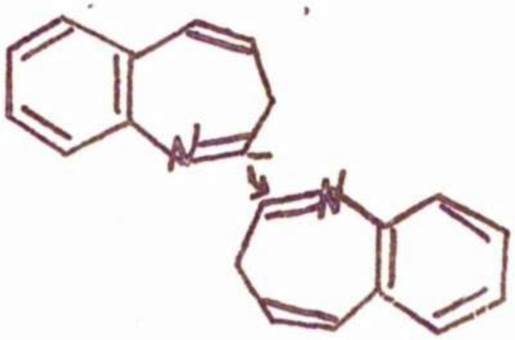


CXXVII

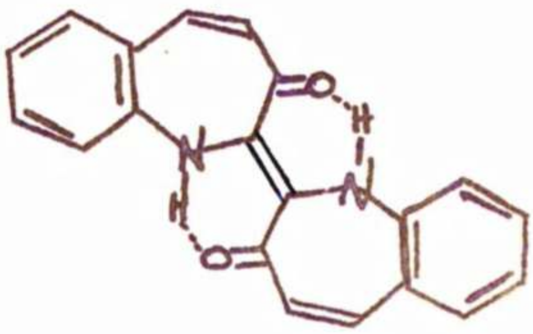
giving the azatropone (CXXVII). The reaction was carried out using sodium hydride, as base, in anhydrous tetrahydrofuran, and yielded a deep purple compound m.p. 158-159°, which had a tendency to autoxidise in solution. The compound has an empirical formula $C_{10}H_7NO$ which fits the structure (CXXVII), but a mass spectral analysis revealed that it was a dimer,

$C_{20}H_{14}N_2O_2$. The infrared spectrum of the compound in carbon tetrachloride shows no appreciable absorption between 3500 and 1615 cm.$^{-1}$ and the nuclear magnetic resonance spectrum is simple, suggesting a symmetrical structure, and showed a 4 proton quartet, i.e. doublets centred at 3.03τ and 3.77τ respectively, j = 12 c.p.s., an aryl multiplet at 2.95τ, equivalent to 8 protons, and a broad (2 protons) singlet (NH or OH) at -0.9τ.

The spectral evidence, coupled with the known[98] reactions of 'activated' anils of the type (CXXII) suggest the structure (CXXVIII) for the purple compound.



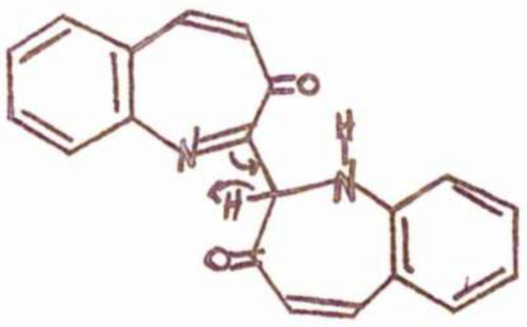
CXXVIIa CXXVII



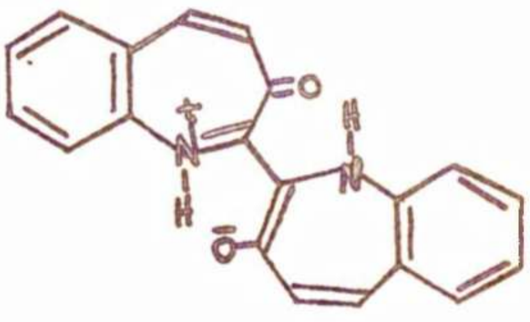
CXXVIII

It is proposed that the expected reaction, i.e. elimination of the sulphonyl group, takes place initially to form the azatropone (CXXVII), which can then form the anion (CXXVIIa), due to the electron withdrawing effect of the neighbouring groups.

By analogy with the mechanism proposed[98] for the formation of the dimer (CXXV), the present dimerisation is seen as the addition of the anion (CXXVIIa) and a proton, to the C=N bond of the azatropone (CXXVII) to form the unsymmetrical compound (CXXIX) which rearranges by a hydride shift, to assume the more stable, intramolecularly hydrogen bonded structure



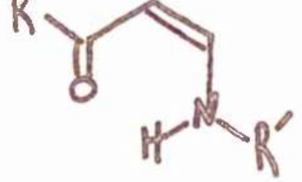
CXXIX



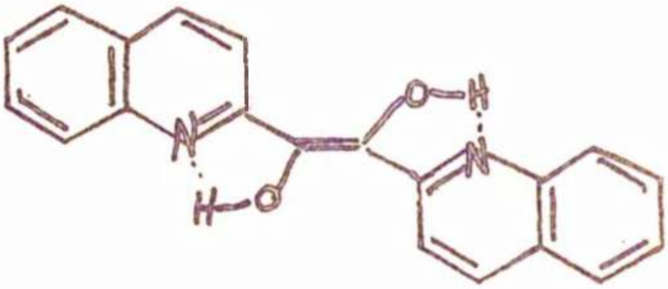
CXXX

(CXXVIII). The colour of this compound is probably due to the contribution of charged resonance structures such as (CXXX), although their contribution will be small owing to the high degree of covalent bonding possible in systems of this type[103].

The complete loss of infrared absorptions recognisably due to secondary amine or carbonyl stretching, has been observed by other workers[104], in acylic compounds of the type (CXXXI; R = Ph. R = C_6H_{11} or $PhCH_2$) which bear an obvious relationship to the proposed structure (CXXVIII).



CXXXI

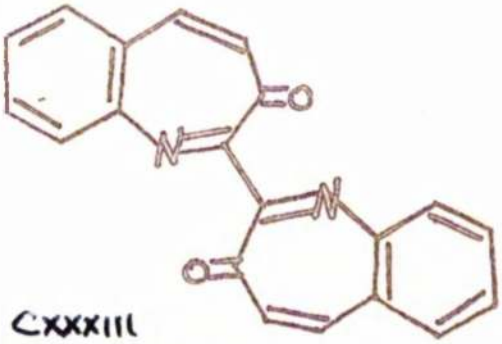


CXXXII

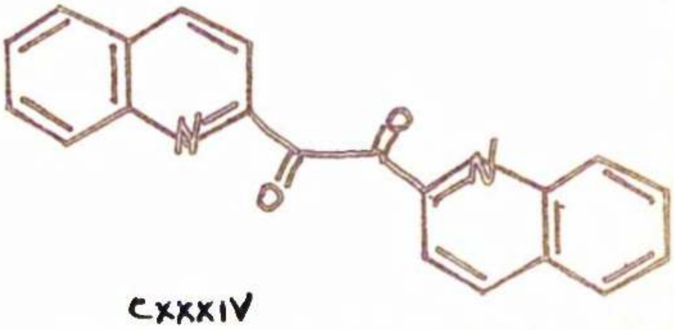
An isomer (CXXXII) m.p. 232-233°, of the compound (CXXVIII) has been described by Buehler[105], and is prepared by the benzoin condensation of quinoline-2-aldehyde. The close similarity, apart from the difference of 70° in melting point, of this compound to the dimer (CXXVIII), e.g. identical molecular formula and colour, lack of infrared absorption between 5000-1615 cm.$^{-1}$, and the likelihood of their having similar n.m.r. spectra, prompted a comparison of the two.

The enediol (CXXXII) has been reported[106] to exhibit absorption in the ultraviolet at 440 m u, whereas the dimer (CXXVIII) has maxima at 270, 370, and 532 m u.

A dilute (purple) solution of the dimer (CXXVIII) in dioxan, becomes yellow after standing for some time in the presence of air, possibly by autoxidation to the bis-azatropone



CXXXIII

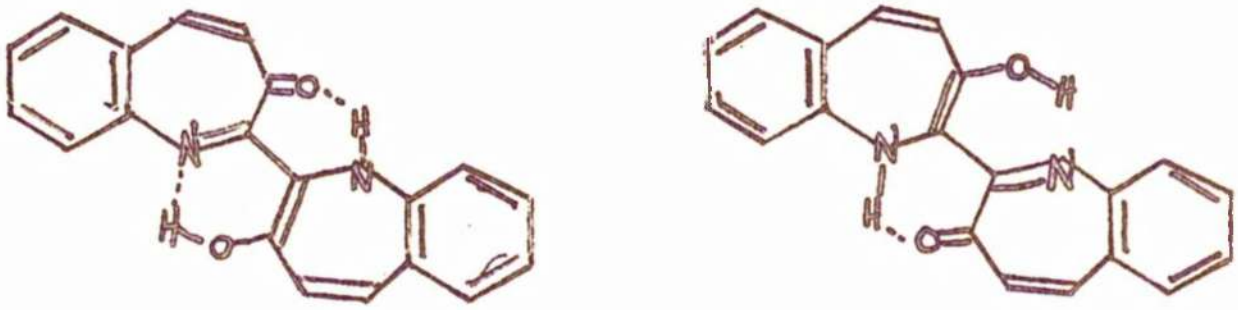


CXXXIV

(CXXXIII), since it is known[106,107] that the enediol (CXXXII) is very readily oxidised to quinaldil (CXXXIV). The ultra-violet spectrum of the solution then exhibits a maximum at 277 m u, whereas quinaldil has a maximum at 340 m u[106].

An x-ray study[108] is being carried out on a crystal of the compound (CXXVIII), and preliminary measurements have confirmed that it is a planar, centrosymmetric molecule as expected, but unfortunately, the more refined calculations, which will define the remainder of the structure, are as yet unavailable.

The compound (CXXVIII) is therefore postulated to



a b

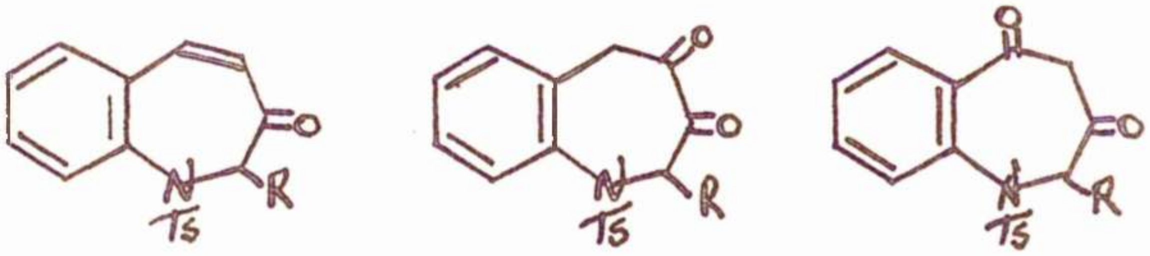
CXXXV

be a resonance hybrid of the two forms (CXXXV; a and b) as the main contributing structures.

The slight paramagnetic shift (about 0.3τ) observed in the n.m.r. spectrum of the dimer (CXXVIII), for the two vinyl protons [compared with the precursor (CXXXVIa; R = H)] could possibly be attributed to the development of a ring current[15,109].

but since the shift is rather small, it may only be due to changes in the environment, e.g. the development of planarity.

The usefulness of the sulphonamide elimination reaction for the final step in the preparation of monomeric azepinones, will undoubtedly be enhanced in the future by the use of suitable blocking groups in the β-position, e.g. as in the compounds (CXXXVI; a, b or c) where R would be an alkyl or aryl group. It is reasonable to suppose that a variety of interesting azatropones and azatropolones would then become available by this route.

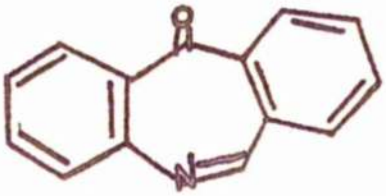


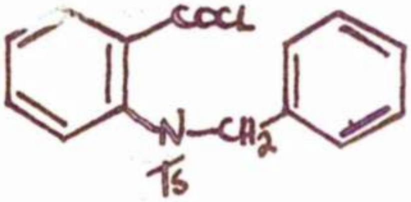
(a) (b) (c)

CXXXVI

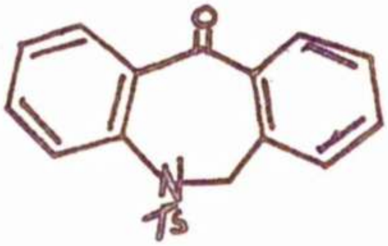
Dibenzazatropone

There is only one unknown simple isomeric dibenzazatropone (CXXXVII), other than the one prepared by Proctor[45] which has been already described. A synthesis of this unknown compound was attempted via the Friedel-Crafts ring closure of the acid chloride (CXXXVIII) at low temperatures, in order to obtain the compound (CXXXIX) which was expected to undergo elimination to yield the dibenzazatropone (CXXXVII). The cyclisation

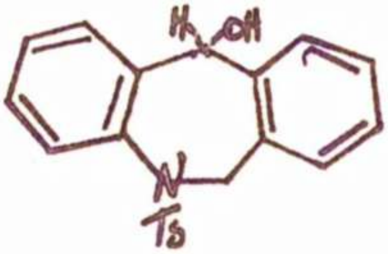

CXXXVII



CXXXVIII



CXXXIX



CXL

step gave a low yield of a compound m.p. 171°, shown by elemental, and mass spectral analysis to have a molecular formula $C_{21}H_{17}NO_{3}S$, exactly that of the desired compound (CXXXIX). The infrared spectrum showed no absorption for NH or OH, but did display a carbonyl peak at 1634 cm.$^{-1}$. On the basis of the n.m.r. spectrum of the compound, the formula (CXXXIX) was initially discounted due to the presence of a signal at 3.2τ(singlet) which gave a poor integral equivalent to either 4 or 5 protons. However, on reduction of the compound with sodium borohydride a compound ($C_{21}H_{19}NO_{3}S$) m.p. 148° was obtained displaying hydroxyl absorption and no carbonyl absorption in the infrared. The n.m.r. spectrum was now consistent with the alcohol (CXL), and the peak which was previously a singlet had become merged as a multiplet in the aryl region, and was therefore in fact due to the four aryl protons of the toluene-p-sulphonyl group. It has been occasionally noticed in these laboratories^{120} that the n.m.r. spectrum of a toluene-p-sulphonyl group can give rise to a singlet in the aryl region. A re-examination of the n.m.r. spectrum of the compound (CXXXIX) now suggests that it is actually consistent with this formula. The spectra are detailed in the appendix.

An elimination reaction on the compound (CXXXIX) has not, as yet, been performed, but such a reaction should be possible, and it will be of interest to determine whether the product is monomeric or dimeric.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES

Melting Points:- were determined on a Gallenkamp Melting Point Apparatus and are uncorrected.

Infrared Spectra:- were generally measured as potassium chloride discs (1%), or as specified in other cases.

Nuclear Magnetic Resonance Spectra:-were measured on a Perkin-Elmer 40 M/C spectrometer.

Reagents. The silica gel used for chromatography was Hopkin and Williams M.F.C. Grade. Alumina used was Spence's 'Activated Alumina Ungraded', and was deactivated by exposing to the atmosphere for varying periods of time.

Thin Layer Chromatography:- is referred to throughout as T.L.C. and was performed on 5 x 15 cm. plates coated with Merck's Kieselgel G.

o-Nitrophenylacetic acid

o-Nitrophenylacetic acid was prepared by the method of May and Mosettig[110], and was obtained as needles, m.p. 136-140° (lit.[110] m.p. 141°).

Ethyl-o-nitrophenylacetate

o-Nitrophenylacetic acid (18.1 g.; 0.1 mole) was dissolved in ethanol (200 ml.) and concentrated sulphuric acid (5 ml.) was added. The mixture was heated under reflux for 4 hrs. After the usual work-up procedure, purification was effected by eluting the ester with benzene through a short alumina column. Evaporation of the eluate under reduced pressure gave yellow prisms of the desired ester (17.6 g., 85%) m.p. 68-69° (lit.[111] m.p. 69°).

Ethyl-o-aminophenylacetate

Ethyl-o-nitrophenylacetate (6.3 g.; 0.03 mole) was hydrogenated over a platinum catalyst (200 mg.) in ethanol, until hydrogen uptake ceased (ca. 0.5 hr.). The solution was filtered and evaporated in vacuo, at room temperature, to give ethyl-o-aminophenylacetate (5.4 g.). The amine formed an acetate, white needles m.p. 66° (lit.[112] m.p. 66°) from ethanol and a benzoate, white needles m.p. 81° (lit.[112] m.p. 82°) from ethanol.

Ethyl-(N-toluene-p-sulphonyl)-o-aminophenylacetate

To ethyl-o-aminophenylacetate (5.4 g.; 0.03 mole) in pyridine (30 ml.) at 0°, was added toluene-p-sulphonylchloride (5.7 g.; 0.03 mole) and the mixture was allowed to stand for

24 hrs. After working-up by conventional procedures, recrystallisation from petroleum-ether (b.p. 60-80°) afforded white prisms of the sulphonamide m.p. 50° (Found: C,60.7; H,5.7; N,4.3; S,9.9. $C_{17}H_{19}NO_4S$ requires C,61.3; H,5.7; N,4.2; S,9.6%). $\nu_{max.}$ (KCL disc) 3290, 1740 cm.$^{-1}$ (NH and C=O respectively).

Reaction of Ethyl-o-aminophenylacetate with Ethyl-bromoacetate

A mixture of ethyl-o-aminophenylacetate (2.32 g.; 7.5 mmole) and ethyl bromoacetate (1.2 g.; 7.5 mmole) was heated at 100° for 6 hrs. The cooled mixture was taken up in chloroform (100 ml.), and the solution was washed with sodium bicarbonate solution (20 ml.; 10%), water, and dried (Na_2SO_4). The solvent was removed by distillation, leaving a red gum (1.52 g.), which was chromatographed on neutral deactivated alumina. Benzene elution yielded, on evaporation of the eluate, a white solid (0.54 g.) m.p. 126-128°. Recrystallisation from petroleum ether (b.p. 60-80°) gave white needles of Ethyl-oxindol-1-ylacetate (317 mg.) m.p. 128-129° (Found: C,65.8; H,5.8; N,6.7. $C_{12}H_{13}NO_3$ requires C,65.7; H,6.0; N,6.4%) $\nu_{max.}$ 1770, 1736 (C=O). N.M.R. data are recorded in the appendix.

Further elution with benzene gave a mixture (0.52 g.) m.p. 107-112°, of the above compound and oxindole (identified by T.L.C.). Continued benzene elution gave oxindole (0.460 g.)

identified by m.p. 125-126°, undepressed on admixture with an authentic sample (lit.[113] m.p. 127°).

Ethyl (N-o-ethoxycarbonylmethylphenyl)-N-toluene-p-sulphonylglycine

To ethyl (N-toluene-p-sulphonyl)-o-aminophenylacetate (6.66 g.; 0.02 mole) dissolved in dry acetone (70 ml.) was added potassium carbonate (3.0 g., anhyd.) followed by ethyl bromoacetate (3.5 g.; 0.0205 mole). The slurry was stirred and refluxed for 3 hrs. The, initially formed, thick slurry became more mobile as the reaction proceeded.

The cooled reaction mixture was filtered and evaporated *in vacuo*, to yield a yellow-brown syrup (8.8 g.).

Chromatography of the syrup on neutral alumina gave on benzene elution, a pale yellow liquid (0.35 g.) smelling strongly of ethyl bromoacetate. Continued elution, and evaporation of the eluate, yielded *Ethyl (N-o-ethoxycarbonylmethylphenyl)-N-toluene-p-sulphonylglycine* (7.6 g.; 91%) as a thick yellow syrup which would not crystallise or distil. (Found: C,60.0; H,6.3; N,3.0. $C_{21}H_{25}NO_6S$ requires C,60.2; H,6.0; N,3.3%) ν_{max} (liq. film) 1720-1740 cm.$^{-1}$ (C=O unresolved).

The above diester (1 g.) and alcoholic potassium hydroxide solution (25 ml.; 1N, 50%) were heated under reflux for 1 hr. Dilution with water and acidification with dilute hydrochloric acid (10%), gave N-(o-carboxymethylphenyl)-N-toluene-p-sulphonylglycine (0.5 g.) as white prisms m.p. 196-197° from aqueous ethanol (Found: C,56.2; H,4.6; N,3.9; S,9.1. $C_{17}H_{17}NO_6S$ requires C,56.2; H,4.7; N,3.9; S,8.8%) ν_{max} (KCL disc) 1730 cm.$^{-1}$ broad (2 x C=O).

Reaction of ethyl N-(o-ethoxycarbonylmethylphenyl)-N-toluene-p-sulphonylglycine with diethyl oxalate

To a cooled (0°) solution of sodium ethoxide, prepared from sodium (0.36 g.), in ethanol (35 ml.), was added diethyl oxalate (1.15 g.) followed by a solution of ethyl N-(o-ethoxycarbonylmethylphenyl)-N-toluene-p-sulphonylglycine (3.31 g.) in ethanol (15 ml.). The solution was stirred for 12 hr. and allowed to come to room temperature. The resultant dark brown solution was poured into water and extracted twice with ether (2 x 150 ml.). The bulked ether extracts were washed, dried (Na_2SO_4) and evaporated in vacuo to a thick oil (2.0 g.). This oil will be termed product A.

The basic aqueous phase was acidified with hydrochloric acid (4N) and extracted with ether. The organic layer was dried and evaporated to a dark brown gum. Trituration of the gum with hot water and filtration yielded pale yellow daliquescent plates of toluene-p-sulphinic acid (0.35 g.) m.p. 78-80° from the cooled filtrate (lit.[79] m.p. 84-85°). Further recrystallisation caused the acid to decompose to di-p-toluene-disulphoxide m.p. 74-76° (lit.[81] m.p. 74-76°) (Found: C,60.2; H,4.9. Calculated for $C_{14}H_{14}S_2O_2$. C,60.0; H,5.0%).

Product A was chromatographed on silica gel, and gave on benzene elution a green solution which on evaporation and recrystallisation from petroleum ether (b.p. 60-80°) yielded 2-ethoxycarbonyl-3-hydroxyquinoline (0.494 g.) as pale green needles m.p. 113° (Found: C,65.8; H,4.9; N,6.55. $C_{12}H_{11}NO_3$ requires C,66.4; H,5.1; N,6.45) ν_{max} (KCL disc) 1678 cm.$^{-1}$ (C=O). N.M.R. data are reported in the appendix.

Further elution of the column with benzene ether (19:1) yielded a red gum (0.94 g.) which failed to crystallise.

Treatment of 2-ethoxycarbonyl-3-hydroxyquinoline (0.11 g.) in pyridine (5 ml.) with toluene-p-sulphonylchloride (0.1 g.) gave after 12 hrs. and working-up by standard procedures 2-ethoxycarbonyl-3-toluene-p-sulphonyloxyquinoline (0.074 g.) m.p. 66° as white prisms from ethanol (Found: C,61.8; H,4.6; N,4.0; S,8.8. $C_{19}H_{17}NO_5S$ requires C,61.5; H,4.6; N,3.8; S,8.6%) ν_{max} (KCL disc) 1740 cm.$^{-1}$ (C=O).

Reaction of ethyl N-(o-ethoxycarbonylmethylphenyl)-N-toluene-p-sulphonylglycine with diethyl oxalate

To a stirred refluxing solution of sodium ethoxide (0.75 g.) in absolute ethanol (20 ml.) in a nitrogen atmosphere, was added a solution of diethyl oxalate (2.33 g.) and ethyl N-(o-ethoxycarbonylmethylphenyl)-N-toluene-p-sulphonylglycine (6.7 g.) in ethanol (20 ml.) over 2 min.

Stirring was continued for 1 hr. while the temperature was allowed to fall to 20°. The mixture was worked up essentially as before and separated into a non-acidic portion, Product A, and an acidic portion Product B.

Product A was a brown gum (3.06 g.). Chromatography on silica gel (benzene elution) yielded a white solid (0.060 g.). Recrystallisation from petroleum ether (b.p. 60-80°) gave 1,2-dihydro-4-ethoxycarbonyl-3-hydroxy-1-toluene-p-sulphonylquinoline (0.030 g.) m.p. 105-106° (Found: C,60.7; H,5.1; N,3.6. $C_{19}H_{19}NO_5S$ requires C,61.1; H,5.1; N,3.8%) ν_{max} (KCL disc) 1658 cm.$^{-1}$ (C=O).

Further elution with benzene gave a green gum (0.450 g.) which on recrystallisation from petroleum ether (b.p. 60-80°) gave 2-ethoxycarbonyl-3-hydroxyquinoline (0.359 g.) m.p. 112°, undepressed on admixture with a sample previously obtained. Elution was continued with benzene ether (19:1) and gave an impure red gum (2.1 g.) which failed to crystallise. An infrared spectral comparison of this material, with the starting diester, suggested that it consisted mainly of the latter.

Product B was a yellow gum (3.5 g.) containing crystalline material (mainly sulphinic acid). Trituration of the gum with cold benzene and filtration, yielded yellow prisms of 3-ethoxalyloxindole (0.212 g.) m.p. 184-186°. Recrystallisation from ethanol gave (0.18 g.) m.p. 186° (lit.[76] m.p. 187°). (Found: C,61.2; H,4.8; N,5.7. Calculated for $C_{12}H_{11}NO_4$. C, 61.8; H,4.8; N,6.0%).

The benzene filtrate was evaporated and extracted with boiling petroleum ether (b.p. 60-80°). On evaporation of the petroleum ether extract, white prisms of di-p-toluene-disulphoxide (0.65 g.) were obtained, m.p. 73-75° undepressed on admixture with a sample previously obtained.

Self-condensation of ethyl N-(o-ethoxycarbonylmethylphenyl)-N-toluene-p-sulphonylglycine

When the previous reaction was carried out, but without the addition of ethyl oxalate, all the compounds previously noted were found to be present with the exception of 3-ethoxalyl-oxindole which could not be detected.

Reaction of ethyl N-(o-ethoxycarbonylmethylphenyl)-N-toluene-p-sulphonylglycine with ethyl oxalate (in aprotic conditions)

To a suspension in dry ether (25 ml.) of dry sodium ethoxide, prepared from sodium (1.38 g.; 0.02 mole), was added a solution of ethyl N-(o-ethoxycarbonylmethylphenyl)-N-toluene-p-sulphonylglycine (8.38 g.; 0.02 mole) and diethyl oxalate (2.92 g.; 0.02 mole) in ether (15 ml.). The mixture was refluxed for 15 min., then evaporated to dryness *in vacuo* and heated for 30 min. *in vacuo*. Working-up as before and separation of the acidic products gave 3-ethoxalyloxindole (0.583 g.; 13%) m.p. 184-185° undepressed on admixture with a genuine sample. N.M.R. data are reported in the appendix.

Hydrolysis of 3-ethoxalyloxindole

3-ethoxalyloxindole (80 mg.) was dissolved in aqueous ethanolic sodium hydroxide (10 ml.; 1.0 N), and allowed to stand for 24 hrs. Acidification with dilute hydrochloric acid (1.0 N) gave, on filtration and recrystallisation of the precipitate from aqueous ethanol, oxindole-3-yl oxalate (20 mg.) m.p. 266-269° (lit.[114] m.p. 265-270°) (Found: N,6.5. Calculated for $C_{10}H_7NO_4$. N,6.8%).

6-oxindol -3-yl-7-oxoquinoxaline

A solution of 3-ethoxalyloxindole (47 mg.), and o-phenylenediamine (25 mg.) in ethanol (5 ml.) was heated under reflux for 2 hrs. The resultant red precipitate was filtered off and yielded 6-oxindol-3-yl-7-oxoquinoxaline (25 mg.) m.p. $>$340° (lit.[76] m.p. $>$240°) as a red powder.

Methylation of 3-ethoxalyloxindole

A solution of 3-ethoxalyloxindole (150 mg.) in dry ether (30 ml.) was treated with an ethereal solution of diazomethane (excess). Evaporation of the solvent gave a red gum which was chromatographed on silica gel (benzene-ether 19:1 elution). The first fraction was a yellow solid which on recrystallisation from Benzene/petroleum ether (b.p. 60-80°) yielded methyl 3-indolinylidene-methoxyacetate (36 mg.) m.p. 143° as yellow needles (Found: C,63.3; H,5.2; N,5.6. $C_{13}H_{13}NO_4$ requires C,63.2; H,5.3; N,5.7%) ν_{max} (KCl disc) 1724, 1692 cm.$^{-1}$ (C=O).

Further elution of the column gave a white solid which on recrystallisation from ethanol yielded a white powder (63 mg.) m.p. 194–195°, for which no structure could be deduced. $\nu_{max.}$ (KCl disc) 1730 cm.$^{-1}$ (C=O).

Preparation of Oxindole

Ethyl-*o*-nitrophenylacetate (1.5 g.) was hydrogenated over platinum (PtO_2, 100 mg.) in ethanol and the resultant solution was filtered and evaporated *in vacuo* to an oil. The oil was heated at 90° for 1 hr. and the solid obtained was recrystallised from petroleum ether (b.p. 60–80°) to yield oxindole (0.7 g.; 75%) m.p. 125–126° (lit.[113] m.p. 127°).

Reaction of oxindole with ethyl oxalate

Oxindole (0.5 g.) was added to a solution of sodium ethoxide, prepared from sodium (0.07 g.) and diethyl oxalate (0.5 g.) in ethanol (20 ml.). The solution was heated under reflux for 5 min. then the solvent was removed *in vacuo* and the residue was heated at 90° for 30 min. Water was added and the solution was extracted with ether. The aqueous layer was acidified with dilute hydrochloric acid and the yellow precipitate was filtered off. Recrystallisation from ethanol yielded 3-ethoxalyloxindole (50 mg.; 8%) m.p. 184–185° (lit.[76] m.p. 186°).

Preparation of ethyl-2,3-dioxycinchoninate

The ester was prepared essentially by the method of

Wislicenus[76] and gave the product (625 mg.) m.p. 210-211° (lit.[76] m.p. 212°).

Methyl-N-toluene-p-sulphonylanthranilate

The sulphonamide was prepared by standard procedures from methyl anthranilate and toluene-p-sulphonylchloride in pyridine, and obtained from ethanol as white prisms m.p. 113° (lit.[37] m.p. 113°).

Methyl-N-ethoxycarbonylmethyl-N-toluene-p-sulphonylanthranilate

A mixture of methyl N-toluene-p-sulphonylanthranilate (16 g.; 0.05 mole), ethyl bromoacetate (8.5 g.; 0.05 mole, 2% excess) and anhydrous pulverised potassium carbonate (10 g.) in dry acetone (150 ml.) was heated and stirred under reflux for 4 hrs. The resultant suspension was filtered and the solids washed with dry acetone. The filtrate and washings were bulked and evaporated to a thick purplish oil which was chromatographed on neutral alumina. Benzene eluted, initially, a mixture of ethyl bromoacetate and methyl N-toluene-p-sulphonylanthranilate (1.6 g.) identified by strong lachrymatory smell and T.L.C. comparison with starting materials. Further elution with benzene ether (19:1) gave a thick syrup (15.6 g.) which crystallised after some days. Recrystallisation from ethanol afforded methyl N-ethoxycarbonylmethyl-N-toluene-p-sulphonylanthranilate (13.5 g.;

69%) as fine white needles m.p. 63° (Found: C, 58.5; H, 5.5; N, 3.5. $C_{19}H_{21}NO_6S$ requires C, 58.3; H, 5.4; N, 3.6%) $\nu_{max.}$ (KCl disc) 1755, 1713 cm.$^{-1}$ (C=O)

Reaction of Methyl N-ethoxycarbonylmethyl-N-toluene-p-sulphonylanthranilate with diethyl malonate

To a solution of sodium ethoxide, prepared by dissolving sodium (0.34 g.; 15 mmole) in ethanol (10 ml.) was added diethyl malonate (0.8 g.; 5 mmole) followed by methyl N-ethoxycarbonylmethyl-N-toluene-p-sulphonylanthranilate (1.95 g.; 5 mmole) in ethanol (10 ml.). The solution turned dark green immediately and it was then heated under reflux for 15 min. The resultant dark brown solution was cooled, poured into water and extracted twice with ether. The bulked ethereal extracts were dried (Na_2SO_4) and evaporated to a brown syrup (1.5 g.).

Chromatography of the product on silica gel gave, on benzene elution, a pale yellow-green solid (0.5 g.) m.p. 110-112°. Two recrystallisations from petroleum ether (b.p. 60-80°) afforded 2-ethoxycarbonyl-3-hydroxyindole (0.26 g.) m.p. 115-116° (lit.[115] m.p. 116-117°) as pale green needles. (Found: C, 64.3; H, 5.4; N, 6.8. Calculated for $C_{11}H_{11}NO_3$: C, 64.3; H, 5.4; N, 6.8%).

Treatment of the above compound with toluene-p-sulphonyl chloride in pyridine for 12 hrs. and working up by standard procedures afforded 2-ethoxycarbonyl-3-toluene-p-sulphonyloxyindole m.p. 152° (Found: C, 60.1; H, 4.7; S, 9.5. $C_{18}H_{17}NO_5S$ requires C, 60.2; H, 4.5; S, 8.9%) $\nu_{max.}$ (KCl disc) 3125 (NH), 1695 cm.$^{-1}$ (C=O).

Further elution of the column with benzene ether (19:1) gave a dark red gum (0.630 g.) which was recrystallised from cyclohexane, then ethanol to yield diethyl-(3-oxo-2-indolyinylidene)-malonate (0.41 g.) m.p. 111-112° as an orange powder. (Found: C, 62.2; H, 5.2; N, 4.9. $C_{15}H_{15}NO_5$ requires C, 62.3; H, 5.2; N, 4.8%) $\nu_{max.}$ 3366 (NH), 1745, 1720, 1689 cm.$^{-1}$ (C=O). N.M.R. data are recorded in the appendix.
The 2,4-dinitrophenylhydrazone of the ester crystallised from ethanol/ethyl acetate as deep violet needles m.p. 209°. (Found: N, 14.9. $C_{21}H_{19}N_5O_8$ requires N, 14.9%). $\nu_{max.}$ (KCl disc) 3330 (NH), 1728, 1676 (C=O).

Continued elution with benzene ether mixtures increasing to pure ether, gave a dark red gum (0.12 g.) which failed to crystallise.

Reaction of methyl N-ethoxycarbonylmethyl-N-toluene-p-sulphonylanthranilate with diethyl malonate.

To a suspension of sodium ethoxide, prepared from sodium (1.38 g.; 0.06 mole), in dry benzene (60 ml.) was added diethyl malonate (3.2 g.; 0.02 mole) followed by methyl N-ethoxycarbonylmethyl-N-toluene-p-sulphonylanthranilate (7.52 g.; 0.02 mole) in benzene (60 ml.). The mixture was heated under reflux (in a nitrogen atmosphere) for 10 min., then evaporated to dryness and heated at 90° in vacuo for 40 min. The mixture was cooled and water and ether was added. The organic layer was separated, washed, dried (Na_2SO_4), and evaporated to a brown gum (5.53 g.). Chromatography of the gum on silica gel with benzene elution gave a yellow gum (2.05 g.). Two recrystallisations from ethanol yielded 2-ethoxycarbonyl-3-hydroxy indole (0.8 g.) m.p. 114-115° undepressed on admixture with a sample previously obtained.

Continued elution with benzene ether (19:1) gave diethyl (3-oxo-2-indolinylidene)-malonate (0.187 g.) as a semi-crystalline gum, identified by infrared comparison with a sample previously obtained.

Further elution with benzene ether (19:1) gave a red solution (blue fluorescing) which evaporated to a red gum. This was purified by repeated crystallisation from ethanol to yield 2,3,3-Triethoxycarbonyl-1,2,3,4-tetrahydroquinol-4-one as pale yellow prisms m.p. 108° (Found: C,59.4; H,5.8; N,3.8. $C_{18}H_{21}NO_7$ requires C,59.5; H,5.8; N,3.9%) ν_{max} 3390 (NH), 1750, 1720, 1692 cm.$^{-1}$ (C=O).

The above compound failed to react with either Brady's reagent or with toluene-p-sulphonyl chloride in pyridine.

Ethyl N-toluene-p-sulphonylaminoacetate

Ethyl N-toluene-p-sulphonylaminoacetate was prepared by standard procedures from ethylaminoacetate hydrochloride and toluene-p-sulphonyl chloride in pyridine, yielding the sulphonamide in 53% yield m.p. 65° (lit.[116] m.p. 64-65°) as fine white needles from petroleum ether (b.p. 80-100°).
(Found: C,51.7; H,6.0; N,5.4; S,12.9. Calculated for $C_{11}H_{15}NO_4S$: C,51.3; H,5.8; N,5.5; S,12.5%).

Diethyl-N-toluene-p-sulphonyliminodiacetate

To a stirred slurry of ethyl N-toluene-p-sulphonylaminoacetate (21 g.) and potassium carbonate (20 g.) in acetone (250 ml.), was added ethyl bromoacetate (14.5 g.) in acetone (50 ml.). The mixture was heated under reflux for 4 hrs., cooled and filtered. The filtrate was evaporated to an oil and chromatographed on silica gel. Benzene elution gave (after discarding a fore-run containing ethyl bromoacetate), diethyl N-toluene-p-sulphonyliminodiacetate (19.58 g.) as a colourless undistillable syrup, shown to be homogeneous by T.L.C. $\nu_{max.}$ (liq. film) 1750 (C=O), 1340, 1163 cm.$^{-1}$ (S=O).

The above diester (1.9 g.) was refluxed with aqueous alcoholic potassium hydroxide solution (20 ml.; 2N) for 1 hr. The resultant solution was acidified and the precipitate

(1.3 g.) was filtered off and recrystallised from aqueous ethanol to yield N-toluene-p-sulphonyliminodiacetic acid as fine white powder m.p. 184-186° (Found: C, 46.5; H, 5.0; N, 4.9. $C_{11}H_{13}NO_6S$ requires C, 46.0; H, 4.5; N, 4.9%). $\nu_{max.}$ (Nujol) 1721 cm.$^{-1}$ (C=O).

Di-(2,2'-ethoxycarbonylethyl)-amine

The disubstituted amine was prepared by the method of McElvain and Stork[117], and gave 22.6 g. of product as a colourless oil, b.p. 121-126°/2 mm. (lit.[117] b.p. 119-125°, 1-2 mm.).

Attempted acyloin cyclisation of di-(2,2'-ethoxycarbonylethyl)amine

Both attempts to cyclise the above compound, under the general reaction conditions described below, led to low yields of intractable oils which were not further investigated.

Attempted acyloin cyclisation of methyl N-(2-methoxycarbonylethyl)-anthranilate (General Procedure).

Liquid ammonia (1 l.) was distilled through potassium hydroxide pellets into a flask at -70°, fitted with a paddle stirrer and a drying tube packed with potassium hydroxide. After addition of ether (750 ml.), the apparatus was flushed with oxygen-free nitrogen, while sodium (6.1 g.) was added in small pieces. The resultant blue solution was stirred for 1 hr., after which methyl-N-(2-methoxycarbonylethyl)-anthranilate

(11.9 g.) in ether (750 ml.) was added dropwise over 2 hrs. with stirring, the blue colour finally giving way to yellow.

After being kept under nitrogen overnight, the mixture was treated with ethanol (30 ml.) and, after 30 min., was extracted with dilute hydrochloric acid (3 x 200 ml. 4N). The extracts were basified with ammonia (d. 0.850), and extracted with chloroform. The organic phase was washed, dried (Na_2SO_4) and evaporated to a dark tar (5.4 g.). T.L.C. revealed the presence of a variety of compounds in the tar.

Chromatography of a portion of the tar (2.7 g.) on neutral deactivated alumina gave the following fractions:-

1) Benzene-chloroform (1:1). A green gum (0.268 g.) which contains recovered methyl-N-(2-methoxycarbonylethyl)-anthranilate and 1,2,3,4-tetrahydro-3-methoxycarbonyl-4-oxo-quinoline. Identified by comparative T.L.C.

2) Chloroform-ethanol (50:1) gave a dark orange gum (1.1 g.) shown by T.L.C. to be a mixture of 3 polar materials.

3) The column was stripped with chloroform-methanol to yield a dark intractable tar (0.32 g.).

Rechromatography of the second fraction gave a homogeneous yellow gum (0.18 g.), which failed to crystallise, and for which no structure could be deduced from elemental analysis. $\nu_{max.}$ (liq. film) 3450-3220 (OH), 1662 cm.$^{-1}$ (C=O).

Oxidation of crude acyloin

A portion (0.68 g.) of the crude product from the previous reaction was dissolved in glacial acetic acid (15 ml.). Bismuth oxide (2.0 g.) was added and the stirred mixture was heated to 90° for 30 min. Working up by standard procedures gave a dark brown solid (0.53 g.). The solid was extracted with hot benzene, which, on cooling, deposited an amorphous powder (56 mg.) m.p. 88-95° for which no structure could be deduced from elemental analysis. $\nu_{max.}$ (KCl disc) 3240 (NH), 1730, 1670 cm.$^{-1}$ (C=O). The material could not be further purified by distillation.

Attempts to prepare quinoxaline or dinitrophenylhydrazone derivatives of the above material gave rise to impure solids.

Ethyl-8-o-toluidinopropionate

The above compound was prepared by the general method of Johnson, Woroch and Buell[118], and gave the product (37 g.; 54%). b.p. 180-184°/14 mm.

N-(3'-Hydroxypropyl)-o-toluidine

To a stirred suspension of sodium (6.0 g.; 0.25 mole) in dry toluene (25 ml.) heated at 60°, was added over 10 min. a solution of N-(2-ethoxycarbonylethyl)-o-toluidine (8.28 g.; 0.04 mole) in ethanol (20 ml.). After the addition was completed a further aliquot of ethanol (40 ml.) was added. Heating was continued for 30 min. The solution was cooled, poured into water and extracted with ether. The organic phase was washed, dried (Na_2SO_4) and evaporated to a yellow oil. Distillation *in vacuo* yielded N-(3'-hydroxypropyl)-o-toluidine (2.86 g.; 44%) as a pale yellow oil b.p. 100-101°/0.15 mm. (lit^{119} b.p. 140°/0.4 mm.). (Found: C,73.2; H,9.0; N,8.3. Calculated for $C_{10}H_{15}NO$: C,72.7; H,9.15; N,8.5%).

The dibenzoate crystallised from petroleum ether (b.p. 60-80°) as white prisms m.p. 140° (Found: C,77.6; H,6.1; N,3.5. Calculated for $C_{24}H_{33}NO_3$: C,77.2; H,6.2; N,3.75%). This product proved identical to material obtained from the crude acyloin product by sodium and alcohol reduction^{40}.

Reactions of 2,3,4,5-Tetrahydro-1-toluene-p-sulphonyl-benz[f]azepin-5-one

4,4,7,9-Tetrabromo-2,3,4,5-tetrahydrobenz[f]azepin-5-one

To a stirred solution of 2,3,4,5-tetrahydrobenz[f]azepin-5-one (20.5 g.; 66 mmole) in chloroform (300 ml.) was added a solution of bromine (20 ml.) in chloroform (50 ml.). The resultant fuming solution was allowed to stand overnight. The yellow precipitate (27.3 g.; 86%) was collected and recrystallisation from ethanol afforded 4,4,7,9-tetrabromo-2,3,4,5-tetrahydrobenz[f]azepin-5-one (25.8 g.) as yellow prisms m.p. 152-153° (Found: C,25.6; H,1.7; N,2.9. $C_{10}H_7Br_4NO$ requires C,25.2; H,1.5; N,2.9%). $\nu_{max.}$ (KCl disc) 3400 (NH), 1680 cm.$^{-1}$ (C=O).

The acetate crystallised from ethanol as white plates m.p. 165-166° (Found: C,27.8; H,1.7; Br,61.0; N,2.9. $C_{12}H_9Br_4NO_2$ requires C,27.7; H,1.7; Br,61.6; N,2.7%).

Hydrolysis of 4,4,7,9-tetrabromo-2,3,4,5-tetrahydrobenz[f]azepin-5-one

A mixture of the tetrabromoketone (11.0 g.), ethanol (250 ml.) and sodium bicarbonate solution (100 ml.; 10%) was heated under reflux for 4 hrs. The mixture was cooled and extracted with chloroform. The organic phase was washed, dried and evaporated to a dark brown tar (7.0 g.). Chromatography of the tar on silica gel (benzene elution with increasing concentrations of chloroform) gave the starting tetrabromide (1.33 g.) m.p. and m.m.p. 151-152°.

Further elution yielded a yellow solid (3.7 g.). Recrystallisation from petroleum ether (b.p. 60-80°) gave *4,7,9-tribromo-2,3,4,5-tetrahydrobenz[f]azepin-5-one* (2.9 g.) as a fine yellow powder m.p. 107° (Found: C,30.0; H,2.0; Br,60.4; N,3.4. $C_{10}H_8Br_3NO$ requires C,30.2; H,2.0; Br,60.3; N,3.5%) $\nu_{max.}$ (KCl disc) 3368 (NH), 1675 cm.$^{-1}$ (C=O).

Continued elution gave a pale green solid (0.154 g.) m.p. 88-90° recrystallisation from ethanol afforded yellow needles of *7,9-dibromo-2,3,4,5-tetrahydrobenz[f]azepin-5-one* (80 mg.) m.p. 91°. (Found: C,37.3; H,3.0; N,4.3. $C_{10}H_9Br_2NO$ requires C,37.6; H,2.8; N,4.4%) ν_{max} (KCl disc) 3316 (NH), 1667 cm.$^{-1}$ (C=O). The *dinitrophenylhydrazone* crystallised from ethyl acetate as fine dark red needles m.p. 274°. (Found: C,38.7; H,2.8; Br,33.4; N,12.6. $C_{16}H_{13}Br_2N_5O_4$ requires C,38.4; H,2.6; Br,33.3; N,12.6%).

One other fraction was obtained as a gum (0.557 g.) on continued elution, and this could not be identified.

7,9-Dibromo-2,3,4,5-tetrahydrobenz[f]azepin-5-one

A mixture of 4,4,7,9-tetrabromo-2,3,4,5-tetrahydrobenz[f]azepin-5-one (4.8 g.; 0.01 mole), zinc dust (20 g.) and methanol (150 ml.) was heated under reflux for 2 hrs. The mixture was cooled and filtered through kieselguhr, poured into water and extracted with ether. The organic layer was washed, dried (Na_2SO_4) and evaporated to a pale yellow solid (3.03 g.; 95%). Recrystallisation from ethanol afforded 7,9-dibromo-2,3,4,5-tetrahydrobenz[f]azepin-5-one (2.8 g.) m.p. 90-91° undepressed on admixture with a sample previously obtained.

Acetylation of the dibromo ketone in acetic anhydride/pyridine had no effect, but refluxing acetic anhydride containing a drop of concentrated sulphuric acid gave after working-up 5-acetoxy-1-acetyl-7,9-dibromo-2,3-dihydrobenz[f]azepine m.p. 157-158° as fine white needles from ethanol. (Found: C,41.9; H,3.2; N,3.3. $C_{12}H_{11}Br_2NO_2$ requires C,41.7; H,3.2; N,3.5%). $\nu_{max.}$ (KCl disc) 1732, (C=O enolacetate) 1650 cm.$^{-1}$ (C=O amide).

Reaction of 4,7,9-tribromo-2,3,4,5-tetrahydrobenz[f]azepin-5-one with zinc and methanol

A mixture of the tribromo ketone (1 g.), zinc dust (5 g.) and methanol (50 ml.) was refluxed for 2 hr. Working-up as before gave 7,9-dibromo-2,3,4,5-tetrahydrobenz[f]azepin-5-one (0.6 g.) m.p. and m.m.p. 88-90°.

4,7,9-Tribromo-2,3,4,5-tetrahydrobenz[f]azepin-5-one

To a stirred solution of 7,9-dibromo-2,3,4,5-tetrahydrobenz[f]azepin-5-one (1.85 g.) in chloroform (50 ml.) was added bromine (0.32 ml.) in chloroform (10 ml.). The solution was left overnight, washed with sodium bicarbonate solution (10%), water, dried, (Na_2SO_4) and evaporated to a green gum. Recrystallisation from ethanol yielded the tribromide (1.59 g.; 59%) m.p. and m.m.p. 107°.

Hydrolysis of 4,7,9-tribromo-2,3,4,5-tetrahydrobenz[f]azepin-5-one

The tribromo amino ketone (0.24 g.) and potassium bicarbonate solution (20 ml., 5%) was heated under reflux for 8 hrs. The solution was cooled and extracted with chloroform (2 x 20 ml.). The organic extracts were bulked and dried (Na_2SO_4) and evaporated to a green gum. Chromatography on neutral alumina, with benzene elution, gave traces of the starting material, and 7,9-dibromo-2,3,4,5-tetrahydrobenz[f] azepin-5-one, (identified by T.L.C.), followed by a yellow gum (70 mg.) which was recrystallised from petroleum ether (b.p. 60-80°) to give a yellow powder (40 mg.) m.p. 155-156°. No structure could be deduced for this compound. (Found: C,36.0; H,2.4%). $\nu_{max.}$ (KCl disc) 3330 (NH), 1664 cm.$^{-1}$ (C=O).

The dinitrophenylhydrazone crystallised as fine red needles m.p. 304-305° from ethanol. (Found: C,37.3; H,2.13; N,14.3%). No structure could be deduced for this compound.

Attempted dehydrobromination of 4,7,9-tribromo-2,3,4,5-tetrahydrobenz[f]azepin-5-one

Anhydrous lithium chloride (5.0 g.) was added to a solution of the tribromoketone (0.5 g.) in dimethyl formamide (30 ml.), and the mixture was heated under reflux for 1 hr. The resultant solution was cooled, poured into water, and extracted with ether. The organic phase was washed, dried (Na_2SO_4) and evaporated to a gum. Recrystallisation from ethanol yielded *7,9-dibromo-4-chloro-2,3,4,5-tetrahydrobenz[f]azepin-5-one* (180 mg.) as yellow blocks m.p. 117° (Found: C,34.3; H,2.7. $C_{10}H_8Br_2ClNO$ requires C,34.0; H,2.3%) $\nu_{max.}$ (KCl disc) 3379 (NH), 1674 cm.$^{-1}$ (C=O).

Attempted Dehydrogenation of 7,9-dibromo-2,3,4,5-tetrahydrobenz[f]azepin-5-one

A solution of the dibromo aminoketone (320 mg.) and 2,3-dichloro-5,6-dicyanobenzo-1,4-quinone (500 mg.) in xylene (25 ml.) was heated under reflux for 6 hr. The solution was poured into ether and extracted twice with alkaline sodium dithionite solution (20 ml., 10%). The organic phase was evaporated *in vacuo* to give a yellow solid (320 mg.). Recrystallisation from ethanol gave recovered starting material (200 mg.) m.p. and m.m.p. 90-91°.

Reaction of 7,9-Dibromo-1,2,3,4-tetrahydrobenz[f]azepin-5-one with Selenium dioxide

To a solution of the dibromo ketone (0.8 g., 2.5 mmole) in glacial acetic acid (15 ml.) was added a solution of selenium dioxide (0.3 g.; 2.5 mmole) in water (2 ml.). The solution was heated under reflux for 3 hrs. and cooled, ether (50 ml.) was added, and then the solution was filtered. The filtrate was washed succesively with water, sodium bicarbonate solution, water and then was dried (Na_2SO_4) and evaporated to a dark gum. Chromatography on neutral alumina gave traces of starting material followed by a yellow gum (200 mg.) which failed to crystallise. The infrared spectrum of this gum showed bands at 3430 (NH), 1737, 1680 cm.$^{-1}$ (C=O). The material (200 mg.) and o-phenylene diamine (150 mg.), were dissolved in ethanol and heated under reflux for 1 hr. The ethanol was removed by distillation and the residue was chromatographed on neutral alumina. Benzene eluted a yellow solid which was recrystallised from petroleum ether (b.p. 60-80°) to yield yellow needles of the quinoxaline derivative of 7,9-dibromo-2,3,4,5-tetrahydrobenz[f]azepin-4,5-dione (62 mg.) m.p. 173° (Found: C,47.7; H,2.8; N,9.9. $C_{16}H_{11}Br_2N_3$ requires C,47.4; H,2.7; N,10.4%).

Hydrolysis of 4,4,7,9-tetrabromo-2,3,4,5-tetrahydrobenz[f] azepin-5-one

The tetrabromo ketone (1 g.) was hydrolysed as described previously (page 86) and the tarry residue (0.327 g.) isolated as before was dissolved in ethanol (20 ml.), o-phenylene diamine (200 mg.) was added and the solution was heated under reflux for 2 hr., then evaporated to dryness. T.L.C. revealed the presence of trace quantities of the quinoxaline isolated in the previous experiment. The residue was not further investigated.

Attempted Hydrolysis of 4,4,7,9-Tetrabromo-2,3,4,5-tetrahydrobenz[f]azepin-5-one

The tetrabromo ketone (1 g.) was suspended in oleum (20 ml.) at 0° and left 16 hrs. The resultant homogeneous solution was poured into crushed ice (200 g.) with stirring. The precipitate was extracted with ether and on working-up gave a quantitative recovery of the starting material m.p. and m.m.p. 151-152°.

Attempted dehydrobromination of 4,4,7,9-tetrabromo-2,3,4,5-tetrahydrobenz[f]azepin-5-one

To a solution of the tetrabromo ketone (2 g.) in benzene (40 ml.), was added sublimed potassium-t-butoxide (0.47 g.). The mixture was heated under reflux for 30 min., then allowed to stand at room temperature for 16 hrs. The mixture was treated with active charcoal (100 mg.) and kieselguhr (2 g.) and warmed for 5 min., then filtered. The filtrate was evaporated to a red gum (1.3 g.), which on recrystallisation from ethanol gave the starting material (1 g.) m.p. and m.m.p. 149-151°.

The mother liquors were found by T.L.C. to contain a complex mixture of polar substances and were not further

Reaction of 4,4,7,9-tetrabromo-2,3,4,5-tetrahydrobenz[f]azepin-5-one with potassium-t-butoxide in dimethyl sulphoxide

To a solution of 4,4,7,9-tetrabromo-2,3,4,5-tetrahydrobenz[f]azepin-5-one (2.4 g.; 5 mmole) in dimethyl sulphoxide (30 ml.) was added sublimed potassium-t-butoxide (0.8 g.; 7 mmole). The red solution was left in a stoppered flask overnight at room temperature, then poured into water and extracted with ether. The organic phase was washed, dried (Na_2SO_4) and evaporated to a red gum (1.95 g.). Chromatography of the gum on silica gel (benzene elution) gave the starting material (0.95 g.) contaminated with a trace of red material.

Further elution with benzene ether gave a red gum (0.5 g.) which was rechromatographed (see below). No other fractions were collected.

The red gum (0.5 g.) was rechromatographed on neutral active alumina which caused extensive decomposition. Benzene ether gradient elution, eluted various trace quantities of coloured materials which were not investigated. Ether elution yielded a yellow solid which on recrystallisation from benzene gave a yellow powder (60 mg.) m.p. 220-221°for which no structure could be deduced from elemental analysis. (Found: C,37.3; H,3.2; N,3.4%). $\nu_{max.}$ (Nujol) 3390 (NH), 1662 cm.$^{-1}$ (C=O).

4-Bromo-4-ethoxycarbonyl-1-toluene-p-sulphonyl-2,3,4,5-tetrahydrobenz[f]azepin-5-one

To a solution of 4-ethoxycarbonyl-1-toluene-p-sulphonyl-2,3,4,5-tetrahydrobenz[f]azepin-5-one[39] (11.6 g.) in chloroform (150 ml.) was added bromine (4.8 g.) in chloroform (50 ml.) with stirring. After 2 hrs., the solution was washed with an aqueous solution containing sodium bicarbonate (5%) and sodium thiosulphate (5%), then water, dried (Na_2SO_4), and evaporated in vacuo to a thick yellow syrup (12.8 g.; 92%). Recrystallisation from ethanol afforded white prisms of the desired product m.p. 78-79° (Found: C,51.6; H,4.45; N,3.4. $C_{20}H_{20}BrNO_5S$ requires C,51.5; H,4.3; N,3.0%). $\nu_{\text{max.}}$ (Nujol) 1740, 1704 $cm.^{-1}$ (C=O).

Attempted Dehydrobromination of 4-Bromo-4-ethoxycarbonyl-1-toluene-p-sulphonyl-2,3,4,5-tetrahydrobenz[f]azepin-5-one

The bromo ester (2.9 g.) was dissolved in collidine (25 ml.) and heated under reflux in a nitrogen atmosphere for 6 hrs. The dark reaction mixture was cooled and poured into ice and dilute hydrochloric acid (4N) and extracted with chloroform. The organic layer was washed, dried (Na_2SO_4), and evaporated in vacuo to a dark gum. Crystallisation from ethanol yielded 2,3,4,5-tetrahydro-1-toluene-p-sulphonylbenz[f]azepin-5-one (1.1 g.) m.p. 122-123° (lit.[39] m.p. 126°), identified by infrared comparison with an authentic sample.

Concentration of the mother liquors gave 4-ethoxy carbonyl-2,3,4,5-tetrahydrobenz[f]azepin-5-one (110 mg.) m.p. 117-119°, undepressed on admixture with an authentic sample.

2,3-Dihydro-1-toluene-p-sulphonylbenz[f]azepine

To a solution of 2,3,4,5-tetrahydrobenz[f]azepin-5-one (9.45 g.) in ethanol (100 ml.) was added sodium borohydride (2.0 g.) in small portions over 1 hr. The solution was left overnight, acidified with dilute hydrochloric acid (3N) and extracted with ether. The organic phase was washed, dried (Na_2SO_4) and evaporated to an oil. A mixture of the oil and toluene-p-sulphonic acid (200 mg.) was heated at 160°/0.01 mm. for 1 hr. Cooling of the mixture gave a crystalline mass which was dissolved in benzene and eluted through a short column of silica gel. Evaporation of the eluate and recrystallisation from ethanol gave the desired product (8.0 g.; 89%) m.p. 106-107°, identified by infrared comparison with a sample m.p. 109°, previously prepared[120] in this laboratory.

2,3-Dihydro-3-hydroxy-1-toluene-p-sulphonylbenz[f]azepine

2,3-Dihydro-1-toluene-p-sulphonylbenz[f]azepine (9.0 g.), N-bromosuccinimide (5.4 g.) and dry carbon tetrachloride (120 ml.) were refluxed[121] for 4 hrs. using a 200 w. bulb. After cooling, filtration and removal of solvent, the residue was dissolved in acetone/water (1.4 l. 1:1) and the solution was heated under reflux for 24 hrs. The acetone was distilled off and the aqueous residue extracted with ether. The organic phase was dried and evaporated to a crystalline mass (9.3 g.), which was chromatographed on silica gel. The benzene eluates were discarded. Benzene ether (9:1) elution gave a white solid (8.4 g.) which was recrystallised from benzene/petroleum ether (b.p. 60-80°) to give the product (7.3 g. 78%) as white prisms m.p. 111°, identified by infrared comparison with a sample m.p. 111°, previously prepared[120] in this laboratory.

2,3-Dihydro-1-toluene-p-sulphonylbenz[f]azepin-3-one

Chromium trioxide (4.0 g.) was added in small portions to pyridine (40 ml.) with swirling and cooling to 0° over a period of 20 min.[122]. To the suspension of the chromium trioxide/pyridine complex was added a solution of 2,3-dihydro-3-hydroxy-1-toluene-p-sulphonylbenz[f]azepine (6.3 g.) in pyridine (70 ml.), with stirring and cooling to 0°. The mixture was allowed to stand at room temperature for 16 hrs., then poured into ice and dilute hydrochloric acid (4N) and extracted with ether (3 x 150 ml.). The organic layer was washed, dried (Na_2SO_4) and evaporated to a yellow solid. Recrystallisation from ethanol afforded the desired product (3.6 g.; 58%) as pale yellow prisms m.p. 150-151°, identified by infrared comparison with a sample m.p. 152° previously prepared in this laboratory[120].

Reaction of 2,3-dihydro-1-toluene-p-sulphonylbenz[f]azepin-3-one with sodium hydride

To a stirred solution of the azepinone (1.05 g.; 33 mmole) in dry tetrahydrofuran (40 ml.), was added sodium hydride (0.075 g.; 3 mmole) in an atmosphere of nitrogen. Stirring was continued for 40 min. The deep purple solution was quickly poured through a 2" thick pad of neutral alumina (deactivated 20 hrs.) and washed with some ether (100 ml.). The filtrate was evaporated _in vacuo_ at 30° to a crystalline mass (about 250 mg.). Recrystallisation from ethanol yielded _2,2'-bi(2,3-dihydro-3-oxo-benz[f]azepinylidene)_ (70 mg.) as purple needles m.p. 158-159° (evacuated m.p. tube). (Found: C,76.2; H,4.8; N,8.9. $C_{20}H_{14}N_2O_2$ requires C,76.5; H,4.5; N,8.9%) mol. wt. (mass spec.) 314. $C_{20}H_{14}N_2O_2$ requires mol. wt. 314.

2,3-Dihydrobenz[f]azepine

To a stirred solution of 2,3,4,5-tetrahydro-1-toluene-p-sulphonylbenz[f]azepin-5-one (12.6 g.) in anhydrous liquid ammonia under reflux, was added sodium in small pellets, until the blue colour just persisted for more than 5 min. Sufficient ammonium chloride (ca. 50 mg.) to destroy the blue colour was added, then the ammonia was allowed to distil off. The residue was shaken with ether and water. The organic layer was dried (Na_2SO_4) and evaporated to an oil (6.4 g.). The oil was reduced with sodium borohydride in ethanol and the product was isolated in the usual manner. Dehydration of the alcohol was effected in a Dean and Stark apparatus by azeotropic removal of water from a benzene solution of the alcohol and toluene-p-sulphonic acid (50 mg.). The resultant solution was eluted through a short silica gel column with benzene. Evaporation of the eluate yielded 2,3-dihydro-benz[f]azepine (4.01 g.; 70%) as a colourless waxy solid m.p. 48°, identified by infrared comparison with an authentic sample (lit.[40] b.p. 95-100/0.4 mm.). The acetate crystallised from ethanol as white prisms m.p. 66° (Found: C,77.4; H,7.1; N,8.0. $C_{12}H_{13}NO$ requires C,77.0; H,7.0; N,7.5%).

4-Bromo-2,3,4,5-tetrahydro-1-toluene-p-sulphonylbenz[f]azepin-5-one

The above compound was prepared by the method of Proctor[39] and gave the bromo ketone (6.4 g.) m.p. 129-131° (lit.[39] m.p. 132°).

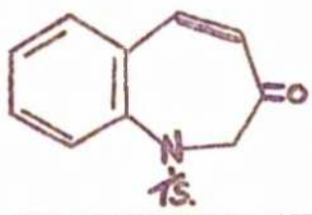
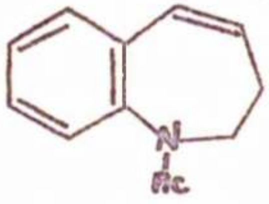
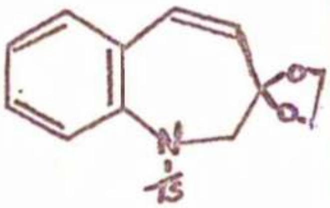
The ethylene ketal of the above compound was prepared by refluxing a solution of the bromo ketone (3.6 g.) redistilled ethylene glycol (2.5 ml.) and toluene-p-sulphonic acid (200 mg.) in dry toluene (120 ml.) in a Dean and Stark apparatus for 72 hrs. Evaporation of the solvent followed by chromatography on neutral alumina with benzene elution, gave the ethylene ketal (2.8 g.) as white prisms m.p. 147° on recrystallisation from ethanol. (Found: N,3.2. $C_{19}H_{20}BrNO_4$ requires N,3.2%). The infrared spectrum showed no absorption due to (C=O) stretching.

Ethylene ketal of 2,3-dihydro-1-toluene-p-sulphonylbenz[f]azepin-3-one

The ketone (3.0 g.), redistilled ethylene glycol (2 ml.), dry benzene (100 ml.), and toluene-p-sulphonic acid (300 mg.) were refluxed in a Dean and Stark apparatus. The solution was cooled, washed with sodium bicarbonate solution (10%) and water, and then dried (Na_2SO_4). Evaporation of the solvent, and recrystallisation of the residue from ethanol yielded the ketal, (2.9 g.) as white prisms m.p. 116°. (Found: C,64.5; H,5.6; N,3.9. $C_{19}H_{19}NO_4S$ require C,63.9; H,5.3; N,3.9%). The infrared spectrum showed no absorption due to (C=O) stretching.

Hydroxylation experiments

Attempts were made to hydroxylate the following compounds with the reagents shown. The times of reaction and percentage recovery of starting material are given. No other compounds were isolated.

Compound	Hydroxylating agent used	Solvent	Reaction time	% Recovery of staring material
 	OsO_4	T.H.F.	120 hrs.	86%
	$KMnO_4$	Acetone	1.5 hrs.	70%
 	$KMnO_4$	Acetone	24 hrs.	80%
 	OsO_4	Ether	150 hrs.	55%

<u>Ethylene ketal of 4,5-dibromo-2,3,4,5-tetrahydro-1-toluene-p-sulphonylbenz[f]azepin-3-one</u>

To a solution of the ethylene ketal of 2,3-dihydro-1-toluene-p-sulphonylbenz[f]azepin-3-one (0.9 g.; 25 mmole) in chloroform (20 ml.) containing pyridine (1 drop) was added bromine (0.4 g.; 25 mmole) in chloroform (10 ml.). The solution was left at room temperature for 3 hrs., washed with sodium hydrogen carbonate solution, water, dried (Na_2SO_4) and evaporated to a gum. Recrystallisation from ethanol yielded the <u>product</u> (410 mg.) as white prisms m.p. 161-162°. (Found: C,43.9; H,3.8; N,2.7. $C_{19}H_{19}Br_2NO_4S$ requires C,44.1; H,3.7; N,2.7%). The infrared spectrum showed no absorption due to (C=O) stretching.

Attempted hydrolysis and dehydration of the product from the preceding experiment

The dibromo ketal (100 mg.) was dissolved in aqueous acetone (20 ml.; 50%) and heated under reflux for 24 hrs. The acetone was removed by distillation and the aqueous residue was extracted twice with ether. The organic layer was dried and evaporated to a gum (70 mg.). The infrared spectrum showed absorption in the (OH) stretching region but no peaks due to (C=O) stretching.

Without further purification the gum was heated with toluene-p-sulphonic acid (5 mg.) at 150°/0.1 mm. for 1 hr. Chromatography of the residue on silica gel, with benzene ether (19:1) elution, gave a gum (30 mg.) which failed to crystallise. $\nu_{max.}$ 1755, 1682 $cm.^{-1}$.

N-Benzyl-N-toluene-p-sulphonylanthranilic acid

A mixture of methyl-N-toluene-p-sulphonylanthranilate (31 g.; 0.1 mole) benzyl bromide (18 g.; 0.11 mole), anhydrous potassium carbonate (15 g.), and dry acetone (200 ml.) was heated under reflux for 6 hrs.

The insoluble solids were removed by filtration and the filtrate was evaporated to a thick oil. Chromatography of the oil on silica gel with benzene elution, gave (after discarding the fore-run containing benzyl bromide) a thick oil (37 g.) which gave a single spot on T.L.C. The oil was dissolved in aqueous methanol (250 ml.; 50%) and sodium hydroxide solution (50 ml.; 20%) and refluxed for 1 hr. The cooled solution was extracted with ether.

The aqueous phase was separated and acidified with dilute hydrochloric acid. The precipitate was filtered off and recrystallisation from aqueous methanol afforded N-benzyl-N-toluene-p-sulphonylanthranilic acid (31 g.; 82%) as white needles m.p. 160-162°. (Found: C,66.1; H,5.0; N,3.95; S,8.8. $C_{21}H_{19}NO_4S$ requires C,66.2; H,5.0; N,3.7; S,8.4%).

N-Benzyl-N-toluene-p-sulphonylanthraniloyl chloride

N-Benzyl-N-toluene-p-sulphonylanthranilic acid (31 g.), and thionyl chloride (20 ml.) were heated together under reflux for 1 hr. The excess thionyl chloride was removed by distillation, leaving the acid chloride as a yellow crystalline fuming solid. The acid chloride (1 g.) and aniline (1.5 g.) were dissolved in benzene (30 ml.) and heated under reflux for 30 min. The cooled solution was washed with sodium bicarbonate solution (10%) dilute hydrochloride acid (2N) and water, dried and evaporated to a yellow solid. Recrystallisation from ethanol yielded the anilide, as fine yellow prisms m.p. 132°. (Found: C,70.7; H,5.2; N,6.2. $C_{27}H_{24}N_2O_3S$ requires C,71.0; H,5.3; N,6.15%).

Attempted Friedel-Crafts cyclisation of N-Benzyl-N-toluene-p-sulphonylanthraniloyl chloride.

To a stirred solution at -75° of the acid chloride (31.6 g.) in methylene chloride (500 ml.) was added aluminium chloride (25 g. finely powdered). The mixture was allowed to come to room temperature over 4-5 hrs. The mixture was poured into a mixture of ice and dilute hydrochloric acid (4N), shaken and separated. The organic layer was washed with dilute sodium hydroxide solution (2N), water, then dried (Na_2SO_4) and evaporated to a yellow oil. Chromatography of the oil on silica gel, with benzene elution gave a white solid m.p. 65-67° which on recrystallisation from petroleum ether (b.p. 60-80°) afforded toluene-p-sulphonyl chloride (3.8 g.) m.p. 68-69° undepressed on admixture with an authentic sample (lit.[123] m.p. 69°).

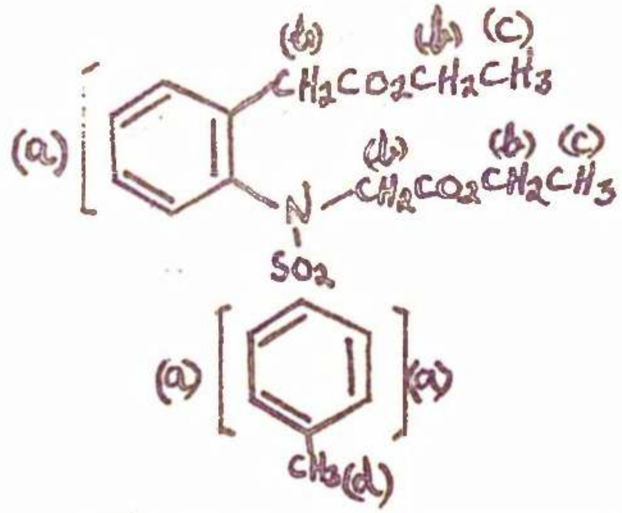
Further elution with benzene gave a pale yellow solid which on repeated recrystallisation from ethanol yielded a substance (1.2 g.) as yellow needles m.p. 171° (Found: C,69.2; H,4.85; N,3.95; S,9.3. $C_{21}H_{17}NO_3S$ requires C,69.4; H,4.7; N,3.9; S,8.8%) m.w. found (mass spec.) 363. $C_{21}H_{17}NO_3$ requires 363. $\nu_{max.}$ (Nujol) 1634 cm.$^{-1}$ (C=O). N.M.R. data are reported in the appendix.

Reduction of unknown substance from the above experiment

The substance m.p. 171° (450 mg.) was reduced with sodium borohydride/ethanol by standard proceduress to yield on recrystallisation from ethanol white prisms of a substance (200 mg.) m.p. 147-148° (Found: C,68.7; H,5.1; N,3.7. $C_{21}H_{19}NO_3S$ requires C,69.0; H,5.2; N,3.8%). N.M.R. data are reported in the appendix.

APPENDIX

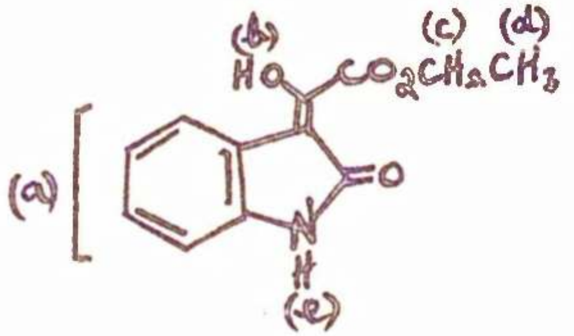
DETAILS OF NUCLEAR MAGNETIC RESONANCE SPECTRA



Ethyl N-(o-ethoxycarbonyl methylphenyl)-N-toluene-p-sulphonylglycine.

Integral:- 8:8:5.7:3.

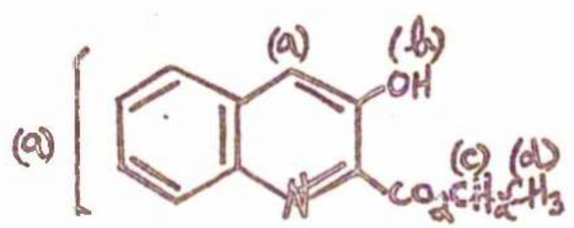
τ values:- (a) 2.4-3.2 (m); (b) 5.6-6.4 (m); (c) 8.74,8.81 (2 x t); (c) 7.6 (s)



3-Ethoxalyloxindole

Integral:- 4:1.2:2:3:1.

τ values:- (a) 2.75 (m); (b) -4.15 (s); (c) 5.57 (q); (d) 8.74 (t) (e) -2.0 (s).

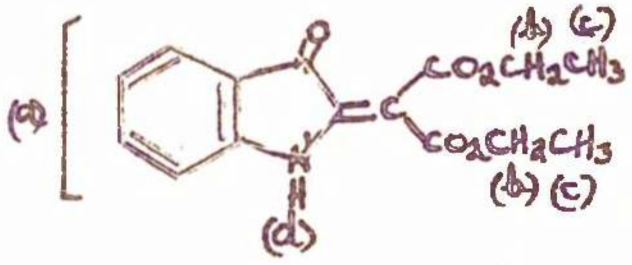


2-Ethoxycarbonyl-3-hydroxyquinoline.

Integral:- 5:1.5:2:3

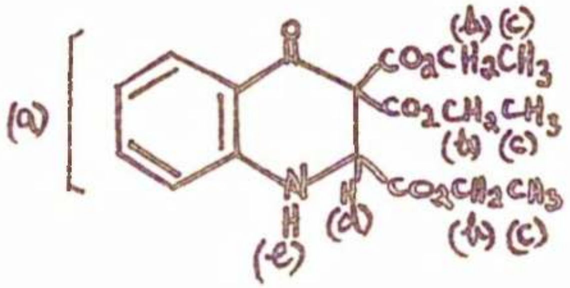
τ values:- (a) 2.2-2.7 (m); (b) -0.45 (s); (c) 5.35 (q); (d) 8.46 (t).

(s) = singlet, (t) = triplet, (q) = quartet, (m) = multiplet



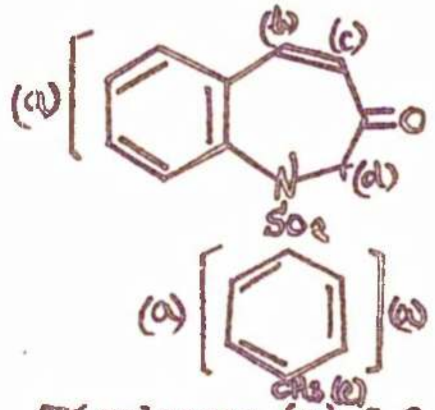
Diethyl-(3-oxo-2-indol-
inylidene)-malonate.
Integral:- 3.7;3.7:6:1

τ values:- (a) 2.2-3.2 (m); (b) 5.56,5.69 (2 x q); (c) 8.61,8.69 (2 x t); (d) 0.78 (s).



2,3,3-Triethoxycarbonyl-
1,2,3,4-tetrahydroquinol-4-one.
Integral:- 4:6:9:1:1

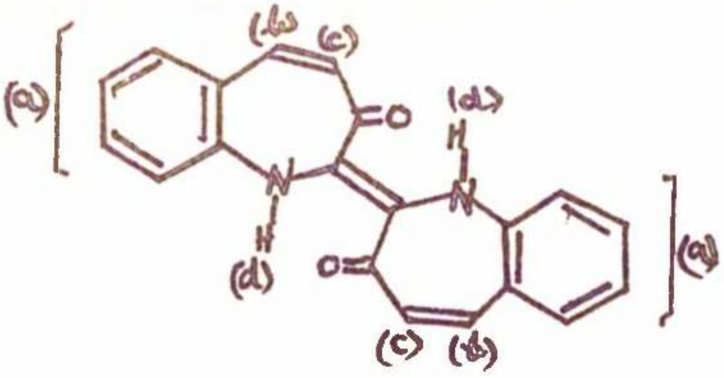
τ values:- (a) 2.2-3.1 (m); (b) 5.4-6.3 (3 x q); (c) 8.67,8.79, 9.2 (3 x t); (d) 5.32 (s); (e) 4.24 (s).



2,3-dihydro-1-toluene-p-
sulphonylbenz[f]azepin-3-one
Integral:- 8.5:1:1:2:3.

τ values:- (a) 2.2-3.0 (m); (b) 3.2 (d); (c) 4.25 (d); (d) 5.2-6.0 (m); (e) 7.6 (s).

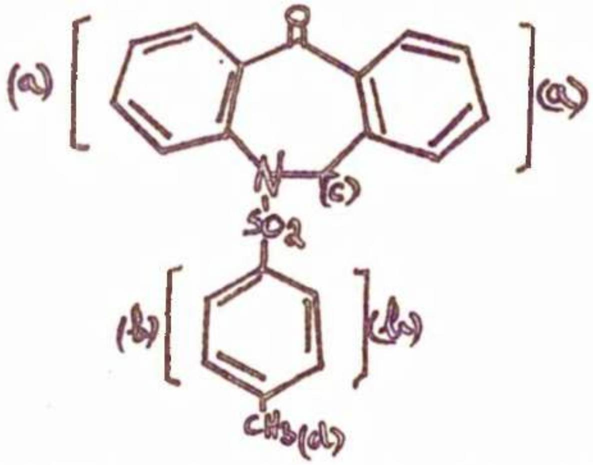
(s) = singlet, (d) = doublet, (t) = triplet, (q) = quartet,
(m) = multiplet



Bis(2,3-dihydro-3-oxo-benz[f]azepinylidene).

Integral:- 4:1:1:0.7

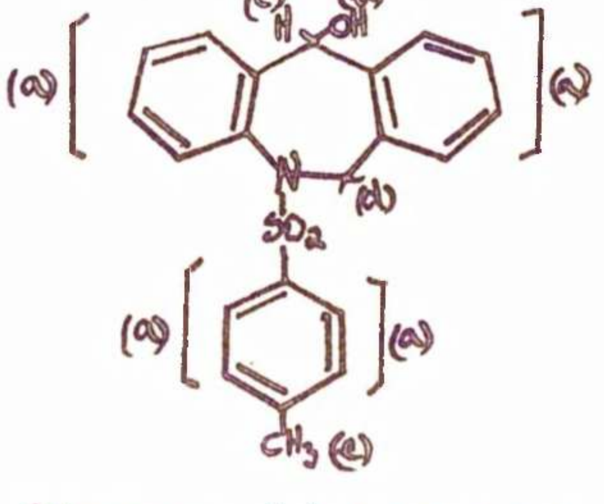
τ values:- (a) 2.6-3.4 (m); (b) 3.05 (d); (c) 3.76 (d); (d) -0.9 (s).



2,5-Dihydro-1-toluene-p-sulphonyl-dibenz[c,f]azepin-5-o

Integral:- 8.8:4.6:1.9:3

τ values:- (a) 1.6-2.8 (m); (b) 3.2 (s); (c) 4.9 (s); (d) 7.77 (s



2,5-Dihydro-5-hydroxy-1-toluene-p-sulphonyl-dibenz[c,f] azepin-5-one.

Integral:- 13.5:0.8:0.7:1.8:3

τ values:- (a) 2.3-3.0 (m); (b) 4.2 (s); (c) 7.25 (s); (d) 5.0 (d); (e) 7.62 (s).

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