An Investigation of the Chemistry of

Cinnolines and Benzoxazines

being a Thesis

presented by

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to the

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in application for

THE DEGREE OF DOCTOR OF PHILOSOPHY

St. Andrews

June 1975

DECLARATION

I declare that this thesis is based on the results of experiments carried out by me, that it is my own composition, and has not previously been presented for a Higher Degree.

The work was carried out in the Department of Chemistry of the University of St. Andrews, under the supervision of Dr. R. K. Mackie since 1st October 1972, the date of my admission as a research student.

CERTIFICATE

I hereby certify that John James Aitken, B. Sc. has spent eleven terms at research work under my supervision, has fulfilled the conditions of the Resolution of the University Court 1967, No. 1, and is qualified to submit the accompanying thesis in application for the degree of Doctor of Philosophy.

R. K. Mackie.

Director of Research.

ACKNOWLEDGEMENTS

I should like to record my appreciation of the help and encouragement given to me over the last three years by Dr. Ray Mackie.

I am indebted to the Mrs. Purdie Fund of the University of St. Andrews for a research grant during the period 1972-75, and to Professors Lord Tedder and P. A. H. Wyatt for research facilities in the Department during this time.

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Finally I am grateful to Mrs. E. J. West and Mr. T. McQueen for their help in the production of this thesis.

SUMMARY

The synthesis of a series of 6-substituted 4-methylcinnolines is described along with their oxidation and the separation of the oxidation products. An unsuccessful attempt to study the photolysis of some of the cinnolines and thus correlate their photochemistry with their mass spectral fragmentation is also described.

4-Methyl-6-nitrocinnoline 2-oxide was successfully prepared confirming that 4-methylcinnoline 2-oxide can be nitrated at the 6-position.

In attempting to prepare 4-methyl-6-nitrocinnoline an intermediate in the reaction scheme was found to have a 3,1-benzoxazine structure which was found to give an interesting mixture of products when hydrolysed in concentrated HCl. Hence several series of 3,1-benzoxazines were synthesised and their hydrolyses compared. A mechanism is proposed to explain the products formed.

Several saturated 1,2-dihydro-3,1-benzoxazines were also synthesised and a proof of their cyclic structure by various spectroscopic methods described.

Since the o-aminophenylcarbinols formed in the benzoxazine hydrolysis were found to dealkylate at various rates, several ortho and para substituted dimethylphenylcarbinols were synthesised and treated with concentrated HCl in the same way as the benzoxazines. The products of the reactions and their separation (where it was possible) is described.

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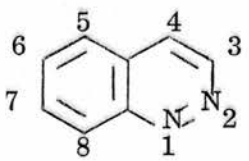
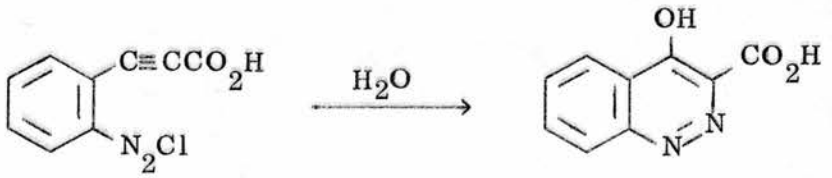
Part I

Introduction.

The cinnoline ring system (1) was first prepared in 1883[1] by von Richter who, in the course of experiments designed to convert o-nitrophenylpropiolic acid into o-hydroxyacetophenone, found that the diazonium chloride derived from o-aminophenylpropiolic acid (2) was transformed on heating into a nitrogenous derivative (3). The new ring system was named cinnoline from analogy with quinoline. In the following year,



(1)



(2) (3)

Widman[2] prepared 4-methylcinnoline-7-carboxylic acid (5) by diazotisation of 2-(2-amino-4-carboxyphenyl)-propene (4). In 1909 Stoermer and his co-workers[3,4] found that this reaction could also be used to prepare 4-arylcinnolines. This general preparation is known as the Widman-

(4) (5)

Stoermer synthesis. Unsubstituted cinnoline was first prepared by Busch in 1897[5].

Cinnoline itself is a pale yellow solid, like many of its alkyl derivatives. However the parent compound (1) is fairly unstable and rapidly

liquifies and turns green on standing in the air[6], though apparently with little decomposition[7]. Its best method of storage is under nitrogen at 0°. It melts at 40-41°[7] but when crystallised from ether forms an etherate complex melting at 24-25°[5].

The parent compound is toxic and shows antibacterial action against Escherichia coli[5]. Neither cinnoline itself nor any of its derivatives have so far been found in nature. Cinnoline (1, 2-diazanaphthalene) is numbered according to IUPAC nomenclature as indicated in (1).

Cinnoline, with a pK_a of 2.70[8] or 2.29[9] in water at 20°, is a weak base when compared to quinoline (pK_a of 4.94 in water at 20°[8]) or isoquinoline (pK_a of 5.40 in water at 20°[9]).

The first and second ionisation potentials of cinnoline have been determined by photoelectron spectroscopy to be 8.51 eV and 9.03 eV respectively. The first I.P. corresponds to loss of non-bonding electrons ("lone pair" electrons) from nitrogen, and the second is a π ionisation. In comparison the first I.P. of phthalazine (lone pair, non-bonding electron ionisation) is 8.68 eV[10] while that of quinoline (π ionisation) is 8.62 eV.

Several molecular orbital calculations of the π - electron density distribution have been made by the Hückel method[11-14]. Although these are not in complete agreement with each other, all four locate the highest electron density for the ring carbon atoms at positions 5 and 8, indicating that electrophilic substitution should occur preferentially at these sites. This is borne out experimentally, at least for simple electrophilic substitution reactions such as nitration[7,15,16] and agrees with results of calculations by Dewar[17,18]. There appears to be some

disagreement about the relative electron densities of N-1 and N-2. Experimentally it is known that cinnoline undergoes N-oxidation[19,20], protonation[21], and alkylation[22] preferentially at N-2. The 2-cinnolinium ion has been calculated to be slightly more stable than the 1-cinnolinium ion[21]. Recent molecular orbital calculations by Palmer and co-workers[23] indicate that the electron densities are essentially equal at N-1 and N-2 for cinnoline, 4-methylcinnoline, 3-methylcinnoline, and 3,4-dimethylcinnoline, leading Palmer to conclude that preferential N-2 protonation is simply a result of steric hindrance to N-1 protonation by the peri C-8 proton. This agrees with experimental work by Palmer and McIntyre[24] where such a steric effect was claimed to be balanced by a substituent in the 3-position.

Cinnoline has been well characterised spectroscopically. The infrared absorption spectrum has been recorded and absorption modes have been assigned to the bands where possible[25,26]. Its Raman spectrum has also been recorded[26]. The ultraviolet absorption spectrum of cinnoline has been compared to those of naphthalene and phthalazine[27].

The proton nmr spectrum has been well studied[28] and more recently a study of the ^{13}C nmr spectrum of cinnoline has been published[29].

Mass spectral studies show that cinnoline fragments upon electron impact to lose first molecular nitrogen and then acetylene[30,31]. The structure of the C_8H_6 cation resulting from the initial loss of nitrogen is unknown, even though 3- and 4-deuteriocinnoline and 3,4-dideuteriocinnoline have been prepared and subjected to mass spectral analysis in an attempt to elucidate the structure of this cation. Incorporation of

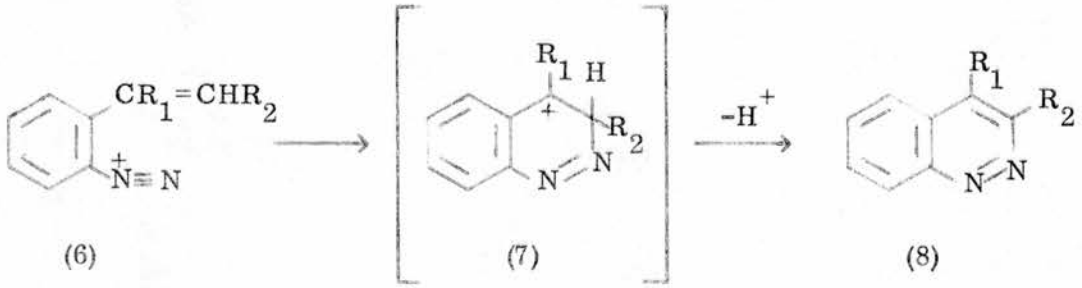
deuterium into the acetylene arising by fragmentation of the C_8H_6 cation is completely random[31].

Only a little experimental work has been done on electrophilic substitution reactions of cinnoline. Dewar[17] determined on the basis of molecular orbital calculations that the 5- and 8-positions should be the most reactive towards simple electrophilic substitution while the 4-position should be the least reactive. This is confirmed experimentally in the case of nitration in sulphuric acid which results in 33% of 5-nitrocinnoline and 28% of 8-nitrocinnoline as the sole nitration products[7,15]. The species nitrated is not cinnoline itself but the protonated 2-cinnolinium cation. At 80°, in 76-83% sulphuric acid, this cation is nitrated 287 times more slowly than the isoquinolinium cation. This gives some indication of the deactivating power of the unprotonated N-1 atom on the nitration of the 2-cinnolinium ion[16].

Alkylcinnolines are generally solids, ranging in colour from colourless to orange-red, but are mostly yellow. They are basic and form a number of salts, including picrates, hydrochlorides and methiodides. Very little has been published about their actual basic strengths, but the alkylcinnolines areexpected to be somewhat more basic than cinnoline itself, in accordance with the usual slight base - strengthening effect of alkyl groups in heterocyclic bases. Like cinnoline itself, the basic centre of 3-, 4-, and 8-methylcinnoline is at N-2. This is known by molecular orbital calculations and by experimentation[32]. The experimental proof was obtained by showing that the ultraviolet spectra of protonated 3-, 4-, and 8-methylcinnoline are very similar to the spectra of the corresponding

2,3-, 2,4-, and 2,8-dimethylcinnolinium perchlorates while the spectra of the 1,3-, 1,4-, and 1,8-dimethylcinnolinium perchlorates are distinctly different[32]. The infrared spectra of several alkylcinnolines have been recorded[33,34], as have the proton nmr spectra[35-37]. Their mass spectra have also been reported[30,31,38].

The most widely used method to prepare cinnolines having an alkyl group at the 4-position is the Widman-Stoermer synthesis. By this method, a diazotised o-aminoaryl olefin (6) (R_1 = alkyl, aryl, or heteroaryl; R_2 = hydrogen, alkyl, aryl, or heteroaryl) cyclises to give the cinnoline (8).



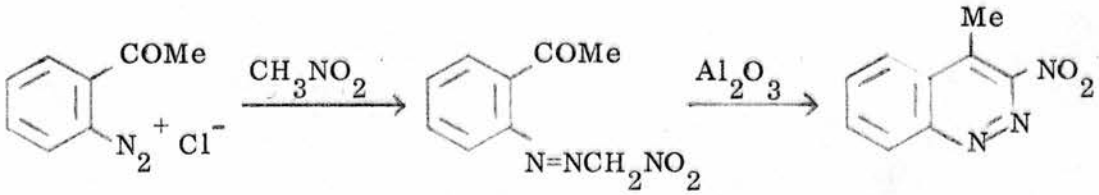
(6) (7) (8)

So far, unsubstituted cinnoline or cinnolines substituted only in the benzenoid ring or only at position 3 have not been prepared by this method (i.e. R_1 = H). That is all cinnolines prepared by the Widman-Stoermer method are substituted at the 4-position. Attempts to prepare cinnoline-4-carboxylic acids, with R_1 the electron attracting carboxyl group have also met with failure[39].

The other chief methods include the Borsche synthesis which involves the diazotisation and cyclisation of 2-aminoacetophenones (9) to yield 4-hydroxycinnolines (10). A modification of the Borsche synthesis was devised by Baumgarten[40] who coupled diazotised 2-aminoacetophenone with nitromethane in a dilute basic solution. Cyclisation of the product (11) in the presence of aluminium oxide then gives 4-methyl-3-nitrocinnoline (12)

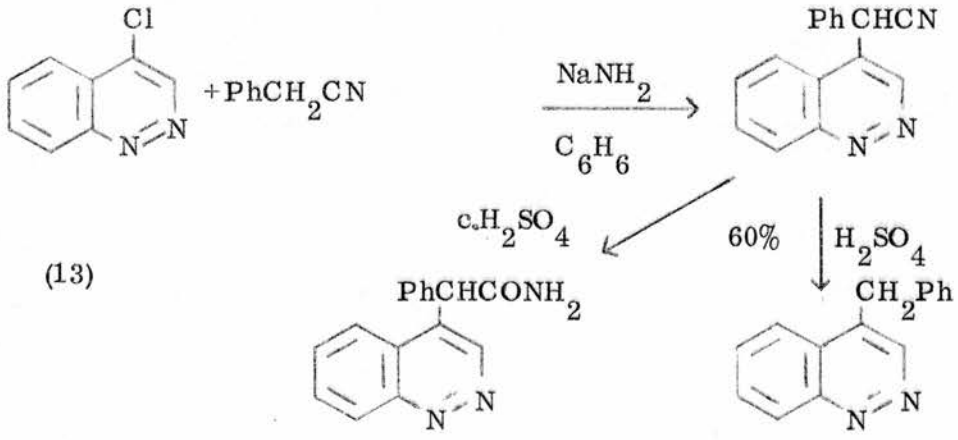
(9) (10)

in a yield of 59%.



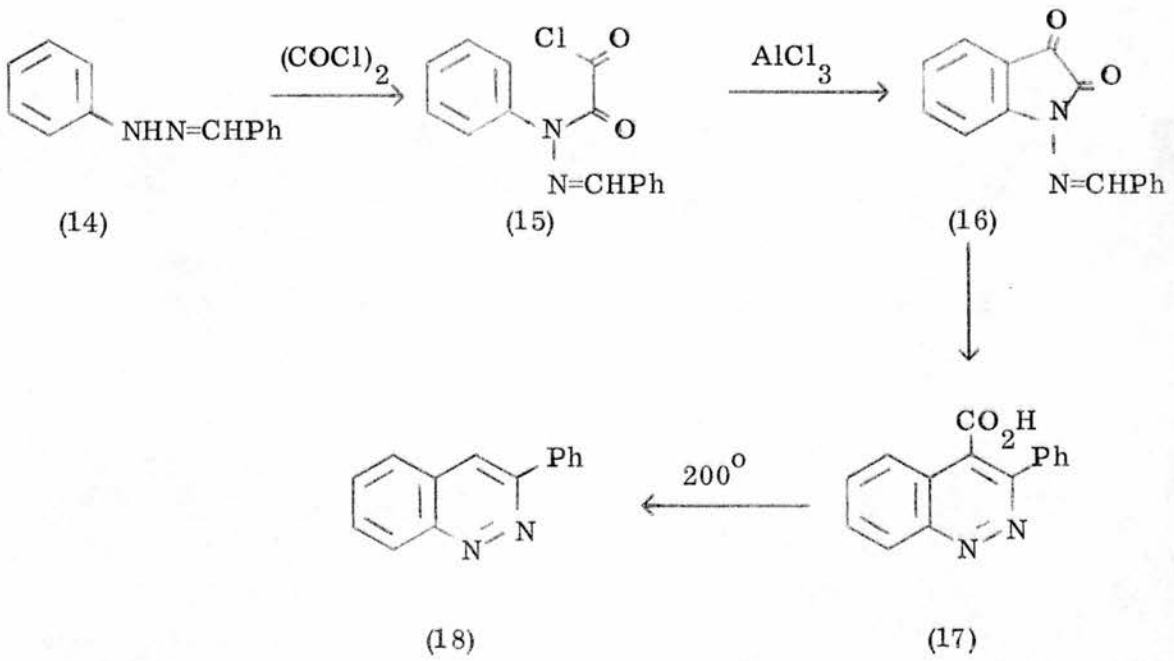
(11) (12)

Another method of synthesis of alkylcinnolines is by nucleophilic displacement of chloride ion from 4-chlorocinnoline (13) as in the example shown.



(13)

Phenylhydrazone derivatives provide another route to aryl-cinnolines. It was first encountered by Stollé and Becker[41] in the course of an unsuccessful attempt to prepare N-aminoisatin. Benzaldehyde phenylhydrazone (14), when allowed to react with excess oxalyl chloride, yields N-benylideneamino-N-phenyloxamyl chloride (15), which can be



(14) (15) (16)

(18) (17)

cyclised by aluminium chloride in chloroform solution[33] or in methylene chloride[42] to give N-benzylideneaminoisatin (16), which when treated with hot aqueous caustic soda gives 3-phenylcinnoline-4-carboxylic acid (17) in 75-85% yields[33,42]. Rearrangement of the isatin to the cinnoline almost certainly proceeds first by alkaline hydrolysis of the amide linkage in the isatin to open the ring. This would be followed by a recyclisation and aromatisation to give the cinnoline. The carboxyl group of (17) can then be thermally removed to give 3-phenylcinnoline (18) in 51-74% yields[33].

The failure of the Widman-Stoermer synthesis for R_1 = H (6) is explicable when one considers that the success of the reaction depends upon the stability of the intermediate benzylic carbonium ion (7), or to be more exact, it depends upon the energy difference between the diazonium ion (6) and the transition state leading to (7). In the most successful reactions R_1 is an electron donating group which can stabilise (7) by

charge delocalisation, hence lowering the energy of the transition state between (6) and (7) and thus increasing the rate of the reaction. Even when R_1 is a heteroaryl group such as 2-pyridyl, charge delocalisation in (7) by the pyridyl ring can occur and the reaction is successful. Apparently when R_1 is hydrogen or carbonyl, the energy difference between (6) and the transition state leading to (7) is high enough to be essentially insurmountable.

It has been shown by Simpson[43] that production of 3-substituted 4-arylcinnolines is independent of the steric configuration of the parent aminophenyl olefins, as in the case for example of 4-phenyl-3-methylcinnoline. Stoermer and Fincke[3], who first prepared this compound, obtained a crystalline amino olefin by dehydration of the carbinol prepared from 2-amino benzophenone and ethyl magnesium iodide. Simpson however obtained an oily olefin which converted into two crystalline stereoisomeric hydrochlorides. One of these was probably identical with the salt prepared by Stoermer and Fincke from their crystalline amino olefin while the other was found to be a mixture. However each salt on diazotisation gave an almost quantitative yield of cinnoline, clearly proving the irrelevance of steric configuration.

Nitration of 4-methylcinnoline in concentrated H_2SO_4 solution produces approximately 28% of 4-methyl-8-nitrocinnoline and about 13% of a second mononitro isomer, thought to be 4-methyl-5-nitrocinnoline[44], while cinnoline itself is converted by nitration into a mixture of 5- and 8-nitrocinnoline. This is in good agreement with the nitration of quinoline which gives 5- and 8-nitroquinoline when nitrated with fuming HNO_3 and

oleum[45], while lepidine (4-methylquinoline) gives the 8-nitro isomer as major product[46,47] plus a minor product, possibly the 5-nitro isomer[48]. Schofield[49] proposed that from these results the steric effect of the 4-methyl group should mean that 4-methylcinnoline would give only the 8-nitro isomer and in fact found this to be true under the conditions used (concentrated HNO_3 at 0^o) which were less severe than those of Curd et al.[45].

A methyl group on position 4 has been shown to be more acidic than one in position 3, since 4-methylcinnoline reacts with chloral in pyridine solution while under the same conditions 3-methylcinnoline does not react[50].

On nitrosation with ethyl nitrite in ethanolic hydrochloric acid, 4-methylcinnoline gives the oxime of 4-cinnolinecarboxaldehyde (19) in 80% yield[51].

(19)

Cinnoline N-oxides

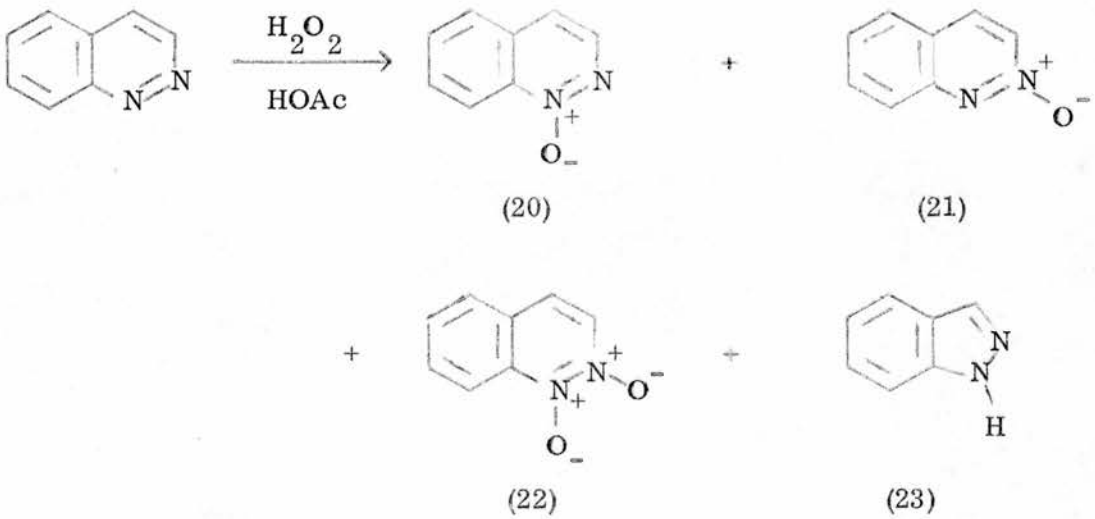
Upon oxidation of cinnoline or substituted cinnolines to their mono N-oxides one is faced with the problem of determining whether the product obtained is a 1-oxide or a 2-oxide. Originally this problem was solved by Ogata and co-workers[19,52] by using previous work on oxidation of substituted pyridazines which were known to oxidise to give only the 1-oxide[53,56]. This problem is now much more easily resolved by the use of ultraviolet

spectroscopy and proton nmr spectroscopy[19, 52, 57]. In their proton nmr spectra, it is notable that the H-8 proton signal of the 1-oxides appears at a lower field than the other protons of the benzenoid ring, although this same proton in the 2-oxides remains buried in the multiplet signal of the remaining aromatic protons. Ogata attributes this downfield shift of the H-8 proton, which is at the peri-position to the N-oxide group of the cinnoline 1-oxides, to a magnetic anisotropy effect of the N-oxide group. It is also of interest that the coupling constant ($J_{3,4}$) between protons H-3 and H-4 is 6.0 to 6.2 Hz in cinnoline 1-oxide and 7.0 Hz in cinnoline 2-oxide.

The mass spectra of cinnoline 1- and 2-oxides, 1,2-dioxide and various alkyl derivatives of these have been investigated[31].

The first reported preparation of cinnoline N-oxides is that of Atkinson and Simpson[58] in 1947; they found that the treatment of certain 3,4-disubstituted cinnolines with hydrogen peroxide in acetic acid produces the corresponding mono N-oxides in 80-90% yields. Many cinnolines were oxidised by them in this way and all were formulated as being the 1-oxides. This assignment was made on the erroneous assumption[59] that the basic centre of the 4-substituted cinnolines was N-1 and was not proven experimentally. Subsequent work has shown that in general the presence of a bulky 3-substituent in the cinnoline ring (in the absence of an 8-substituent) causes the 1-oxide to be the principal isomer. When no 3-substituent is present, the 2-oxide is usually the predominant isomer.

When Ogata et al.[19, 52] treated cinnoline with hydrogen peroxide in acetic acid at 70° for 6 h there was obtained a mixture of cinnoline



(20) (21)

(22) (23)

1-oxide (20) and cinnoline 2-oxide (21), the ratio being 1:1.4. When this reaction was repeated under similar conditions by Suzuki and co-workers the separate oxides were again isolated but this time cinnoline 1,2-dioxide (22) and indazole (23) were also found in low yield[20,60].

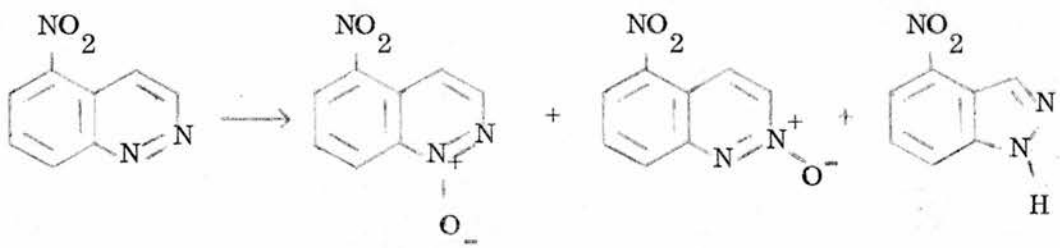
When cinnoline is heated with hydrogen peroxide in acetic acid at 110-120° for 8 h the yield of the dioxide is increased to 13%. A mechanism to explain the appearance of the ring contracted product, indazole, has not yet been advanced, although it has been suggested[61] that the loss of the C-3 carbon from the cinnoline ring is a possible pathway in its conversion to indazole, since 3-arylcinnolines have been found to yield the separate oxides, indazole and the aryl carboxylic acid from the 3-aryl group, but the 3-aryl indazole has not been found.

Treatment of the mono 1- and 2-oxides with hydrogen peroxide in acetic acid at 110-120° gives the dioxide in 25% and 4% yields respectively[20,60].

When 4-methylcinnoline is allowed to react with hydrogen peroxide in acetic acid at 70° for 6 h there is produced a mixture in good yield of both 4-methylcinnoline 1-oxide and 4-methylcinnoline 2-oxide in the

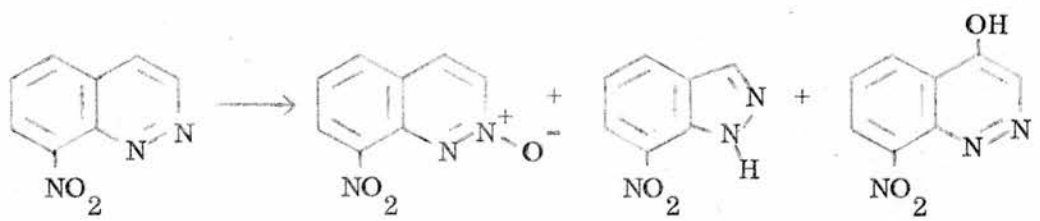
ratio of 1:2[19,52] together with a small amount (about 4%) of 4-methylcinnoline 1,2-dioxide [62].

If 5-nitrocinnoline (24) is oxidised by hydrogen peroxide in acetic acid at 60-70° for 8 h, or with persulphuric acid[63], there is obtained a



(24) (25) (26) (27)

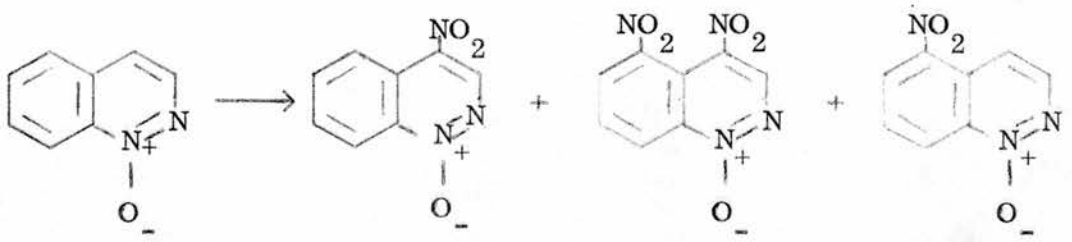
mixture of 5-nitrocinnoline 1-oxide (25), 5-nitrocinnoline 2-oxide (26), and the ring contracted product 4-nitroindazole (27) in 18, 43, and 16% yields respectively. However when 8-nitrocinnoline (28) is treated with hydrogen peroxide in acetic acid at 60-70° for 8 h, no 1-oxide is



(28) (29) (30) (31)

obtained. Instead a mixture of 8-nitrocinnoline 2-oxide (29), 7-nitroindazole (30), and 8-nitro-4-cinnolinol (31) in 20, 45 and 3% yields is obtained.

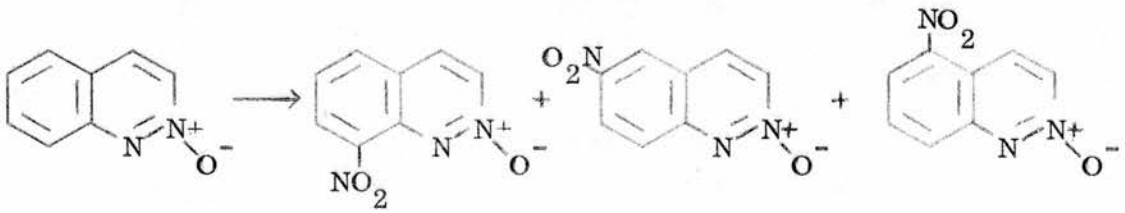
When cinnoline 1-oxide (32) is treated with a mixture of nitric acid and sulphuric acid, 4-nitrocinnoline 1-oxide (33) is obtained in yields ranging from 3 to 64% depending upon the reaction conditions[64,65]. The best yields of the 4-nitro isomer have been obtained when the N-oxide



(32) (33) (34) (35)

is allowed to stand in the mixed acid at room temperature for 8 h and then the mixture is heated at 50° for 1 h. When the mixture of HNO_3 and H_2SO_4 is replaced with a mixture of fuming HNO_3 and H_2SO_4 only small amounts of the 4-nitro isomer are realized but 44-50% yields of 4, 5-dinitrocinnoline 1-oxide (34) are then obtained. Once, a small amount (2%) of 5-nitrocinnoline 1-oxide (35) was detected.

Nitration of cinnoline 2-oxide (36) gives different results from the nitration of the 1-oxide. Thus when cinnoline 2-oxide is allowed to react with a mixture of nitric and sulphuric acids, or with potassium nitrate in sulphuric acid, there is obtained a mixture of 8-nitrocinnoline 2-oxide (37), 6-nitrocinnoline 2-oxide (38), and 5-nitrocinnoline 2-oxide



(36) (37) (38) (39)

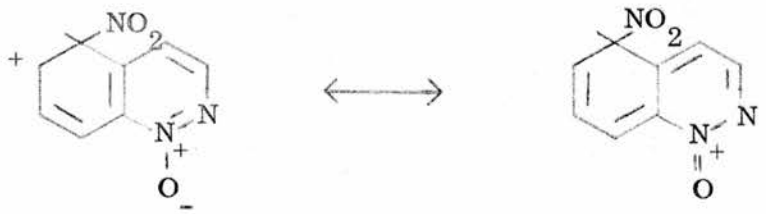
(39), the mixture of nitrated products being obtained in yields ranging from 0.6 to 97% depending upon the nitrating conditions[66, 67].

In several nitration experiments in which cinnoline 2-oxide is

nitrated with potassium nitrate in sulphuric acid there are obtained individual yields of up to 72% of the 8-nitro isomer, 25% of the 6-nitro isomer, and 21% of the 5-nitro isomer, depending upon the reaction conditions. With one exception, where the total yield of the three nitrated products was only 2.1% , the principal product in each individual experiment is the 8-nitro isomer. This can be rationalised by considering the stabilisation of the intermediates in the nitration. When nitration

(40) (41)

(42) (43)



(44) (45)

by the nitronium ion occurs at position 6 or 8 the resultant positive charge at position 5 or 7 can be stabilised (40-43), whereas when nitration occurs at position 5 the charge cannot be delocalised in the case of the 2-oxide while it can in the case of the 1-oxide (44, 45).

Several nitrated N-oxides have been found to display antifungal, antibacterial, and anticancer activity. It is claimed that 3-methoxy-4-nitrocinnoline 1-oxide is useful as an antifungal agent[68], while 3-nitrocinnoline 1-oxide and 6-nitrocinnoline 2-oxide show strong activity against Ehrich tumour cells and certain species of bacteria[69]. The preparation of nitrocinnoline N-oxides by nitration of the corresponding cinnoline N-oxides is outlined in a patent which claims that compounds such as 4-nitrocinnoline 1-oxide, 5-nitrocinnoline 1-oxide, 4, 5-dinitrocinnoline 1-oxide, 5-nitrocinnoline 2-oxide, 3-nitrocinnoline 2-oxide, 6-nitrocinnoline 2-oxide, and 3-nitrocinnoline 1-oxide are useful as bactericides, fungicides, and cancer remedies[70]. Another patent[71] claims 4-nitrocinnoline 1-oxide and 5- or 8-nitrocinnoline 2-oxides as bactericides.

Although the photolysis of cinnoline oxides has been very little studied[72,73] there is evidence of photochemical reactions similar to those of other aromatic amine N-oxides. One type of rearrangement is that which results in the formation of a lactam (46). This has been

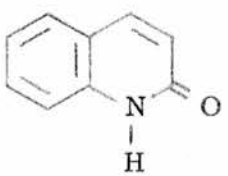
(46)

observed in the pyridine, quinoline, isoquinoline, quinazoline and pyrazine series. Another is the apparent direct ring contraction to five - membered rings observed in the pyridine (47), quinoline,

(47)

phenanthridine, pyridazine and pyrazine series. In addition to these more complex reactions it has been found in most cases that deoxygenation to the parent system takes place.

Some aromatic amine N-oxides have been the subject of examinations by mass spectrometry[31,74-83]. It has been suggested that there could be a correlation between the reactions of the positive ions of the aromatic amine N-oxides formed by electron impact in the mass spectrometer, and of the electronically excited species formed by the action of light. In some cases, striking similarities have been found, probably the best examples being quinoline N-oxide and isoquinoline N-oxide, whose fragmentation routes appear to follow the same pattern



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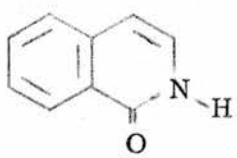


(49)

as their photoisomers, carbostyril (48) and isocarbostyril (49) respectively[82,83]. However before taking the analogy between these two processes too far it must be remembered that the conditions in which the two sets of reactions take place are vastly different, the mass spectral

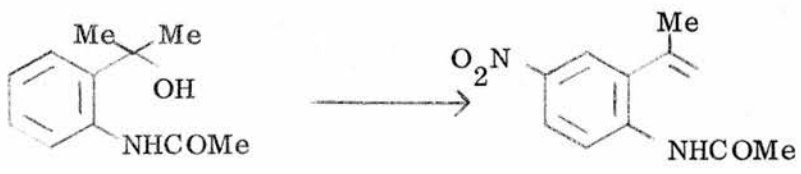
taking place in the gas phase while the photochemical take place in solution at normal temperature and pressure.

Results and Discussion

In order to prove unambiguously the structure of a nitro-4-methylcinnoline-2-oxide[84] which could not be identified from nmr further than knowing that the nitro group was in either the 6- or 7-position, it was decided to attempt to prepare 4-methyl-6-nitrocinnoline (51) by putting the nitro group into the ring before cyclisation of the heteroring and then oxidising the cinnoline and separating the oxides by column chromatography.

The Widman - Stoermer synthesis requires the preparation of 2-(2-amino-5-nitrophenyl)-propene (50), the amide of which was reported to have been synthesised by Atkinson and Simpson[59] by nitration of 2-(2-N-acetylaminophenyl)-propan-2-ol (52) using concentrated H_2SO_4

(50) (51)

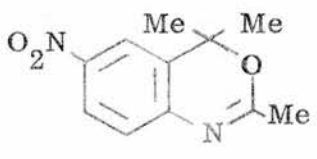


(52) (53)

and concentrated HNO_3 at -15^{o}. Hence it was assumed that having prepared this amido olefin (53) basic hydrolysis would yield the amino olefin (50). However when the nitration was repeated and the product

worked up it was found that although it had the molecular formula for the amido olefin (53), $C_{11}H_{12}N_2O_3$, it certainly could not have that structure since the nmr spectrum indicated that there was no -NH proton and no olefinic protons. It did however indicate three methyl groups two of which were equivalent. The infrared spectrum also showed the absence of a -NH bond and also the absence of any carbonyl group although there was a strong absorption at 1634 cm^{-1} which is only slightly low for an amide carbonyl, but this was subsequently assigned to the $\diagdown C{=}N-$.

On the basis of this information the compound was assigned the structure 2,4,4-trimethyl-6-nitro-3,1-benzoxazine (54). For comparison the amino olefin (50) was later acetylated to give the amido olefin (53) which Atkinson and Simpson believed they had prepared and was found to have a melting point of 84° which coincidentally is very close to the



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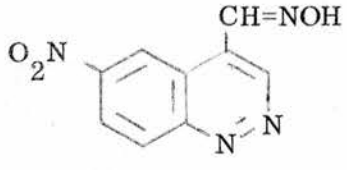


(55)

melting point of the benzoxazine (mp 86°). This product showed both -NH and carbonyl absorptions in the infrared spectrum and the presence of olefinic protons in the nmr spectrum.

Having established that the benzoxazine was in fact the product of the reaction, it was assumed that it could be easily hydrolysed by acid to yield the ortho amino olefin (50). However although enough of the

amino olefin was in fact prepared this way the hydrolysis of the benz-oxazineproved to be much more complex than was expected and this will be discussed in more detail in Part II.

Preparation

When the olefin was isolated the diazotisation was carried out in hydrochloric acid and the resultant product found to be a dark red solid, mp 236°, which was insoluble in most organic solvents. From its accurate mass measurement (218.0443) the molecular formula would seem to be $C_9H_6N_4O_3$ (requires 218.0440) and from other spectroscopic evidence, mainly nmr, which shows the absence of any methyl group and the presence of a proton which could be the aldehydic proton on C-4, it is proposed that it has structure (55) which is the oxime of 6-nitro-4-cinnolinecarboxaldehyde. Its nmr spectrum is rather complex but by expanding both the 100 MHz and 220 MHz spectra assignments were tentatively made. The solution was made up in d_6-dimethylsulphoxide. At lowest field is the proton on C-3 which appears at 12.74 δ as a singlet. Then H-5 appears at 9.84 δ and is split by H-7, the $H_{5,7}$ coupling constant being 2.6 Hz. The aldehydic proton on C-4 appears as a singlet at 8.75 δ and is superimposed on the H-8 proton which appears at 8.71 δ and is ortho split by H-7 with $J_{7,8}$ being 9.5 Hz. The H-7 proton occurs at 8.57 δ and is ortho coupled to H-8 and meta coupled to H-5. The meta coupling constant is 2.7 Hz. As there were solubility problems, the resolution of the spectrum was not of a particularly high standard and the para coupling constant ($J_{5,8}$) could not be easily measured accurately but was of the order of 0.7 Hz.

Finally the hydroxyl proton appears as a singlet at 3.39 δ .

After many more attempts at the cyclisation eventually the required cinnoline could be consistently synthesised by using a mixture of hydrochloric acid and acetic acid. The diazotisation was carried out at 0^{o} for 12 min after which the ice bath was removed and then the mixture was basified after a further 8 min. In this way 4-methyl-6-nitrocinnoline was consistently synthesised in ca. 90% yield of crude material. This was recrystallised from water to give a yellow crystalline product.

Each of 4-methyl-, 6-bromo-4-methyl-, and 4, 6-dimethyl-cinnolines was prepared in a similar way by the Widman-Stoermer synthesis from the corresponding 2-(2-aminophenyl)-propene. These were all stored out of direct light as it is known that some cinnolines are light sensitive[6].

Oxidation

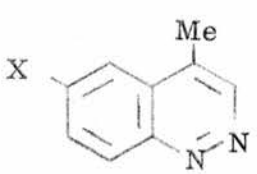
The oxidation of these cinnolines was effected by the use of peracetic acid as described by Palmer and Russell[35]. In each case the ratio of 1-oxide to 2-oxide in the crude oxidation mixture could be determined by using the nmr integral, althought the results cannot be trusted quantitatively and should only be looked at qualitatively. (It would be realistic to put an accuracy of $\pm$ 10% on the figures obtained). In the case of the 4, 6-dimethylcinnoline the estimation was also done using a Du Pont 310 Curve Resolver to find the area under the expanded methyl signals. However the curve resolver was set up to measure Gaussian curves and the nmr signals are recorded as Laurentian curves and so although this gives an approximate ratio , the result obtained

using the nmr integral is probably better even though the answer is probably subject to an error of $\pm$ 10% .

In the case of 4-methylcinnoline no dioxide was found, unlike the results of Palmer and Russell. However the dioxide was produced in the case of the 4, 6-dimethylcinnoline which had also been oxidised by Palmer and Russell but who had not found any dioxide. In the oxidation of 4-methyl-6-nitrocinnoline there was virtually none of the 1-oxide produced and this is probably due to the fact that the N-1 nitrogen atom is in a para position to the nitro group and because of the very large electron withdrawing capacity of that group, that part of the molecule is polarised in such a way that the N-1 atom could be envisaged as having a partial positive character which means that N-oxidation at that position is retarded. The same sort of effect is produced if a strong electron withdrawing group is attached at position 4 (para to N-1 across the heteroring) such as a carboxylic acid group[35]. 8-Nitrocinnoline also does not yield the 1-oxide[63].

The separation of the oxides was achieved by the use of column chromatography. Initially silica was used as the adsorbant

Table 1 Melting points of cinnolines and their oxides and oxidation ratio.



(56)

X	mp/°C (recrystallisation solvent)	N-1 : N-2	N-1 mp/°C	N-2 mp/°C	dioxide mp/°C
H	71-2[a] (petrol)	1 : 2.8	90-2[b]	143-5[c]	
Me	74-5[d] (hexane)	1 : 2.1 (1 : 1.5)[e]	146-8[f]	225-6[g]	206 (d)
Br	134 (d)[h] (H_2O)	1 : 1.6	204 (d)	223	
NO_2	130 (d) (hexane)	>1 : 10		260	

a. Lit. 72-3[59] b. Lit. 94-5[35] c. Lit. 147-8[35] d. Lit. 75-6[35]

e. using curve resolver f. Lit. 160-1[35] g. Lit. 230-1[35]

h. Lit. 128-9[35]

for column packing and for thin layer chromatography of the fractions but it was found that the oxides were very difficult to separate and that separation was much better when alumina was used. Hence all subsequent columns were packed with alumina and alumina tlc plates also used. It was found that the best eluant for the column was 10% chloroform in benzene and the tlc plates were developed in pure chloroform. Recovery from the columns was at least 90%.

As in the case of the parent cinnolines, their oxides were kept excluded from the light as at least some of them were found to be light sensitive.

When 4-methyl-6-nitrocinnoline 2-oxide was isolated it was found that its nmr spectrum was identical to the spectrum obtained by Mackie[84] under whose nitrating conditions (1 : 1 (v/v) concentrated H_2SO_4 : concentrated HNO_3 at 0°) 4-methylcinnoline 2-oxide can be nitrated

successfully at position 6, something which had not been achieved previously.

Spectra

The nmr spectra of the cinnolines were very readily interpreted in most cases, especially in the case of the 6-substituted ones which then gave 1, 2, 4 splitting patterns for the aromatic protons. The nmr data for these is shown in Table 2.

In each case the proton attached to position 3 is at lowest field due to its position adjacent to the two nitrogen atoms doubly bonded to each other which has a serious deshielding effect on H-3. When position 6 is substituted with an electron releasing group (in this case methyl), H-3 moves slightly upfield while it is pulled even further downfield in the case of the electron attracting nitro group. In each case except

Table 2 NMR data for 6-substituted 4-methylcinnolines (56)[b]

X	H_3	H_5	H_7	H_6	H_8	Me	J_{ortho}/ Hz	J_{meta}/ Hz	J_{para}/ Hz
H	9.13	8.02--7.70[a]			8.49	2.67		2.6	0.7
Me	9.04	7.86	7.81	-	8.35	2.60	8.8	1.9	0.6
Br	9.16	8.14	7.87	-	8.37	2.65	9.0		
NO_2	9.37	8.97	8.55	-	8.72	2.85	9.2	2.1	0.7

a. H_5, H_7, H_8 occurred as a complex multiplet b. chemical shifts are δ

for the 6-nitro compound the next lowest field proton is the H-8 proton which is pulled sharply downfield when it has the nitro group meta to it. Since a nitro group has most influence on positions ortho and para to it,

it is perhaps not surprising that the C-5 proton is pulled very much further downfield and in fact appears at even lower field than the H-8 proton (8.72 δ) at 8.97 δ . The position of the 4-methyl group remains fairly constant although the nitro group at position 6 pulls it down by 0.2 ppm from its position in the unsubstituted 4-methylcinnoline to 2.85 δ.

In the case of pure 1- and 2-oxides it is normally fairly easy to assign them as being the 1-oxide or the 2-oxide since the H-8 proton is always well downfield from the other aromatics in the case of the 1-oxide. According to Ogata et al.[19] this is caused by the presence of the magnetic anisotropy of the N-O group. There is also the effect of the electric field produced by the N-O group and of the lone pair electrons on the oxygen atom. This is an effect analogous to that of the carbonyl or nitro groups. It is therefore reasonable to expect that the proton at the peri position to the N-O group of the cinnoline 1-oxide should have its signal at lower field than the other protons.

The nmr data for the cinnoline 1-oxides and the cinnoline 2-oxides is tabulated in Tables 3 and 4 respectively while Table 5 shows the data for the only dioxide produced, 4,6-dimethylcinnoline 1,2-dioxide.

As in the case of the cinnolines themselves, the spectra of the cinnoline oxides do not show any abnormal substituent effects with respect to the unsubstituted 4-methylcinnoline taken as standard. In the case of the 6-nitro substitution the electron withdrawing group has a severe deshielding effect on all the protons, which is especially noticeable

Table 3 NMR data for cinnoline 1-oxides (56)[b]

X	H_3	H_8	H_5	H_7	Me	J_{ortho}/ Hz	J_{meta}/ Hz	J_{para}/ Hz
H	8.12	8.65	7.98 - 7.64[a]		2.58			
Br	8.16	8.54	8.05	7.81	2.55	9.1	2.0	0.4
Me	8.08	8.54	7.61	7.55	2.54	8.9	1.8	
NO_2	8.31	8.88	8.83	8.48	2.68	9.2	2.2	

a. complex multiplet b. chemical shifts are δ

Table 4 NMR data for cinnoline 2-oxides (56)[b]

X	H_3	H_8	H_5	H_7	Me	J_{ortho}/ Hz	J_{meta}/ Hz
H	8.08	7.94 - 7.32[a]			2.62		
Br	8.08	7.82 - 7.68[a]			2.59		
Me	8.05	7.78	7.60	7.56	2.58	9.4	
NO_2	8.18	8.04	8.78	8.54	2.71	9.1	2.2

a. complex multiplet b. chemical shifts are δ

Table 5 NMR data for 4,6-dimethylcinnoline 1,2-dioxide[b]

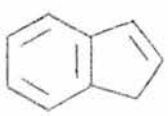
	H_8	H_3	H_5	H_7	Me
Dioxide	8.27	7.97	7.68 - 7.53[a]		2.57

a. broad multiplet b. chemical shifts are δ

with the protons ortho to it showing a shift of almost one ppm downfield. The methyl substituent causes corresponding upfield shifts because of its shielding effect although the shifts with respect to the unsubstituted compound are not nearly so great (ca. 0.3 ppm). Halogen (in this case bromo) substitution does not have a very significant effect with the largest effect as expected on the meta position (H-8) with an upfield shift of ca. 0.1 ppm. Again the coupling constants are normal with the ortho coupling ca. 9.0 Hz and meta ca. 2.0 Hz.

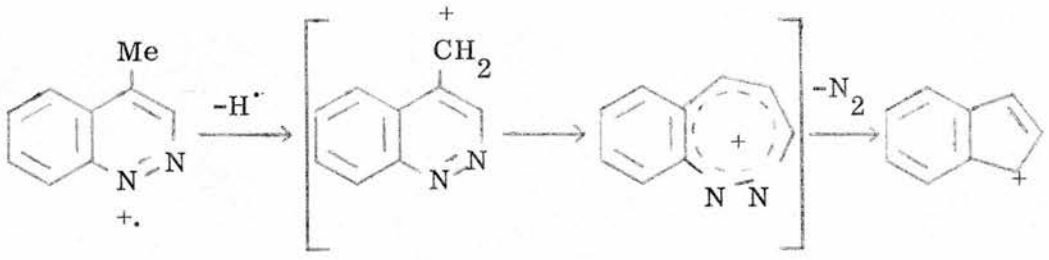
It should be noted that although nmr data has been given for 4-methyl-6-nitrocinnoline 1-oxide, there is no experimental proof to substantiate its existence apart from the nmr spectrum. As only a few milligrams were isolated, melting point and analysis could not be done and even the nmr had to be run by spectrum accumulation due to the weakness of the solution. However the nmr spectrum is not inconsistent with its being the 1-oxide.

The mass spectra of the cinnolines show that the principal initial fragmentation involves the synchronous loss of a molecule of nitrogen and a proton, followed by the loss of the 6-substituent, which is replaced by a proton giving a fragment of m/e 115, the base peak or the next largest in the spectrum of each of the cinnolines prepared. Palmer et al.[31] compared the spectra of some cinnolines below m/e 116 with those of α-methylstyrene, propenylbenzene and indene (57) and found that the spectrum of indene was almost identical and conclude that the ions at m/e 115 are probably identical to those of indene. Elkins and Brown[30] came to



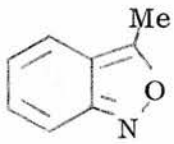
(57)

Scheme 1



similar conclusions about the structure of the m/e 115 fragment and the initial breakdown is probably as shown in Scheme 1. Palmer claims that there is a second minor breakdown pathway involving the loss of only a single nitrogen atom. By the use of ^{15}N at position 1 they were able to show that it was the N-2 atom that is lost. However the spectra of the cinnolines being studied at present did not show this fragmentation pattern.

In all the spectra of the mono oxides prepared the molecular ion was the base peak. It appears from the spectra that deoxygenation is the principal process. One marked difference between the two sets of isomers is the presence of m/e 43, which in each case is the second most intense peak in the spectrum, in the spectra of the 1-oxides and its almost complete absence in the spectra of the 2-oxides. Although Palmer suggests that 1-oxides lose HCN this fragmentation was not evident even with an ionisation energy of 20 eV. However the presence of m/e 43 in each of the spectra of the 1-oxides is in agreement with their findings and so almost certainly means that HCN is lost since they propose that an initial loss of HCN, followed by a recyclisation, results in an anthranil structure (58) which has in its mass spectrum a large m/e 43

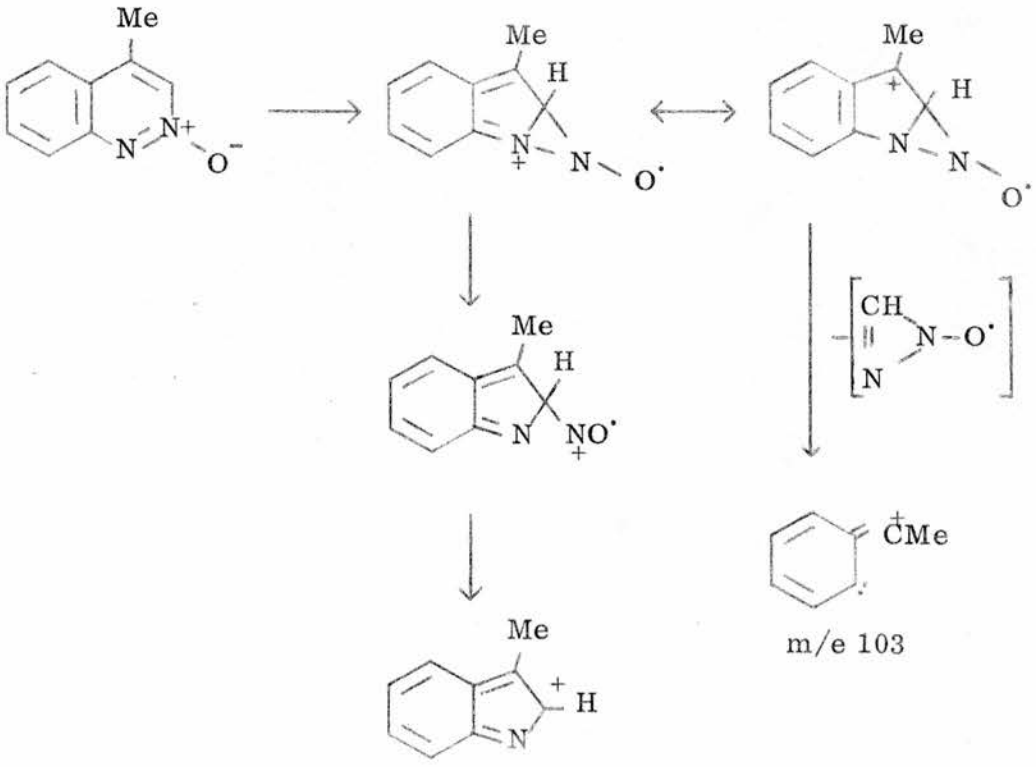


(58)

peak due to CH_3CO^+. However under the mass spectral conditions used in this study simple deoxygenation seems to be fairly important also, leading to a fragmentation pattern similar to that of the cinnolines.

The most abundant initial loss in the spectra of the 2-oxides appears to be the loss of the oxygen atom, after which the cinnoline fragments as before. Initial loss of 30 (nitric oxide) also seems to have some significance as shown in Scheme 2.

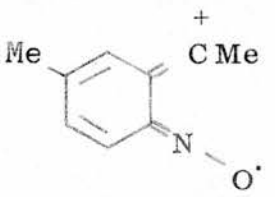
Scheme 2



m/e 103

m/e 130

There appear to be several competitive mechanisms in the initial fragmentation pattern of the dioxide of 4,6-dimethylcinnoline. The deoxygenation pattern is present (m/e 174) and also the initial loss of nitric oxide (m/e 160). There is also the successive loss of two atoms of oxygen resulting in an ion at m/e 158 which then breaks down as the cinnoline. However the base peak in the dioxide appears at m/e 147 and is due to the loss of CHNO which results in a cation of structure (59).



(59)

This can then recyclise to the anthranil structure and results in a substantial m/e 43 ion, CH_3CO^+.

Photolysis

As it was known that some of the N-oxides, notably 4-methylcinnoline 1-oxide appear to undergo some kind of change on standing in the air and light, it was wondered whether any reaction could be detected by photolysing them. Initially experiments were carried out using ca. $2x10^{-3}$M solutions of the particular oxide being studied in acetonitrile and using a low pressure mercury source of light. Quartz was used for all walls between the lamp and solution. Efficient cooling of the lamp and solution was necessary and both a water jacket between the lamp and solution and a flow of compressed air around the lamp were required. The initial experiments involved the 4-methyl-6-bromocinnoline 2-oxide. After photolysis for 6 h in acetonitrile the solvent was evaporated to leave a very tarry looking product. When this was examined by tlc there was a large amount of tarry residue left at the bottom of the plate and the only mobile spot corresponded to the 2-oxide itself. In an

attempt to cut down on the extent of decomposition, the experiment was repeated but this time the lamp was switched on for one hour only. In this case an nmr was run on the product, which again was rather tarry, in order to get a more quantitative assessment of the products, but it was found that the only product to show up in the spectrum was 6-bromo-4-methylcinnoline 2-oxide. The experiments were repeated using 4-methylcinnoline 2-oxide in acetonitrile. After 1 h, tlc showed only starting material plus a little tar. A further 2 h resulted only in the formation of more tar. The solvent was changed from acetonitrile to methanol but photolysis for a further hour resulted only in an even higher tar : starting material ratio.

In order to try to reduce the severity of the reaction conditions in an attempt to cut down the amount of total degradation, one of the quartz sleeves was replaced by a pyrex sleeve which cut down the amount of short wavelength ultraviolet light reaching the solution. With this alteration made, 6-bromo-4-methylcinnoline 2-oxide was photolysed for 2 h as a methanolic solution. After this time no apparent change had taken place, with complete recovery of the 2-oxide. It was then photolysed for a total of 24 h but even after this period no change had taken place.

Finally 4-methylcinnoline 1-oxide, which rapidly turns green on standing in air was photolysed under these conditions for 24 h in methanol. After this time there had been complete degradation into a tar which would not run at all on a tlc plate.

One cannot draw many conclusions from these results apart from

the fact that it appears that when the molecule gains sufficient energy to begin to breakdown the degradation is either very easy and advantageous energy-wise or the intermediates formed are extremely unstable and result in the total degradation of the molecule rather than into isolable intermediates.

Experimental

2-(2-Aminophenyl)-propan-2-ol [59]

(a) Methyl iodide (500 g; 3.52 mole) in ether (200 ml) was added dropwise on to magnesium turnings (100g; 4.12 mole) well covered with ether. After the addition the mixture was heated under reflux for 30 min and then cooled to 0^{o}.

(b) Methyl anthranilate (100g; 660 mmole) in ether (400 ml) was added dropwise to the Grignard solution. When the addition was complete the mixture was heated under reflux for 5 h. After cooling in an ice bath, any remaining Grignard was decomposed by cautiously adding ice. Saturated ammonium chloride solution (200 ml) and concentrated HCl (450 ml) were added to destroy the excess magnesium and dissolved the hydroxides formed. The solution was then neutralised with concentrated ammonia solution. The mixture was extracted with ether (2x100 ml) and the combined extracts dried over anhydrous Na_2SO_4. The solvent was then evaporated under reduced pressure to yield a crude red brown oil. This was distilled to give a very viscous colourless oil. Yield (crude): 98.13g (98%). It had bp 86-92^{o} (0.07 mm); λ_{max} 239 (ϵ 7860) and 288 nm (2400); ν_{max} 3520, 3460, 3375 (all part of one large broad absorption), and 1615 cm^{-1}; δ ($CDCl_3$) 7.04 - 6.42 (4H, m), 3.90 (3H, br), and 1.50 (6H, s); m/e 151 (51%), 136 (31), 133(100), 132 (71), 118 (98), 117 (36), 91 (46), and 43 (33). (Found: C, 71.76; H, 8.81; N, 9.19. $C_9H_{13}NO$ requires C, 71.52; H, 8.61; N, 9.27%).

2-(2-N-Acetylaminophenyl)-propan-2-ol (52)

2-(2-Aminophenyl)-propan-2-ol (98 g; 649 mmole) was dissolved in water

(1450 ml) by adding concentrated HCl (52.5 ml) and stirring vigorously for about 45 min. Acetic anhydride (75.3 ml; 81 g; 794.1 mmole) was then stirred in and immediately sodium acetate (98 g; 1.19 mole) in water (290 ml) was added. The solution was stirred vigorously and cooled to 0^{o} as beige coloured crystals precipitated. These were filtered off, washed with a little cold water and recrystallised from aqueous ethanol. Yield: 102.71g (82%). It had mp 144-6^{o} [Lit.[59] 146-7^{o}]; λ_{max} 239 nm (ϵ 12,470); ν_{max} 3350, 3285, and 1655 cm^{-1}; δ ($CDCl_3$) 10.01 (1H, br), 8.18 (1H, d), 7.11 (3H, m), 3.28 (1H, br), 2.02 (3H, s), and 1.62 (6H, s); m/e 193 (20%), 178 (7), 175 (5), 160 (35), 136 (42), 134 (22), 133 (43), 132 (100), 118 (45), and 43 (59).

2,4,4-Trimethyl-6-nitro-3,1-benzoxazine (54)

2-(2-N-Acetylaminophenyl)-propan-2-ol (10 g; 51.8 mmole) was added over 30 min to a stirred 5:2 mixture (v/v) of fuming HNO_3 and concentrated H_2SO_4 (60 ml). The reaction mixture was kept at -25^{o} using a solid CO_2/acetone bath. After the addition the stirred solution was kept at this temperature for a further 15 min. The solution was then poured on to ice (600 g) and basified with concentrated ammonia. A yellow solid precipitated and this was filtered and washed with a little water. The crude product was recrystallised firstly from aqueous ethanol and then from petroleum ether (bp 40-60^{o}). Yield: 11.10 g (97%). It had mp 86^{o}; λ_{max} 225 (ϵ 9590) and 321 nm (11,500); ν_{max} 1634, 1604, 1571, and 1370 cm^{-1}; δ (d_6-acetone) 8.11 - 8.03 (2H, m), 7.17 (1H, dd), 2.09 (3H, s), and 1.68 (6H, s); m/e 220 (9%), 205 (100), 159 (45), 131 (16), 130 (17), 117 (10), 75 (14), and 43 (71). (Found: C, 60.08;

H, 5.52; N, 12.77. $C_{11}H_{12}N_2O_3$ requires C, 60.00; H, 5.45; N, 12.72%).

2-(2-N-Acetylamino-5-nitrophenyl)-propene (53)

2-(2-Amino-5-nitrophenyl)-propene (200 mg; 1.12 mmole) was treated with acetic anhydride (0.5 ml; 0.54 g; 5.29 mmole). The mixture was heated on a steambath for 10 min. Water (5 ml) was added dropwise to the mixture, followed by concentrated ammonia solution (1.0 ml). A yellow oil was formed and this was extracted into ether (2 x 25 ml). After the combined ether fractions had been dried over Na_2SO_4 the solvent was removed under reduced pressure. The crude yellow solid was recrystallised from aqueous ethanol. Yield: 140 mg (56%). It had mp 84°; mixed mp with 2,4,4-trimethyl-6-nitro-3,1-benzoxazine (mp 86°) of 68-81°; λ_{max} 307 nm (ϵ 9350); ν_{max} 3340, 1681, 1579, 1535, 1379, and 1349 cm^{-1}; δ (d_6-acetone) 8.45 (1H, d), 8.09 (1H, dd), 7.98 (1H, d), 5.43 (1H, m), 5.13 (1H, m), 2.15 (3H, s), and 2.11 (3H, m) (NH did not appear); m/e (220 absent), 177 (97%), 160 (18), 148 (23), 132 (32), 131 (63), 130 (39), 117 (29), and 43 (100), (Found: C, 60.01; H, 5.46; N, 12.67. $C_{11}H_{12}N_2O_3$ requires C, 60.00; H, 5.45; N, 12.72%).

2-(2-Amino-5-nitrophenyl)-propan-2-ol

2,4,4-Trimethyl-6-nitro-3,1-benzoxazine (7.50 g; 34.1 mmole) in concentrated HCl was heated under reflux for 60 min. The solution was then basified with concentrated ammonia solution and then extracted with ether (3 x 100 ml). The combined fractions were dried over Na_2SO_4 and the solvent was evaporated. Recrystallisation of the crude solid from ethanol/petroleum ether (bp 60-80°) yielded the carbinol, 880 mg (13%). The

composition of the evaporated mother liquor (4.92 g) was found to be 2-(2-amino-5-nitrophenyl)-propan-2-ol (42%), 2-(2-amino-5-nitrophenyl)-propene (30%), starting benzoxazine (18%) and 4-nitroaniline (10%). The recrystallised carbinol was then recrystallised from water. It had mp 137.5 - 8.5°; λ_{max} 231 (ϵ 6390), 255 (3480), 297 (1840), 320 (2420), and 378 nm (14,410); ν_{max} 3515, 3420, 3345, 3230, 1639, 1571, and 1373 cm^{-1}; δ (d_6- acetone) 7.95 - 7.79 (2H, m), 6.70 (1H, dd), 6.42 (2H, s), 4.56 (1H, s), and 1.64 (6H, s); m/e 196 (42%), 181 (50), 178 (100), 163 (62), 148 (62), 117 (88), and 42 (45). (Found: C, 55.20; H, 6.36; N, 14.35. $C_9H_{12}N_2O_3$ requires C, 55.10; H, 6.12; N, 14.29%).

2-(2-Amino-5-nitrophenyl)-propene (50)

2-(2-Amino-5-nitrophenyl)-propan-2-ol (1.96 g; 10 mmole) was dissolved in benzene (100 ml) and, after adding I_2 (ca. 100 mg), the mixture was heated under reflux for 20 h. Using a Dean-Stark trap, approximately 0.12 ml water (6.7 mmole) was collected. After washing the mixture with a saturated solution of sodium thiosulphate (ca. 150 ml) and then with water (2 x 100 ml), the organic layer was dried over Na_2SO_4 and then evaporated to give the crude product. This was distilled to give a mobile pale yellow oil. Yield: 1.44 g (81%). It had bp 148° (0.5 mm); λ_{max} 261 (ϵ 3830) and 363 nm (13,700); ν_{max} 3500, 3395, 1621, 1578, and 1335 cm^{-1}; δ (d_6- acetone) 7.93 - 7.84 (2H, m), 6.78 (1H, dd), 5.70 (2H, s), 5.35 (1H, m), 5.09 (1H, m), and 2.07 (3H, m); m/e 178 (100%), 177 (9), 163 (3), 132 (10), 131 (22), 130 (34), 117 (53), 115 (22), and 77 (26). (Found C, 60.55; H, 5.56; N, 15.52. $C_9H_{10}N_2O_2$ requires C, 60.67; H, 5.62; N, 15.73%).

4-Methyl-6-nitrocinnoline (51)

2-(2-Amino-5-nitrophenyl)-propene (534 mg; 3 mmole) was suspended in concentrated HCl (5 ml) and glacial acetic acid (2 ml). Sodium nitrite (207 mg; 3 mmole) in water (15 ml) was added to the stirred solution which was kept at 0^{o} in an ice bath. A slight oiliness appeared and the suspension dissolved into a yellow solution. After 12 min the ice bath was removed and 8 min later the solution was basified with ammonia which caused a yellow solid to precipitate. This plus the mother liquor was extracted into chloroform (2 x 25 ml) and the combined extracts were dried before removal of the solvent. The product was purified on an alumina column eluted with 2% chloroform in benzene and then recrystallised from water. Yield (crude): 502 mg (88%). It had mp 130^{o} (d); λ_{max} 255 (ϵ 12,070), 327 (5240), and 350 nm (5430); ν_{max} 1620, 1580, 1528, 1379, and 1348 cm^{-1}; δ ($CDCl_3$) 9.37 (1H, s), 8.97 (1H, d), 8.72 (1H, d), 8.55 (1H, dd), and 2.85 (3H, s); m/e 189 (38%), 159 (5), 131 (5), 116 (5), 115 (48), 103 (6), 89 (19), 44 (77), and 43 (100). (Found: C, 56.55; H, 3.80; N, 22.33. $C_9H_7N_3O_2$ requires C, 57.14; H, 3.70; N, 22.22%). Although it was repeatedly recrystallised and showed up as a single spot on a tlc plate this analysis could not be improved. Accurate mass: 189.0537. ($C_9H_7N_3O_2$ requires 189.0538).

It should be noted that this adaptation of the standard Widman-Stoermer synthesis[59] using concentrated HCl and glacial acetic acid was arrived at only after many futile attempts, each of which resulted in the isolation of a dark red solid which it is proposed may be the oxime of 6-nitro-4-cinnoline carboxaldehyde. A typical preparation is:

2-(2-Amino-5-nitrophenyl)-propene (520 mg; 2.92 mmole) was converted to its hydrochloride by adding a 1:1 (v/v) mixture of concentrated HCl and glacial acetic acid (20 ml) and this was then dissolved by adding water (30 ml), stirring all the time. Sodium nit rite (410 mg; 5.94 mmole) in water (7 ml) was added dropwise. The colour changed from pale yellow to deep red and after stirring for 10 min the solution became brown and after being left stirring overnight it had become deep purple. The solution was basified and a dark red precipitate was filtered off. Yield: 500 mg (78% if proposed structure is correct). It had mp 236°; λ_{max} 236, 262, 308, and 363 cm^{-1}; ν_{max} 2850 (br), 1613, 1580, 1536, and 1351 cm^{-1}; δ (d_6-DMSO) 12.74 (1H, s), 9.64 (1H, d), 8.71 (2H, d), 8.57 (1H, dd), and 3.39 (1H, s); m/e 218 (100%), 200 (22), 173 (14), 127 (23), 100 (33), 99 (23), 89 (34), and 43 (25). (Found: C, 48.31; H, 3.14; N, 24.95. $C_9H_6N_4O_3$ requires C, 49.50; H, 2.76; N, 25.68%). No satisfactory method of recrystallisation was found and this analysis could not be improved. Accurate mass: 218.0443. ($C_9H_6N_4O_3$ requires 218.0440).

2-(2-Aminophenyl)-propene

2-(2-Aminophenyl)-propan-2-ol (10.0 g; 66.2 mmole) was dehydrated in a similar manner to the 5-nitro compound described previously to yield a crude brown oil which was distilled to give an almost colourless mobile oil. Yield: 7.30 g (84%). It had bp 48-60° (0.5 mm) [Lit.[6] 83.5 - 87.5° (1-2 mm)]; λ_{max} 215 (ϵ 12,830), 234 (5330), and 294 nm (1420); ν_{max} 3470 and 3380 cm^{-1}; δ ($CDCl_3$) 7.10 - 6.92 (2H, m), 6.78 - 6.56 (2H, m), 5.25 (1H, m), 5.02 (1H, m), 3.74 (2H, br),

and 2.04 (3H, m); m/e 133 (100%), 118 (51), 117 (39), 91 (51), 77 (21), and 65 (26). (Found: C, 81.04; H, 8.08; N, 10.34. $C_9H_{11}N$ requires C, 81.20; H, 8.27; N, 10.53%).

4-Methylcinnoline

2-(2-Aminophenyl)-propene (250 mg; 1.88 mmole) was dissolved in concentrated HCl (5 ml) and water (5 ml) was then added to dissolve the white hydrochloride. After cooling in ice, sodium nitrite (200 mg; 2.9 mmole) in water (4 ml) was added to the red solution, which became progressively darker until it was virtually black. The solution was heated to 60° and after stirring had been continued at this temperature for about 20 min the colour lightened and became yellowish and the β-naphthol coupling reaction was negative. The solution was allowed to cool, before being extracted with ether (2 x 30 ml) and then petroleum ether (bp 60-80°) (2 x 30 ml). After the combined extracts had been dried over Na_2SO_4 the solvent was evaporated to give a dark green solid which was recrystallised at -78° from petroleum ether (bp 60-80°) plus a drop of ethanol, to give a yellow light sensitive solid. Yield (crude): 200 mg (74%). It had mp 69-71° [Lit.[35] 72°]; λ_{max} 223 (ϵ 46,930), 281 (3310), 290 (3410), and 321 nm (3250); ν_{max} 1619 and 1576 cm^{-1}; δ ($CDCl_3$) 9.13 (1H, s), 8.49 (1H, m), 8.02 - 7.70 (3H, m), and 2.67 (3H, s); m/e 144 (73%), 116 (12), 115 (100), 89 (11), and 63 (12).

Methyl 5-bromoanthranilate

Bromine (8.0 g; 50 mmole) in methanol (250 ml) was added dropwise over a period of 45 min to a stirred solution of methyl anthranilate

(7.55 g; 50 mmole) in methanol (500 ml). The methanol was evaporated to leave the hydrobromide salt, 14.77 g, a pale yellow solid. The hydrobromide (10.0 g) was dissolved in hot ethanol (100 ml) and a saturated solution of $NaHCO_3$ was added until the solution was basic (100 ml). The solution was extracted with ether (3 x 100 ml) and the combined extracts were dried over Na_2SO_4 and then evaporated to give a yellowish white solid. This was shown by nmr and tlc to be mainly methyl 5-bromoanthranilate but also contained two other components which were later shown to be methyl 3-bromoanthranilate and a dibromo isomer. The mixture was therefore loaded on to an alumina column (30 x 2 cm) and by elution with benzene the pure methyl 5-bromoanthranilate was isolated. Yield: 5.50 g (48%). It had mp 72-3° [Lit.[85] 74°]; λ_{max} 258 (ϵ 9600) and 350 nm (4400); ν_{max} 3470, 3375, and 1690 cm^{-1}; δ ($CDCl_3$) 7.95 (1H, d), 7.31 (1H, dd), 7.54 (1H, d), and 3.86 (3H, s); m/e 231 (72%), 229 (74), 199 (100), 197 (100), 172 (35), 170 (36), 91 (33), 90 (41), and 63 (51). (Found C, 41.64; H, 3.53; N, 6.12. $C_8H_8BrNO_2$ requires C, 41.74; H, 3.48; N, 6.09%).

2-(2-Amino-5-bromophenyl)-propan-2-ol

The method was similar to the preparation of 2-(2-aminophenyl)-propan-2-ol using methyl iodide (81.0 g; 570 mmole) and magnesium turnings (16.2 g; 666 mmole) for the Grignard and adding to this methyl 5-bromoanthranilate (25.3 g; 110 mmole). Yield: 24.87 g (99%). It had mp 62.5 - 3.5°; λ_{max} 249 (ϵ 12,420) and 301 nm (2370); ν_{max} 3390, 3320, and 3280 (br) cm^{-1}; δ ($CDCl_3$) 7.14 (1H, d), 7.09 (1H, dd), 6.44 (1H, d), 3.73 (3H, br), and 1.59 (6H, s); m/e 231 (30%), 229 (31),

213 (99), 211 (100), 198 (30), 196 (27), 131 (40), 117 (71), and 43 (41). (Found: C, 46.84; H, 5.35; N, 6.27. $C_9H_{12}BrNO$ requires C, 46.96; H, 5.22; N, 6.09%).

2-(2-Amino-5-bromophenyl)-propene

2-(2-Amino-5-bromophenyl)-propan-2-ol (24.9 g; 108.3 mmole) in benzene (200 ml) was heated under reflux for 86 h. A catalytic amount of toluene-p-sulphonic acid was added to the solution and a Dean-Stark trap was used to collect the water which was azeotroped off. The benzene solution was then washed with triethylamine and then with water (3 x 200 ml). The organic layer was dried over Na_2SO_4 and then evaporated to give the crude product which was purified by distillation. Yield: 12.76 g (56%). It had bp 88 - 95° (0.1 mm); λ_{max} 245 (ϵ 8600) and 307 nm (1970); ν_{max} 3480 and 3395 cm^{-1}; δ ($CDCl_3$) 7.15 - 7.02 (2H, m), 6.50 (1H, d), 5.26 (1H, m), 5.02 (1H, m), 3.76 (2H, br), and 2.01 (3H, m); m/e 213 (95%), 211 (100), 198 (16), 196 (15), 132 (12), 131 (54), 130 (24), 130 (24), and 117 (77). (Found: C, 50.89; H, 4.82; N, 6.65. $C_9H_{10}BrN$ requires C, 50.94; H, 4.72; N, 6.60%).

6-Bromo-4-methylcinnoline

2-(2-Amino-5-bromophenyl)-propene (500 mg; 2.36 mmole) was dissolved in concentrated HCl (10 ml) and water (10 ml) by vigorous stirring. The solution was cooled to 5° and sodium nitrite (184 mg; 2.67 mmole) in water (10 ml) was added. After about 2 h the β-naphthol test was still positive and so the solution was heated to 60°. The solution became darker until it was dark red. It was basified and extracted with chloroform

(2 x 30 ml). After drying the organic layer the solvent was evaporated and the crude product was then recrystallised from hexane. Yield (crude): 470 mg (89%). It had mp 134-5° [Lit.[35] 128-9°]; λ_{max} 235 (ϵ 48,450), 298 (5450), and 323 nm (3410); ν_{max} 1600 and 1569 cm^{-1}; δ ($CDCl_3$) 9.16 (1H, s), 8.37 (1H, d), 8.14 (1H, d), 7.88 (1H, dd), and 2.65 (3H, s); m/e 224 (76%), 222 (79), 116 (13), 115 (100), 114 (19), 89 (22), and 43 (20). (Found: C, 48.04; H, 3.15; N, 12.80. $C_9H_7BrN_2$ requires C, 48.45; H, 3.16; N, 12.56%). Accurate mass: 223.9767. ($C_9H_7BrN_2$ requires 223.9772).

Methyl 5-methylanthranilate

5-Methylanthranilic acid (23.0 g; 152.3 mmole) was dissolved in saturated methanolic HCl (600 ml) and heated under reflux for 4.5 h. The methanol was then evaporated and the residue dissolved in water and basified with saturated $NaHCO_3$ solution. It was then extracted with ether (2 x 300 ml) and after drying the combined extracts over Na_2SO_4, the solvent was evaporated and the product recrystallised from aqueous methanol. Yield: 20.68 g (82%). It had mp 62° [Lit.[85] 62°]; λ_{max} 248 (ϵ 7340) and 345 nm (4680); ν_{max} 3480, 3371 and 1681 cm^{-1}; δ ($CDCl_3$) 7.66 (1H, d), 7.09 (1H, dd), 6.58 (1H, d), 5.54 (2H, br), 3.85 (3H, s), and 2.22 (3H, s); m/e 165 (62%), 134 (25), 133 (100), 106 (23), 104 (27), and 77 (20).

2-(2-Amino-5-methylphenyl)-propan-2-ol

The method was similar to the preparation of 2-(2-aminophenyl)-propan-2-ol using methyl iodide (100.0 g; 704 mmole) and magnesium turnings

(20.0 g; 823 mmole) for the Grignard and adding to this methyl 5-methylanthranilate (22.7 g; 137.6 mmole). Yield: 17.05 g (76%). It had bp 150-64° (0.1 mm); λ_{max} 238 (ϵ 8190) and 294 nm (2010); ν_{max} 3370 (br) cm^{-1}; δ ($CDCl_3$) 6.89 (1H, d), 6.85 (1H, dd), 6.50 (1H, d), 3.72 (3H, br), 2.21 (3H, s), and 1.60 (6H, s); m/e 165 (42%), 150 (23), 147 (100), 132 (55), 117 (41), 91 (13), and 43 (58). (Found: C, 72.83; H, 9.18; N, 8.23. $C_{10}H_{15}NO$ requires C, 72.72; H, 9.09; N, 8.48%).

2-(2-Amino-5-methylphenyl)-propene

2-(2-Amino-5-methylphenyl)-propan-2-ol (36.97 g; 224.1 mmole) was dehydrated by a method similar to that used to dehydrate 2-(2-amino-5-bromophenyl)-propan-2-ol. The dehydration took 22 h and water (3.7 ml; 205.6 mmole) was collected in the Dean-Stark trap. Yield (crude): 32.78 g (100%). It had bp 64-78° (0.1 mm); λ_{max} 297 nm (ϵ 1950); ν_{max} 3470 and 3380 cm^{-1}; δ ($CDCl_3$) 6.90 - 6.78 (2H, m), 6.57 (1H, d), 5.25 (1H, m), 5.02 (1H, m), 3.64 (2H, br), 2.21 (3H, s), and 2.04 (3H, m); m/e 147 (100%), 146 (53), 132 (26), 131 (19), 130 (20), 117 (25), and 106 (24). (Found: C, 81.64; H, 9.21; N, 9.25. $C_{10}H_{13}N$ requires C, 81.63; H, 8.84; N, 9.52%).

4,6-Dimethylcinnoline

2-(2-Amino-5-methylphenyl)-propene (19.23 g; 130.8 mmole) was dissolved in concentrated HCl (100 ml) and water (200 ml) and, after cooling to 5°, to this was added sodium nitrite (14.0 g; 202.9 mmole) in water (100 ml). The colour changed from colourless to yellow during the 30 min stirring. The solution was then basified and extracted with chloroform (2 x 200 ml)

and after the combined extracts were dried over Na_2SO_4 the solvent was evaporated and the crude product recrystallised from hexane. Yield after crystallisation: 8.91 g (43%). It had mp 74-5° [Lit.[35] 75-6°]; λ_{max} 230 (ϵ 50,750), 296 (4410), and 319 nm (3240); ν_{max} 1623 cm^{-1}; δ ($CDCl_3$) 9.04 (1H, s), 8.35 (1H, d), 7.86 (1H, d), 7.81 (1H, dd), 2.60 (3H, s), and 2.58 (3H, s); m/e 158 (100%), 129 (37), 128 (39), 127 (19), 119 (10), 115 (82), and 43 (27).

6-Bromo-4-methylcinnoline 1-oxide and 2-oxide

In a manner similar to Palmer and Russell[35], 6-bromo-4-methylcinnoline (8.24 g; 37.0 mmole) was dissolved in glacial acetic acid (30 ml) and 30% H_2O_2 (15 ml). This mixture was heated on a steambath for 3 h after which time a further portion of H_2O_2 (15 ml) was added and the heating continued for a further 3 h. The solution was then neutralised with saturated Na_2CO_3 solution and extracted with chloroform (2 x 200 ml). After the combined extracts had been dried over Na_2SO_4 the solvent was evaporated to leave the crude oxidation mixture (5.87 g). At this stage an nmr spectrum was run to confirm the presence of N-oxide functions at positions N-1 and N-2 and also to estimate the ratio of the two products (1 : 1.6). Thin layer chromatography on silica confirmed the presence of two products but column chromatography of the mixture (1.50 g) on silica (40 x 3 cm) failed to separate the isomers when eluted with either benzene or chloroform. Hence the mixture (1.50 g; 6.28 mmole) was loaded on to an alumina column (40 x 3 cm) and eluted with 10% chloroform in benzene. In this way 6-bromo-4-methylcinnoline 1-oxide, 65 mg (3%) and then 6-bromo-4-methylcinnoline 2-oxide, 130 mg (6%)

were isolated along with mixed fractions (950 mg). 6-Bromo-4-methylcinnoline 1-oxide had mp 204° (d); λ_{max} 224 (ϵ 19,850), 240 (24,420), 260 (sh) (7840), 279 (7110), 315 (4470), 328 (4650), and 354 nm (7110); ν_{max} 1579, 1331, and 1164 cm^{-1}; δ ($CDCl_3$) 8.54 (1H, d), 8.16 (1H, s), 8.05 (1H, d), 7.81 (1H, dd), and 2.55 (3H, s); m/e 240 (97%), 238 (100), 224 (7), 222 (7), 184 (19), 182 (20), and 43 (88). The compound was recrystallised from benzene/petroleum ether (bp 60-80°) but did not analyse successfully. Accurate mass: 237.9741. ($C_9H_7BrN_2O$ requires 237.9742. 6-Bromo-4-methylcinnoline 2-oxide had mp 223°; λ_{max} 227 (ϵ 29,010), 263 (30,400), 269 (sh) (26,850), 307 (8540), 351 (5580), and 355 nm (sh) (5350); ν_{max} 1591 and 1223 cm^{-1}; δ ($CDCl_3$) 8.08 (1H, s), 8.00 - 7.76 (3H, m), and 2.59 (3H, s); m/e 240 (97%), 238 (100), 224 (6), 222 (6), 129 (33), 115 (21), 103 (26), 102 (64), and 77 (49). (Found: C, 45.33; H, 3.03; N, 12.02. $C_9H_7BrN_2O$ requires C, 45.19; H, 2.93; N, 11.72%).

4-Methylcinnoline 1-oxide and 2-oxide

4-Methylcinnoline (4.0 g; 27.8 mmole) was oxidised by the same method as 6-bromo-4-methylcinnoline using glacial acetic acid (20 ml) and 30% H_2O_2 (2 x 10 ml), resulting in the isolation of the crude oxidation mixture, 3.92 g, which from its nmr spectrum had composition 1 : 2.8 1-oxide : 2-oxide. Chromatography of part of the mixture (2.82 g; 17.63 mmole) on alumina (40 x 3 cm) gave 4-methylcinnoline 1-oxide, 280 mg (9%), followed by 4-methylcinnoline 2-oxide, 240 mg (8%), plus fractions of mixed oxides (1.93 g). 4-Methylcinnoline 1-oxide had mp 90-2° [Lit.[35] 94-5°]; λ_{max} 229 (ϵ 22,460), 252 (7540), 288 (sh)

(3670), 306 (sh) (5010), 317 (5210), 356 (8210), and 367 nm (sh) (7690); ν_{max} 1580 and 1231 cm^{-1}; δ ($CDCl_3$) 8.65 (1H, m), 8.12 (1H, s), 7.98 - 7.64 (3H, m), and 2.58 (3H, s); m/e 160 (100%), 144 (13), 133 (3), 115 (25), 104 (25), 103 (15), 78 (25), 77 (47), and 43 (73). 4-Methylcinnoline 2-oxide had mp 143-5° [Lit.[35] 147-8°]; λ_{max} 221 (ϵ 25,610), 261 (28,170), 307 (6020), 346 (5250), and 356 nm (sh) (4990); ν_{max} 1601 and 1229 cm^{-1}; δ ($CDCl_3$) 8.08 (1H, s), 7.94 - 7.32 (4H, m), and 2.62 (3H, s); m/e 160 (100%), 144 (13), 130 (4), 115 (26), 103 (36), and 77 (43).

4,6-Dimethylcinnoline 1-oxide, 2-oxide and 1,2-dioxide

4,6-Dimethylcinnoline (7.0 g; 44.3 mmole) was oxidised in the same way using glacial acetic acid (35 ml) and 30% H_2O_2 (2 x 17.5 ml) to give the crude oxidation mixture, 6.37 g, the composition of which was 1 : 2.1 1-oxide : 2-oxide plus a small amount of dioxide. Chromatography of the mixture (2.0 g; ca. 11.5 mmole) on alumina (20 x 4 cm) gave 4,6-dimethylcinnoline 1-oxide, 380 mg (16%), 4,6-dimethylcinnoline 2-oxide, 670 mg (28%), and unlike Palmer and Russell, also a small amount of 4,6-dimethylcinnoline 1,2-dioxide, 70 mg (3%), as well as fractions of mixed oxides (740 mg). 4,6-Dimethylcinnoline 1-oxide had mp 146-8° [Lit.[35] 160-1°]; λ_{max} 234 (ϵ 28,010), 255 (sh), (8930), 279 (5900), 312 (5070), 325 (5450), 354 (8630), and 364 nm (sh) (8250); ν_{max} 1580 and 1231 cm^{-1}; δ ($CDCl_3$) 8.54 (1H, d), 8.08 (1H, s), 7.61 (1H, d), 7.55 (1H, dd), 2.58 (3H, s), and 2.54 (3H, s); m/e 174 (100%), 158 (24), 129 (11), 128 (14), 118 (30), 115 (40), 91 (27), and 43 (66). 4,6-Dimethylcinnoline 2-oxide had mp 225-6° [Lit.[35] 230-1°];

λ_{max} 223 (ϵ 30,660), 264 (34,070), 269 (sh) (33,310), 309 (6960), 349 (5750), and 358 nm (sh) (5600); ν_{max} 1597 and 1225 cm^{-1}; δ ($CDCl_3$) 8.05 (1H, s), 7.78 (1H, d), 7.64 - 7.52 (2H, m), 2.58 (3H, s), and 2.54 (3H, s); m/e 174 (100%), 173 (18), 158 (9), 144 (4), 128 (10), 117 (15), 115 (37), 103 (13), and 91 (27). 4,6-Dimethylcinnoline 1,2-dioxide had mp 206° (d); λ_{max} 234 (ϵ 16,190), 275 (37,700), and 340 nm (6900); ν_{max} 1610, 1550, and 1268 cm^{-1}; δ ($CDCl_3$) 8.27 (1H, d), 7.97 (1H, s), 7.68 - 7.53 (2H, m), and 2.57 (6H, s); m/e 190 (10%), 174 (10), 173 (54), 160 (5), 158 (11), 147 (100), 118 (55), 115 (93), 114 (41), and 43 (35). (Found: C, 62.51; H, 5.14; N, 14.74. $C_{10}H_{10}N_2O_2$ requires C, 63.15; H, 5.26; N, 14.74%). Repeated crystallisations from benzene/petroleum ether (bp 40-60°) failed to improve this analysis. Accurate mass: 190.0737. ($C_{10}H_{10}N_2O_2$ requires 190.0742).

4-Methyl-6-nitrocinnoline 1-oxide and 2-oxide

4-Methyl-6-nitrocinnoline (4.20 g; 22.2 mmole) was oxidised in the same way using glacial acetic acid (17.5 ml) and 30% H_2O_2 (2 x 8.75 ml) to yield a crude oxidation mixture (680 mg) which nmr showed to be almost totally 2-oxide. Chromatography of part of the mixture (600 mg ; 2.93 mmole) on alumina (20 x 3 cm) yielded 4-methyl-6-nitrocinnoline 2-oxide, 210 mg (5%). However the first fractions of 2-oxide to come off the column were contaminated with a trace of 1-oxide. As these had run together down the column and also in view of how little there was, it was decided not to separate the 1-oxide further by chromatography. It was found that the 2-oxide in the mixture recrystallised from acetone and that the 1-oxide remained in the mother liquor. Hence by evaporation of this,

a few milligrams of 4-methyl-6-nitrocinnoline 1-oxide were obtained. This was sufficient only for obtaining a microcell nmr by spectrum accumulation. 4-Methyl-6-nitrocinnoline 1-oxide had δ ($CDCl_3$) 8.88 (1H, d), 8.83 (1H, d), 8.48 (1H, dd), 8.31 (1H, s), and 2.68 (3H, s). 4-Methyl-6-nitrocinnoline 2-oxide had mp 260° (d); λ_{max} 221 (ε 21,120), 254 (19,880), 336 (13,990), and 349 nm (sh) (11,650); ν_{max} 1611, 1509, 1348, and 1238 cm^{-1}; δ ($CDCl_3$) 8.78 (1H, d), 8.54 (1H, dd), 8.18 (1H, s), 8.04 (1H, d), and 2.71 (3H, s); m/e 205 (100%), 189 (4), 175 (13), 147 (5), 129 (7), 115 (6), 104 (11), 103 (5), 102 (12), and 77 (24). (Found: C, 52.25; H, 3.54; N, 20.45. $C_9H_7N_3O_3$ requires C, 52.68; H, 3.41; N, 20.48%). Accurate mass: 205.0484. ($C_9H_7N_3O_3$ requires 205.0487).

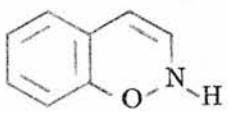
Photolysis of some substituted 4-methylcinnoline oxides

Each of the cinnoline oxides was photolysed as ca. 2×10^{-3} M solution in both acetonitrile and methanol. The photolysis apparatus consisted of an outer jacket (50 mm diam.) filled with solution (70 ml) and which had a sinter at its base through which compressed air was blown to ensure efficient mixing of the solution. This solution was contained between this outer jacket and an inner double jacket through which cooling water flowed. The outer wall of this double jacket was made of quartz and the inner wall could be either quartz or pyrex. Inside this water jacket was placed the low pressure mercury lamp. Air was pumped around the lamp to help prevent overheating. After each solution had been photolysed for the appropriate time, the solvent was evaporated from the solution under reduced pressure and the product examined by nmr or tlc.

Part II

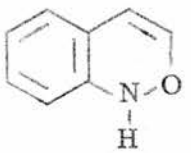
Introduction

By their very nomenclature, benzoxazines define their structure - a benzene ring fused to a six-membered hetero-ring containing one nitrogen atom and one oxygen atom. These hetero-atoms may be positioned at various places - there are eight isomers - which results in a numbering system to differentiate between them as shown [(60) - (67)]. For the tautomeric forms, the position of the mobile hydrogen is indicated by the



1,2-

(60)



2,1-

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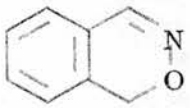

2,3,1-

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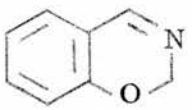

1,3,2-

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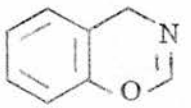
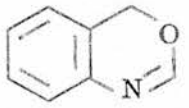


1,3,4-

(64)



3,1,4-

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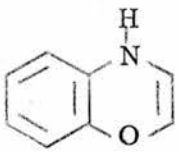
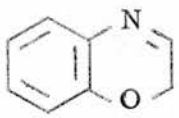


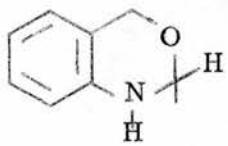
1,4-

(66)



1,4,2-

(67)



(68)

third number. As there is only one type of unsaturated 3,1-benzoxazine, the third number will be omitted and all will be referred to simply as 3,1-benzoxazines. In all the structures shown one bond in the hetero-ring is unsaturated. If this particular bond is saturated then the compounds

become dihydrobenzoxazines - for example 1,2-dihydro-3,1-benzoxazine (68).

The structure of these dihydrobenzoxazines can be written as two tautomers - a cyclic form (69) and an open chain form (70). In fact it is

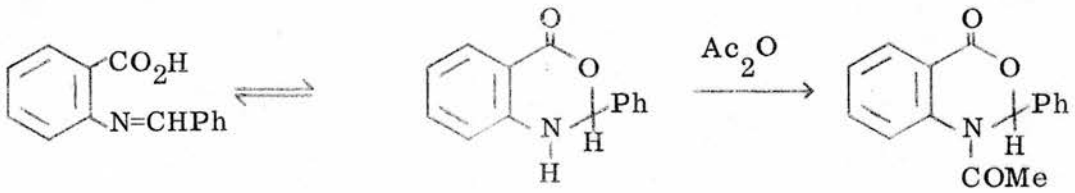
(69) (70)

quite difficult to distinguish between these two tautomers by methods such as proton nmr, mass spectrometry and infrared spectroscopy, since the nmr spectra would not be expected to be very different, they have the same mass, and the absence of >C=N vibration in the infrared must be treated with some caution since p-hydroxybenzalaniline in which no ring closure can occur lacks this band completely[86]. Eventually a combination of ^{13}C nmr and ultraviolet spectroscopy on these and some similar model compounds which were known to be either ring or open chain compounds was used to decide that the compounds are in fact cyclic. This is in agreement with work on γ-hydroxy imines which definitely cyclise to tetrahydro-1,3-oxazines[87]. On the other hand Witkop and Beiler[88] found that the open chain (71) was preferred to the cyclic tautomer (72),

(71) (72)

although they suggested that this equilibrium was sensitive to substituents.

Snyder et al. concluded[89] that benzalanthranilic acid (73) exists in equilibrium with its cyclic form (74) and that it is in its cyclic form that it

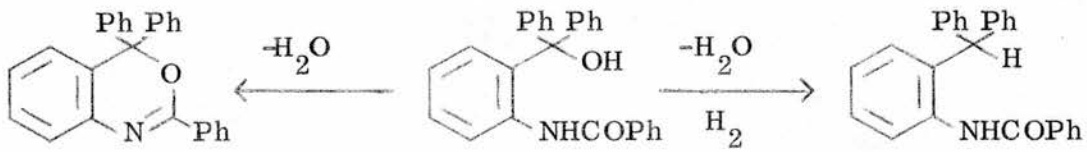


(73) (74) (75)

reacts with acetic anhydride to give what they called a "metoxazine" derivative (75). They suggested that the cyclic tautomer is formed from the open chain structure by intramolecular addition of the carboxyl group to the double bond. Up until the publication of this paper it had been thought that the acetic anhydride reacted with the double bond of the open chain form.

Holly and Cope made an extensive study[90] of many dihydrobenzoxazines using ultraviolet spectroscopy to show whether they had cyclic or open chain type structures. Paal and Laudenheimer had described[91] a number of condensation products between acetone and several aldehydes with o-aminobenzyl alcohol as azomethines (open chain Schiff bases) but did not consider the cyclic structures. Thus Holly and Cope condensed o-aminobenzyl alcohol with numerous aldehydes and ketones and also synthesised several Schiff bases (which were known to have open chain structures). All the condensation products were then compared by their ultraviolet spectra to the open chain Schiff bases, and they concluded that the condensation products had cyclic structures.

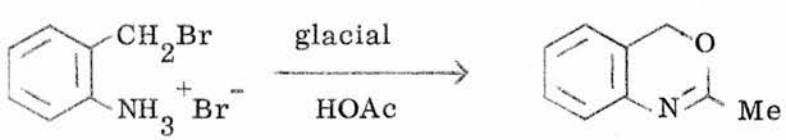
As was seen in Part I there can also be confusion as to the structure of the unsaturated benzoxazines, as when Atkinson and Simpson[59] almost certainly prepared 2,4,4-trimethyl-6-nitro-3,1-benzoxazine and thought it was the amido olefin (53). Since the widespread use of nmr however this particular problem has been greatly eased. A similar difficulty was encountered by Petyunin et al.[92] who, in a reaction using N-benzoyl-2-aminotriphenylcarbinol (77) found water had been eliminated, and concluded



(76) (77) (78)

that the product could be the benzoxazine (76) or the triphenylmethane derivative (78). Since they did not know whether hydrogen was evolved in their reaction they could not give preference to either structure. However they synthesised the benzoxazine (76) independently and found that its mixed melting point with their product was not depressed.

The synthesis of 3,1-benzoxazines normally uses an ortho aminobenzyl alcohol or an anthranilic acid or similar compound, for example 2-aminobenzyl bromide hydrobromide (79).



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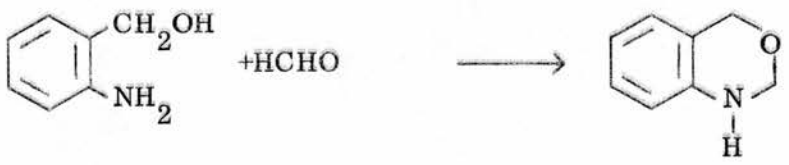
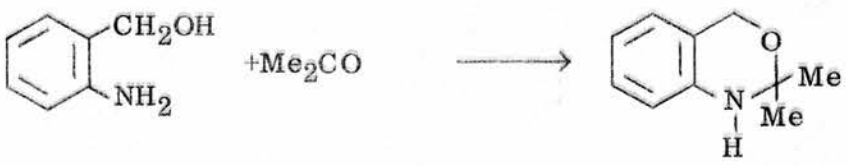
The saturated benzoxazines can be prepared by condensation of ortho aminobenzyl alcohol (80) with aldehydes or ketones in benzene for



(80) (81)

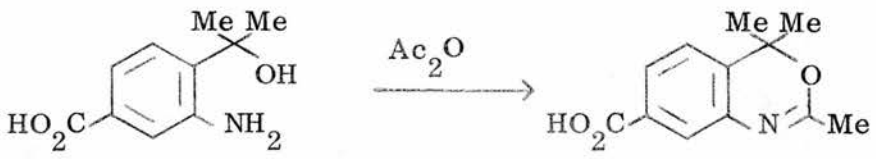


(82)

example, sometimes with a catalytic amount of glacial acetic acid. The cyclic structures of these compounds (81, 82) is supported by their molecular refractions and ultraviolet absorptions[90].

One of the first 3,1-benzoxazines to be synthesised was the 7-carboxylic acid (83) by Widman[93] in 1883.

The preparation of benzoxazones allows access to many benzoxazines. A typical method[94] is the dehydration of 2-amido benzoic acids (84). These benzoxazones can then react[95] with Grignard reagents to give the corresponding benzoxazines (85). Grignard reagents can also be reacted[96] with substituted 3,4-dihydro-4-oxoquinazolines (86).



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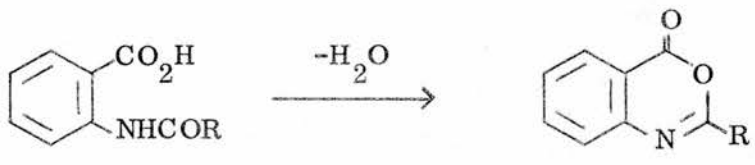

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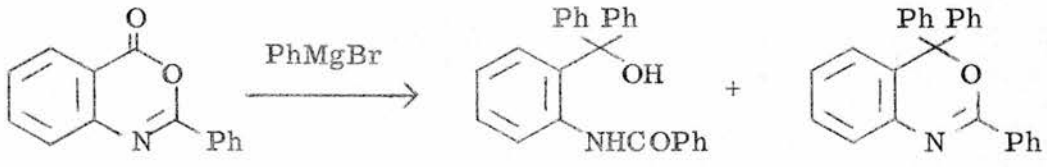
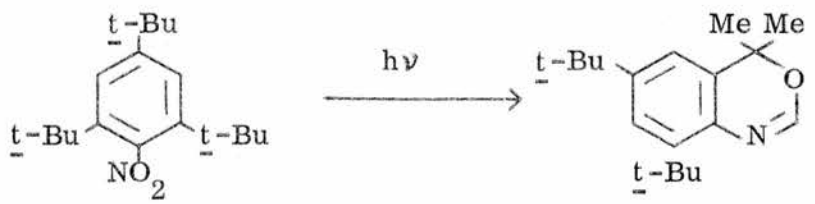


(85)

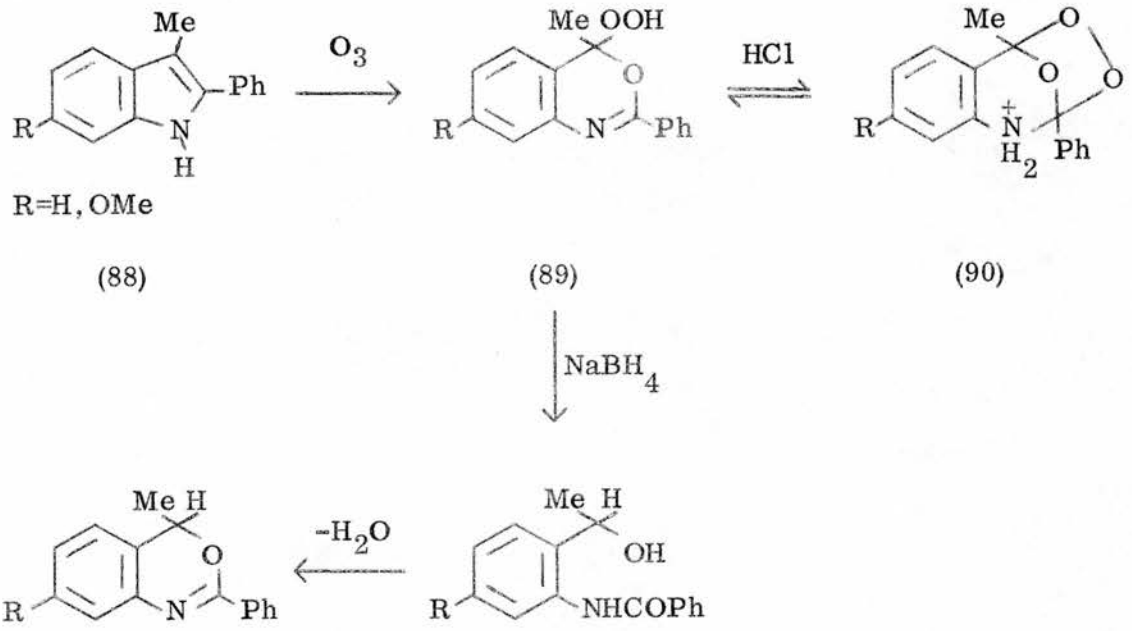
(86) R=Et or Pr^n ; R^1=Ph or p-C_6H_4Me

Among the products of the photolysis of crystalline 2-nitro-1,3,5-tri-tert-butylbenzene[97] followed by column chromatographic separation is 6,8-di-tert-butyl-4,4-dimethyl-3,1-benzoxazine (87) though this is produced in very small yield (2%).



(87)

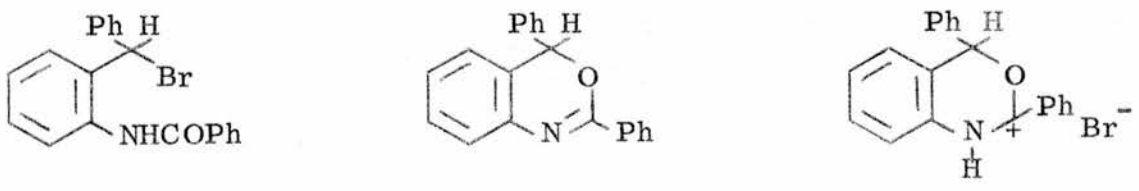
Benzoxazines may also be synthesised from their hydroperoxides as demonstrated by Patrick and Witkop in the early 1950's[98, 99]. They describe how the ozonolysis of substituted 2-phenylindoles (88) yield 2-phenyl-3,1-benzoxazine hydroperoxides (89) which were shown to be in



(88) (89) (90)

equilibrium with the ring tautomeric isozonides (90). Reduction followed by dehydration of the hydroperoxides yield the parent benzoxazines.

While trying to prepare the benzhydryl bromide (91) by passing

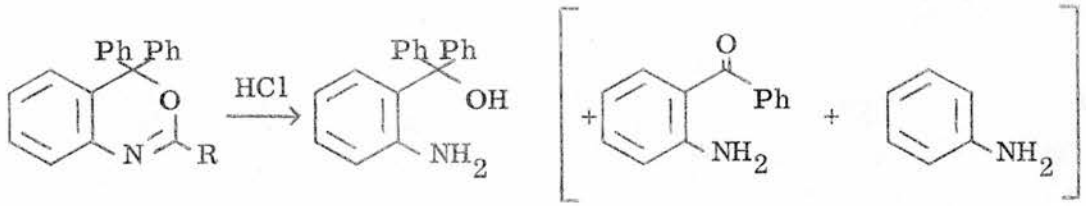


(91) (92) (93)

HBr through a benzene solution of o-benzamidobenzhydrol, Singh et al.[100] found the product to be the 3,1-benzoxazine (92) which probably formed via the cyclic intermediate (93).

Substituted 3,1-benzoxazines are basic oils or solids and are stable to alkali. They form salts with acids and most of these are hydrolysed by water to form acetylated ortho aminobenzyl alcohols. In one case[101], treatment with P_2S_5 resulted in the replacement of oxygen with sulphur.

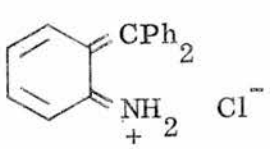
The chemistry of benzoxazines does not seem to have been very well documented but one or two general reactions are known. Hydrolysis by hot hydrochloric acid is reported[96] to result in the production of the ortho amino carbinol but with small amounts of ortho aminobenzophenone (in the case of a 4,4-diphenyl-3,1-benzoxazine (94)) and aniline also



(94)

produced. Hot hydrochloric acid or acetic acid causes ring opening when R = Me but when R = Et or n-Pr the ring opened product immediately cyclises again. The paper also shows that the benzophenone and aniline obtained in small quantitites from the acid hydrolysis of the benzoxazine are also obtained (in small quantities) on prolonged treatment of the carbinols with acid. It proposes that they result from intermediates (95, 96).

Alkylation of a benzoxazine (97) was attempted by Lednicer and



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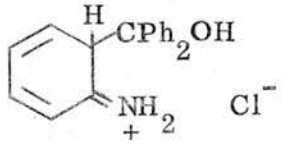
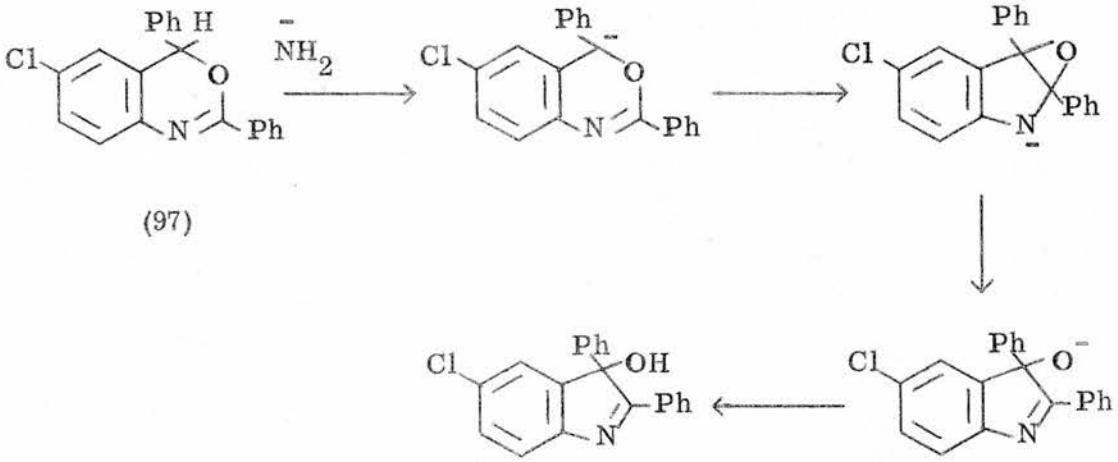


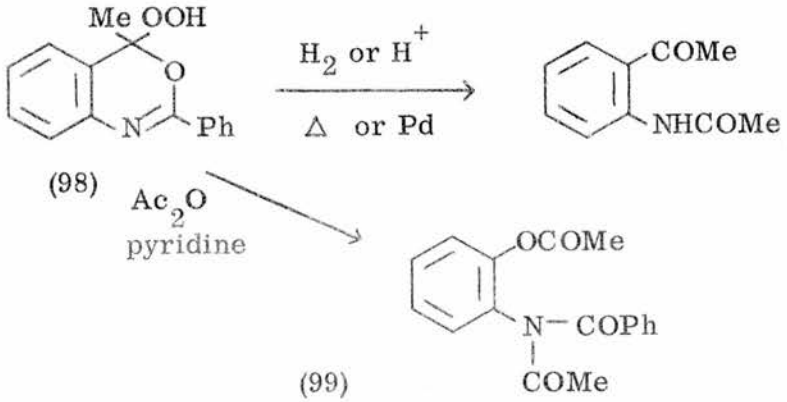
(96)

Emmert[102] using benzyl chloride and liquid ammonia. However the reaction was not successful.



(97)

Witkop and Patrick[98] have described reactions of the hydroperoxide (98) with acetic anhydride and pyridine and its reduction. The product from the acetic anhydride and pyridine reaction (99) had no precedent and

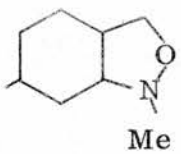


(98)

(99)

coul d not be obtained by any other synthesis.

The formation of a bicyclic tetrahydro-3,1-oxazine (101) photochemically has been studied in detail[103]. Irradiation of the fused



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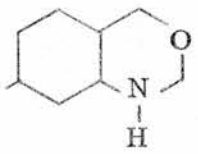

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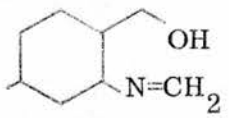
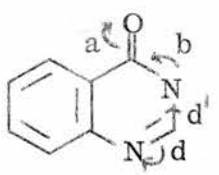


(102)

bicyclic isoxazolidine (100) in hexane with ultraviolet light gave a mixture from which (101) was isolated. It is believed to proceed through (102). The benzoxazine (101) can also be formed from (100) by heating with potassium tert-butoxide in DMSO.

It is interesting to note the difference in the electrophilicities of C-2 and C-4 in 3,1-benzoxazones and their diazo analogues (quinazolones). A study has been made of these[104] in which it was shown that in (103)



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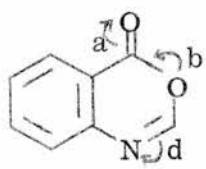


(104)

polarisation a is followed by b, and so process d assisted by the inductive d' is the only way in which an electrophilic centre may be developed in the molecule and so any nucleophilic attack takes place at C-2. However in the case of the benzoxazone (104), again a may be followed by b but because of the comparative difficulty in forming an O^+ type cation (cf. cations from ketones and ketimines are R_2C^+-OH and $R_2C=\overset{+}{N}H_2$),

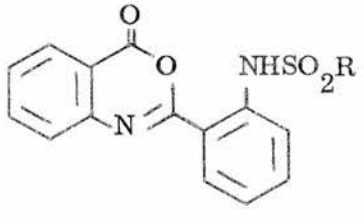
C-4 retains greater electrophilic properties than imparted to C-2 by process d.

In the late 1930's it was found[105] that among the substances which accelerate the vulcanisation of rubber are those which have four carbon atoms, one nitrogen atom, and one oxygen or sulphur atom, one of the carbons being between the oxygen (or sulphur) and the nitrogen and linked directly to a non-nuclear mercapto sulphur atom (105). It was found that

(105)

these could easily be made from 2-(2-aminophenyl)-propan-2-ol heated under reflux with carbon disulphide and potassium hydroxide.

Several molecules with 3,1-benzoxazine skeletons have been cited in the literature as having interesting properties. Compound (106) has

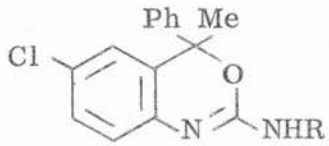


R = 2- or 4- MeC_6H_4-

(106)

been found to be an extremely intense green to yellow-green lumiphor[106].

When psychotropic 2-amino-4-methyl-4-phenyl-6-chloro-3,1-benzoxazines (107) were studied, it was shown[107] that these have weak toxicity and have sedative and anticonvulsive activity. When R = Et it



R = H, Et, Me, iso-Pr.

(107)

was found[108] that animal tests indicated the compound to be considered as a tranquilising drug with additional stimulating properties. The central depressant properties of 3,1-benzoxazine derivatives have also been studied[109].

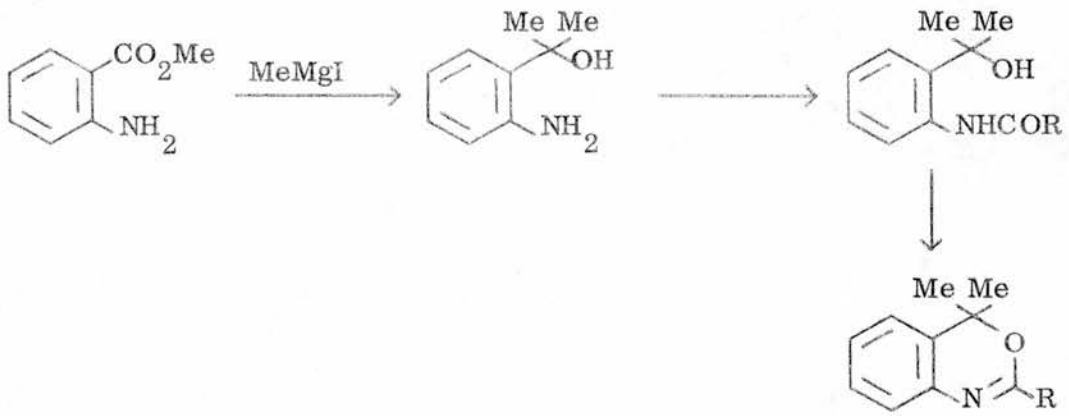
Results and Discussion

Preparation of 2,4,4-trimethyl-3,1-benzoxazines.

The preparation of these 3,1-benzoxazines can be partially generalised although it proved to be extremely difficult to synthesise two of them and these will be discussed separately.

The most general method is to react methyl magnesium iodide with methyl anthranilate to form 2-(2-aminophenyl)-propan-2-ol. This can then be acetylated and dehydrated to the benzoxazine as shown in Scheme 3. When substituents were required in position 6 or 7 of the product

Scheme 3

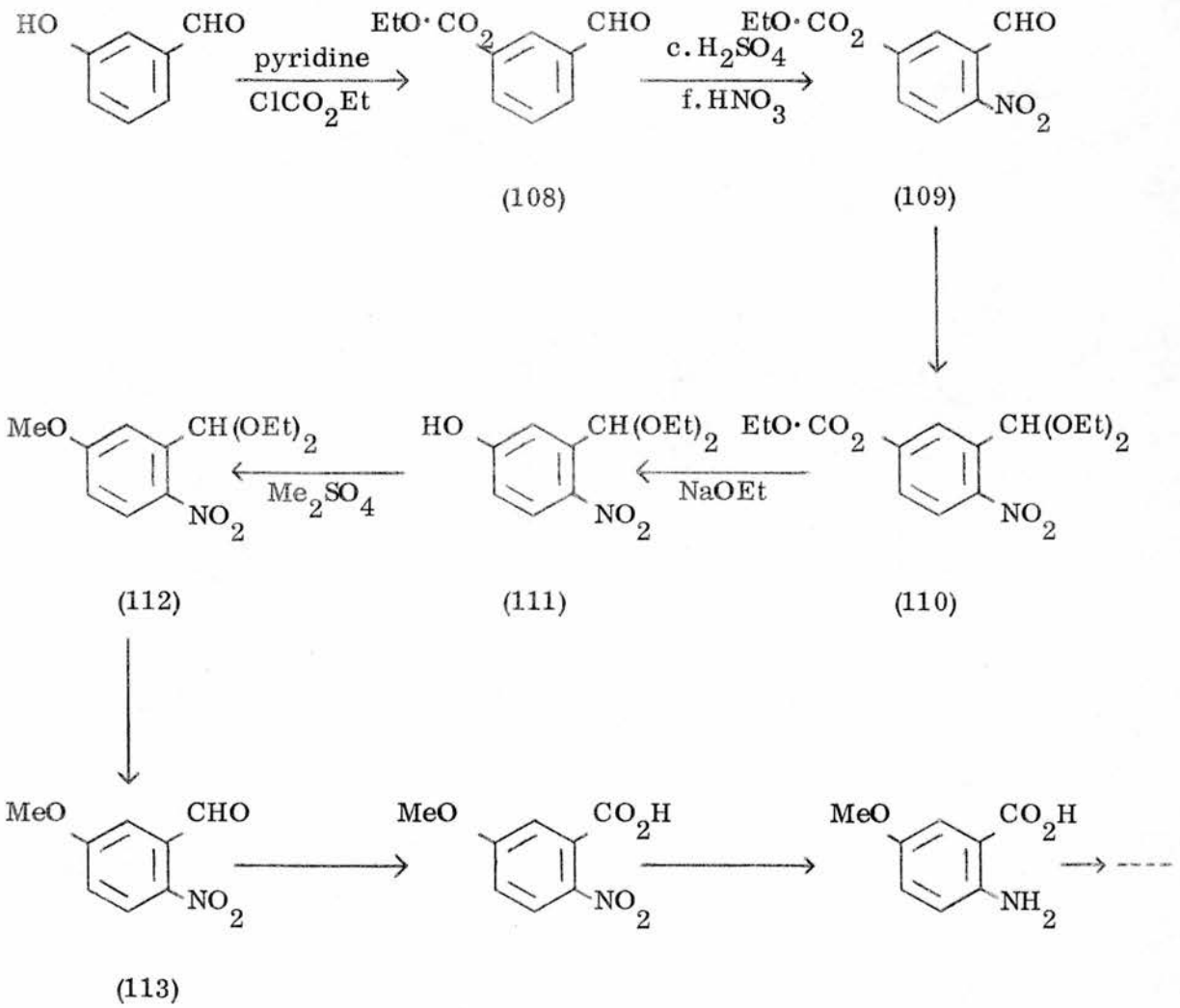


they were introduced into the methyl anthranilate (at position 5 or 4 respectively) with the exception of the 6-nitro benzoxazine. As was seen in Part I this was introduced when the amide was nitrated which also caused cyclisation.

The 6-methoxy compound proved to be the most difficult of the 6-substituted benzoxazines to synthesise. Initially Scheme 4 was followed[110-115]. When the o-ethyl carbonate of 3-hydroxybenzaldehyde

(108) was nitrated to yield (109) this was hydrolysed by base in an attempt to give 5-hydroxy-2-nitrobenzaldehyde but in fact very little of this was produced, possibly due to a Cannizarro type of reaction on the aldehyde.

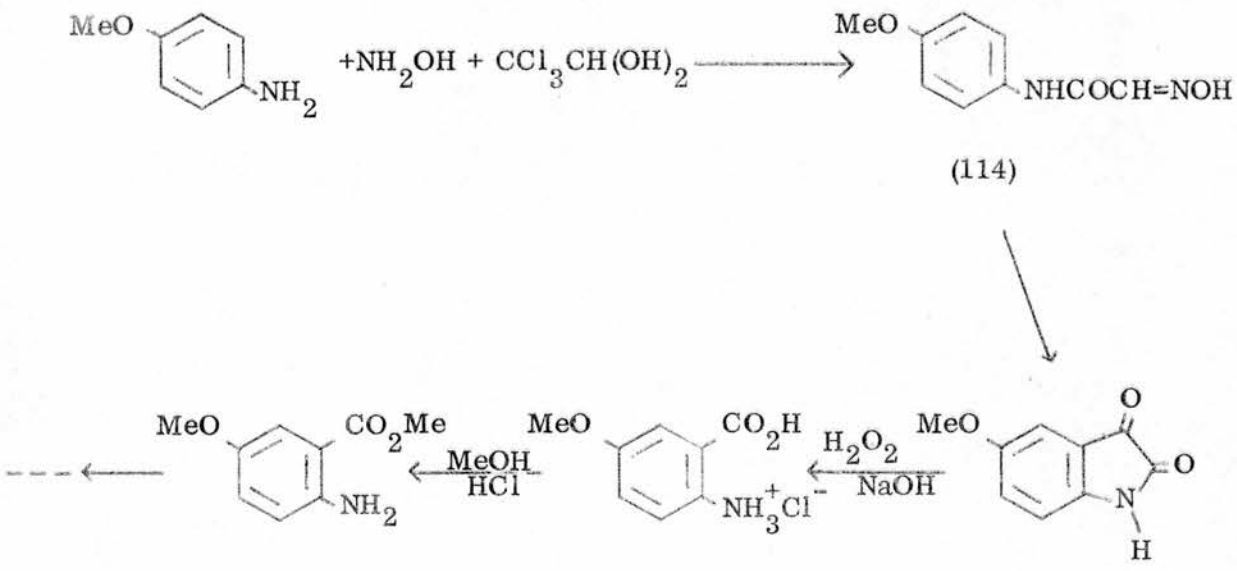
Scheme 4



Hence in subsequent attempts, the aldehyde was protected as the acetal. However even with this protection each step proceeded in much lower yield than claimed and the methylation, either as shown, or of 5-hydroxy-2-nitrobenzaldehyde was particularly poor. A second method of synthesis

was then tried (Scheme 5). Although this reaction scheme[116-119] appears to be fairly straightforward, many problems were encountered, notably the fact that the cyclisation of 4-methoxyisonitrosoacetanilide (114) to

Scheme 5



5-methoxyisatin (115) using "concentrated" H_2SO_4 [116] did not appear to work while use of 89% H_2SO_4 [119] did achieve cyclisation though in fairly low yield. Cyclisation using polyphosphoric acid was also tried[120] to see if the yield could be improved but it was not.

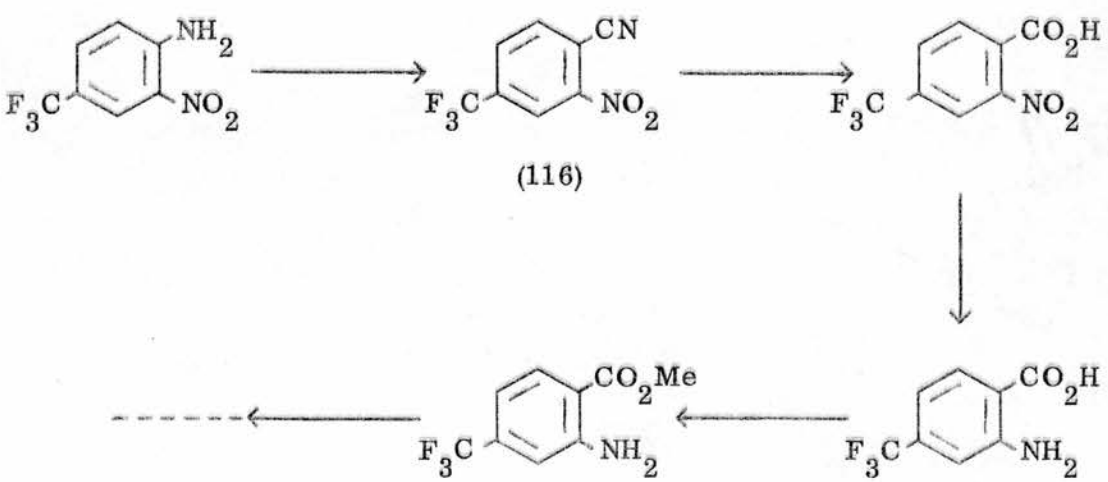
The synthesis of 2,4,4-trimethyl-7-trifluoromethyl-3,1-benzoxazine also proved to be rather difficult and is shown in Scheme 6. The yields were found to be much lower than claimed[121] notably in the isolation of the nitrile (116).

Hydrolysis

Having obtained 2,4,4-trimethyl-6-nitro-3,1-benzoxazine (54)

while attempting to make 2-(2-N-acetylamino-5-nitro-phenyl)-propene in

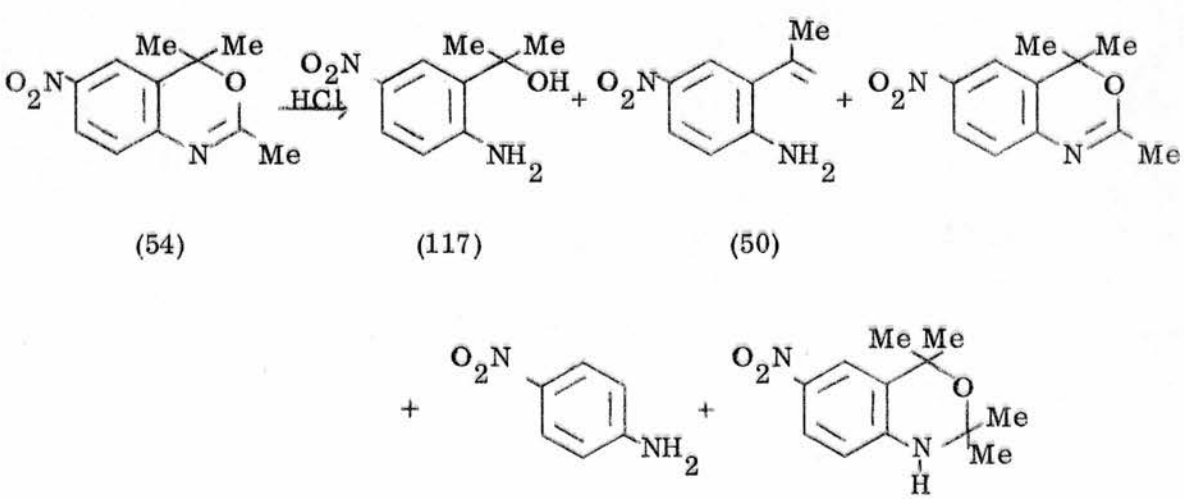
Scheme 6



(116)

order to prepare 2-(2-amino-5-nitrophenyl)-propene to use for cyclisation to a cinnoline (see Part I), the benzoxazine was hydrolysed in concentrated HCl in the expectation of forming 2-(2-aminophenyl)-propan-2-ol. However the product in fact proved to be a mixture (Scheme 7), the composition of

Scheme 7



(54) (117) (50)

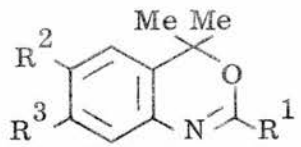
(118)

which changed with respect to time, but which contained carbinol (117), olefin (50), starting material and 4-nitroaniline. The hydrolysis was repeated for a period of 24 h, aliquots being taken at various time intervals and after being basified and extracted with ether, the composition of each mixture was determined by nmr. It was found that the concentration of benzoxazine fell steadily as the hydrolysis time proceeded, while the carbinol and olefin concentrations increased fairly rapidly to a maximum of about 35% and 30% respectively after 30 min and then decreased more slowly. The percentage of 4-nitroaniline in the mixture increased steadily until, after just 6 h, it was approaching 100%, which it had reached within 24 h.

By chance, some of the hydrolysis (30 min) mixture was left for almost 8 weeks in the acid solution. After working up this solution it was found that a further product was now present. This was found by accurate mass, analysis, and proton nmr to be 1,2-dihydro-2,2,4,4-tetramethyl-6-nitro-3,1-benzoxazine (118). This was confirmed by independent synthesis followed by mixed melting point.

Several series of 3,1-benzoxazines (Table 6) were then prepared and their hydrolysis products examined in this way (Table 7). It was found that after 24 h some of the benzoxazines also gave substituted quinolines as additional hydrolysis products.

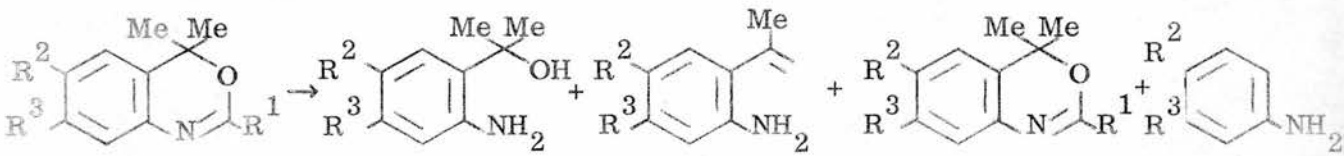
Table 6



Compound	R^1	R^2	R^3	mp/°C	bp/°C(mm)
119	Me	H	H		74-80 (0.3)
120	Me	Me	H		140-55 (0.2)
121	Me	MeO	H		125-40 (0.1)
122	Me	Br	H		90-100 (0.1)
54	Me	NO_2	H	85.5-86	
123	Me	H	Me		120-8 (0.1)
124	Me	H	Cl		118-25 (0.1)
125	Me	H	CF_3	29-31	135-45 (0.1)
126	Ph	H	H		160-75 (0.1)
127	p-$MeOC_6H_4$	H	H		180-95 (0.2)
128	p-ClC_6H_4	H	H	65	
129	p-$O_2NC_6H_4$	H	H	117-8	

At this stage it seems reasonable to propose the mechanism shown in Scheme 7. From this scheme it can be seen that two of the methods by which the hydrolysis could proceed is either through an amide intermediate (132) or by way of a benzyl ester (138). Evidence disfavours the route using the amide intermediate since it is known that the acid hydrolysis

Table 7 Hydrolysis products at various times for the reaction:



(i) (ii) (iii) (iv)

Compound	T/h	(i)	(ii)	(iii)	(iv)	Notes
119	0.5	34.1	14.2	50.6	1.0	
	2	37.2	21.2	20.6	20.8	
	4	36.2	17.8	11.2	34.8	
	6	20.0	12.3	6.4	61.3	
	24				100	a
120	0.5			100		
	2			100		
	4	43.7	29.6	9.2	17.5	
	6	40.0	24.7	4.0	31.3	
	24		trace		100	b
121	0.5	trace	trace	100		
	2	28.5	30.8	40.7		
	4	44.4	38.9	11.1		c
	6	41.5	48.0			c
	24					d
122	0.5	2.4		97.6		
	2	32.6	33.8	31.4	2.3	
	4	36.3	38.2	9.1	16.5	
	6	31.7	26.7	4.9	36.6	
	24	9.9	7.0		84.1	e

Table 7 (cont'd)

Compound	T/h	(i)	(ii)	(iii)	(iv)	Notes
54	0.5	36.5	28.5	9.5	25.6	
	2	21.9	17.0	7.6	53.5	
	4	3.6	5.9		90.6	
	6	1.3			98.7	
	24				100	
123	0.5	30.1	trace	60.2	9.7	
	2	28.7	trace		71.3	
	4				100	
	6				100	
	24				100	
124	0.5	4.9	8.5	81.4	5.2	
	2	20.8	17.2	7.1	54.9	
	4	5.8	4.2	1.5	88.5	
	6				100	
	24				100	
125	0.5	trace	trace	100		
	2	47.2	35.0	17.8		
	4	47.5	38.8	10.1	3.5	
	6	53.5	30.9	9.3	6.3	
	24	34.5	17.1		48.4	

Table 7 (cont'd)

Compound	T/h	(i)	(ii)	(iii)	(iv)	Notes
126	0.5			100		
	2	25.3	15.5	49.9	9.3	
	4	31.9	19.3	18.5	30.3	
	6	26.6	16.9	8.8	47.7	
	24				92.6	f
127	0.5			100		
	2	17.2	4.7	78.1		
	4	19.1	6.8	66.8	7.4	
	6	26.8	13.1	41.3	18.8	
	24	14.6		8.0	77.4	a
128	0.5			100		
	2	15.7	13.6	59.5	11.2	
	4	37.1	23.4	22.4	17.1	
	6	37.3	21.4	7.7	33.6	
	24				92.2	g
129	0.5	19.6		80.4		
	2	38.7	17.5	41.5	2.3	
	4	48.0	21.7	23.5	6.8	
	6	46.5	23.4	14.4	15.7	
	24	29.3	11.7	7.4	45.8	h

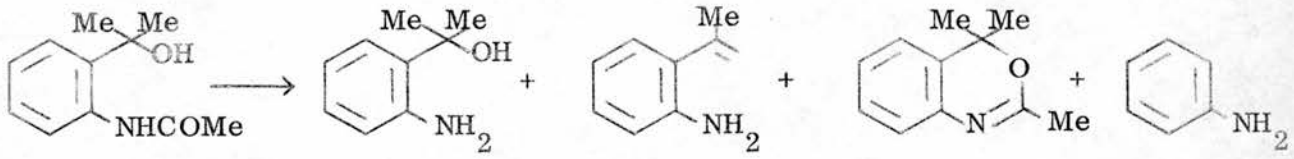
a. trace 2,4-dimethylquinoline b. trace 2,4,6-trimethylquinoline

c. 5-10% of unidentified material d. constituents not identified

e. trace 6-bromo-2,4-dimethylquinoline f. 7.4% 2,4-dimethylquinoline

g. 7.8% 2,4-dimethylquinoline h. 5.8% 2,4-dimethylquinoline

Table 8 Hydrolysis products of 2-(2-N-acetylaminophenyl)-propan-2-ol.



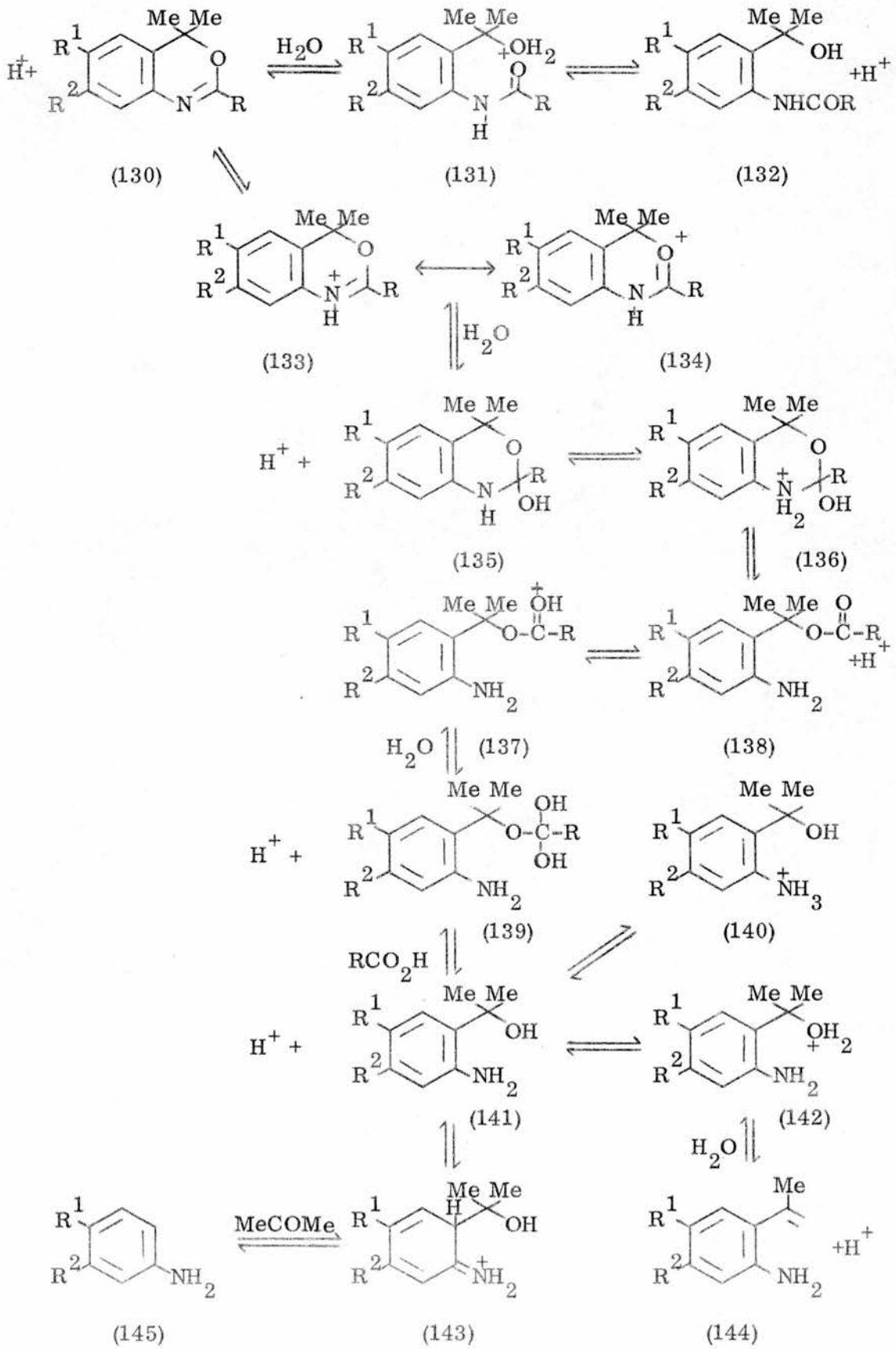
(i) (ii) (iii) (iv) (v)

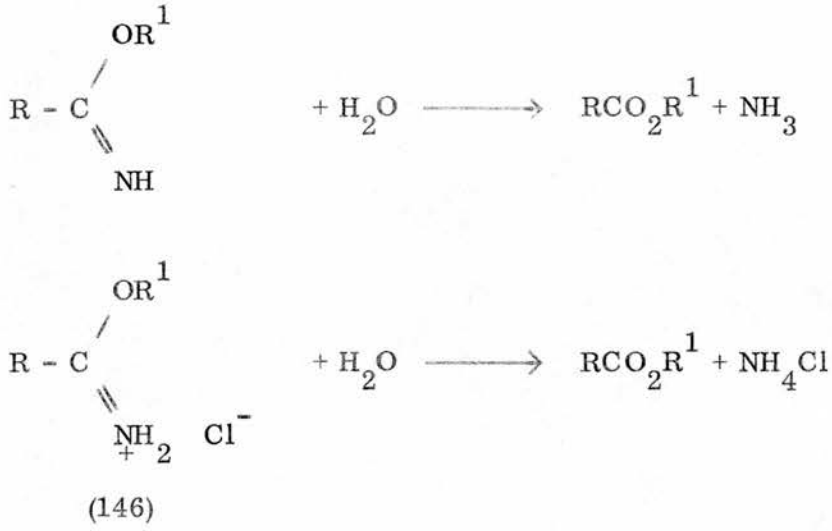
T[a]/h	(i)	(ii)	(iii)	(iv)	(v)	Notes
0.5		7.3	trace	92.7		
2		42.2	25.3	27.2	5.3	
4		35.8	20.0	10.3	33.9	
6		24.7	13.6	6.7	55.0	
24					94.8	b

a. for 10 min (iv) = 100% b. 5.2% 2,4-dimethylquinoline

of amides is slow[122] and also it is known that the decomposition of imidate esters (which the benzoxazine (130) can be considered as) by water undergoes two concurrent reactions[123]. The first is decomposition into a nitrile and an alcohol or phenol while the second is hydrolysis to an ordinary ester and ammonia. It is known that the first reaction is accelerated by bases while the second one is accelerated by acids. Hence the imido ester hydrochloride (146) (analogous to intermediate (133)) is normally decomposed by water to give the ordinary ester and ammonium chloride.

Scheme 7

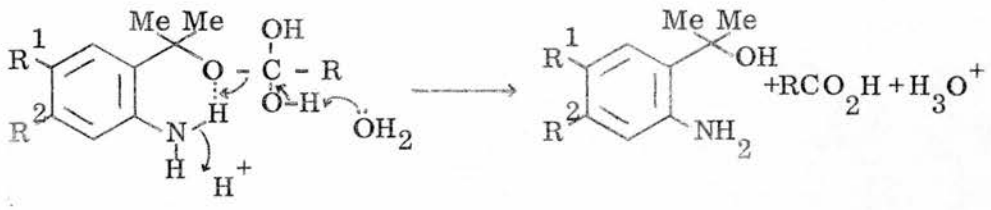




(146)

Since the presence of neither the ester nor the amide was ever detected in the nmr spectra of any of the products, the amide intermediate (132) (R = Me; $R^1 = R^2 = H$) was synthesised and treated with concentrated HCl under exactly the same hydrolysis conditions as those used for the benzoxazines. As can be seen from Table 8 all the amide had disappeared within the first 10 min of the reaction but instead of hydrolysing, cyclisation had taken place to give the benzoxazine (130) (R = Me; $R^1 = R^2 = H$). Hence it appears that the equilibria (130)⇌(131) and (131)⇌(132) both lie very much towards the left.

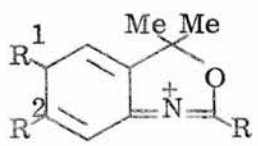
The fact that no benzyl ester was seen in the nmr is probably due to the fact its hydrolysis is very rapid because of neighbouring group participation by the ortho amino group. This could greatly increase the rate of the reaction since the (138)⇌(137) equilibrium could be pushed to the right as could the (137)⇌(139) equilibrium since hydrogen bonding between a nitrogen proton and the ester oxygen would make the carbonyl group more liable to protonate and the carbon more electron deficient and hence assist the attack by a water molecule to give (139). This could then be hydrolysed possibly by a concerted mechanism as shown.



(139)

The initial protonation of the benzoxazine could be of either nitrogen or oxygen but it is more likely to be of nitrogen since this can then be written as the resonance stabilised forms (133) and (134) whereas this cannot be done if the protonation of oxygen is proposed.

The relative rates of the 6-substituted benzoxazines may be explained by consideration of the substituent R^1 on intermediate (136). If R^1 is a good electron donating group, it increases the base strength of an amino group para to it and therefore the equilibrium (135)⇌(136) will lie to the right. It could be argued that the substituent will have a lesser effect on the equilibrium (130)⇌(133) because of the reduced possibility of delocalisation into the ring of the lone pair of electrons on nitrogen in (130) by a contribution from structures such as (147) in which there would be a six-membered ring with a linear C = N = C unit in it. Hence when R^1 is electron releasing then (136) is stabilised and so the (136)⇌(138) equilibrium probably lies towards the left. This means that a relatively low proportion of the reaction mixture proceeds as far as (138) and so degradation of (130) is slow



(147)

relative to the situation when R^1 is electron withdrawing. In this situation the equilibrium (135)⇌(136) will lie on the left since structure (136) is destabilised because protonation of (135) will not be fast as the lone pair on nitrogen will tend to be delocalised into the ring. However when (136) does form it will then cleave to give (138) very rapidly since the situation at (138) is similar to that at (135) in that the nitrogen is not protonated and hence this structure is stable relative to (136). Hence the (136)⇌(135) and (136)⇌(138) equilibria compete against each other causing the rapid formation of (138). As can be seen from Table 7 the initial hydrolysis of (130) when $R^1 = NO_2$ is very fast and so the tendency appears to be for (136) to form (138) at the expense of (135). This could be because the neighbouring group assisted hydrolysis of the benzyl ester (138) which has already been discussed would be assisted even more when R^1 is electron withdrawing due to stronger hydrogen bonding.

When R^1 is electron donating and (136) is stabilised it might be expected that species such as (136) should be present in the mixture before work up but since the work up of the hydrolysis mixtures involves quenching the reaction mixture by strong base then this would remove the proton and mean that the (135)⇌(136) equilibrium would be pushed completely to the left and (135) then revert to starting benzoxazine.

Having considered the situation at (136) the next rate determining stage appears to be at (141). If R^1 is electron withdrawing then the (141)⇌(140) equilibrium is not favoured since the electron withdrawing R^1 group reduces the electron density on the nitrogen of (141) and makes (140) less likely to form and, while structure (143) is also not favoured its

equilibrium with (145) is probably almost irreversible and so any (143) which does form is immediately removed and this then pulls the (141)⇌(143) equilibrium to the right. The (143)⇌(145) equilibrium is probably almost completely over to the right since a substituted aniline (145) in acetone and concentrated HCl did not give any carbinol (141) when heated under reflux. Hence for $R^1 = NO_2$ the initial removal of benzoxazine is very fast but there is quite a large build-up of carbinol since (141) is stable relative to both (140) and (143).

On the other hand when R^1 is electron donating then (140) is considerably stabilised relative to (141) and so the concentration of carbinol and, by proton transfer to (142) and then to (144), also olefin rise to very high levels and the rate of dealkylation is slowed down. In fact in the case of the 6-methoxy benzoxazine the existence of p - anisidine was not certain since although there was 5-10% of unidentified material after 4-6 h there was no p - anisidine identified after 24 h.

When the substituent R^2 is varied it appears that the initial decomposition of benzoxazine is slower than for the completely unsubstituted case but then (for R^2 = Me) the decomposition is extremely fast with only small amounts of carbinol and olefin forming. This can be rationalised by consideration of (141). Since (136) is not particularly affected by the 7-substituent, the (136)⇌(138) equilibrium will probably not lie very far to the right and so the initial decomposition of (130) is fairly slow. However when intermediate (141) is reached its equilibrium with (143) (and (140)) will probably be pulled very far to the right since the electron donating methyl group could stabilise the positive charge on nitrogen and since the

(143)⟹(145) equilibrium is almost irreversible the production of (143) is favoured at the expense of (140). However in the case of the CF_3 group structure (141) will be stable relative to either (140) or (143) because of its inductive effect and so the concentration of carbinol builds up to a large value (over 50% after 6 h).

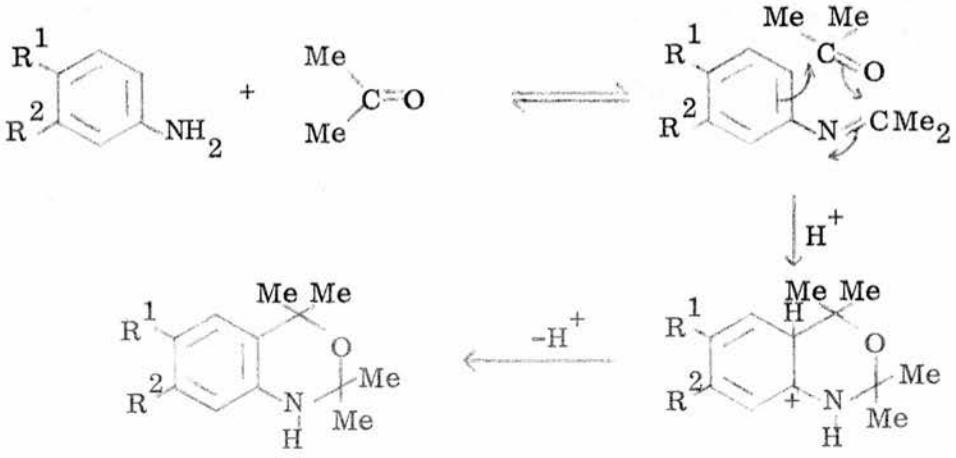
Substitution of a phenyl or substituted phenyl group at R in place of methyl slows down the initial decomposition of the benzoxazine (in each case over 80% of the mixture is benzoxazine after 30 min) as might be expected if structures (133) and (134) are considered. In both cases C-2 is electron deficient and so the nucleophilic attack can take place. When R = Me then this deficiency tends to be overcome and the formal positive charge delocalised giving (133) and (134) relatively more stability and hence these species exist longer and have a greater opportunity to be attacked by a water molecule. However if R = Ph the electron deficiency on C-2 is increased and the positive charge cannot be delocalised and so species (133) and (134) are even more unstable and so their equilibria with (130) will be pushed towards the right and hence there is less chance of attack by water. It is also known[124] that when the imidate ester (146) has R = Ar greater resistance to hydrolysis is noted.

The relative rates of the substituted phenyl groups on position 2 are difficult to rationalise. Although there is not much difference between them (and none would be expected since this group is lost as the corresponding benzoic acid) it appears that total production of (145) after 24h is greatest in the case of phenyl and 4-chlorophenyl and lowest in the case of 4-nitrophenyl. The slowness of the 4-nitrophenyl group could be caused by

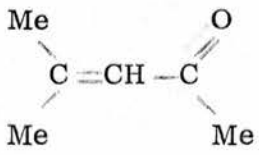
an extension of the argument used above that an electron withdrawing group at position 2 slows down the reaction, although this particular compound is the only one which hydrolyses at all during the first 30 min. One factor which could cause the variations is the fact that in some cases the benzoic acid was precipitated in the reaction mixture as it was produced (R = C_6H_4Cl and $C_6H_4NO_2$) although this seems unlikely as the strength of the concentrated HCl would not be expected to be affected by the presence of a few mmoles of a benzoic acid.

It was found that when the reaction mixture (R = Me; $R^1 = NO_2$; R^2 = H) was left for several weeks that a small amount of 1,2-dihydro-2,2,4,4-tetramethyl-6-nitro-3,1-benzoxazine (118) was produced. Since the nitro compound dealkylates very fast it seems likely that most of the reaction mixture was in the form of protonated aniline and as it has been shown that the carbinol is not produced when aniline and acetone in concentrated HCl are heated under reflux, then it seems probable that the dihydro-3,1-benzoxazine forms by successive condensation of 2 moles of acetone to give first the Schiff base and then the benzoxazine as shown in Scheme 8.

Scheme 8



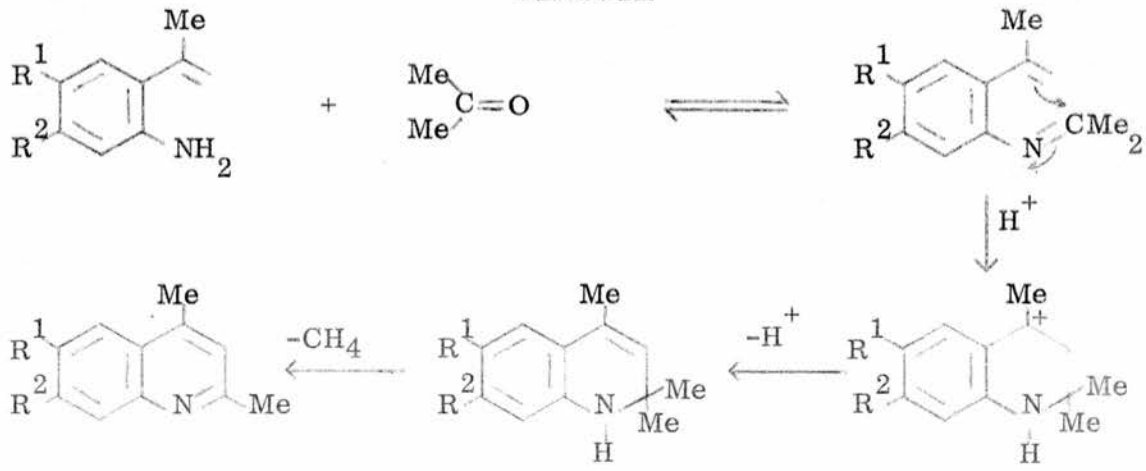
Although it was found that no carbinol was formed when acetone and 4-nitroaniline were heated under reflux with concentrated HCl, it was found that after 6 h ca. 4% yield of 1,2-dihydro-2,2,4,4-tetramethyl-6-nitro-3,1-benzoxazine (118) was obtained from the mixture. Its existence was confirmed by its accurate mass, 236.1167. ($C_{12}H_{16}N_2O_3$ requires 236.1161). To show whether this yield could be increased by prolonged hydrolysis the reflux time was increased to 65 h and it was found that although there was a trace of the dihydro-3,1-benzoxazine another product, mesityl oxide (148) was shown to be present to the extent of ca. 23%. This is formed by the acid catalysed condensation of acetone with itself.



(148)

The presence of substituted quinolines can be accounted for by condensation of one mole of acetone with the olefin (144) to form the Schiff base followed by cyclisation to give the appropriately substituted 1,2-dihydro-2,2,4-trimethylquinoline which are known[125-127] to lose methane to give the corresponding 2,4-dimethyl-quinolines (Scheme 9).

Scheme 9



Saturated 3,1-benzoxazines

The actual structure of the saturated 1,2-dihydro-2,2,4,4-tetramethyl-6-nitro-3,1-benzoxazine (118) was not easy to prove. As can be seen there is the possibility of tautomeric equilibrium between it and the

(118) (149)

open chain structure (149). The infrared spectrum shows an absorption at 3314 cm^{-1} which could be either an -OH or -NH stretching frequency although it is much sharper than is usual for an -OH stretch. Mass spectrometry confirms its empirical formula from its accurate mass, 236.1151. ($C_{12}H_{16}N_2O_3$ requires 236.1161). Proton nmr cannot resolve the problem since the only significant difference in the two structures for nmr is the OH in one case and the NH in the other, both of which occur simply as broad singlets. In this case the protons ortho to the nitro group show up at 7.90 δ while the meta proton, split by the adjacent proton appears at 6.69 δ. Underneath this signal the NH (or OH) is partially hidden. The geminal dimethyl protons at position 2 appear as a singlet at 1.44 δ while those at position 4 appear at 1.57 δ. The fact that both sets of geminal dimethyl groups appear as singlets seems at first sight to favour the open chain tautomer (149) since in that case there should be free rotation around each ring - carbon bond, although the groups attached to the N=C might have been expected to be slightly different due to the asymmetry

caused by the lone pair on the nitrogen, while in the cyclic sturcture the methyl groups would probably be expected to be non-equivalent. Hence the spectrum was also recorded at -60^{o} to show whether the methyl groups could be slowed down in the open chain tautomer or if each pair of geminal dimethyl groups in the ring tautomer could be rendered non-equivalent. However the low temperature caused no change apart from pulling the NH (or OH) proton out from underneath the aromatic signals.

The best evidence was from a combination of quantitative ultra-violet spectroscopy and proton and ^{13}C nmr. Several Schiff bases were synthesised for comparison, some of which could cyclise and some of which could not. In each case the amine was condensed with the carbonyl compound under dehydrating conditions (Tables 9, 10). In the case of (156) no condensation took place while in the case of (155) when acetone was condensed with o-toluidine, 1,2-dihydro-2,2,4,8-tetramethylquinoline was isolated as had been reported previously[128,129].

The fact that more difficulty was encountered when trying to synthesise the open chain compounds suggests that if cyclisation can occur it will make the reaction easier. In the open chain form of (150) and (153), the benzylic proton would occur below 8 δ. In fact no such signal was observed and this in itself is good evidence for the cyclic structures. The nmr of (150) shows the geminal dimethyl protons as separate singlets, while in (151) both sets of geminal dimethyl groups are singlets. Similarly the methylene protons in (152) are equivalent while in (153) they are no longer indentical and are coupled to each other giving an AB signal pattern. This is in agreement with the results for 1,3-benzodioxans[130] and is

Table 9

Compound	R^1	R^2	R^3	R^4	mp/°C
150	Me	Me	Ph	H	73-3.5
151	Me	Me	Me	Me	65-6
152	H	H	Me	Me	117-9[a]
153	H	H	Ph	H	119-20[b]

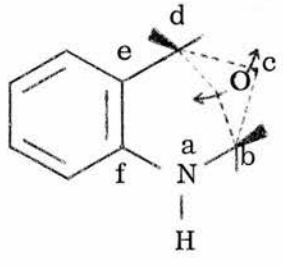
a. Lit.[90] 123 b. Lit.[86] 121-4

Table 10

Compound	R^1	R^2	bp/°C
154	H	Ph	192 (29 mm)[a]
155	Me	Me	b
156	Et	Et	c

a. Lit.[144] 307 (775 mm) b. product found to be 1,2-dihydro-2,2,4,8-tetramethylquinoline bp 78-80 (0.3 mm) [Lit.[128] 131 (6mm)] c. this condensation did not take place

consistent with having the hetero-ring rigid and planar around 5 atoms (4 bonds), or all 6 atoms. As it seems very unlikely that a ring containing both oxygen and nitrogen could be totally planar, it is much more likely that the ring is rigid[131,132] and planar from atom b round to atom d through a, f, and e and that c - d and c - b bonds can flex up and down so that the oxygen atom is below the plane of the ring half the time and above it the other half, thus creating a symmetrical environment with respect to substituents on b or d. When b is asymmetrically substituted [(150), (153)] then the geminal dimethyl groups on d (150) or the methylene protons (153) are no longer equivalent. This model necessitates that the nitrogen atom is sp^2 hydbridised so that the N-H bond is also in the plane of the molecule and the lone pair is in a p orbital perpendicular to the plane.



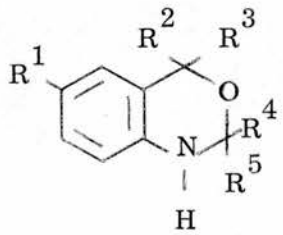
The ultraviolet spectrum of (154), which is definitely not cyclic should resemble those of (150) - (153) if they have the open chain structure. As can be seen from Table 11 it is completely different from

Table 11

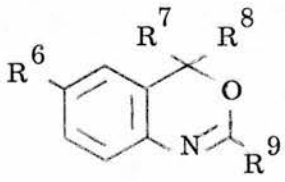
Compound	λ_1/nm	ϵ_1	λ_2/nm	ϵ_2
150	240	9290	289	1840
151	239	7040	291	1645
152	244	7830	295	2020
153	245	8750	291	1950
154	260	15,280	319	5280

that of compounds (150) - (153) which is further proof of their cyclic structure.

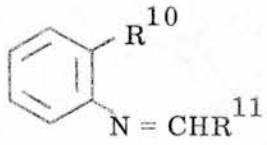
Table 12



(i)



(ii)



(iii)

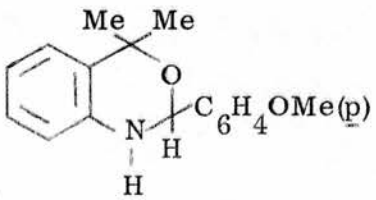
Compound	R	C_2/ppm
118	$R^1 = NO_2$; $R^2 = R^3 = R^4 = R^5 = Me$	82.6
152	$R^1 = R^2 = R^3 = H$; $R^4 = R^5 = Me$	81.8
153	$R^1 = R^2 = R^3 = R^4 = H$; $R^5 = Ph$	85.1
157	$R^1 = H$; $R^2 = \underline{t}$-Bu; $R^3 = R^4 = R^5 = Me$	81.6
54	$R^6 = NO_2$; $R^7 = R^8 = R^9 = Me$	163.5
119	$R^6 = H$; $R^7 = R^8 = R^9 = Me$	159.9
154	$R^{10} = Me$; $R^{11} = Ph$	159.1

^{13}C nmr probably provides the best evidence for the cyclic structure. As can be seen from Table 12, in structures of the type (ii) and (iii), C-2 has a shift of the order of 160 ppm downfield from TMS. Now if the unknown structure is of the open chain type it would have a N=C-2 bond and so the chemical shift of C-2 would be expected to be of this order. However the C-2 shift is almost constant, being 83 ppm $\pm$2

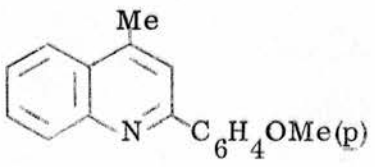
downfield from TMS and consequently the nitrogen is almost certainly not unsaturated which favours the cyclic structure (i).

Hence the proton nmr, ultraviolet spectra, and most especially the ^{13}C nmr provide overwhelming evidence in favour of the saturated 3,1-benzoxazine type structure (i) for these compounds.

The hydrolysis of one of these saturated benzoxazines (158) was studied under the same conditions which were used for the unsaturated compounds. It was found that after only 30 min there was no benzoxazine left in the mixture. Hence the nmr was recorded 10 min after the start



(158)

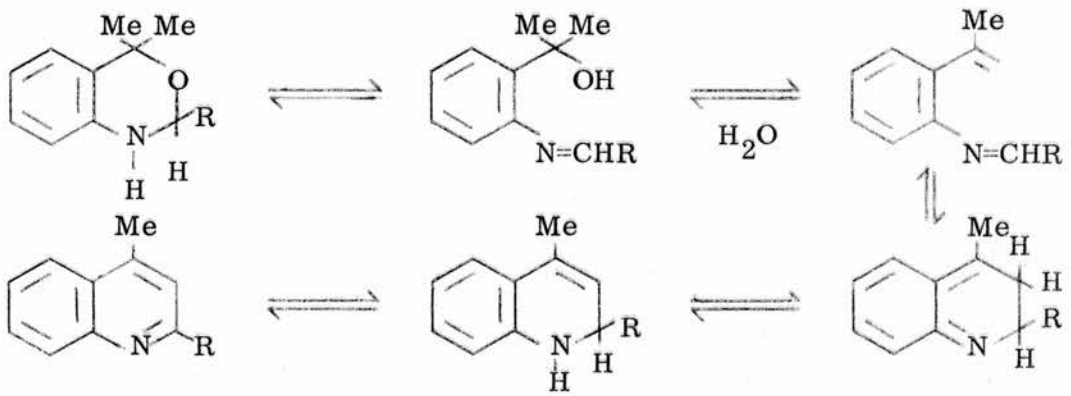


(159)

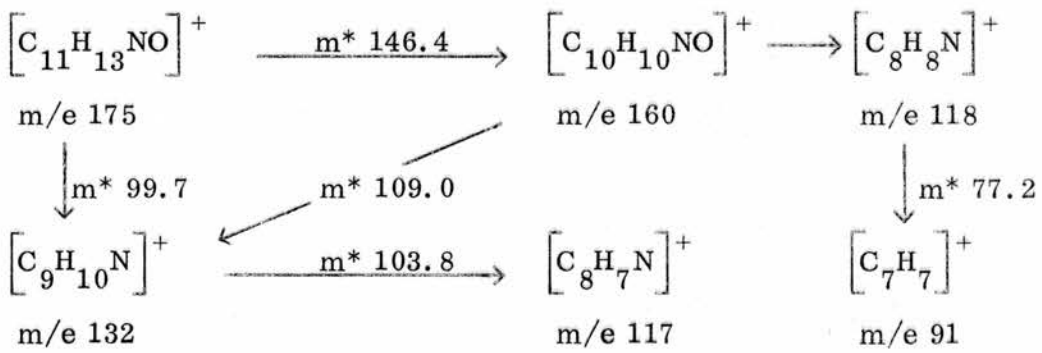
and this showed a similar pattern to the unsaturated benzoxazine hydrolysis, with signals corresponding to the carbinol and the olefin. After 30 min however the nmr was very complex with tlc showing the presence of three components. Although each of these was not successfully separated one of them was identified as 2-(4-methoxyphenyl)-4-methylquinoline (159) by its accurate mass, 249.1154. ($C_{17}H_{15}NO$ requires 249.1154). This is probably formed as shown in Scheme 10.

The mass spectral fragmentation pattern of the substituted 3,1-benzoxazines is shown in Scheme 11 using 2,4,4-trimethyl-3,1-benzoxazine as being a typical member of the series.

Scheme 10



Scheme 11



All of the processes shown were confirmed by the presence of metastable peaks and by high resolution measurements. Comparison of the spectra below m/e 131 of all the substituted benzoxazines (54), (119) - (129) show them to be essentially identical. It appears that substitution in position 7 instead of 6 makes no difference as the fragmentation of 2,4,4,6-tetramethyl-3,1-benzoxazine and 2,4,4,7-tetramethyl-3,1-benzoxazine are virtually identical.

Experimental

The synthesis of 2-(2-aminophenyl)-propan-2-ol, 2-(2-N-acetyl-aminophenyl)-propan-2-ol (52), 2,4,4-trimethyl-6-nitro-3,1-benzoxazine (54), methyl 5-bromoanthranilate, 2-(2-amino-5-bromophenyl)-propan-2-ol, methyl 5-methylanthranilate, and 2-(2-amino-5-methylphenyl)-propan-2-ol have been described in Part I.

2,4,4-Trimethyl-3,1-benzoxazine (119)

2-(2-N-Acetylaminophenyl)-propan-2-ol (10.0 g; 51.8 mmole) was heated under reflux with excess acetic anhydride (30 ml; 32.4 g; 317.6 mmole) for 15 min. The solution was allowed to cool and then the acetic anhydride was distilled off under reduced pressure (bp 40° (15 mm)). The residual oil was heated under reflux with NaOH solution (30 ml x 5M) for 30 min and then the mixture extracted with ether (2 x 50 ml). After the combined extracts had been dried over anhydrous Na_2SO_4, the solvent was evaporated under reduced pressure. The crude product was then purified by distillation. Yield: 6.71 g (74%). It had bp 74-80° (0.3 mm); λ_{max}^{133} 260 nm (ϵ 5970); ν_{max} 1640 and 1605 cm^{-1}; δ ($CDCl_3$) 7.29 - 6.95 (4H, m), 2.08 (3H, s), and 1.58 (6H, s); m/e 175 (27%), 160 (100), 133 (14), 132 (46), 118 (15), 117 (12), 91 (17), and 43 (21). (Found: C, 75.63; H, 7.49; N, 7.86. $C_{11}H_{13}NO$ requires C, 75.43; H, 7.43; N, 8.00%).

2-(2-N-Acetylamino-5-methylphenyl)-propan-2-ol

2-(2-Amino-5-methylphenyl)-propan-2-ol (6.60 g; 40.0 mmole) was treated with acetic anhydride (5.02 ml; 5.40 g; 52.9 mmole) and sodium

acetate (6.54 g; 79.7 mmole) by the method used to synthesise 2-(2-N-acetylaminophenyl)-propan-2-ol. The product was recrystallised from methanol. Yield: 6.35 g (77%). It had mp 139-40°; λ_{max} 247 nm (ϵ 13,500); ν_{max} 3360 (br), 3290 (br), and 1668 cm^{-1}; δ ($CDCl_3$) 9.97 (1H, br), 8.01 (1H, d), 6.99 (2H, m), 3.66 (1H, br), 2.26 (3H, s), 1.99 (3H, s), and 1.60 (6H, s); m/e 207 (29%), 174 (15), 150 (36), 146 (100), 124 (48), 106 (20), and 43 (95). (Found: C, 69.77; H, 8.51; N, 6.50. $C_{12}H_{17}NO_2$ requires C, 69.57; H, 8.21; N, 6.76%).

2,4,4,6-Tetramethyl-3,1-benzoxazine (120)

2-(2-N-Acetylamino-5-methylphenyl)-propan-2-ol (4.14 g; 20.0 mmole) was dissolved in concentrated H_2SO_4 (25 ml) and warmed on a steambath for 8 min[99]. The mixture was then poured on to ice, basified with concentrated ammonia and extracted into ether (3 x 50 ml). The combined ether extracts were dried and then evaporated to yield the crude product which was purified by distillation. Yield: 3.40 g (90%). It had bp 140-55° (0.2 mm); λ_{max} 262 nm (ϵ 10,320); ν_{max} 1652, 1641, and 1612 cm^{-1}; δ ($CDCl_3$) 7.00 (2H, m), 6.85 (1H, br), 2.30 (3H, s), 2.07 (3H, s), and 1.57 (6H, s); m/e 189 (31%), 174 (100), 146 (40), 132 (14), 131 (14), 117 (6), 91 (6), and 43 (44). (Found: C, 76.21; H, 8.16; N, 7.18. $C_{12}H_{15}NO$ requires C, 76.19; H, 7.94; N, 7.41%).

3-Carbethoxybenzaldehyde (108)

A solution of ethyl chloroformate (1.09 g; 10.0 mmole) in dry benzene (20 ml) was slowly added to a stirred solution of 3-hydroxybenzaldehyde (1.22 g; 10.0 mmole) in dry pyridine (0.8 ml; 790 mg; 10.0 mmole)

and dry benzene (25 ml). After stirring for ca. 10 min an oil formed which then crystallised. This solid pyridine hydrochloride was filtered off and the filtrate washed with dilute HCl before drying and evaporation of the solvent. The product was not distilled due to possible decomposition. Yield: 1.75 g (90%). It had ν_{max} 1752 and 1695 cm^{-1}; δ ($CDCl_3$) 9.97 (1H, s), 7.80 - 7.30 (4H, m), 4.32 (2H, q), and 1.38 (3H, t); m/e 194 (11%), 122 (99), 121 (100), 93 (24), and 65 (27).

5-Carbethoxy-2-nitrobenzaldehyde (109)

3-Carbethoxybenzaldehyde (3.88 g; 19.9 mmole) was dropped into a stirred mixture of concentrated H_2SO_4 (30 ml) and fuming HNO_3 (6 ml) at ca. -5^{o}. The mixture was stirred for 1.5 h and then poured on to ice (100 g) and a yellow solid precipitated on scratching and after being filtered off and washed with cold water, was recrystallised from aqueous ethanol. Yield: 4.08 g (85%). It had mp 58-60° [Lit.[115] 63-5°]; ν_{max} 1756, 1687, 1585, and 1365 cm^{-1}; δ ($CDCl_3$) 10.41 (1H, s), 8.17 (1H, d), 7.72 (1H, d), 7.57 (1H, dd), 4.36 (2H, q), and 1.40 (3H, t); m/e 239 (absent), 168 (100%), 122 (31), 109 (14), 92 (29), 76 (54), and 75 (57).

5-Carbethoxy-2-nitrobenzaldehyde diethyl acetal (110)

5-Carbethoxy-2-nitrobenzaldehyde (2.39 g; 10.0 mmole) in ethanol (50 ml) was heated under reflux with toluene p - sulphonic acid (5 mg) added as dehydrating agent. After 1.5 h, the mixture was cooled and allowed to stand overnight before removal of the solvent. Yield: 2.71 g (87%). It had ν_{max} 1768, 1532, and 1370 cm^{-1}; δ ($CDCl_3$) 7.85 (1H, d), 7.64 (1H, d), 7.30 (1H, dd), 6.04 (1H, s), 4.34 (2H, q), 3.80 - 3.36

(4H, m), 1.39 (3H, t), and 1.22 (6H, t).

5-Methoxy-2-nitrobenzaldehyde (113)

5-Carbethoxy-2-nitrobenzaldehyde diethyl acetal (3.13 g; 10.0 mmole) in NaOEt solution (20 ml x 1.5M; 30 mmole) was heated under reflux for 10 min. To this solution was then added NaOH solution (40 ml x 1.5M; 60 mmole) followed by Me_2SO_4 (2.86 ml; 3.78 g; 30 mmole). Having ensured that the solution was basic, the mixture was heated under reflux for 30 min. The solution was then acidified with dilute HCl and water (200 ml) was added. The solution was heated under reflux for 1.5 h and then extracted into ether (2 x 200 ml). The combined extracts were then dried and evaporated. Although this experiment was repeated several times, in each case the product was 5-hydroxy-2-nitrobenzaldehyde, 1.51 g (90%). This was then methylated[134,135]. 5-Hydroxy-2-nitrobenzaldehyde (1.00 g; 6.0 mmole) in water (2.5 ml) was heated on a steambath. NaOH solution (2.0 ml x 5M) was heated to ca. 100° and added in one portion. The heating was continued and Me_2SO_4 (0.78 ml; 1.04 g; 8.25 mmole) was added slowly over ca. 20 min and then after a further 15 min Me_2SO_4 (0.16 ml; 210 mg; 1.67 mmole) was added at the same rate as before. The mixture was now slightly acidic and after heating for a further 10 min the mixture was made slightly basic by the addition of NaOH solution (0.33 ml x 5 M) and then a further portion of Me_2SO_4 (0.16 ml; 210 mg; 1.67 mmole) was added. This alternate addition of NaOH solution and Me_2SO_4 was repeated twice so that a total of 14.93 mmole Me_2SO_4 had been added. 15 min after the last addition of Me_2SO_4 the mixture was made alkaline by the addition of NaOH

solution (0.75 ml x 5 M). The solution was then cooled and extracted with ether (3 x 60 ml). The combined extracts were then dried and evaporated. The crude product was recrystallised from ethanol. Yield: 170 mg (16%).

As these yields were too poor to enable methyl 5-methoxyanthranilate to be synthesised this way, the procedure was abandoned at this point.

4-Methoxyisonitrosoacetanilide[116,119,120,136] (114)

To chloral hydrate (90.0 g; 540 mmole) and water (1200 ml) were added in turn hydrated Na_2SO_4 (1300 g), p-anisidine (61.5 g; 500 mmole) in water (300 ml) to which concentrated HCl (43.0 g; 520 mmole) had been added, and a solution of hydroxylamine hydrochloride (110.0 g; 1.58 mole) in water (500 ml). The mixture was warmed until it was heating under reflux (taking as close to 60 min as possible) and then heated under reflux for 2 min and allowed to cool. The precipitate was filtered off and recrystallised from aqueous ethanol. Yield: 77.67 g (80%). It had mp 189-90° [Lit.[116] 181-2°]; ν_{max} 3270 (br), 1658, and 1612 cm^{-1}; δ (d_6-DMSO) 10.0 (1H, br), 7.66 (1H, s), 7.61 (2H, d), 6.90 (2H, d), 3.73 (3H, s), and 3.47 (1H, br); m/e 194 (43%), 149 (59), 134 (27), 123 (28), 122 (100), 108 (50), and 44 (51).

5-Methoxyisatin (115)

H_2SO_4 (755 g x 89% (w/w)) was warmed to 75-8° and to this was added 4-methoxyisonitrosoacetanilide (111.0 g; 570 mmole) small portions at a time with stirring. After the addition, the temperature was maintained for 5 min and then the solution was cooled and poured on to ice (ca. 2500 g). The product was filtered off as a dark red sludge and recrystallised three times from glacial acetic acid. Yield: 28.3 g (28%). It had mp 196-9°

[Lit.[116] 200-1°]; ν_{max} 3180 (br), 1750, 1732, and 1640 cm^{-1}; δ (d_6-DMSO) 7.56 (1H, d), 6.97 (1H, dd), 6.82 (1H, d), 4.00 (1H, br), and 3.73 (3H, s); m/e 177 (2%), 133 (58), 105 (96), 78 (56), and 52 (100).

Methyl 5-methoxyanthranilate[116-118]

5-Methoxyisatin (13.6 g; 77.0 mmole) was dissolved in NaOH solution (136.7 ml x 1.25 M) and oxidised by the dropwise addition of 30% H_2O_2 solution (20.4 ml) until the reaction cooled down (ca. 60 min). The solution was made acidic with dilute HCl and filtered from any insoluble residue. The filtrate was evaporated to dryness and then the residue extracted into hot ethanol (80 ml). After cooling the extract the product was precipitated by the addition of ether. Yield: 6.46 g (41%). 5-Methoxyanthranilic acid hydrochloride (2.02 g; 9.93 mmole) in saturated methanolic HCl (100 ml) was heated under reflux for 1.5 h after which the methanol was evaporated and the residue dissolved in water and basified with saturated $NaHCO_3$ solution. It was then extracted with ether (2 x 200 ml) and then the combined extracts were dried and evaporated and the product recrystallised from water. Yield: 1.22 g (67%). It had mp 34-6°; ν_{max} 3495, 3390, and 1695 cm^{-1}; δ ($CDCl_3$) 7.35 (1H, d), 6.94 (1H, dd), 6.61 (1H, d), 5.38 (2H, br), 3.85 (3H, s), and 3.74 (3H, s); m/e 181 (100%), 166 (44), 150 (25), 149 (61), 134 (85), and 106 (73).

2-(2-Amino-5-methoxyphenyl)-propan-2-ol

The method was similar to that used to prepare 2-(2-aminophenyl)-propan-2-ol using methyl iodide (17.0 g; 119.7 mmole), magnesium

(3.50 g; 144.0 mmole) and methyl 5-methoxyanthranilate (3.90 g; 21.6 mmole). Yield (crude): 3.79 g (97%). It had bp 175-90° (0.1 mm); λ_{max} 238 (ϵ 7500) and 303 nm (2540); ν_{max} 3450 (br) and 3370 (br) cm^{-1}; δ ($CDCl_3$) 6.72-6.46 (3H, m), 3.86 (3H, br), 3.69 (3H, s), and 1.58 (6H, s); m/e 181 (25%), 163 (40), 151 (54), 148 (69), 120 (37), 119 (100), and 43 (36). (Found: C, 66.36; H, 8.36; N, 7.68. $C_{10}H_{15}NO_2$ requires C, 66.30; H, 8.29; N, 7.73%).

2-(2-N-Acetylamino-5-methoxyphenyl)-propan-2-ol

Acetylation of 2-(2-amino-5-methoxyphenyl)-propan-2-ol (2.75 g; 15.2 mmole) was carried out using the same method as for 2-(2-aminophenyl)-propan-2-ol, using acetic anhydride (1.88 ml; 2.03 g; 19.9 mmole) and sodium acetate (2.45 g; 29.8 mmole). However in this case when the reaction mixture was poured into water no solid was precipitated. Hence the oily product mixture was extracted with ether (3 x 50 ml) and then the combined ether layers were washed with dilute NaOH solution (50 ml x 1 M) and then dried and evaporated to yield the crude product which was recrystallised from water. Yield: 2.27 g (67%). It had mp 141-2°; λ_{max} 251 nm (ϵ 11,920); ν_{max} 3200 (br) and 1649 cm^{-1}; δ ($CDCl_3$) 9.81 (1H, br), 8.02 (1H, d), 6.72 (2H, m), 3.74 (3H, s), 3.64 (1H, br), 2.02 (3H, s), and 1.59 (6H, s); m/e 223 (45%), 190 (21), 163 (49), 162 (95), 148 (83), 124 (24), and 43 (100). (Found: C, 64.72; H, 7.98; N, 5.99. $C_{12}H_{17}NO_3$ requires C, 64.57; H, 7.67; N, 6.28%).

6-Methoxy-2,4,4-trimethyl-3,1-benzoxazine (121)

The method was similar to the preparation of 2,4,4,6-tetramethyl-3,1-

benzoxazine using 2-(2-N-acetylamino-5-methoxyphenyl)-propan-2-ol (1.27 g; 5.67 mmole) in concentrated H_2SO_4 (5.7 ml). Yield: 680 mg (58%). It had bp 125-40° (0.1 mm); λ_{max} 267 (ϵ 11,840) and 277 nm (sh) (10,530); ν_{max} 1644 cm^{-1}; δ ($CDCl_3$) 7.07 (1H, d), 6.75 (1H, dd), 6.61 (1H, d), 3.78 (3H, s), 2.07 (3H, s), and 1.58 (6H, s); m/e 205 (18%), 190 (54), 162 (25), 148 (36), 147 (14), 118 (11), 91 (16), and 43 (100). (Found: C, 70.46; H, 7.51; N, 6.71. $C_{12}H_{15}NO_2$ requires C, 70.24; H, 7.31; N, 6.82%).

2-(2-N-Acetylamino-5-bromophenyl)-propan-2-ol

2-(2-Amino-5-bromophenyl)-propan-2-ol (5.0 g; 21.7 mmole) was dissolved in glacial acetic acid (10 ml) and acetic anhydride (10.0 ml; 10.9 g; 106.9 mmole) was added. The mixture was warmed on a steam-bath for 5 min and then poured into cold water (100 ml). As this was stirred, the amide precipitated and was filtered off, washed with a little water and recrystallised from aqueous methanol. Yield: 5.44 g (92%). It had mp 139.5-40.5°; λ_{max} 252 nm (ϵ 16,420); ν_{max} 3315 and 1661 cm^{-1}; δ ($CDCl_3$) 9.95 (1H, br), 8.06 (1H, d), 7.19 (2H, m), 3.18 (1H, s), 2.05 (3H, s), and 1.60 (6H, s); m/e 273 (22%), 271 (23), 255 (13), 253 (16), 240 (20), 238 (21), 212 (38), 210 (31), 131 (59), and 43 (100). (Found: C, 48.26; H, 5.28; N, 5.10. $C_{11}H_{14}BrNO_2$ requires C, 48.53; H, 5.15; N, 5.15%).

6-Bromo-2,4,4-trimethyl-3,1-benzoxazine (122)

The method was similar to that used for the synthesis of 2,4,4-trimethyl-3,1-benzoxazine using 2-(2-N-acetylamino-5-bromophenyl)-propan-2-ol

(2.50 g; 9.19 mmole) and acetic anhydride (30 ml; 32.4 g; 317.6 mmole). Yield: 1.42 g (61%). It had bp 90-100° (0.1 mm); λ_{max} 267 nm (ϵ 11,380); ν_{max} 1639 cm^{-1}; δ ($CDCl_3$) 7.30 (1H, dd), 7.13 (1H, d), 6.93 (1H, d), 2.06 (3H, s), and 1.56 (6H, s); m/e 255 (32%), 253 (32), 240 (97), 238 (100), 212(13), 210 (14), 131 (52), 117 (15), and 43 (55). (Found: C, 52.02; H, 4.81; N, 5.45. $C_{11}H_{12}BrNO$ requires C, 51.97; H, 4.72; N, 5.51%).

2-(2-N-Acetylamino-4-methylphenyl)-propan-2-ol

2-(2-Amino-4-methylphenyl)-propan-2-ol was prepared by the action of methyl magnesium iodide on methyl 4-methylanthranilate[137] using a method analogous to that used in the preparation of 2-(2-aminophenyl)-propan-2-ol. By a method similar to that used for 2-(2-aminophenyl)-propan-2-ol the aminocarbinol (1.49 g; 9.03 mmole) was acetylated with acetic anhydride (1.14 ml; 1.22 g; 11.96 mmole) and sodium acetate (1.49 g; 17.53 mmole). Yield: 1.71 g (91%). It had mp 158° (from aq. MeOH); λ_{max} 246 nm (ϵ 11,850); ν_{max} 3230 and 1665 cm^{-1}; δ ($CDCl_3$) 9.92 (1H, br), 8.03 (1H, d), 7.08 (1H, d), 6.80 (1H, dd), 3.04 (1H, br), 2.28 (3H, s), 2.04 (3H, s), and 1.61 (6H, s); m/e 207 (12%), 174 (19), 150 (33), 147 (20), 146 (64), 132 (22), and 43 (100). (Found: C, 69.47; H, 8.24; N, 6.88. $C_{12}H_{17}NO_2$ requires C, 69.56; H, 8.21; N, 6.76%).

2,4,4,7-Tetramethyl-3,1-benzoxazine (123)

2-(2-N-Acetylamino-4-methylphenyl)-propan-2-ol (820 mg; 3.96 mmole) was cyclised using concentrated H_2SO_4 (10 ml) using a method similar to that required to prepare 2,4,4,6-tetramethyl-3,1-benzoxazine.

Yield: 540 mg (72%). It had bp 120-8° (0.1 mm); λ_{max} 263 nm (ϵ 6740); ν_{max} 1644 cm^{-1}; δ ($CDCl_3$) 6.94 (3H, s), 2.30 (3H, s), 2.09 (3H, s), and 1.58 (6H, s); m/e 189 (23%), 174 (100), 147 (11), 146 (42), 132 (14), 131 (14), 117 (8), 91 (8), and 43 (75). (Found: C, 76.26; H, 7.65; N, 7.39. $C_{12}H_{15}NO$ requires C, 76.19; H, 7.94; N, 7.41%).

2-(2-Amino-4-chlorophenyl)-propan-2-ol

4-Chloroanthranilic acid (21.5 g; 125.4 mmole) was esterified by the same method used for 5-methylanthranilic acid using saturated methanolic HCl (600 ml). Yield: 20.67 g (87%). It had mp 67-8° [Lit.[85] 68-9°]. This ester (22.8 g; 122.9 mmole) was then treated with MeMgI (700 mmole) by a method similar to that used to prepare 2-(2-aminophenyl)-propan-2-ol. Yield: 21.54 g (94%). It had bp 122-6° (0.15 mm); ν_{max} 3470 (br) and 3380 cm^{-1}; δ ($CDCl_3$) 6.94 (1H, d), 6.56 (2H, m), 3.92 (3H, br), and 1.55 (6H, s); m/e 187 (9%), 185 (26), 172 (10), 170 (33), 169 (36), 167 (100), 154 (31), 152 (71), 131 (21), 117 (74), and 43 (36). The nmr spectrum showed the product to contain a trace of the olefin obtained by its dehydration.

2-(2-N-Acetylamino-4-chlorophenyl)-propan-2-ol

The method was similar to that used for acetylating 2-(2-aminophenyl)-propan-2-ol using 2-(2-amino-4-chlorophenyl)-propan-2-ol (10.0 g; 53.9 mmole), acetic anhydride (7.09 ml; 7.52 g; 73.7 mmole), and sodium acetate (9.20 g; 108.2 mmole). Yield: 9.77 g (80%). It had mp 152.5° (from aq. MeOH); λ_{max} 246 nm (ϵ 13,120); ν_{max} 3415, 3310, and 1674 cm^{-1}; δ ($CDCl_3$) 10.02 (1H, br), 8.30 (1H, d), 7.12 (1H, d),

6.94 (1H, dd), 3.18 (1H, br), 2.08 (3H, s), and 1.62 (6H, s); m/e 229 (4%), 227 (11), 196 (8), 194 (20), 169 (18), 168 (47), 167 (50), 166 (100), 152 (38), 131 (35), and 43 (80). (Found: C, 57.81; H, 6.31; N, 6.10. $C_{11}H_{14}ClNO_2$ requires C, 58.02; H, 6.15; N, 6.15%).

7-Chloro-2,4,4-trimethyl-3,1-benzoxazine (124)

The cyclisation of 2-(2-N-acetylamino-4-chlorophenyl)-propan-2-ol (5.0 g; 22.0 mmole) by concentrated H_2SO_4 (25 ml) was effected by a method similar to the one used to prepare 2,4,4,6-tetramethyl-3,1-benzoxazine. Yield: 4.25 g (92%). It had bp 118-25° (0.1 mm); λ_{max} 265 nm (ϵ 6140); ν_{max} 1646 cm^{-1}; δ ($CDCl_3$) 7.07 (2H, m), 6.94 (1H, d), 2.09 (3H, s), and 1.57 (6H, s); m/e 211 (6%), 209 (17), 194 (100), 168 (9), 166 (24), 153 (2), 151 (3), 131 (15), and 43 (66). (Found: C, 62.82; H, 5.78; N, 6.76. $C_{11}H_{12}ClNO$ requires C, 63.00; H, 5.73; N, 6.68%).

2-Nitro-4-trifluoromethylbenzonitrile[121] (116)

2-Nitro-4-trifluoromethylaniline (41.2 g; 200 mmole) was added with stirring to water (500 ml) and concentrated H_2SO_4 (150 ml) and the mixture was heated until a clear solution resulted and then cooled to 0°. Sodium nitrite (16.5 g; 240 mmole) in water (30 ml) was added over a period of 30 min. The temperature was allowed to rise to 5-10° and maintained for several hours. Any insoluble material was filtered off and the clear diazonium solution was added slowly with stirring into a cold solution of potassium nickelocyanide prepared from KCN (70.0 g; 1.08 mole) in water (300 ml) and $NiSO_4$ (60.0 g; 388 mmole) in water

(100 ml) to which anhydrous Na_2CO_3 (400 g) in water (650 ml) had been added. During the addition, which was done in an ice bath, the pH was checked to ensure the solution remained basic. The mixture was then heated to 30-5° for 30 min and allowed to stand overnight. It was then heated to 70° for 30 min and allowed to cool. A black solid was filtered off and steam distilled. (Sometimes the reaction yielded a black sludge and when this happened the mother liquor was decanted off and the residue steam distilled). The distillation was continued until no more yellow colour came over (ca. 6 l distillate) and since the product did not precipitate the distillate had to be extracted with ether (3 x 1000 ml). After drying the combined extracts the solvent was evaporated to yield a yellow oil, 9.50 g, which was found from tlc to be a mixture of product and starting amine. This mixture (14.63 g) was loaded on to alumina (40 x 3 cm) which was eluted with benzene. The starting amine was recovered first (2.30 g) followed by 2-nitro-4-trifluoromethylbenzonitrile, 10.25 g (15%) which crystallised on standing. It had mp 44-5° [Lit.[121] 44.5-5.5°]; δ (3:1 C_6D_6 : CCl_4) 7.90 (1H, br), 7.12 (1H, dd), and 6.92 (1H, m).

2-Nitro-4-trifluoromethylbenzoic acid

2-Nitro-4-trifluoromethylbenzonitrile (9.02 g; 41.8 mmole) in 55% (v/v) H_2SO_4 (165 ml) was heated at 165° for 1.5 h. It was then cooled and poured on to ice and basified with NaOH solution (2.5 M) followed by re-acidification with concentrated HCl and extracted into ether (2 x 200 ml). After the combined extracts were dried the solvent was evaporated to leave the crude 2-nitro-4-trifluoromethylbenzoic acid, 6.61 g (67%).

This had mp 119-24°. [Lit.[121] 140-40.5°]; δ (d_6-acetone) 8.90 - 7.82 (3H, m), and 7.30 (1H, br).

2-Amino-4-trifluoromethylbenzoic acid

2-Nitro-4-trifluoromethylbenzoic acid (6.25 g; 26.6 mmole) was introduced in small portions to a stirred mixture of iron powder (8.70 g; 155.8 mmole) and NH_4Cl (4.35 g; 81.3 mmole) in water (135 ml) at 50°. The mixture was then heated under reflux for 60 min, cooled and extracted with ether (2 x 100 ml). The combined extracts were dried and evaporated to leave the crude 2-amino-4-trifluoromethylbenzoic acid, 2.05 g (38%). This had mp 148-53° [Lit.[121] 175-7°]; δ ($CDCl_3$) 8.15 - 6.82 (3H, m) and 6.00 (3H, br).

2-(2-Amino-4-trifluoromethylphenyl)-propan-2-ol

2-Amino-4-trifluoromethylbenzoic acid (2.05 g; 10 mmole) was esterified with saturated methanolic HCl (50 ml) in a manner similar to that used to prepare methyl 5-methylanthranilate. Yield (crude): 2.15 g (98%). This ester (2.10 g; 9.59 mmole) was then treated with MeMgI (50 mmole) by the same method as that used to prepare 2-(2-aminophenyl)-propan-2-ol. Yield (crude): 2.02 g (96%). This was not distilled but used crude. It had δ ($CDCl_3$) 7.26 - 6.64 (3H, m), 3.80 (3H, br), and 1.64 (6H, s).

2-(2-N-Acetylamino-4-trifluoromethylphenyl)-propan-2-ol

2-(2-Amino-4-trifluoromethylphenyl)-propan-2-ol (2.02 g; 9.22 mmole) was acetylated by the method used to prepare 2-(2-N-acetylaminophenyl)-propan-2-ol with acetic anhydride (1.14 ml; 1.23 g; 12.06 mmole) and sodium acetate (1.49 g; 18.2 mmole). Yield: 1.05 g (44%). It had

mp 161-2° (from aq. EtOH); λ_{max} 246 nm (ϵ 14,570); ν_{max} 3325 (br), 3270, and 1667 cm^{-1}; δ (d_6-acetone) 10.62 (1H, br), 8.78 (1H, m), 7.42 (2H, m), 2.84 (1H, br), 2.11 (3H, s), and 1.68 (6H, s); m/e 261 (8%), 243 (6), 228 (8), 204 (5), 201 (9), 200 (13), 186 (4), 166 (2), 117 (3), and 43 (100). (Found: C, 54.92; H, 5.03; N, 5.21. $C_{12}H_{14}F_3NO_2$ requires C, 55.17; H, 5.36; N, 5.36%).

2,4,4-Trimethyl-7-trifluoromethyl-3,1-benzoxazine (125)

2-(2-N-Acetylamino-4-trifluoromethylphenyl)-propan-2-ol (1.03 g; 3.95 mmole) was cyclised using concentrated H_2SO_4 (5 ml) by a method similar to that used to prepare 2,4,4,6-tetramethyl-3,1-benzoxazine. Yield: 720 mg (75%). It had bp 135-40° (0.1 mm); mp 29-31°; λ_{max} 261 nm (ϵ 7980); ν_{max} 1641 cm^{-1}; δ ($CDCl_3$) 7.36 (2H, m), 7.17 (1H, d), 2.12 (3H, s), and 1.62 (6H, s); m/e 243 (2%), 228 (23), 200 (6), 185 (2), 159 (3), 117 (3), and 43 (100). (Found: C, 59.15; H, 4.88; N, 5.67. $C_{12}H_{12}FNO$ requires C, 59.26; H, 4.94; N, 5.76%).

2-(2-N- Benzoylaminophenyl)-propan-2-ol

2-(2-Aminophenyl)-propan-2-ol (3.02 g; 20 mmole) was suspended in NaOH solution (60 ml x 2 M) and benzoyl chloride (2.31 ml; 2.81 g; 20 mmole) was added with stirring. Almost immediately the product precipitated and was filtered off, washed with a little water and recrystallised from aqueous ethanol. Yield: 3.83 g (75%). It had mp 156°; λ_{max} 218 (ϵ 15,930) and 272 nm (13,740); ν_{max} 3345, 3250, and 1652 cm^{-1}; δ ($CDCl_3$) 8.40 (1H, m), 7.89 (2H, m), 7.50-6.90 (6H, m), 3.18 (1H, br), and 1.66 (6H, s); m/e 255 (6%), 240 (1), 196 (10), 133 (13), 132 (37),

105 (100), and 77 (95). (Found: C, 75.52; H, 6.93; N, 5.26. $C_{16}H_{17}NO_2$ requires C, 75.29; H, 6.67; N, 5.49%).

4,4-Dimethyl-2-phenyl-3,1-benzoxazine (126)

By a method analogous to that used to prepare 2,4,4,6-tetramethyl-3,1-benzoxazine 2-(2-N-benzoylaminophenyl)-propan-2-ol (2.55 g; 10 mmole) was cyclised using concentrated H_2SO_4 (20 ml). Yield: 2.12 g (89%). It had bp 160-75° (0.1 mm); λ_{max} 229 (ϵ 19,280) and 302 nm (14, 870); ν_{max} 1628 cm^{-1}; δ ($CDCl_3$) 8.16 (2H, m), 7.60 - 6.95 (7H, m), and 1.69 (6H, s); m/e 237 (31%), 222 (100), 132 (33), 117 (5), 105 (63), 91 (25), and 77 (77). (Found: C, 81.21; H, 6.17; N, 5.83. $C_{16}H_{15}NO$ requires C, 81.01; H, 6.33; N, 5.91%).

2-(2-N-4-Methoxybenzoylaminophenyl)-propan-2-ol

p-Anisic acid (15.20 g; 100 mmole) and thionyl chloride (14.28 g; 120 mmole) plus a drop of pyridine were heated under reflux for 3 h. After removal of the thionyl chloride, the product was distilled. Yield: 14.47 g (85%). It had bp 81-6° (0.2 mm) [Lit.[139] 145° (14 mm)]; mp 24° [Lit.[138] 22°]. 2-(2-Aminophenyl)-propan-2-ol (2.28 g; 15 mmole) was then acylated with 4-methoxybenzoyl chloride (2.56 g; 15 mmole) by the same method as was used to prepare 2-(2-N-benzoylaminophenyl)-propan-2-ol. Yield: 2.33 g (54%). It had mp 127-8° (from aq. EtOH); λ_{max} 278 nm (ϵ 20,310); ν_{max} 3335 (br), 3220 (br), and 1639 cm^{-1}; δ ($CDCl_3$) 8.34 (1H, m), 7.80 (2H, d), 7.39-6.94 (3H, m), 6.82 (2H, d), 3.77 (3H, s), and 1.63 (6H, s) (the NH and OH protons were not observed); m/e 285 (3%), 267 (2), 135 (100), 133 (19), 132 (13), 92 (10), and 77 (28). (Found: C, 71.66; H, 6.60; N, 5.07. $C_{17}H_{19}NO_3$ requires C, 71.58;

H, 6.67; N, 4.91%).

2-(4-Methoxyphenyl)-4,4-dimethyl-3,1-benzoxazine (127)

2-(2-N-4-Methoxybenzoylaminophenyl)-propan-2-ol (1.46 g; 5.12 mmole) was cyclised with concentrated H_2SO_4 (5 ml) by the method used to prepare 2,4,4,6-tetramethyl-3,1-benzoxazine. Yield: 1.06 g (77%). It had bp 180-195° (0.2 mm); λ_{max} 226 (ϵ 17,420), 260 (7740), and 307 nm (22,900); ν_{max} 1624 cm^{-1}; δ ($CDCl_3$) 8.10 (2H, d), 7.32 - 7.05 (4H, m), 6.93 (2H, d), 3.81 (3H, s), and 1.66 (6H, s); m/e 267 (39%), 252 (93), 135 (100), 132 (25), 117 (4), 91 (19), and 43 (29). (Found: C, 76.66; H, 6.55; N, 5.13. $C_{17}H_{17}NO_2$ requires C, 76.40; H, 6.37; N, 5.24%).

2-(2-N-4-Chlorobenzoylaminophenyl)-propan-2-ol

4-Chlorobenzoic acid (30.3 g; 193.6 mmole) and thionyl chloride (41.67 g; 350.2 mmole) were heated under reflux as in the preparation of 4-methoxybenzoyl chloride to yield 4-chlorobenzoyl chloride, 27.5 g (81%). It had bp 75-8° (0.4 mm) [Lit.[85] 220-2°; 118° (18 mm)]. 2-(2-Aminophenyl)-propan-2-ol (3.02 g; 20 mmole) was then acylated using 4-chlorobenzoyl chloride (3.50 g; 20 mmole) by the same method used to prepare 2-(2-N-benzoylaminophenyl)-propan-2-ol. Yield: 5.24 g (90%). It had mp 121-2°; λ_{max} 232 (ϵ 14,780) and 275 nm (13,270); ν_{max} 3350 (br), 3265 (br), and 1653 cm^{-1}; δ ($CDCl_3$) 8.37 (1H, m), 7.79 (2H, d), 7.34 (2H, d), 7.26 - 6.92 (3H, m), 3.27 (1H, br), and 1.66 (6H, s) (either the OH or NH proton was not observed); m/e 291 (2%), 289 (6), 258 (4), 256 (10), 141 (35), 139 (100), 132 (99), and 111 (50). (Found: C, 66.14; H, 5.31; N, 4.86. $C_{16}H_{16}ClNO_2$ requires C, 66.32;

H, 5.53; N, 4.84%).

2-(4-Chlorophenyl)-4,4-dimethyl,3,1-benzoxazine (128)

By a method similar to that used to prepare 2,4,4,6-tetramethyl-3,1-benzoxazine 2-(2-N-4-chlorobenzoylaminophenyl)-propan-2-ol (2.89 g; 9.98 mmole) was cyclised in concentrated H_2SO_4 (20 ml). Yield: 2.03 g (75%). It had mp 65° (from aq. EtOH); λ_{max} 229 (ϵ 16,850), 236 (16,510), and 306 nm (16,180); ν_{max} 1622 cm^{-1}; δ ($CDCl_3$) 8.08 (2H, d), 7.38 (2H, d), 7.30-7.05 (4H, m), and 1.68 (6H, s); m/e 273 (9%), 271 (23), 258 (39), 256 (100), 141 (20), 139 (62), 132 (50), 111 (57), 91 (55), and 43 (62). (Found: C, 70.58; H, 5.23; N, 4.92. $C_{16}H_{14}ClNO$ requires C, 70.72; H, 5.16; N, 5.16%).

2-(2-N-4-Nitrobenzoylaminophenyl)-propan-2-ol

4-Nitrobenzoic acid (33.40 g; 200 mmole) and thionyl chloride (41.67 g; 350.2 mmole) were heated under reflux as in the preparation of 4-methoxybenzoyl chloride to yield 4-nitrobenzoyl chloride, 33.0 g (89%). It had mp 72-3° [Lit.[139] 72-3°]. 2-(2-Aminophenyl)-propan-2-ol (3.02 g; 20 mmole) was then acylated using 4-nitrobenzoyl chloride (3.71 g; 20 mmole) in the same way used to synthesise 2-(2-N-benzoylaminophenyl)-propan-2-ol. Yield: 4.32 g (72%). It had mp 160-1° (from aq. EtOH); λ_{max} 245 (ϵ 17,090) and 302 nm (8730); ν_{max} 3360 (br), 3220 (br), 1661, 1529, and 1351 cm^{-1}; δ ($CDCl_3$) 8.52 (1H, m), 8.38 (2H, d), 8.18 (2H, d), 7.43 - 6.99 (3H, m), 5.48 (1H, br), 2.90 (1H, br), and 1.68 (6H, s); m/e 300 (12%), 282 (12), 150 (55), 133 (35), 132 (100), 117 (14), and 104 (53). (Found: C, 63.64; H, 5.26; N, 9.33. $C_{16}H_{16}N_2O_4$

requires C, 64.00; H, 5.33; N, 9.33%).

4,4-Dimethyl-2-(4-nitrophenyl)-3,1-benzoxazine (129)

The method used to prepare 2,4,4,6-tetramethyl-3,1-benzoxazine was used to cyclise 2-(2-N-4-nitrobenzoylaminophenyl)-propan-2-ol (2.40 g; 8 mmole) with concentrated H_2SO_4 (20 ml). Yield: 1.91 g (85%). It had mp 117-8° (from aq. EtOH); λ_{max} 247 (ϵ 15,400) and 343 nm (12,790); ν_{max} 1622, 1522, and 1351 cm^{-1}; δ ($CDCl_3$) 8.27 (4H, s), 7.34 - 7.11 (4H, m), and 1.71 (6H, s); m/e 282 (21%), 267 (100), 221 (34), 150 (25), 132 (76), 117 (48), 91 (53), and 43 (73). (Found: C, 68.27; H, 5.03; N, 10.21. $C_{16}H_{14}N_2O_3$ requires C, 68.09; H, 4.96; N, 9.93%).

Hydrolysis of unsaturated 3,1-benzoxazines

The benzoxazine (5 mmole) in concentrated HCl was heated under reflux and after 30 min, 2, 4, 6, and 24 h aliquots (9 ml) were taken. These were each basified with ammonia and extracted with ether (2 x 25 ml). If required, the aqueous layer was acidified and the acetic or substituted benzoic acids recovered by ether extraction or filtration. The ether extracts of the basic solutions were dried and evaporated and the nmr spectrum of each was obtained. By use of its integral and by comparison to spectra of the starting benzoxazine, correspondingly substituted carbinol, olefin, and aniline the composition of each mixture was calculated.

1,2-Dihydro-4,4-dimethyl-2-phenyl-3,1-benzoxazine (150)

2-(2-Aminophenyl)-propan-2-ol (500 mg; 3.31 mmole) and benzaldehyde (351 mg; 3.31 mmole) in ethanol (20 ml) were heated under reflux for 3 h.

The solvent was evaporated and the resulting oil crystallised on standing and was recrystallised from ethanol. Yield 470 mg (59%). It had mp 73-3.5°; λ_{max} 240 (ϵ 9290), and 289 nm (1840); ν_{max} 3475 cm^{-1}; δ (d_6-acetone) 7.63 - 6.62 (9H, m), 5.34 (1H, br), 5.64 (1H, s), 1.61 (3H, s), and 1.51 (3H, s); m/e 239 (6%), 206 (12), 133 (45), 130 (17), 118 (37), 117 (29), 115 (13), 91 (56), 77 (100), and 43 (25). (Found: C, 79.86; H, 7.50; N, 5.74. $C_{16}H_{17}NO$ requires C, 80.30; H, 7.16; N, 5.85%).

1,2-Dihydro-2,2,4,4-tetramethyl-3,1-benzoxazine (151)

2-(2-Aminophenyl)-propan-2-ol (500 mg; 3.31 mmole) in acetone (25 ml), with toluene-p-sulphonic acid (5 mg) added, was heated under reflux for 2 h. The solvent was evaporated and the resulting oil crystallised on standing and was recrystallised from ethanol. Yield: 510 mg (80%). It had mp 65-6°; λ_{max} 239 (ϵ 7040) and 291 nm (1645); ν_{max} 3345 cm^{-1}; δ (d_6-acetone) 7.11 - 6.53 (4H, m), 5.09 (1H, br), 1.45 (6H, s), and 1.34 (6H, s); m/e 191 (17%), 176 (85), 173 (13), 158 (100), 134 (87), 133 (47), 130 (17), 118 (39), 117 (29), 115 (21), 91 (44), and 43 (51). (Found: C, 74.67; H, 9.45; N, 7.27. $C_{12}H_{17}NO$ requires C, 75.35; H, 8.96; N, 7.32%). This analysis could not be improved. Accurate mass 191.1302. ($C_{12}H_{17}NO$ requires 191.1310).

1,2-Dihydro-2-(4-methoxyphenyl)-4,4-dimethyl-3,1-benzoxazine (158)

2-(2-Aminophenyl)-propan-2-ol (695 mg; 4.60 mmole) and p-anisaldehyde (680 mg; 5 mmole) in benzene (30 ml), with toluene-p-sulphonic acid (5 mg), were heated under reflux for 60 min. A Dean-Stark trap was

used to collect the water which was azeotroped off. The solvent was then evaporated to leave an oil which crystallised on standing and was recrystallised from aqueous ethanol. Yield: 950 mg (77%). It had mp 98-8.5°; λ_{max} 225 (ϵ 16,590), 240 (12,030), and 288 nm (2570); ν_{max} 3490 and 3465 cm^{-1}; δ ($CDCl_3$) 7.50 (2H, d), 7.18 - 6.58 (6H, m), 5.58 (1H, s), 3.78 (3H, s), 1.64 (3H, s), and 1.58 (3H, s); m/e 269 (9%), 254 (9), 133 (100), 132 (30), 118 (20), and 91 (16). (Found: C, 76.03; H, 7.42; N, 4.97. $C_{17}H_{19}NO_2$ requires C, 75.84; H, 7.06; N, 5.20%).

1,2-Dihydro-4,4-dimethyl-2-(4-nitrophenyl)-3,1-benzoxazine

By a method similar to that used for its condensation with p-anisaldehyde 2-(2-aminophenyl)-propan-2-ol (695 mg; 4.60 mmole) was condensed with 4-nitrobenzaldehyde (750 mg; 4.97 mmole). Yield: 1.0 g (77%). It had mp 130° (from aq. EtOH); λ_{max} 257 nm (ϵ 15,380); ν_{max} 3395, 1519, and 1351 cm^{-1}; δ ($CDCl_3$) 8.26 (2H, d), 7.79 (2H, d), 7.25 - 6.68 (4H, m), 5.74 (1H, s), 3.70 (1H, br), 1.66 (3H, s), and 1.61 (3H, s); m/e 284 (15%), 269 (16), 133 (100), 132 (51), 118 (40), and 91 (27). (Found: C, 67.61; H, 5.93; N, 9.68. $C_{16}H_{16}N_2O_3$ requires C, 67.61; H, 5.63; N, 9.86%).

By the same method it was attempted to prepare 2,2-diethyl-1,2-dihydro-4,4-dimethyl-3,1-benzoxazine, 2-tert-butyl-1,2-dihydro-2,4,4,-trimethyl-3,1-benzoxazine, and 1,2-dihydro-4,4-dimethyl-3,1-benzoxazine using diethyl ketone, tert-butyl methyl ketone, and formaldehyde respectively, but in each case starting materials were recovered under the conditions used.

1,2-Dihydro-2,2,4,4-tetramethyl-6-nitro-3,1-benzoxazine (118)

2,4,4-Trimethyl-6-nitro-3,1-benzoxazine (5.50 g) was hydrolysed in the normal way with concentrated HCl (100 ml) for 60 min. However in this case some of the solution was allowed to stand for 8 weeks before it was basified with ammonia and extracted with ether. In addition to the usual products, 2-(2-amino-5-nitrophenyl)-propan-2-ol, 2-(2-amino-5-nitrophenyl)-propene, some starting material, and 4-nitroaniline, repeated recrystallisations from aqueous ethanol produced a small yield of 1,2-dihydro-2,2,4,4-tetramethyl-6-nitro-3,1-benzoxazine. It had mp 158-60°; λ_{max} 229 (ϵ 5710), 258 (2970), and 385 nm (14,150); ν_{max} 3325, 1531, and 1375 cm^{-1}; δ (d_6-acetone) 7.90 (2H, m), 6.76 (1H, br), 6.68 (1H, d), 1.56 (6H, s), and 1.44 (6H s); m/e 236 (6%), 221 (81), 203 (23), 179 (57), 178 (26), 148 (57), 130 (27), 117 (37), and 43 (100). Accurate mass 236.1151. ($C_{12}H_{16}N_2O_3$ requires 236.1161). (Found: C, 60.94; H, 6.91; N, 11.85. $C_{12}H_{16}N_2O_3$ requires C, 61.02; H, 6.78; N, 11.86%).

This was also made independently with 2-(2-amino-5-nitrophenyl)-propan-2-ol (170 mg; 0.87 mmole) in acetone (25 ml) with one drop concentrated HCl. The mixture was heated under reflux for 20 min and then basified with ammonia and the acetone evaporated. The residue was extracted into ether (2 x 25 ml) and then the combined extracts were dried before evaporation of the solvent. The product was recrystallised from aqueous ethanol. Yield: 190 mg (93%). It had mp 151-2° and mixed mp with the analytical sample of 155-6°. Its infrared and nmr spectra were identical to that of the analytical sample.

2-Aminobenzyl alcohol[140]

Anthranilic acid (11.70 g; 85.4 mmole) was placed in an extraction thimble in a continuous ether extractor between a condenser and a three necked flask containing $LiAlH_4$ (7.80 g; 205.3 mmole) in dry ether (600 ml). The ether was heated under reflux until all the anthranilic acid had been dissolved (ca. 1.5 h). The solution was then cooled and, after the excess $LiAlH_4$ had been destroyed, was basified with 10% NaOH solution and the ether layer separated and to this added the ether extracts (2 x 50 ml) of the aqueous layer. The combined ether extracts were dried before evaporation of the solvent. Yield: 10.25 g (97%). It had mp 76-7° [Lit.[140] 82°].

1,2-Dihydro-2,2-dimethyl-3,1-benzoxazine (152)

2-Aminobenzyl alcohol (1.0 g; 8.13 mmole) in a 1:1 (v/v) mixture of dry benzene and acetone (35 ml) was heated under reflux for 18 h over anhydrous $CaSO_4$. A Dean-Stark trap was used to collect the water. After the solvent was evaporated the residual oil crystallised on standing. Yield: 610 mg (46%). It had mp 117-9° [Lit.[90] 123°]; λ_{max} 244 (ϵ 7830) and 295 nm (2020); ν_{max} 3310 cm^{-1}; δ (d_6-acetone) 7.05-6.50 (4H, m), 5.25 (1H, br), 4.73 (2H, s), and 1.36 (6H, s); m/e 163 (30%), 148 (100), 130 (60), 106 (76), 105 (48), 104 (73), 78 (62), and 77 (47).

1,2-Dihydro-2-phenyl-3,1-benzoxazine (153)

2-Aminobenzyl alcohol (1.0 g; 8.13 mmole) and benzaldehyde (1.20 g; 11.32 mmole) in ethanol (30 ml) were heated under reflux for 45 min. The solvent was then evaporated and the solid recrystallised from

aqueous ethanol. Yield: 1.35 g (79%). It had mp 119-20° [Lit.[86] 121-4°]; λ_{max} 245 (ϵ 8750) and 291 nm (1950); ν_{max} 3350 cm^{-1}; δ ($CDCl_3$) 7.62 - 6.63 (9H, m), 5.54 (1H, s), 5.11 (1H, d), 4.88 (1H, d), and 4.00 (1H, br); m/e 211 (35%), 180 (8), 106 (14), 105 (48), 91 (26), and 77 (100).

1-(2-Aminophenyl)-ethanol

2-Aminoacetophenone (6.60 g; 48.9 mmole) in dry ether (50 ml) was added dropwise to $LiAlH_4$ (1.86 g; 48.9 mmole) in dry ether (100 ml) at such a rate as to just maintain gentle refluxing. After the addition the mixture was heated under reflux for 30 min and then, after destroying any residual $LiAlH_4$, the mixture was extracted into ether (2 x 200 ml). The combined extracts were dried and evaporated and the crude product distilled. Yield: 4.71 g (70%). It had bp 115-25° (2 mm) [Lit.[141] 119° (1.5 mm)]; mp 55-7° [Lit.[142] 57°].

1,2-Dihydro-2,2,4-trimethyl-3,1-benzoxazine

1-(2-Aminophenyl)-ethanol (411 mg; 3 mmole) in acetone (20 ml) with toluene-p-sulphonic acid (5 mg) was heated under reflux for 30 min. The solvent was then evaporated and the product recrystallised from petroleum ether (bp 60-80°). Yield: 110 mg (21%). It had mp 54-6°; λ_{max} 243 (ϵ 8470) and 294 nm (2020); ν_{max} 3350 cm^{-1}; δ ($CDCl_3$) 7.16 - 6.52 (4H, m), 4.97 (1H, q), 3.87 (1H, br), 1.52 (3H, d), 1.46 (3H, s), and 1.41 (3H, s); m/e 177 (24%), 162 (48), 144 (13), 120 (48), 119 (45), 117 (16), and 43 (29). (Found: C, 74.92; H, 8.63; N, 7.73. $C_{11}H_{15}NO$ requires C, 74.58; H, 8.48; N, 7.91%).

By the same method it was attempted to prepare 1,2-dihydro-2,4-dimethyl-3,1-benzoxazine, 2-ethyl-1,2-dihydro-2,4-dimethyl-3,1-benzoxazine, 2-tert-butyl-1,2-dihydro-2,4-dimethyl-3,1-benzoxazine, and 1,2-dihydro-2-(4-methoxyphenyl)-4-methyl-3,1-benzoxazine using acetaldehyde, ethyl methyl ketone, tert-butyl methyl ketone, and 4-methoxybenzaldehyde respectively with benzene as solvent in the latter two cases. However under the conditions used starting materials were recovered in each case.

2-(2-Aminophenyl)-3,3-dimethyl-butan-2-ol

2-Aminoacetophenone (3.86 g; 28.6 mmole) was treated with tert-butylmagnesium chloride (100 mmole) in the usual way. Yield: 4.92 g (89%). It had bp 148-60° (0.1 mm); ν_{max} 3460 (br) and 3360 cm^{-1}; δ ($CDCl_3$) 7.02 - 6.50 (4H, m), 3.96 (3H, br), 1.59 (3H, s), and 0.98 (9H, s); m/e 193 (3%), 136 (100), 135 (29), 120 (59), 118 (63), 92 (37), and 43 (52).

4-tert-Butyl-1,2-dihydro-2,2,4-trimethyl-3,1-benzoxazine (157)

2-(2-Aminophenyl)-3,3-dimethyl-butan-2-ol (772 mg; 40 mmole) in acetone (50 ml) with toluene-p-sulphonic acid (5 mg) was heated under reflux for 4 h. The solvent was evaporated and the residual oil distilled. Yield: 800 mg (86%). It had bp 110-30° (0.15 mm); ν_{max} 3480 and 3370 cm^{-1}; δ ($CDCl_3$) 7.18 - 6.49 (4H, m), 3.39 (1H, br), 1.54 (3H, s), 1.45 (3H, s), 1.29 (3H, s), and 0.89 (9H, s); m/e 233 (1%), 218 (2), 176 (100), 158 (33), 135 (16), 134 (16), 120 (25), and 43 (35).

N-Benzylidene o - toluidine[143] (154)

o-Toluidine (12.7 g; 118.7 mmole) and benzaldehyde (10.6 g; 100 mmole) were gently warmed for 30 min. The solution was allowed to cool and then extracted into ether (200 ml) and washed with dilute acetic acid (50 ml). The etheral layer was dried and evaporated to leave a crude oil which was distilled. Yield: 7.57 g (33%). It had bp 192° (29 mm) [Lit.[143] 307° (775 mm)]; λ_{max} 260 (ϵ 15,280) and 319 nm (5280); ν_{max} 1632 cm^{-1}; δ (d_6-acetone) 8.41 (1H, s), 7.94 (2H, m), 7.46 (3H, m), 7.26 - 6.88 (4H, m), and 2.32 (3H, s); m/e 195 (100%), 194 (82), 118 (93), 117 (17), and 91 (39).

Attempted preparation of N-isopropylidene o-toluidine[144] (155)

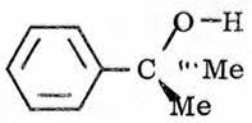
o-Toluidine (21.4 g; 200 mmole) in acetone (5.8 g; 100 mmole) was heated under reflux with I_2 (250 mg) for 40 h. During this time the temperature of the solution rose from 80° to 101°. The solution was then distilled and the fraction with bp 78-80° (0.3 mm) was collected. However this was subsequently shown to be 1,2-dihydro-2,2,4,8-tetramethylquinoline, 4.90 g (26%). It had bp 78-80° (0.3 mm) [Lit.[128] 131° (6 mm)]; λ_{max} 234 (ϵ 23,450), 266 (1900), and 334 nm (2260); ν_{max} 3395 cm^{-1}; δ ($CDCl_3$) 6.91 (1H, d), 6.83 (1H, d), 6.50 (1H, t), 5.23 (1H, m), 3.46 (1H, br), 2.03 (3H, s), 1.95 (3H, m), and 1.24 (6H, s); m/e 187 (8%), 172 (100), 171 (11), 157 (3), and 115 (4).

Part III

Introduction

Dimethylphenylcarbinol (2-phenylpropan-2-ol) and the corresponding compounds substituted in the ortho and para positions in the ring have been studied to show the existence of H-bonding especially in the ortho substituted cases and the possibility of two conformations of the hydroxyl group in the other cases.

Oki and Iwamura[145,146] have shown that when the possibility



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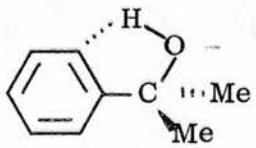
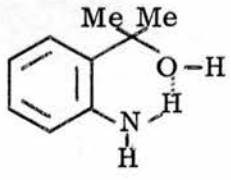


(161)

of H-bonding of the hydroxyl to an ortho substituent does not exist the hydroxyl group can have its proton lying either over the π -electron cloud of the benzene ring (161) or away from it (160). This gives rise to a doublet for the O-H stretch in the infrared, when well resolved, the peak at lower wavenumber corresponding to structure (161) in which interaction can take place. These two conformations should also give rise to differing OH signals in their nmr spectra, but the nmr spectrum of the system studied usually shows a single OH proton, owing to the rapid exchange between, and consequent averaging of, the protons of various kinds. This interaction with the π -electrons is not present to nearly the same extent when an ortho substituent is present to which the hydroxyl group can hydrogen bond as in (162) - (165), although the

O-H stretching absorptions in the infrared are broadened by these varying types of OH.



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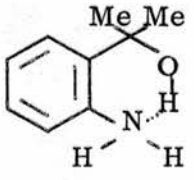

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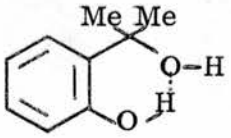

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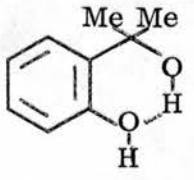


(165)

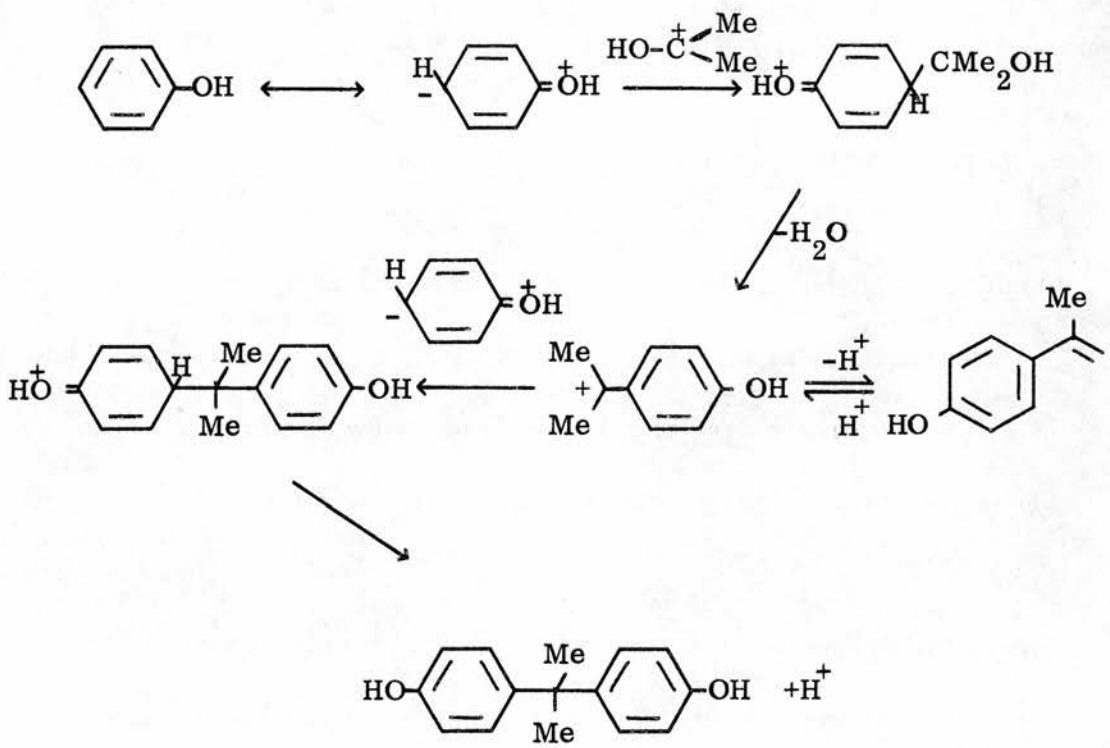
Acid catalyses the dehydration of these dimethylphenylcarbinols and in some cases the carbinol dehydrates even at room temperature. An example of this is when the phenyl ring is para substituted with a dimethylamino group[145], when only the substituted α-methylstyrene was isolated.

As was stated in Part II it is known[96] that one of the hydrolysis products of 2-substituted 4,4-diphenyl-3,1-benzoxazines is o-aminotriphenylcarbinol and this then yields small amounts of benzophenone and aniline. Hence it is known that an o-amino substituted benzyl alcohol can dealkylate by prolonged treatment with concentrated HCl.

Alkylation of phenols is known to take place in the formation of Bisphenol A (166) which is formed from phenol and acetone in the presence of acid[147]. It is thought that it is formed by the condensation of a molecule of protonated acetone with phenol in its quinonoid canonical form (as shown in Scheme 12) and then after elimination of a molecule of water repetition of the process gives Bisphenol A which, since the

development of epoxy resins in 1938 has found significant industrial application.

Scheme 12



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Results and Discussion

After the hydrolysis of the 3,1-benzoxazines had shown comparative ease of dealkylation in concentrated HCl several ortho and para substituted dimethylphenylcarbinols were prepared in order to investigate the products of their reaction with concentrated HCl, to show whether an ortho amino group was required for dealkylation.

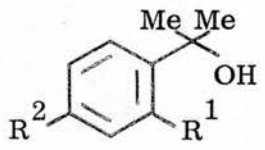
The carbinols were prepared from the appropriately substituted methyl benzoate with methyl magnesium iodide except for the para methoxy compound and dimethylphenylcarbinol itself, both of which were found to contain large amounts of the dehydration product when prepared that way. Instead, they were synthesised from phenyl (or p-methoxyphenyl) magnesium bromide and acetone. In the case of dimethylphenylcarbinol it had to be used almost immediately since it dehydrated readily on standing. The p-amino carbinol was synthesised by nitrating cumene and separating from the product mixture the para isomer. This was then oxidised to the carbinol and then the nitro group reduced.

Each in turn was then treated in exactly the same way as the benzoxazines. However the results in this case were entirely qualitative since the carbinols, apart from the amino substituted ones, were insoluble in concentrated HCl and so the aliquots taken after given periods of time only contained acid soluble products. In each case some of the acid insoluble material was also taken but this could not be done quantitatively.

It was found that only (168) which is in fact the ortho amino compound gave products corresponding to the benzoxazine hydrolysis.

Table 13

Mp and bp data for carbinols.



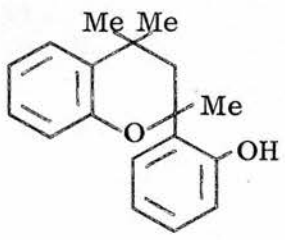
Cpd	R^1	R^2	mp/ °C	bp/ °C
167	H	H		58-67 (0.1 mm)[a]
168	NH_2	H		86-92 (0.07 mm)
169	OH	H	38-40[b]	73-81 (0.1 mm)
170	OMe	H		64-76 (0.1 mm)[c]
171	H	NH_2		78-83 (0.05 mm)[d]
172	H	OH	124-6[e,f]	
173	H	OMe		80-2 (0.15 mm)[g]

a. Lit.[148] 90-2 (11mm) b. Lit.[149] 41-44 c. Lit.[150] 195-200 (760 mm) d. Lit.[151] 110-1 (0.2 mm) e. softens at 112-8 f. Lit.[149,152,153] 102-10 (d); 107; 174.1-4.8 g. Lit.[154] 122 (13 mm)

After 24 h there had been virtually quantitative conversion to aniline, while after shorter times there was a mixture of carbinol, olefin, and aniline.

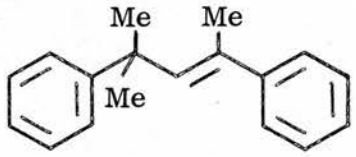
When that carbinol had its amino group replaced by a hydroxyl group (169), within 30 min the carbinol had formed a type of cyclic

dimer, 2-hydroxy-2,4,4-trimethylflavan (174); accurate mass 268.1473. ($C_{18}H_{20}O_2$ requires 268.1463). It is known that this is a by-product in the formation of Bisphenol A from phenol and acetone[147], by the dimerisation of 2-(2-hydroxyphenyl)-propene in acid.



(174)

When this type of product cannot form as is the case when the hydroxyl group of the carbinol is replaced by a methoxy group, another type of condensation appears to take place. When 2-(2-methoxyphenyl)-propan-2-ol (170) is treated in the usual way with concentrated HCl the product is again the result of dimerisation with the loss of two moles of water. Now, as cyclisation cannot occur, the initial dehydration must be at the tertiary alcohol centre to give 2-(4-methoxyphenyl)-propene. The dimerisation of α-methylstyrene in H_2SO_4 has been analysed by nmr[155] and glc[156] and has been shown to result in 6 components, 5 of which (175-179) were identified. The nmr of this mixture was very complex and was assigned only after separating the components by preparative glc and then running the nmr spectrum of each. The principal mass spectral fragments and their intensities are shown in Table 14. The mixture from the reaction involving 2-(2-methoxyphenyl)-propan-2-ol (170) was examined by glc (3% APL at 245°) but the separation was very poor, the chromatogram showing one peak with a very slight shoulder on its more volatile side. The mixture was also chromatographed on



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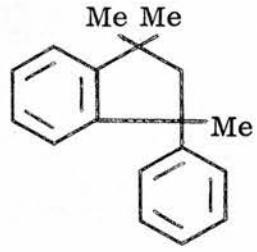

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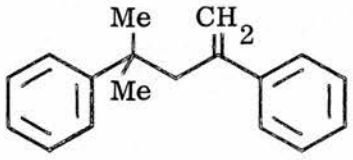

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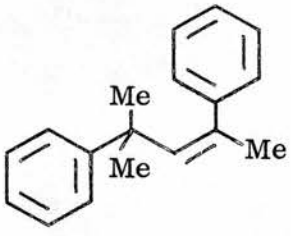

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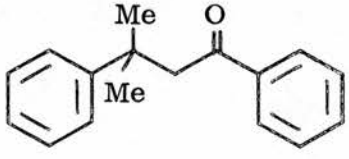


(179)

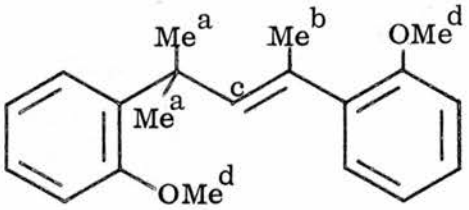
alumina and distilled [bp 150-90° (0.2 mm)] but its nmr spectrum still showed it to be a mixture of probably 3 compounds. Its accurate mass, 296.1779 ($C_{20}H_{24}O_2$ requires 296.1776) confirms the molecular forumula corresponds to structures analogous to the α-methylstyrene products (175-178) with o-methoxy groups in the rings. Analysis of the mixture gave 81.35% C and 8.67% H. Since $C_{20}H_{24}O_2$ requires C, 81.04% and H, 8.16% it can be seen that there is almost certainly no isomer corresponding to structure (179). (This is confirmed by the

Table 14 Mass spectral data for 175-178[a]

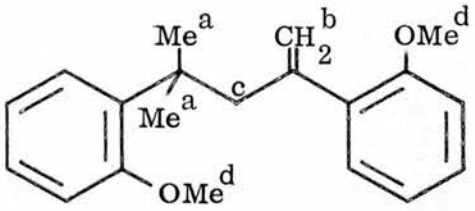
m/e / Cpt.	236	221	143	128	119	115	105	103	91	77
175	33	40	47	40	20	50	67	40	100	43
176	7	100	48	21	-	10	14	10	59	21
177	4	15	15	7	100	8	5	7	91	15
178	6	12	39	10	100	13	13	11	100	28

a. Intensities relative to base peak = 100%

absence of a carbonyl absorption in the infrared). As two of the possible structures are cis/trans isomers and it is known that these can sometimes be separated by the impregnation of the silica tlc plates with $AgNO_3$, as first demonstrated by de Vries[157], the mixture was examined on tlc plates coated with a 10% (w/w) mixture of $AgNO_3$ in silica. It was found that separation of all three isomers was excellent when benzene was used as eluent and so the mixture (200 mg) was loaded on to two preparative tlc plates and by this means the three isomers were separated and their nmr spectra obtained. The spectra showed each isomer to be $>$ 90% pure. The isomers (180-182) were identified as the structures corresponding to (175), (178), and (177). From the nmr spectrum of the mixture they were present in 45, 34, and 21% respectively. The structure corresponding to (176) was discounted because all three spectra showed the presence of olefinic protons, as shown in Table 15. The spectrum of structure (182) was the easiest to recognise, since it has no single methyl group and also is the only



(180)



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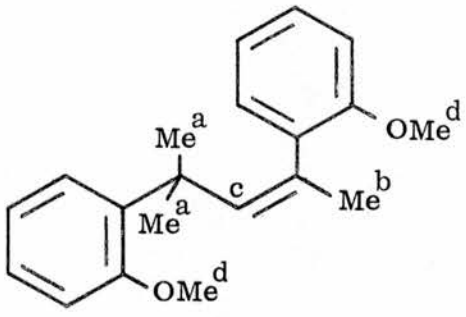

(181)

structure to have a terminal olefinic group (at 3.09 δ). Structures (180) and (181) have very similar spectra but in the case of (180) the olefinic proton c is at lower field than the corresponding proton in (181)

Table 15 NMR data for (180) - (182)[a]

	a	b	c	d	Aromatics
180	1.26(s)	1.91(m)	5.94(m)	3.82(s), 3.67(s)	7.46-6.38(m)
181	1.53(s)	1.47(m)	5.79(m)	3.79(s), 3.70(s)	7.48-6.73(m)
182	1.28(s)	4.95(m), 4.85(m)	3.09(s)	3.73(s), 3.64(s)	7.16-6.50(m)

a. chemical shifts are δ

since it is forced to lie between the peripheries of two equally close phenyl groups, while in (181) it is only correspondingly close to one of these rings, the other one now being in a trans position to it. By a similar argument the single methyl group b lies equally close to one of the rings in both structures but in (181) free rotation of the other ring means that the methyl group is very much further away from that ring for part of the time than it can be in structure (180) and so the methyl group in (180) is more deshielded and occurs at lower field (1.91 δ) than in (181) (1.47 δ). The principal mass spectral breakdown is shown in Table 16.

Table 16 Mass spectral data for (180) - (182)[a]

m/e	296	281	173	135	121	105	91	84	77	43
180	24	18	88	61	64	59	88	100	48	33
m/e	296	281	173	135	133	121	105	91	77	43
181	18	10	35	27	22	27	25	37	27	100
m/e	296	281	175	149	121	91	86	84	77	47
182	6	2	21	100	47	50	52	80	18	27

a. Intensities relative to base peak = 100%

When dimethylphenylcarbinol (167) itself was treated with acid the nmr spectrum obtained was very complex but was almost identical to the spectrum obtained when α -methylstyrene was given the same treatment.

When the carbinol was substituted with a para amino group (171) it was found to dehydrate very readily. On treatment with acid it was found to have an extremely complex nmr spectrum which did not noticeably change after the initial aliquot was taken (30 min). It did seem to have a spectrum analogous to that obtained from the crude mixtures when methoxy was the substituent, with many olefinic protons apparent. TLC on silica, alumina or $AgNO_3$ impregnated silica did not resolve the mixture. In an attempt to improve the resolution of the tlc, one of the aliquots was methylated with methyl iodide. Although nmr showed that methylation had taken place, the resolution by tlc was not improved. The accurate mass, 266.1792 ($C_{18}H_{22}N_2$ requires 266.1783) indicates that dimerisation with the loss of two moles of water has again taken place.

In the case of the p-hydroxy compound (172) the flavan corresponding to the one isolated from the reaction with (169) formed, 4'-hydroxy-2,4,4-trimethylflavan. For the flavan to form there must be some ortho hydroxy carbinol present. Hence some dealkylation must take place followed by realkylation preferentially at the ortho position. It has been reported[158] that in the alkylation of phenols para substitution is thermodynamically favoured, but that ortho alkylation takes place faster. Hence if the ortho isomer is removed before equilibrium is reached, as is the case if it cyclises to the flavan, then it is the ortho isomer which is predominantly formed.

2-(4-Methoxyphenyl)-propan-2-ol (173) gave an nmr which was not readily interpretable, but it did resemble the nmr spectra of the products

from ∝-methylstyrene and from 2-(2-methoxyphenyl)-propan-2-ol. Neither normal tlc nor the use of plates spread with $AgNO_3$ impregnated silica resolved the mixture and when injected into a glc column (3% APL at 245°) the chromatogram indicated three components, but from the extreme broadness of the peaks it seemed possible that pyrolysis of the components might be occuring on the column. The nmr spectrum showed five overlapping methoxy signals, confirming that it was a mixture of several components, probably corresponding to analogues of the products of dimerisation of ∝-methylstyrene. The presence of just such a compound with formula $C_{20}H_{24}O_2$ was confirmed by the accurate mass measurement, 296.1785 ($C_{20}H_{24}O_2$ requires 296.1776). Dealkylation followed by realkylation in the ortho position does not appear to take place since tlc of the mixture from the para compound did not show any component comparable to those isolated from the ortho methoxy mixture. The nmr spectrum did not show any signals corresponding to (180 - 182) either.

Ortho substituted carbinols tended to be more stable than the para substituted isomers, probably due to intramolecular hydrogen bonding. From nmr studies[159] it has been shown that ortho aminobenzyl alcohols show quasibicyclic structures stabilised by intramolecular hydrogen bonding. It is also interesting to compare the infrared absorptions of 2-(2-aminophenyl)-propan-2-ol and 2-(2-amino-5-nitrophenyl)-propan-2-ol. In the former there is a broad, largely unresolved area of absorption for the O-H and N-H stretches whereas in the nitro compound the N-H and O-H absorptions are well resolved and this could be due to the fact

that amino and nitro groups para to each other have the quinonoid structure (183) as one of their canonical forms, which means that the lone pair on

(183)

nitrogen is no longer available for hydrogen bonding.

Thus it would appear that there are several different pathways which these carbinols may take in the presence of concentrated HCl.

The first is dealkylation which appears to occur to the largest extent with the ortho amino substitution. This is probably because in the

(184)

acidic solution the protonated species (184) can hydrogen bond as shown. In this way the proton bonded to oxygen would be expected to be appreciably more acidic than normal and hence dealkylation is assisted. Presumably it is the absence of this hydrogen bonding which prevents the rapid dealkylation of the para amino compound. The para hydroxy compound must also dealkylate since this, followed by realkylation in the ortho

position is the only explanation of how the flavan is produced. As has already been shown this is because the kinetically more stable ortho substituted product is removed to form the even more stable flavan and so the thermodynamically more stable para substituted product is gradually removed.

The hydroxy carbinols (both ortho and para) form the second type of reaction which occurs since they are the only ones to form the cyclic flavans as products.

In the third type of reaction at least some of the products appear to be formed by dimerisation with the loss of two molecules of water but this time the products are not cyclic. In the cases of the unsubstituted dimethylphenylcarbinol and in the methoxy substituted cases cyclisation is impossible and these, along with the para amino compound all appear to dehydrate and then dimerise to form products analogous to those of α-methylstyrene. In one case the products were in fact identified as just such analogues (180-182).

Experimental

The synthesis of 2-(2-aminophenyl)-propan-2-ol (168) has already been described in Part I.

2-Phenylpropan-2-ol (167)

Acetone (2.9 g; 50 mmole) was added to phenyl magnesium bromide made from magnesium (2.5 g; 102.9 mmole) and bromobenzene (17.3 g; 110.2 mmole). The Grignard reaction was performed in the usual way to give the crude product. Yield: 4.02 g (59%). It had bp 58-67° (0.1 mm) [Lit.[148] 90-2° (11 mm)]; ν_{max} 3400 (br) cm^{-1}; δ ($CDCl_3$) 7.64-7.28 (5H, m), 2.39 (1H, br), and 1.58 (6H, s); m/e 136 (1%), 121 (11), 118 (45), 117 (34), 103 (39), 91 (21), 77 (61), and 43 (100).

2-(2-Hydroxyphenyl)-propan-2-ol (169)

Methyl salicylate (15.2 g; 100 mmole) was added to MeMgI (500 mmole) in the usual way. Yield (crude): 13.81 g (91%). It had bp 73-81° (0.1 mm); mp 38-40° [Lit.[149] 41-4°]; ν_{max} 3320 (br) cm^{-1}; δ ($CDCl_3$) 9.10 (1H, br), 7.20-6.69 (4H, m), 3.42 (1H, br), and 1.60 (6H, s); m/e 152 (2%), 137 (4), 134 (22), 119 (27), 91 (100), 77 (20), and 43 (70).

2-(2-Methoxyphenyl)-propan-2-ol (170)

Methyl 2-methoxybenzoate (16.6 g; 100 mmole) was added to MeMgI (500 mmole) in the usual way. Yield: 14.58 g (88%). It had bp 64-76° (0.1 mm) [Lit.[150] 195-200° (760 mm)]; ν_{max} 3550 (br) and 3450 (br) cm^{-1}; δ ($CDCl_3$) 7.38-6.82 (4H, m), 4.16 (1H, br), 3.82 (3H, s), and 1.58 (6H, s); m/e 166 (7%), 151 (100), 148 (1), 133 (34), 121 (18), 105 (50), 91 (16), 77 (29), 65 (16), and 43 (100).

2-(4-Aminophenyl)-propan-2-ol (171)

(a)[160] A mixture of concentrated H_2SO_4 (75 g) and concentrated HNO_3 (55 g) was stirred dropwise into cumene (86.0 g; 716.7 mmole) at 45°. The temperature was maintained within a few degrees of 45° while the mixture was stirred vigorously for 2 h. The nitration products were then separated off, washed with water, 5% $NaHCO_3$, and again with water. After drying this solution over Na_2SO_4, the crude mixture, 56.14 g, was separated by means of a 30 inch spinning band column. 4-Nitrocumene had bp 179-80° (78 mm) [Lit.[160] 131° (14 mm)].

(b)[161] 4-Nitrocumene (2.5 g; 15.15 mmole) was added to a solution of acetic anhydride (10.2 ml; 10.97 g; 107.5 mmole) and glacial acetic acid (8.8 ml). Chromium trioxide (1.22 g; 12.2 mmole) was added over 3 h whilst stirring with the temperature between 23 and 30°. The solution was then stirred for 4 days and then poured on to ice. $NaHCO_3$ (2.7 g; 32.1 mmole) was stirred in and the solution left to stand overnight before extracting with ether (2 x 10 ml). The combined extracts were washed with water, $NaHCO_3$ solution, and again with water before being dried and evaporated to yield 2-(4-nitrophenyl)-propan-2-ol, 1.23 g (45%). It had bp 124° (0.7 mm) [Lit.[161] 121° (2 mm)].

(c)[162] Hydrazine hydrate (2 ml x 60% solution; ca. 24 mmole) was added to 2-(4-nitrophenyl)-propan-2-ol (1.0 g; 5.52 mmole) in ethanol (100 ml). After the solution had been warmed on a steambath a small amount of Raney nickel was added. After some initial frothing the solution changed from brown to almost colourless. More catalyst was then added to destroy any excess hydrazine and the solution was heated under reflux

until no more effervesence was observed. The nickel was filtered off and the product obtained by pouring the solution on to ice and extracting into ether. After the extracts were dried and evaporated the product was carefully distilled. It was found that unless a very good vacuum was used ($<$ 0.1 mm) the product tended to dehydrate when distilled. It had bp 78-83 (0.05 mm) [Lit.[151] 110-1° (0.2 mm)]. Due to extensive decomposition during distillation it was not possible to calculate an overall yield or to obtain an analysis. The compound after distillation was shown to be $>$ 90% pure by nmr. It had δ ($CDCl_3$) 7.27 (2H, d), 6.64 (2H, d), 2.87 (3H, br), and 1.52 (6H, s).

2-(4-Hydroxyphenyl)-propan-2-ol (172)

Methyl 4-hydroxybenzoate (7.60 g; 50 mmole) was added to MeMgI (400 mmole) in the usual way. Yield: 5.18 g (68%). It had mp 124-6° (softened at 112-8°) (from EtOH) [Lit.[149,152,153] 102-10° (d); 107°; 174.1-4.8°]; ν_{max} 3400 and 3125 (br) cm^{-1}; δ (d_6-acetone) 8.08 (1H, br), 7.35 (2H, d), 6.77 (2H, d), 3.86 (1H, s), and 1.48 (6H, s); m/e 152 (3%), 137 (27), 134 (3), 119 (3), 91 (3), 77 (4), 65 (7), and 43 (100). (Found: C, 71.40; H, 8.21. $C_9H_{12}O_2$ requires C, 71.05; H, 7.95%).

2-(4-Methoxyphenyl)-propan-2-ol (173)

Acetone (580 mg; 10 mmole) was added to 4-methoxyphenyl magnesium bromide prepared from 4-bromoanisole (5.61 g; 30 mmole) and magnesium (730 mg; 30 mmole) in the usual way. The product was found to be contaminated with some 4-bromoanisole but was successfully purified

by fractional distillation. Yield: 1.02 g (62%). It had bp 80-2° (0.15 mm) [Lit.[154] 122° (13 mm)]; ν_{max} 3430 (br) cm^{-1}; δ ($CDCl_3$) 7.36 (2H, d), 6.82 (2H, d), 3.72 (3H, s), 2.45 (1H, br), and 1.51 (6H, s); m/e 166 (5%), 151 (29), 148 (1), 109 (6), 91 (2), 77 (8), 65 (6), and 43 (100).

2'-Hydroxy-2,4,4-trimethylflavan (174)

When 2-(2-hydroxyphenyl)-propan-2-ol (5.0 g; 32.9 mmole) in concentrated HCl (50 ml) was heated under reflux for 24 h, neutralised with ammonia, extracted into ether and then the ether extracts dried and evaporated, a solid was obtained which was recrystallised from petroleum ether (bp 60-80°). It had mp 92-4° [Lit.[163] 97°]; ν_{max} 3400 (br) cm^{-1}; δ ($CDCl_3$) 8.10 (1H, br), 7.38-6.72 (8H, m), 2.62 (1H, d), 2.07 (1H, d), 1.70 (3H, s), 1.42 (3H, s), and 1.15 (3H, s); m/e 268 (20%), 253 (11), 225 (9), 147 (38), 135 (94), 134 (54), 121 (35), 119 (40), 107 (54), 91 (100), and 43 (35). (Found: C, 80.04; H, 7.94. $C_{18}H_{20}O_2$ requires C, 80.60; H, 7.46%). Accurate mass 268.1473 ($C_{18}H_{20}O_2$ requires 268.1463).

Appendix

Materials and Apparatus

Ultraviolet and visible spectra were obtained on a Unicam SP800 instrument. When possible, analytical samples were used and all were recorded as solutions in methanol.

Infrared spectra were measured with a Perkin Elmer 257 spectrometer. Solids were recorded as nujol mulls while oils were recorded as liquid films.

Proton nmr spectra were run on a Varian HA 100 spectrometer operating at 100 MHz. They were recorded as 10% (w/v) solutions with tetramethylsilane as internal reference. When coupling constants were measured sweep width of the spectrum was 100 Hz. 220 MHz spectra were recorded at PCMU on a HR 220 spectrometer.

^{13}C nmr spectra were recorded at Edinburgh University by Dr. A. Boyd on a XL 100 spectrometer operating at 25.2 MHz.

Mass spectra were recorded and molecular weights determined on an AEI MS 902 instrument.

Melting points were determined in open capillaries and are uncorrected.

Column chromatography was carried out on either activated alumina type H 100/200 mesh or silica gel grade M60.

Thin layer chromatography was done on silica (MN Kieselgel G) coated plates or alumina (MN Aluminium oxide G) coated plates, the layer of adsorbant being 0.25 mm. When the adsorbant was impregnated with $AgNO_3$, the proportion used was 10% (w/w) of $AgNO_3$ to silica.

Preparative plates had a layer thickness of 1 mm.

Concentrated H_2SO_4 had density 1.84, concentrated HNO_3 1.42, fuming HNO_3 1.50, concentrated HCl 1.18, and concentrated ammonia solution 0.88.

Abbreviations

s :	singlet
d :	doublet
dd :	double doublet
t :	triplet
q :	quartet
m :	multiplet
br :	broad
sh :	shoulder
(d) :	with decomposition (after melting point)
TMS :	tetramethylsilane
DMSO :	dimethylsulphoxide
APL :	Apiezon L

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