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DOCTOR OF PHILOSOPHY

by

WILLIAM DAWSON

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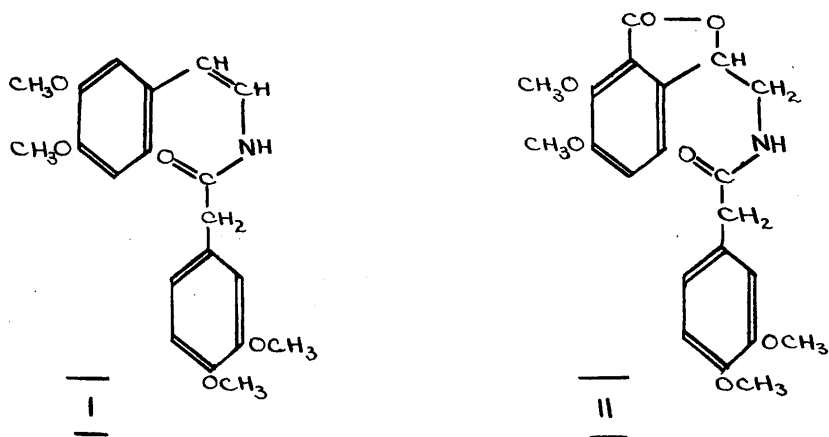
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The author wishes to express his sincere gratitude to Professor F.S. Spring for his supervision and constant interest in the progress of this work, and to Dr. H.R. Bentley and Dr. G.T. Newbold for their readily given advice and help. Thanks are also due to the Department of Scientific and Industrial Research for financial provision and to The Royal Technical College where the research programme was carried out.

SUMMARY.Part I - An Examination of Synthetic Routes to Papaverine.

In an attempt to establish a new synthesis of the alkaloid papaverine, four possible routes were examined.

3:4-Dimethoxyphenylacetyl chloride was condensed with ethyl aminoacetate giving ethyl 3:4-dimethoxyphenylacetamidoacetate, which on hydrolysis formed the free acid. Condensation of this acid and 3:4-dimethoxybenzaldehyde led to the formation of 2-(3:4'-dimethoxybenzyl)-4-(3:4'-dimethoxybenzal)-oxazol-5-one which underwent ring opening with sodium carbonate to α -(3:4'-dimethoxyphenylacetamido)-3:4-dimethoxycinnamic acid. Decarboxylation of the acid gave β -(3:4'-dimethoxyphenylacetamido)-3:4-dimethoxystyrene (I).

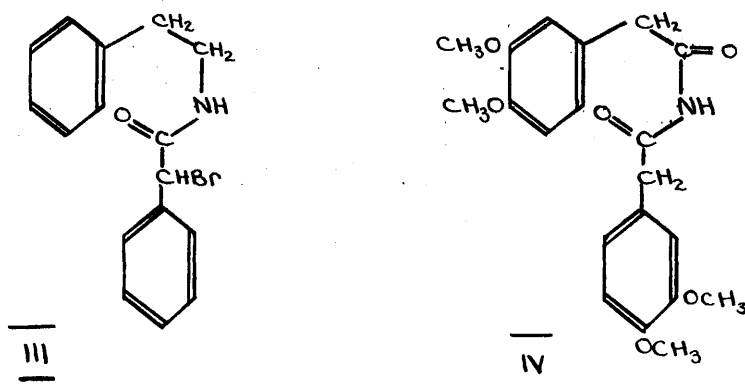


The structure of this material was confirmed by hydrogenation to homoveratroyl-homoveratrylamine. All attempts to ring close this substance with the elimination of the elements of water to papaverine failed. The theoretical aspects of this failure are discussed.

Using op~~ianic~~ acid, a possible synthetic route was investigated. The acid condensed with nitromethane giving nitromethylmeconin, reduction of which formed aminomethylmeconin hydrochloride. Acylation with 3:4-dimethoxyphenylacetyl chloride led to the formation of the desired 3:4-dimethoxyphenylacetamido-methylmeconin (II). It was however found impossible to eliminate the lactone ring and convert this compound either to papaverine or an isoquinoline derivative.

An examination of the ring closure of 2-(α -bromophenylacetamido)-1-phenyl-ethane (III) was made in the hope that during this reaction the excess hydrogen atoms of the heterocyclic ring formed, would be removed by reductive dehalogenation. Instead of the expected product, 1-benzyl-isoquinoline however, 1-benzyl-3:4-dihydroisoquinoline was produced. When the reaction was examined using 2-(α -chloro-3':4'-dimethoxyphenylacetamido)-1-(3':4'-dimethoxyphenyl)-ethane, no evidence of reductive dehalogenation was found.

An approach to a papaverine synthesis was made through dihomoveratramide (IV) by treatment of this substance with phosphorus oxychloride to form 3-chloro papaverine. The diamide was found to be unstable to the action of this reagent and gave homoveratramide. An



alternative synthesis of 3-hydroxy-isoquinolines was established. Methyl 2-acetyl-4:5-dimethoxyphenylacetate with ammonia gave 6:7-dimethoxy-3-hydroxy-1-methyl-isoquinoline and similarly methyl 2-benzoyl-4:5-dimethoxyphenylacetate formed 6:7-dimethoxy-3-hydroxy-1-phenyl-isoquinoline. When the reaction was examined using methyl 4:5-dimethoxy-2-phenylacetyl-phenylacetate, the product isolated was 6:7-dimethoxy-2-hydroxy-3-phenyl-1:4-naphthoquinone. Methyl 4:5-dimethoxy-2-(3':4'-dimethoxyphenylacetyl)-phenylacetate also formed 6:7-dimethoxy-3-(3':4'-dimethoxyphenyl)-2-hydroxy-1:4-naphthoquinone.

In conjunction with this work, the Schiff's base formed by the condensation of 2-(3':4'-dimethoxyphenyl)-2-methoxy-ethylamine and 3:4-dimethoxybenzaldehyde was shown to rearrange giving 1:2-dihydro-6:7-dimethoxy-1-(3':4'-dimeth-

oxyphenyl)-isoquinoline.

Part II - Synthetic Studies in 1:4-Oxazine
Chemistry

In an extension of the synthetic route to 5-hydroxy-1:4-oxazines discovered by Newbold, Spring and Sweeny (J.1950, 909.), the synthesis of phenyl substituted 5-hydroxy-1:4-oxazines was successfully carried out by this method. At the same time various condensations of difunctional compounds to 1:4-oxazines were examined. Bromoacetal was condensed with ethanolamine forming 2-amino-ethoxy-acetaldehyde diethylacetal which was converted into dihydro-1:4-oxazine. 2-Amino-1-hydroxy-propane in a similar manner gave (2-amino-1-methyl-ethoxy)-acetaldehyde diethylacetal which was converted to 2-methyl-dihydro-1:4-oxazine. The extension of this reaction to fully unsaturated 1:4-oxazines was examined.

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Part One.

An Examination of Synthetic Routes

to

Papaverine.

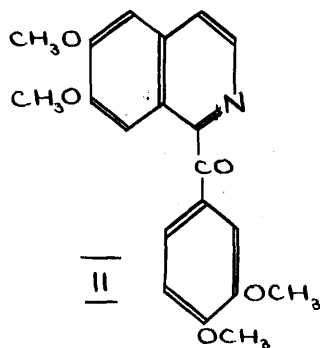
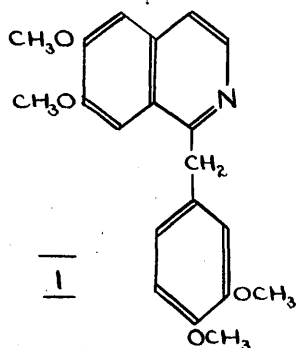
INTRODUCTION.

The alkaloid papaverine, first isolated by Merck (1) from papaver somniferum L in 1848, occurs as one of the minor constituents of opium. The separation of this alkaloid from the opium extract, a matter to which a large amount of attention has been given by Hesse and others (2) resulted in the development of several methods whereby the pure alkaloid may be obtained. It has been characterized by the preparation of its acid oxalate, picrate and hydrochloride, and investigation by Warren (3) has led to specific colour reactions with sulphuric acid and formaldehyde by which the presence of the base may be detected.

The pharmacological action of papaverine lies in its spasmolytic activity, first observed by Pal (4) the general effect of the drug being intermediate between that of morphine and codeine. Reviews published by Raymond (5) and Blicke (6) give a detailed account of the action of papaverine and its derivatives.

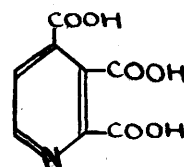
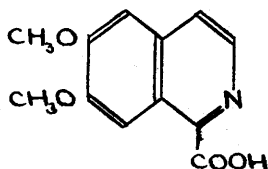
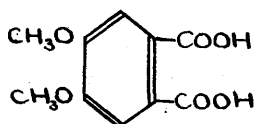
The elucidation of the chemical structure of papaverine was due primarily to the classical work of Goldschmiedt and collaborators (7) extending over ten years which led to the establishment of its structure as

1 - (3:4'- dimethoxybenzyl) - 6:7-dimethoxyisoquinoline(I)

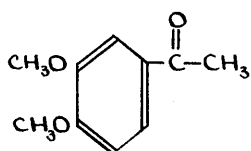


The degradative evidence on which this structure was based may be summarised briefly.

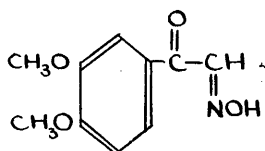
Oxidation of papaverine with potassium permanganate yielded the simpler products metahemipinic acid (III) and 6:7 - dimethoxyisoquinoline - 1 - carboxylic acid (IV). The attachment of a veratryl residue to the isoquinoline nucleus was deduced from degradative examination of papaveraldine, (II) an oxidation product of papaverine. Further oxidation of papaveraldine yields pyridine-2:3:4-tricarboxylic acid (V), thereby signifying that the veratryl residue is attached to C₁.



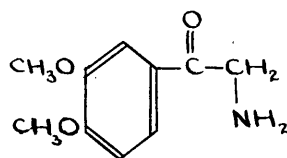
The structure suggested on the basis of this work was established unequivocally from a total synthesis of the alkaloid by Pictet and Gams (8). Veratrole was condensed with acetyl chloride giving acetoveratrone (VI) which was then converted through the isonitrosoketone (VII) which was then converted through the isonitrosoketone (VIII)



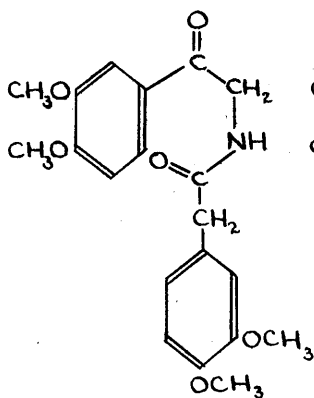
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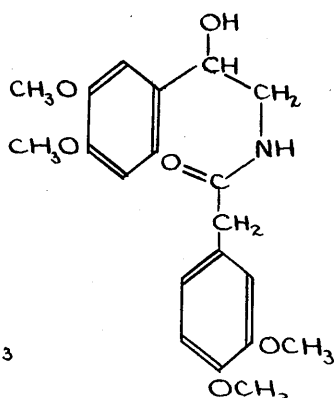
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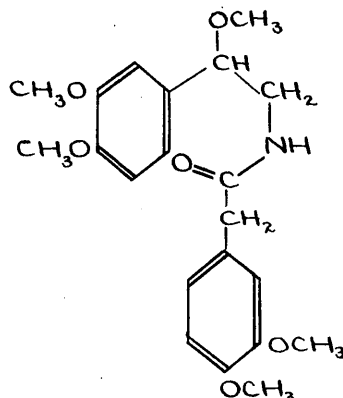
VIII



IX



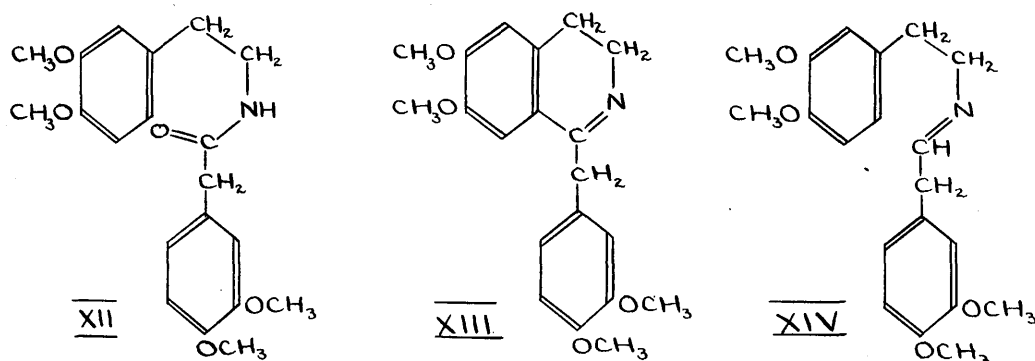
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XI

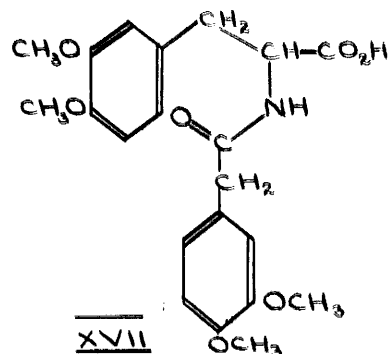
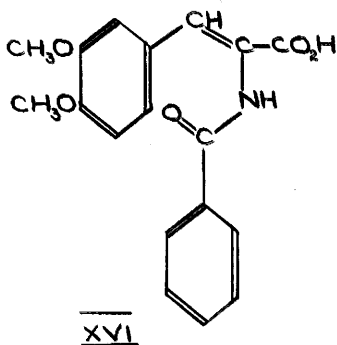
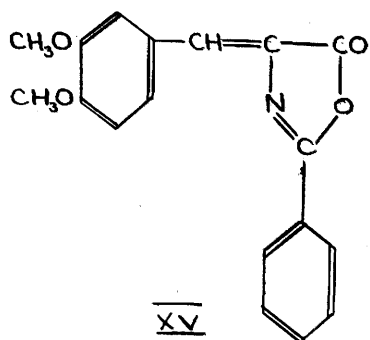
to ω -aminoacetoveratrone (VIII). Acylation of (VIII) with homoveratroyl chloride gave ω -homoveratramidoacetoveratrone (IX) which on reduction gave the secondary alcohol (X). Elimination of two molecules of water from (X) effects ring closure with formation of papaverine. The synthesis of papaverine has been further refined by several workers in an effort to increase the /

the overall yield of the base. Rosenmund (9) and Mannich and Walther (10) carried out the synthesis via 1-(3':4'-dimethoxyphenyl)-2-(3':4'-dimethoxyphenylacetamido)-1-methoxyethane (XI) ring closure with phosphorus oxychloride giving papaverine, while Spath and Berger (11) effected the ring closure of (XII) to 3:4-dihydropapaverine (XIII), catalytic dehydrogenation of which gave papaverine. Spath and Berger (12) have also successfully ring closed

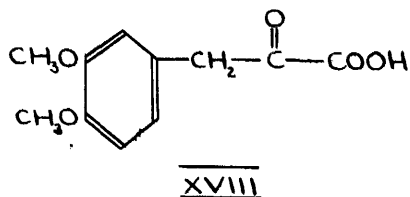


the Schiff's base (XIV) obtained by the condensation of homoveratraldehyde and homoveratrylamine, to give tetrahydropapaverine.

A review of German processes given in B.I.O.S. report No.1774 reveals that in addition to the above syntheses one other variation attributed to Boehringer (13) has been employed. Treatment of 4-(3':4'-dimethoxybenzal)-2-phenyl-oxazol-5-one (XV) with sodium carbonate gives α -benzamido-3:4-dimethoxycinnamic acid (XVI) which self-condenses in the presence of ammonia and calcium hydroxide to give α -(3':4'-dimethoxyphenylacetamido)-3:4-dimethoxyphenylpropionic acid (XVII). Presumably the reaction takes place



through the intermediate keto acid (XVIII), two molecules of which condense with ammonia to yield (XVII). Ring closure of this compound followed by dehydrogenation and decarboxylation gives papaverine.



A number of products allied to papaverine have been synthesised and described by Buck, Haworth and Perkin (14) Slotta and Hoberlandt, (15), Kindler (16), Keimatsu (17) and Sugasawa (18), while work on intermediates has been contributed by Bide and Wilkinson (19).

THEORETICAL.

The synthesis of papaverine from
3-(3:4-dimethoxyphenylacetamido)-3:4-dimethoxystyrene
(XIV) has been reported by
Kobayashi and co-workers (17). This reaction
has been carried out in a solution of
methyl acetate and acetic acid (17).
The reaction is carried out in a
methyl acetate-acetic acid system.

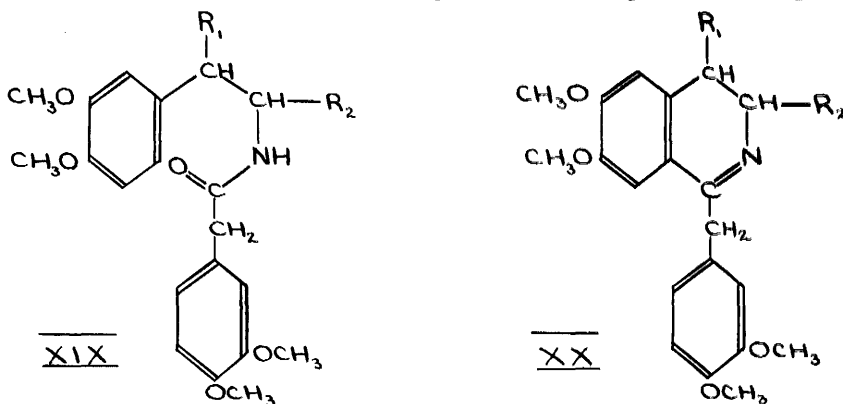
Attempted Synthesis of Papaverine

from

β -(3:4'-Dimethoxyphenylacetamido)-3:4-dimethoxystyrene.

Attempted Synthesis of Papaverine-dimethoxystyrene
Dimethoxyphenylacetamido)-3:4-dimethoxystyrene.

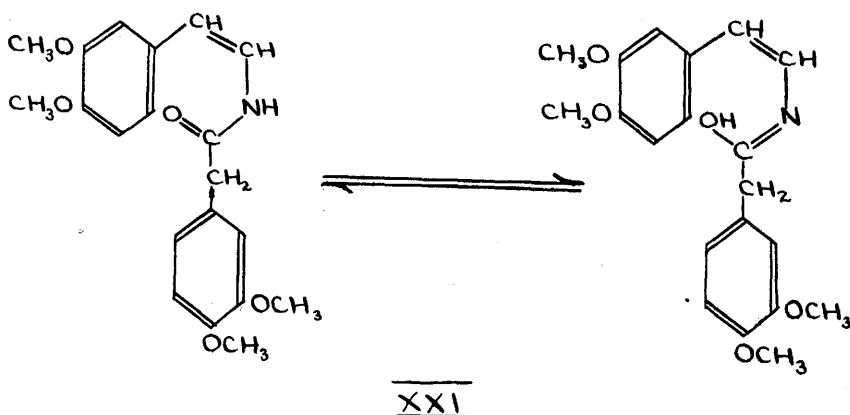
The application of isoquinoline syntheses to the production of papaverine has followed strictly conventional lines (8,9,10,11,12). With one exception (12) the desirable intermediate has been a substituted acylated β -phenylethylamine of structure (XIX) which by ring closure with suitable dehydrating agents as prescribed



by Spath et alia (20) has given the required dihydroisoquinoline (XX). The groups R_1 and R_2 have been of such a nature that they can be eliminated easily to a fully aromatic compound. In some cases (XIX $R_1 = OH$, $R_2 = H$), (XIX $R_1 = OMe$, $R_2 = H$) this elimination has been affected simultaneously with ring closure; in others (XIX $R_1 = H$, $R_2 = COOH$), (XIX $R_1 = R_2 = H$) it has necessitated a further operation such as dehydrogenation. The ring closure of these amides has not proven difficult since the preliminary step appears to be the formation of a substituted dihydroisoquinoline (XX)

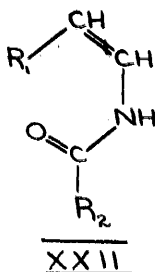
and it has been found that dihydroisoquinolines are easily formed from amides (XIX $R_1 = R_2 = H$).

In a search for a new synthesis of papaverine we have attempted to establish a route which would not involve as the final stage the dehydrogenation of a dihydropapaverine, since this step has not always proven efficient (21) in previous cases. Therefore the problem has been to establish an intermediate amide which would proceed by ring closure direct to papaverine. It can be seen that this condition would be fulfilled by β -(3:4'- dimethoxyphenylacetamido) - 3:4 - dimethoxystyrene (XXI) since it possesses the necessary substituted amide structure, and also contains a double bond in the potential 3:4 positions. It has been suggested by Pictet and Gams (loc. cit.) that this substance may be the intermediate



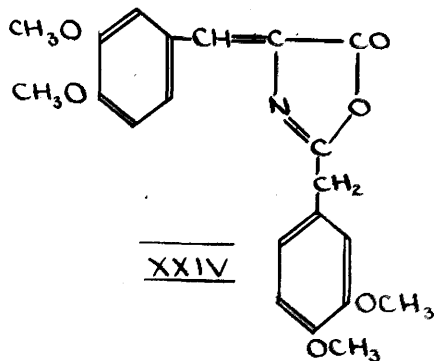
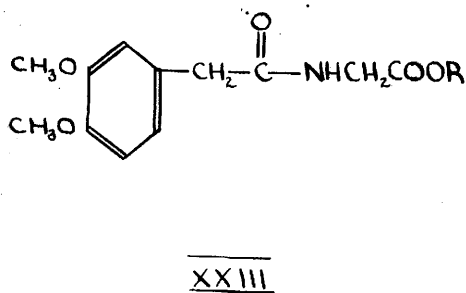
formed in the synthesis of papaverine from the substituted acylated β -phenylethylamine (XIX $R_1 = OH$, $R_2 = H$). On the other /

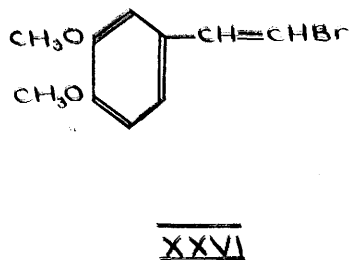
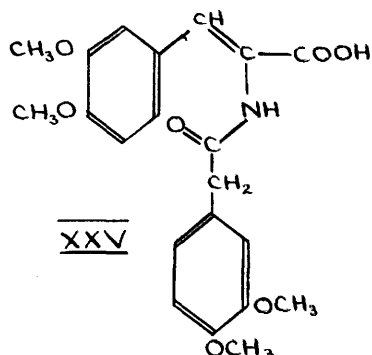
other hand Rosenmund, Nothnagel and Riesenfeldt (loc.cit) and Sugawara (loc.cit) failed to effect the cyclisation of the substituted amides (XXII $R_1 = C_6H_5$ or $(C_2H_5O)_2 C_6H_5-$, $R_2 = C_6H_5$ or $(CH_3O)_3 C_6H_2-$). However serious discrepancies



in the physical constants of the intermediates exists between the authors. For this reason it was decided that the investigation of a possible route to papaverine through the substituted styrene (XXI) was worthy of investigation.

Two methods were considered for the synthesis of β - (3:4' - dimethoxyphenylacetamido) - 3:4 - dimethoxystyrene. (a) Preparation of 2 - (3:4' dimethoxybenzyl) - 4 - (3:4' - dimethoxybenzal) - oxazol - 5 - one (XXIV) followed by opening of the oxazalone ring and decarboxylation.





(b) Condensation according to the method of Rosenmund et alia (9) of β -bromo - 3:4 - dimethoxystyrene (XXVI) with 3:4 - dimethoxyphenylacetamide to give β -(3:4'-dimethoxyphenylacet:amido) - 3:4 - dimethoxystyrene (XXI).

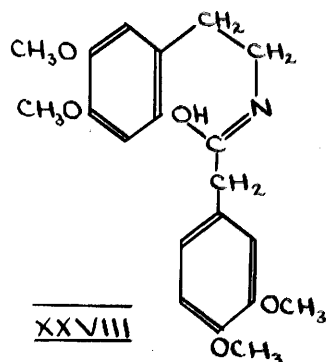
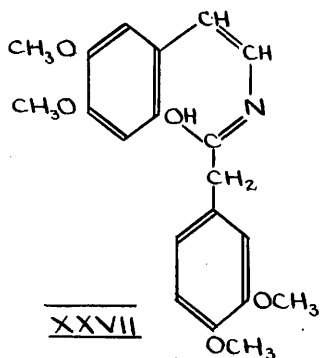
Method (b) presents the difficulty of synthesizing the required styrene and also the fact that the authenticity of other amides prepared by this method has been questioned (18). Method (a) appeared more suitable and it was therefore decided to pursue this route. Homoveratric acid was prepared by the method of Organic Syn. Vol. II 333 . The acid chloride was formed by the action of phosphorus pentachloride and distillation under vacuum gave the chloride as a pale yellow oil, which solidified to a low melting solid. This substance has been described as a viscous oil(22). Attempted acylation of glycine with this acid chloride to give 3:4 - dimethoxyphenyl acetamido-acetic acid (XXIII R=H) was unsuccessful. Attempts to effect the acylation by treatment of an aqueous solution of glycine with the acid chloride in the presence of sodium hydroxide under varying conditions all resulted in the formation of 3:4 - dimethoxyphenylacetic acid . The use of sodium carbonate gave similar results. Refluxing the acid/

acid chloride with glycine suspended in benzene was likewise unsuccessful, using methyl and ethyl aminoacetates however, the required acylation was readily achieved to give ethyl 3:4 - dimethoxyphenylacetamido - acetate (XXIII R=C₂H₅) and methyl 3:4 - dimethoxyphenylacetamido - acetate (XXIII. R=CH₃). Hydrolysis of these esters to the corresponding acid proved difficult, the use of aqueous alkali resulting in preferential fission of the amide linkage with the production of 3:4 - dimethoxyphenylacetic acid. The required hydrolysis of the esters (XXIII R=C₂H₅ or CH₃) to 3:4 - dimethoxyphenylacetamido-acetic acid (XXIII R=H) was eventually carried out using sodium ethoxide in dry ethanol in the presence of the theoretical amount of water.

The formation of 2-(3:4' - dimethoxybenzyl) - 4 - (3:4' - dimethoxybenzal) - oxazol - 5 - one (XXIV) was accomplished in poor yield. The low yield was not unexpected since a review of the chemistry of oxazolones (23) revealed that in cases where the 2 position was occupied by a benzyl group (24,25), i.e., using phenylacetamido-acetic acid, poor yields were obtained. Treatment of the oxazolone(XXIV) with sodium carbonate gave α - (3:4' - dimethoxyphenylacetamido) - 3:4 - dimethoxycinnamic acid (XXV). This acid when heated in quinoline in the presence of copper chromite gave the desired β - (3:4' - dimethoxy:phenylacetamido) - 3:4 - dimethoxystyrene (XXI). The structure of the last compound was established unequivocally by hydrogenation which gave (N -(3:4' - dimethoxyphenyl)-ethyl) - 3:4 - dimethoxyphenylacetamide (XII) identical with a specimen prepared according/

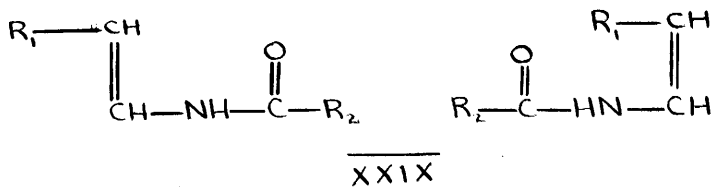
according to the method of Spath (11) .

Ring closure of (XXI) to papaverine was then attempted. Using a wide variety of dehydrating agents and different reaction conditions no basic material was isolated and in numerous cases starting material was recovered unchanged. At the same time unsuccessful attempts were made to ring close α -(3:4'-dimethoxyphenylacetamido) - 3:4 - dimethoxycinnamic acid(XXV) and its methyl ester. These results seem rather unexpected, since one might expect the greater tendency to full aromatisation of (XXVII) to facilitate the elimination of water



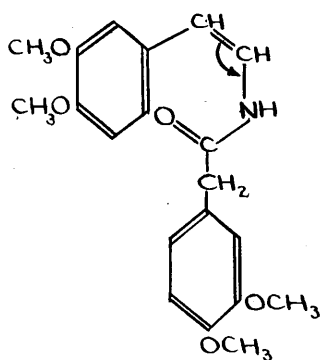
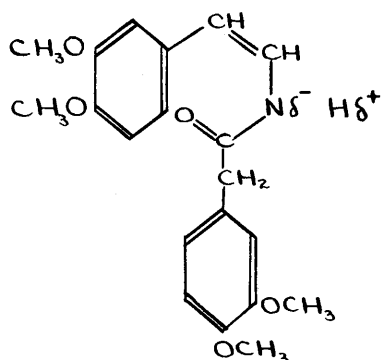
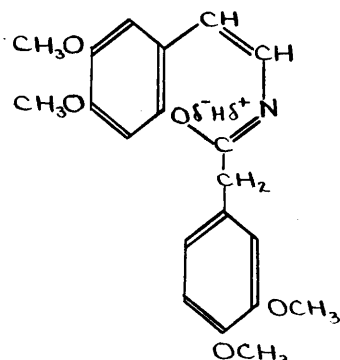
compared with (XXVIII). This, however, supports the observations of Rosenmund et alia(9) and Sugasawa(18) to which reference has already been made, and provides further evidence of the impossibility of converting the amides (XXII) into isoquinolines.

In order to explain this failure to produce papaverine under what would appear to be the most favourable circumstances, it is suggested that the introduction of the double bond gives rise to the possibility of cis-trans isomerism with the formation of the isomers (XXIX)



If, as may be the case, the trans form is the stable isomer, then cyclisation to a heterocyclic ring would be very difficult and would explain the experimental impossibility of achieving the synthesis. Against this theory however it must be noted that no other form of β -(3':4' - dimethoxyphenylacetamido) - 3:4 - dimethoxystyrene has been isolated. Also exposure of this material to the action of ultra-violet light according to the method used by Hartley(35) to convert trans-azobenzene into the cis-form did not isomerise(XXI). An attempt to ring close this amide to an isoquinoline in the presence of ultra-violet light, using phosphorus oxychloride as the condensing agent was also unsuccessful.

A further explanation for the behaviour of this compound can also be offered. The presence of the double bond in the potential 3:4-position creates in the position α to the nitrogen

XXXXXXIXXXII

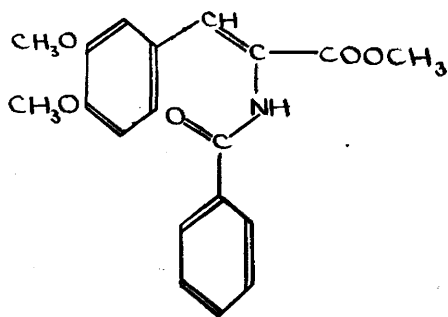
atom a high degree of electron density (XXX). This must confer on the nitrogen atom an increased nucleophilic character (XXXI) which will affect the equilibrium between structures (XXXI) and (XXXII) in favour of the amide form. It is not unlikely that in the formation of an isoquinoline ring of this type, the essential preliminary stage is the intermediate formation of the enolic form of the amide (XXXII). From an electronic standpoint we can say that the presence of the double bond in the potential 3:4 position prevents the formation of the enolic form of the amide, and since this is an essential step in the formation of an isoquinoline compound, the presence of the double bond will prevent the ring closure.

The Attempted Ring Closure
of
3:4-Dimethoxyphenylacetamido-methylmeconin.

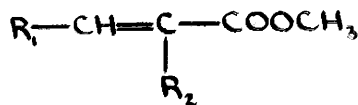
Attempted Ring Closure of 3:4 - Dimethoxyphenylacetamido-methylmeconin.

With the failure of the previous synthesis attention was next turned to an examination of possible methods of saturating the double bond with groupings which could be eliminated after cyclisation. In the first place it was found that bromination of β -(3:4' - dimethoxyphenylacetamido) - 3:4 - dimethoxystyrene (XXI) produced copious evolution of hydrogen bromide and did not give a homogeneous product. In view of the high reactivity of the carbon atoms C_6 and C_6' in the benzene nuclei present, it was clear that aromatic substitution was proceeding in preference to, or as well as, addition to the double bond.

Examination of methyl α -(3:4' - dimethoxyphenylacetamido) - 3:4 - dimethoxycinnamic acid (XXV) showed that this substance can be regarded as a substituted acrylic ester of type (XXXIV)

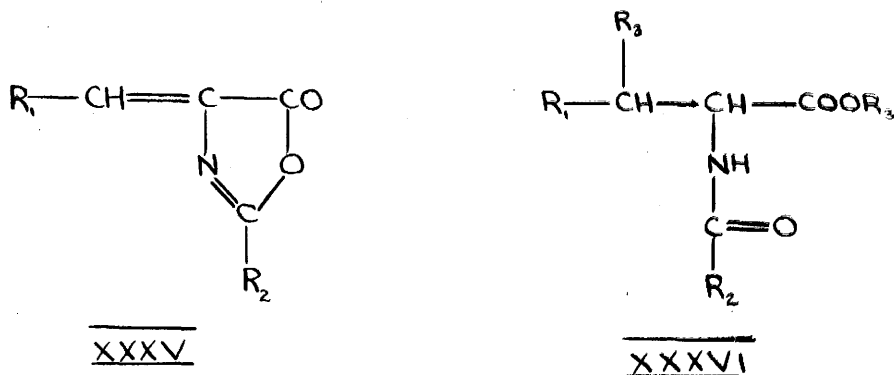


XXXIII



XXXIV

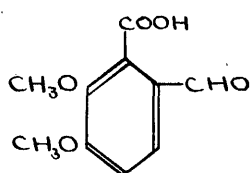
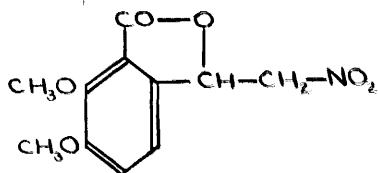
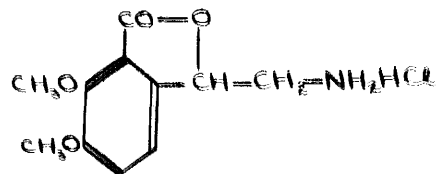
Rehberg, Dixon and Fisher (26) have found that in the presence of alkaline catalysts, α - β unsaturated esters add methanol across the double bond. Accordingly methyl α -benzamido - 3:4 - dimethoxycinnamate (XXXIII) was treated under a variety of conditions with methanol and sodium. However, only starting material was recovered in all cases. In addition the unsaturated oxazolones of type (XXXV, R_1R_2 = aliphatic groups) have been shown by Carter Stevens and Ney (27) to be capable of ring opening and simultaneous addition to the double bond



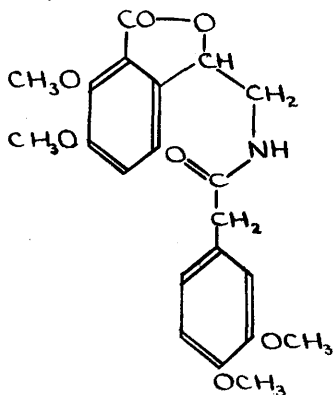
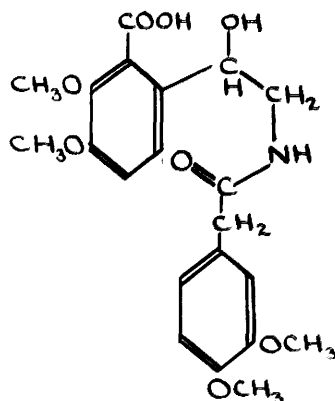
to give (XXXVI $R_3 = C_6H_5S-$). Treatment of 2 - phenyl - 4 - (3:4' - dimethoxybenzal) - oxazol - 5 - one (XXXV $R_1 = (CH_3O)_2C_6H_3-$, $R_2 = C_6H_5-$) with methanolic sodium methoxide, however, gave in quantitative yield methyl α -benzamido - 3:4 - dimethoxycinnamate (XXXIII). In both cases it must be assumed that the presence of aromatic substituents and groups materially affects the reactivity of the double bond and prevents the addition of methanol.

A novel method of blocking the double bond presents itself on examination of the chemistry of opianic acid (XXXVII). /

(XXXVII). Rodionow and Kogan (28) discovered that opianic acid on treatment with nitromethane gave nitromethylmeconin

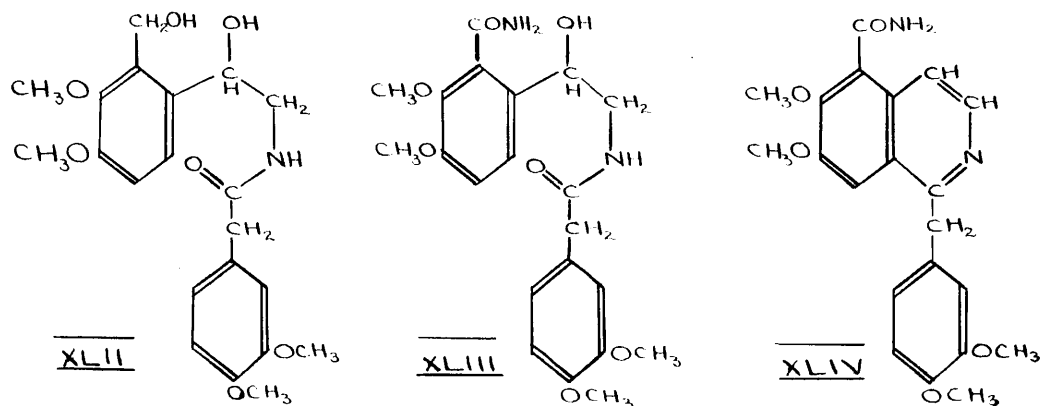
XXXVIIXXXVIIIXXXIX

(XXXVIII). This substance offers a route to 3:4 - dimethoxyphenylacetamido-methylmeconin (XL) in which the potential 3:4 double bond has been removed by lactonisation with the carboxyl group. It was hoped that cyclisation of this compound would be accompanied by loss of carbon dioxide to give papaverine.

XLXLI

Accordingly nitromethylmeconin (XXXVIII) was prepared by the method of Kogan. An attempt to prepare this substance by an adaptation of the methods described for similar condensations in B.I.O.S. report No.1774 led to the quantitative separation of methyl opianate. Reduction of nitromethylmeconin under pressure gave aminomethylmeconin hydrochloride (XXXIX).
Acylation/

Acylation of this base with 3:4 - dimethoxyphenylacetyl chloride gave 3:4 - dimethoxyphenylacetamido-methylmeconin (XL), the desired intermediate. This compound could not, however, be ring closed to an isoquinoline derivative by any of the dehydrating agents employed, and attempts to remove the lactone ring by heating the amide at high temperatures both at atmospheric and under reduced pressure gave only starting material. Refluxing in quinoline in the presence of copper chromite did not decompose the amide. On the basis of this evidence it was assumed that the well known stability of 8-lactones was preventing the formation of an isoquinoline structure. Accordingly efforts were directed towards rupturing the lactone by chemical methods. On treatment of the amide with sodium carbonate solution at reflux no solution of the amide occurred whereas with dilute sodium hydroxide on heating the amide dissolved, but acidification reformed the lactone, thereby demonstrating that the free acid (XLI) formed by hydrolysis of the lactone was unstable. An attempt to convert the sodium salt of this acid into its methyl ester also gave the lactone. An attempt to reduce the amide with lithium aluminium hydride to give (XLII) was unsuccessful. Finally treatment of the amide (XL) with ethanolic ammonia formed (XLIII), the lactone group having undergone the conventional fission with the formation of an amide and alcohol grouping.



When 2:3 - dimethoxy - 6 - (2' - (3:4-dimethoxyphenylacetamido) - 1' - hydroxy - ethyl) - benzamide (XLIII) was treated with dehydrating agents with the object of preparing (XLIV), in every case 3:4 - dimethoxyphenylacetamido-methylmeconin(XL) was obtained the lactone ring having reformed in preference to isoquinoline ring formation. Attempts to benzoylate the hydroxyl group in an endeavour to prevent this reaction also gave a quantitative yield of the original lactone (XL). In view of this fact this approach was abandoned.

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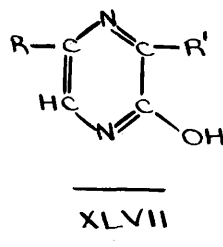
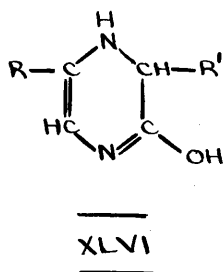
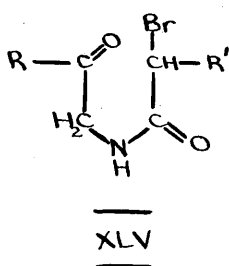
Attempted Papaverine Synthesis

by

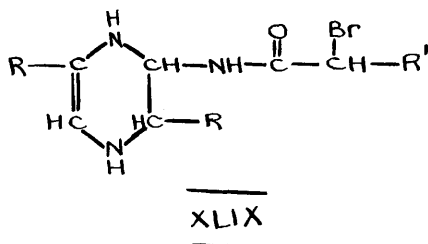
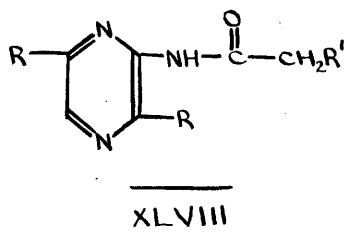
Reductive Dehalogenation.

Attempted Papaverine Synthesis by Reductive Dehalogenation.

Newbold, Spring and Sweeny (29) in the synthesis of pyrazine derivatives have found that the action of ammonia on bromoacylamidoketones of structure (XLV) does

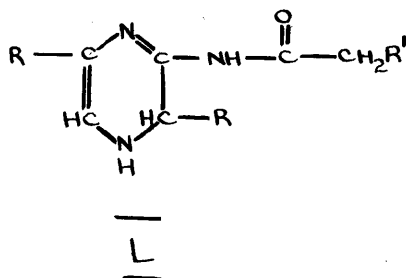


not give the expected pyrazine (XLVII) via the unstable dihydropyrazine (XLVI) but instead forms the acylamido-pyrazine (XLVIII). The explanation for the formation of



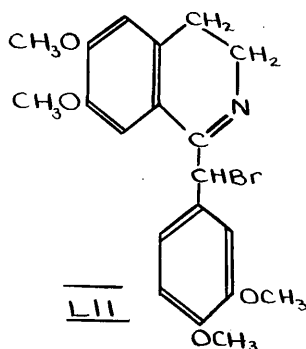
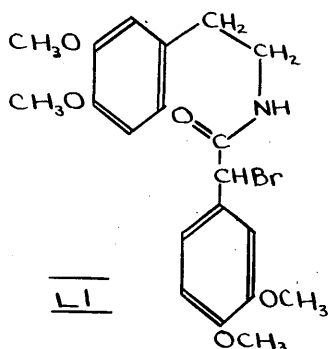
this pyrazine is that two molecules of the bromoacylamidoketone have condensed with ammonia giving the intermediate formation of a tetrahydrobromoacylamidopyrazine (XLIX).

This



compound is then converted to an unstable dihydropyrazine (L) by the process of reductive dehalogenation. The bromine in the acylamido side chain is removed as hydrogen bromide and at the same time replaced by a further hydrogen atom. Thus this mechanism has been effective in removing two hydrogen atoms from the heterocyclic ring. Completion of the reaction is brought about by the spontaneous dehydrogenation of the dihydroacylamidopyrazine to the fully aromatic base (XLVIII). The noteworthy point in this synthesis is that dehalogenation of the side chain has removed two hydrogen atoms from the heterocyclic ring.

A similar reaction was attempted with the object of achieving a papaverine synthesis. Acylation of homoveratrylamine, (β -3:4-dimethoxyphenylethylamine) with α -bromo-3:4-dimethoxyphenylacetyl chloride should give the substituted

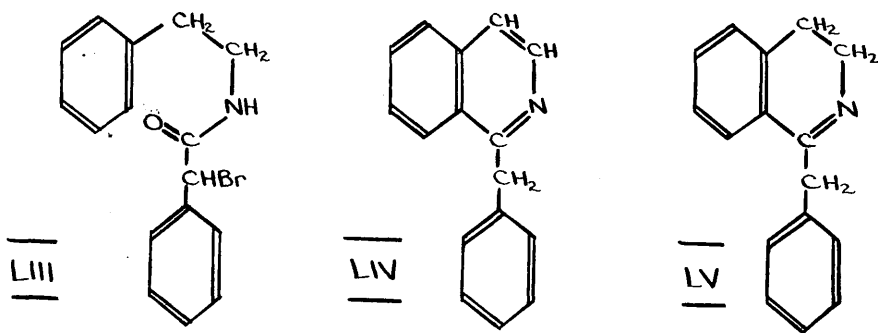


amide (LI) cyclisation of which might be expected to give the intermediate dihydroisoquinoline (LII). This compound contains the elements essential for a reductive dehalogenation namely, a dihydroaromatic ring system and a halogen atom conveniently placed in the side chain attached to the heterocyclic ring.

Hence/

Hence ring closure to a dihydroisoquinoline (LII) might occur simultaneously with the elimination of hydrogen bromide to give papaverine.

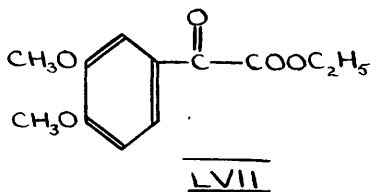
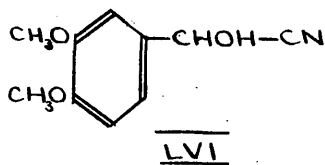
To test the validity of this hypothesis, the reaction was examined first in the case of the non-methoxylated isoquinoline ring system, 1-benzyl-isoquinoline (LIV). β -Phenylethylamine was condensed with α -bromophenylacetyl chloride to give 2-(α -bromophenylacetamido)-1-phenyl-ethane (LIII). This compound was ring closed with difficulty



in boiling tetralin containing phosphorus pentoxide to give in poor yield a basic pale yellow oil. This base contained no halogen and gave a crystalline picrate identified as 1-benzyl-3:4-dihydroisoquinoline picrate by means of a mixed melting point with an authentic specimen. Dehydrogenation of the base gave 1-benzyl-isoquinoline. The elimination of halogen followed by replacement with hydrogen to give 1-benzyl-3:4-dihydroisoquinoline is difficult to explain, but in this connection Brodrick (45) has shown that at high temperatures 1-benzyl-3:4-dihydroisoquinoline dehydrogenates by disproportionation losing two hydrogen atoms

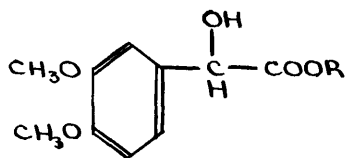
and forms as a degradation product isoquinoline. If this occurred during the experiment described above, dehalogenation may have resulted from utilisation of the liberated hydrogen.

To obviate the necessity of using such powerful dehydrating conditions, the synthesis was attempted from (LI) where the presence of the methoxyl groups activates the benzene nuclei, and facilitates ring closure. Homoveratrylamine was prepared by the method of Kindler(31) employing the refinements of Bide and Wilkinson (19). The production of α - bromo - 3:4 - dimethoxyphenylacetyl chloride was found to be impossible by the Hell, Volhard, Zelensky method (37) since free halogen caused substitution in the aromatic nucleus of 3:4 - dimethoxyphenylacetic acid. It was decided therefore to use the more readily available α - chloro - 3:4 - dimethoxyphenylacetyl chloride since this substance could be readily prepared by treatment of 3:4 - dimethoxymandelic acid with a suitable chlorinating agent. The problem therefore resolves itself into a synthesis of 3:4 - dimethoxymandelic acid (LVIII R=H) The most direct approach to this substance appeared to be from the readily available vertraldehyde cyanhydrin (LVI) but this

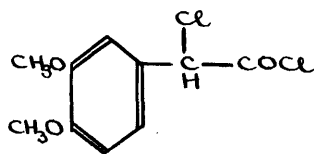


failed owing to the resistance of the cyanhydrin to hydrolysis Eventually a method due to Kindler (33) was employed.
Veratrole/

Veratrole was condensed in nitrobenzene with ethyl oxalyl chloride to give ethyl 3:4-dimethoxyphenylglyoxylate (LVIII).



LVIII

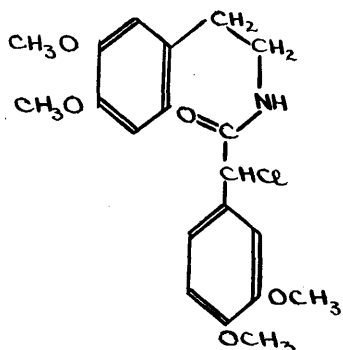


LIX

This ester was reduced catalytically to give ethyl 3:4-dimethoxymandelate (LVIII, R=Et). Hydrolysis of the ester to the free acid (LVIII, R=H) was easily accomplished. The acid on treatment with phosphorus pentachloride in dry chloroform gave α -chloro-3:4-dimethoxyphenylacetyl chloride (LIX).

Acylation of homoveratrylamine with this acid chloride formed 2-(α -chloro-3':4'-dimethoxyphenylacetamido)-1-(3:4'-dimethoxyphenyl)-ethane (LX). Repeated attempts to ring close this amide gave small quantities of a very unstable base.

This substance could not be characterised by the formation of a crystalline derivative, and by virtue



LX

of its behaviour could not be papaverine the expected product of reductive dehalogenation.

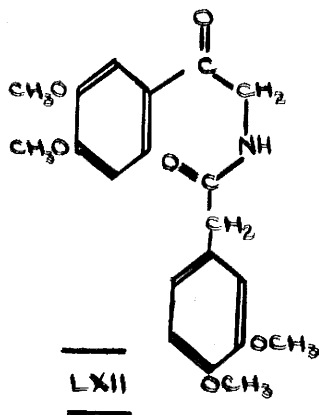
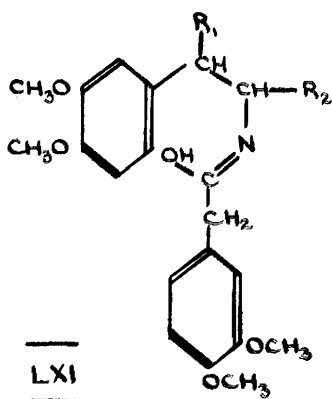
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3 - Hydroxyisoquinolines
and
2-Hydroxy-1:4-Naphthoquinones.

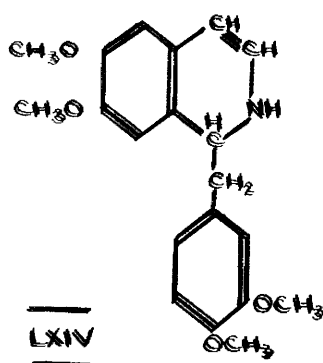
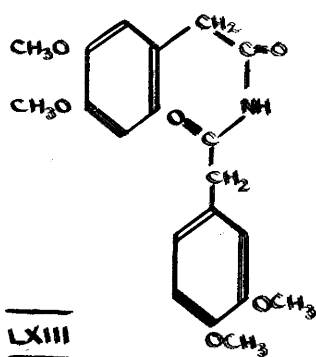
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3-Hydroxyisoquinolines and 2-Hydroxy-1:4-Naphthoquinones.

In the formation of isoquinolines from amides of the type (LXI) the preliminary stage is probably the formation of the enolic form of the amide, as depicted, followed by elimination of the elements of water. If we include a

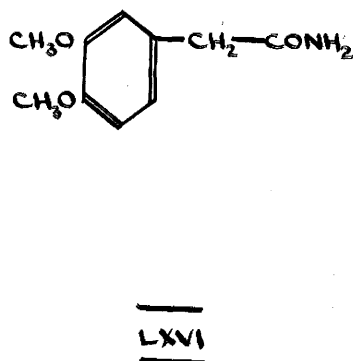
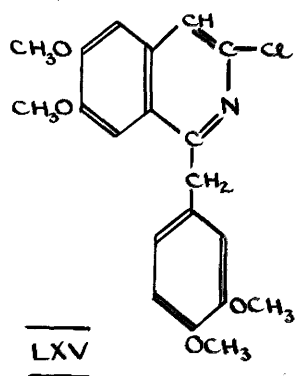


further enolisable oxygen atom in the amido side chain we have two possible structures ω -homoveratramido-acetoveratrone (LXII) and dihomoveratramide (LXIII). Buck *et alia* (38) have examined the action of phosphorus oxychloride on

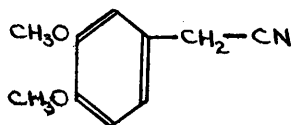


LXII) and claim that this forms after further reduction and dehydration 1:2-dihydropapaverine (LXIV). This evidence has been repudiated by Robinson (29) who has

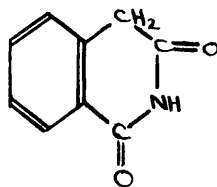
shown that the true product is 3:4-dihydropapaverine (XIII). Dihomoveratramide (LXIII) has been synthesised by Sugasawa (40) who has examined its reduction to homoveratroyl-homoveratrylamine (XII). No account of the action of phosphorus oxychloride on this substance has been described. It can be seen that the action of a chlorinating and dehydrating agent on the enolic form of dihomoveratramide (LXIII) can be postulated as forming 3-chloropapaverine (LXV) from which the parent base could be readily obtained by dehalogenation. In order to examine the feasibility of this synthesis,



dihomoveratramide was prepared according to the method of Sugasawa. This compound was refluxed in benzene with phosphorus oxychloride and yielded quantitatively 3:4-dimethoxyphenylacetamide (LXVI). When a higher boiling solvent, toluene, was employed a high yield of 3:4-dimethoxyphenylacetonitrile (LXVII) was recovered from the reaction mixture. It appears therefore that the diamide is not sufficiently stable to the action of



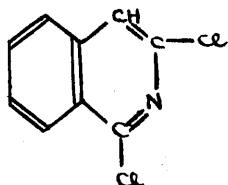
LXVII



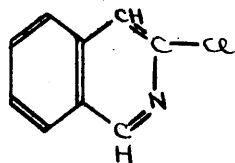
LXVIII

phosphorus oxychloride thereby precluding the possibility of isoquinoline formation. When attempts were made to effect the ring closure using phosphorus pentachloride under less severe experimental conditions, mixtures of 3:4-dimethoxyphenylacetamide (LXVI) and 3:4-dimethoxyphenylacetonitrile (LXVII) were obtained.

The 3-chloro or 3-hydroxy derivatives of papaverine which were envisaged as intermediates formed by the action of phosphorus oxychloride on dihomoveratramide have not been previously described, and in consequence of this examination of the literature was made in an effort to achieve a synthesis of one or both compounds. 3-Halogenated isoquinolines have been synthesised by Gabriel and co-workers (44) who treated homophthalimide (LXVIII) with phosphorus oxychloride to obtain 1:3-dichloroisoquinoline (LXIX). Dehalogenation of this compound was said to give

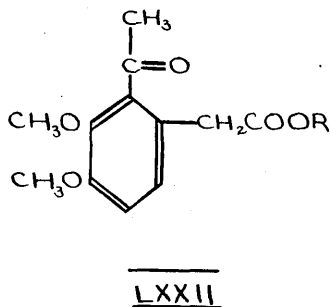
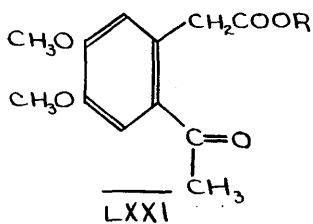


LXIX

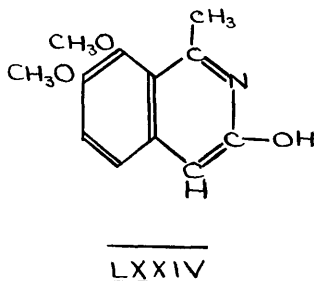
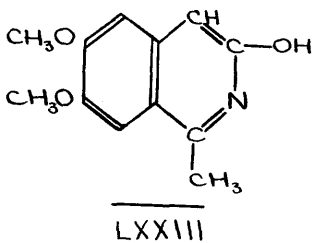


LXX

3-chloroisoquinoline but the proof offered by these workers that dehalogenation had occurred at the 1-position was not conclusive. It has been shown by Dr. H.R. Bentley (private communication) that ethyl 3:4-dimethoxyphenylacetate condenses under the influence of aluminium chloride with acetyl chloride to give either ethyl 2-acetyl-4:5-dimethoxyphenylacetate (LXXI) R = C₂H₅) or ethyl 2-acetyl-3:4-dimethoxyphenylacetate (LXXII R = C₂H₅) and that treatment of this ketone with

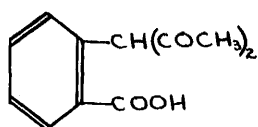
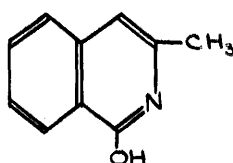


concentrated aqueous ammonia forms either 6:7-dimethoxy-3-



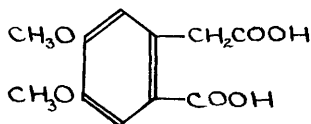
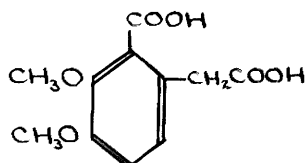
hydroxy-1-methyl-isoquinoline (LXXIII) or 7:8-dimethoxy-3-hydroxy-1-methyl-isoquinoline(LXXIV). The mechanism of this reaction is apparently the formation of the amide from the ester followed by ring closure and elimination of the elements of water. There is an analogy to this reaction in/

in the work of Hurtley (30) who showed that evaporation to dryness of an aqueous solution of the ammonium salt of (LXXV) gave rise to a product formulated as the isoquinoline derivative (LXXVI). This route gives the desired 3-hydroxy-

LXXVLXXVI

isoquinoline derivatives and a study of its extension was made.

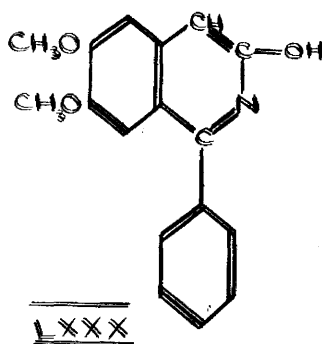
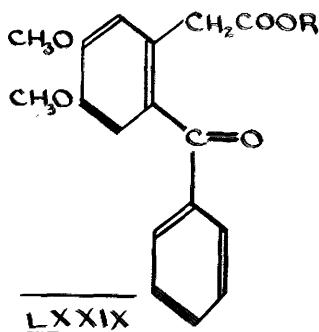
Methyl 3:4-dimethoxyphenylacetate was condensed with acetyl chloride to give either (LXXI R = CH₃) or (LXXII R = CH₃). This ester was oxidised with sodium hypochlorite according to the method used by Smith(41) for the oxidation of acetyl-vanillin to vanillin 5-carboxylic acid and gave a dibasic acid C₁₁H₁₂O₆ m.p. 216°. 2-Carboxy-4:5-dimethoxy-phenylacetic acid (LXXVII) is described by Robinson (42)

LXXVIILXXVIII

as melting 215°, while 2-carboxy-3:4-dimethoxyphenylacetic acid (LXXVIII) is stated by Schopf (43) to have a m.p. 115-7°
From/

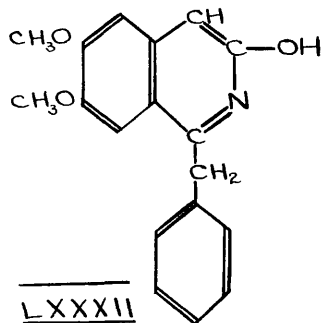
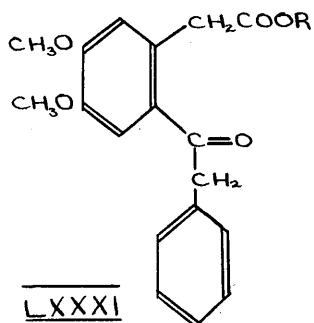
From these facts it is clear that the dibasic acid is 2-carboxy-4:5-dimethoxyphenylacetic acid (LXXVII) and hence the original ester is methyl 2-acetyl-4:5-dimethoxyphenyl:acetate (LXXI, $R=CH_3$). This ester on hydrolysis gave 2-acetyl-4:5-dimethoxyphenylacetic acid (LXXI, $R=H$), and on treatment with concentrated aqueous ammonia gave 6:7-dimethoxy-3-hydroxy-1-methyl-isoquinoline (LXXVIII) which formed a well defined picrate and showed identical physical properties to the product of Bentley.

With benzoyl chloride, methyl 3:4-dimethoxyphenyl:acetate condensed to give methyl 2-benzoyl-4:5-dimethoxy:phenylacetate (LXXIX, $R=CH_3$). The 2-position was preferred in view of the structural investigation of the previous case.

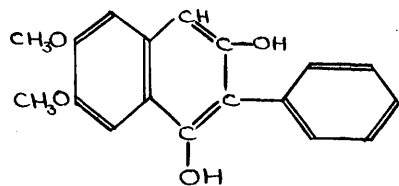
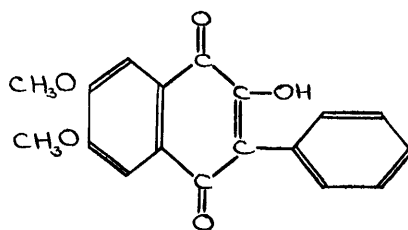


The ester hydrolysed readily to the corresponding acid (LXXIX, $R=H$) and with ethanolic ammonia formed 6:7-dimethoxy-3-hydroxy-1-phenyl-isoquinoline (LXXX).

In a similar manner condensation of phenylacetyl chloride and methyl 3:4-dimethoxyphenylacetate formed methyl 4:5-dimethoxy-2-phenylacetyl-phenylacetate (LXXXI $R=CH_3$).

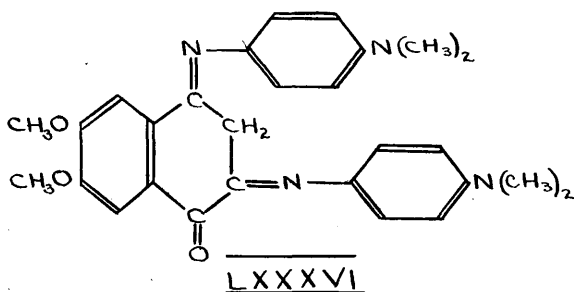
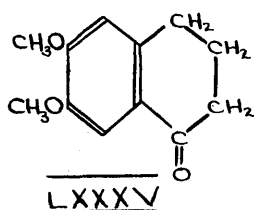


This substance on treatment with aqueous ammonia or aqueous sodium hydroxide solution did not form the expected isoquinoline (LXXXII) or the colourless acid (LXXXI R=H) respectively, but instead yielded the same product, a bright red crystalline compound m.p. 255° of molecular formula $C_{18}H_{14}O_5$. This compound showed typical phenolic properties and formed a monoacetate $C_{20}H_{16}O_6$, a monobenzoate $C_{25}H_{18}O_6$, and a monomethyl ether $C_{19}H_{16}O_5$, all of which were highly coloured, indicating that the chromophoric group was unaffected by derivative formation. Methoxyl determination by the Zeisel method indicated the presence of two methoxyl groups, whereas the starting material (LXXXI R = CH₃) possessed three methoxyl groups. In view of the reagents which were used to bring about the transformation it was anticipated that hydrolysis of the ester group had taken place as a primary step in the reaction. Examination shows that an intramolecular Claisen type of condensation could be effected to give 1:3-dihydroxy-6:7-dimethoxy-2-phenyl-naphthalene (LXXXIII). It has been shown by Volhard (32) and Soliman (34) that these dihydric phenols undergo atmospheric/

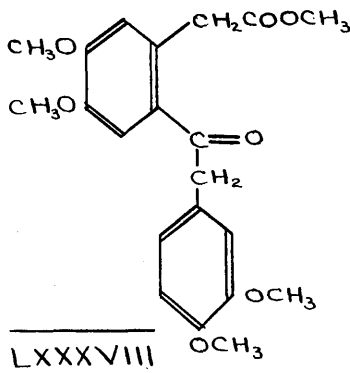
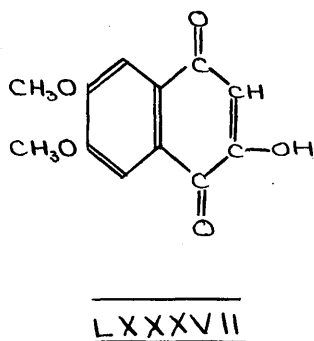
LXXXIIILXXXIV

atmospheric oxidation in alkaline solution with considerable ease to give the corresponding 2-hydroxy-1:4-naphthoquinones. If such a reaction occurred in the above case the product would be 6:7-dimethoxy-2-hydroxy-3-phenyl-1:4-naphthoquinone (LXXXIV). This compound possesses the required chemical properties and agrees with the analytical evidence. Support for this structure was obtained by treatment of methyl 4:5-dimethoxy-2-phenylacetyl-phenylacetate (LXXXI, R=CH₃) with sodium ethoxide in ethanol, air being rigorously excluded from the experiment. This led to the isolation of a colourless phenolic compound which oxidised with great rapidity, when exposed to the atmosphere, to a red compound identical with the substance obtained in the previous treatment of this ester. Also the red phenolic substance yielded with acetic anhydride and zinc dust a colourless triacetate, a typical reaction of 2-hydroxy-1:4-naphthoquinones.

In order to establish this structure an alternative synthesis was undertaken, 6:7-dimethoxy-1-keto-1:2:3:4-tetrahydronaphthalene (LXXXV) was condensed with nitrosodimethylaniline to give 6:7-dimethoxy-2:4-di-(4-dimethyl:

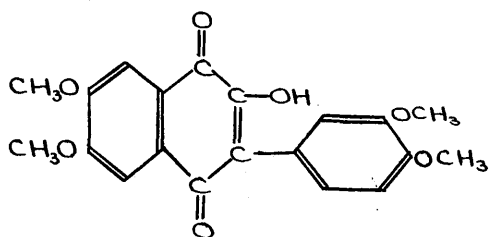


:aminophenylimino)-1-keto-1:2:3:4-tertahydronaphthalene
(LXXXVI) which on hydrolysis yielded 6:7-dimethoxy-2-



hydroxy-1:4-naphthoquinone (LXXXVII). This compound was condensed with benzene diazonium chloride according to the method of Neunhoffer (36) and gave 6:7-dimethoxy-2-hydroxy-3-phenyl-1:4-naphthoquinone (LXXXIV) as bright red needles m.p. 255°. This substance showed no depression in melting point on admixture with the compound obtained from methyl 4:5-dimethoxy-2-phenylacetyl-phenylacetate (LXXXI, R=CH₃) and exhibited identical light absorption characteristics. Therefore the structure of that compound is unequivocally established as (LXXXIV).

Finally 3:4-dimethoxyphenylacetylchloride was condensed with methyl 3:4-dimethoxyphenylacetate to give methyl/



LXXXIX

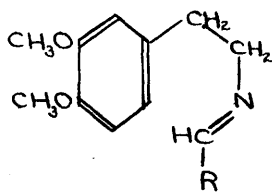
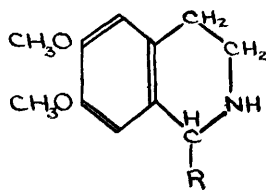
methyl 4:5-dimethoxy-2-(3':4'-dimethoxyphenylacetyl)-phenylacetate (LXXXVIII). This ester on treatment with either aqueous ammonia or aqueous sodium hydroxide solution formed 6:7-dimethoxy-3-(3':4'-dimethoxyphenyl)-2-hydroxy-1:4-naphthoquinone (LXXXIX), a bright red compound possessing similar properties to the previous 1:4-naphthoquinone.

Starting with the cyclic aldehyde derived
from the aldehyde structure, the synthesis
of the ring (1:2) has also been carried
out by the reaction of the cyclic
aldehyde with the cyclic aldehyde
derived from the aldehyde structure, and
the product is a cyclic aldehyde of the
type cyclic aldehyde. Several
examples of the synthesis of the

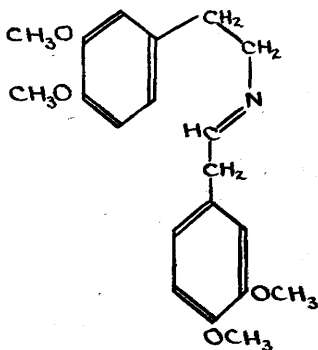
1:2 - Dihydroisoquinolines.

1:2 - Dihydroisoquinolines.

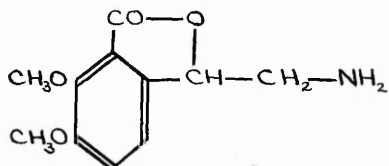
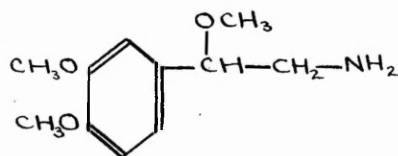
In conjunction with the work already described examination of the formation of substituted isoquinolines from Schiff's bases of the type (XC) has also been undertaken. Decker (46) Buck (47) and Weinbach (48) have all described syntheses of tetrahydroisoquinoline derivatives (XCI) from Schiff's bases produced by condensation of homoveratrylamine with various aromatic aldehydes. Spath(12) has also attempted the synthesis of tetrahydropapaverine by this route

XCXCI

using (XCII) as the intermediate Schiff's base.

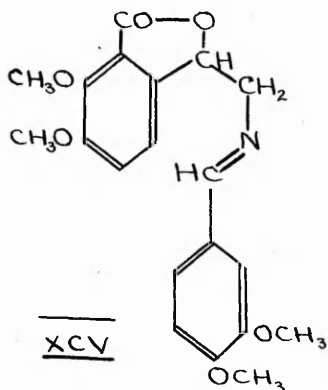
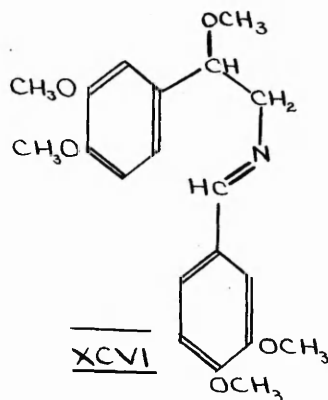
XCII

No description has been given of isoquinoline syntheses via Schiff's bases from the amines aminomethylmeconin (XCIII) and 2-(3:4'-dimethoxyphenyl)-2-methoxyethylamine (XCIV).

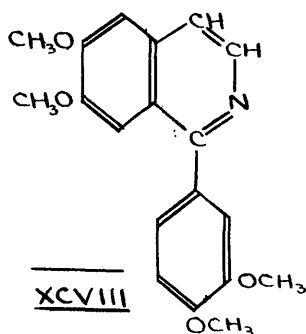
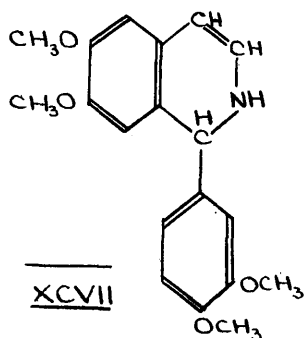
XCIIIXCIV

Since both these bases are capable of forming isoquinoline:
:line derivatives other than tetrahydroisoquinolines by
elimination of substituents from the heterocyclic ring, exam:
:ination of their derivatives was considered of sufficient
novelty, and hence undertaken.

Aminomethylmeconin hydrochloride was treated with 3:4-dimethoxybenzaldehyde in the presence of potassium acetate and gave N-(3:4'-dimethoxybenzylidene)-aminomethylmeconin (XCV). This material on treatment with any of the agents capable of bringing about rearrangement to an isoquinoline yielded aminomethylmeconin hydrochloride quantitatively.

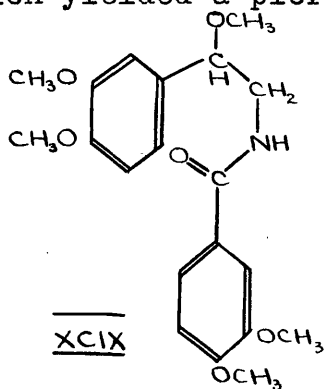
XCVXCVIXCV

2-(3':4'-Dimethoxyphenyl)-2-methoxyethylamine was obtained by the catalytic reduction of 2-(3':4'-dimethoxyphenyl)-2-methoxy-nitroethane, prepared according to the method of B.I.O.S. report No.1774. The base was condensed with 3:4-dimethoxybenzaldehyde to give N-(3':4'-dimethoxybenzylidene)-2-(3':4'-dimethoxyphenyl)-2-methoxyethylamine (XCVI). Treatment of this substance with the reagents described in the literature for similar rearrangements did not yield any basic products. However, when the substance was suspended in concentrated hydrochloric acid it formed a deep red hydrochloride, which when refluxed in ethylene glycol monomethyl ether rearranged to give a pale yellow hydrochloride. Analysis of this substance corresponded to the molecular formula $C_{19}H_{22}O_4NCl$ or $C_{19}H_{20}O_4NCl$. On this basis the product could be formulated as the hydrochloride of 1:2-dihydro-6:7-dimethoxy-1-(3':4'-dimethoxyphenyl)-isoquinoline (XCVII) or if the base had also undergone spontaneous dehydrogenation as the hydrochloride of 6:7-dimethoxy-1-(3':4'-dimethoxyphenyl)-isoquinoline (XCVIII).



The behaviour and stability of this type of dihydroisoquinoline is unknown, Consequently the completely aromatic isoquinoline must be considered.

The hydrochloride decomposed readily giving the free base m.p. 164°, which yielded a picrate. An authentic specimen of 6:7-dimethoxy-1-(3':4'-dimethoxyphenyl)-isoquinoline was prepared. Veratroyl chloride was condensed with 2-methoxy-2-(3':4'-dimethoxyphenyl)-ethylamine to give 2-(3':4'-dimethoxybenzamido-)-1-(3':4'-dimethoxyphenyl)-1-methoxy-ethane (XCIX). When this substance was refluxed in toluene with phosphorus oxychloride it formed 6:7-dimethoxy-1-(3':4'-dimethoxyphenyl)-isoquinoline (XCVIII) m.p. 159° which yielded a picrate.



This authentic specimen showed a large depression in melting point on admixture with the base obtained from N-(3':4'-dimethoxybenzylidene)-2-methoxy-2-(3':4'-dimethoxyphenyl)-ethylamine (XCVI). In view of this fact, this base is therefore/

therefore formulated as 1:2-dihydro-6:7-dimethoxy-1-(3:4'-dimethoxyphenyl)-isoquinoline (XCVII). This structure is supported by light absorption characteristics of the compound. In the region 2200-2500A it shows much lower intensity of absorption than authentic 6:7-dimethoxy-1-(3:4'-dimethoxyphenyl)-isoquinoline, a difference which might be expected in view of the decreased conjugation in the dihydro compound.

EXPERIMENTAL.

(All m.p.'s are uncorrected).

3:4-Dimethoxyphenylacetic Acid. This compound was prepared from 2-phenyl-4-(3:4'-dimethoxybenzal)-oxazol-5-one in 60% yield (190 g.) by the method of Organic Syn., Vol.11, 333.

3:4 -Dimethoxyphenylacetyl Chloride,

(cf. Pictet, Ber., 1909, 42, 1985).

3:4-Dimethoxyphenylacetic acid (5.0 g.) was dissolved in dry chloroform (30 c.c.) and treated portionwise with phosphorus pentachloride (4.5 g.). When the vigorous reaction had ceased the solvent and phosphorus oxychloride were removed by distillation under vacuum. Distillation of the residue gave 3:4-dimethoxyphenylacetyl chloride (4.5 g.) as a light yellow oil, b.p. 120-125°/16²mm. The product solidified to a colourless solid m.p. 46°.

Ethyl Aminoacetate.

(cf. Fischer, Ber., 1901, 34, 436).

Glycine (100 g.) was suspended in dry ethanol (500 c.c.) and heated on a water bath. Dry hydrogen chloride was introduced until solution was complete (two hours). The solution on cooling deposited ethyl aminoacetate hydrochloride in quantitative yield. The hydrochloride (50 g.) was dissolved in water (25 c.c.), ether (100 c.c.) added, and the mixture treated at -10° with sodium hydroxide solution (40 c.c. of 33%). After addition/

addition of sufficient potassium carbonate to convert the aqueous layer to a thick paste, the ethereal solution was separated and the paste extracted with ether (3 x 100 c.c.) The ether extract was dried, first over potassium carbonate, then for one hour over calcium oxide, and distilled. Ethyl aminoacetate (25 g.) was obtained as a colourless oil b.p.59°/20 mm.

Methyl Aminoacetate was prepared in a similar manner using methanol instead of ethanol. Glycine (100 g.) gave methyl aminoacetate (20 g.) as a colourless oil b.p.50°/45 mm.

Ethyl 3:4-Dimethoxyphenylacetamido-acetate.

Freshly prepared ethyl aminoacetate (5.5 g., 2 mols.) was dissolved in dry chloroform (25 c.c.) and cooled to -10°. 3:4-Dimethoxyphenylacetyl chloride (5.5 g., 1 mol.) in dry chloroform (25 c.c.) was added dropwise with stirring over one hour and the reaction mixture stirred for a further hour. The precipitate (ethyl aminoacetate hydrochloride) was removed and the solution washed successively with dilute hydrochloric acid, saturated sodium hydrogen carbonate solution, and water. After drying (sodium sulphate) the solvent was removed under reduced pressure leaving a pale brown oil which solidified on cooling. Crystallisation from ether gave ethyl-3:4-dimethoxyphenylacetamido-acetate as colourless slender needles (5.0 g.; 75% of theory) which melted after four crystallisations at 78°. The substance is soluble in

all common solvents except light petroleum.

Found: C, 59.8; H, 7.1; N, 5.0%.

$\text{C}_{14}\text{H}_{19}\text{O}_5\text{N}$ requires: C, 59.8; H, 6.8; N, 5.0%.

Methyl 3:4-Dimethoxyphenylacetamido-acetate. This compound was prepared by the same procedure using methyl amino-acetate (9.0g., 2 mols.) and 3:4-dimethoxyphenylacetyl chloride (10.g., 1 mol.). Methyl 3:4-dimethoxyphenyl-acetamido-acetate was obtained as colourless needles (.8.0g.) m.p. 91° after four crystallisations from ether; it is soluble in all common solvents except light petroleum.

Found: C, 58.3; H, 6.7; N, 5.4%.

$\text{C}_{13}\text{H}_{17}\text{O}_5\text{N}$ requires: C, 58.4; H, 6.4; N, 5.2%.

3:4-Dimethoxyphenylacetamido-acetic acid.

Ethyl-3:4-dimethoxyphenylacetamido-acetate (31g.) was dissolved in absolute ethanol (100 c.c.) and treated with sodium ethoxide (2.54g. sodium in ethanol (50c.c.)). Water (2.0g.) was added and the mixture shaken for two hours. The sodium salt of 3:4-dimethoxyphenylacetamido acetic acid was collected and dissolved in water (100 c.c.) The solution on acidification gave the required acid, in quantitative yield; it crystallised from water in small colourless needles m.p. 154° after four crystallisations.

Found: C, 56.8; H, 5.8; N, 5.7%.

$\text{C}_{12}\text{H}_{15}\text{O}_5\text{N}$ requires: C, 56.9; H, 6.0; N, 5.5%.

2-(3':4'-Dimethoxybenzyl)-4-(3':4'-dimethoxybenzal)-oxazol-5-one.

3:4-Dimethoxyphenylacetamido-acetic acid (25.5g.) was added to a mixture of sodium acetate (15.0g.) acetic anhydride (26.5g.), 3:4-dimethoxybenzaldehyde (15.1g.) (prepared by the method of Organic Syn., Vol. II, 619) and heated, first on a water bath for two hours, then for fifteen minutes at 110°. After cooling, methanol (30c.c.) was added and left overnight. 2-(3':4'-dimethoxybenzyl)-4-(3':4'-dimethoxybenzal)-oxazol-5-one (10.0g., 25% of theory) was collected and crystallised from benzene, forming circular clusters of yellow needles m.p. 161° after five crystallisations.

Found: C, 66.25; H, 5.4; N, 3.6%.

$C_{21}H_{21}O_6N$ requires: C, 65.8; H, 5.5; N, 3.7%.

α-(3':4'-Dimethoxyphenylacetamido)-3:4-dimethoxycinnamic Acid

(a) 2-(3':4'-Dimethoxybenzyl)-4-(3':4'-dimethoxybenzal)-oxazol-5-one (4.0g.) was heated to 120° with sodium carbonate (1.25g.) and water (10c.c.) for half an hour, cooled and acidified with dilute hydrochloric acid. The precipitate was collected and α-(3':4'-dimethoxyphenylacetamido)-3:4-dimethoxycinnamic acid (3.7g; 75% of theory) crystallised from methanol as colourless clusters m.p. 190° after four crystallisations.

(b) 2-(3':4'-Dimethoxybenzyl)-4-(3':4'-dimethoxybenzal)-oxazol-5-one (4.0g.) was refluxed with sodium carbonate solution (200 c.c. of 10%) until all had dissolved (twenty minutes). After heating for a further half hour, the solution was

cooled, acidified and the product (3.8 g.) collected. It crystallised from methanol m.p. 190°.

Found: C,62.8; H,5.9; N,3.6%

$C_{21}H_{23}O_7N$ requires: C,62.8; H,5.8; N,3.5%

The methyl ester was prepared by treating a suspension of the acid (0.5 g.) in ether with ethereal diazomethane solution at 0° overnight. Crystallisation from benzene/light petroleum (b.p. 40-60°) gave colourless needles (260 mg) m.p.127° after four crystallisations.

Found: C,63.9; H,6.3%

$C_{22}H_{25}O_7N$ requires: C,63.6; H,6.0%

β -(3:4'-Dimethoxyphenylacetamido)-3:4-dimethoxystyrene.

α -(3:4'-Dimethoxyphenylacetamido)-3:4-dimethoxycinnamic acid (3.0 g.) was added to quinoline (15 c.c.) together with copper chromite (0.5 g.) prepared according to Adkins and Connor. J. Amer. Chem. Soc. 1931, 53, 1091. The solution was maintained at 170-180° for twenty minutes when evolution of carbon dioxide ceased. On cooling, the solution was poured into dilute hydrochloric acid, the yellow-white precipitate collected, and refluxed with sodium carbonate solution. Filtration and crystallisation from methanol gave β -(3:4'-dimethoxyphenylacetamido)-3:4-dimethoxystyrene (1.5 g.) as felted colourless needles m.p.177° after five crystallisations.

Found: C,67.4; H,6.5; N,3.9%

$C_{20}H_{23}O_6N$ requires: C,67.2; H,6.5; N,3.9%

Homoveratroyl-homoveratrylamine. (N-(β -(3':4'-dimethoxyphenyl)-ethyl)-3:4-dimethoxyphenylacetamide).

β -(3':4'-Dimethoxyphenylacetamido)-3:4-dimethoxystyrene (100 mg.) was hydrogenated in ethyl acetate using platinum black as catalyst. One mole of hydrogen was absorbed. The product obtained on evaporation and crystallisation from chloroform/light petroleum, melted at 123-124° after four crystallisations.

This material was undepressed in melting point on admixture with an authentic specimen of homoveratroyl-homoveratrylamine obtained by the action of homoveratroyl chloride on homoveratrylamine according to the method of Spath and Berger, Ber., 1927, 60, 704.

Found: C, 66.8; H, 7.2; N, 4.1%

Calc. for $C_{20}H_{25}O_5N$: C, 66.8; H, 7.0; N, 3.9%

Attempted ring closure of α -(3':4'-dimethoxyphenylacetamido)-3:4-dimethoxycinnamic acid.

I. To a suspension of α -(3':4'-dimethoxyphenylacetamido)-3:4-dimethoxycinnamic acid (1g.) in dry toluene (10c.c.) was added at 60° phosphorus oxychloride (5c.c.), and the solution refluxed. After heating for twenty minutes, during which time a deep red colour developed, the solution was cooled, and the solvents removed. Only a tarry non-crystalline residue could be isolated from the residual material.

II. α -(3':4'-Dimethoxyphenylacetamido)-3:4-dimethoxycinnamic acid (1g.) was added to a mixture of phosphorus pentachloride (0.5g.) and phosphorus oxychloride (5c.c.) at 15°. The temperature was raised to 40° for twenty minutes when evolution of hydrochloric acid occurred. On cooling and pouring into water only an intractible tar was isolated.

III. A solution of α -(3':4'-dimethoxyphenylacetamido)-3:4-dimethoxycinnamic acid (1g.) in concentrated sulphuric acid (5c.c.) was heated to 100°. Considerable destruction of organic material occurred over a period of ten minutes and no basic or acidic organic products were isolated.

IV. α -(3':4'-Dimethoxyphenylacetamido)-3:4-dimethoxycinnamic acid (1g.) was dissolved in ethanol (5 c.c.) and concentrated sulphuric acid (3c.c.) added. The solution was refluxed for one hour, then cooled. From this solution only starting material (0.8g.) was obtained.

V. To syrupy phosphoric acid (10 c.c.) was added α -(3':4'-dimethoxyphenylacetamido)-3:4-dimethoxycinnamic acid (1g.) and the mixture heated to 150° for one hour. From the cooled solution starting material (0.75g.) was recovered as the only product.

Attempted ring closure of β -(3':4'-dimethoxyphenylacetamido)-3:4-dimethoxystyrene.

I. β -(3':4'-Dimethoxyphenylacetamido)-3:4-dimethoxystyrene (1g.) was treated with concentrated sulphuric acid (5 c.c.) at room temperature for fourteen days. The precipitated solid was collected and crystallised from methanol to give starting material (0.7g.). No basic material was found in the filtrate.

II. A solution of β -(3':4'-dimethoxyphenylacetamido)-3:4-dimethoxystyrene (1g.), in toluene (5c.c.) was treated with phosphorus oxychloride (5c.c.). The solution was refluxed for one hour, cooled and the solvents removed. No basic material could be separated from the gum obtained.

III. A solution of β -(3':4'-dimethoxyphenylacetamido)-3:4-dimethoxystyrene (1g.) in xylene (10c.c.) was treated with phosphorus pentoxide (2g.) and refluxed for one hour. After filtration of the insoluble solid, ~~and~~ solution in water, no basic material was isolated.

IV. β -(3':4'-Dimethoxyphenylacetamido)-3:4-dimethoxystyrene (1g.) was treated with phosphorus oxychloride (10c.c.) and heated to 40°, when phosphorus pentachloride (2g.) was added. After /

heating for one hour, the solvent was removed and the residue decomposed with water. No basic substance was isolated from the residual material.

V. To syrupy phosphoric acid (5 c.c.) was added β -(3':4'-dimethoxyphenylacetamido)-3:4-dimethoxystyrene (1g) and the mixture heated to 150° for one hour. After cooling and solution in water, starting material (0.8 g.) was recovered.

VI. To β -(3':4'-dimethoxyphenylacetamido)-3:4-dimethoxystyrene (1 g.) in ethanol (5 c.c.) was added concentrated sulphuric acid (5 c.c.) The mixture was refluxed for one hour, cooled and added to water. Starting material (0.9 g.) was recovered from the solution.

VII. A solution of β -(3':4'-dimethoxyphenylacetamido)-3:4-dimethoxystyrene (1 g.) in liquid hydrogen fluoride (10 c.c.) was allowed to stand overnight. Removal of the acid gave β -(3':4'-dimethoxyphenylacetamido)-3:4-dimethoxystyrene (0.9 g.) as the only product.

VIII. β -(3':4'-dimethoxyphenylacetamido)-3:4-dimethoxystyrene (1 g.) was refluxed with Boron trifluoride-acetic acid complex for one hour. After removal of the solvent, no basic substance was isolated from the residual material.

IX. To a solution of phosphorus oxychloride (4 c.c.) in pyridine (8 c.c.) was added β -(3':4'-dimethoxyphenylacetamido)-3:4-dimethoxystyrene (1 g.) and the mixture heated to 60° for one hour. After cooling and removal of the solvent the residue was dissolved in methanol from which starting material (0.9 g.) crystallised.

Methyl α -benzamido-3:4-dimethoxycinnamate.

2-Phenyl-4-(3:4'-dimethoxybenzal)-oxazol-5-one (30.9 g.) prepared by the method of Organic Syn. Vol. II, 55 was added portionwise with cooling and stirring over one hour to a solution of sodium methoxide (sodium (2.3 g.) in methanol (50 c.c.)). A further quantity of methanol (150 c.c.) was added and the mixture stirred overnight at room temperature. The precipitate (26 g.) was collected and crystallised from methanol giving methyl α -benzamido-3:4-dimethoxycinnamate as plates melting 147° , undepressed on admixture with an authentic specimen prepared by the method of Kropp and Decker, Ber., 1909, 42, 1185.

Found: C, 66.7; H, 5.6; N, 4.0%.

Calc. for $C_{19}H_{19}O_5N$: C, 66.8; H, 5.6; N, 4.1%.

Methyl opianate.

Opianic acid (20 g.) was dissolved with warming in methanol (25.5 g.) and water (19 g.). Nitromethane (6.5 g.), prepared according to the method of Organic Syn., Coll. Vol. I, 393, ethylene diamine (0.5 g.), glacial acetic acid (0.7 g.) were added at 30° , and the mixture stirred at this temperature for eighteen hours. On cooling a crystalline product (20 g.) was given which after three crystallisations from methanol appeared as colourless shimmering plates m.p. 98° . The material gave a depression of fifteen degrees on admixture with opianic acid.

Found: C,58.6; H,5.4%

Calc. for methyl opianate

$C_{11}H_{12}O_5$: C,58.9; H,5.4%

Methyl opianate (0.5 g.) on heating with sodium carbonate (5 c.c. of 10%), cooling, and acidification gave opianic acid, melting after recrystallisation from water at 147° , undepressed in melting point on admixture with authentic specimen of opianic acid.

Nitromethylmeconin.

(cf. Radionow, Kogan, Ber., 1924, 57(2), 1442).

To opianic acid (33.8 g.) dissolved in ethanol (1400 c.c.) was added nitromethane (10.8 g.) at room temperature, and solution cooled to 0° . Potassium hydroxide (50 c.c. of 50%) in ethanol (80 c.c.), previously cooled to 5° , was added dropwise. After a short period of time the solution became cloudy and yielded a white precipitate. On standing one hour without previously filtering, an excess of hydrochloric acid (10%) was added at $0^{\circ} - 5^{\circ}$.

The ensuing precipitate (a mixture of potassium chloride and nitromethylmeconin) was collected next morning carefully washed with water, and crystallised from alcohol as colourless plates melting at 166° .

Found: C,51.8; H,4.5; N,5.4%

Calc. for $C_{11}H_{11}O_6N$: C,52.2; H,4.4; N,5.5%

Light absorption (ethanol):

Maximum at 3060 A. (ϵ max. = 4,420).

Amino-methylmeconin.

(cf. Dey, Arch. Pharm. 1937, 275, 397).

Nitromethylmeconin (10 g.) in ethanol (500 c.c.) was hydrogenated at temperature of 60° and 15 ats. pressure using platinum oxide (2.5 g.) as catalyst. The theoretical amount of hydrogen was absorbed. Hydrochloric acid (10 c.c. concentrated) was added and the solution was evaporated to give a white precipitate of aminomethylmeconin hydrochloride melting, on crystallisation three times from ethanol as colourless needles, at 247-248° (decomp.)

Found: C, 50.6; H, 5.5; N, 5.3%

Calc. for $C_{11}H_{14}O_4NCl$: C, 50.8; H, 5.4; N, 5.4%

Light absorption (ethanol):

Maximum at 3050A. (ϵ max. = 4,620.)

The base gave a picrate crystallising from ethanol as yellow needles m.p. 204°.

Found: C, 45.4; H, 3.9; N, 12.6%.

$C_{17}H_{16}O_4N_4$ requires: C, 45.1; H, 3.6; N, 12.4%.

From the mother liquors a small amount of a further hydrochloride was obtained melting on crystallisation from ethanol 171°.

Light absorption (ethanol):

Maximum at 3020A. ϵ max. = 5,700.

Found: C, 54.9; H, 5.9; N, 4.0%.

3:4 Dimethoxyphenylacetamido-methyl meconin.

To a mixture of aminomethylmeconin hydrochloride (6 g.) in dry chloroform (100 c.c.) was added 3:4-dimethoxy-

phenylacetyl chloride (4.9 g.) in dry chloroform (25 c.c.) at 0°. N-methyl-morpholine (4.9 g.), prepared by the method of Atherton, Openshaw, Todd, J., 1945, 660, in dry chloroform (30 c.c.), was added dropwise with cooling and stirring over fifteen minutes. The solution was kept at 0° for a further thirty minutes, filtered free from N-methyl-morpholine hydrochloride, and washed successively with dilute hydrochloric acid, saturated sodium bicarbonate solution, and water. After drying (sodium sulphate) the solvent was removed under reduced pressure and a gum (7.2 g.) was obtained. 3:4-Dimethoxyphenylacetamido-methyl-meconin crystallised from benzene in small colourless prisms melting after four crystallisations at 131°.

Found: C, 63.1; H, 5.8; N, 3.8%.

$\begin{matrix} \text{C} & \text{H} & \text{O} & \text{N} \\ 21 & 23 & 7 & \end{matrix}$ requires: C, 62.8; H, 5.8; N, 3.5%

Light absorption (ethanol):

Maxima at 2870A $\epsilon_{\text{max.}} = 2,305$

3070A $\epsilon_{\text{max.}} = 2,575$

Sodium methoxide on nitromethylmeconin.

Nitromethylmeconin (5 g.) was dissolved in methyl alcohol (25 c.c.) at 0° and sodium methoxide (2g. sodium in methanol (25 c.c.)) added slowly with stirring. The suspension of nitro compound turned yellow and went into solution. After a few minutes a white precipitate appeared. On heating the solution to 35° for twenty minutes, cooling, then adding acetic acid (10 c.c.) in methanol (25 c.c.), the substance redissolved, and in a

moment reprecipitated. Evaporation under reduced pressure gave a residue which crystallised from ethanol/water to give starting material in high yield.

Action of sodium hydroxide on 3:4-Dimethoxyphenylacetamido-methylmeconin.

3:4-Dimethoxyphenylacetamido-methylmeconin (0.5 g.) warmed with sodium hydroxide (0.2 g.) in water (5 c.c.) until solution took place. On acidification of part of the solution a substance precipitated which on filtration and crystallisation from benzene melted 130° , and was undepressed on admixture with starting material.

The remainder of the solution was treated at 30° with methyl sulphate (2 c.c.) and sodium hydroxide (10 c.c. of 5%), added dropwise with stirring. After cooling no ester separated and nothing could be extracted from solution.

2:3-Dimethoxy-6-(2'-(3:4-dimethoxyphenylacetamido)-1'-hydroxyethyl)-benzamide.

3:4-Dimethoxyphenylacetamido-methylmeconin (5.0 g.) was dissolved in ethanol (10 c.c.) and added carefully to ethanolic ammonia (100 c.c. of 50%). After standing overnight at 0° , 2:3-dimethoxy-6-(2'-(3:4-dimethoxyphenylacetamido)-1'-hydroxy-ethyl)-benzamide (2.8 g.) crystallised out. This material separated from ethanol as small white needles m.p. 185° after four crystallisations.

Found: C, 60.4; H, 6.4; N, 7.0%

$C_{21}H_{26}O_7N_2$ requires: C, 60.3; H, 6.2; N, 6.7%

Light absorption (ethanol):

Maxima at 2260A. ($\epsilon_{\max} = 15,700$)

and 2800A. ($\epsilon_{\max} = 5,110$).

Attempted Formation of Benzoyl derivative.

2:3-Dimethoxy-6-(2'-(3:4-dimethoxyphenylacetamido)-1'-hydroxy-ethyl)-benzamide (0.5 g.), suspended in pyridine (5.0 c.c.), was treated with benzoyl chloride (0.5 c.c.) in pyridine (5.0 c.c.). Evolution of heat occurred and the substance dissolved. After leaving overnight, the solvents were removed under reduced pressure and the residue decomposed with water. The amorphous solid obtained (350mg.) crystallised from benzene/light petroleum (b.p.40-60°) m.p. 128-130° as colourless prisms, which were undepressed in melting point on admixture with an authentic specimen of 3:4-dimethoxyphenylacetamido-methyl meconin.

Found: C, 62.9; H, 5.5%.

$C_{21}H_{23}O_7N$ requires: C, 62.8; H, 5.8%

β -Phenylethylamine. This base was prepared from benzyl cyanide by the method of Organic Syn. Coll. Vol. I, 107.

2-Phenylacetamido-1-phenyl-ethane.

(cf. Pictet and Kay, Ber., 1909, 42, 1977.)

β -Phenylethylamine (20 g.) was treated, with stirring and cooling to 0°, with phenylacetyl chloride (14 g.) in the presence of excess sodium hydroxide solution (20%).

The solid amorphous product obtained was crystallised from benzene/light petroleum m.p. 93°. The yield was quantitative.

Found: C, 80.0; H, 7.4; N, 6.0%

Calc. for $C_{16}H_{17}ON$: C, 80.3; H, 7.2; N, 5.9%

1-Benzyl-3:4-dihydroisoquinoline.

2-Phenylacetamido-1-phenyl-ethane (20g.) was dissolved in toluene (20 c.c.) and phosphorus pentoxide (50g.) added. The mixture was refluxed for one hour, cooled and the base obtained by dissolving the solid residue in water, making alkaline, and extracting with ether. Removal of the ether and distillation of the oily base at $125^{\circ}/10^{-2}$ mm. gave 1-benzyl-3:4-dihydroisoquinoline as a pale yellow oil with distinctive odour. The picrate crystallised from ethanol, melted at 176° . The yield (12g.) represents sixty-four per cent of theoretical.

1-Benzyl-isoquinoline.

1-Benzyl-3:4-dihydroisoquinoline (2g.) was heated to $200-220^{\circ}$ in the presence of 30% palladium charcoal (0.5g.) in a stream of carbon dioxide. When the theoretical amount of hydrogen had been evolved, the base was extracted with ether, the solution dried (sodium sulphate), and the ether removed. Distillation of the residual oil at $128^{\circ}/10^{-3}$ mm. gave 1-benzyl-isoquinoline (1.2g.) which solidified on cooling at 0° and crystallised from chloroform/light petroleum as colourless prisms m.p. 54° .

Found: C, 87.5; H, 5.9; N, 6.0%

Calc. for $C_{16}H_{13}N$: C, 87.7; H, 6.0; N, 6.4%

α -Bromophenylacetyl chloride.

Phenylacetic acid (100g.) was heated to 150° and phosphorus trichloride (2 c.c.) added. Bromine (42 c.c.) was introduced dropwise over two hours, and the solution heated for a further hour when the evolution of hydrogen bromide ceased. The liquid was cooled to 30° and phosphorus pentachloride (130g.) added portionwise. When the reaction had ceased the solution was decanted from the excess phosphorus pentachloride and carefully fractionated twice under vacuum giving α -bromophenylacetyl chloride b.p. 130-4°/30 mm. in 60% yield.

2-(α -Bromophenylacetamido)-1-phenyl-ethane.

β -Phenylethylamine (25g.) was stirred vigorously with 10% sodium carbonate (400 c.c.) at 0° and α -bromophenylacetyl chloride (60g.) added. After stirring for a further two hours the white solid mass obtained was crystallised from benzene/light petroleum (b.p. 40-60°) giving

2-(α -bromophenylacetamido)-1-phenyl-ethane as colourless prismatic needles m.p. 72°.

Found: C, 60.5; H, 5.3; N, 4.5%

$C_{16}H_{16}ONBr$ requires: C, 60.4; H, 5.1; N, 4.4%

1-Benzyl-3:4-dihydroisoquinoline.

2-(α -Bromophenylacetamido)-1-phenyl-ethane (20g.) was dissolved in dry tetralin (300 c.c.) containing phosphorus pentoxide (60g.), the mixture heated at 120° for half an hour, then refluxed for fifteen minutes. Phosphorus pentoxide (50g.) was then added and the heating repeated for

fifteen minutes. After cooling, the solid residue was dissolved in water (250 c.c.), containing concentrated hydrochloric acid (5 c.c.). The mixture was steam distilled to remove traces of tetralin, the aqueous solution rendered alkaline, and extracted with ether. After drying (solid potassium hydroxide) evaporation gave 1-benzyl-3:4-dihydro-isoquinoline (5.0g.) which distilled at $125-127^{\circ}/10^{-3}$ mm.

The picrate was obtained as small yellow prisms from ethanol melting at 178° after eight crystallisations.

Found: C, 58.7; H, 3.9; N, 12.5%

$C_{22}H_{18}O_7N_4$ requires: C, 58.7; H, 4.0; N, 12.4%

1-Benzyl isoquinoline.

The isoquinoline base obtained above (0.5g.) was treated with (30%) palladium charcoal (0.2g.) at 200° in a stream of carbon dioxide. After hydrogen ceased to be evolved (one hour) the mixture was cooled and extracted with ether. Removal of the solvent gave an oil which on solution in chloroform/light petroleum formed large colourless prisms melting 54° . This material gave no depression in melting point on admixture with an authentic specimen of 1-benzyl-isoquinoline.

The picrate which crystallised from ethanol in small yellow prisms melting at 178° after five crystallisations was undepressed on admixture with an authentic specimen.

Veratryl alcohol.

Veratraldehyde (150g.) was dissolved in methanol (75 c.c.) and hydrogenated at atmospheric pressure using palladium oxide (2g.) as catalyst. Distillation of the solution after absorption of the theoretical amount of hydrogen gave two products:

The first, homoveratrole (40g.) b.p. $115^{\circ}/17$ mms. and solidifying on cooling to low melting solid.

$$n_{20}^D = 1.530 (1.527)$$

The second, veratryl alcohol (100g.) b.p. $180-185^{\circ}/17$ mms.

$$n_{20}^D = 1.554 (1.553).$$

Homoveratryl chloride.

Veratryl alcohol (80g.) was added dropwise with stirring to thionyl chloride (65g.) and calcium chloride (2g.). The reaction temperature was maintained at $35-40^{\circ}$. After the addition, the solution was stirred for a further half hour, treated with dry ether (200 c.c.), calcium carbonate (5g.) and allowed to stand overnight.

The ethereal solution was filtered, washed with water, then carefully with sodium carbonate solution. The extract was dried (calcium chloride) and evaporation gave a dark oil which on distilling at $165^{\circ}/2$ mm. solidified to a yellow solid (61g.).

This material was very unstable and was employed directly in the following stage.

Homoveratryl cyanide.

Homoveratryl chloride (60g.) was dissolved in benzene (150 c.c.) and placed in a two litre flask. The mixture was heated on a steam bath and vigorously stirred. Potassium cyanide (70g.) in water (250 c.c.) was added inside two minutes and the mixture heated and stirred for four hours. The residue was taken up in ether (200 c.c.), dried over calcium chloride, and distilled to give homoveratryl cyanide (37g.) b.p. 164°/7mm..

Found: C,67.6; H,6.3; N,8.0%

Calc. for $C_{10}H_{11}O_2N$: C,67.8; H,6.3; N,7.9%

Homoveratrylamine

Homoveratryl cyanide (37g.), dissolved in ethanol (50 c.c.) was added to ammonia (100 c.c.) and Raney nickel (10g.), and hydrogenated at 60° and 75ats. pressure. Removal of the catalyst and solvents gave homoveratrylamine (30g.), b.p. 125-7°/5mm., as a pale yellow viscous oil with a distinct ammoniacal odour.

Homoveratroyl -homoveratrylamine

Homoveratrylamine (1g.) was acylated with homoveratroyl chloride (1.9g.) according to the method of Pictet, Ber. 1909, 42,1987. The product

was crystallised from chloroform/light petroleum (b.p. 40-60°) in colourless needles melting 123-124°.

Found: C, 66.8; H, 7.2; N, 4.1%

Calc. for $C_{20}H_{25}O_5N$: C, 66.8; H, 7.0; N, 3.9%

Ethyl oxalyl chloride.

Prepared by the method of Kindler, Ber., 1943, 76B, 308.

To diethyl oxalate (240g.) was added phosphorus pentachloride (290g.) and the mixture heated to 95-100° for four days. Distillation under reduced pressure removed the phosphorus oxychloride. The remainder was heated to 95-98° with palladium black (0.5g.) at ordinary pressures until the evolution of ethyl chloride ceased. The acid chloride was then distilled at reduced pressure to give a clear liquid (60g.) of pungent odour boiling 39°/18 mms. or 134-136° at ordinary pressure.

Veratrole.

Guaiacol (50g.) was placed in a one litre flask and boiling water (150 c.c.) added. The mixture was heated on a water bath with stirring and 20% sodium hydroxide (120 c.c.) added, followed by dimethyl sulphate (50 c.c.), dropwise over half an hour. A further (10 c.c.) was added followed by sodium hydroxide (20 c.c.) after fifteen minutes. This procedure was repeated twice. The solution was made strongly alkaline with sodium hydroxide (50 c.c.). After cooling, the product was extracted with ether, dried (sodium sulphate) and distilled b.p. 206°. The yield was 80% of theoretical.

Ethyl 3:4-dimethoxyphenylglyoxylate.

Into a three necked flask equipped with a dropping funnel and mercury seal stirrer was introduced dry nitrobenzene (75 c.c.) and aluminium chloride (25g.) added slowly with external ice-cooling. When all the chloride had dissolved, ethyl oxalyl chloride (16g.) was added and veratrole (25g.) dropwise with further stirring. A deep red colour developed and after complete addition the mixture was stirred for five hours at room temperature. Ether (150 c.c.) and ice (100g.) were added with vigorous stirring. The ether solution was successively treated with water, saturated sodium bicarbonate and sodium chloride solution, dried (sodium sulphate) and ether, nitrobenzene, removed by distillation under reduced pressure. The residue gave on distillation ethyl 3:4-dimethoxyphenylglyoxylate (17g.) as a pale yellow oil b.p. 150-160°/0.3 mm. solidifying to a colourless solid melting 42°. The yield represents 60% of theoretical.

Found: C, 60.3; H, 5.5%.

Calc. for $C_{12}H_{14}O_5$: C, 60.5; H, 5.9%

The 2:4-dinitrophenylhydrazone crystallised from ethanol as orange-red leaflets m.p. 179° after four crystallisations.

Found: C, 52.0; H, 4.0; N, 13.7%

$C_{18}H_{18}O_8N_4$ requires: C, 51.7; H, 4.3; N, 13.4%.

Ethyl 3:4-dimethoxymandelate.

Ethyl 3:4-dimethoxyphenylglyoxylate (16g.) was dissolved in ethanol (30 c.c.) and shaken at room temperature with palladium black and hydrogen. On absorption of the theoretical amount of hydrogen the mixture was filtered and evaporated at reduced pressure.

The product was obtained as a colourless viscous oil (13g.) b.p. 153-156°/1 mm.

3:4-Dimethoxymandelic acid.

Ethyl 3:4-dimethoxymandelate (40g.) was refluxed with a ten per cent excess of 10% sodium hydroxide for one hour, the solution cooled and acidified with dilute hydrochloric acid. Evaporation of the aqueous solution under reduced pressure to dryness gave a white solid which was extracted by chloroform. To the heated chloroform solution was added benzene and the chloroform removed by evaporation. On cooling 3:4-dimethoxymandelic acid (35g.) crystallised in colourless aggregates of prisms melting at 105° after four crystallisations.

Found: C, 56.7; H, 5.6%

Calc. for $C_{10}H_{12}O_5$: C, 56.6; H, 5.7%.

 α -Chloro-3:4-dimethoxyphenylacetyl chloride.

3:4-Dimethoxymandelic acid (24g.) was dissolved in dry chloroform (100 c.c.) and phosphorus pentachloride (50g.) added portionwise. On cessation of the reaction the solvent and phosphorus oxychloride were removed under reduced pressure.

The acid chloride was obtained by distillation at $120^{\circ}/5 \times 10^{-2}$ mm. as a pale yellow oil solidifying to a white solid. This material decomposes rapidly on standing at 0° .
2-(α -chloro-3:4'-dimethoxyphenylacetamido)-1-(3:4'-dimethoxyphenyl)-ethane.

α -Chloro-3:4-dimethoxyphenylacetyl chloride (10g.) was dissolved in dry benzene (25 c.c.), and added dropwise with cooling to β -3:4-dimethoxyphenylethylamine (7.6g.) in benzene (25 c.c.). The mixture was stirred for one hour, then 2N sodium hydroxide (20 c.c.) added. Stirring was continued for one hour, the benzene layer washed successively with water, dilute hydrochloric acid solution, sodium hydroxide solution, then dried (sodium sulphate). Chromatography of the residual gum obtained on removal of the solvent gave as a separate fraction 2-(α -chloro-3:4'-dimethoxyphenylacetamido)-1-(3:4'-dimethoxyphenyl)-ethane (10.8g.) which crystallised from light petroleum (b.p. $60-80^{\circ}$) as small colourless prisms m.p. 108° .

Found: C, 61.2; H, 6.2; N, 3.5; Cl, 7.9%

$C_{20}H_{24}O_5$ NCl requires: C 61.0; H, 6.1; N, 3.6; Cl, 9.0%

Dihomoveratramide.

(cf. Sugawara J. Pharm. Soc. Japan, 1936, 194).

To an intimate mixture of 3:4-dimethoxyphenylacetic acid (2.4g.) and 3:4-dimethoxyphenylacetonitrile (2.16g.) was

added acetic anhydride (0.5 c.c.) and the substances heated in a sealed tube to 200° for ten hours. The contents were extracted with ethyl acetate, washed successively with sodium carbonate solution and water, then dried (sodium sulphate). After removal of the solvent the residue (2.0g.) was crystallised from ethyl acetate/light petroleum (b.p.40-60°) to give dihomoveratramide as colourless needles m.p.114°.

Found: C,64.5; H,6.2%

Calc. for $C_{20}H_{23}O_6N$: C,64.3; H,6.2%

Phosphorus oxychloride on dihomoveratramide.

Dihomoveratramide (1.0g.) was added to a mixture of toluene (10 c.c.) and phosphorus oxychloride (5 c.c.), the solution refluxed for two hours, cooled and the solvents removed under reduced pressure. The residue was dissolved in ethanol (10 c.c.), ammonia (2 c.c.) added, the ethanol removed and the residue extracted with benzene (3x20 c.c.). This solution on chromatography gave 3:4-dimethoxyphenylacetonitrile (100 m.g.) m.p.65°, and homoveratramide (300 mg.) m.p. 147°.

Methyl 2-acetyl-4:5-dimethoxyphenylacetate.

To a suspension of finely powdered aluminium chloride (6.0g.) in dry carbon disulphide (60 c.c.). was added methyl 3:4-dimethoxyphenylacetate (9.5g.) and acetyl chloride (3.5g.) The mixture was refluxed for one hour, cooled and the solvent decanted from the solid complex which was decomposed with ice-water. Extraction with ether (5x150 c.c.) and evaporation

of the ether to low bulk gave methyl 2-acetyl-4:5-dimethoxyphenylacetate (3.5g.) as colourless needles which crystallised from ether/light petroleum (b.p. 60-80°), m.p. 114°.

Found: C, 62.7; H, 6.7%

$C_{13}H_{16}O_5$ requires: C, 61.9; H, 6.4%

The substance forms a 2:4-dinitrophenylhydrazone crystallising from ethyl acetate as red needles m.p. 194°.

Found: C, 53.9; H, 4.9; N, 13.7%

$C_{19}H_{20}O_8N_4$ requires: C, 52.8; H, 4.7; N, 13.0%

2-Acetyl-4:5-dimethoxyphenylacetic acid.

Methyl 2-acetyl-4:5-dimethoxyphenylacetate (200 mg.) was shaken overnight with sodium hydroxide solution (10 c.c. of 5%). Acidification to pH-4 gave 2-acetyl-4:5-dimethoxyphenylacetic acid (100 mg.) as colourless needles crystallising from ethanol m.p. 175°.

Found: C, 60.3; H, 6.3%

$C_{12}H_{14}O_5$ requires: C, 60.5; H, 5.9%

2-Carboxy-4:5-dimethoxyphenylacetic acid.

Methyl 2-acetyl-4:5-dimethoxyphenylacetate (150 mg.) was suspended in 10% sodium hydroxide solution (10 c.c.) and heated to 80° for 15 minutes when solution occurred. After cooling to room temperature, sodium hypochlorite solution (from chlorine and 20% sodium hydroxide solution (6 c.c.)) was added with stirring over half an hour. The solution was heated to reflux for a further 15 minutes, cooled and acidified to pH4. The precipitate of 2-carboxy-4:5-

dimethoxyphenylacetic acid was collected and crystallised from water as colourless needles m.p. 216° . Robinson (J. 1907, 1082) quotes m.p. 215° .

Found: C, 55.3; H, 5.3%

Calc. for $C_{11}H_{12}O_6$: C, 55.0; H, 5.0%

6:7-Dimethoxy-3-hydroxy-1-methyl-isoquinoline.

Methyl 2-acetyl-4:5-dimethoxyphenylacetate (200 mg.) was shaken overnight at room temperature with concentrated aqueous ammonia (10 c.c.). The light yellow precipitate of 6:7-dimethoxy-3-hydroxy-1-methyl-isoquinoline (110 mg.) was collected by filtration and crystallised from ethanol as light yellow prisms m.p. 286° (decomp.). The compound is sparingly soluble in water, more soluble in ethanol with a green fluorescence. With ferric chloride in ethanol it gives a blue colouration.

Found: C, 65.7; H, 6.0; N, 6.6%

$C_{12}H_{13}O_3N$ requires: C, 65.7; H, 6.0; N, 6.4%

Light absorption (ethanol).

Maximum at 2540A ($\epsilon_{\text{Max.}} = 27,000$)

The base yields a picrate with ethanolic picric acid, which crystallises from ethanol as yellow prisms m.p. $236-9^{\circ}$.

Found: C, 48.9; H, 4.2%

$C_{18}H_{16}O_{10}N_4$ requires: C, 48.2; H, 3.6%

Methyl 2-benzoyl-4:5-dimethoxyphenylacetate.

To a suspension of finely powdered aluminium chloride (5.0g.) in dry carbon disulphide (60 c.c.) as added benzoyl chloride (5.1g.) and methyl 3:4-dimethoxyphenylacetate (7.5g.) The mixture was heated to reflux for one hour, cooled and the solvent decanted from the solid complex, which was then decomposed with ice-water. Extraction with ether (3x100 c.c.) and evaporation gave a gum which was dissolved in chloroform, washed successively with sodium carbonate solution and water, then dried (sodium sulphate). The residual oil on removal of the solvent was distilled at $100/10^{-2}$ mm. to remove impurities. The non-distillable fraction crystallised from benzene/light petroleum (b.p. $60-80^{\circ}$) to give methyl 2-benzoyl-4:5-dimethoxyphenylacetate (1.5g.) as colourless prismatic needles m.p. 108° .

Found: C, 69.3; H, 6.1%

$C_{18}H_{18}O_5$ requires: C, 68.8; H, 5.8%

2-Benzoyl-4:5-dimethoxyphenylacetic acid.

Methyl 2-benzoyl-4:5-dimethoxyphenylacetate (100 mg.) was heated to reflux with 5% sodium hydroxide solution (10 c.c.) for half an hour when solution occurred. Acidification to pH 4 gave 2-benzoyl-4:5-dimethoxyphenylacetic acid (80 mg.) which was obtained from aqueous methanol as long colourless needles m.p. 163° .

Found: C, 69.0; H, 5.9%

$C_{17}H_{16}O_5$ requires : C, 68.0; H, 5.4%

6:7-Dimethoxy-3-hydroxy-1-phenyl-isoquinoline.

Methyl 2-benzoyl-4:5-dimethoxyphenylacetate (800 mg.) was heated in an autoclave with 50% ethanolic ammonia (20 c.c.) for four hours at 135°. Removal of the solvents gave 6:7-dimethoxy-3-hydroxy-1-phenyl-isoquinoline (200 mg.) as bright yellow prisms crystallising from light petroleum (b.p.60-80°), m.p. 247-9°.

Found: N, 4.9%

$C_{17}H_{15}O_3N$ requires: N, 5.0%

Light absorption. (ethanol)

Maximum at 2,500A. ($\epsilon_{max.} = 28,600$)

Methyl 4:5-dimethoxy-2-phenylacetyl-phenylacetate.

To a suspension of finely powdered aluminium chloride (12.8g.) in dry carbon disulphide (120 c.c.) was added phenylacetyl chloride (14.8g.) and methyl 3:4-dimethoxyphenylacetate (20.0g.). The mixture was refluxed for one hour, cooled and the solvent decanted from the solid complex which was then decomposed with ice-water. Extraction with ether (6x150 c.c.) and evaporation to low bulk gave methyl 4:5-dimethoxy-2-phenylacetyl-phenylacetate (10.0g.) which crystallised from chloroform/light petroleum (b.p.60-80°) as colourless needles m.p. 94°.

Found: C, 69.9; H, 6.2%

$C_{19}H_{20}O_5$ requires : C, 69.5; H, 6.1%

The substance forms a 2:4-dinitrophenylhydrazone which crystallised from ethanol as red needles m.p. 148°.

Found: C, 60.0; H, 5.3; N, 10.3%

$C_{25}H_{24}O_8N_4$ requires: C, 59.0; H, 4.8; N, 11.0%

6:7-Dimethoxy-2-hydroxy-3-phenyl-1:4-naphthoquinone.

(a) Methyl 4:5-dimethoxy-2-phenylacetyl-phenylacetate (200 mg.) was shaken for two days with concentrated aqueous ammonia (10 c.c.) when solution occurred with development of a deep red colour. Removal of the ammonia and acidification of the residue gave 6:7-dimethoxy-2-hydroxy-3-phenyl-1:4-naphthoquinone which crystallised from methanol (60 mg.) as long red needles m.p. 255°. The material gives a red brown colour with ferric chloride in ethanol.

(b) Methyl 4:5-dimethoxy-2-phenylacetyl-phenylacetate (200 mg.) was shaken for two days with 5% sodium hydroxide (10 c.c.) when solution occurred giving a deep violet colouration. The solution was acidified, the precipitate collected and crystallised from methanol (100 mg.) as red needles m.p. 255°, undepressed in melting point on admixture with the above specimen.

Found: C, 70.0; H, 4.8; OCH_3 , 19.7%

$C_{18}H_{14}O_5$ requires : C, 69.7; H, 4.5; $2OCH_3$, 18.8%

Light Absorption (ethanol)

Maxima at 2,800A ($\epsilon_{max.} = 31,600$)

and 3,350A ($\epsilon_{max.} = 1,010$)

The substance forms a monoacetate which crystallised from chloroform/methanol as yellow micro prisms m.p. 218-20°.

Found: C,68.2; H,4.8%

$C_{20}H_{16}O_6$ requires: C,68.2; H,4.6%

It also yields a mono-benzoate as orange prisms from chloroform/methanol m.p. 232°.

Found: C,72.4; H,4.6%

$C_{25}H_{18}O_6$ requires: C,72.4; H,4.4%

3-Phenyl-2:6:7-trimethoxy-1:4-naphthoquinone.

6:7- Dimethoxy-2-hydroxy-3-phenyl-1:4-naphthoquinone (100 mg.) was suspended in excess ethereal diazomethane solution. When the vigorous reaction had ceased, 3-phenyl-2:6:7-trimethoxy-1:4-naphthoquinone (100 mg.) was crystallised from chloroform/methanol giving yellow micro prisms m.p. 214°.

Found: C,70.3; H,4.7 ; OCH_3 ,29.5%

$C_{19}H_{16}O_5$ requires: C,70.4; H,5.0; $3OCH_3$,28.7%

6:7-Dimethoxy-3-phenyl-1:2:4-trihydroxy-naphthalene-triacetate

6:7-Dimethoxy-2-hydroxy-~~2~~-phenyl-1:4-naphthoquinone (300 mg.) was added to acetic anhydride (5 c.c.) containing zinc dust (300 mg.) and concentrated sulphuric acid (0.1 c.c.). The mixture was refluxed for 20 minutes, the acetic anhydride solution decanted from the residue, then decomposed with water. After standing overnight, the white solid of 6:7-dimethoxy-3-phenyl-1:2:4-trihydroxy-naphthalene tri-

acetate (200 mg.) was collected and crystallised from ethanol as colourless needles m.p. 175-7°.

Found: C, 66.1; H, 5.5%

$C_{24}H_{22}O_8$ requires: C, 65.7; H, 5.1%

6:7-Dimethoxy-2:4-di-(4-dimethylaminophenylimino)-1-keto-1:2:3:4-tetrahydronaphthalene.

6:7-Dimethoxy-1-keto-1:2:3:4-tetrahydronaphthalene (5.2g.), prepared according to the methods of Haworth J. 1932, 1487 and Martin J. Amer. Chem. Soc., 1936, 58, 1438, was added in ethanol (50 c.c.) to a solution of nitroso-dimethylaniline (7.5g.) in ethanol (100 c.c.), containing 10% sodium hydroxide solution (5 c.c.). After standing overnight at room temperature, the precipitate of 6:7-dimethoxy-2:4-di-(4-dimethylaminophenylimino)-1-keto-1:2:3:4-tetrahydronaphthalene (5.5g.) was collected, and crystallised from ethyl acetate as small permanganate coloured needles m.p. 230°.

Found: N, 11.9%

$C_{28}H_{30}O_3N_4$ requires: N, 11.9%

6:7-Dimethoxy-2-hydroxy-1:4-naphthoquinone.

The anil (10g.) was dissolved in 10% sulphuric acid solution (300 c.c.) and refluxed for one hour. The solution was cooled, the solid collected and dried, then extracted with boiling benzene (2x500 c.c.). Concentration gave 6:7-dimethoxy-2-hydroxy-1:4-naphthoquinone (800 mg.) as small clusters of brown orange needles m.p. 212° (decomp.).

The substance gives a pale red ferric chloride colour, is soluble in sodium hydroxide forming a red solution and gives a purple colour with concentrated sulphuric acid.

Found: C, 61.4; H, 4.5 %

$C_{12}H_{11}O_5$ requires: C, 61.3; H, 4.7 %

6:7-Dimethoxy-2-hydroxy-3-phenyl-1:4-naphthoquinone

Aniline (290 mg.) in water (12 c.c.) containing concentrated hydrochloric acid (0.36 c.c.) was diazotised at 0°. This solution was added over five minutes to a solution of 6:7-dimethoxy-2-hydroxy-1:4-naphthoquinone (560 mg.) in 5% potassium hydroxide solution, (24 c.c.) with stirring at 45°. After a further 20 minutes at 45°, the solution was brought to pH 6 with dilute acetic acid and filtered. The filtrate was acidified with dilute hydrochloric acid and the pale yellow solid (160 mg.) collected and dried. Crystallisation from ethanol gave a red orange material (50 mg.) which was chromatographed on calcium carbonate using benzene as solvent. Evaporation of the eluate and crystallisation of the red residue from methanol gave 6:7-dimethoxy-2-hydroxy-3-phenyl-1:4-naphthoquinone (10 mg.) as small red needles m.p. 255°, undepressed in melting point on admixture with the previous specimen.

Light absorption. (ethanol).

Maxima at 2,800A ($\epsilon_{\text{max.}} = 32,000$)

and 3,350A ($\epsilon_{\text{max.}} = 970$)

Methyl 4:5-dimethoxy-2-(3':4'-dimethoxyphenylacetyl)-phenylacetate.

To nitrobenzene (50 c.c.), cooled to 0°, was added dry powdered aluminium chloride (7.0g.) and the mixture stirred until solution occurred. 3:4-Dimethoxyphenylacetyl chloride (7.0g.) was introduced then methyl 3:4-dimethoxyphenylacetate (10g.), dropwise with stirring over one hour. The solution was stirred at room temperature overnight then ether (100 c.c.) added along with sufficient ice to decompose the aluminium complex. The ether extract was washed successively with dilute hydrochloric acid, saturated sodium hydrogen carbonate solution, water and dried (sodium sulphate). The solvents were removed by steam distillation and the residue extracted with benzene, washed and dried as previously. Removal of the benzene gave a semi-solid which on solution in benzene/light petroleum (b.p.60-80°) deposited methyl 4:5-dimethoxy-2-(3':4'-dimethoxyphenylacetyl)-phenylacetate (1.7g.) as colourless rosettes of prisms m.p. 132°.

Found: C,65.2; H,6.5%

$C_{21}H_{24}O_7$

requires: C,64.9; H,6.2%

The substance gives a 2:4- dinitrophenylhydrazone, obtained from ethanol as red needles m.p. 150°.

Found: C,57.3; H,5.2%

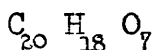
$C_{27}H_{28}O_{10}N_4$

requires: C,57.0; H,5.0%

6:7-Dimethoxy-3-(3':4'-dimethoxyphenyl)-2-hydroxy-1:4-naphthoquinone.

Methyl 4:5-dimethoxy-2-(3':4'-dimethoxyphenylacetyl)-phenylacetate (850mg.) was suspended in 5% sodium hydroxide solution (50 c.c.) and shaken for two days. Solution occurred with the development of a deep violet colouration. Acidification to pH 4 gave 6:7-dimethoxy-3-(3':4'-dimethoxyphenyl)-2-hydroxy-1:4-naphthoquinone which crystallised from methanol (200 mg.) as long red needles m.p. 226°. The substance gives a dark green colour with ferric chloride.

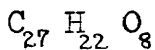
Found: C, 65.0; H, 5.1%



requires: C, 64.9; H, 4.9%

The substance gives a monobenzoate as orange prisms from chloroform/methanol m.p. 206°.

Found: C, 68.3; H, 4.4%



requires: C, 68.3; H, 4.7%

N-(3:4-Dimethoxybenzylidene)-aminomethylmeconin.

Aminomethylmeconin hydrochloride (2.33g.) was dissolved in ethanol (60 c.c.) containing potassium hydroxide (0.51g.). 3:4-Dimethoxybenzaldehyde (1.5g.) in ethanol (10 c.c.) was added and the solution refluxed for three hours. The solvent was removed and the residue heated at 100° for one hour giving N-(3:4-dimethoxybenzylidene)-aminomethylmeconin (2.0g.) which crystallised from aqueous methanol as colourless needles m.p. 142°.

Found: C, 64.5; H, 5.7; N, 4.1%

$C_{20}H_{21}O_6N$ requires: C, 64.7; H, 5.7; N, 3.8%

Light absorption (ethanol)

Maxima at 2720A (ϵ max. = 14,980)

and 3050A (ϵ max. = 14,600)

Attempted rearrangement of N-(3:4-dimethoxybenzylidene)-aminomethylmeconin.

N-(3:4-Dimethoxybenzylidene)-aminomethylmeconin (5.0g.) was dissolved in concentrated hydrochloric acid (25 c.c.) and left standing for three days. The precipitate (2.2g.) was collected and crystallised from aqueous ethanol, giving colourless needles m.p. $247-8^{\circ}$. This material was undepressed in melting point on admixture with an authentic specimen of aminomethylmeconin hydrochloride.

2-Methoxy-2-(3:4'-dimethoxyphenyl)-ethylamine

2-Methoxy-2-(3:4'-dimethoxyphenyl)-nitroethane (50g.), prepared according to the method of B.I.O.S. report no. 1774, was dissolved in ethyl acetate (100 c.c.) and hydrogenated at 75ats. pressure and 60° for 24 hours, when the theoretical amount of hydrogen was absorbed. Platinum oxide was used as catalyst. Removal of the solvent and distillation gave 2-methoxy-2-(3:4'-dimethoxyphenyl)-ethylamine (30g.) as a colourless oil b.p. $125^{\circ}/10^2$ mm., solidifying to a white solid m.p. 40° .

N-(3':4'-Dimethoxybenzylidene)-2-methoxy-2-(3':4'-dimethoxyphenyl)-ethylamine.

To 2-methoxy-2-(3':4'-dimethoxyphenyl)-ethylamine (5.0g.) in ethanol (10 c.c.) was added 3:4-dimethoxybenzaldehyde (3.95g.) in ethanol (25 c.c.). After refluxing for one hour, the solvent was removed and the residue heated on a water bath for one hour. N-(3':4'-dimethoxybenzylidene)-2-methoxy-2-(3':4'-dimethoxyphenyl)-ethylamine (quantitative yield) crystallised from benzene/light petroleum (b.p.40-60°) as colourless needles m.p. 108°.

Eound: C,66.9; H,6.9; N,4.0%

$C_{20}H_{24}O_5N$ requires; C,67.0; H,6.7; N,3.9%

Light absorption.(ethanol)

Maxima at 2280A ($\epsilon_{max.} = 25,800$)

and 2700A ($\epsilon_{max.} = 19,600$)

and 3000A ($\epsilon_{max.} = 12,400$)

1:2-Dihydro-6:7-dimethoxy-1-(3':4'-dimethoxyphenyl)-isoquinoline hydrochloride.

N-(3':4'-Dimethoxybenzylidene)-2-methoxy-2-(3':4'-dimethoxyphenyl)-ethylamine (5.0g.) was dissolved in concentrated hydrochloric acid (50 c.c.) and left for seven days. The deep red solution was added to water (200 c.c.) and the red precipitate collected and dried (1.9g.). This was dissolved in ethylene glycol monomethyl ether (15 c.c.), refluxed for two hours, cooled and ether (50 c.c.) added. 1:2-Dihydro-6:7-dimethoxy-1-(3':4'-dimethoxyphenyl)-isoquin-

-oline hydrochloride (300 mg.) separated and crystallisation from ethanol/ether gave this compound as pale yellow micro-needles m.p. 236° .

Found: C, 62.8; H, 5.8; N, 3.9%

$C_{19}H_{22}O_4NCl$ requires: C, 62.7; H, 6.1; N, 3.85%

Light absorption. (ethanol)

Maximum at 3000A ($\epsilon_{max.} = 17,000$)

1:2-Dihydro-6:7-dimethoxy-1-(3:4'-dimethoxyphenyl)-isoquinoline

The above hydrochloride (250mg.) was dissolved in aqueous ethanol (10 c.c.) and concentrated ammonia (1 c.c.) added. The solvents were removed and 1:2-dihydro-6:7-dimethoxy-1-(3:4-dimethoxyphenyl)-isoquinoline (150mg.) crystallised from benzene/light petroleum (b.p. $40-60^{\circ}$) as colourless clusters of needles m.p. 164° .

Found: N, 3.8%

$C_{19}H_{21}O_4N$ requires: N, 4.4%

Light absorption. (ethanol)

Maxima at 2240A ($\epsilon_{max.} = 33,460$)

and 2980A ($\epsilon_{max.} = 18,400$)

The base gives a picrate crystallising from ethanol as yellow prisms m.p. 194° .

3:4-Dimethoxybenzoyl chloride.

(cf. Edwards J. 1925, 195.)

3:4-Dimethoxybenzoic acid (12g.), prepared by the method of Edwards, J. 1925, 195, was suspended in chloroform

(100 c.c.) and phosphorus pentachloride (12.0g.) added portionwise. When the vigorous reaction had ceased, the solvents were removed and 3:4-dimethoxybenzoyl chloride (8.0g.) distilled as a colourless oil b.p. $120^{\circ}/10\text{mm.}^{-2}$, solidifying to a white solid m.p. 69° .

2-(3':4'-Dimethoxybenzamido)-1-(3':4'-dimethoxyphenyl)-1-methoxy-ethane.

To 2-methoxy-2-(3':4'-dimethoxyphenyl)-ethylamine (5.14g.) dissolved in dry chloroform (50 c.c.), was added, dropwise with stirring, and cooling to 0° , 3:4-dimethoxybenzoyl chloride (4.88g.) in chloroform (25 c.c.). N-methyl-morpholine (2.5g.) in chloroform (25 c.c.) was then added dropwise over half an hour, and the reaction mixture stirred for a further hour. The solution was filtered from N-methyl-morpholine hydrochloride, washed successively with dilute hydrochloric acid, saturated sodium hydrogen carbonate solution, water and dried (sodium sulphate). On removal of the solvent 2-(3':4'-dimethoxybenzamido)-1-(3':4'-dimethoxyphenyl)-1-methoxy-ethane (7.1g.) was obtained, crystallising from benzene/light petroleum (b.p. $60-80^{\circ}$) as colourless prisms m.p. 130° .

	Found:	C, 63.6;	H, 6.9;	N, 4.0%
$\text{C}_{20}\text{H}_{25}\text{O}_6\text{N}$	requires:	C, 64.0;	H, 6.7;	N, 3.7%

6:7-Dimethoxy-1-(3:4'-dimethoxyphenyl)-isoquinoline.

To 2-(3:4'-dimethoxybenzamido)-1-(3:4'-dimethoxyphenyl)-1-methoxy-ethane (2.0g.) dissolved in dry toluene (10 c.c.), was added phosphorus oxychloride (3 c.c.) and the solution refluxed for one hour, cooled and the solvents removed under reduced pressure. The residue was extracted with dilute hydrochloric acid (25 c.c.), this solution neutralised with ammonia and 6:7-dimethoxy-1-(3:4'-dimethoxyphenyl)-isoquinoline (0.9g.) collected. Crystallisation from benzene/light petroleum (b.p.60-80°) gave the base as colourless prisms m.p. 159°.

Found: C,70.3; H,5.0; N,4.5%

$C_{19}H_{19}O_4N$ requires: C,70.1; H,5.9; N,4.3%

Light absorption. (ethanol)

Maximum at 2580A ($\epsilon_{max.} = 44,000$)

The base forms a picrate which crystallises from ethanol as yellow prisms m.p. 170°.

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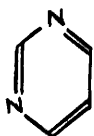
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Part Two.

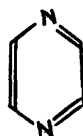
Synthetic Studies in

1:4-Oxazine Chemistry.

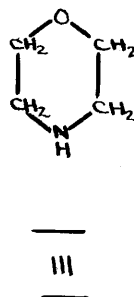
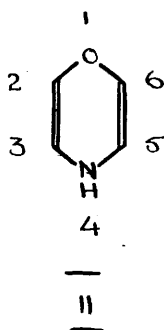
While synthesis of six membered rings with two hetero-atoms are among the earliest described in heterocyclic chemistry (1), it appears that the detailed study of such systems has been restricted to pyrimidine and pyrazine compounds (1) . The occurrence of natural products possessing



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these structures has given impetus to the chemical investigation and syntheses of their derivatives, leading to the extension and development of their chemistry (2,3,4). No analogous fields exist in the oxazine ring systems, particularly the 1:4-oxazines (II). It is therefore not

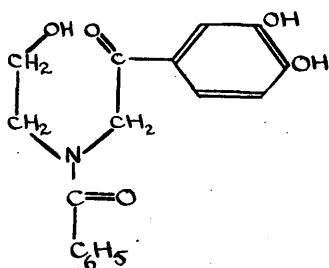


unexpected that efforts to enlarge the chemistry of this class of compounds have not been made.

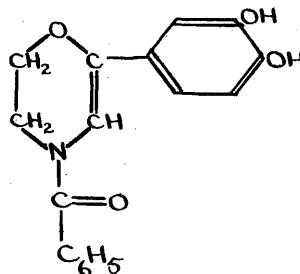
The earliest synthetic work on 1:4-oxazines is that of Knorr (5) who showed that treatment of diethanolamine and its O-derivatives with various reagents gave tetrahydro-1:4-oxazine (III), the so-called morpholine, because of its mistaken connection with a structural portion of the alkaloid

morphine (6). A large number of tetrahydro-1:4-oxazines substituted in the 4-position have been prepared by similar methods, in connection with the application of N-derivatives of morpholine as chemotherapeutic agents (7).

There have been few syntheses of unsaturated 1:4-oxazines. Hill and Powell (8), in the preparation of amines of the procaine type related to adrenaline, obtained, by the cyclisation of N-(3:4-dihydroxyphenacyl)-N-(2-hydroxyethyl)-benzamide (IV) a compound which they suggested to be 2-(3':4'-dihydroxyphenyl)-4-benzoyl-5:6-dihydro-1:4-oxazine (V), but no further evidence was offered by these authors

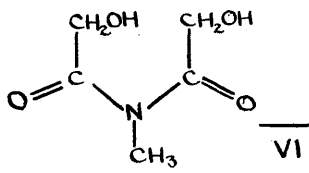


IV

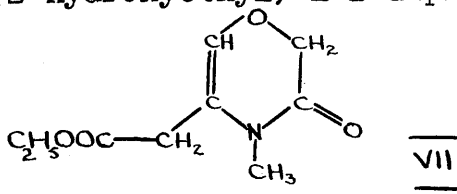


V

regarding the validity of this postulation. Lukes and Storm (9) describe the treatment of N-Methyl-diglycollimide (VI) with ethyl bromoacetate to give ethyl 4-methyl-3-oxo-2:3-dihydro-1:4-oxazine-5-acetate (VII) while Lutz and others (10) during investigation of new types of antimalarials, prepared from N-ethyl-N-(2'-hydroxyethyl)-1:2-diphenyl-2-

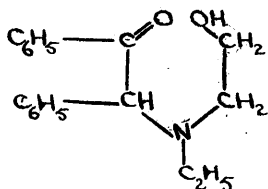


VI

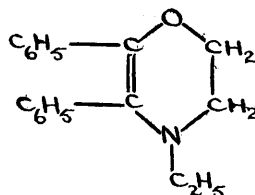


VII

keto-ethylamine (VIII) a compound declared to be 4-ethyl-2:3-diphenyl-5:6-dihydro-1:4-oxazine (IX). Finally Newbold, Spring and Sweeny (11) while investigating syntheses of

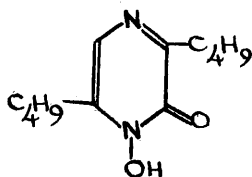


VIII

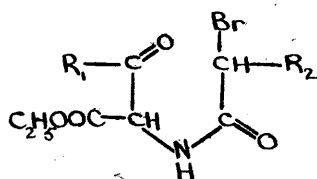


IX

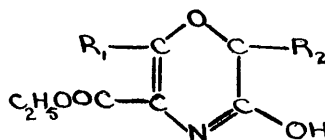
pyrazines related to aspergillic acid (X) found that bromo-acylamidoketo esters (XI) with basic reagents gave in high yield 5-hydroxy-1:4-oxazines (XII). This represents the



X



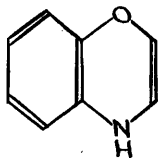
XI



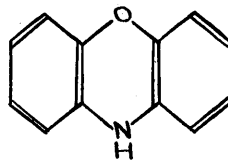
XII

first general method of synthesis of fully unsaturated 1:4-oxazines.

Apart from these syntheses of uncondensed 1:4-oxazines, the preparation of phenoxazines (XIII) and (XIV)



XIII

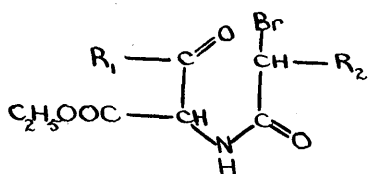


XIV

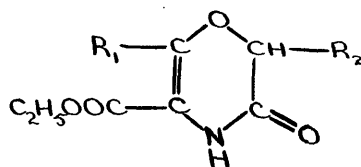
has been commercially undertaken in virtue of their valuable properties as dyestuffs (12).

THEORETICAL.

In their discovery of a synthetic route to 5-hydroxy-1:4-oxazines, Newbold, Spring, and Sweeny (11) demonstrated that treatment of bromoacylamidoketo esters (XV) with ammonia or sodium ethoxide led to the formation the 1:4-oxazine esters (XVI). Thus ethyl α -(α' -bromopropionamido)-



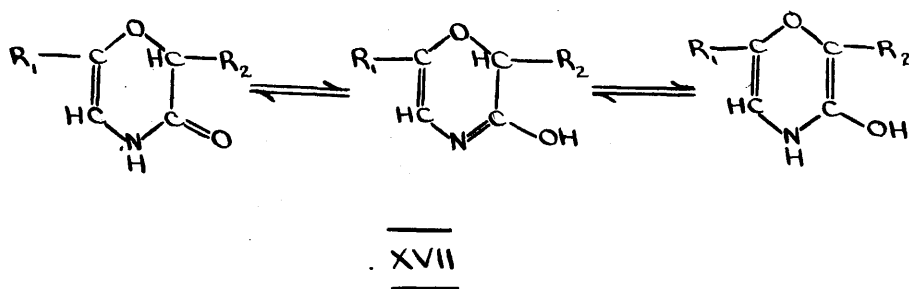
XV

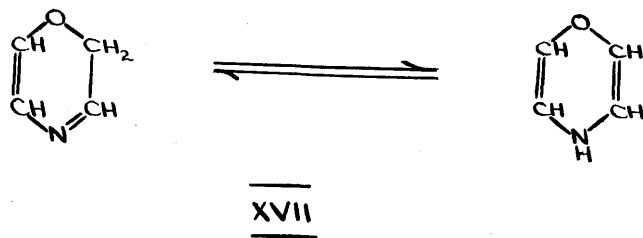


XVI

β -ketobutyrate (XV $R_1 = R_2 = \text{CH}_3$) gave ethyl 5-hydroxy-2:6-dimethyl-1:4-oxazine-3-carboxylate (XVI $R_1 = R_2 = \text{CH}_3$), and ethyl α -bromoacetamido- β -ketobutyrate (XV, $R_1 = \text{CH}_3$, $R_2 = \text{H}$) gave ethyl 5-hydroxy-2-methyl-1:4-oxazine-3-carboxylate (XVI $R_1 = \text{CH}_3$, $R_2 = \text{H}$). When however the reaction was investigated using a phenyl substituted case, ethyl α -(α' -bromophenylacetamido)- β -ketobutyrate (XV $R_1 = \text{CH}_3$, $R_2 = \text{C}_6\text{H}_5$), isolation of the desired 1:4-oxazine was not accomplished. It was suggested by Sweeny (13) that steric hinderance due to the large dimension of the adjacent phenyl group was preventing the elimination of the elements of hydrogen bromide.

The object of the synthetic studies described in this part of the thesis has been to extend further the chemistry of 1:4-oxazines containing two double bonds in the ring. In the realisation of this aim, the field of work may be considered to fall into three inter-related sections. Firstly a re-examination of the synthesis of phenyl substituted 5-hydroxy-1:4-oxazines was undertaken in order to extend the generality of the reaction to include both alkyl and aryl substituents. This work was considered of importance since the previous failure to isolate a suitably substituted 1:4-oxazine confines the synthetic route to the narrower limits of alkyl substituted 1:4-oxazines. Secondly the investigation of the reactions of 5-hydroxy-1:4-oxazines was commenced in an attempt to eliminate the 5-hydroxyl group. The tautomeric structures of 5-hydroxy-1:4-oxazines (XVII) indicate that the presence of the -OH group adjacent to the heterocyclic nitrogen atom might by virtue of its keto-enolic tautomerism confer a degree of stability on the ring system which it would not possess in a completely unsubstituted ring (XVIII). In this case a low degree of aromaticity





due to the ability of the ring system to accommodate only two double bonds is not unexpected. It remained therefore to be seen whether the system possessed sufficient stability to exist as an entity. Finally a survey of possible synthetic routes to 1:4-oxazines not containing a hydroxyl group was envisaged in order to contribute further evidence on the question of ring stability in the 1:4-oxazines.

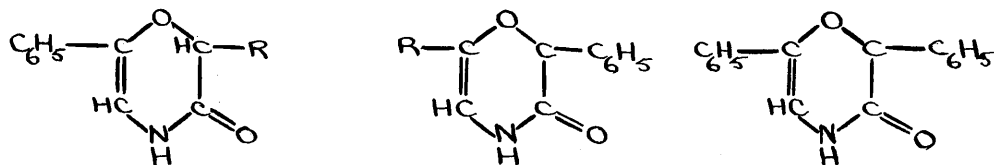
Phenyl -5- Hydroxy- 1:4 - Oxazines.

... 5-hydroxy-1,4-oxazine (X) is
... with the product of Seelye (1)
... substance with radial edges
... chromatographic examination of it



Phenyl-5-Hydroxy-1:4-Oxazines.

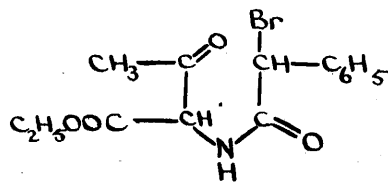
The synthesis of phenyl substituted 5-hydroxy-1:4-oxazines is necessarily confined to the 2- and 6- substituted cases (XIX) since the final ring closure of the intermediate



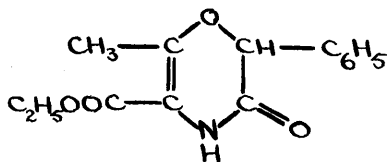
—
XIX
—

bromoacylamidoketo esters takes place by means of elimination of the elements of hydrogen bromide between these two positions. Accordingly their syntheses was attempted.

Condensation of ethyl α -amino- β -ketobutyrate hydrochloride with α -bromophenylacetyl chloride gave ethyl α -(α' -bromophenylacetamido)- β -ketobutyrate (XX) identical in physical properties with the product of Sweeny (loc. cit.). Treatment of this substance with sodium ethoxide in dry ethanol followed by chromatographic examination of the resultant

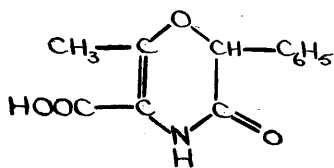


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XX
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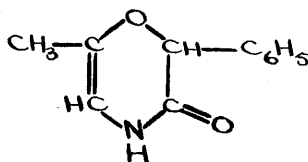


—
XXI
—

intractible gum led to the isolation of ethyl 5-hydroxy-2-methyl-6-phenyl-1:4-oxazine-3-carboxylate (XXI) in poor yield. This substance showed the light absorption characteristics of the type anticipated for a phenyl substituted 1:4-oxazine. The ester was readily hydrolysed to 5-hydroxy-2-methyl-6-phenyl-1:4-oxazine-3-carboxylic acid (XXII). This acid decarboxylated on heating above its melting point



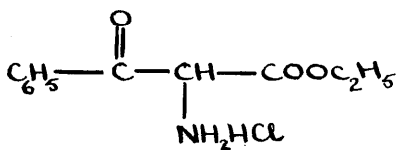
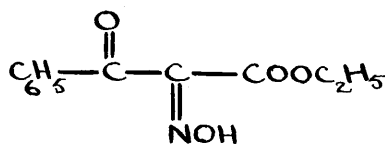
XXII



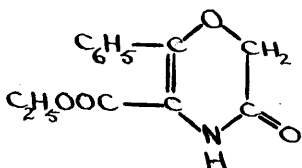
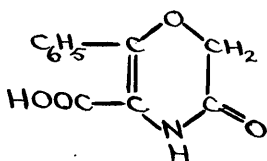
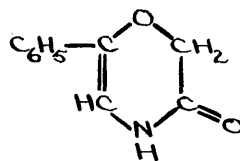
XXIII

to give the parent 1:4-oxazine, 5-hydroxy-2-methyl-6-phenyl-1:4-oxazine (XXIII).

For the production of 2-phenyl-1:4-oxazines, the synthesis of ethyl α -amino- β -keto- β -phenyl-propionate hydrochloride (XXIV) was necessary. This was achieved via ethyl β -keto- α -oxo-amino- β -phenyl-propionate (XXV) by adaptation of the method of Forsyth and Pyman (14). Acylation of the amine hydrochloride with bromoacetyl chloride gave ethyl α -bromoacetamido- β -keto- β -phenyl-propionate (XXIX, R = H), giving the claret red ferric chloride colour characteristic of these keto esters. With sodium

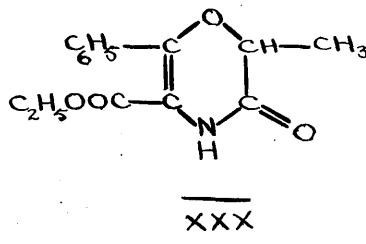
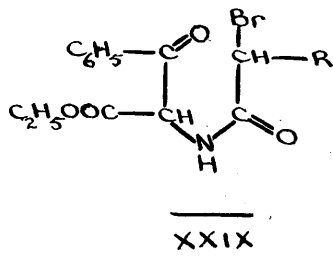
XXIVXXV

ethoxide as previously described, ethyl 5-hydroxy-2-phenyl-1:4-oxazine-3-carboxylate (XXVI) was obtained. This ester which showed two maxima of light absorption at 2,200 Å

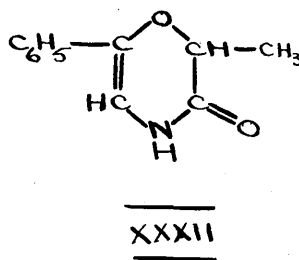
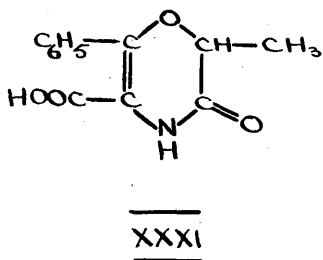
XXVIXXVIIXXVIII

($\epsilon_{\text{max}} = 12,400$) and 3,050 Å ($\epsilon_{\text{max}} = 9,580$), hydrolysed to give 5-hydroxy-2-phenyl-1:4-oxazine-3-carboxylic acid (XXVII). When heated to 230° the acid was smoothly converted into 5-hydroxy-2-phenyl-1:4-oxazine (XXVIII).

Similarly condensation of α -bromopropionyl chloride and ethyl α -amino- β -keto- β -phenyl-propionate hydrochloride gave ethyl α -(α' -bromopropionamido)- β -keto- β -phenyl-propionate (XXIX, R = CH₃). This was converted in very poor yield into ethyl-5-hydroxy-6-methyl-2-phenyl-1:4-oxazine-3-carboxylate (XXX). Hydrolysis of this ester gave 5-hydroxy-6-methyl-2-phenyl-1:4-oxazine-3-carboxylic acid (XXXI) and decarboxylation led to the formation of



5-hydroxy-6-methyl-2-phenyl-1:4-oxazine (XXXII). The ester showed light absorption characteristics very similar to the previous



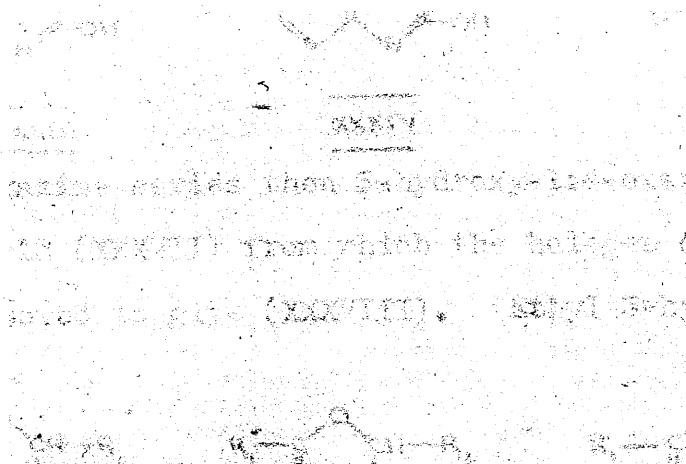
2-phenyl-1:4-oxazine ester, having two maxima, at 2,190A ($\epsilon_{\max} = 12,960$) and 3,060A ($\epsilon_{\max} = 10,100$).

Finally with α -bromophenylacetyl bromide the amine hydrochloride gave ethyl α -(α' -bromophenylacetamido)- β -keto- β -phenyl-propionate (XXIX, R = C₆H₅), showing a claret-red ferric chloride colour. All attempts to cyclise this product to ethyl 5-hydroxy-2:6-diphenyl-1:4-oxazine-3-carboxylate failed. The gum obtained on treatment of the compound with sodium ethoxide did not exhibit any light absorption at 3,060A and hence the expected 1:4-oxazine was not present in an impure state. Also treatment of the keto ester with ammonia according to the method of Sweeny (loc.cit)

proved fruitless. The use of sodium tert. butoxide according to the method of Ramsey (15) was similarly unsuccessful.

Summarising, therefore, the synthetic route from bromoacylamidoketo esters to 1,4-oxazines discovered by Sweeny et alia (11) is perfectly general in its application both with respect to alkyl and aryl ring substituents although in the most sterically hindered case (XXIX, R = C₆H₅) the ring closure does not appear possible. It may also be noted that the ease of synthesis is considerably decreased in aryl substituted cases as shown by the poorer yields.

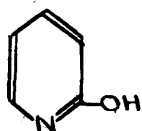
Condensation Reactions.
and Dihydro -1:4- Oxazines.



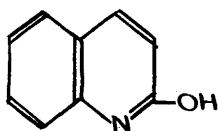
Condensation Reactions and Dihydro-1:4-Oxazines.

With the successful extension of the synthesis of 5-hydroxy-1:4-oxazines to include phenyl substituted cases, attention was turned to the problem of the synthesis of 1:4-oxazines containing no hydroxyl substituent. This object can be achieved either by elimination of the -OH grouping from known 5-hydroxy-1:4-oxazines or via a direct total synthesis.

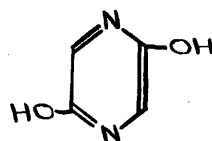
The removal of the hydroxyl group of 5-hydroxy-1:4-oxazines by replacement with halogen was examined, since it has been shown by Roth (16), Fischer (17), and Gallagher and others (18) in the 2-OH-pyridine (XXXIII), 2-OH-quinoline (XXXIV) and 2:5-dihydroxy-pyrazine (XXXV) series respectively, that -OH groups adjacent to nitrogen atoms are directly replacable by halogen. If analogous behaviour was exhibited



XXXIII

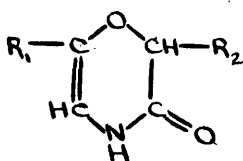


XXXIV

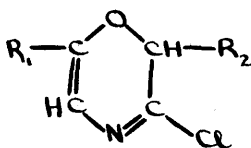


XXXV

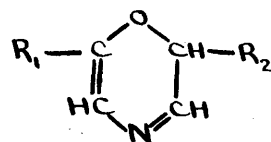
in the oxazine series then 5-hydroxy-1:4-oxazine (XXXVI) would yield (XXXVII) from which the halogen could be successfully removed to give (XXXVIII). Ethyl 5-hydroxy-2-methyl-



XXXVI



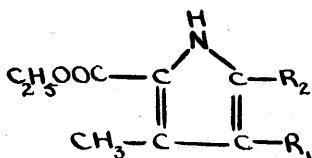
XXXVII



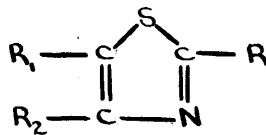
XXXVIII

1:4-oxazine-3-carboxylate (XVI, $R_1 = \text{CH}_3$, $R_2 = \text{H}$) was prepared and its behaviour on treatment with chlorinating agents was examined. In all cases amorphous products were isolated, and no evidence of the formation of halogenated 1:4-oxazines obtained. Similar treatment of 5-hydroxy-2-methyl-1:4-oxazine also gave intractable products. From these series of experiments it was concluded that the instability of the 1:4-oxazine ring system was preventing halogenation. This view is in accord with the observations of Sweeny (13) who found that fission of the ring of ethyl 5-hydroxy-2:6-dimethyl-1:4-oxazine-3-carboxylate (XVI, $R_1 = R_2 = \text{CH}_3$) occurred easily. This approach was therefore abandoned in favour of a direct synthetic route.

A synthesis of fully unsaturated 1:4-oxazines appeared to be possible through the condensation of two difunctional compounds. Knorr (19), using the aminoketo ester (XLI) and a ketone accomplished the synthesis of a pyrrole (XXXIX) while Hantsch (20) similarly condensed the bromoketone (XLII) with thioamides to give thiazoles (XL). In a similar type

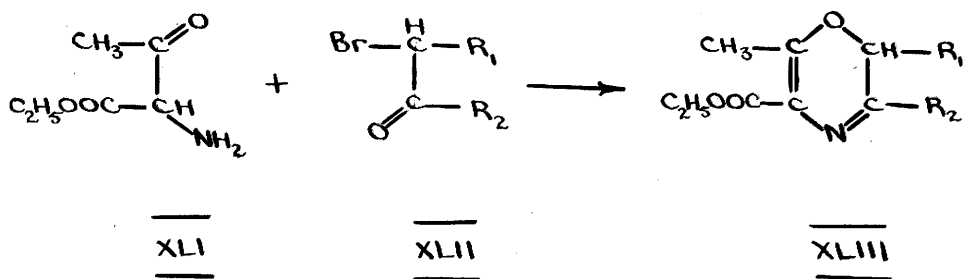


XXXIX

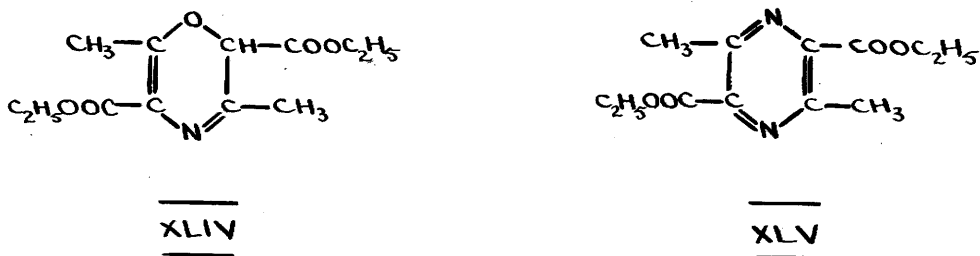


XL

of synthesis for the 1:4-oxazine system, condensation of the aminoketo ester (XLI) with the bromoketone (XLII) might give the desired 1:4-oxazine (XLIII). To examine the feasibility

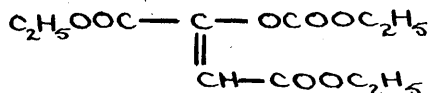


of this route ethyl α -amino- β -ketobutyrate hydrochloride was shaken in ethanolic solution in the presence of a base with ethyl α -bromoacetoacetate in an attempt to form ethyl 2:5-dimethyl-1:4-oxazine-3:6-dicarboxylate (XLIV). From the



reaction, however, a quantitative yield of ethyl 2:5-dimethyl-pyrazine-3:6-dicarboxylate (XLV) was isolated. The liberated ethyl α -amino- β -ketobutyrate had undergone self-condensation with the exclusion of the ethyl α -bromoaceto-

to carbon linkage, the formation of an ether linkage (L) is not unknown. For example Boese and others (22) have shown that ethyl oxalacetate reacts with ethyl chloroformate to give ethyl O-carbethoxyoxalacetate (LII). Ultimately the

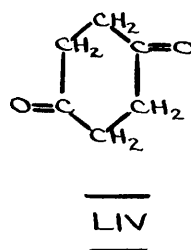
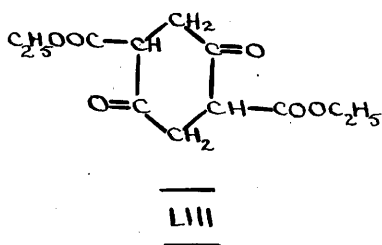


LII

reaction which proceeds will depend on the collective effect of the $-\text{COOC}_2\text{H}_5$ group and $-\text{NHAc}$. group on the enolisation of the ketonic group. As no parallel case has been described in the literature, the reaction was investigated.

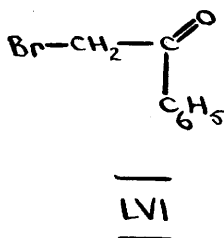
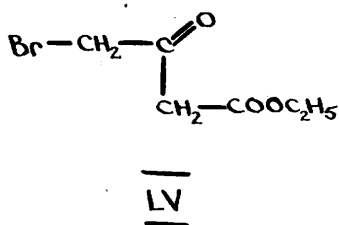
The synthesis of ethyl α -acetamido- β -ketobutyrate (XLVI) has been previously described. Cerchez(23) prepared the compound by direct acylation of the amine, while Wiley and Borum (24) obtained (XLVI) by reduction of ethyl β -keto- α -oximino-butyrate in the presence of acetic anhydride. These authors, however, disagree regarding the physical properties of the substance, Cerchez quoting m.p. 141° while Wiley and Borum describe the compound as a low melting solid. In order to clarify this position, ethyl α -amino- β -ketobutyrate hydrochloride was acylated with acetyl chloride to give a colourless solid m.p. $45-8^\circ$ which formed a 2:4-dinitrophenylhydrazone, analysing for the dinitrophenylhydrazone of ethyl α -acetamido- β -ketobutyrate. Hydrogenation of ethyl β -keto- α -oximino-butyrate in acetic anhydride gave the same material. It was concluded that the

product described by Cerchez (23) could not be ethyl α -acetamido- β -ketobutyrate. The condensation of this compound with ethyl α -bromoacetoacetate was then attempted in ethanol containing a molar proportion of sodium ethoxide. The reaction product isolated however was identified as ethyl succinoyl-succinate (LIII), readily converted by the

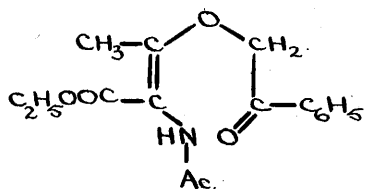


method of Meerwein (25) into 1:4-cyclohexadione (LIV), which in turn was characterised by the formation of a bis-2:4-dinitrophenylhydrazone analysing for the molecular formula $C_{18}H_{16}O_8N_8$. The formation of (LIII) is to be attributed to the ready rearrangement of ethyl α -bromoacetoacetate to ethyl δ -bromoacetoacetate (LV) (26) which self-condenses to ethyl succinoyl-succinate (27).

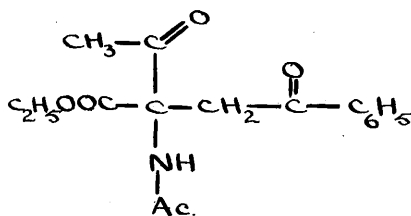
Attention was next turned to the use of an α -bromo-ketone incapable of undergoing rearrangement. Such a substance is ω -bromoacetophenone (LVI) where the presence of



only one methylene group renders self-condensation impossible. Treatment of this bromoketone with ethyl α -acetamido- β -keto-butyrates (XLVI) in an identical manner gave a product $C_{16}H_{19}O_5N$ corresponding to either (LVII) or (LVIII). The substance shows one maximum of light absorption at 2,240A ($\epsilon_{max} = 16,980$) presumably caused by the benzene ring present, and yielded a bis-2:4-dinitrophenylhydrazone of molecular formula $C_{28}H_{27}O_{11}N_9$. As formula (LVII) is a

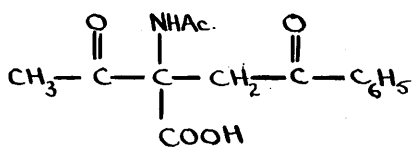


LVII

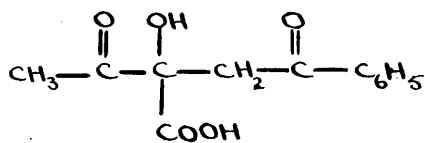


LVIII

monoketone it must be excluded and formula (LVIII) attributed to the condensation product. Further support for this conclusion was obtained by hydrolysis of the product with sodium hydroxide. This gave an acid $C_{14}H_{15}O_5N$ which must be 3-Acetamido-2:5-diketo-5-phenyl-pentan-3-oic acid (LIX). On refluxing this acid with sodium hydroxide solution complete degradation of the molecule occurred to give ammonia and acetophenone. The initial reaction is probably the hydrolysis of the acetyl group



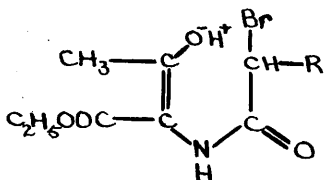
LIX



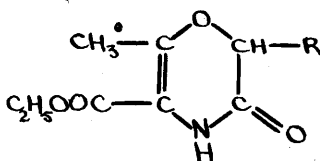
LX

and replacement of amino by hydroxyl to give (LX). Further degradation gives acetic acid and benzoylacetic acid which loses carbon dioxide to yield acetophenone.

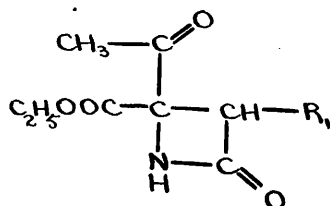
Although this work establishes that the synthesis of 1:4-oxazines from ethyl α -acetamido- β -ketobutyrate is not possible, it does enable the mechanism of 1:4-oxazine formation from bromoacylamido ketones to be more clearly understood. Two mechanisms can be proposed for the transformation of (LXI) into (LXII).



LXI



LXII



LXIII

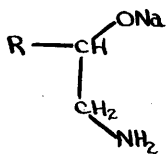
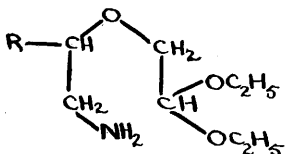
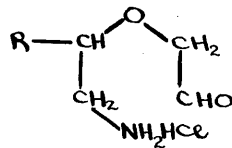
1. The collective effect of a carbethoxy and an acetamido grouping in (LXI) is such that the ketone exists wholly in the enolic form. Therefore treatment with a base forms an ether in the usual phenol type condensation, as for example in the synthesis of aryloxyacetic acids (28).

2. The action of sodium ethoxide on (LXI) can lead to the formation of either (LXII) or (LXIII). The former is a six-membered ring possessing the stability associated with such a system, while the latter is a four-membered heterocyclic ring which owing to strain would present considerable synthetic difficulties.

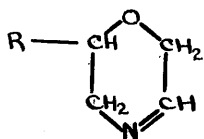
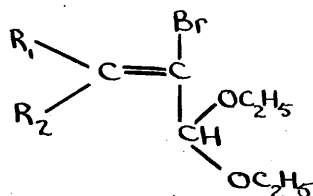
The first mechanism cannot be correct since the condensation of ethyl α -acetamido- β -ketobutyrate and ω -bromoacetophenone did not form an ether, therefore the correct reason for the formation of (LXII) from (LXI) is that in a reaction where the possibility exists of forming either a four or six-membered ring, the inherent strain associated with four membered ring formation will prevent this reaction occurring, and lead to preferential six-membered ring formation.

An examination of these failures to condense difunctional intermediates into 1:4-oxazines indicates that while the elimination of water between a carbonyl and amino group via Schiff's base formation takes place readily, the formation of an ether, by elimination of hydrogen bromide is a slow reaction. In view of this fact, the use of an intermediate

in which a preformed ether linkage had been established, was examined. The sodium salt of ethanolamine (LXIV R = H)

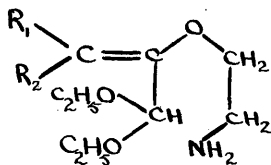
LXIVLXVLXVI

was condensed with bromoacetal to give 2-aminoethoxy-acetaldehyde diethylacetal (LXV R = H). When dissolved in concentrated hydrochloric acid 2-aminoethoxy-acetaldehyde hydrochloride (LXVI R = H) was formed, which on treatment with basic reagents yielded dihydro-1:4-oxazine (LXVII R = H) isolated as its picrate. Spectrophotometric determination

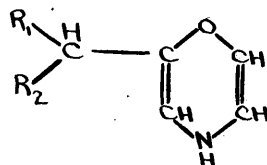
LXVIILXVIII

of the molecular weight (see appendix) was in good agreement with that required by dihydro-1:4-oxazine picrate. Similarly 1-amino-2-hydroxy-propane gave (2-amino-1-methyl-ethoxy)-acetaldehyde diethylacetal (LXV, $R = CH_3$) which formed with hydrochloric acid (2-amino-1-methyl-ethoxy)-acetaldehyde hydrochloride (LXVI, $R = CH_3$). Ring closure was achieved in a manner similar to the previous case to give 2-methyl-dihydro-1:4-oxazine (LXVII, $R = CH_3$).

In order to adapt this synthesis for the production of a fully unsaturated 1:4-oxazine, it is necessary to employ an α - β unsaturated bromoacetal of the type (LXVIII) where the double bond attached directly to the heterocyclic ring would remove the excess hydrogen atoms by forming as the intermediate (LXIX), which would rearrange to (LXX). This



LXIX

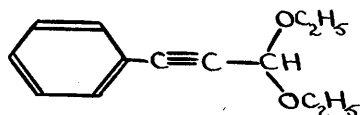


LXX

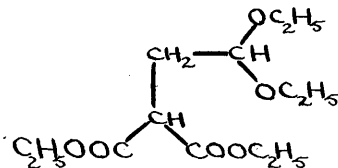
device has been successfully employed by Ramsay and Spring (30) in the synthesis of pyrazine hydroxamic acids.

Accordingly α -bromocinnamaldehyde diethylacetal (LXVIII, $R_1 = H$, $R_2 = C_6H_5$) was treated with the sodium salt of

ethanolamine to form (LXIX, $R_1 = H$, $R_2 = C_6H_5$) but this led to the formation of phenylacetylenealdehyde diethylacetal (LXXI). The ethanolamine derivative functioning merely as



LXXI



LXXII

as a basic reagent, removing the elements of hydrogen bromide. To prevent this side reaction, the acetal (LXVIII, $R_1 = R_2 = COOEt$) was synthesised from ethyl 1:1-diethoxy-propane-3:3-dicarboxylate (LXXII) (29), and employed in a similar manner. Condensation occurred with vigorous decomposition, but no crystalline product could be obtained from the reaction mixture. It was therefore concluded that although this route is capable of producing dihydro-1:4-oxazines, the introduction of a further double bond by the above method either forms unstable intermediates or gives (LXX) which is itself unstable.

These varied attempts to form fully unsaturated 1:4-oxazines by condensation reactions, although failing in this object, do suggest that the stability of the fully unsaturated 1:4-oxazine ring system is not comparable with

that of the aromatic heterocyclic ring systems for example pyrazine. To achieve their synthesis a new route which does not permit the synthesis in the final stage of a more stable alternative system will require to be found.

EXPERIMENTAL.Ethyl oximinoacetoacetate.

(cf. Adkins and Reeve, J. Amer. Chem. Soc., 60, 1328.)

Ethyl acetoacetate (750g.) was dissolved in glacial acetic acid (840 c.c.) and a solution of sodium nitrite (450g.) in water (1000 c.c.) added dropwise with stirring over one hour at 0°. Stirring was continued for a further hour, the solution diluted with water (3000 c.c.) and left overnight at room temperature. The solution was extracted with ether, the ether removed, and ethyl oximinoacetoacetate distilled under vacuum at 132°/7mm. The distillate (650g.) solidified to a colourless solid, which crystallised from toluene m.p. 58°.

Ethyl α -amino- β -ketobutyrate hydrochloride.

(cf. Gabriel and Posner, Ber., 1894, 27, 1141.)

Ethyl oximinoacetoacetate (9.0g.) was added in small portions over 15 minutes to a solution of stannous chloride (27g.) in concentrated hydrochloric acid (45 c.c.) at 0°. Tin (9.0g.) was then added, the mixture heated to 90° for ten minutes, diluted to 1000 c.c. with water and saturated with hydrogen sulphide till the solution was free of tin salts. After filtering, the solution was evaporated to dryness under reduced pressure (below 50°), the residue extracted with dry ethanol (50 c.c.) and filtered. After removing the solvent from the filtrate, the residue was crystallised from dry ethanol/

ether giving ethyl- α -amino- β -ketobutyrate hydrochloride as practically colourless prisms m.p. 95° . Yield 7.0g; 70% of theory. The product is highly hygroscopic.

α -Bromophenylacetyl bromide.

(Fourneau and Nicolitsch Bull. Soc. Chim. 43, 1239 (1928)).

Phenylacetyl chloride was obtained from phenylacetic acid and thionyl chloride in 83% yield as a light yellow oil b.p. $112^{\circ}/26$ mm. A mixture of the acid chloride (100g.) and bromine (130g.) was heated on an oil bath at $140-150^{\circ}$ for two hours and the product distilled under reduced pressure to give α -bromophenylacetyl bromide as a pale yellow oil b.p. $151^{\circ}/32$ mm. in 94% yield.

Ethyl α -(α' -bromophenylacetamido)- β -ketobutyrate.

A stirred suspension of ethyl α -amino- β -ketobutyrate hydrochloride (7.0g.) in dry chloroform (100 c.c.), to which was added a solution of α -bromophenylacetyl bromide (10.6g.) in dry chloroform (50 c.c.) was cooled to 0° and treated with N-methyl-morpholine (7.7 g.) in dry chloroform (25 c.c.), added dropwise during 30 minutes; the reaction mixture was stirred for 1 hour at 0° , then washed successively with water, dilute hydrochloric acid, saturated sodium hydrogen carbonate solution, and water, dried (sodium sulphate) and the chloroform removed under reduced pressure. The residue, which solidified, was crystallised from light petroleum (b.p. $100-20^{\circ}$) from which ethyl α -(α' -bromophenylacetamido)- β -ketobutyrate (10.0g.) separated as colourless prisms m.p. $68-70^{\circ}$.

Found: C,49.2; H,4.7; N,4.1%

$C_{14}H_{16}O_4N$ requires: C,49.1; H,4.7; N,4.1%

Ethyl 5-hydroxy-2-methyl-6-phenyl-1:4-oxazine -3-carboxylate.

A solution of ethyl α -(α' -bromophenylacetamido)- β -ketobutyrate (4.0g.) in dry ethanol (20 c.c.) was added at 0° to a solution of sodium ethoxide, from sodium (0.35g.) and ethanol (10 c.c.). After leaving overnight at 15°, the solvent was removed under reduced pressure and the residue extracted with boiling benzene (3x25 c.c.). This solution was chromatographed giving as a separate fraction ethyl 5-hydroxy-2-methyl-6-phenyl-1:4-oxazine-3-carboxylate (0.64g.) which separated as colourless needles from light petroleum (b.p.40-60°) m.p. 102°.

Found: C,64.1; H,5.5; N,5.6%

$C_{14}H_{15}O_4N$ requires: C,64.4; H,5.8; N,5.4%

Light absorption. (ethanol)

Maximum at 2820A ($\epsilon_{max} = 6,270$)

5-Hydroxy-2-methyl-6-phenyl-1:4-oxazine-3-carboxylic acid.

A suspension of ethyl 5-hydroxy-2-methyl-6-phenyl-1:4-oxazine-3-carboxylate (300mg.) in aqueous sodium hydroxide (15 c.c. of 0.1N) was shaken at 15°. After sixteen hours when solution was complete, the mixture was acidified to pH 4 with hydrochloric acid and evaporated to half bulk under reduced pressure. After cooling to 0°, the crystalline solid was separated, washed with ethanol and dried. 5-Hydroxy-2-methyl-6-phenyl-1:4-oxazine-3-carboxylic acid separates from aqueous methanol as colourless

prisms m.p. 200° (decomp.).

Found: C, 62.1; H, 4.5; N, 6.3%

$C_{12}H_{11}O_4N$ requires: C, 61.8; H, 4.8; N, 6.0%.

Light Absorption (Ethanol).

Maxima at 2320 Å ($\epsilon_{\max}=8,900$).

and 2820 Å ($\epsilon_{\max}=7,220$).

5-Hydroxy-2-methyl-6-phenyl-1:4-oxazine.

5-Hydroxy-2-methyl-6-phenyl-1:4-oxazine-3-carboxylic acid (150 mg.) was kept at 230° for 15 minutes at atmospheric pressure. The product was sublimed at 100°/10⁻¹ mm. Crystallisation from light petroleum (b.p. 40-60°) gave 5-hydroxy-2-methyl-6-phenyl-1:4-oxazine (10 mg.) as colourless prismatic nodules m.p. 82°.

Found N, 7.4%.

$C_{11}H_{11}O_2N$ requires: N, 7.4%.

Ethyl benzoylacetate.

This ester was obtained from ethyl acetoacetate (267g.) and ethyl benzoate (600g.) according to the method of Organic Synthesis Vol.23, 35. The yield (200g.) b.p. 130-5°/3 mm. was 52% of theoretical.

Ethyl β -keto- α -oximino- β -phenyl-propionate.

(cf. Forsyth and Pyman, J. (1925) 573).

Into a three necked flask equipped with stirrer, dropping funnel and thermometer was placed ethyl benzoylacetate (50.0g.) and glacial acetic acid (60 c.c.). With cooling to 0° sodium nitrite (30g.) in water (60 c.c.) was added dropwise over half an hour, when the solution solidified. Water (50 c.c.)

was added, the suspension stirred for two hours, collected and washed with water. Crystallisation from a mixture of benzene/light petroleum (b.p. 40-60°) gave ethyl β -keto- α -oximino- β -phenyl-propionate (quantitative yield) as colourless needles m.p. 115-7°.

Found: C, 59.5; H, 4.8; N, 6.4%.

Calc. for $C_{11}H_{11}O_4N$: C, 59.7; H, 5.0; N, 6.3%

Ethyl α -amino- β -keto- β -phenyl-propionate Hydrochloride.

(Forsyth and Pyman J. 1925, 573).

Ethyl β -keto- α -oximino- β -phenyl-propionate (25g.) was added portionwise over one hour to a stirred solution of stannous chloride (54g.) in concentrated hydrochloric acid (90 c.c.) cooled to 0°. Tin (10g.) was added and the solution heated to 90° for fifteen minutes then added to water (3,000 c.c.). The solution was saturated with hydrogen sulphide until free from tin salts, filtered, and the filtrate evaporated under reduced pressure (below 50°) to dryness. The residue was extracted with hot chloroform (3x100 c.c.). Removal of the solvent gave ethyl α -amino β -keto- β -phenyl-propionate hydrochloride as a colourless very hygroscopic solid. Yield(10g.).

Ethyl α -bromoacetamido- β -keto- β -phenyl-propionate.

Ethyl α -amino- β -keto- β -phenyl-propionate hydrochloride (2.1g.) was suspended in chloroform (50 c.c.) and cooled to 0°. With stirring bromoacetyl chloride (1.4g.) in chloroform (25c.c.) was added. N-methylmorpholine (2.0g.) in chloroform (25c.c.) was then added dropwise during fifteen minutes.

The chloroform solution was filtered, washed successively with dilute hydrochloric acid, saturated solution of sodium hydrogen carbonate and water, then dried (sodium sulphate). Removal of the solvent gave ethyl- α -bromoacetamido- β -keto- β -phenyl-propionate (2.0g.) which crystallised from light petroleum (b.p. 40-60°) as colourless prisms m.p. 71°.

Found: C, 47.8; H, 4.5; N, 4.6%.

$C_{13}H_{14}O_4NBr$ requires: C, 47.6; H, 4.3; N, 4.3%

Light absorption. (ethanol).

Maximum at 2,500 A ($\epsilon_{max}=13,440$).

Ethyl 5-hydroxy-2-phenyl-1:4-oxazine-3-carboxylate.

Ethyl α -bromoacetamido- β -keto- β -phenyl-propionate (2.0g.) was dissolved in dry ethanol (5 c.c.) and treated with sodium ethoxide, from sodium (0.16g.) and ethanol (15 c.c.) at 0°. On standing overnight ethyl 5-hydroxy-2-phenyl-1:4-oxazine-3-carboxylate (0.85g.) separated. It crystallised from light petroleum (b.p. 60-80°) as colourless needles m.p. 120°.

Found: C, 63.3; H, 5.4; N, 5.4%.

$C_{13}H_{13}O_4N$ requires: C, 63.1; H, 5.3; N, 5.7%.

Light absorption (ethanol).

Maxima at 2,220 A ($\epsilon_{max}=12,400$).

and 3,050 A ($\epsilon_{max}=9,580$).

5-Hydroxy-2-phenyl-1:4-oxazine-3-carboxylic Acid.

A suspension of ethyl 5-hydroxy-2-phenyl-1:4-oxazine-3-carboxylate (500 mg.) was shaken for 15 hours with sodium hydroxide solution (40c.c. of 0.1 N). The small residue was

removed and the filtrate acidified to pH4. The crystalline solid, 5-hydroxy-2-phenyl-1:4-oxazine-3-carboxylic acid (250 mg), was separated and crystallised from methanol as colourless needles m.p. 214-16° (decomp.)

Found: C, 60.2; H, 3.9; N, 6.4%.

$C_{11}H_9O_4N$ requires: C, 60.3; H, 4.1; N, 6.4%.

Light absorption (ethanol).

Maxima at 2,180 Å ($\epsilon_{max} = 10,890$).

and 3,030 Å ($\epsilon_{max} = 9,200$).

5-Hydroxy-2-phenyl-1:4-oxazine.

5-Hydroxy-2-phenyl-1:4-oxazine-3-carboxylic acid (250 mg.) was kept at 230° for ten minutes when evolution of carbon dioxide ceased. The crystalline residue was sublimed at 120°/10 mm. Crystallisation from benzene gave 5-hydroxy-2-phenyl-1:4-oxazine (100 mg.) as colourless plates m.p. 182°.

Found: C, 69.1; H, 5.5; N, 7.8%

$C_{10}H_9O_2N$ requires: C, 68.6; H, 5.2; N, 8.0%

Light absorption. (ethanol).

Maxima at 2,180 Å ($\epsilon_{max} = 8,530$)

and 3,050 Å ($\epsilon_{max} = 13,640$)

α-Bromopropionyl chloride.

(Weinig Ann., 280, 247. Auwers and Bernhardt Ber. 24, 2219).

A mixture of propionic acid (136g.) and red phosphorus (10g.) was treated with bromine (600g.) added dropwise over four hours at 90°. The mixture was then distilled under reduced pressure giving two main fractions (a) b.p. 40-60°/5-10 m.m. and (b) 90-100°/10 mm.

Fraction (b) α -bromopropionic acid (65g.) was refluxed on a steam bath with a 10% excess of thionyl chloride. Fractional distillation of the products gave α -bromopropionyl chloride as a light yellow oil b.p. 135^o/760 mm. Yield 80%

Ethyl α -(α' -bromopropionamido)- β -keto- β -phenyl-propionate.

A stirred suspension of ethyl α -amino- β -keto- β -phenyl-propionate hydrochloride (12.9g.) in dry chloroform (150 c.c.) to which was added a solution of α -bromopropionyl chloride (9.2g.) in dry chloroform (50 c.c.) was cooled to 0^o and treated with N-methyl-morpholine (10.4g.) in dry chloroform (50 c.c.) added dropwise during one hour; the reaction mixture was stirred for one hour at 0^o, then washed successively with water, dilute hydrochloric acid, saturated sodium hydrogen carbonate solution, and water, dried (sodium sulphate), and the chloroform removed under reduced pressure. The residue which solidified gave ethyl α -(α' -bromopropionamido)- β -keto- β -phenyl-propionate (8.0g) which separated from a mixture of chloroform/light petrol (b.p. 60-80^o) as colourless needles m.p. 54^o.

Found: C, 49.4; H, 4.7; N, 4.1%.

$\begin{matrix} \text{C} & \text{H} & \text{O} & \text{NBr} \\ 14 & 16 & 4 & \end{matrix}$ requires: C, 49.1; H, 4.7; N, 4.1%.

Light Absorption. (ethanol).

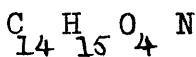
Maximum at 2,500 A $\epsilon_{\text{max}} = 7,310$.

Ethyl 5-hydroxy-6-methyl-2-phenyl-1:4-oxazine-3-carboxylate.

To ethyl α -(α' -bromopropionamido)- β -keto- β -phenyl-propionate (1.0g.) dissolved in ethanol (5.0 c.c.) was added at 0^o a solution of sodium ethoxide, from sodium (0.08g.) and ethanol (5.0 c.c.). After standing overnight, the solvent was removed under reduced pressure and the residue

refluxed with light petroleum (b.p. 60-80°, 3x10 c.c.). Evaporation of the light petroleum gave ethyl 5-hydroxy-6-methyl-2-phenyl-1:4-oxazine-3-carboxylate (50 mg.) as colourless needles m.p. 126°.

Found: C,64.3; H,5.3; N,5.5%.



requires: C,64.4; H,5.8; N,5.4%.

Light absorption. (ethanol).

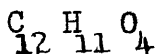
Maxima at 2190 A ($\epsilon_{\text{max}} = 12,960$).

and 3060 A ($\epsilon_{\text{max}} = 10,100$).

5-Hydroxy-6-methyl-2-phenyl-1:4-oxazine-3-carboxylic acid.

Ethyl 5-hydroxy-6-methyl-2-phenyl-1:4-oxazine-3-carboxylate (90 mg.) was suspended in aqueous sodium hydroxide solution (25 c.c. of 0.1 N) and shaken for four days. The suspension was then heated to 60° for five hours when solution was complete. Cooling and acidification at pH4 gave a crystalline solid (50 mg.) of 5-hydroxy-6-methyl-2-phenyl-1:4-oxazine-3-carboxylic acid which separated from aqueous methanol as clusters of colourless prisms m.p. 212° (decomp.)

Found: C,61.9; H,4.8; N,5.8%



requires: C,61.8; H,4.8; N,6.0%.

Light absorption (ethanol).

Maxima at 2170 A ($\epsilon_{\text{max}} = 11,880$).

and 3070 A ($\epsilon_{\text{max}} = 9,670$).

5-Hydroxy-6-methyl-2-phenyl-1:4-oxazine.

5-Hydroxy-6-methyl-2-phenyl-1:4-oxazine-3-carboxylic acid (50mg.) was kept at 250° for ten minutes when evolution

of carbon dioxide ceased. The residue was sublimed at $120^{\circ}/10^{-2}$ mm. Crystallisation from benzene/light petroleum (b.p. $40-60^{\circ}$) gave 5-hydroxy-6-methyl-2-phenyl-1:4-oxazine (8 mg.) as colourless needles m.p. 143° .

Found: C, 69.4; H, 5.8; N, 7.7%.

$C_{11}H_{11}O_2N$ requires: C, 69.8; H, 5.9; N, 7.4%.

Light absorption (ethanol).

Maxima at 2200 Å ($\epsilon_{\max}=8,200$)

and 3040 Å ($\epsilon_{\max}=13,060$).

Ethyl α -(α' -bromophenylacetamido)- β -keto- β -phenyl-propionate

A stirred suspension of ethyl α -amino- β -keto- β -phenyl-propionate hydrochloride (2.4g.) in dry chloroform (50 c.c.), to which was added a solution of α -bromophenylacetyl bromide (2.78g.) in dry chloroform (25 c.c.) was cooled to 0° and treated with N-methyl-morpholine (2.02g.) in dry chloroform (25 c.c.) added dropwise during one hour; the reaction mixture was stirred for one hour at 0° , then washed successively with water, dilute hydrochloric acid, saturated sodium hydrogen carbonate, and water, dried (sodium sulphate) and the chloroform removed under reduced pressure. The residue which solidified gave ethyl α -(α' -bromophenylacetamido)- β -keto- β -phenyl-propionate (3.6g.) which separated as rosettes of colourless needles from a mixture of chloroform/light petroleum (b.p. $60-80^{\circ}$) m.p. 102° .

Found: C, 56.8; H, 4.2; N, 3.6%.

$C_{19}H_{18}O_4NBr$ requires: C, 56.4; H, 4.5; N, 3.5%.

Light Absorption. (ethanol).

Maximum at 2500 Å ($\epsilon_{\max}=14,950$).

Ethyl α -bromoacetamido- β -keto-butyrate.

This compound was prepared according to the method of Newbold, Spring, Sweeny (J. 1950, 909). Ethyl α -amino- β -keto-butyrate hydrochloride (14.2g.), condensed with bromoacetyl chloride (12.3g.), gave ethyl α -bromoacetamido- β -keto-butyrate (16.0g.) m.p. 99° after crystallisation from light petroleum b.p. ($60-80^{\circ}$).

Ethyl 5-hydroxy-2-methyl-1:4-oxazine-3-carboxylate.

Ethyl α -bromoacetamido- β -keto-butyrate (12.0g.) was dissolved in dry ethanol (75 c.c.) and treated with sodium ethoxide from sodium (1.2g.) and ethanol (20 c.c.). Ethyl 5-hydroxy-2-methyl-1:4-oxazine-3-carboxylate (6.0g.) m.p. 115° after crystallisation from light petroleum b.p. ($60-80^{\circ}$), was collected next day. Sweeny (J. 1950,909) quotes m.p. 112° .

Ethyl α -bromoacetoacetate.

(cf. Conrad, Ber., 29, 1044).

Ethyl acetoacetate (50g.) treated with bromine (62g.) gave ethyl α -bromoacetoacetate (31g.) b.p. $98^{\circ}/4$ mm.

Attempted condensation of ethyl α -bromoacetoacetate and Ethyl α -amino- β -keto-butyrate hydrochloride.

Ethyl α -amino- β -keto-butyrate hydrochloride (5.0g.) was dissolved in ethanol (10 c.c.) and ethyl α -bromoacetoacetate (5.8g.) added. Potassium acetate (2.3g.) was then added in the form of a fine powder. The mixture was shaken overnight. Filtration of the solid sodium chloride and removal of solvent gave ethyl 2:5-dimethyl-pyrazine-3:6-

dicarboxylate (2.0g.) crystallising from light petroleum (b.p. 40-60°) as feathery needles m.p. 86°.

Found: C, 56.3; H, 6.1; N, 10.8%.

Calc. for $C_{12}H_{16}O_4N_2$: C, 57.1; H, 6.4; N, 11.1%

Light absorption. (ethanol).

Maximum at 2880 A ($\epsilon_{max} = 11,600$).

Attempted condensation of bromoacetal and ethyl α -amino- β -ketobutyrate hydrochloride.

Ethyl α -amino- β -ketobutyrate hydrochloride (5.0g.) was dissolved in ethanol (10 c.c.) and bromoacetal (6.0g.) added. N-methyl-morpholine (4.7g.) was added dropwise and the solution shaken overnight. Removal of the precipitated solid and evaporation of the solvent gave ethyl 2:5-dimethyl-pyrazine-3:6-dicarboxylate (1.8g.) which crystallised from light petroleum b.p. (40-60°) m.p. 86°.

Ethyl α -acetamido- β -ketobutyrate.

(a) To a stirred suspension of ethyl α -amino- β -keto-butyrate hydrochloride (7.0g.) in dry chloroform (100 c.c.) was added dropwise acetyl chloride (3.04g.) in chloroform (25 c.c.). With cooling to 0°, N-methyl-morpholine (7.8g.) in chloroform (25 c.c.) was added over half an hour and the reaction mixture stirred for a further one hour. The solution, filtered from N-methyl-morpholine hydrochloride, was washed successively with water, dilute hydrochloric acid, saturated sodium hydrogen carbonate solution, and dried (sodium sulphate). Removal of the solvent gave a pale yellow oil which solidified on standing to a colourless solid m.p. 45-48° b.p. 118°/0.1mm.

Found: C,51.5; H,6.7%

Calc. for $C_8H_{13}O_4N$: C,51.3; H,7.0%

This substance gave a 2:4-dinitrophenylhydrazone crystallising from ethanol as yellow micro-needles m.p. 202° .

Found: C,46.0; H,4.6; N,18.1%

$C_{14}H_{17}O_7N_5$ requires: C,45.8; H,4.7; N,19.2%

(b) (cf. Wiley and Borum, J. Amer. Chem. Soc., 1948, 1666.)

Ethyl oximinoacetoacetate (30g.) in acetic anhydride (100 c.c.) was shaken for twelve hours with hydrogen at a pressure of 50 lbs. /sq.in. in the presence of palladium charcoal (8.0g.). Removal of the excess acetic anhydride and distillation of the residue gave ethyl α -acetamido β -keto-butyrate (26g.) b.p. $118^\circ/0.1\text{mm.}$ as a colourless oil solidifying to a white solid m.p. 48° .

This material gave a 2:4-dinitrophenylhydrazone m.p. 202° , undepressed in melting point on admixture with the previous specimen.

Condensation of ethyl α -bromoacetoacetate and ethyl α -acetamido β -ketobutyrate.

To sodium (0.615g.) dissolved in ethanol (20 c.c.) was added at 0° ethyl α -acetamido- β -ketobutyrate (5.0g.) in ethanol (10 c.c.), followed by ethyl α -bromoacetoacetate (5.6g.) which had been redistilled two days previously, dissolved in ethanol (10 c.c.). After ten minutes a vigorous reaction ensued, heat developed and a crystalline precipitate deposited. Removal of this precipitate after twenty

four hours gave sodium bromide (2.5g.) and a white colourless compound (1.9g.) crystallising from light petroleum (b.p. 60-80°) in long colourless needles m.p. 130°.

Found: C, 55.7; H, 6.3%.

Calculated for ethyl

succinoyl-succinate $C_{12}H_{16}O_6$ C, 56.2; H, 6.3%.

The substance gave a deep red ferric chloride colour.

1:4-Cyclohexadione. (cf. Meerwein Ann (1913) 398, 248).

Ethyl succinoyl-succinate (600 mg.) was heated with water (2 c.c.) in a sealed tube at 200° for half an hour. The water was removed and the residue, 1:4-cyclohexadione (200mg.), crystallised from light petroleum (b.p. 40-60°) as colourless needles m.p. 78°.

The diketone formed a bis-2:4-dinitrophenylhydrazone crystallising from benzene/ethanol as yellow micro-needles m.p. 236°.

Found: C, 45.4; H, 3.1; N, 23.6%.

$C_{18}H_{16}O_8N_8$ requires: C, 45.8; H, 3.4; N, 23.7%.

Ethyl 3-acetamido-2:5-diketo-5-phenyl-pentane-3-carboxylate.

To sodium (0.62g.) dissolved in dry ethanol (20c.c.) was added at room temperature ethyl α -acetamido- β -ketobutyrate (5.0g.) in ethanol (10c.c.). ω -Bromoacetophenone (5.3g.) prepared by the method of Organic, Syn. Vol. II, 480. dissolved in ethanol (20c.c.) was then added, and the mixture allowed to stand overnight. The deposit of sodium bromide was removed, and the solvents distilled under reduced pressure. The residual viscous oil was extracted with benzene and a

further quantity of sodium bromide discarded. Removal of the solvents gave ethyl-3-acetamido-2:5-diketo-5-phenyl-pentane-3-carboxylate (4.1g.) which was obtained from benzene/light petroleum (b.p.60-80°) as colourless prisms m.p. 120°.

Found: C,63.6; H,6.1; N,4.7%.

$C_{16}H_{19}O_5N$ requires: C,62.9; H,6.3; N,4.6%.

Light Absorption (ethanol).

Maximum at 2,240A ($\epsilon_{max.}=16,980$).

The compound forms a bis-2:4-dinitrophenylhydrazone crystallising from methanol as reddish-orange prisms m.p. 148°.

Found: C,49.9; H,4.1%.

$C_{28}H_{27}O_{11}N_9$ requires: C,50.5; H,4.1%.

3-Acetamido-2:5-diketo-5-phenyl-pentan-3-oic acid.

Ethyl 3-acetamido-2:5-diketo-5-phenyl-pentane-3-carboxylate (500 mg.) was shaken for six days with 5% sodium hydroxide solution (20 c.c.). After acidification with dilute hydrochloric acid and standing at 0° overnight 3-acetamido-2:5-diketo-5-phenyl-pentan-3-oic acid (200 mg.) deposited. Crystallisation from aqueous methanol gave the acid as long colourless needles m.p. 194°.

Found: C,60.8; H,5.5% Equivalent wt. 280

$C_{14}H_{15}O_5N$ requires: C,60.65; H,5.45% Equivalent wt. 277.

Action of sodium hydroxide on 3-acetamido-2:5-diketo-5-phenyl-pentan-3-oic Acid.

3-Acetamido-2:5-diketo-5-phenyl-pentan-3-oic acid (100 mg.) was refluxed in 5% sodium hydroxide solution (25c.c.)

Dihydro-1:4-oxazine.

2-Aminoethoxy-acetaldehyde hydrochloride (300mg.) was suspended in ethanol (20 c.c.) and 10% sodium hydroxide (20 c.c.) added. The solution was distilled, and the distillate (30 c.c.) collected. After acidification with hydrochloric acid, the solution was evaporated under reduced pressure to a small volume. Addition of ethanolic picric acid gave dihydro-1:4-oxazine crystallising from ethyl acetate as yellow prisms m.p. 157-9°.

Found: N, 17.5%

$C_{10}H_{10}O_8N_4$ requires: N, 17.8%

1-Amino-2-hydroxy-propane.

This substance was prepared according to the method of Levene and Walti, J. Biol. Chem., 1927, 71, 461. Propylene oxide (15g.) gave 1-amino-2-hydroxy-propane (12g.) b.p. 156-162°.

(2-Amino-1-methyl-ethoxy)-acetaldehyde diethylacetal.

Sodium (6.0g.) was dissolved in 1-amino-2-hydroxy-propane (25 c.c.) and the excess base removed by distillation at reduced pressure. To the residue was added bromoacetal (50g.) and the mixture shaken overnight. After filtration of the precipitated sodium bromide, the filtrate was distilled under reduced pressure giving (2-amino-1-methyl-ethoxy)-acetaldehyde diethylacetal (20g.) as a colourless oil b.p. 84-8°/10⁻² mm.

Found: C, 56.1; H, 10.5; N, 7.0%.

$C_9 H_{21} O_3 N$ requires: C, 56.5; H, 11.1; N, 7.3%.

Equivalent weight by titration Found 189.

Required 191.

(2-Amino-1-methyl-ethoxy)-acetaldehyde hydrochloride.

(2-Amino-1-methyl-ethoxy)-acetaldehyde-diethylacetal (5.0g.) was dissolved in hydrochloric acid/water 1:2 (25 c.c.) and left overnight. Evaporation of the water left (2-amino-1-methyl-ethoxy)-acetaldehyde hydrochloride (2.5g.) crystallising from ethyl acetate/ethanol as colourless prisms m.p. 132°.

Found: C, 38.7; H, 7.5; N, 9.0%.

$C_5 H_{12} O_2 NCl$ requires: C, 39.1; H, 7.9; N, 9.1%

2-Methyl-dihydro-1:4-oxazine.

(2-Amino-1-methyl-ethoxy)-acetaldehyde hydrochloride (500 mg.) was dissolved in ethanol (20c.c.) and potassium hydroxide (1.0g.) dissolved in ethanol (5c.c.) added. The precipitated salts were removed by filtration and the filtrate evaporated to small volume and extracted with ether (3x10 c.c.). The ether was removed and ethanolic picric acid added to residue 2-methyl-dihydro-1:4-oxazine picrate was obtained as small yellow needles from ethanol m.p. 188°.

Found: C, 40.4; H, 3.9%.

$C_{11} H_{12} O_8 N_4$ requires: C, 40.3; H, 3.7%.

α -Bromocinnamaldehyde diethylacetal.

α -Bromocinnamaldehyde was prepared according to the method of Straus, Ber., 49, 2876. To α -bromocinnamaldehyde (75g.) was added ethyl orthoformate (57g.), ethyl alcohol (61g.) and concentrated hydrochloric acid (0.25 c.c.). The mixture was refluxed for half an hour then distilled.

α -Bromocinnamaldehyde diethylacetal (110g.) was obtained as a colourless oil b.p. $158^{\circ}/12\text{mm}$.

Attempted condensation of α -bromocinnamaldehyde diethylacetal and ethanalamine.

Sodium (2.4g.) was dissolved in ethanalamine (30 c.c.) and the excess base distilled under reduced pressure. α -Bromocinnamaldehyde diethylacetal (28.5g.) was added to the residue and shaken overnight. After addition of dry ethanol (25 c.c.), the solution was refluxed for one hour. Removal of the ethanol and distillation under vacuum gave phenylacetylenealdehyde diethylacetal (15g.) b.p. $76^{\circ}/10^{-3}\text{mm}$.

This material gave a 2:4-dinitrophenylhydrazone crystallising from ethanol m.p. 192° .

Found: C, 58.4; H, 3.6; N, 18.1%

$\begin{matrix} \text{C}_{15} & \text{H}_{16} & \text{O}_4 & \text{N}_4 \end{matrix}$

requires: C, 58.1; H, 3.2; N, 18.0%

Ethyl 1:1-diethoxy-propane-3:3-dicarboxylate

(cf. Perkin, J., 1899, 14.)

To sodium (14.2g.) dissolved in ethanol (200 c.c.) was added ethyl malonate (100g.) and bromoacetal (80g.)

The solution was heated in an autoclave to 150° for six hours, the precipitated sodium bromide removed by filtration, and the residue distilled under reduced pressure. Ethyl 1:1-diethoxy-propane-3:3-dicarboxylate (50g.) was obtained as a colourless oil b.p. 132-4°/4mm. in 40% yield.

The substance yielded a 2:4-dinitrophenylhydrazone crystallising from ethanol as yellow plates m.p. 90°.

Found: C,46.7; H,5.0; N,14.4%

$C_{15}H_{18}O_8N_4$ requires: C,47.1; H,4.8; N,14.7%

Ethyl 2-bromo-1:1-diethoxy-prop-2:3-ene-3:3-dicarboxylate.

Ethyl-1:1-diethoxy-propane-3:3-dicarboxylate (15g.) in carbon tetrachloride (100 c.c.) was refluxed and bromine (17.4g.) in carbon tetrachloride (10 c.c.) added dropwise with stirring over one hour. The solution was washed successively with sodium carbonate solution and water, dried (sodium sulphate), and the solvent removed. Distillation gave ethyl 2-bromo-1:1-diethoxy-prop-2:3-ene-3:3-dicarboxylate (5.0g.) as a colourless oil b.p. 148°/4mm.

Found: C,45.1; H,5.6; Br,22.2%

$C_{13}H_{21}O_6Br$ requires: C,44.3; H,6.0; Br,22.6%

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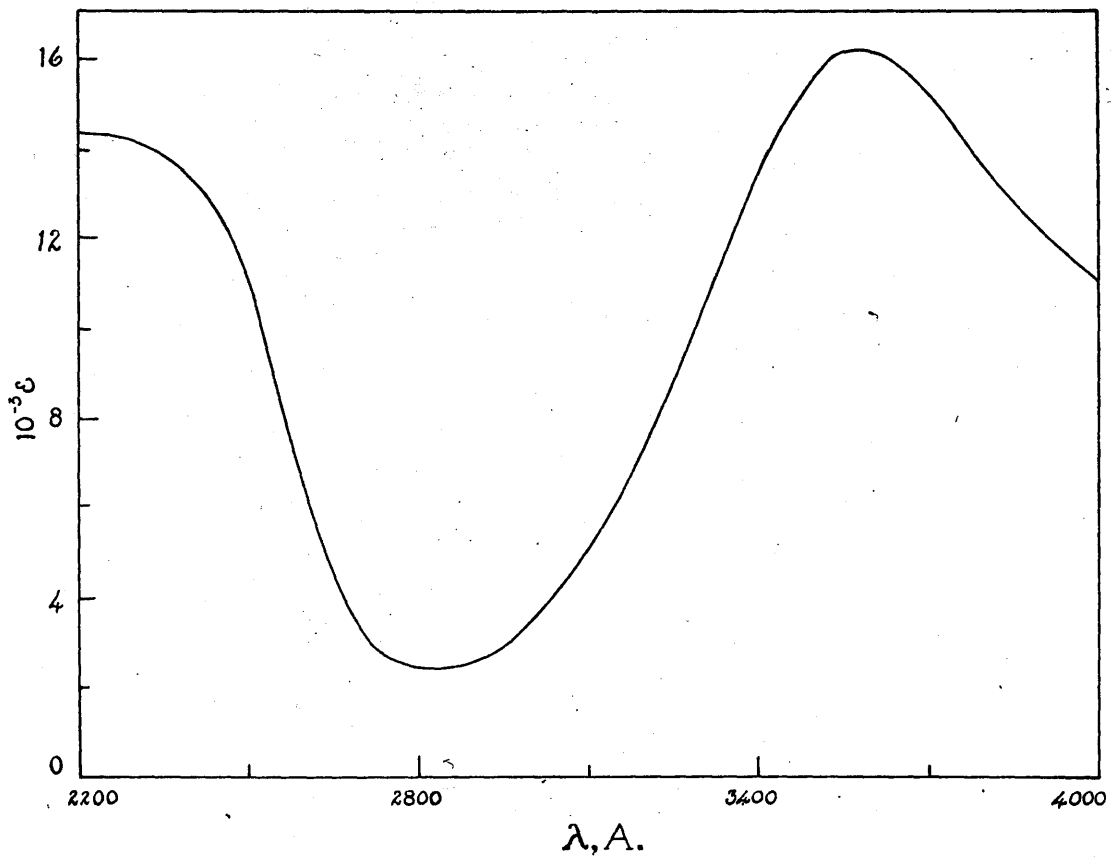
A P P E N D I X.

...	1.100	0.518
...	1.090	0.490
...	1.422	0.500
...	1.227	0.497
...	1.100	0.418

Ethanollic solutions of picric acid exhibit high intensity absorption between 2000-2500 A and between 3500-4000 A (fig.I). Few colourless organic compounds show absorption of appreciable intensity between 3500-4000 A. These facts led to the investigation of the possibility of determining molecular weights of bases and hydrocarbons by the measurement of the intensity of light absorption of their picrates within the region 3500-4000 A. By using a Unicam photoelectric spectrophotometer of the compensating cell type, the light absorption characteristics of a number of picrates were examined. Table I lists the observed intensity of absorption of these picrates at 3800 A, a wave length chosen from the high intensity band of picric acid (3400-4000 A) at a point remote from the region 2000-3500 A in which high intensity absorption is frequently observed in colourless compounds. This choice is to a certain extent arbitrary, similar results to those described being obtained by measurement of the intensity of absorption at other wave lengths within the high intensity band of picric acid.

Table I.

Picrate.	c(mg./100 ml.)	$\log \left(\frac{I_0}{I} \right)_{3800}$	ϵ_{3800} .
Ethanolamine	1.109	0.512	13,390
Piperidine	1.090	0.469	13,510
Morpholine	1.462	0.620	13,400
2-Amino-pyrazine	1.137	0.472	13,450
N-Ethyl aniline	1.196	0.459	13,430
Picric Acid	1.107	0.650	13,450



Picric Acid in ethanol.

Fig. 1.

Apart from the weighing operation, the accuracy of the determination depends on the high sensitivity of the photoelectric spectrophotometer, the value of $\log(I_0/I)$ being repeatedly reproducible with an accuracy of $\pm 1.0\%$. The average value of ϵ_{3800} for the five picrates listed in Table I is 13,440, in excellent agreement with the observed value for picric acid. As required by the constant value for ϵ_{3800} it was found that the bases corresponding to the picrates listed in Table I show no appreciable absorption at 3800 A.

By assuming the average value 13,440 for ϵ_{3800} , the molecular weights of a number of picrates were determined by the spectrophotometric method, the relationship $M = 13,440 C, n/\log I_0/I$ being used where n is the molar ratio of picric acid: base or picric acid; hydrocarbon in the picrate and C is measured in g/l. The values obtained for a number of mono-picrates, matched quartz cells of 1 cm. thickness being used, are shown in Table II, whole number atomic weights were employed.

Table II /

Table 11

Picrate.	c(mg./100ml.)	$\log\left(\frac{I_0}{I}\right)_{3800}$	M found	M calc.	Error%
Acenaphthene	2.801	0.990	380	383	-0.8
1-Bromonaphthalene	1.353	0.420	433	436	-0.7
2-Methoxynaphthalene	1.161	0.401	389	387	0.5
2:5-Dichloroaniline*	1.421	0.485	394	391	0.8
Quinoline	1.319	0.491	361	358	0.8
8-Hydroxyquinoline	1.388	0.498	375	374	0.3
Adenine	1.361	0.500	366	364	0.5
2-Methyl-pyridine	1.165	0.490	320	322	-0.6
N-methyl-morpholine	1.300	0.525	333	330	0.9
4-Methyl-glyoxaline	1.959	0.850	310	311	-0.3
Carbazole	1.327	0.443	403	396	1.8
Cocaine	2.159	0.550	528	532	-0.8
Narcotine	2.938	0.615	642	642	0.0
Strychnine	2.481	0.598	558	563	-0.9
Vomicine	2.530	0.558	609	609	0.0

* 2:5-Dichloroaniline picrate separates from water as needles m.p. 86° . (Found: C, 37.0; H, 2.3; N, 13.9%
 $C_6H_5NCl_2, C_6H_3O_7N_3$ requires: C, 36.8; H, 2.1; N, 14.3%)

A determination of the molecular weight of cordycepin, a metabolic product isolated from the cultures of the mould *cordyceps militaris* (LINN) Link, was carried out using its monopicate with the following result:-

	c(mg./100ml.)	$\log\left(\frac{I_0}{I}\right)$	M
Cordycepin picrate	1.036	0.288	483

This value corresponds to a molecular weight of 254 for cordycepin which is in close agreement both with that of 247 ± 10 obtained by the X-ray crystallographic method, and with that of 251 required by $C_{10}H_{13}O_3N_5$ subsequently shown by analytical and degradative examination to be the molecular formula of cordycepin (Cunningham, Ph.D. Thesis 1951.)

The accuracy of this method is dependant upon the exact determination of the molecular extinction coefficient at the chosen wave length. A small error in the wavelength determination mechanism of the instrument employed may lead to an appreciable error in the value of ϵ . Experience has shown that such variations can occur (the value $\epsilon_{3800} = 13,200$) was obtained as the average for 12 picrates examined in a second spectrophotometer similar to the one described above. For this reason it is desirable that the spectrophotometer employed for molecular weight determination should be standardised against a number of picrates of known molecular weight, matched quartz cells being used in the same aspect .