(a) 2:3-DIHYDRO-3-OXOBENZ-1:4-OXAZINES.

(b) A NOTE ON LYCORINE.

THESIS

submitted by

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for the Degree of Ph.D.

of Glasgow University.

Glasgow. October 1954.

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SUMMARY.

Part I. The chemistry of the 2:3-dihydro-3-oxobenz-1:4-oxazines is reviewed, and a general method for their N-methylation developed. The possession of a feebly reactive methylene group is demonstrated in the formation of a benzylidene derivative by 2:3-dihydro-3-oxobenz-1:4-oxazine and its N-methyl derivative. Reduction of 2:3-dihydro-4-methyl-3-oxobenz-1:4-oxazine with lithium aluminium hydride is shown to give 2:3-dihydro-4-methyl-benz-1:4-oxazine.

The reaction with aluminium chloride whereby chloroacetyl-N-methyl-o-anisidide yields 2:3-dihydro-4-methyl-3-oxobenz-1:4-oxazine and, hence, a mixture of hydroxy-1-methyloxindoles is investigated and a search made for other examples of analogous rearrangements. The formation of benzoxazine derivatives from chloroacetyl-o-anisidides appears to be general, and proceeds through demethylation to chloroacetyl-o-amido phenols, which are isolable only when the nitrogen atom does not carry a methyl substituent, and which yield the corresponding benzoxazines on dissolution in alkali. The rearrangement of these oxazines to oxindoles appears to depend on two factors (a) the presence of an N-methyl

substituent (b) the stability of the compound at the high reaction temperatures used. Hence, no oxindoles could be obtained from benz-1:4-oxazines which did not carry an N-methyl group. 2:3-Dihydro-2:4-dimethyl-3-oxobenz-1:4-oxazine rearranges to a single product, 7-hydroxy-1:3-dimethyloxindole, which is identified by conversion to, and independent synthesis of, 7-methoxy-1:3-dimethylindole. No oxindoles could be obtained, either, from 2:3-dihydro-6-hydroxy-4-methyl-3-oxobenz-1:4-oxazine, 2:3-dihydro-7-hydroxy-4-methyl-3-oxobenz-1:4-oxazine (or the corresponding N-methylanilides), or 5:6-benz-2:3-dihydro-4-methyl-3-oxobenz-1:4-oxazine owing to their instability in the high temperature melt. Incidentally to the preparative work entailed in this study, a convenient preparation of 2:4-dimethoxynitrobenzene is evolved.

The action of aluminium chloride on β-chloropropionyl-o-anisidide and -N-methyl-o-anisidide, leading to 3:4-dihydrocarbostyrils is examined. In each case a single product is obtained and is identified as 3:4-dihydro-8-hydroxycarbostyril and its N-methyl derivative respectively.

Part II. Lycorine is obtained from the bulbs of Narcissus pseudonarcissus. The products of fusing the

alkaloid with potassium hydroxide are examined, but although the formation of indole, or a simple indole derivative, is indicated by colour reactions, conclusive proof is still lacking. Attempts to dehydrate lycorine under mild conditions failed.

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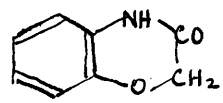
INTRODUCTION.



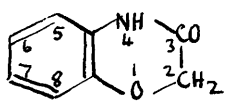
(I)

2:3-Dihydro-3-oxobenz-1:4-oxazine (I), also called benzmorpholone, phenmorpholone, or o-aminophenoxyacetic anhydride, was first described in 1879 by Fritzsche[1], who obtained it by the reduction of o-nitrophenoxyacetic acid with stannous chloride and hydrochloric acid during an attempt to prepare derivatives of o-aminophenoxyacetic acid, and who reported its melting point as 143-144°. Since then other workers have also obtained the substance as colourless needles, m.p. 172°, usually during the course of reduction experiments with o-nitrophenoxyacetic acid. Numerous substituted 2:3-dihydro-3-oxobenz-1:4-oxazines are described in the literature, but no concise account of their properties or reactivity has been published. The purpose of this section is, therefore, to summarise briefly the chemistry of these compounds.

It might be mentioned here that the

N-alkylated 2:3-dihydro-3-oxobenz-1:4-oxazines were found to be active against cramp and, at one time in the history of these compounds, a method for the preparation of the alkyl derivatives appears in the Patent literature(2).

Arsonic acids containing the 2:3-dihydro-3-oxobenz-1:4-oxazine nucleus have also been synthesised by Newbery, Phillips, and Stickings(3) and tested for their activity against Venereal Disease.



The 2:3-dihydro-3-oxobenz-1:4-oxazine ring system is numbered as shown above.

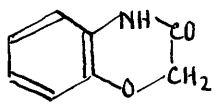
2:3-Dihydro-3-oxobenz-1:4-oxazine crystallises from water as colourless needles, m.p. 173° (corr.)(4). Its aqueous solution is neutral to litmus(5) but it is soluble in sodium or potassium hydroxides, although insoluble in ammonium hydroxide. 2:3-Dihydro-3-oxobenz-1:4-oxazine, dissolved in alkali, is precipitated from solution, on standing, by the carbon

dioxide of the air[1]. It is soluble in concentrated sulphuric acid, being reprecipitated by the addition of water, and it is slightly more soluble in concentrated hydrochloric acid than it is in pure water[1].

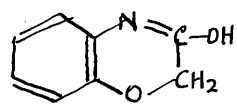
Thate[5] was able to prepare the potassium salt of o-aminophenoxyacetic acid from 2:3-dihydro-3-oxo-benz-1:4-oxazine by boiling with alkali, and from this the lead and silver salts by treatment with the appropriate lead or silver compound.

Fritzsche[1], as stated before, first obtained 2:3-dihydro-3-oxobenz-1:4-oxazine as colourless needles, m.p. 143-144° by reduction of o-nitrophenoxyacetic acid with stannous chloride and hydrochloric acid. Thate[5] next obtained the compound, m.p. 169° by the reduction of the nitro- acid with iron filings and acetic acid. He then went on to show that reduction with stannous chloride and hydrochloric acid gave a mixture of 2:3-dihydro-3-oxobenz-1:4-oxazine and a monochloro-derivative and suggested that Fritzsche's compound was a mixture of the two latter compounds. However, Duparc[6] also claims to have isolated a form of 2:3-dihydro-3-oxo-benz-1:4-oxazine of m.p. 144°, and he suggests that this is the enol form of the compound, but he was unable to

obtain an acetyl derivative, even with acetic anhydride at 180°, or a methyl derivative. He therefore concludes that there is insufficient evidence for his former hypothesis to be tenable.

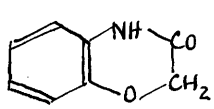


m.p. 173°

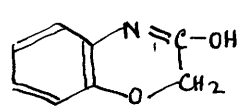


m.p. 144°.

Wheeler and Barnes[7] investigated more fully the properties of 2:3-dihydro-3-oxobenz-1:4-oxazines. They discovered that sodium, potassium, and silver salts could be prepared and that the sodium or potassium salts reacted to give derivatives of (I) and the silver salts derivatives of (II).



(I)



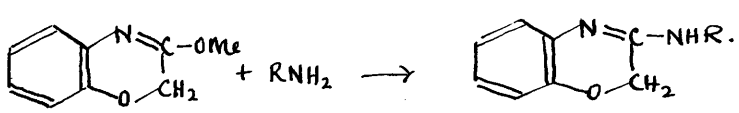
(II)

Reaction of methyl or ethyl iodide with the potassium derivative gave 2:3-dihydro-4-methyl-3-oxobenz-1:4-oxazine, or the 4-ethyl derivative. That the

methyl group was attached to the nitrogen atom was shown by degradation to o-methylaminophenol.

The silver salts are prepared by the action of silver nitrate on the sodium or potassium salt, and are stable to light, water, and alcohol. The salt is easily reduced by phenol, as are the silver salts of formanilide and 2:4-dichloroformanilide. Heating the silver salt with methyl iodide at 115-120° gives the methyl ether of (II). The ethyl, isopropyl, isobutyl, and isoamyl derivatives can be similarly prepared. The silver salt reacts with acetyl chloride to form the N-acetyl derivative.

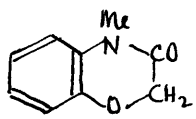
When the methyl ether of (II) is mixed with an amine, a crystalline solid separates. This has the general formula (III). R can be either alkyl or aryl[7].



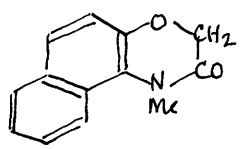
(III)

Lees and Shedden[8] attempted to reduce some 2:3-dihydro-3-oxobenz-1:4-oxazines electrolytically.

They found that, under the conditions of electrolysis the oxazine ring was remarkably unstable and that, for the most part, reduction gave degradation products such as acetamidophenols and ethylaminophenols. However, 2:3-dihydro-4-methyl-3-oxobenz-1:4-oxazine (IV) and 5:6-benz-2:3-dihydro-4-methyl-3-oxobenz-1:4-oxazine (V) gave a little of the corresponding 2:3-dihydrobenz-1:4-oxazine.



(IV)

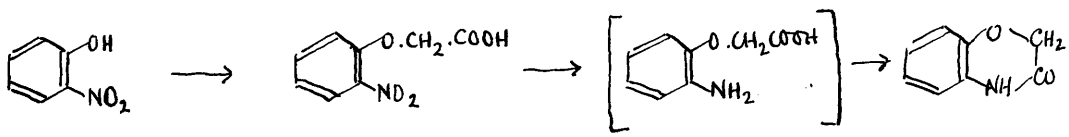


(V)

In the present work, it has been found that reduction of 2:3-dihydro-4-methyl-3-oxobenz-1:4-oxazine with lithium aluminium hydride affords 2:3-dihydro-4-methylbenz-1:4-oxazine, identical in properties to that obtained by Knorr[9, 10]. This result is in accordance with experimental work carried out by various people[11, 12, 13] on the reduction of amides with lithium aluminium hydride. They showed that reduction affords the corresponding amine.

SYNTHESIS.

There are two main recorded routes to this type of compound. In one, the appropriate o-nitrophenol is converted into the o-nitro- (VI) and, hence, into the o-aminophenoxyacetic acid (VII), which is never isolated but, under the reducing conditions, undergoes spontaneous dehydration to the dihydrobenz-1:4-oxazine (I).

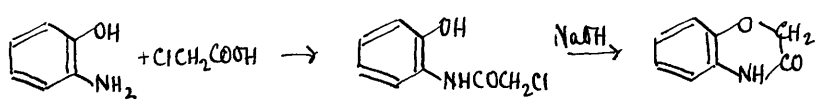


(VI) (VII) (I).

This method has been used for the synthesis of (I) by Fritzsche[1], Bischoff[14], and Jacobs and Heidelberger[4]. The 2-methyl derivative of (I) was prepared also in this way by Bischoff[15], and the 6-, 7-, and 8-methyl derivatives by Minton and Stephen[16]. The 5-, 6-, 7-, and 8-amino- derivatives of (I) were prepared by Newbery and Phillips[17] by reduction of the corresponding dinitrophenoxyacetic acids. The 6-amino- derivative was also prepared by Howard[18].

The second synthetic method utilises

o-aminophenol as starting material. The o-aminophenol (VIII) is condensed with chloroacetyl chloride, the product being chloroacetyl-o-amidophenol (IX). When (IX) is dissolved in dilute sodium hydroxide, hydrochloric acid is eliminated and (I) crystallises out after a short time. This method has been used for the preparation of (I) by Aschan[19], and v. Auwers and Frese[20]. Puxeddu and Sanna[21, 22, 23] and Sanna and Vacca[24] have also used this method with success for the preparation of 2:3-dihydro-3-oxobenz-1:4-oxazines related to 6-allyl-2:3-dihydro-8-methoxy-3-oxobenz-1:4-oxazine, which they isolated from 5-chloroacetamidoeugenol by the action of alkali. The 2-isobutyl and the 2-isopropyl derivatives of (I) were the compounds which they synthesised.



(VIII) (IX) (I).

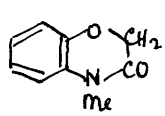
Both of these routes have been followed in the present work to prepare known and new compounds of this class. In the first route, the metal-acid methods of reducing the o-nitrophenoxyacetic acid were

superseded by reduction using palladium black in acetic acid. Reduction by this means took place rapidly and smoothly, excellent yields of the product being obtained in every case. The hitherto unknown 5-methyl derivative of (I) was prepared in this way.

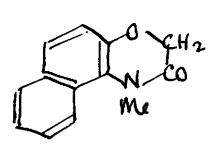
The second route was especially useful, and certain modifications were introduced. o-Methoxyanilines were used in place of o-aminophenols. These were condensed with chloroacetyl chloride, in benzene, together with either one mole excess of the base or with one mole of pyridine to combine with the hydrochloric acid produced. It was found that this condensation was practically quantitative in the cold. Heating of the benzene-pyridine solution to complete the reaction was unnecessary and merely caused the reaction mixture to turn brown. Since the starting materials were o-methoxyanilines, demethylation had to be carried out after condensation. This was conveniently achieved by mixing the methoxychloroacetanilide with powdered anhydrous aluminium chloride and heating the mixture to 80-100° for a short time. Decomposition of the resulting complex with iced hydrochloric acid gave the demethylated compound in good yield. Heating the aluminium chloride/o-methoxychloroacetanilide melt at

160° for a protracted time (one hour) in certain cases resulted in the direct formation of the 2:3-dihydro-3-oxobenz-1:4-oxazine. When these o-methoxy-chloroacetanilides had been previously N-methylated, the product, at both temperatures, was the 2:3-dihydro-4-methyl-3-oxobenz-1:4-oxazine.

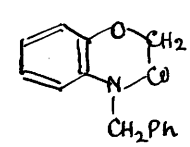
N-Alkyl and -arylalkyl derivatives of 2:3-dihydro-3-oxobenz-1:4-oxazine have been known for some considerable time and they have been prepared in diverse ways. Wheeler and Barnes[7] prepared 2:3-dihydro-4-methyl-3-oxobenz-1:4-oxazine (IV) by heating 2:3-dihydro-3-oxobenz-1:4-oxazine with methyl iodide in sodium methoxide solution at 135°, while Lees and Shedden[8] prepared 5:6-benz-2:3-dihydro-4-methyl-3-oxo-benz-1:4-oxazine (X) by the action of methyl iodide on the unsubstituted oxazine, in alcohol, at 100°.



(IV)



(X)



(XI)

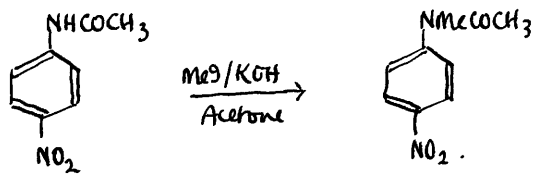
Preiswerk and Meyer[2] prepared 4-benzyl-2:3-dihydro-3-oxobenz-1:4-oxazine (XI) and

various other N-benzylated 2:3-dihydro-3-oxobenz-1:4-oxazines by heating the appropriate benz-1:4-oxazine with potassium carbonate and benzyl chloride at 160° for six hours.

During the course of the present work, it was discovered that 2:3-dihydro-3-oxobenz-1:4-oxazine could be methylated in about 50% yield by treatment with dimethyl sulphate in alkali. However, it was found that this method failed completely with the 5- and 8-methyl derivatives, due to their insolubility in alkali. Accordingly, a more general method of N-alkylation was sought.

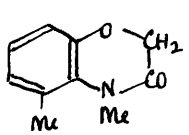
Pachter and Kloetzal[25] discovered that simple anilides could be alkylated quickly and in good yield by refluxing the anilide with alkyl iodide and solid potassium hydroxide in acetone. In this way they succeeded in alkylating, in almost 100% yield, compounds such as p-nitroacetanilide (XII) which could not be alkylated by other methods. Now, 2:3-dihydro-3-oxobenz-1:4-oxazine is a cyclic anilide, and as such should be readily alkylated by this method. This was found to be the case. Refluxing the free imido-compound with methyl iodide and powdered potassium hydroxide in "Analar" acetone for a few

minutes afforded excellent yields of the N-methylated products.

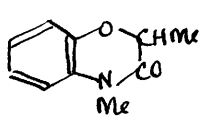


(XII).

2:3-Dihydro-4-methyl-3-oxobenz-1:4-oxazine (IV), 2:3-dihydro-4:5-dimethyl-3-oxobenz-1:4-oxazine (XIII), 5:6-benz-2:3-dihydro-4-methyl-3-oxobenz-1:4-oxazine (X), and 2:3-dihydro-2:4-dimethyl-3-oxobenz-1:4-oxazine (XIV) were prepared in excellent yields by this method. 4-Benzyl-2:3-dihydro-3-oxobenz-1:4-oxazine (XI) was also prepared, using the corresponding benzyl chloride, although in this case the yield was slightly poorer.



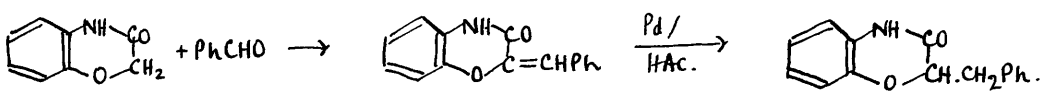
(XIII)



(XIV)

METHYLENE REACTIVITY OF 2:3-DIHYDRO-3-OXOBENZ-1:4-OXAZINE.

Although derivatives of the enol form (II) of 2:3-dihydro-3-oxobenz-1:4-oxazine have been reported by Wheeler and Barnes[7], who prepared various 3-substituted derivatives by condensing the methyl ether of the enol form (II) with various amines, there has been, so far, no mention of the methylene reactivity, or its absence, of the compound. Since the methylene group is activated by the presence of the adjacent carbonyl group, 2:3-dihydro-3-oxobenz-1:4-oxazine should be capable of being condensed with reagents such as benzaldehyde.

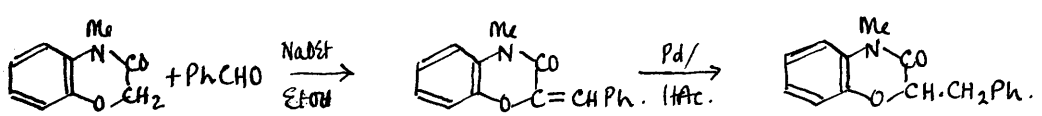


(I) (XV) (XVI)

When the compound was refluxed with benzaldehyde and freshly fused sodium acetate in acetic anhydride for some time, i.e. under the conditions of the Perkin condensation, a substance which analysed for the expected condensation product, 2-benzylidene-2:3-dihydro-3-oxobenz-1:4-oxazine (XV), was obtained, but in very poor yield. It crystallised from alcohol as long, pale

yellow, needles and on reduction with palladium black in acetic acid it absorbed one mole of hydrogen giving colourless needles of 2-benzyl-2:3-dihydro-3-oxo-benz-1:4-oxazine (XVI).

Condensation of 2:3-dihydro-4-methyl-3-oxo-benz-1:4-oxazine (IV) with benzaldehyde afforded slightly better results. The condensation was attempted by dissolving (IV) and benzaldehyde in alcohol containing sodium methoxide and leaving aside in the cold for a few days. This method gave no product. However, when (IV) was refluxed with benzaldehyde in alcoholic sodium ethoxide for 24 hours, concentration of the reaction mixture gave a product which separated as long, yellow, needles and analysed for the expected condensation product, 2-benzylidene-2:3-dihydro-4-methyl-3-oxobenz-1:4-oxazine (XVII). Again the yield was poor.



(IV) (XVII) (XVIII)

A third repetition of the reaction, this time using sodamide in benzene as the condensing agent,

gave much better results, the product being isolated in 32% yield. Reduction of (XVII) with palladium black in acetic acid resulted in the absorption of one mole of hydrogen and the formation of 2-benzyl-2:3-dihydro-4-methyl-3-oxobenz-1:4-oxazine (XVIII) as a colourless oil, which, even after distillation, did not crystallise. An attempt to improve the yield of the condensation product by using toluene as a solvent was unsuccessful, a lower yield being obtained.

An attempted Mannich condensation with 40% formaldehyde and aqueous dimethylamine failed, starting material being recovered in good yield. (IV) also failed to condense with o-chlorobenzaldehyde.

On the other hand, condensation of (IV) with diethyl oxalate or m-chlorobenzaldehyde gave small quantities of crystalline materials which did not have the expected composition.

From the foregoing series of reactions, it would appear that, as is to be expected, 2:3-dihydro-3-oxobenz-1:4-oxazine and its derivatives contain a reactive methylene group. It would appear, also, that this methylene reactivity is very feeble, requiring the

strongest condensing conditions for reaction.

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SYNTHESIS OF 2:4-DIMETHOXYANILINE.

During the course of this work it became necessary to prepare a considerable quantity of 2:4-dimethoxyaniline. This is readily obtainable from the corresponding dimethoxynitrobenzene by reduction. However, a search of the literature on the subject revealed that, although 2:4-dimethoxynitrobenzene was known, it had been prepared by diverse and more or less complicated ways. For example, Blanksma[26] prepared it from 5-chloro-2-nitroanisole by heating this substance with sodium methoxide and methanol at 150°, while Vermeulen[27] prepared it from 2:5-dinitroanisole by boiling with the same reagents. In fact, most of the recorded syntheses involve replacement of another atom or group through heating with sodium methoxide. In no case had it been obtained by a simple nitration of resorcinol dimethyl ether.

Since nitration of resorcinol dimethyl ether with fuming nitric acid in acetic acid gives 4:6-dinitroresorcinol dimethyl ether[28], and none of the

methods of nitrating resorcinol gives an appreciable quantity of the 4-nitro isomer, other conditions for the mono-nitration of resorcinol dimethyl ether were sought.

Cook et al.[29, 30] have shown that when a methoxy compound with a free para position is sulphonated with concentrated sulphuric acid, it sulphonates in this position, and that, under suitable conditions of dilution, this sulphonic acid group can be replaced to give the mono-nitro derivative. Arni[31] has succeeded in preparing 4-nitro-3-phenyl methyl ether by this method. The reaction was applied, therefore, to resorcinol dimethyl ether.

A solution of the sulphonic acid in concentrated sulphuric acid was prepared. A constant weight (5g.) of this mixture was taken and various quantities of water and concentrated nitric acid were added. The mixture was allowed to stand overnight and the product was then worked up. The results are shown in table I.

The experiment was repeated, this time using glacial acetic acid as a solvent. Resorcinol dimethyl ether was dissolved in glacial acetic acid and

TABLE I.

Volume of water.	Volume of conc. nitric acid.	Remarks.
0.25ml.	1 ml.	Small amount of solid m.p. 120-130° obtained.
0.5 ml.	1 ml.	Small amount of solid m.p. 120-130° obtained.
0.75ml.	1 ml.	No product.
1.0 ml.	1 ml.	No product.
1.5 ml.	1 ml.	No product.
2.0 ml.	1 ml.	No product.
2.5 ml.	1 ml.	No product.
3.0 ml.	1 ml.	No product.

TABLE II.

Volume of acetic.	Volume of sulphuric.	Volume of water.	Volume of nitric.	Yield.
1 ml.	1 ml.	0.75 ml.	1 ml.	0.15g; 11%.
2 ml.	1 ml.	0.75 ml.	1 ml.	0.20g; 15%.
3 ml.	1 ml.	0.75 ml.	1 ml.	0.25g; 19%.
4 ml.	1 ml.	0.75 ml.	1 ml.	0.25g; 19%.
5 ml.	1 ml.	0.75 ml.	1 ml.	0.30g; 23%.
6 ml.	1 ml.	0.75 ml.	1 ml.	0.30g; 23%.

concentrated sulphuric acid added slowly. The solution was heated to 50° for a few minutes to promote sulphonation, and then cooled. Water, followed by nitric acid was added and the solution left overnight. After addition of more water, the product was worked up. The results are shown in tables II and III.

An attempt was made to catalyse the reaction by means of the addition of a small amount of mercuric nitrate. A second series of experiments, similar to those in table III, but with the addition of a very small amount of mercuric nitrate after the water, was run. In all cases the yield was diminished and not increased as had been hoped. The results are shown in table IV.

From the foregoing results, it would appear that there are optimum values for dilution, both with water and acetic acid, before nitration. At best, however, the yield is only in the region of 35%. This was borne out when the experiment was repeated on a larger (20g.) scale. The yield remained reasonably constant at 30-35%.

Another method of nitration was attempted.

TABLE III.

Volume of acetic.	Volume of sulphuric.	Volume of water.	Volume of nitric.	Yield.
5 ml.	1 ml.	0.25ml.	1 ml.	0.30g; 23%.
5 ml.	1 ml.	0.50ml.	1 ml.	0.40g; 30%.
5 ml.	1 ml.	0.75ml.	1 ml.	0.45g; 34%.
5 ml.	1 ml.	1.00ml.	1 ml.	0.50g; 38%.
5 ml.	1 ml.	1.50ml.	1 ml.	0.35g; 26%.

TABLE IV.

Volume of acetic.	Volume of sulphuric.	Volume of water.	Volume of nitric.	Yield.
5 ml.	1 ml.	0.25ml.	1 ml.	0.20g; 15%.
5 ml.	1 ml.	0.50ml.	1 ml.	0.35g; 26%.
5 ml.	1 ml.	0.75ml.	1 ml.	0.35g; 26%.
5 ml.	1 ml.	1.00ml.	1 ml.	0.35g; 26%.
5 ml.	1 ml.	1.50ml.	1 ml.	0.20g; 15%.

Menke[32] has shown that a mixture of copper nitrate and acetic anhydride can be used as a mild nitrating agent. When this method was applied to resorcinol dimethyl ether, reaction appeared to take place, and when the reaction mixture was worked up 2:4-dimethoxynitrobenzene was obtained. The yields by this method are in the region of 70%.

---oooOOOooo---

ACTION OF ALUMINIUM CHLORIDE ON O-METHOXYCHLOROACETANILIDES AND 2:3-DIHYDRO-3-OXOBENZ-1:4-OXAZINES.

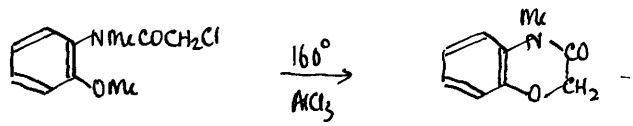
One important ring closure brought about by anhydrous aluminium chloride is the cyclisation of an -haloacetanilide, with the elimination of hydrogen chloride, to give an oxindole. The reaction was first utilised by Stolle[33].

The Stolle oxindole synthesis is one of the most recently devised of the major oxindole syntheses, and was first used by Stolle in 1914 for the preparation of 1-ethyl and 1-phenyl oxindole[33]. The aniline and the acid chloride can be considerably varied and still yield anilides which are capable of conversion to oxindoles. In particular, p-anisidine[34] and N-methyl-p-anisidine[35] have been converted to oxindoles in this way.

α-Chlorohalides of propionic acid have also been used in place of the simple chloroacetyl chloride[35, 36, 37]. In this case, 3-alkyloxindoles result

In general, the ease of ring closure varies

with the degree of substitution of the anilide. The more highly substituted the anilide, the more easily does the ring closure take place and thus, the lower the reaction temperature required. In particular, the presence of an N- substituent is important. In many cases, oxindoles cannot be obtained, under the Stolle conditions, if there is no substituent on the nitrogen atom. In fact, oxindole itself cannot be obtained from chloroacetanilide with Stolle's experimental conditions[38]. Stolle himself recommended the method only for the preparation of 1-alkyloxindoles. Recently, however, Abramovich and Hey[39] have prepared oxindole from chloroacetanilide by fusion with an aluminium chloride/sodium chloride melt for a very short time.

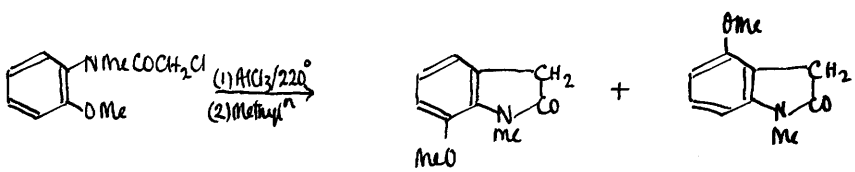


(XIX) (IV)

Interest arose in the Stolle reaction as applied to chloroacetyl-N-methyl-o-anisidide (XIX) when, thereby, Cook, Loudon, and McCloskey[40] attempted to prepare 7-methoxy-1-methyloxindole a material which was not available in quantity by any of the usual synthetic

routes. They discovered that at relatively low temperatures (ca. 160°) the product was the 2:3-dihydro-4-methyl-3-oxobenz-1:4-oxazine (IV).

The product of the high temperature reaction (220°) was not homogeneous, and by methylation was found to yield two isomeric methoxy-1-methyloxindoles, (XX) and (XXI), which were identified by independent syntheses and by reduction to the corresponding known methoxy-1-methylindoles.



(XIX) (XX) (XXI)

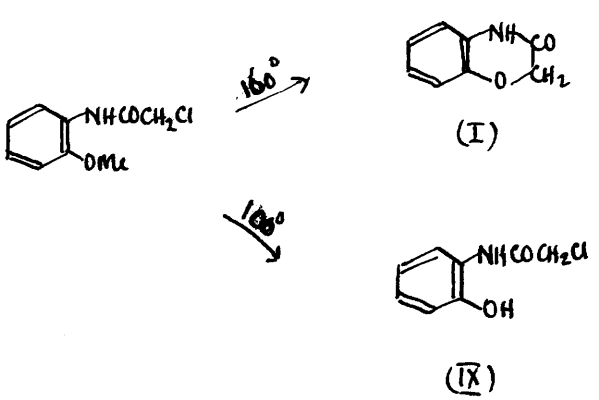
The rearrangement involved in this production of 4-methoxy-1-methyloxindole has some novel features; moreover this type of ring opening and recyclisation is quite unexplored and it was therefore of interest to examine more closely these reactions and their potentialities for synthesis.

Kretz, Muller, and Schlittler[41], who simultaneously reported this reaction, failed to observe

that the product was not homogeneous and assigned the 7-hydroxy-1-methyloxindole structure to the compound which is now shown to be 4-hydroxy-1-methyloxindole.

Cyclisation of chloroacetyl-o-anisidide and chloroacetyl-N-methyl-o-anisidide.

The action of anhydrous aluminium chloride on chloroacetyl-o-anisidide is two-fold. At lower temperatures (ca. 100°) the product is chloroacetyl-o-amidophenol (IX) and at higher temperatures (160°) 2:3-dihydro-3-oxobenz-1:4-oxazine (I) is obtained. Prolonged treatment at elevated temperatures (220°) with anhydrous aluminium chloride failed to produce any rearrangement to an oxindole. This result is in agreement with Stolle's original work, in as much as he recommended his reaction only for the preparation of 1-alkyloxindoles.



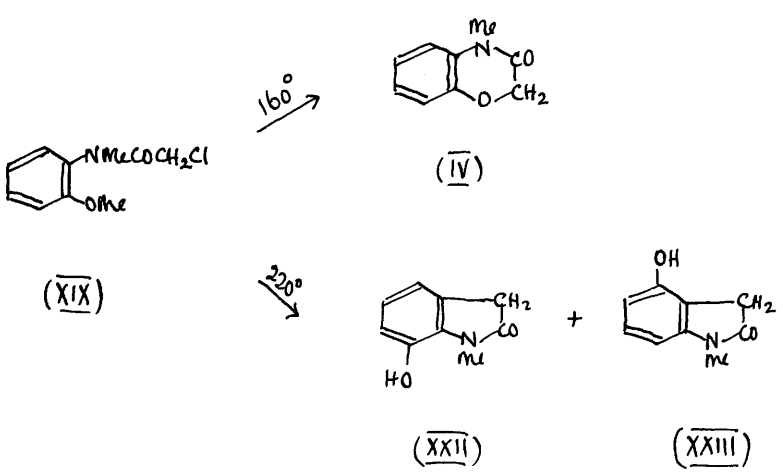
When the pre-formed oxazine (I) was fused with anhydrous aluminium chloride at 220° for 20 minutes, cooling and decomposition of the resulting complex gave a solid of m.p. 114-115°, after recrystallisation from water. Boiling this material to small bulk with dilute hydrochloric acid resulted in the recovery of the oxazine (I), m.p. 167-171° and mixed m.p. with an authentic specimen of (I), 169-171°. The solid, m.p. 114-115°, has a mixed m.p. 125-128° with chloroacetyl-o-amidophenol (IX:m.p.136°), and would thus appear to be a mixture of (I) and (IX), in agreement with the analytical results. (Found: C, 57.32; H, 4.97. Calculated for $C_8H_8O_2NCl.C_8H_7O_2N$: C, 57.4; H, 4.52%.). Indeed, a simple mixture of these two compounds has m.p. 112-116°.

v. Auwers and Frese[20] obtained a similar product, m.p. 114-115° by the action of chloroacetyl chloride on o-aminophenol in weakly alkaline solution, wherein some formation of the oxazine (I) would be expected. They, however, regarded the compound as an allotropic modification of chloroacetyl-o-amidophenol, but gave no analytical figures.

The action of anhydrous aluminium chloride on chloroacetyl-N-methyl-o-anisidide, however, is much

more complicated.

Chloroacetyl-N-methyl-o-anisidide (XIX) was prepared by condensing N-methyl-o-anisidine with chloroacetyl chloride, in benzene, in the presence of pyridine. It was obtained as a solid (cf. Cook et al.[40] who obtained it as an oil). Cook et al.[40] have already shown that fusion of this compound with anhydrous aluminium chloride at 220° gives a mixture of the two isomeric hydroxy-1-methyloxindoles, 7-hydroxy-1-methyl oxindole (XXII) and 4-hydroxy-1-methyloxindole (XXIII), and that at lower temperatures (160°) the product is 2:3-dihydro-4-methyl-3-oxobenz-1:4-oxazine (IV). Methylation of the phenolic product of the fusion at 220° then gave a mixture of the 4- and 7-methoxy-1-methyloxindoles which could be separated by fractional crystallisation from ether.



In the present work these results have been confirmed and the fusions have been more closely investigated. Attempts have also been made to obtain other methods of separating the isomers formed, particularly at the hydroxyoxindole stage.

Chloroacetyl-*N*-methyl-*o*-anisidide was fused with anhydrous aluminium chloride at various temperatures between 180° and 220° for an hour. It was found that there was no specific temperature above which only the oxindole was formed and under which the product was solely the benz-1:4-oxazine. In practice, as the temperature of fusion was raised, the ratio of oxindole to benz-1:4-oxazine became greater until, at 220° the product consisted almost entirely of hydroxyoxindole.

Various attempts were made to separate the two hydroxyoxindoles at this stage. Crystallisation from several solvents was tried; water achieved a partial separation, but the substances did not crystallise well. Chromatography on alumina was ineffective, but chromatography, in methanol, on a charcoal column also achieved a partial separation.

Alkylation of the phenolic product.

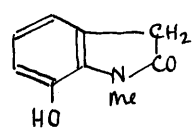
The yield of methyl ethers of the hydroxy-1-methyloxindoles obtained by methylation with dimethyl sulphate in alkali was very poor. A certain amount of polymerisation appeared to take place on distillation of the product and a glassy solid, which was not investigated, was left in the distilling flask.

It was found that a better yield of the methyl ethers could be obtained by methylating the compounds with methyl iodide and powdered potassium carbonate in acetone[42]. Although, on distillation, some resinification still took place, it was considerably less than in the previous case.

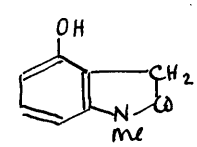
Separation was effected by crystallisation from ether, the method used by Cook et al.[40], in which the 4-methoxy-1-methyloxindole is less soluble and crystallises out first. The second crop consists of a mixture of crystals of the 4- and 7- isomers, and can be readily separated mechanically. Further recrystallisation yields pure samples of each.

4- and 7-Hydroxy-1-methyloxindole.

After separation, both the 7- and 4-methoxy-1-methyloxindoles were demethylated by heating with anhydrous aluminium chloride at 100°. Recrystallisation afforded pure specimens of 4-hydroxy-1-methyloxindole (XXIII) and 7-hydroxy-1-methyloxindole (XXII). Since Cook et al.[40] have already orientated the two isomeric methoxy-1-methyloxindoles, there is no ambiguity as to the structures of these two hydroxy-1-methyloxindoles.



(XXII)

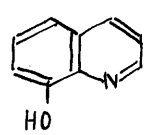


(XXIII)

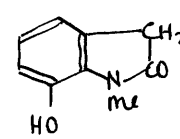
When the melting points of these hydroxy-1-methyloxindoles are compared with that reported by Kretz, Muller, and Schlittler[41] for "7-hydroxy-1-methyl oxindole", it at once emerges that these authors had really isolated the 4-hydroxy isomeride. As found in the present work, 7-hydroxy-1-methyloxindole (XXII) has m.p. 275-277°, while 4-hydroxy-1-methyloxindole (XXIII) has m.p. 230-232°. Kretz, Muller, and Schlittler quote

227-228° as the melting point of their "7-hydroxy-1-methyl oxindole".

Some of the reactions of these two hydroxy-1-methyloxindoles have been studied. 7-Hydroxy-1-methyl oxindole contains a hydroxyl group peri to a heterocyclic tertiary nitrogen atom, just the conditions which favour the formation of metallic complexes in 8-hydroxyquinoline (XXIV). The reaction of solutions of 7-hydroxy-1-methyl oxindole (XXII) toward metals was therefore investigated, but in no instance was a complex comparable to that formed by 8-hydroxyquinoline obtained.



(XXIV)

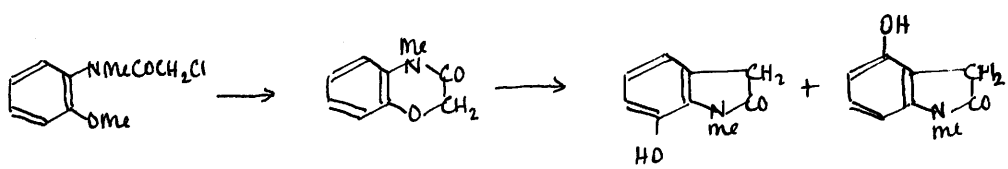


(XXII)

It is a property of m-aminophenols and their mono- or dialkyl derivatives that they give coloured dyestuffs (rhodamines) when fused with phthalic anhydride in the presence of zinc chloride. Only 4-hydroxy-1-methyloxindole (XXIII) is a derivative of a m-aminophenol, and when both (XXII) and (XXIII) were condensed with phthalic anhydride, only (XXIII) gave a

dyestuff.

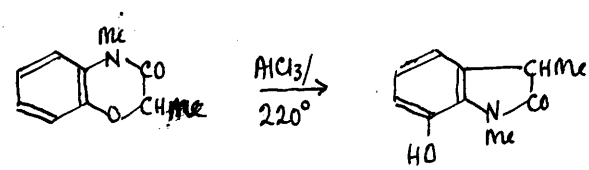
In the foregoing series of experiments, the reaction by which (XXIII) is formed by a double rearrangement of (XIX) is unusual. It is the first instance to be reported of the production of two isomeric oxindoles during a Stolle cyclisation, and, as such, is of considerable interest. In the subsequent series of experiments, specific search was made for parallel cases, but none was found.



(XIX) (IV) (XXII) (XXIII)

Rearrangement of 2:3-dihydro-2:4-dimethyl-3-oxo-benz-1:4-oxazine.

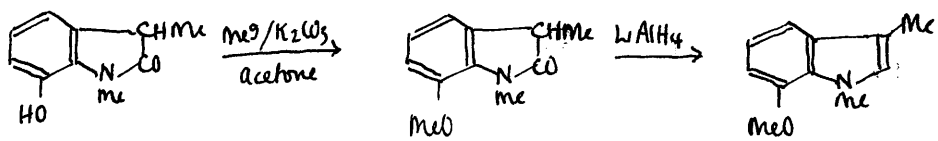
2:3-Dihydro-2:4-dimethyl-3-oxo-benz-1:4-oxazine (XIV) was prepared by condensing -chloropropionyl chloride with o-anisidine in benzene solution, demethylating, and ring-closing the product in dilute sodium hydroxide. Subsequent N-methylation with potassium hydroxide and methyl iodide in acetone afforded the required product in good yield.



(XIV) (XXV).

Treatment of this compound with anhydrous aluminium chloride at 220° for one hour, followed by decomposition of the cooled, powdered complex, afforded a solid which appeared to be homogeneous. It could be purified by chromatography, in methanol, on a charcoal column, only one substance being obtained. Recrystallisation gave 7-hydroxy-1:3-dimethyloxindole (XXV).

Methylation, whether of the crude material or the purified 7-hydroxy-1:3-dimethyloxindole, with potassium carbonate and methyl iodide in acetone, followed by distillation of the product under reduced pressure, gave only one fraction, as a light yellow oil, which soon solidified. Recrystallisation gave 7-methoxy-1:3-dimethyloxindole (XXVI), as clusters of needles.

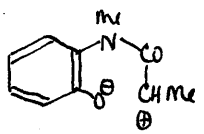


(XXV) (XXVI) (XXVII)

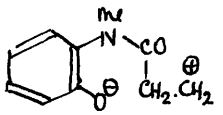
Reduction of the compound, in ether, with an ethereal suspension of lithium aluminium hydride[43] gave a compound which had an indole-like odour, gave a positive Ehrlich's indole test with p-dimethylamino-benzaldehyde, and formed a chocolate coloured picrate. On the basis of these observations and the analytical figures for the base, its picrate, and the picrate of the corresponding indolene, which is also obtained in small quantity during the course of the reduction, the structure (XXVII) of 7-methoxy-1:3-dimethylindole was assigned to it, and its precursors were assumed to be substituted in the appropriate positions.

Ultra-violet spectra determinations seemed to be in agreement with this assumption, in that the spectra of (XXVII) and its precursors were very similar to the spectra of 7-methoxy-1-methylindole and its precursors.

Prior to this proof of the oxindole structure of (XXV) and (XXVI), it was possible, although not perhaps probable, that an intermediate (XXVIII) might have given rise to another intermediate (XXIX) and that, in view of the generally greater ease of forming a six-membered ring, the final product might have been a quinoline derivative.



(XXVIII)

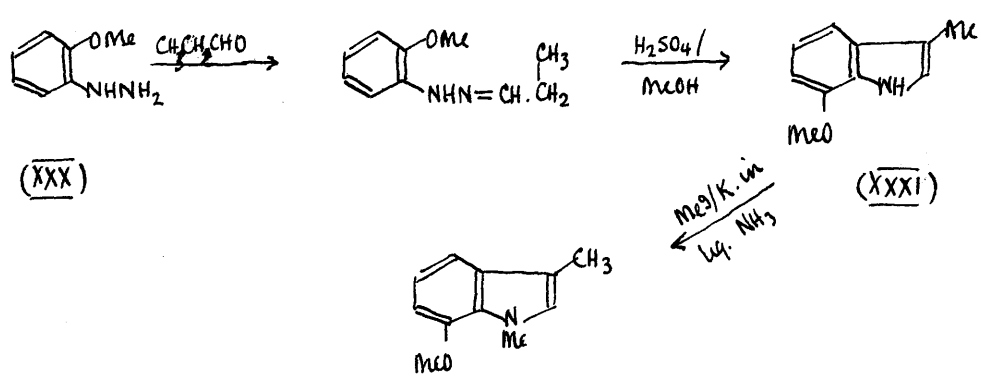


(XXIX)

The postulate that the foregoing series of compounds contains the substituent in the 7- position, however, assumes that there has been no double rearrangement during the reaction with aluminium chloride, and thus it became necessary at this stage to carry out a separate, unambiguous synthesis of the hitherto unknown 7-methoxy-1:3-dimethylindole.

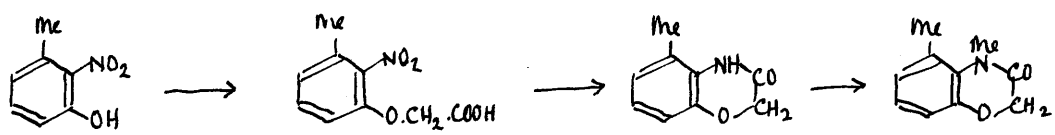
7-Methoxy-3-methylindole has been synthesised before[40, 44], and Cook et al.[40] have shown that 7-methoxyindole can be N-methylated by the action of methyl iodide and sodamide in liquid ammonia. Plieniger[45] and Potts and Saxton[46] have since shown that indoles can, in general, be N-alkylated in this way.

Accordingly, o-methoxyphenylhydrazine (XXX) was condensed with propaldehyde and converted, by means of sulphuric acid and methanol, to 7-methoxy-3-methylindole (XXXI). When (XXXI) was dissolved in liquid ammonia and methylated, purification of the product in petroleum ether (60-80°) on alumina gave 7-methoxy-1:3-dimethylindole (XXVII) which was identical in all respects with that prepared by the action of aluminium chloride on 2:3-dihydro-2:4-dimethyl-3-oxobenz-1:4-oxazine.



Rearrangement of 2:3-dihydro-4:5-dimethyl-3-oxo-benz-1:4-oxazine.

2:3-Dihydro-4:5-dimethyl-3-oxo-benz-1:4-oxazine (XIII) was prepared by condensing chloroacetic acid with o-nitro-m-cresol (XXXII), followed by reduction and N-methylation of the product in the usual way. The intermediate oxazine (XXXIII) is the only one of the four isomeric 2:3-dihydro-3-oxobenz-1:4-oxazines, derived from toluene, which was not prepared by Minton and Stephen[16].



(XXXII) (XXXIII) (XIII)

Treatment of (XIII) with aluminium chloride at 220° afforded an alkali soluble gum, indicating some rearrangement. Reprecipitation from the alkaline solution again gave a gum which was methylated with dimethyl sulphate. Distillation of the product afforded a yellow oil which distilled over a range of temperature, and which solidified on cooling. After recrystallisation, the solid melted over a range of temperature and was

obviously a mixture. Attempts at a separation by crystallisation were unsuccessful.

Wahl and Livovschi[47] demonstrated by the action of aluminium chloride on chloroacetanilides derived from C-dimethyl anilines that migration of nuclear methyl groups takes place under the conditions of the Stolle reaction. Other cases of the migration of nuclear alkyl groups under the influence of anhydrous aluminium chloride have been reported[48, 49]. Whether the mixture of products obtained by the action of aluminium chloride on 2:3-dihydro-4:5-dimethyl-3-oxo-benz-1:4-oxazine arises from a migration of the C-methyl group or from a double rearrangement of the oxazine ring is impossible to determine without separation and adequate identification of the products.

Cyclisation of β-chloropropionyl-o-anisidide and of β-chloropropionyl-N-methyl-o-anisidide.

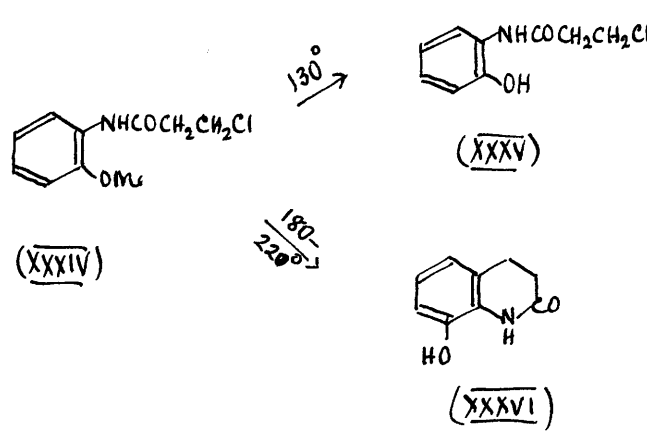
Mayer, Zutphen, and Philipps[50] introduced a modification of Stolle's oxindole synthesis for the synthesis of 3:4-dihydrocarbostyrils. They showed that cyclisation of -chloropropionyl derivatives of many anilines with anhydrous aluminium chloride gave

the corresponding 3:4-dihydrocarbostyril.

In this section, their work as applied to the --chloropropionyl derivative of o-aminophenol has been repeated and extended to show that there has been no rearrangement during cyclisation. In addition, the corresponding 3:4-dihydro-8-hydroxy-1-methylcarbostyril has been prepared from β-chloropropionyl-N-methyl-o-anisidide.

The required anisidides were prepared by condensing β-chloropropionyl chloride with o-anisidine and N-methyl-o-anisidine respectively, in benzene solution.

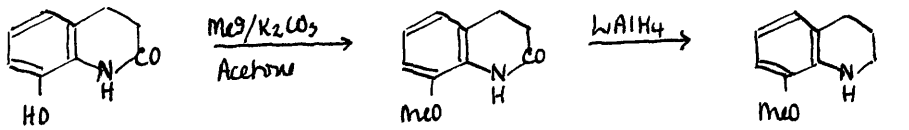
When β-chloropropionyl-o-anisidide (XXXIV) was heated with anhydrous aluminium chloride at 130°, the product was β-chloropropionyl-o-amidophenol (XXXV).



(XXXIV) (XXXV) (XXXVI)

Reaction at higher temperatures (160-220°), however, afforded a product which did not contain chlorine and was presumably 3:4-dihydro-8-hydroxycarbostyril (XXXVI). (XXXV) and (XXXVI) agree in melting point with the compounds previously obtained by Mayer[50].

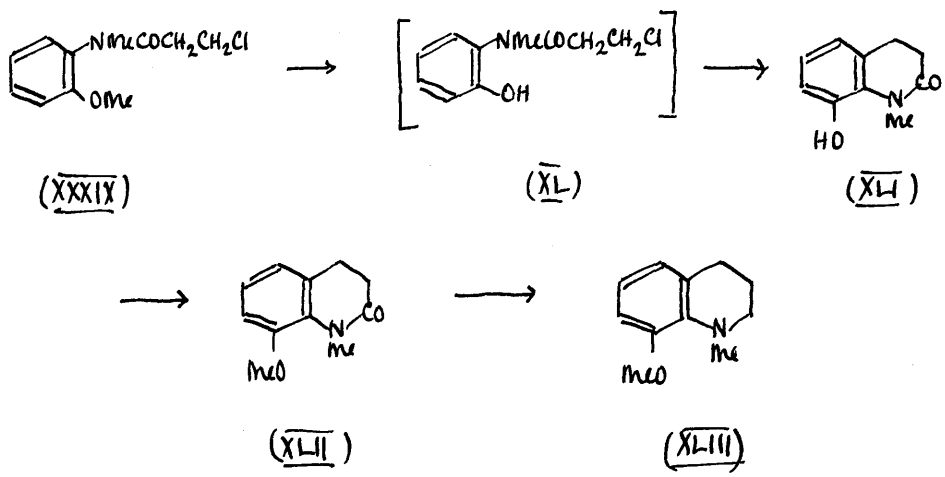
Methylation of (XXXVI) with potassium carbonate and methyl iodide in acetone gave 3:4-dihydro-8-methoxycarbostyril (XXXVII), which, on reduction in ether with an ethereal suspension of lithium aluminium hydride, gave 1:2:3:4-tetrahydro-8-methoxyquinoline (XXXVIII). This compound gave a benzoyl derivative which had m.p. and mixed m.p. 131-132° with an authentic specimen prepared from 8-hydroxyquinoline by methylation and reduction.



(XXXVI) (XXXVII) (XXXVIII)

On the other hand, cyclisation of β-chloropropionyl-N-methyl-o-anisidide (XXXIX) with anhydrous aluminium chloride took place even more readily. At the lowest reaction temperatures (80-100°)

cyclisation took place, and the intermediate β-chloropropionyl-N-methyl-o-amidophenol (XL) could not be isolated. The product in all cases was 3:4-dihydro-8-hydroxy-1-methylcarbostyril (XLI), and methylation of this with potassium carbonate and methyl iodide gave 3:4-dihydro-8-methoxy-1-methylcarbostyril (XLII). Reduction of (XLII) with lithium aluminium hydride afforded 1:2:3:4-tetrahydro-8-methoxy-1-methylquinoline (XLIII), identified as its platinichloride.

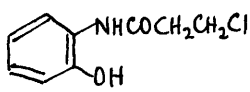


(XXXIX) (XL) (XLI) (XLII) (XLIII)

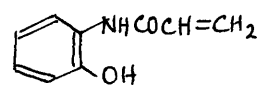
o-Acrylamidophenol.

When β-chloropropionyl-o-amidophenol (XXXV) was dissolved in dilute sodium hydroxide and the solution acidified, there was obtained a compound which did not contain chlorine. The compound was assigned the structure

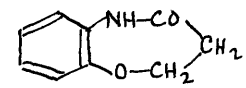
of o-acrylamidophenol (XXXVa), rather than that of the seven-membered cyclic amide (XXXVb), due to its ease of solubility in alkali, the facile absorption of one mole of hydrogen on reduction with palladium black in acetic acid, and the similarity of its Ultra-violet absorption spectra in ethanol, dilute sodium hydroxide, and ethanol containing a small amount of sodium methoxide.



(XXXV)



(XXXVa)

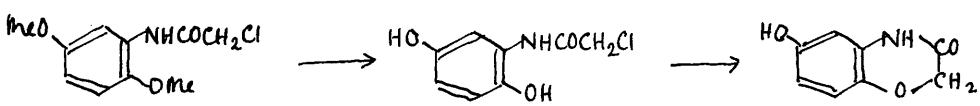


(XXXVb)

Cyclisation of chloroacetyl-2:5-dimethoxyanilides.

Chloroacetyl-2:5-dimethoxyanilide and chloroacetyl-2:5-dimethoxy-N-methylanilide were prepared by condensing the corresponding aniline with chloroacetyl chloride in benzene.

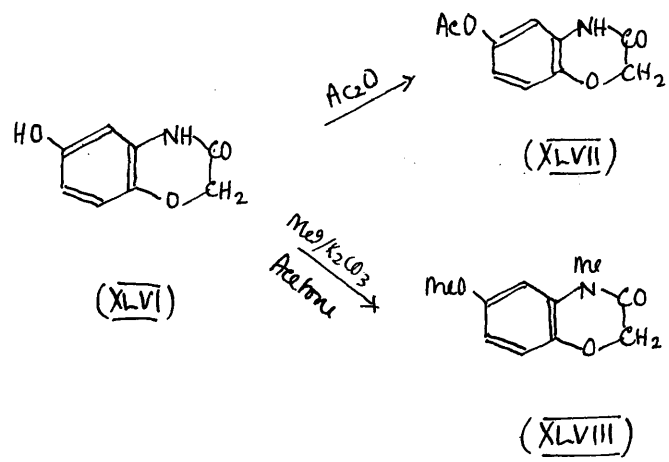
Fusion of chloroacetyl-2:5-dimethoxyanilide (XLIV) with anhydrous aluminium chloride in the temperature range 100-160°, or with a sodium chloride/aluminium chloride melt at 150°, gave only the demethylated product, chloroacetyl-2:5-dihydroxyanilide (XLV). Unlike the fusion of chloroacetyl-o-anisidide, the corresponding 2:3-dihydro-3-oxobenz-1:4-oxazine was not obtained. Fusion at higher temperatures (200°) resulted in excessive decomposition of the material and no identifiable product was obtained.



(XLIV) (XLV) (XLVI)

When (XLV) was dissolved in dilute sodium hydroxide, acidification gave 2:3-dihydro-6-hydroxy-3-oxo-

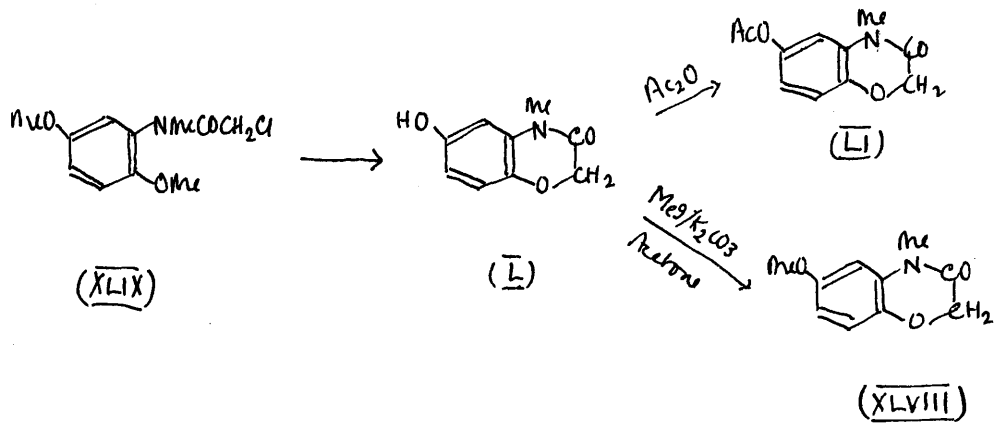
benz-1:4-oxazine (XLVI), which could be acetylated with acetic anhydride giving 6-acetyl-2:3-dihydro-3-oxo-benz-1:4-oxazine (XLVII), and which on methylation with potassium carbonate and methyl iodide unexpectedly gave 2:3-dihydro-6-methoxy-4-methyl-3-oxobenz-1:4-oxazine (XLVIII).



Fusion of chloroacetyl-2:5-dimethoxy-N-methylanilide (XLIX) with anhydrous aluminium chloride at 150°, or with a sodium chloride/aluminium chloride melt at 150°, afforded good yields of 2:3-dihydro-6-hydroxy-4-methyl-3-oxobenz-1:4-oxazine (L). At lower temperatures (ca. 100°), fusion gave rise to a little (L), but mostly starting material was recovered. Chloroacetyl-2:5-dihydroxy-N-methylanilide could not be isolated.

At higher fusion temperatures (200°), much

decomposition took place, and only a small amount of (L) was obtained. There was no trace of oxindole formation.



(XLIX) (L) (LI) (XLVIII)

When (L) was treated with acetic anhydride, it formed an acetyl derivative, 6-acetyl-2:3-dihydro-4-methyl-3-oxobenz-1:4-oxazine (LI), and methylation with potassium carbonate and methyl iodide gave (XLVIII), identical with that obtained from the methylation of (XLVI).

Attempted cyclisation of α:α-dichloroacetyl-o-anisidide.

α:α-Dichloroacetyl-o-anisidide was prepared by condensing o-anisidine with dichloroacetyl chloride.

Treatment of α:α-dichloroacetyl-

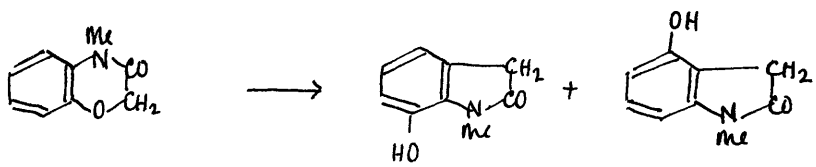
o-anisidide with aluminium chloride at 120° afforded α:α-dichloroacetyl-o-amidophenol, which was reprecipitated unchanged from its alkaline solution by the addition of acid. There is no evidence of the formation of the expected benz-1:4-oxazine as in other similar cases. Fusion with aluminium chloride or with an aluminium chloride/sodium chloride melt at 180° gave only α:α-dichloroacetyl-o-amidophenol.

This failure to undergo ring closure even to 2-chloro-2:3-dihydro-3-oxobenz-1:4-oxazine is not the only instance of the inactivity of two chlorine atoms attached to the same carbon atom. Stolle was unable to obtain 3-chloro-1-methyloxindole from α:α-dichloroacetyl-N-methylanilide, although the corresponding trichloroacetanilides cyclise very readily to 3:3-dichloro-oxindoles[52]. The inactivity of these chlorine atoms is further evident in the fact that α:α-dichloroacetyl-o-anisidide could be N-methylated with potassium hydroxide and methyl iodide in acetone (see later).

Mechanism of the rearrangement.

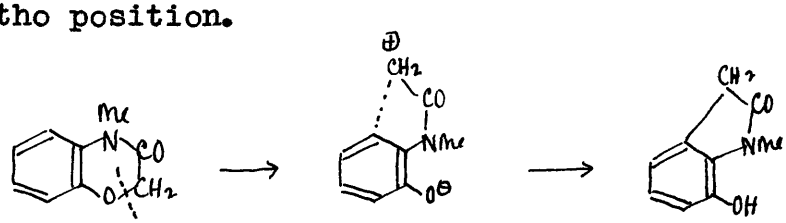
The mechanism by which molecular rearrangements are brought about is of interest, but the precise mechanism is often difficult to determine experimentally.

In the rearrangement of (IV) we have to account for the formation of the two isomeric hydroxy-oxindoles, (XXII) and (XXIII).



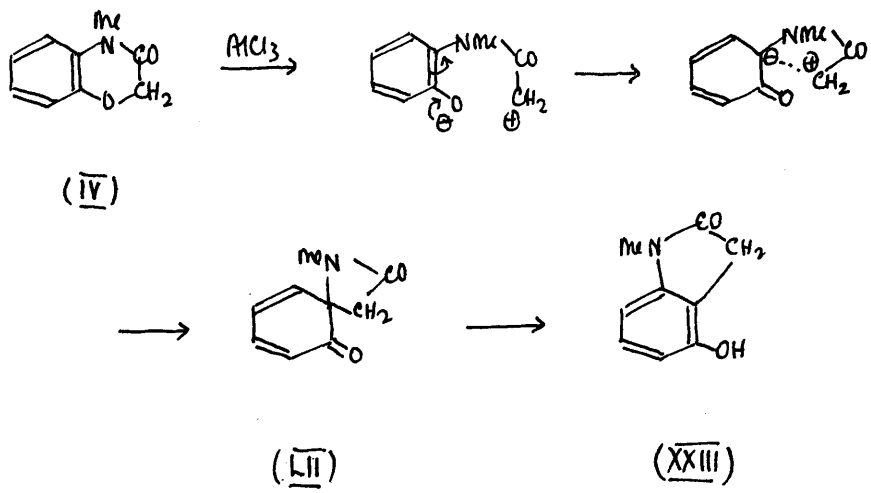
(IV) (XXII) (XXIII)

The formation of (XXII) can be readily explained by the scission of the ether linkage under the influence of aluminium chloride, and recyclisation in the free ortho position.



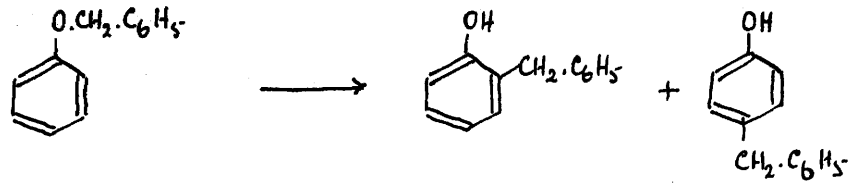
(IV) (XXII)

The production of (XXIII), however, is by no means so readily explained. A mechanism involving migration of the nitrogen atom is considered to be the most likely. Electrons are released from the donor oxygen atom, resulting in the distribution of charges as shown, followed by the formation of a bond with the electrophilic methylene group, giving the intermediate (LII). This intermediate yields the product by migration of the nitrogen atom.



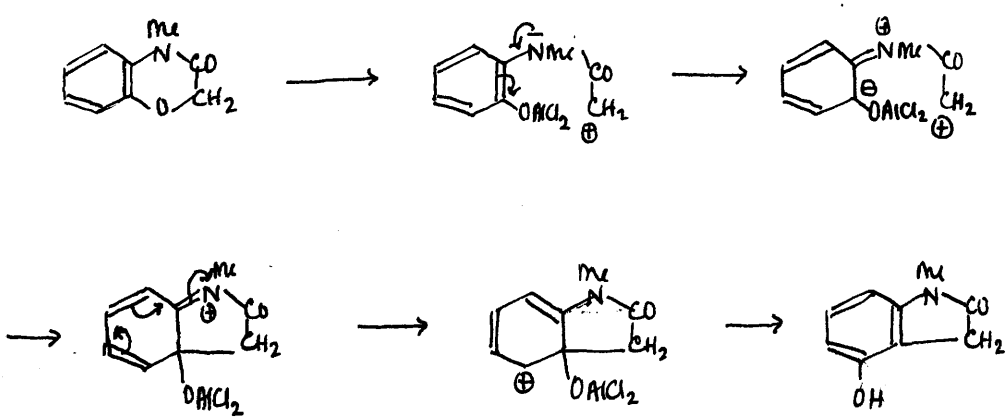
(IV) (LII) (XXIII)

A migration, somewhat similar to that envisaged for the production of the intermediate (LII), was reported by Behaghel and Friensehner[52], who observed that benzylphenyl ether (LIII) undergoes a Fries type rearrangement to give a mixture of o-benzylphenol (LIV) and p-benzylphenol (LV).



(LIII) (LIV) (LV)

A mechanism involving the migration of the oxygen atom might also be considered. In this case, the nitrogen atom acts as the electron donor, ring closure takes place with the electrophilic $-CH_2^+$ group, and the product is formed by the migration of the oxygen atom to the adjacent positively charged centre.

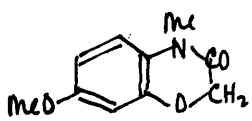


(XXIII)

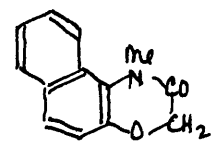
This mechanism is much less likely, however, since it ignores completely the strong electron

donating capacity of the oxygen atom. Also, the release of electrons from the nitrogen atom will be hindered by the presence of the adjacent carbonyl group.

With a view to determining which, if either, of these two mechanisms is applicable to the rearrangement of 2:3-dihydro-4-methyl-3-oxobenz-1:4-oxazine, the synthesis of two additional benz-1:4-oxazines, namely 2:3-dihydro-7-methoxy-4-methyl-3-oxobenz-1:4-oxazine (LVI) and 5:6-benz-2:3-dihydro-4-methyl-3-oxobenz-1:4-oxazine (X), was undertaken.



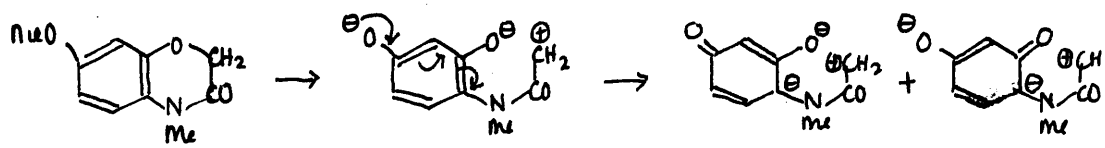
(LVI)



(X)

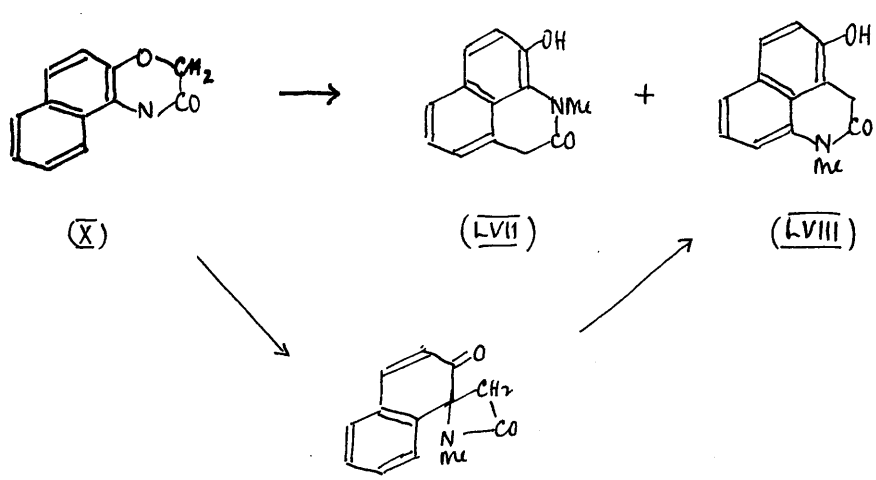
If (LVI) rearranges (or in the cyclisation of chloroacetyl-2:4-dimethoxy-N-methylanilide), the formation of the postulated intermediate should be favoured by the presence of a hydroxyl group (in the first instance the action of aluminium chloride will be to demethylate the methoxyl group) at position 7- in the molecule, since we now have two electron donating atoms in the molecule, thus increasing the electron availability

at the critical position in the benzene ring, as shown.



Treatment of the compound with aluminium chloride under varying conditions, however, failed to yield any hydroxyoxindole.

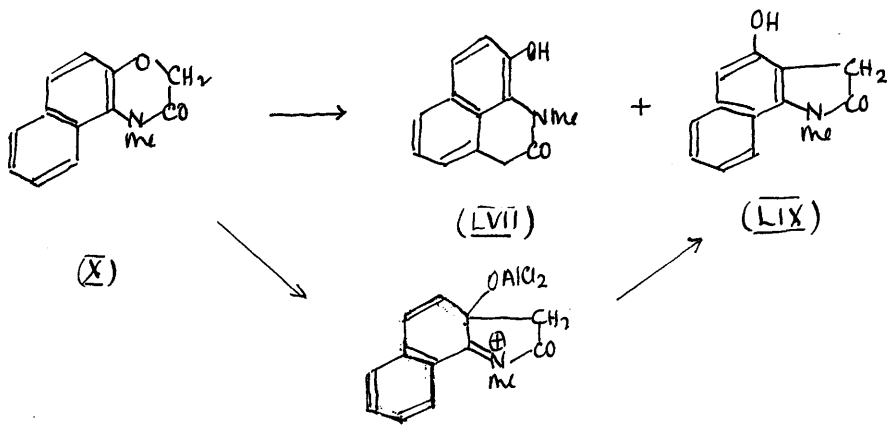
If rearrangement of (X) takes place at all, the products expected by the first mechanism (the nitrogen migration) would be (LVII) and (LVIII), since the peri position is the only one available for recyclisation.



(X) (LVII) (LVIII)

Rearrangement of similar cyclic ethers of -naphthol to the peri position has been observed[53].

On the other hand, if the second (hydroxyl migration) mechanism is applicable, the products should be (LVII) and (LIX).



No phenolic product, however, could be obtained by the action of aluminium chloride on (X).

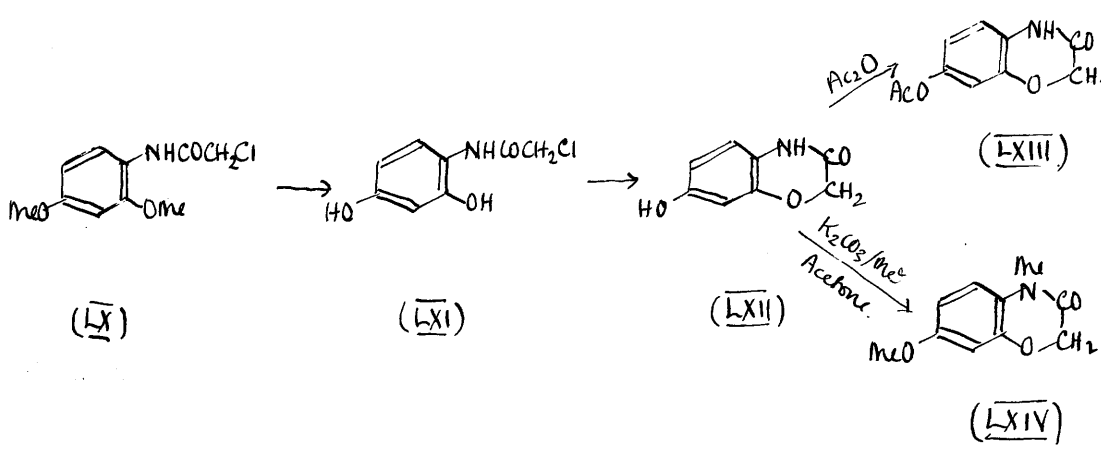
Cyclisation of chloroacetyl-2:4-dimethoxyanilides.

Chloroacetyl-2:4-dimethoxyanilide and chloroacetyl-2:4-dimethoxy-N-methylanilide were obtained by condensing chloroacetyl chloride with the respective anilines.

Chloroacetyl-2:4-dimethoxyanilide (LX),

when fused with anhydrous aluminium chloride at temperatures up to 160°, or at 150° with an aluminium chloride/sodium chloride melt, affords chloroacetyl-2:4-dihydroxyanilide (LXI). At 200° extensive decomposition takes place.

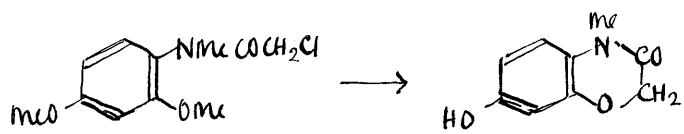
Dissolution of (LXI) in dilute sodium hydroxide and subsequent reprecipitation with acid gives 2:3-dihydro-7-hydroxy-3-oxobenz-1:4-oxazine (LXII), acetylation of which affords 7-acetyl-2:3-dihydro-3-oxo-benz-1:4-oxazine (LXIII), and methylation with potassium carbonate and methyl iodide gives 2:3-dihydro-7-methoxy-4-methyl-3-oxobenz-1:4-oxazine (LXIV).



(LX) (LXI) (LXII) (LXIII) (LXIV)

When chloroacetyl-2:4-dimethoxy-N-methyl-anilide (LXV) is fused, at 150°, with either anhydrous aluminium chloride or an aluminium chloride/sodium

chloride melt, the product is 2:3-dihydro-7-hydroxy-4-methyl-3-oxobenz-1:4-oxazine (LXVI), and at lower temperatures a mixture of (LXVI) and starting material is obtained. Chloroacetyl-2:4-dihydroxy-N-methylanilide was not isolated.



(LXV) (LXVI).

Fusion at 200° again resulted in considerable decomposition, but a small quantity of a red solid was isolated from the mother liquors of the fusion, after standing in the air for a few days. This crystallised from alcohol as red needles, and gave a blue solution in dilute sodium hydroxide. It is probably some oxidation product, but was not further identified.

Attempted rearrangement of 5:6-benz-2:3-dihydro-3-oxo-benz-1:4-oxazine and its 4-methyl derivative.

5:6-Benz-2:3-dihydro-3-oxobenz-1:4-oxazine was prepared by the method of Lees and Shedden[8] and N-methylated by the general proceedure using potassium

hydroxide and methyl iodide in acetone.

Attempted rearrangement of 5:6-benz-2:3-dihydro-3-oxobenz-1:4-oxazine with anhydrous aluminium chloride at 180° was inconclusive, the product after decomposition of the complex being a black powder, insoluble in organic solvents, and in alkali.

Fusion of 5:6-benz-2:3-dihydro-4-methyl-3-oxobenz-1:4-oxazine with aluminium chloride at various temperatures also failed to produce any appreciable quantity of alkali soluble product. The dark powder, which was the product of reaction at 220°, was insoluble in alkali but a portion was soluble in benzene, giving a brown solution with a green fluorescence. Fusion at 150° also gave a dark, solid product and extraction with benzene gave the same brown solution with a green fluorescence, but containing no alkali soluble material. Chromatography, on alumina, of the dried benzene solution and elution with dry benzene gave a little starting material, but further elution with benzene/methanol gave a green fluorescent eluate. Evaporation of this to dryness gave a reddish-brown amorphous solid which could not be obtained crystalline from any of the usual solvents and which was not further investigated.

Fusion of 5:6-benz-2:3-dihydro-4-methyl-3-oxobenz-1:4-oxazine in an aluminium chloride/sodium chloride melt, followed by decomposition of the complex, afforded a purplish solid which on recrystallisation after charcoaling proved to be a good return of starting material.

Miscellaneous fusions.

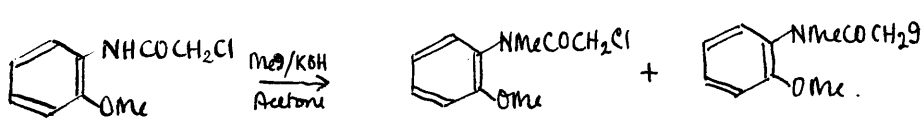
When 4-benzyl-2:3-dihydro-3-oxobenz-1:4-oxazine, prepared from 2:3-dihydro-3-oxobenz-1:4-oxazine by benzylation with potassium hydroxide and benzyl chloride in acetone, was fused with anhydrous aluminium chloride at 100°, the resulting product was partially soluble in alkali and reprecipitation with acid gave an almost colourless solid which was not obtained pure for analysis. It is possibly 7-hydroxyoxindole, since Stolle[51] found that ring closure of N-benzyl-chloroacetanilides are frequently accompanied by debenzylation.

Fusion of 2:3-dihydro-4-methyl-benz-1:4-oxazine, obtained from 2:3-dihydro-4-methyl-3-oxobenz-1:4-oxazine by reduction with lithium aluminium

hydride, with aluminium chloride at 140° resulted in the recovery of starting material in good yield. When the fusion was carried out at 220°, a little starting material was recovered, but extensive decomposition took place. In neither case was any phenolic material isolated.

Attempted N-methylation of chloroacetanilides.

During the course of this work, it was desired to prepare N-methylchloroacetanilides. As mentioned previously, Pachter and Kloetzal[25] developed a method for the N-methylation of aryl amides. When this reaction was applied to chloroacetanilides, however, the product was seldom that expected, but was usually an oil, which, in the case of chloroacetyl-o-anisidide, on distillation decomposed to give vapours of iodine. The product is possibly a mixture of the expected compound and another compound in which the chlorine has been replaced by iodine.



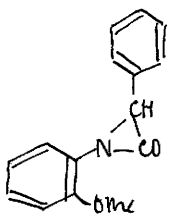
The conversion to the iodo compound is probably brought about by the Finkelstein reaction, in which treatment of a chloro or bromo compound with sodium iodide in acetone causes replacement of the chlorine or bromine atom by iodine[54]. In the foregoing methylation, potassium iodide is formed in the reaction.

In two instances, however, the expected N-methyl compound was obtained. When α:α-dichloroacetyl-o-anisidide was methylated with potassium hydroxide and methyl iodide in acetone, α:α-dichloroacetyl-N-methyl-o-anisidide was obtained in good yield. This again shows the inactivity of the α:α-chlorine atoms.

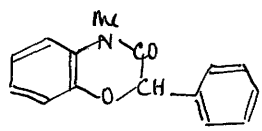
Also, when α-chlorophenylacetyl-o-anisidide was similarly methylated, two products were obtained, one of which was the expected α-chlorophenylacetyl-N-methyl-o-anisidide, as shown by comparison with an authentic specimen prepared from α-chlorophenylacetyl chloride and N-methyl-o-anisidine. The other product of this reaction was a high-melting crystalline solid, which did not contain chlorine, and analysed for $C_{15}H_{13}O_2N$. The compound could, therefore, have any one of the three structures (LXVII), (LXVIII), or (LXIX). Although azacyclopropanes (ethyleneimines), particularly phenyl

derivatives, are readily obtained by the action of potassium hydroxide on α-chloroamines[55, 56, 57], there is no evidence of the formation of azacyclopropanones, such as (LXVII), under the same conditions.

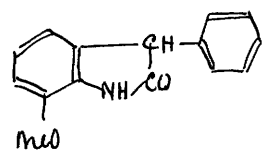
The formation of the 2:3-dihydro-3-oxobenz-1:4-oxazine structure (LXVIII) would require demethylation of the methoxyl group, a reaction which takes place in the presence of potassium hydroxide only when there is a strongly negative substituent (e.g. NO_2 or COOH) in the molecule[58]. Thus it would appear that the most likely structure for the compound is that of a methoxyoxindole (LXIX).



(LXVII)



(LXVIII)



(LXIX)

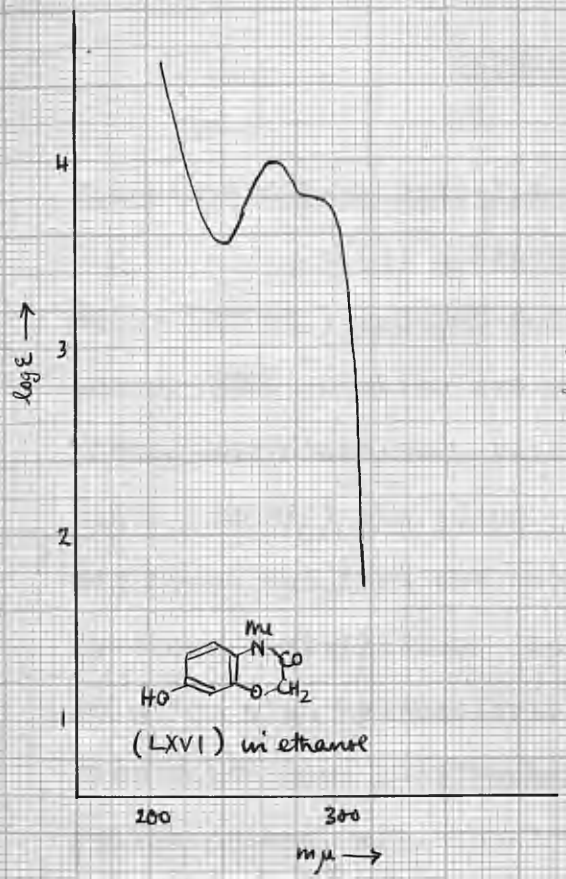
Ultra-violet spectra of the compounds.

The ultra-violet spectra of many of the foregoing compounds have been determined. In general, the substituted chloroacetanilides, 2:3-dihydro-3-oxobenz-1:4-oxazines and derivatives not hydroxylated in the benzene

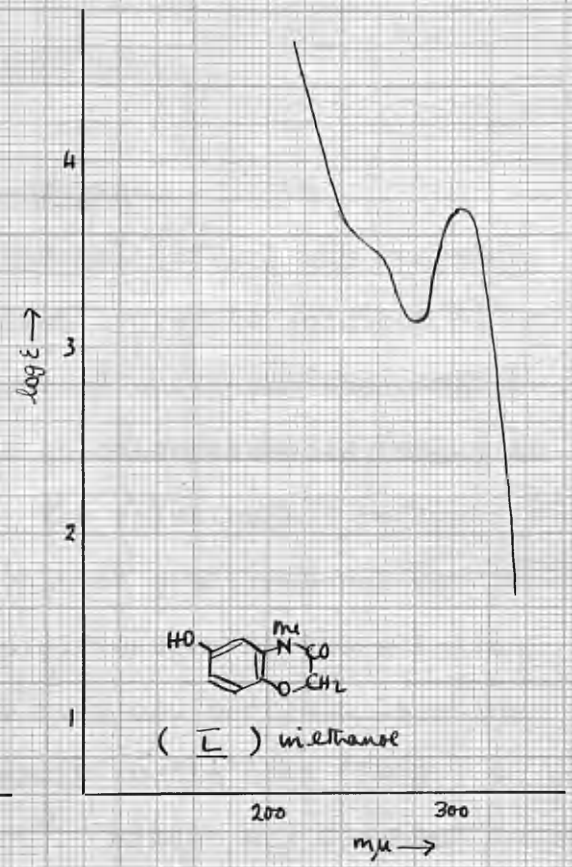
ring, and the substituted oxindoles all have a somewhat similar spectrum, having two peaks, one at 2400-2600 Å. and the other at 2800-3000 Å.

2:3-Dihydro-3-oxobenz-1:4-oxazines hydroxylated in the benzene ring, and their derivatives, have a modified spectrum. Where the hydroxyl group is para to the oxygen atom of the oxazine ring, the compound has a well-defined peak at ca. 3000 Å. and an inflexion at 2450-2550 Å. Where the hydroxyl group is meta to this oxygen atom, the spectrum shows a peak at ca. 2650 Å., which is not so well-defined, and an inflexion at about 2900 Å.

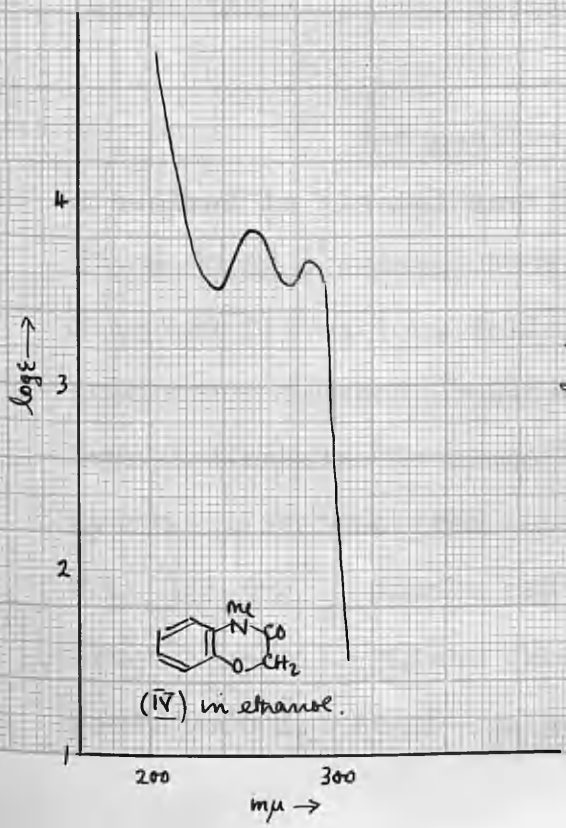
A selection of typical curves is given, and maxima for the various compounds are quoted throughout the experimental text.



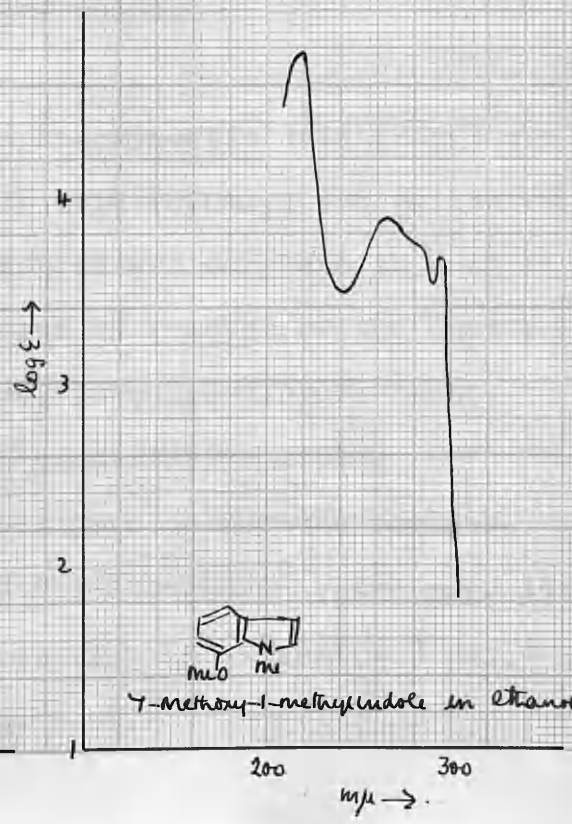
(LXVI) in ethanol



(L) in ethanol



(IV) in ethanol.



4-Methoxy-1-methylindole in ethanol

EXPERIMENTAL.

2:3-Dihydro-3-oxobenz-1:4-oxazine.

(a) o-Nitrophenol (139g.) was suspended in water (800ml.) and 50% sodium hydroxide solution (160g.) added. The solution was warmed until all the o-nitrophenol had dissolved, then chloroacetic acid (95g.) in water (200ml.) was added. The solution was refluxed for six hours and then the unchanged o-nitrophenol was removed by steam distillation. Acidification of the alkaline solution with hydrochloric acid and recrystallisation from water gave o-nitrophenoxy acetic acid (100g.) as pale yellow prisms, m.p. 156-157°. Minton and Stephen[16] report 156.5° as the melting point.

The o-nitrophenoxyacetic acid (25g.) was dissolved in glacial acetic acid (200ml.) and palladium black (0.5g.) added. Reduction was complete in a short time and filtration, followed by removal of the acetic acid under reduced pressure, gave 2:3-dihydro-3-oxobenz-1:4-oxazine in almost quantitative yield. Recrystallisation from water gave colourless needles, m.p. 171-172°. Jacobs and Heidleberger[4] give m.p. 173-173.5° (corr.). Light absorption in ethanol:- λ max. 2550, 2860 Å. Log.ε 3.73, 3.59.

(b) o-Anisidine (33g.) was dissolved in glacial acetic acid (165ml.) and saturated sodium acetate solution (250ml.) was added. Chloroacetyl chloride (33ml.) was then added to the cooled, well-stirred solution. When addition was complete, the reaction mixture was set aside at 0° overnight and the resultant crystals filtered off. The mother liquors were diluted and again set aside, when a further crop of crystals were obtained. In all, 50g. of chloroacetyl-o-anisidide resulted.

Chloroacetyl-o-anisidide (20g.) was heated at 180° with aluminium chloride (40g.) for an hour and the resultant melt cooled, powdered, and decomposed with ice (250g.) and dilute hydrochloric acid. The product was recrystallised from water (charcoal) as colourless needles, m.p. 171-172°.

2:3-Dihydro-4-methyl-3-oxobenz-1:4-oxazine.

(a) 2:3-Dihydro-3-oxobenz-1:4-oxazine (0.5g.) was dissolved in concentrated sodium hydroxide (5ml) and dimethyl sulphate (1ml.) added. The solution was boiled for ten minutes under reflux, a further 2ml. of concentrated sodium hydroxide added, and the whole refluxed for a further ten minutes. After cooling and acidifying, 2:3-dihydro-4-methyl-3-oxobenz-1:4-oxazine

separated on standing, and recrystallisation from petroleum ether (40-60°) gave the product, m.p. 57-58°.

(b) 2:3-Dihydro-3-oxobenz-1:4-oxazine (10g.) was dissolved in "Analar" acetone (250ml.) and powdered potassium hydroxide (14g.) added. The solution was gently refluxed and methyl iodide (15g.) was run in, in two portions, at an interval of ten minutes. After twenty minutes refluxing in all, the solution was cooled, filtered, and concentrated. Addition of water (100ml.) precipitated an oil which soon solidified, and recrystallisation from petroleum ether (40-60°) afforded 2:3-dihydro-4-methyl-3-oxobenz-1:4-oxazine as colourless needles, m.p. 57-58°. Wheeler and Barnes[7] give m.p. 58-59°. The yield was 90% of the theoretical. Light absorption in ethanol:- λ max. 2540, 2850 Å. Log. ε 3.78, 3.64.

2-Benzylidene-2:3-dihydro-3-oxobenz-1:4-oxazine.

2:3-Dihydro-3-oxobenz-1:4-oxazine (1.5g.), benzaldehyde (1.1g.), acetic anhydride (3.1g.), and freshly fused sodium acetate (0.6g.) were mixed together and refluxed for eight hours. The reaction mixture was then poured into much water, giving an oil which gradually turned solid. Treatment of this with dilute sodium hydroxide

gave a colourless, alkali soluble fraction, which proved to be unchanged starting material, and a yellow fraction which was insoluble in alkali. Crystallisation of the yellow solid from ethanol gave 2-benzylidene-2:3-dihydro-3-oxobenz-1:4-oxazine as pale yellow needles, m.p. 260-261°. (Found: C, 75.88; H, 4.97; N, 6.19. $C_{15}H_{11}O_2N$ requires: C, 75.92; H, 4.67; N, 5.90%.). Light absorption in ethanol:- λ max. 2570, 3350 Å. Log.ε 4.19, 4.29.

2-Benzyl-2:3-dihydro-3-oxobenz-1:4-oxazine.

2-Benzylidene-2:3-dihydro-3-oxobenz-1:4-oxazine (82mg.) was dissolved in glacial acetic acid (5ml.), palladium black added, and the solution hydrogenated. Reduction was complete in an hour and the solution was then filtered and the acetic acid removed under reduced pressure. Recrystallisation of the solid residue from petroleum ether (60-80°) gave 2-benzyl-2:3-dihydro-3-oxobenz-1:4-oxazine as colourless needles, m.p. 158-159°. (Found: C, 74.81; H, 4.89; N, 6.15. $C_{15}H_{13}O_2N$ requires C, 75.29; H, 5.45; N, 5.85%.). Light absorption in ethanol:- λ max. 2520, 2810 Å. Log.ε 3.83, 3.66.

2-Benzylidene-2:3-dihydro-4-methyl-3-oxobenz-1:4-oxazine.

2:3-Dihydro-4-methyl-3-oxobenz-1:4-oxazine (0.8g.) was dissolved in dry benzene (25ml.) and freshly

distilled benzaldehyde (0.53g.), followed by sodamide (0.3g.) added. The solution was refluxed until the evolution of ammonia had almost ceased (ca. 12 hours), and the yellow solution was then cooled, washed with water, dried, and concentrated. Crystallisation of the residue from ethanol afforded 2-benzylidene-2:3-dihydro-4-methyl-3-oxobenz-1:4-oxazine as yellow needles, m.p. 155-156°. (Found: C, 76.19; H, 5.35; N, 5.78. $C_{16}H_{13}O_2N$ requires C, 76.48; H, 5.21; N, 5.58%.). Light absorption in ethanol:- λ max. 2700, 3370 Å. Log.ε 4.15, 4.28.

2-Benzyl-2:3-dihydro-4-methyl-3-oxobenz-1:4-oxazine.

2-Benzylidene-2:3-dihydro-4-methyl-3-oxobenz-1:4-oxazine (0.2g.) was dissolved in glacial acetic acid (5ml.) and reduced by hydrogenation over palladium black (0.1g.). Filtration of the solution, followed by removal of the acetic acid under reduced pressure gave 2-benzyl-2:3-dihydro-4-methyl-3-oxobenz-1:4-oxazine as a colourless oil which could not be solidified, even after distillation.

2:3-Dihydro-4-methylbenz-1:4-oxazine.

To lithium aluminium hydride (2g.), suspended in ether (100ml.), was added an ethereal solution of 2:3-dihydro-4-methyl-3-oxobenz-1:4-oxazine

(5g. in 100ml. ether) slowly, with stirring and exclusion of moisture. The reaction mixture was set aside for 48 hours, and then water (25ml.), followed by 2N hydrochloric acid (25ml.) was carefully added. The ether layer was separated, dried, and concentrated. Distillation of the residual oil gave 2:3-dihydro-4-methylbenz-1:4-oxazine as a colourless oil, b.p. $61^{\circ}/5x10^{-5}$ m.m. Knorr[9] gave b.p. 261° at atmospheric pressure.

Hydrochloride. The oil (0.5g.), dissolved in absolute alcohol (5ml.), was saturated with dry hydrogen chloride and set aside for a short time. Crystals of the hydrochloride were obtained which, after recrystallisation from alcohol, has m.p. 168-169°. (Found: C, 58.27; H, 6.26; N, 7.62. Calculated for $C_9H_{12}ONCl$: C, 58.22; H, 6.52; N, 7.55%.). Knorr[9] reported m.p. 162° and Lees and Shedden[8] m.p. 167-168°. Light absorption in ethanol:- λ max. 2580, 2980 Å. Log. ε 3.82, 3.56.

Methiodide. The oil (0.5ml.), methyl alcohol (0.5ml.), and methyl iodide (0.5ml.) were mixed together and set aside at 0° overnight. Crystals of the methiodide separated and, after recrystallisation from methanol, the colourless spears had m.p. 198-200°. Knorr[10] gave m.p. ca. 200° and Lees and Shedden m.p. 195-200°.

Picrate. The oil (0.25g.) was dissolved in absolute alcohol (5ml.) and a saturated solution of picric acid in

alcohol (5ml.) added. After a short time, leaflets of the picrate were obtained, m.p., after recrystallisation from alcohol, 149-150°. (Found: C, 47.68; H, 4.02; N, 14.96. $C_{15}H_{14}O_8N_4$ requires: C, 47.62; H 3.73; N, 14.81%.).

Resorcinol dimethyl ether.

Resorcinol (55g.) was dissolved in a solution of potassium hydroxide (56g.) in water (600ml.) and the mixture cooled in an ice-salt bath. Dimethyl sulphate (126g.) was added slowly over a period of an hour, with stirring. The solution was then heated to 60° for a further hour, cooled, and extracted with ether. After drying the extract over sodium sulphate, the ether was removed and the residue of resorcinol dimethyl ether distilled as an almost colourless oil, b.p. 209-211°.

1:3-Dimethoxybenzene-4-sulphonic acid.

Concentrated sulphuric acid (13.5g.) was slowly added to resorcinol dimethyl ether (13g.) at room temperature, with stirring. The resulting pinkish syrup contained a solution of the sulphonic acid in excess sulphuric acid.

Attempted nitration of 1:3-dimethoxybenzene-4-sulphonic acid.

Various quantities of water and concentrated

nitric acid were added to the sulphonic acid solution (5g.) and the mixture set aside for 16 hours. Water (10ml.) was then added and the product filtered off and washed with a further quantity of water (20ml.), dried, and weighed.

(b) Resorcinol dimethyl ether (1g.) was dissolved in glacial acetic acid (various quantities) and sulphuric acid (1ml.) added. The solution was then heated to 70° until a drop added to water (2ml.) gave no turbidity (5mins.), thus ensuring complete sulphonation. After cooling, water (0.75ml.) followed by concentrated nitric acid (1ml.) was added and the solution left overnight. Water (25ml.) was added and the reaction mixture extracted with benzene (75ml.), the extract dried, and passed through a column of alumina from which the product was readily eluted with benzene. Removal of the benzene gave almost pure 2:4-dimethoxy-nitrobenzene.

2:4-Dimethoxynitrobenzene.

Acetic anhydride (30g.) was added to copper nitrate (10g.) and resorcinol dimethyl ether (11.8g.) added with brisk stirring, the temperature being kept below 30°. After 4 hours the reaction mixture was poured into water (300ml.), the suspension extracted with benzene, and the extract washed with dilute sodium hydroxide followed by

water, before drying. Purification on alumina, as before, and recrystallisation from alcohol gave 2:4-dimethoxynitrobenzene as colourless crystals, m.p. 75-76°. Vermeulen[27] gave m.p. 76-77°. The yield was 70% of the theoretical.

Chloroacetyl-o-amidophenol.

Chloroacetyl-o-anisidide was heated with twice its weight of anhydrous aluminium chloride at 100° for twenty minutes. Subsequent cooling, powdering, and decomposition of the melt, followed by crystallisation of the product from benzene gave chloroacetyl-o-amidophenol as stout, colourless needles, m.p. 135.5-136.5°. (Found: C, 51.43; H, 4.33. Calculated for $C_8H_8O_2NCl$: C, 51.77; H, 4.34%.). Aschan[19] reports m.p. 136°.

N-Methyl-o-anisidine.

o-Anisidine (47g.) was acetylated by dissolving it in dry benzene (800ml.) and running in, slowly, acetyl chloride (30g.). After standing overnight, the filtered, acid washed, and dried benzene solution was concentrated to give crude acetyl-o-anisidide (63g.) which was dissolved in "Analar" acetone. Powdered potassium hydroxide (75g.) was added and the solution refluxed gently while adding methyl iodide (75g.) in two portions at a ten minute interval. After 30 minutes, the cooled,

filtered, and concentrated solution was diluted with water (250ml.) and the resulting oil was extracted with ether. Removal of the ether, without drying, gave acetyl-N-methyl-o-anisidide (41g.) which was hydrolysed by boiling for six hours with 30% sulphuric acid (300ml.). The solution was then made alkaline with sodium hydroxide and the resultant dark oil extracted with ether. Concentration, after drying, and distillation of the residue afforded N-methyl-o-anisidine as a yellow oil, b.p. 226-228°. Cook et al.[40] give b,p, 228-230°.

(b) o-Anisidine (110g.) was dissolved in water (2 l.) and concentrated hydrochloric acid (75ml.). Acetic anhydride (105g.), followed by sodium acetate (132g.) in water (400ml.), was then added and the acetyl-o-anisidide which separated was filtered, washed, and dried. It (110g.) was then dissolved in xylene (600ml.) and added to a cooled suspension of atomised sodium (16g.) in a further 200ml. of xylene. After heating to 140° until no sodium remained, methyl iodide (45g.) was run in slowly and the reaction completed by gentle heating. The xylene was distilled off and the residue hydrolysed by boiling for six hours with 30% sulphuric acid. The solution was then made alkaline, extracted with ether, and the ether extract dried, concentrated, and distilled to give N-methyl-o-anisidine as a yellow oil b.p. 226-228°

Chloroacetyl-N-methyl-o-anisidide.

N-Methyl-o-anisidine (5.4g.) was dissolved in benzene (25ml.) and pyridine (3.2g.) added. Chloroacetyl chloride (4.5g.) was then added dropwise to the cooled, stirred, solution and the reaction mixture allowed to stand overnight. After filtration and washing with dilute hydrochloric acid followed by water until the washings were neutral, the benzene solution was dried and the benzene removed under reduced pressure. The resulting oil, which soon solidified, was recrystallised from petroleum ether (40-60°) and chloroacetyl-N-methyl-o-anisidide was obtained as colourless rods, m.p. 49-50°. (Found: C, 56.35; H, 5.50; $C_{10}H_{12}O_2NCl$ requires: C, 56.21; H, 5.66%.). Cf. Cook et al.[40] who obtained it as an oil.

Action of anhydrous aluminium chloride on chloroacetyl-N-methyl-o-anisidide.

(a) At 180°. Chloroacetyl-N-methyl-o-anisidide (2.5g.) and aluminium chloride (3.2g.) were intimately mixed and heated at 180° for an hour. The melt was then cooled, powdered, and added to a mixture of ice (20g.) and dilute hydrochloric acid (5ml.). The gummy solid so obtained was dissolved in ether and the ether solution washed with dilute sodium hydroxide solution and then with water until the washings were

neutral. When the ether extract was dried over sodium sulphate and the ether removed, there was obtained 2:3-dihydro-4-methyl-3-oxobenz-1:4-oxazine (1.4g.), which, after recrystallisation from petroleum ether (40-60°), had m.p. and mixed m.p. with an authentic specimen, 57-58°. Acidification of the alkaline washings gave a trace of a phenolic substance.

(b) At 200°. Chloroacetyl-N-methyl-o-anisidide (3g.) was mixed with aluminium chloride (5g.) and heated at 200° for an hour. Decomposition of the melt, followed by extraction and washing with dilute sodium hydroxide as above, afforded, from the ether solution, 2:3-dihydro-4-methyl-3-oxobenz-1:4-oxazine (1g.), m.p. and mixed m.p. 57-58°. Acidification of the alkaline washings afforded a quantity of mixed hydroxy-1-methyl oxindoles (0.5g.).

(c) At 220°. Fusion of a mixture of chloroacetyl-N-methyl-o-anisidide (3g.) and aluminium chloride (4g.) at 220° for an hour and subsequent treatment as in (a) and (b), gave only a trace of 2:3-dihydro-4-methyl-3-oxobenz-1:4-oxazine in the ether solution. Acidification of the alkaline extract, however, gave 2.1g. of the mixed hydroxy-1-methyloxindoles.

Action of aluminium chloride on 2:3-dihydro-3-oxo-benz-1:4-oxazine.

2:3-Dihydro-3-oxobenz-1:4-oxazine (3g.) was heated at 220° with aluminium chloride (6g.) for 20 minutes. The melt was cooled, powdered, and decomposed with ice (20g.) and dilute hydrochloric acid (5ml.). Crystallisation of the resulting solid from water after charcoaling gave colourless needles, m.p. 114-115°. Boiling the substance to small bulk with 2N hydrochloric acid gave 2:3-dihydro-3-oxobenz-1:4-oxazine, m.p. 167-171° and mixed m.p. 169-171°, and the compound had mixed m.p. with chloroacetyl-o-amidophenol (m.p. 136°), 125-128°. (Found: C, 57.32; H, 4.97. $C_8H_8O_2NCl.C_8H_7O_2N$ requires: C, 57.40; H, 4.52%.)

4- and 7-Methoxy-1-methyloxindoles.

(a) The mixture of 4- and 7-hydroxy-1-methyloxindoles (6.3g.) was dissolved in 7.5% sodium hydroxide solution (25ml.) and cooled in ice-water. Dimethyl sulphate (5ml.) was added slowly, with shaking, and the solution was then heated on the water-bath for 30 minutes, a little sodium hydroxide being added at intervals to preserve the alkalinity. After cooling, the solution was extracted with ethyl acetate, the extract dried over sodium sulphate and the ethyl acetate removed.

Distillation of the residue gave a mixture of the two isomeric methoxy-1-methyloxindoles as a yellow oil, b.p. 140-160°/1m.m., which soon solidified. The yield of the methylated product was poor, being in the range 20-30%.

(b) The mixture of hydroxy-1-methyloxindoles (2.8g.) was dissolved in "Analar" acetone (50ml.) and potassium carbonate (5.6g,) added. The solution was gently refluxed and methyl iodide (3g.) was added in two portions at an interval of an hour. Refluxing was continued for two hours in all, then the solution was cooled, filtered, concentrated, and diluted with water (25ml.). After extraction of the resultant gummy precipitate with ethyl acetate and drying the extract over sodium sulphate, the ethyl acetate was removed and the residue distilled, giving the oily mixture of the two methoxy-1-methyloxindoles as before. Yields of 60-70% could be obtained by this method.

Separation of 4- and 7-methoxy-1-methyloxindoles.[40]

The mixture of 4- and 7-methoxy-1-methyl oxindoles (12g.) was finely powdered and extracted five times in a Buchner funnel with 25ml. portions of ether. The white residue consisted of almost pure 4-methoxy-1-methyloxindole (4g.). The filtrate was concentrated slowly at room temperature and deposited a further

quantity of 4-methoxy-1-methyloxindole (0.5g.). Further concentration of the ether solution on a steam-bath and cooling to 0° gave yellowish needles, m.p. 76-80°, consisting mainly of the 7-isomer, but also containing some 4-methoxy-1-methyloxindole. These were redissolved in ether and passed through an alumina column in ether (300ml.). The eluate was concentrated to small bulk and allowed to crystallise slowly at room temperature. Two types of crystals were obtained, stout prisms of the 4-isomer (1.5g.) and long pointed leaflets of 7-methoxy-1-methyloxindole (4.5g.). They were easily separated mechanically.

4-Methoxy-1-methyloxindole crystallised from water as shiny plates, m.p. 136-137° and mixed m.p. with an authentic specimen 135-136°. Light absorption in ethanol:- λ max. 2510, 2810 Å. Log. ε 3.67, 3.32.

7-Methoxy-1-methyloxindole crystallised as colourless needles from petroleum ether (60-80°), m.p. 101-102° and mixed m.p. with an authentic specimen, 99-100°. Light absorption in ethanol:- λ max. 2530, 2950 Å. Log. ε 3.95, 3.50.

4-Hydroxy-1-methyloxindole.

4-Methoxy-1-methyloxindole (0.2g.) was heated with aluminium chloride (0.4g.) at 120° for 20

minutes, when the melt was cooled, powdered, and added to a little ice-cold 2N hydrochloric acid. The white solid so obtained was recrystallised from hot water after charcoaling, and afforded 4-hydroxy-1-methyloxindole as colourless, irregular plates, m.p. 230-232°. (Found: C, 66.07; H, 5.53. $C_9H_9O_2N$ requires: C, 66.24; H, 5.56%.) Light absorption in ethanol:- λ max. 2520, 2800 Å. Log.ε 3.83, 3.37.

7-Hydroxy-1-methyloxindole.

7-Methoxy-1-methyloxindole (0.2g.) was treated as above with aluminium chloride (0.4g.) and the solid obtained from the decomposition of the melt was crystallised from glacial acetic acid after charcoaling. 7-Hydroxy-1-methyloxindole was obtained as colourless rhombs, m.p. 275-277°. (Found: C, 66.04; H, 5.64. $C_9H_9O_2N$ requires: C, 66.24; H, 5.56%.). Light absorption in ethanol:- λ max. 2450, 2860 Å. Log. ε 3.82, 3.52.

Rhodamine test with 4- and 7-hydroxy-1-methyloxindoles.

When a small quantity of 4-hydroxy-1-methyl oxindole was fused with excess phthalic anhydride and a trace of zinc chloride, and the melt dissolved in dilute sodium hydroxide, a red fluorescent solution of the corresponding rhodamine dyestuff was obtained.

Acidification of the alkaline solution with hydrochloric acid gave a bright red precipitate of the rhodamine salt. 7-Hydroxy-1-methyloxindole did not give this test.

α-Chloropropionyl chloride.

α-Chloropropionic acid (25g.) was added slowly to thionyl chloride (35g: 21ml.), gently heated on the water-bath. After addition was complete, the solution was refluxed for three hours, with the exclusion of moisture. The reaction mixture was then distilled, unchanged thionyl chloride coming over at 77°. The fraction b.p. 105-110° was pure α-chloropropionyl chloride. (20.8g.)

α-Chloropropionyl-o-anisidide.

o-Anisidine (36.8g.) was dissolved in dry benzene (500ml.) and the solution cooled with running water. α-Chloropropionyl chloride (19.3g.) was then added dropwise with continuous stirring. After addition was complete, the reaction mixture was allowed to stand overnight at room temperature. It was then filtered, washed with water then dried over sodium sulphate. The benzene was then removed and the α-chloropropionyl-o-anisidide (31.8g.) obtained as a light yellow oil.

2:3-Dihydro-2-methyl-3-oxobenz-1:4-oxazine.

To α-chloropropionyl-o-anisidide (34g.) was added anhydrous aluminium chloride (30g.), and the mixture reacted spontaneously, white fumes being given off with a temperature rise to 120°. The temperature was maintained at this level for 30 minutes with frequent stirring, then the cooled, powdered melt was added to ice (250g.) and dilute hydrochloric acid (20ml.). The resulting product, which is crude -chloropropionyl-o-amidophenol, was left in contact with the acid solution at room temperature for two hours, then filtered off and dissolved in dilute sodium hydroxide (250ml.), from which the product is deposited as almost colourless needles on standing. A further quantity of product was obtained by acidifying the alkaline mother liquors. Recrystallisation from benzene after charcoaling gave colourless needles of 2:3-dihydro-2-methyl-3-oxobenz-1:4-oxazine, m.p. 143-144°. Cook et al.[40] give m.p. 144.5-145.5° (corr.).

2:3-Dihydro-2:4-dimethyl-3-oxobenz-1:4-oxazine.

2:3-Dihydro-2-methyl-3-oxobenz-1:4-oxazine (10.1g.) was dissolved in "Analar" acetone and potassium hydroxide (12.4g.) added. Methyl iodide (12.8g.) was then added to the gently refluxing solution in two portions at ten minutes interval. Refluxing was continued for 20

minutes in all, then the solution was cooled, filtered, and concentrated to small volume. Water (100ml.) was added and the resulting oil which was precipitated crystallised after standing for a short time. Recrystallisation from petroleum ether (40-60°) gave 2:3-dihydro-2:4-dimethyl-3-oxobenz-1:4-oxazine (11g.) as colourless needles, m.p. 49.5-50°. (Found: C, 67.51; H, 6.00. $C_{10}H_{11}O_2N$ requires: C, 67.77; H, 6.26%.). Light absorption in ethanol:- λ max. 2550, 2860 Å. Log.ε 4.01, 3.90.

7-Hydroxy-1:3-dimethyloxindole.

2:3-Dihydro-2:4-dimethyl-3-oxobenz-1:4-oxazine (5g.) was intimately mixed with aluminium chloride (10g.) and heated to 220° on an oil bath with frequent stirring. After an hour, the melt, which by now had thickened considerably, was cooled, powdered, and added to ice (20g.) and dilute hydrochloric acid (5ml.). A grey solid was obtained (4.5g.), which, after purification on a charcoal column and crystallisation from methanol, afforded colourless prisms of 7-hydroxy-1:3-dimethyl oxindole, m.p. 224-226°. (Found: C, 67.62; H, 6.61; N, 7.55. $C_{10}H_{11}O_2N$ requires: C, 67.77; H, 6.26; N, 7.92%.) Light absorption in ethanol:- λ max. 2490, 2970 Å. Log.ε 3.87, 3.57.

7-Methoxy-1:3-dimethyloxindole.

7-Hydroxy-1:3-dimethyloxindole (2g.) was dissolved in "Analar" acetone and methylated in the usual way with potassium carbonate (1.5g.) and methyl iodide (2g.). The solution was refluxed for 4 hours, then cooling, filtering, concentrating, and adding water (10ml.) precipitated an oil which was extracted with ether. The ether extract was washed with dilute sodium hydroxide, then with water and dried over sodium sulphate. Removal of the ether gave an oil which was distilled in vacuo, b.p. 146-148°/9.8x10^{-2}m.m. and which solidified on cooling. Recrystallisation from petroleum ether (40-60°) gave colourless needles of 7-methoxy-1:3-dimethyloxindole, m.p. 65-66°. (Found: C, 68.88; H, 6.55; N, 7.51. $C_{11}H_{13}O_2N$ requires: C, 69.09; H, 6.84; N, 7.33%.). Light absorption in ethanol:- λ max. 2520, 2930 Å. Log.ε 3.92, 3.50.

7-Methoxy-1:3-dimethylindole.

(a) 7-Methoxy-1:3-dimethyloxindole (0.5g.) was dissolved in dry ether (15ml.) and added to a suspension of lithium aluminium hydride (0.2g.) in dry ether (25ml.). The reaction mixture was set aside for 5 hours, then water (10ml.), followed by 4% hydrochloric acid (5ml.) was added. The ether layer was separated, washed with water, and dried over sodium sulphate. The

ether was removed, and the oily residue obtained solidified on cooling. Crystallisation from petroleum ether (40-60°) gave colourless rhombs of 7-methoxy-1:3-dimethylindole, m.p. 68-69°. (Found: C, 75.47; H, 7.13; N, 8.66. $C_{11}H_{13}ON$ requires: C, 75.40; H, 7.48; N, 7.99%.). Light absorption in ethanol:- λ max. 2260, 2730, 2880, 3000 Å. Log.ε 4.69, 3.74, 3.78, 3.78.

Picrate. The substance forms a chocolate brown picrate when solutions of it and picric acid in ether are mixed. Chocolate brown needles from ethanol, m.p. 163-164°. (Found: C, 50.30; H, 3.80; N, 14.10. $C_{17}H_{16}O_8N_4$ requires C, 50.50; H, 3.99; N, 13.86%.).

(b) 7-Methoxy-3-methylindole (1.2g.) in ether (10ml.) was added slowly, with stirring, to a solution of potassium (0.29g.) in liquid ammonia (25ml.) containing a crystal of ferric nitrate, the solution being kept at -40°. When addition of the indole was complete, methyl iodide (1.1g.), in ether (5ml.), was run in. The reaction mixture was kept for 45 minutes at -40°, then the cooling bath removed and the ammonia allowed to evaporate at room temperature overnight. The ether was then removed and the residue purified by passage through an alumina column in dry petroleum ether (40-60°). Concentration of the first fraction of the eluate gave

7-methoxy-1:3-dimethylindole as colourless plates, m.p. 69-70°. The mixed m.p. with a sample obtained from 2:3-dihydro-2:4-dimethyl-3-oxobenz-1:4-oxazine was 68-69°.

Picrate. The picrate was obtained by mixing ethereal solutions of the indole and picric acid as before. It was obtained as chocolate brown needles from ethanol, m.p. and mixed m.p. with the previous sample 162-163°.

7-Methoxy-1:3-dimethylindoline picrate.

This substance is obtained as a by-product in the reduction of 7-methoxy-1:3-dimethyloxindole with lithium aluminium hydride. After separation of the ether layer, the acid solution is made alkaline with dilute sodium hydroxide. Extraction of this with ether, washing with water and drying over sodium sulphate, followed by addition of ethereal picric acid gives a precipitate of 7-methoxy-1:3-dimethylindoline picrate. The substance forms yellow rectangular plates from ethanol, m.p. 135-136°. (Found: C, 50.62; H, 4.77; N, 13.95. $C_{17}H_{18}O_8N_4$ requires C, 50.25; H, 4.46; N, 13.79%.).

7-Methoxy-3-methylindole[40].

o-Methoxyphenylhydrazine (13g.) was mixed with freshly distilled propaldehyde (10ml.) with shaking and cooling. The oily hydrazone which separated was

washed with a little water, then dissolved in a mixture of sulphuric acid (3ml.) and ethanol (35ml.). The reaction was completed by heating on the water bath for 30 minutes then water (100ml.) was added and the solution extracted with ether. The ether extract was washed, dried, concentrated, and the residue distilled. 7-Methoxy-3-methylindole was obtained as a yellow oil, b.p. 91°/ 1.5×10^{-5} m.m. Cook et al.[40] give b.p. 150°/15m.m. Picrate. The compound formed a picrate as red needles from ethanol, m.p. 154-155°. Blaikie and Perkin[44] give m.p. 156°, and Cook et al., 158.5-159° (corr.).

2-Nitro-m-cresol.[59]

m-Cresol (43.2g.) was added slowly to fuming sulphuric acid (20% SO_3: 160ml.) and heated to 50-60° on the water bath for 30 minutes. The solution was cooled in an ice-salt mixture and concentrated nitric acid (9.3ml.) in fuming sulphuric acid (20% SO_3: 21.3ml.) was added over an hour. The solution was left for 36 hours at room temperature, then water (50ml.) was added and the whole distilled with superheat steam. The product was obtained as a yellow oil which was used without further purification. The yield was 21.5g.

2-Nitro-3-methylphenoxyacetic acid.

2-Nitro-m-cresol (21.5g.) was dissolved in sodium hydroxide solution (12.4g. in 200ml. water), heated to boiling, and chloroacetic acid (14.6g.) added. The solution was refluxed for 3 hours and then the unchanged 2-nitro-m-cresol was removed by steam distillation. Acidification of the alkaline solution with concentrated hydrochloric acid gave the phenoxyacetic acid, which was recrystallised from water, m.p. 194-196°. (Found: C, 51.45; H, 4.30. $C_9H_9O_5N$ requires: C, 51.23; H, 4.30%.). The yield was 75% of the theoretical.

2:3-Dihydro-5-methyl-3-oxobenz-1:4-oxazine.

2-Nitro-3-methylphenoxyacetic acid (8g.) was dissolved in glacial acetic acid (40ml.) and palladium black (0.4g.) added. Hydrogenation was complete in a short time, when the palladium black was filtered off and the acetic acid removed under reduced pressure. The resulting solid residue was recrystallised from water after charcoaling and gave 2:3-dihydro-5-methyl-3-oxobenz-1:4-oxazine as colourless needles, m.p.188-190°. (Found: C, 66.53; H, 5.73. $C_9H_9O_2N$ requires: C, 66.25; H, 5.56%.)

2:3-Dihydro-4:5-dimethyl-3-oxobenz-1:4-oxazine.

2:3-Dihydro-5-methyl-3-oxobenz-1:4-oxazine

(2g.) was dissolved in "Analar" acetone (50ml.) and methylated in the usual way with potassium hydroxide (2g.) and methyl iodide (2g.). After 15 minutes, cooling, filtering, and concentrating the solution, followed by addition of water (20ml.) precipitated an oil which rapidly crystallised. Recrystallisation from petroleum ether (60-80°) gave 2:3-dihydro-4:5-dimethyl-3-oxo-benz-1:4-oxazine as rectangular plates, m.p. 86-87°. (Found: C, 67.68; H, 6.14. $C_{10}H_{11}O_2N$ requires: C, 67.80; H, 6.26%.)

Action of aluminium chloride on 2:3-dihydro-4:5-dimethyl-3-oxobenz-1:4-oxazine.

When 2:3-dihydro-4:5-dimethyl-3-oxo-benz-1:4-oxazine (3.2g.) was fused with aluminium chloride (7g.) at 220° for 30 minutes, the initially light-coloured, mobile melt became gradually dark and viscous. Decomposition with ice (20g.) and dilute hydrochloric acid (5ml.) resulted in a gummy solid which was left overnight at 0°. The supernatant liquid was then decanted off, the gum washed with water, and dissolved in dilute sodium hydroxide. Filtration of this solution, followed by acidification with hydrochloric acid again gave a gum (2g.) which was redissolved in dilute sodium hydroxide and methylated with dimethyl sulphate (3ml.). The reaction

mixture was set aside for 20 hours, then extracted with ether, the ether extract dried over sodium sulphate and the ether removed. The residue was distilled at 14m.m. pressure and the product was obtained as a yellow oil, boiling over a 30° range of temperature. It was dissolved in petroleum ether (60-80°) and chromatographed on alumina. Elution with benzene gave a yellow solution and removal of the benzene left an oily residue which solidified. Recrystallisation from petroleum ether (60-80°) gave feathery crystals, m.p. 50-62°. Attempted separation of this mixture by crystallisation from various solvents failed.

β-Chloropropionyl chloride.

Thionyl chloride (35g.) was added to β-chloropropionic acid (25g.) and the mixture refluxed gently with the exclusion of moisture. After 3 hours, the excess thionyl chloride was distilled off and the residue distilled under reduced pressure. β-Chloropropionyl chloride (22g.) was obtained as a colourless liquid, b.p. 74°/55m.m.

β-Chloropropionyl-o-anisidide.

β-Chloropropionyl o-Anisidine (40g.) was dissolved in dry benzene (500ml.) and β-chloropropionyl chloride (20g.)

added slowly to the well-stirred, cooled solution. When addition was complete, the reaction mixture was allowed to stand overnight, then filtered and washed with a little dilute hydrochloric acid followed by water until the washings were neutral, and dried over sodium sulphate. Removal of the benzene gave a yellow oil which soon solidified and recrystallisation from petroleum ether (60-80°) afforded β-chloropropionyl-o-anisidide (33g.) as yellowish leaflets, m.p. 67-68°. (Found: C, 56.34; H, 5.64; N, 6.43. $C_{10}H_{12}O_2NCl$ requires: C, 56.21; H, 5.66; N, 6.56%.). Light absorption in ethanol:- λ max. 2450, 2830 Å. Log.ε 3.99, 3.66.

β-Chloropropionyl-o-amidophenol.

β-Chloropropionyl-o-anisidide (5g.) was mixed with anhydrous aluminium chloride (6g.) and heated at 130° on the oil bath for 10 minutes, when the melt had become almost solid. It was cooled, powdered, and added to ice (20g.) and dilute hydrochloric acid (5ml.), when an almost colourless solid was obtained. Recrystallisation from benzene, after charcoaling, gave β-chloropropionyl-o-amidophenol as colourless irregular plates, m.p. 122-123°. (Found: C, 54.09; H, 5.20; N, 7.23. Calculated for $C_9H_{10}O_2NCl$: C, 54.14; H, 5.05; N, 7.02%.). Mayer, Zutphen, and Philipps[50] gave m.p. 125°.

3:4-Dihydro-8-hydroxycarbostyril.

β-Chloropropionyl-o-anisidide (5g.) was mixed with anhydrous aluminium chloride (10g.) and heated on the oil bath at 220° for an hour with intermittent stirring. Decomposition of the melt in the usual way with ice (20g.) and dilute hydrochloric acid (5ml.) gave a yellow solid (2.5g.) which, after recrystallisation from water, afforded 3:4-dihydro-8-hydroxycarbostyril as almost colourless plates, m.p. 193-194°. (Found: C, 66.37; H, 5.67; N, 8.40. Calculated for $C_9H_9O_2N$: C, 66.24; H, 5.56; N, 8.58%.). Mayer, Zutphen, and Philipps[50] give m.p. 195° for this compound. Light absorption in ethanol:- λ max. 2500, 2910 Å. Log. ε 3.95, 3.73.

3:4-Dihydro-8-methoxycarbostyril.

3:4-Dihydro-8-hydroxycarbostyril (0.5g.) was dissolved in "Analar" acetone (20ml.) and methylated with potassium carbonate (1.5g.) and methyl iodide (1g.) by refluxing for $2\frac{1}{2}$ hours. Addition of water after filtering, cooling, and concentrating gave an oil which soon solidified, and recrystallisation from petroleum ether (60-80°) afforded 3:4-dihydro-8-methoxycarbostyril as irregular prisms, m.p. 97-98°. (Found: C, 67.96; H, 6.42; N, 8.10. $C_{10}H_{11}O_2N$ requires: C, 67.77; H, 6.26; N, 7.92%.). Light absorption in ethanol:- λ max. 2500, 2840 Å. Log. ε 4.00,

3.58.

1:2:3:4-Tetrahydro-8-methoxyquinoline.

(a) 3:4-Dihydro-8-methoxycarbostyril (0.6g.) was dissolved in dry ether (50ml.) and added to an ethereal suspension of lithium aluminium hydride (0.3g.). The reaction mixture was set aside for two hours, then water (10ml.), followed by dilute hydrochloric acid (5ml.), was added and the acid layer separated off. This was made alkaline with dilute sodium hydroxide and extracted with ether. Removal of the ether from the dried extract gave 1:2:3:4-tetrahydro-8-methoxyquinoline as an oil which formed a benzoyl derivative when shaken with benzoyl chloride and dilute sodium hydroxide. Recrystallisation from dilute alcohol gave this derivative as colourless rhombs, m.p. 131-132°. Troge and Krückeberg[60] give m.p. 136° for this compound.

(b) 8-Methoxyquinoline (1g.) was reduced with iron filings and hydrochloric acid during the course of 2 days. The excess iron was then filtered off, the filtrate made alkaline with sodium hydroxide, and extracted with ether. After drying, removal of the ether gave 1:2:3:4-tetrahydro-8-methoxyquinoline as an oil which on benzoylation with benzoyl chloride in dilute sodium

hydroxide gave a benzoyl derivative, m.p. 131-132° after recrystallisation from dilute alcohol. It had mixed m.p. 131-132° with the previous benzoyl derivative.

8-Methoxyquinoline.

8-Hydroxyquinoline (10g.) was dissolved in potassium hydroxide solution (5.8g. in 150ml. water) and dimethyl sulphate (10g.) added slowly, with stirring, at room temperature. The reaction mixture was set aside overnight and then heated to 70° for 30 minutes, care being taken that the solution was still alkaline at the end of that time. The resulting oil was extracted with ether, dried, and distilled as a bright yellow oil, b.p. 91°/ 3×10^{-4} m.m. It formed a picrate, m.p. 161-162°, as yellow needles from alcohol. (Found: C, 49.53; H, 3.23; N, 14.52. Calculated for $C_{16}H_{12}O_8N_4$: C, 49.49; H, 3.12; N, 14.43%.). Frankel and Grauer[61] report m.p. 143° for this derivative.

β-Chloropropionyl-N-methyl-o-anisidide.

N-Methyl-o-anisidine (10.5g.) was dissolved in dry benzene (250ml.) and pyridine (5.7g.) added. β-Chloropropionyl chloride (9.8g.) was then run in slowly, with exclusion of moisture, to the well-stirred solution. After standing overnight, the benzene solution was washed first with water, then with dilute hydrochloric acid, and

finally with water, dried, and the benzene removed. β-Chloropropionyl-N-methyl-o-anisidide was obtained as an oil which did not solidify.

3:4-Dihydro-8-hydroxy-1-methylcarbostyril.

To the oily β-chloropropionyl-N-methyl-o-anisidide (2g.) was added anhydrous aluminium chloride (4g.) and the mixture was heated on the oil bath at 110° for an hour. Addition of the cooled, powdered melt to ice (10g.) and dilute hydrochloric acid (3ml.) gave an almost colourless, alkali soluble solid. Recrystallisation from benzene after charcoaling gave stout needles of 3:4-dihydro-8-hydroxy-1-methylcarbostyril, m.p. 195-196°. (Found: C, 68.04; H, 6.55; N, 7.84. $C_{10}H_{11}O_2N$ requires: C, 67.77; H, 6.26; N, 7.92%.). Light absorption in ethanol:- λ max. 2490, 2890 Å. Log.ε 3.96, 3.67.

3:4-Dihydro-8-methoxy-1-methylcarbostyril.

3:4-Dihydro-8-hydroxy-1-methylcarbostyril (0.7g.) was dissolved in "Analar" acetone and methylated with potassium carbonate (1g.) and methyl iodide (2g.) by refluxing for 3 hours. Addition of water (10ml.) to the cooled, filtered, and concentrated solution precipitated an oil which solidified overnight. Recrystallisation from petroleum ether furnished 3:4-dihydro-8-methoxy-1-methyl

carbostyril as colourless rhombs, m.p. 85-86°. (Found: C, 69.15; H, 6.79; N, 7.40. $C_{11}H_{13}O_2N$ requires: C, 69.09; H, 6.84; N, 7.33%.). Light absorption in ethanol:- λ max. 2510, 2900 Å. Log.ε 4.07, 3.73.

1:2:3:4-Tetrahydro-8-methoxy-1-methylquinoline.

3:4-Dihydro-8-methoxy-1-methylcarbostyril (0.5g.) was dissolved in ether (50ml.) and added to a suspension of lithium aluminium hydride (0.3g.) in ether (25ml.). The reaction mixture was set aside for 5 hours and then water (10ml.), followed by dilute hydrochloric acid (5ml.), was added. The ether layer was separated off and the acid solution was made alkaline with dilute sodium hydroxide, extracted with ether and the ether extract dried. Removal of the ether gave 1:2:3:4-tetrahydro-8-methoxy-1-methylquinoline as an oil which furnished a platinichloride when treated with an aqueous solution of platinum chloride. Recrystallisation from water gave the derivative as reddish-yellow prisms, m.p. 198° (dec.). Fischer and Köhn[62] give m.p. 199° (dec.) for this derivative of 1:2:3:4-tetrahydro-8-methoxy-1-methyl quinoline.

o-Acrylamidophenol.

β-Chloropropionyl-o-amidophenol (1g.) was

dissolved in dilute sodium hydroxide (10ml.). The solution was set aside for 2 hours, then dilute hydrochloric acid was added until the solution was just acid, and the solution extracted with ether. Removal of the ether from the dried extract gave an oil which soon solidified on being treated with a little benzene. Recrystallisation from benzene after charcoaling gave a compound as rectangular plates, m.p. 122-123° and mixed m.p. with β-chloropropionyl-o-amidophenol (m.p. 122-123°), 95-100°. The compound contained no chlorine and was soluble in dilute alkali. It was assigned the structure of o-acrylamidophenol. (Found: C, 66.50; H, 5.85; N, 8.78. $C_9H_9O_2N$ requires: C, 66.24; H, 5.56; N, 8.58%.). Light absorption in ethanol:- λ max. 3000 Å. Log.ε 3.9. Light absorption in dilute sodium hydroxide:- λ max. 2330, 3280 Å. Log.ε 4.6, 3.78. Light absorption in ethanol/ sodium methoxide:- λ max. 2400, 3000 Å. Log.ε 3.89, 3.82.

Chloroacetyl-2:5-dimethoxyanilide.

2:5-Dimethoxyaniline (12g.) was dissolved in dry benzene (300ml.) and pyridine (6.2g.) added. Chloroacetyl chloride (8.9g.) was run in slowly to the well-stirred solution, with exclusion of moisture, and after addition was complete the solution was set aside overnight. The solution was then filtered, washed with

dilute hydrochloric acid followed by water, and dried over sodium sulphate. After removal of the benzene, the residue solidified on cooling and recrystallisation from petroleum ether (60-80°) gave chloroacetyl-2:5-dimethoxy anilide as colourless plates, m.p. 76-77°. (Found: C, 53.11; H, 5.03; N, 6.38. $C_{10}H_{12}O_3NCl$ requires: C, 52.41; H, 5.28; N, 6.11%.).

Chloroacetyl-2:5-dihydroxyanilide.

Chloroacetyl-2:5-dimethoxyanilide (2g.) was added portionwise to a melt consisting of aluminium chloride (10g.) and sodium chloride (4g.) at 140°. After 10 minutes at this temperature the melt was cooled, powdered, and added to ice (20g.) and dilute hydrochloric acid (5ml.). An almost colourless solid was obtained, which, after recrystallisation from water (charcoal) afforded chloroacetyl-2:5-dihydroxyanilide as brownish needles, m.p. 196-197°. (Found: C, 47.77; H, 3.91; N, 6.89. $C_8H_8O_3NCl$ requires: C, 47.66; H, 4.00; N, 6.95%.).

The same compound is also obtained by fusion of chloroacetyl-2:5-dimethoxyanilide with twice its weight of aluminium chloride at 100° or 150°.

Methylation of chloroacetyl-2:5-dihydroxyanilide with diazomethane.

Chloroacetyl-2:5-dihydroxyanilide (0.5g.) was dissolved in ether (25ml.) and an ethereal solution of diazomethane, prepared from isonitrosomethylurea (0.75g.), was added. Slow effervescence took place and the reaction mixture was set aside overnight. The ethereal solution was then washed with a little dilute sodium hydroxide, then with dilute hydrochloric acid, finally with water, and dried over sodium sulphate. Removal of the ether and crystallisation of the solid residue from petroleum ether (60-80°) gave colourless plates of chloroacetyl-2:5-dimethoxyanilide, m.p. and mixed m.p. with an authentic sample 76-77°.

2:3-Dihydro-6-hydroxy-3-oxobenz-1:4-oxazine.

Chloroacetyl-2:5-dihydroxyanilide (1.4g.) was dissolved in dilute sodium hydroxide (10ml.), with the formation of a transient green colour. The solution eventually became brown and, after a short time, began to deposit a brown solid. This was filtered off and the mother liquors were extracted with ether after acidification. The ether extract was dried, the ether removed, and the solid obtained added to that which had precipitated from solution. Recrystallisation from

water after charcoaling gave 2:3-dihydro-6-hydroxy-3-oxobenz-1:4-oxazine as colourless needles, m.p. 249-250°. (Found: C, 58.32; H, 4.42; N, 8.18. $C_8H_7O_3N$ requires: C, 58.18; H, 4.37; N, 8.48%.). Light absorption in ethanol:- λ max. 3020 Å. Log. ε 3.69. Inflexion at 2480-2600 Å. Log. 3.56-3.48.

Acetyl derivative. Acetylation by dissolution in alkali, adding ice, and shaking with excess acetic anhydride gave the acetyl derivative, aolourless needles from water, m.p. 161-162°. (Found: C, 58.64; H, 4.66; N, 6.87. $C_{10}H_9O_4N$ requires: C, 57.97; H, 4.38; N, 6.76%.)

Action of aluminium chloride at 220° on chloroacetyl-2:5-dimethoxyanilide.

Aluminium chloride (5g.) and chloroacetyl-2:5-dimethoxyanilide (2g.) were heated together at 220° for 30 minutes. Subsequent decomposition of the melt gave a very dark solid which was practically insoluble in ether and alkali, and afforded no identifiable product.

Attempted O-methylation of 2:3-dihydro-6-hydroxy-3-oxobenz-1:4-oxazine.

When 2:3-dihydro-6-hydroxy-3-oxobenz-1:4-oxazine was dissolved in "Analar" acetone and methylated

with potassium carbonate and methyl iodide in the usual manner, the product was a solid, m.p. 75-76°, which proved to be identical with 2:3-dihydro-6-methoxy-4-methyl-3-oxo-benz-1:4-oxazine (mixed m.p. 76-77°) when compared with an authentic specimen.

2:5-Dimethoxy-N-methylaniline.

2:5-Dimethoxyaniline (14.9g.) was dissolved in dry benzene (500ml.) and pyridine (7.7g.) added. Acetyl chloride (7.6g.) was then run in slowly to the stirred solution, moisture being excluded. The reaction mixture was set aside overnight, then filtered, washed with dilute hydrochloric acid followed by water, dried, and the benzene removed. Recrystallisation of the solid residue from benzene afforded 2:5-dimethoxyacetanilide as colourless spears (16g.), m.p. 92-93°.

2:5-Dimethoxyacetanilide (11g.) was dissolved in "Analar" acetone (400ml.) and methylated with potassium hydroxide (8g.) and methyl iodide (12g.) in the usual way. The resultant oil obtained by the addition of water (100ml.) was extracted with ether and the ether removed without drying the extract. The resulting oily 2:5-dimethoxy-N-methylacetanilide (10.2g.) was hydrolysed by refluxing for 6 hours with 30% sulphuric acid (100ml.) and the solution was then made alkaline and the

precipitated oil extracted with ether. Removal of the ether from the dried extract gave 2:5-dimethoxy-N-methylaniline which distilled as an almost colourless oil, b.p. 68-71°/ 1.8×10^{-4} m.m.

Chloroacetyl-2:5-dimethoxy-N-methylanilide.

2:5-Dimethoxy-N-methylaniline (4.5g.) was dissolved in dry benzene (250ml.) and pyridine (2.1g.) added. Chloroacetyl chloride (3.05g.) was slowly run in with stirring and exclusion of moisture, then the reaction mixture was set aside overnight. Removal of the benzene from the washed (dilute hydrochloric acid then water) and dried solution gave an oil which afforded crystals of chloroacetyl-2:5-dimethoxy-N-methylanilide, m.p. 67-68°, (Found: C, 54.54; H, 5.44; N, 6.20. $C_{11}H_{14}O_3NCl$ requires: C, 54.29; H, 5.55; N, 5.76%.), from petroleum ether (40-60°).

2:3-Dihydro-6-hydroxy-4-methyl-3-oxobenz-1:4-oxazine.

Chloroacetyl-2:5-dimethoxy-N-methylanilide (1g.) was added to a melt consisting of aluminium chloride (5g.) and sodium chloride (2g.) at 140°. The temperature was maintained at this level for 15 minutes, then addition of the cooled powdered melt to a mixture of ice (10g.) and dilute hydrochloric acid (3ml.) gave a grey solid.

Recrystallisation of this from water afforded 2:3-dihydro-6-hydroxy-4-methyl-3-oxobenz-1:4-oxazine as colourless needles, m.p. 208-209°. (Found: C, 60.43; H, 4.86; N, 8.02. $C_9H_9O_3N$ requires: C, 60.33; H, 5.06; N, 7.82%.). Light absorption in ethanol:- λ max. 3030 Å. Log. ε 3.72. Inflexion at 2480-2600 Å. Log.ε 3.60-3.47.

Acetyl derivative. Acetylation in ice-cold dilute sodium hydroxide with acetic anhydride gave the acetyl derivative, colourless needles from water, m.p. 93-94°. (Found: C, 59.57; H, 4.72; N, 6.56. $C_{11}H_{11}O_4N$ requires: C, 59.72; H, 5.01; N, 6.53%.).

2:3-Dihydro-6-hydroxy-4-methyl-3-oxobenz-1:4-oxazine was also obtained by fusion of chloroacetyl-2:5-dimethoxy-N-methylanilide (2g.) with aluminium chloride (5g.) alone at 140°.

2:3-Dihydro-6-methoxy-4-methyl-3-oxobenz-1:4-oxazine.

2:3-Dihydro-6-hydroxy-4-methyl-3-oxobenz-1:4-oxazine (0.5g.) was dissolved in "Analar" acetone and methylated in the usual way with potassium carbonate and methyl iodide. The resultant product, which was first obtained as an oil, soon solidified and recrystallisation from petroleum ether (60-80°) gave 2:3-dihydro-6-methoxy-4-methyl-3-oxobenz-1:4-oxazine as colourless plates, m.p. 77-78°. (Found: C, 62.50; H, 5.67; N, 7.48. $C_{10}H_{11}O_3N$

requires: C, 62.16; H, 5.74; N, 7.25%.). Light absorption in ethanol:- λ max. 3000 Å. Log. ε 3.73. Inflexion at 2440-2570 Å. Log. ε 3.60-3.52.

Action of aluminium chloride at 220° on chloroacetyl-2:5-dimethoxy-N-methylanilide.

Treatment of chloroacetyl-2:5-dimethoxy-N-methylanilide (2g.) with aluminium chloride (5g.) at 220° for an hour resulted in the formation of a dark, viscous melt. Decomposition with iced hydrochloric acid in the usual way gave a bluish-black solid which was insoluble in alkali. It was partially soluble in methanol, and purification on a charcoal column gave a small quantity of 2:3-dihydro-6-hydroxy-4-methyl-3-oxobenz-1:4-oxazine, m.p. and mixed m.p. with an authentic specimen, 206-207°.

Dichloroacetyl chloride.

Thionyl chloride (11.9g.) was added to dichloroacetic acid (12.9g.) and the whole refluxed, with the exclusion of moisture, until the evolution of hydrogen chloride had practically ceased. The product was then distilled, b.p. 104-106°.

Dichloroacetyl-o-anisidide.

o-Anisidine (11.6g.) was dissolved in dry benzene (200ml.) and the dichloroacetyl chloride (6.9g.) added slowly with stirring and exclusion of moisture. The reaction mixture was allowed to stand overnight, then it was filtered, washed with dilute hydrochloric acid followed by water, dried over sodium sulphate, and the benzene removed on the steam bath. The resulting oil solidified on cooling and recrystallisation from petroleum ether (60-80°) gave dichloroacetyl-o-anisidide as long, colourless spears, m.p. 92-93°. (Found: C, 46.28; H, 3.74; N, 6.06. $C_9H_9O_2NCl_2$ requires: C, 46.18; H, 3.87; N, 5.98%.).

Dichloroacetyl-o-amidophenol.

Dichloroacetyl-o-anisidide (2.4g.) was mixed with aluminium chloride (2g.) and heated at 120° for 15 minutes. The cooled, powdered melt was added to ice (10g.) and dilute hydrochloric acid (3ml.) and the solid product was allowed to stand overnight. Filtration and recrystallisation from benzene afforded dichloroacetyl-o-amidophenol as colourless rods, m.p. 132-133°. (Found: C, 43.70; H, 3.44; N, 6.22. $C_8H_7O_2NCl_2$ requires: C, 43.66; H, 3.21; N, 6.37%.).

Action of aluminium chloride at 180° on dichloroacetyl-o-anisidide.

Dichloroacetyl-o-anisidide (2g.) and powdered aluminium chloride (4g.) were mixed and heated at 180° for 30 minutes. The melt turned very dark during the course of the reaction, indicating some degree of decomposition. After cooling, the powdered complex was decomposed with ice (10g.) and dilute hydrochloric acid (3ml.). Extraction of the resulting solid with benzene gave only dichloroacetyl-o-amidophenol, m.p. and mixed m.p. 129-131°, and a dark, insoluble residue.

Action of aluminium chloride/sodium chloride melt at 180° on dichloroacetyl-o-anisidide.

To a melt consisting of aluminium chloride (6g.) and sodium chloride (10g.) was added dichloroacetyl-o-anisidide (2g.). The temperature was raised to 180° and maintained at this for 30 minutes, then the melt was cooled, powdered, and added to ice (10g.) and dilute hydrochloric acid (3ml.). A dark brown solid was again obtained and extraction with benzene gave only dichloroacetyl-o-amidophenol, m.p. and mixed m.p. 128-130°

2:4-Dimethoxyaniline.

2:4-Dimethoxy-nitrobenzene (25g.) was dissolved in glacial acetic acid (500ml.) and palladium black (0.3g.) added. Reduction with hydrogen was complete in six hours, when the solution was filtered and the acetic acid removed under reduced pressure. The residue was distilled in vacuo, giving 2:4-dimethoxyaniline (18.5g.) as an almost colourless oil, b.p. 75-80°/ 6×10^{-3} m.m. The oil was a solid at 0°.

The acetyl derivative was obtained by suspending the amine (0.5g.) in ice-cold water, adding excess acetic anhydride, and shaking for 15 minutes. 2:4-Dimethoxyacetanilide separated as colourless crystals, m.p. 115-116° after recrystallisation from water. Vermeulen[63] gives m.p. 117°.

Chloroacetyl-2:4-dimethoxyanilide.

2:4-Dimethoxyaniline (18g.) was dissolved in benzene (500ml.) and pyridine (9.2g.) added. Chloroacetyl chloride (15.3g.) was run in slowly, with stirring and exclusion of moisture, and the reaction mixture allowed to stand overnight. Removal of the benzene from the filtered, washed and dried solution gave a solid residue, which after recrystallisation from petroleum ether (60-80°) afforded chloroacetyl-2:4-dimethoxyanilide

m.p. 90-90.5°. Jacobs and Heidelberger[64] quote m.p. 90° (corr.).

Chloroacetyl-2:4-dihydroxyanilide.

Chloroacetyl-2:4-dimethoxyanilide (2g.) was added to a melt of aluminium chloride (10g.) and sodium chloride (4g.) at 140°. The temperature was maintained at this level for 15 minutes, when the melt was cooled, powdered, and added to ice (20g.) and dilute hydrochloric acid (5ml.). The resulting solid, after recrystallisation from water (charcoal) gave chloroacetyl-2:4-dihydroxyanilide as pale brown plates (1.7g.), m.p. 179-180°. (Found: C, 47.92; H, 4.32: N, 7.30. $C_8H_8O_3NCl$ requires: C, 47.66; H, 4.00; N, 6.95%.).

Fusion of chloroacetyl-2:4-dimethoxyanilide with its own weight of aluminium chloride at 100° or 150° for periods up to an hour, followed by similar treatment of the powdered melt, also gives the same compound.

2:3-Dihydro-7-hydroxy-3-oxobenz-1:4-oxazine.

Chloroacetyl-2:4-dihydroxyanilide (1.7g.) was dissolved in dilute sodium hydroxide solution (10ml.), filtered, and set aside for an hour. The solution was then acidified with dilute hydrochloric acid and, since only a small amount of solid separated, the solution was

saturated with ammonium sulphate and extracted with ether. The extract was dried, concentrated, and the resulting dark solid recrystallised from a little water after charcoaling. 2:3-Dihydro-7-hydroxy-3-oxobenz-1:4-oxazine was obtained as colourless needles, m.p. 208-209°. (Found: C, 58.23; H, 4.50; N, 8.56. $C_8H_7O_3N$ requires: C, 58.18; H, 4.37; N, 8.48%.). Light absorption in ethanol:- λ max. 2680 Å. Log. ε 3.91. Inflexion at 2840-2940 Å. Log. ε 3.78-3.72.

The acetyl derivative was obtained by acetylating the phenol in ice-cold dilute sodium hydroxide solution with acetic anhydride, and it formed colourless rods from water, m.p. 216-217°. (Found: C, 57.96; H, 4.21; N, 6.79. $C_{10}H_9O_4N$ requires: C, 57.97; H, 4.38; N, 6.76%.).

Fusion of chloroacetyl-2:4-dimethoxyanilide with aluminium chloride at 220°.

Fusion of chloroacetyl-2:4-dimethoxyanilide with twice its own weight of aluminium chloride for an hour at 220°, followed by decomposition of the melt in the usual way, resulted in the formation of a dark powder which was insoluble in alkali and the usual organic solvents and which yielded no identifiable product.

2:4-Dimethoxy-N-methylaniline.

2:4-Dimethoxyaniline (8.7g.) was dissolved in a solution of concentrated hydrochloric acid (4.6ml.) in water (120ml.), and acetic anhydride (6.5g.) run in slowly to the cooled, stirred solution. When addition was complete, a solution of sodium acetate (8g.) in water (20ml.) was added. This caused the separation of the solid acetyl derivative. This was filtered off and dried (9.5g.) then dissolved in "Analar" acetone (250ml.) and methylated by refluxing gently with potassium hydroxide (6.7g.) and methyl iodide (10.5g.) for 15 minutes. Cooling, filtering, and concentrating the solution, followed by the addition of water (150ml.) precipitated a colourless oil which was allowed to stand overnight at 0°, when it crystallised in large colourless plates, which, however, melted before reaching room temperature. The oil was extracted with ether, the ether removed without drying, and the residue hydrolysed by boiling with 30% sulphuric acid (100ml.) for 6 hours. The reaction mixture was then made alkaline with potassium hydroxide, and the precipitated oil extracted with ether. Removal of the ether from the dried extract and distillation of the residue in vacuo afforded 2:4-dimethoxy-N-methylaniline as an almost colourless oil (4.2g.), b.p. $66\text{-}68^{\circ}/3\times10^{-4}$ m.m.

Benzoylation of a small amount with benzoyl

chloride in dilute sodium hydroxide solution, afforded a benzoyl derivative as colourless needles, m.p. 173-174°, from ethanol. (Found: C, 70.60; H, 5.99; N, 5.27. $C_{16}H_{17}O_5N$ requires: C, 70.83; H, 6.32; N, 5.16%.).

Chloroacetyl-2:4-dimethoxy-N-methylanilide.

2:4-Dimethoxy-N-methylaniline (4g.) was dissolved in benzene (250ml.) and pyridine (1.9g.), followed dropwise by chloroacetyl chloride (2.7g.), added. The reaction mixture was set aside overnight, then removal of the benzene from the washed and dried solution gave chloroacetyl-2:4-dimethoxy-N-methylanilide as an oil which could be crystallised at 0° from petroleum ether (40-60°), but which was gummy at room temperature.

2:3-Dihydro-7-hydroxy-4-methyl-3-oxobenz-1:4-oxazine.

Aluminium chloride (10g.) and sodium chloride (4g.) were fused together at 140° and chloroacetyl-2:4-dimethoxy-N-methylanilide (2g.) added in small portions. The temperature was maintained at this level for 30 minutes, then the cooled, powdered melt was added to ice (20g.) and dilute hydrochloric acid (5ml.). A gummy solid was obtained, which on charcoaling in aqueous solution and filtering subsequently deposited 2:3-dihydro-7-hydroxy-4-methyl-3-oxobenz-1:4-oxazine as colourless needles,

m.p. 181-182°. (Found: C, 60.60; H, 5.28: N, 8.66. $C_9H_9O_3N$ requires: C, 60.33; H, 5.05; N, 7.82%.). Light absorption in ethanol:- λ max. 2640 Å. Log. ε 3.90. Inflexion at 2840-2940 Å. Log. ε 3.78.

Fusion of chloroacetyl-2:4-dimethoxy-N-methylanilide with an equal weight of aluminium chloride alone at 120° also yields the same compound.

Fusion of chloroacetyl-2:4-dimethoxy-N-methylanilide with aluminium chloride at 220°.

Aluminium chloride (5g.) and chloroacetyl-2:4-dimethoxy-N-methylanilide (2g.) were heated together at 220° for an hour. The viscous black melt was cooled, powdered, and added to ice (10g.) and dilute hydrochloric acid (3ml.), giving a black gum which was partially soluble in alkali. Acidification of the alkaline solution gave a dark brown solid which could not be crystallised from any of the usual organic solvents.

The mother liquors from the black gum, on standing (3 days), deposited a brownish solid which was soluble in alkali, giving a deep purple solution. Recrystallisation from alcohol gave a small quantity of red needles, m.p. 260° (dec.). (Found: C, 54.14; H, 4.18%.).

Attempted O-methylation of 2:3-dihydro-7-hydroxy-3-oxo-benz-1:4-oxazine.

An attempt to O-methylate this compound with potassium carbonate and methyl iodide in acetone gave, as with the 6-hydroxy isomer, the O- and N-methylated product, 2:3-dihydro-7-methoxy-4-methyl-3-oxobenz-1:4-oxazine, as colourless needles from petroleum ether (40-60°), m.p. 74-75°. (Found: C, 62.17; H, 5.10; N, 6.89. $C_{10}H_{11}O_3N$ requires: C, 62.16; H, 5.74; N, 7.25%.). Light absorption in ethanol:- λ max. 2620, 2880 Å. Log. ε 3.96, 3.82.

1-Nitro-2-naphthoxyacetic acid.

β-Naphthol (14.4g.) was dissolved in a solution of potassium hydroxide (12g.) in water (250ml.). Chloroacetic acid was added and the solution refluxed for 3 hours. The solution was then cooled and the potassium salt of -naphthoxyacetic acid which separated was filtered off, dissolved in hot water, and acidified with hydrochloric acid. The acid solution was cooled and the crude -naphthoxyacetic acid (20g.) filtered off, dissolved in glacial acetic acid (125ml.) and nitric acid (d. 1.42: 14ml.) added with stirring. The solution was set aside for 2 hours and the 1-nitro-2-naphthoxyacetic acid which separated was filtered off.

5:6-Benz-2:3-dihydro-3-oxobenz-1:4-oxazine.

1-Nitro-2-naphthoxyacetic acid (5g.) was dissolved in methanol (200ml.) and palladium black (0.2g.) added. Hydrogenation took place rapidly and smoothly, the 5:6-benz-2:3-dihydro-3-oxobenz-1:4-oxazine being precipitated as it was formed. After filtration, the precipitate was dissolved in glacial acetic acid, filtered again to remove catalyst, concentrated, and allowed to crystallise. 5:6-Benz-2:3-dihydro-3-oxobenz-1:4-oxazine was obtained, in 85-90% yield, as colourless needles, m.p. 215-216°. Lees and Shedden[8] give m.p. 215-216°.

Action of aluminium chloride on 5:6-benz-2:3-dihydro-3-oxobenz-1:4-oxazine.

When 5:6-benz-2:3-dihydro-3-oxobenz-1:4-oxazine (2g.) was heated for 30 minutes at 200° with aluminium chloride (4g.), and the resulting complex decomposed with ice (10g.) and dilute hydrochloric acid (3ml.), the product was a black, amorphous solid which was insoluble in dilute sodium hydroxide or in any of the usual organic solvents.

5:6-Benz-2:3-dihydro-4-methyl-3-oxobenz-1:4-oxazine.

5:6-Benz-2:3-dihydro-3-oxobenz-1:4-oxazine (8g.) was dissolved in "Analar" acetone (150ml.) and

methylated by refluxing for 20 minutes with potassium hydroxide (5.5g.) and methyl iodide (8.5g.). Addition of water (50ml.) to the cooled, filtered, and concentrated solution precipitated an oil which soon solidified and recrystallisation of this from ethanol after charcoaling gave 5:6-benz-2:3-dihydro-4-methyl-3-oxobenz-1:4-oxazine as colourless needles, m.p. 83-84°. Lees and Shedden[8] give m.p. 84-85°.

Action of aluminium chloride at 150° on 5:6-benz-2:3-dihydro-4-methyl-3-oxobenz-1:4-oxazine.

When 5:6-benz-2:3-dihydro-4-methyl-3-oxobenz-1:4-oxazine (2g.) was fused with aluminium chloride (4g.) at 150° for 30 minutes, decomposition of the melt with ice (10g.) and dilute hydrochloric acid (3ml.) gave a dark amorphous solid. Extraction of this with benzene gave a brown solution with a green fluorescence, but extraction of this solution with dilute sodium hydroxide afforded no alkali soluble material. The dry benzene solution was chromatographed on alumina, a little starting material being recovered from the benzene eluate. Further elution with 10% methanol in benzene again gave the green-fluorescent solution, concentration of which afforded a brown amorphous solid which could not be obtained crystalline.

Fusion with aluminium chloride at 220° gave similar results, although more decomposition occurred at this temperature.

Action of aluminium chloride/sodium chloride melt at 160° on 5:6-benz-2:3-dihydro-4-methyl-3-oxobenz-1:4-oxazine.

To a melt consisting of aluminium chloride (4g.) and sodiun chloride (5g.) at 160° was added 5:6-benz-2:3-dihydro-4-methyl-3-oxobenz-1:4-oxazine (1g.). The temperature was maintained at this level for an hour, then the purple melt was decomposed as usual. Recrystallisation of the purplish solid obtained from petroleum ether (60-80°) gave colourless needles, m.p. and mixed m.p. with starting material 83-84°.

4-Benzyl-2:3-dihydro-3-oxobenz-1:4-oxazine.

2:3-Dihydro-3-oxobenz-1:4-oxazine (4.2g.) was dissolved in "Analar" acetone (100ml.) and refluxed for six hours with potassium hydroxide (5.5g.) and benzyl chloride (3.6g.). The solution was then cooled, filtered, and concentrated before the addition of water (25ml.) which precipitated an oil. This was extracted with ether, the extract dried, and the ether removed. The resulting oil was distilled, b.p. 166-168°/3.5×10^{-2} m.m., and the solid distillate recrystallised from petroleum

ether (60-80°) as colourless rods of 4-benzyl-2:3-dihydro-3-oxobenz-1:4-oxazine, m.p. 70-71°. (Found: C, 75.17; H, 5.40. Calculated for $C_{15}H_{13}O_2N$: C, 75.29; H, 5.47%.). Preiswerk and Meyer[2] give m.p. 71°.

Action of aluminium chloride on 4-benzyl-2:3-dihydro-3-oxobenz-1:4-oxazine.

4-Benzyl-2:3-dihydro-3-oxobenz-1:4-oxazine (2g.) was fused with aluminium chloride (4g.) for 30 minutes at 120°. Decomposition of the melt with ice and hydrochloric acid gave a gummy, non-crystalline solid which was dissolved in ether and extracted with dilute sodium hydroxide (5ml.). 4-Benzyl-2:3-dihydro-3-oxobenz-1:4-oxazine, m.p. 66-68° and mixed m.p. 68-69° was recovered from the washed and dried ether layer.

Acidification of the alkaline extract afforded a solid, m.p. 62-66°, which was soluble in benzene and could be precipitated therefrom by petroleum ether (60-80°), but did not crystallise from the pure solvents or from a mixture of them. Other solvents were tried, also with lack of success.

Action of aluminium chloride on 2:3-dihydro-4-methylbenz-1:4-oxazine.

When 2:3-dihydro-4-methylbenz-1:4-oxazine

(2g.) was fused with aluminium chloride (4g.) at 150°, for 30 minutes, and the melt cooled and decomposed with ice (10g.) and dilute hydrochloric acid, the product was an oil which was extracted with ether. Removal of the ether from the dried extract allowed the residue to be identified as a good return of starting material by formation of its picrate and its methiodide.

Fusion of 2:3-dihydro-4-methylbenz-1:4-oxazine (2g.) with aluminium chloride (4g.) at 220° resulted in some decomposition. Addition of the cooled, powdered melt to ice (10g.) and dilute hydrochloric acid (3ml.) again gave an oil, in smaller quantity, which was identified as starting material.

In neither case was there any appreciable alkali-soluble material produced.

Attempted methylation of chloroacetyl-o-anisidide.

Chloroacetyl-o-anisidide (36g.) was dissolved in "Analar" acetone (250ml.) and the usual methylation proceedure carried out with potassium hydroxide (10.1g.) and methyl iodide (25.6g.). After an hour, the cooled, filtered, and concentrated solution was diluted with water (100ml.) and the resulting viscous yellow oil extracted with ether, the extract dried, and the ether removed. On distillation of the residue under

reduced pressure, partial decomposition took place, with the evolution of iodine vapours. A viscous yellow oil distilled, b.p. 180° (oil bath temperature)/10^{-3}m.m., which could not be crystallised even by seeding with a crystal of an authentic specimen of chloroacetyl-N-methyl-o-anisidide

Dichloroacetyl-N-methyl-o-anisidide.

Dichloroacetyl-o-anisidide (12g.) was dissolved in "Analar" acetone and potassium hydroxide (15g.) added. After methylation in the usual way with methyl iodide (12g.), cooling, filtering, and concentrating, followed by addition of water (50ml.) gave an oil which soon solidified. Recrystallisation from petroleum ether (60-80°) afforded dichloroacetyl-N-methyl-o-anisidide as colourless needles, m.p. 74-75°. (Found: C, 48.94; H, 4.63; N, 5.75. $C_{10}H_{11}O_2NCl_2$ requires: C, 48.41; H, 4.47; N, 5.65%.).

α-Chloro-α-phenylacetyl chloride.

Thionyl chloride (23.8g.) was added to mandelic acid (15.2g.) and the mixture heated to 110° (oil bath) until no further evolution of hydrogen chloride took place. The excess thionyl chloride was removed and the residue distilled at 108-110°/20m.m. (5.9g.).

The acid chloride formed an amide when it (0.5g.) was mixed with excess ammonia (s.g. 0.880.), m.p. 120-121° after recrystallisation from benzene. Michael and Jeanpretre[65] give m.p. 116° for this derivative.

-Chloro- -phenylacetyl-o-anisidide.

α-Chloro-α-phenylacetyl chloride (8.7g.) was condensed with o-anisidine (11.4g.) in benzene (100ml.). After standing overnight, isolation of the product in the usual way gave α-chloro-α-phenylacetyl-o-anisidide as clusters of rhombs from petroleum ether (60-80°), m.p. 103-104°. (Found: C, 65.73; H, 5.12; N, 5.26. $C_{15}H_{14}O_2NCl$ requires: C, 65.34; H, 5.12; N, 5.08%.).

N-Methylation of α-chloro-α-phenylacetyl-o-anisidide.

α-Chloro-α-phenylacetyl-o-anisidide (6g.) was dissolved in "Analar" acetone and methylated with potassium hydroxide (8g.) and methyl iodide (6g.) in the usual way. After cooling, filtering, and concentrating, addition of water gave a brown oil, which was separated off. Trituration with a little methanol gave a brown solution from which was deposited colourless crystals. Recrystallisation from benzene gave colourless rhombs, m.p. 282-284°, which did not contain halogen. (Found: C, 75.09; H, 5.48; N, 5.55. $C_{15}H_{13}O_2N$ requires: C, 75.29

H, 5.44; N, 5.85%.).

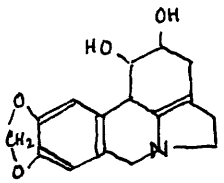
Removal of the methanol from the mother liquors, followed by chromatography of the residue, in ether, on alumina, gave, on concentration of the eluate, a yellow gum which crystallised from petroleum ether (40-60°). Recrystallisation from petroleum ether (60-80°) gave -chloro- -phenylacetyl-N-methyl-o-anisidide, m.p. 82-83°, as colourless prisms. (Found: C, 66.65; H, 5.57; N, 4.85. $C_{16}H_{16}O_2NCl$ requires: C, 66.31; H, 5.57; N, 4.83%.).

α-Chloro-α-phenylacetyl-N-methyl-o-anisidide.

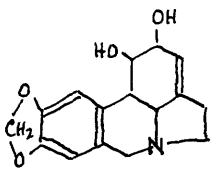
α-Chloro-α-phenylacetyl chloride (1.9g.) was condensed with N-methyl-o-anisidine (1.4g.), in benzene (100ml.), in the presence of pyridine (0.8g.). After standing overnight, the solution was filtered, washed, and dried. Removal of the benzene gave an oil which crystallised from petroleum ether (60-80°), giving rhombs of α-chloro-α-phenylacetyl-N-methyl-o-anisidide, which proved to be identical (m.p. and mixed m.p. 81-82°) with the compound obtained by N-methylation of α-chloro-α-phenylacetyl-o-anisidide.

LYCORINE.

Lycorine is the principal alkaloid of the Amaryllidaceae and was first isolated from Narcissus pseudonarcissus in 1877 by Gerrard[66]. The structural elucidation of lycorine and the other closely related alkaloids of this species has been mainly due to Kondo and his collaborators, who, by means of the usual analytical methods, established beyond all doubt the functional groups present in the alkaloid. From degradative evidence, Kondo proposed (LXX) as the structure of lycorine, although (LXXI) also might well represent the structure, since the only conditions for the placing of the ethylenic bond are that it should be out of conjugation with the aromatic nucleus and that neither of the two vicinal hydroxyl groups should be enolic. (LXX) and (LXXI) both satisfy these conditions.



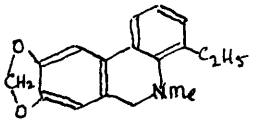
(LXX)



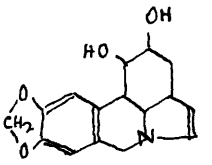
(LXXI)

This work on the elucidation of the structure of lycorine has been reviewed by Cook and Loudon[67] and full references are given there.

More recently, interest in the structure of lycorine has been reawakened by the synthesis, by Kelly, Taylor, and Wiesner[68], of 1-ethyl-9:10-dihydro-10-methyl-6:7-methylenedioxyphenanthridine (LXXII) which they showed to be identical with dihydrolycorineanhydromethine, a compound obtained from lycorine by Hofmann degradation followed by catalytic reduction, although Hey and Turpin[69] report that they have been unable to obtain this compound by the method given by Kelly et al., but isolated only 2'-ethyl-4:5-methylenedioxybenzanilide which they claim to be the usual product of such a reaction.



(LXXII)

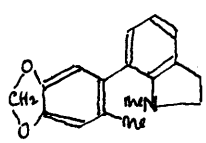


(LXXIII)

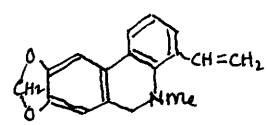
From Emde degradation results, Kelly et al., then proposed for lycorine the formula (LXXIII), in which the ethylenic bond occupies the 4:5-position and not the 4:13-position as postulated by Kondo, since the product

obtained from such a degradation could be more easily explained by this formula. Wiesner, Taylor, and Uyeo[70] further considered that the basicities of lycorine and dihydrolycorine were in agreement with this postulate.

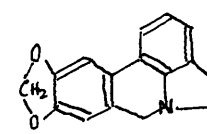
Since then, Taylor, Thomas, and Uyeo[71] have published syntheses of a number of degradation products of lycorine, namely lycorine anhydrohydromethine (LXXIV), lycorine anhydromethine (LXXV), and dihydroisolycorine (LXXVI). However, from a full consideration of the properties of lycorine, they now propose (LXXI) as the structure of lycorine, a structure which has previously been suggested by Cook and Loudon[67], and give a reaction scheme for the formation of the Hofmann and Emde degradation products which takes into account the necessity for the presence both of the double bond and the quaternary nitrogen atom for facile elimination of water from lycorine, under alkaline conditions.



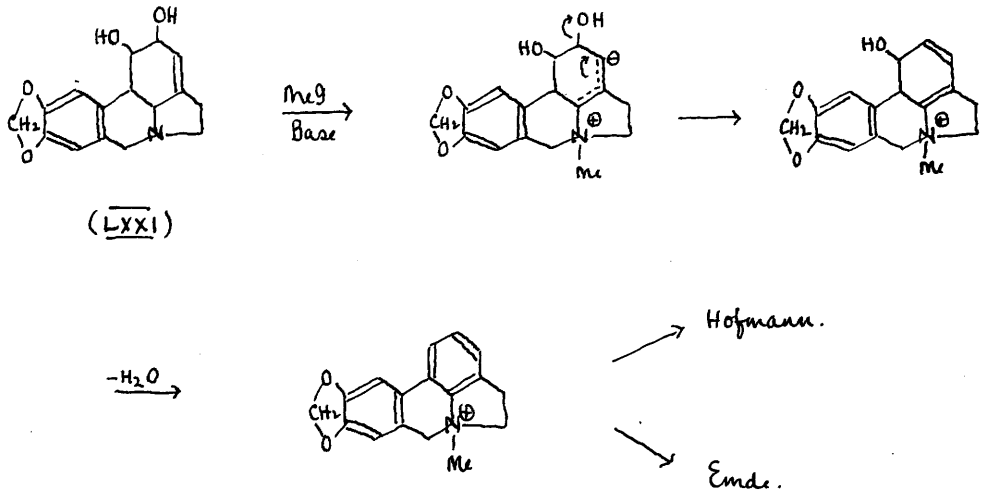
(LXXIV)



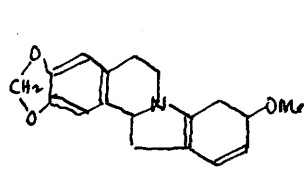
(LXXV)



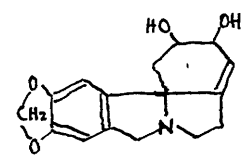
(LXXVI)



About the same time, Robinson and collaborators[72], on considerations based upon the exhaustive methylation processes and on biogenetic schemes, proposed that lycorine had the erythraline skeleton (LXXVII), that its structure could be represented by (LXXVIII), and that the phenanthridine nucleus is produced through molecular rearrangement during Hofmann degradation.



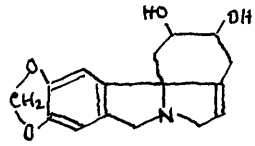
(LXXVII)



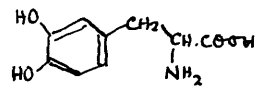
(LXXVIII)

The double bond could be moved into the five-membered ring, as in (LXXIX), but this is not favoured

in view of the proposed biogenetic origin from 3:4-dihydroxyphenylalanine (LXXX).

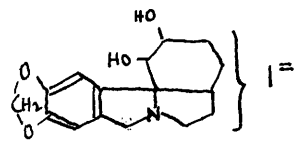


(LXXIX)

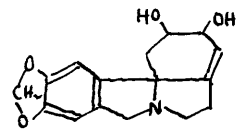


(LXXX)

Subsequently[73], Robinson advanced a further modification in which one of the hydroxyl groups has been moved (LXXXI), and in which there would again be alternative positions for the double bond. The hydroxyl group vicinal to the hydroaromatic block would make the rearrangement to a phenanthridine easier to understand.



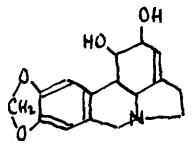
(LXXXI)



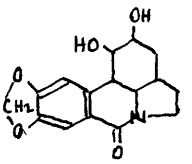
(LXXVIII)

Wiesner, Taylor, and Uyeo[70], commenting on Robinson's formula (LXXVIII) for lycorine, do not believe that an Erythina type rearrangement would be probable under the conditions of the Hofmann or Emde degradation and advance further evidence for their proposed structure

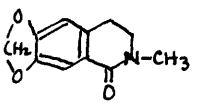
(LXXI) in the similarity of the infra-red spectra of dihydrolycorinone (LXXXII) and oxyhydrastinine (LXXXIII) in the carbonyl region, and in the dissimilarity of the infra-red spectra of (LXXXII) and (LXXXIV).



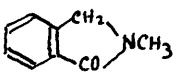
(LXXI)



(LXXXII)



(LXXXIII)

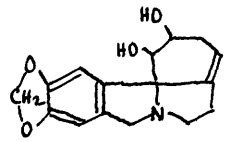


(LXXXIV)

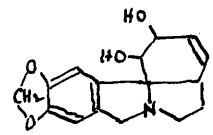
It may well be, however, that mild permanganate oxidation of dihydrolycorine diacetate, followed by hydrolysis, is sufficient to cause the rearrangement to a compound containing a phenanthridine nucleus, although, on the whole, lycorine is remarkably stable.

Govindachari and Thyagarajan[74] have further deduced from infra-red studies of lycorine and dihydrolycorine, that the possibility of the ethylenic linkage being in the 4:13-bridgehead position is completely ruled out in any of the proposed formulae, and also that in Robinson's formula (LXXXI) the double bond must occupy the position shown in (LXXXV) since, if it was in the position shown in (LXXXVI), it would then be

a disubstituted ethylenic linkage whic has a characteristic peak in the infra-red spectrum. The infra-red spectrum of lycorine lacks this peak.



(LXXXV)



(LXXXVI)

At this stage, then, ignoring the final positions of the two non-phenolic hydroxyl groups, the main problem is to decide between the phenanthridine type of structure proposed by Kondo and its slight modification due to Taylor, Wiesner, and others, and the erythraline type of skeleton as envisaged by Robinson. Now, Folkers, Koniuszy, and Shavel[75] have shown that fusion of erythraline, erythratine, and β-erythroidine with molten potassium hydroxide produces an appreciable quantity of indole. It would thus be of interest to apply this reaction to lycorine, although Ewins in 1910[76] was unable to obtain any useful results by this method.

In the present work, lycorine was isolated from Narcissus pseudonarcissus by the method given in Manske and Holmes[67]. When lycorine was fused with

potassium hydroxide at 220°, the odour of indole could be detected quite distinctly. Addition of water, followed by distillation in steam, however, gave no appreciable quantity of indole, although the first few drops of the distillate gave a positive pink colour reaction with p-dimethylaminobenzaldehyde, Ehrlich's reagent for the detection of indoles. Addition of a saturated solution of picric acid failed to produce a picrate, although a reddish solution was obtained.

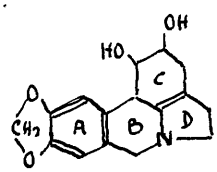
The reaction was extended to lycorine hydrochloride. Again the odour of indole was detected and the distillate gave a positive Ehrlich's indole test, but neither indole itself, nor a solid derivative, could be isolated. These experiments were repeated several times, but, although the odour of indole was apparent each time, attempts at its isolation were fruitless.

The results of these experiments are perhaps not as disappointing as would at first appear, since the quantity of the alkaloid and its hydrochloride available was small. 0.7g. was the maximum quantity used in these experiments and, since in the Erythrina alkaloids 8g. of material gave only 0.16g of indole picrate in the most successful experiment, it is not surprising that the

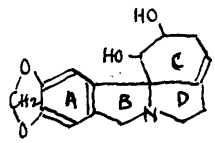
quantity of indole obtained from lycorine was insufficient to furnish a derivative.

Working up of the other products of the fusion gave very small quantities of a neutral substance and an acidic substance which were not identified. Ewins[76] obtained a small quantity of a polyphenolic substance which resisted all attempts at crystallisation.

Lycorine contains two non-phenolic hydroxyl groups and it is known that during the course of the Hofmann and Emde degradations these are eliminated by dehydration, forming an aromatic ring. Now, in the Kondo structure for lycorine (LXX), it might be expected that dehydration would take place under mild conditions with the consequent formation of a fully aromatic ring C.



(LXX)



(LXXXV)

On the other hand, in Robinson's proposed structure (LXXXV), ring C contains a quaternary carbon atom and dehydration to a fully aromatic structure cannot

take place without an accompanying rearrangement. Thus it would seem that ease of dehydration would point to the Kondo structure, although the fact that easy dehydration does not take place does not necessarily establish Robinson's structure.

Various attempts were made to dehydrate lycorine by refluxing it with a trace of iodine[77] in benzene and xylene. In each case, lycorine was recovered unchanged, in high yield, on working up the product.

While, therefore, this brief inquiry has contributed no conclusive results, it affords some indication that the Erythrina type of structure may better accommodate the behaviour of lycorine.

EXPERIMENTAL.

Isolation of lycorine.

The bulbs of Narcissus pseudonarcissus (4 Kg.) were collected, thoroughly washed and dried, then crushed and thinly laid out on wire gauze, allowing free circulation of air round the bulbs. After four days the bulbs were dfy enough to be ground without clogging the mill.

The dry bulb material was then extracted, in several batches, with hot alcohol. Each batch was extracted for 6 hours with 2 litres of alcohol, the hot alcohol removed, and the residue extracted for a further 6 hours with a fresh quantity of alcohol (2 l.). On cooling the alcoholic extract, a precipitate, believed to be a glycoside, was obtained. This was filtered off and retained. The extracts were then combined and concentrated to small volume when a dark, syrupy liquid (ca. 250ml.) resulted. This was treated with an equal volume of water and the resulting tarry precipitate filtered off, resuspended in dilute hydrochloric acid and thoroughly shaken. It was filtered again and the combined filtrates extracted with two portions of ether (150ml. each) and the extract discarded. The solution was made alkaline

with sodium carbonate, and the precipitate which slowly settled was filtered off, resuspended in water, and washed several times with water by decantation before being refiltered.

The crude lycorine (10.8g.) was dissolved in 2N hydrochloric acid (200ml.) and boiled with acid-washed charcoal[78] (2.5g.), filtered, and cooled. After several recrystallisations from 2N hydrochloric acid, pure lycorine hydrochloride (9.2g.) was obtained as light yellow needles, m.p. 207-208°.

Lycorine (7g.) was obtained from the purified hydrochloride by dissolving it in water (200ml.) and adding ammonia (0.880) until a precipitate began to form. The pure lycorine was crystallised from a large quantity of alcohol, in which it is only slightly soluble, m.p. 272-274°.

Potassium hydroxide fusion of lycorine.

Lycorine (or lycorine hydrochloride) (0.7g.) was intimately mixed with "Analar" potassium hydroxide (2g.) and plunged into an oil bath at 190°. After a few minutes the melt became reddish, and frothing occurred. After heating for 30 minutes, the melt was cooled and

water (10ml.) added. When the mixture was steam distilled, the first few drops of the distillate gave a positive Ehrlich's indole test and smelled of indole. Attempts to prepare a picrate by adding a saturated solution of picric acid were unsuccessful as also were attempts to isolate the derivative formed with the sodium salt of naphthaquinone sulphonic acid.

The above experiment was repeated several times and a modified version, in which the vapours of the fusion were passed through a solution of picric acid, was devised. No derivative of indole could be obtained, although the odour of indole was quite distinct.

The solution of the melt in water was allowed to cool, and a yellowish-brown solid which had been precipitated was filtered off, dissolved in benzene, in which it was not completely soluble, and chromatographed on alumina. Elution with benzene or benzene/methanol gave no product, but elution with pure methanol gave a solution with an intense blue-violet fluorescence. Concentration of this solution gave a yellowish solid which was very sparingly soluble in benzene, petroleum ether (60-80^{o}), and dioxan but very soluble in methanol. Crystallisation from methanol by allowing the methanol to evaporate slowly

gave yellow needles, m.p. 262-265° (dec.).

Acidification of the alkaline liquors of the fusion gave a brown solid which was purified somewhat by redissolution in alkali and reprecipitation several times. The solid dissolved in sodium bicarbonate with effervescence and did not give a ferric chloride test for a phenol. Crystallisation from methanol afforded a yellow solid, m.p. 165-170°, which did not sublime at 220°/1m.m. nor from copper powder at 170°/2×10^{-2} m.m.

Attempted dehydration of lycorine.

Lycorine (0.25g.) was refluxed with a crystal of iodine in benzene (50ml.) for $2\frac{1}{2}$ hours. After this time the solution was concentrated somewhat, then cooled and filtered. The resulting solid was recrystallised from alcohol, m.p. 268-270°, mixed m.p. with lycorine, 272-275°. The recovery was 85% of the starting material.

Repetition of the experiment using xylene as the refluxing medium gave similar results.

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