DEAMINOCOLCHINOL METHYL ETHER,

A DEGRADATION PRODUCT OF

COLCHICINE,

And Some Related Topics.

A

THESIS

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Norman Barton, B.Sc.

University of Glasgow,

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ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 – 1346

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PART I. INTRODUCTION.

I.

From the seeds and corms of the meadow saffron (Colchicum autumnale L. (Liliaceae)), which is popularly but erroneously known as the autumn crocus, the substance COLCHICINE is obtained in small quantities. It is not confined to the meadow saffron, but also occurs in other Colchicum and Liliaceous species. Like most other nitrogenous compounds obtained from plant tissues, colchicine shows pronounced physiological effects, and it is probably on account of this that it is included amongst the alkaloids, although it is non-basic, and appears to have a structure which, so far as it is known, is unlike that of any other known alkaloid.

Commercially colchicine is supplied as a yellow powder of melting point 143 - 147°. Crystallization from water gives a trihydrate, whilst from ethyl acetate pale yellow needles, of melting point 155 - 157°, are obtained. It is miscible in all proportions with cold water, aqueous alcohol, or chloroform, but is less soluble in warm water or dry alcohol. With chloroform two crystalline compounds are formed, containing respectively one and two molecules of chloroform to one molecule of colchicine. These decompose at 100° or in water at 50°.

A convenient method of purifying colchicine has recently been described[1]. A chloroform solution of colchicine is passed through a column of alumina, and it is claimed that in this way a product is obtained which crystallizes from ethyl acetate as pale yellow needles, melting point 155°, or from benzene as pale yellow prisms, melting point 140°, containing one molecule of benzene of crystallization.

When colchicine, $C_{22}H_{25}O_6N$, is heated with dilute sulphuric acid or dilute hydrochloric acid, it is hydrolysed to give colchiceine, $C_{21}H_{23}O_6N$, one methoxyl group being converted to a hydroxyl group. This substance crystallizes from water with half a molecule of water of crystallization, and the hemihydrate has a melting point of 139 - 141° in an open tube, or 156 - 162° in a closed tube. The anhydrous substance softens at 161°, and the melt is clear by 172°. Colchiceine is soluble in hot water, alcohol, and chloroform.

Colchicine and colchiceine produce similar physiological effects, but the former is more active and more toxic than the latter, being in fact more toxic than most of the known alkaloids. Nevertheless it has been frequently used, generally as the salicylate, in the treatment of gout; it is said, in fact, that a weak infusion of sliced roots of the meadow saffron is the traditional gypsy remedy for dropsy and gout.

Dustin[2] and Lits[3] showed that colchicine has a striking effect on the dividing cell, for when colchicine is present, cell division, or mitosis, is arrested. This remarkable behaviour at once suggests that colchicine might be of value for the inhibition of tumour growth, and such inhibition has in fact been observed in a number of cases. Thus Amoroso[4] found that it induces regression of tumours in mice, and is effective in treating spontaneous tumours in dogs. Ludford[5] examined the biological effect of colchicine. He confirmed the arrest of cell-division, but, like Dustin, reported that the action was not specific for cancer cells, extending also to normal cells, a fact which reduces its value as a potential agent in the treatment of cancer. Furthermore, on account of the high toxicity of colchicine, the amount necessary to produce an effect on the growth of a tumour closely approaches the lethal dose, and, moreover, a given dose is much more toxic to animals bearing tumours than to normal animals[6]. It is thus clear that colchicine does not at present qualify as a tumour inhibitor. It has, nevertheless, great interest and potentialities, not only in this, but also in certain other directions.

Colchicine inhibits mitosis by interfering, in some way not understood, with the formation of the spindle at the metaphase. In consequence the chromosomes, though they have

divided in the usual way, cannot move to the ends of the spindle as they normally do at the anaphase. If the cell recovers from the colchicine treatment there is a likelihood that resumed mitosis will produce daughter cells containing a multiple number of chromosomes, thereby introducing new characteristics.

The effect is quite specific. Unlike many other agents which have been used to induce this phenomenon of polyploidy, colchicine does not interfere with the other life processes of the chromosomes[7]. In this lies its particular value.

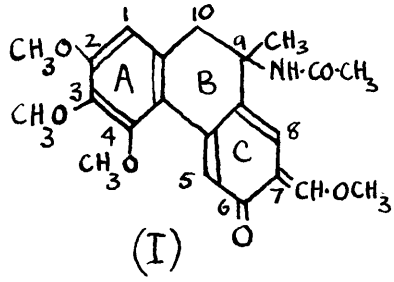
The possibilities thus opened up have been extensively investigated in plants, and some cases of increased size and rate of growth are reported. Interesting and useful developments in this field may be confidently expected.

Therefore, in spite of the fact that other substances, of widely differing chemical structure, have comparable effects on cell-division, colchicine has acquired considerable importance. But incomplete knowledge of its structure is a barrier to complete understanding and exploitation of its biological effects. Structural investigations, begun long before these notable biological properties were recognised, have proved of great chemical interest, and a brief account of these up to 1944 will be found in the following pages.

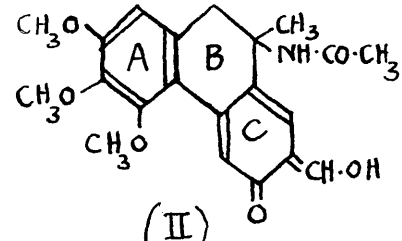
II.

The first sustained chemical studies appear to have been made by Zeisel during the period 1883-1913. These studies were of wide scope, and provided the basis for subsequent advances. Zeisel proposed[8] that colchicine should be formulated as $(CH_3O)_3C_{15}H_9(COOCH_3)(NH.COCH_3)$.

A. Windaus then took up the problem, and his brilliant investigations culminated in a paper published in 1924[9] in which the formula (I) was proposed for colchicine, and (II) for colchiceine, with the proviso that the positions of the substituents in ring C might have to be interchanged, since the available evidence did not distinguish between the alternatives (e.g. between (II) and (III))



(I)



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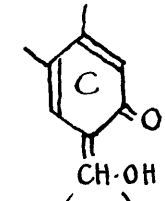
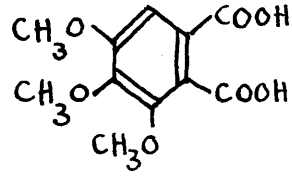


(III)

Windaus's researches will now be summarised, and their implications discussed, taking rings A, C, and B of his formula for colchicine in turn.

III.

The structure of ring A is well established. When colchiceine, the first hydrolysis product of colchicine, is further hydrolysed by treatment with stronger acid, an acetyl group is removed, and the free amine, trimethylcolchicinic acid, results. Windaus found that if colchicine, colchiceine, or trimethylcolchicinic acid is oxidised with hot potassium permanganate, 3:4:5-trimethoxyphthallic acid (IV) is obtained, proving that the methoxyl groups are vicinal.



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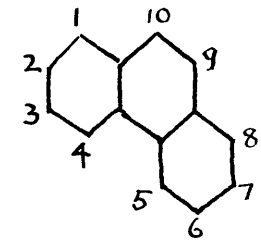
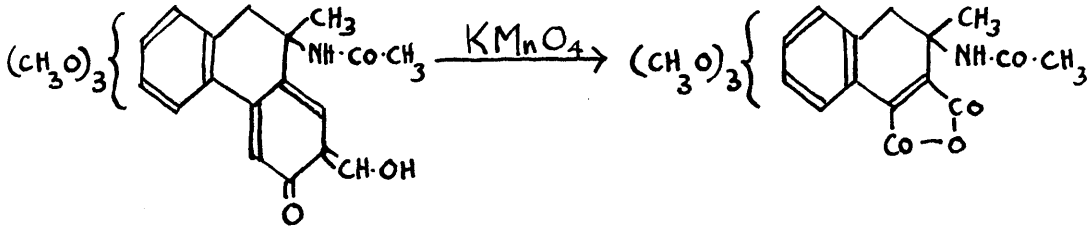


(V)

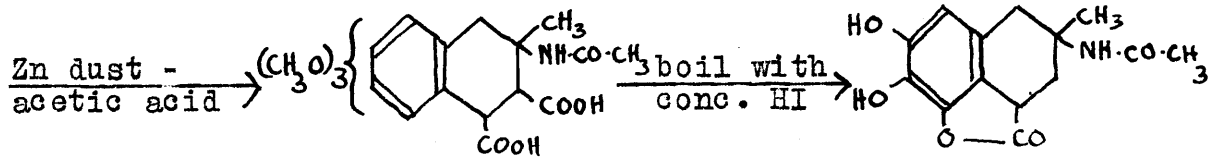
The original compounds are regarded as derived from a phenanthrene structure (V), and the product (IV) indicates either a 1:2:3- or a 2:3:4-trimethoxylated pattern. A decision between the two was reached as follows. N-Benzoyltrimethylcolchicinic acid on oxidation with potassium permanganate gave an anhydride considered to be a naphthalene derivative, and this in turn, when the anhydride ring had been opened by reduction, and the methoxyl groups hydrolysed to hydroxyl groups, yielded a lactone. It was considered

that the lactone was formed by interaction of *peri* substituents, and the whole process was represented thus:-



N-Benzoyltrimethyl-colchicinic acid

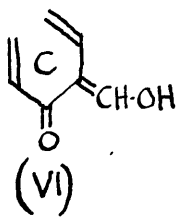
N-Benzoylcolchinic acid anhydride



Accordingly the methoxyl groups were assigned to the 2:3:4 positions.

IV.

Zeisel attributed the weak acidity of colchiceine to a carboxyl group, but Windaus's proposal for ring C differs markedly from this, in that the acidity is attributed to a hydroxymethylene ketone grouping (eg. VI). The evidence



(VI)

offered in support of this structure is of great interest.

In the first place colchiceine, unlike colchicine, gives a green colour with ferric chloride solution. This reaction, typically shown by phenols and enols, but not by carboxylic acids, immediately casts doubt on Zeisel's carboxylic acid formulation. Moreover, like the ortho hydroxy aldehydes of the aromatic series, colchiceine and some of its derivatives give yellow solutions in acids and alkalies.

Trimethylcolchicinic acid, the hydrolysis product of colchiceine, forms a dibenzoate, which does not give a green colour with ferric chloride solution. Apparently one benzoyl group is more easily detached than the other, for by preferential hydrolysis the ability to give a colour with ferric chloride is restored; the resulting compound is therefore designated N-benzoyl trimethylcolchicinic acid. More important, trimethylcolchicinic acid also forms two isomeric dibenzenesulphonyl derivatives, which on hydrolysis both yield the same monobenzenesulphonyl derivative, in which the surviving benzenesulpho group is attached to the nitrogen atom. If trimethylcolchicinic acid is a carboxylic acid

(Zeisel), benzenesulphonic acid must give a mixed acid anhydride, and the appearance of isomerides is unintelligible. Neither can the facts be explained by supposing that the substance is a phenol. On the other hand, Windaus's hydroxymethylene structure might be expected to form cis and trans isomers about the double bond (compare for example Wislicenus and Bindemann[10]). There appears to be no proof that the two dibenzenesulphonyl derivatives are true stereoisomers, and not structural isomers or merely polymorphs, but if they are in fact stereoisomers, their formation must be held to support Windaus's proposal.

Colchiceine treated with bromine water or bromine and acetic acid gives a brominated carboxylic acid with the same number of carbon atoms as colchiceine. This might be explained either by the reaction

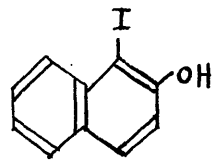
$$= CH.OH \longrightarrow -COOH$$

or by assuming that colchiceine here reacts in the <u>ortho</u> hydroxyaldehyde form, when

$$-CHO \longrightarrow -COOH.$$

The most important single reaction which Windaus recorded as evidence for the hydroxymethylene structure is the action of iodine and potassium hydroxide on colchiceine. In this reaction colchiceine, $C_{21}H_{23}O_6N$, is converted to N-acetyliodocolchinol, $C_{20}H_{22}O_5NI$, in which, Windaus considered, iodine replaces -CHO, and ring C is aromatic.

Experiments carried out by Windaus and Schiele[11] with aromatic ortho and para hydroxyaldehydes demonstrated that these compounds give ortho and para iodophenols with iodine and alkali. Thus β-naphthol-α-aldehyde gives α-iodo-β-naphthol (VII). Claisen[12] converted hydroxymethylene camphor into monobromo camphor (VIII) by the action of



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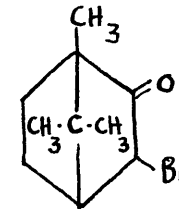
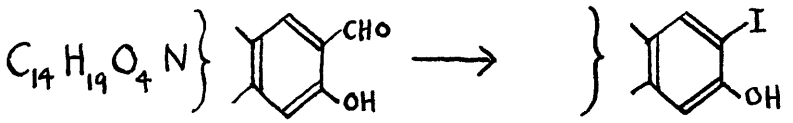
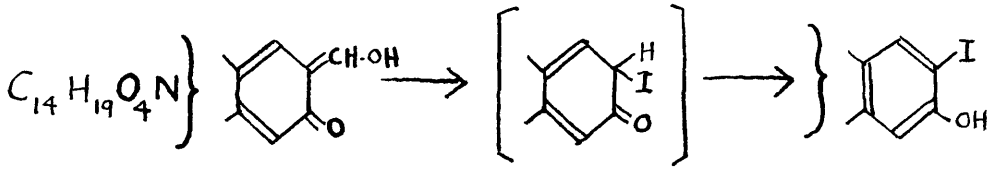


(VIII)

bromine and potassium hydroxide, and Brühl[13] obtained αα-di-iodo camphor by treating the same substance with iodine and potassium hydroxide. These two latter compounds are α-halogeno-ketones, whereas Windaus and Schiele showed that aromatic hydroxyaldehydes give halogeno-phenols. N-Acetyliodocolchinol behaves more like a phenol than a ketone. It is insoluble in water, soluble in dilute potassium hydroxide, is recovered from solutions of its alkali salts by treating with carbon dioxide, does not react with hydroxylamine, is easily acetylated and methylated. Apparently, therefore, one might conclude that colchiceine is an aromatic hydroxyaldehyde, and that the reaction is

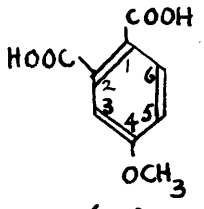


But there are certain differences in behaviour between colchiceine and aromatic ortho hydroxyaldehydes. Thus colchiceine on methylation with methyl iodide gives an easily hydrolysed methyl ether (colchicine)[14], and no phenol methyl ether. Moreover no reaction occurs with aldehydic reagents such as hydroxylamine. Windaus therefore formulated the reaction thus:-



He pointed out, however, that colchiceine does nevertheless show a close relationship to aromatic hydroxyaldehydes; for example it gives yellow solutions in acid and alkali, as mentioned above.

Proof of the structure of the iodine-containing ring of N-acetyliodocolchinol was provided by methylation followed by oxidation with potassium permanganate, whereby an iodomethoxyphthalic acid was obtained. The iodine was removed by treatment with zinc dust and acetic acid, and 4-methoxyphthalic acid (IX) was then obtained. This leaves two



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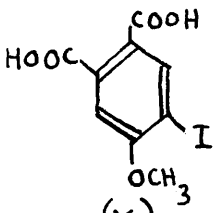

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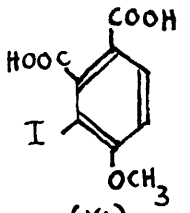
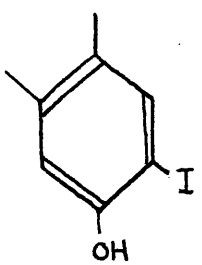


(XI)

alternatives for the original iodo-acid — 4-methoxy-5-iodo- (X), and 3-iodo-4-methoxy-phthalic acid (XI). Grewe[15] later synthesized both these acids, and showed that the iodo-acid from colchicine is identical with (X).

Ring C in N-acetyliodocolchinol can now be represented on the basis of Windaus's proposals by formula (XII), and in colchicine itself by (XIII). In both cases the positions of the substituents may of course require to be interchanged.



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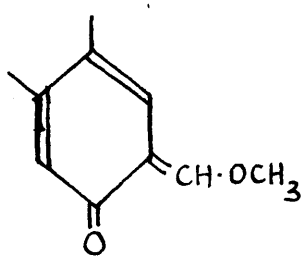


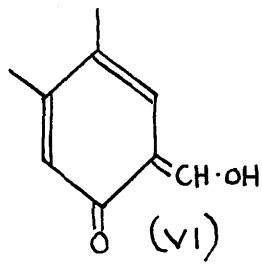
(XIII)

V.

It is perhaps not surprising that Windaus's structure for ring C of colchicine has excited a good deal of discussion and criticism. Windaus himself pointed out that both colchicine and colchiceine are indifferent to reagents

such as hydroxylamine and semicarbazide. Bursian[16] could not bring about reaction between colchicine or colchiceine and maleic anhydride. In addition he found that they did not titrate with perbenzoic acid, but this failure is not a very important observation, since, as Bursian himself states, it is well known that $\alpha\beta$- unsaturated carbonyl compounds either react with difficulty or not at all with perbenzoic acid.

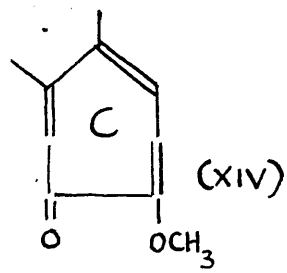
Horning[17] considers that a structure such as (VI)



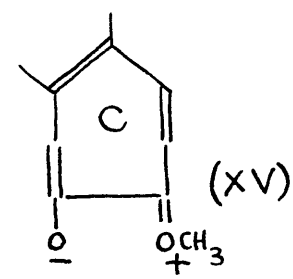
(VI)

would be likely to isomerise during preparation, and this makes the existence of Windaus's structure doubtful.

Dewar[18], in addition to some of the above objections, recalls Bursian's observation (loc.cit.) that the absorption spectra of colchicine and colchiceine are almost identical, thus proving that colchiceine cannot be the isomeric aldehyde, and points out that colchiceine is a much stronger acid than salicylaldehyde. He himself proposes the novel structure (XIV), resonance with (XV) accounting for the



(XIV)



(XV)

stability. This structure, it is claimed, would at once explain the intense ferric chloride reaction of colchiceine, also the existence of two stereoisomeric dibenzenesulphonyl derivatives, which on Dewar's basis would be position isomers. It possibly could explain the isolation by Lettrè and Fernholz[19] of a colchicine isomer when they treated colchiceine with diazomethane. Benzilic acid rearrangement is suggested as an explanation of the facile conversion to benzene derivatives. It is difficult, however, if the structure (XIV) is correct, to see how this or any other likely mechanism could readily explain the important action of iodine and potassium hydroxide on colchiceine. Unfortunately this difficulty is not discussed.

It will be seen, then, that the structure of ring C remains in some doubt, since no conclusive evidence has yet been brought forward in support of any one proposal. However, since the work which is outlined later is mainly of interest in connection with ring B of colchicine, the discussion of the chemistry of ring C must now give place to a consideration of ring B.

VI.

Windaus showed that terephthalic and trimellitic acids are formed when trimethylcolchicinic acid is demethylated, fused with alkali to remove the amino group, then oxidised

by potassium permanganate. He considered that these acids could not arise from either of the two rings whose presence in the colchicine molecule had already been demonstrated, and their formation was therefore indicative of a third six-membered ring. The experimental evidence, including the empirical formula of colchicine as determined by analysis, now indicated that three fused six-membered rings are present in the molecule. That is to say, colchicine is an anthracene or a phenanthrene derivative. In order to relate how Windaus decided between these two alternatives, it is necessary to give in outline the degradations leading to the tetramethoxylated compound deaminocolchinol methyl ether.

N-Acetyliodocolchinol was first methylated, then iodine was removed from the product by treatment with zinc dust and acetic acid. The resulting substance, N-acetylcolchinol methyl ether, gave on hydrolysis the compound colchinol methyl ether. When colchinol methyl ether was subjected to exhaustive methylation, deaminocolchinol methyl ether was formed, a process which Windaus considered to be essentially the aromatisation of colchinol methyl ether[x].

From this point two reactions sufficed to give a known substance. Demethylation with hydriodic acid, and distillation with zinc dust gave a product identified as

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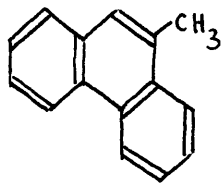
[x] Dr. W. Graham, working in these laboratories, later found that N-acetylcolchinol methyl ether can be converted to deaminocolchinol methyl ether more easily by treating it with phosphorus pentoxide in boiling xylene.

9-methylphenanthrene (XVI). It was obtained in such small quantities that not enough was available to check its identity by preparation of a derivative, and the assertion rests on a single observation that the colchicine degradation product and synthetic 9-methylphenanthrene did not depress each other's melting point. However, Windaus was able to conclude that colchicine is a phenanthrene derivative.



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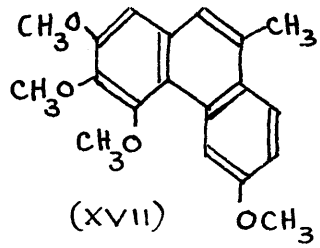

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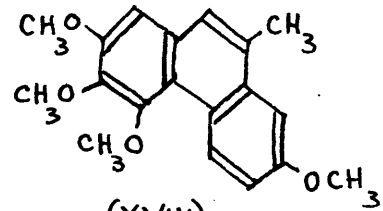

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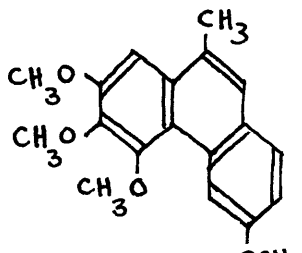

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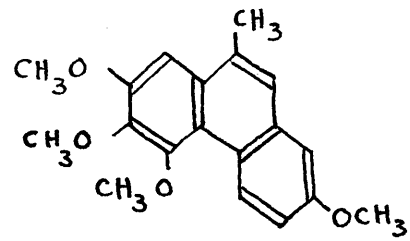
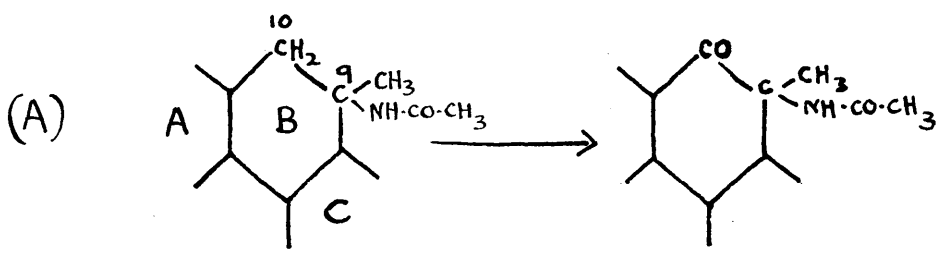


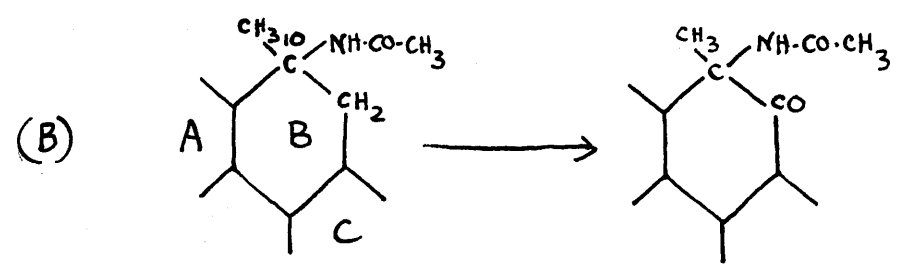
(XX)

Any one of the four structures (XVII) to (XX) for deaminocolchinol methyl ether would be consistent with the production from it of 9-methylphenanthrene (XVI). Windaus

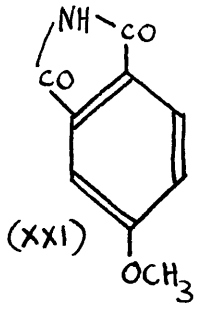
actually suggested that deaminocolchinol methyl ether was either (XVII) or (XVIII), since the evidence outlined below was considered to eliminate the structures (XIX) and (XX).

Zeisel had shown that when colchicine, $C_{22}H_{25}O_6N$, is oxidised with chromic acid it is converted into a carbonyl compound, oxycolchicine, $C_{22}H_{23}O_7N$. Windaus now interpreted this as the oxidation of a methylene group in a 9:10-dihydrophenanthrene derivative. The two substituents postulated for ring B, namely, $-CH_3$ and $-NH.COCH_3$, must, in order to leave an unsubstituted methylene group, be attached to the same carbon atom, and the oxidation may be written either as in (A) or (B):-



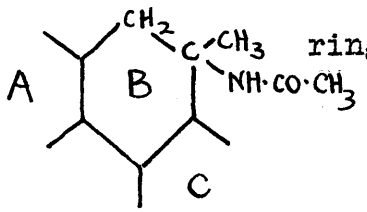


Now partial hydrolysis of N-acetylcolchinol methyl ether, followed by oxidation with chromic oxide, was found



(XXI)

to give 4-methoxyphthalimide (XXI). It would thus appear that the nitrogen atom in N-acetylcolchinol methyl ether is attached to the ring bearing a single methoxyl group (i.e. ring C) through the intervention of one carbon atom only. Hence Windaus concluded that the acetylamino group in colchicine is attached to C9, that is to say, the oxidation of colchicine to oxycolchicine is to be represented as in(A) above. It follows that deaminocolchinol methyl ether, if it is a tetramethoxy methylphenanthrene derivative, must be a 9- and not a 10-methyl derivative.



(XXII)

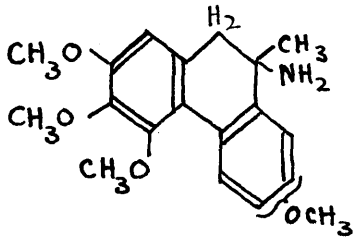
The structure (XXII) was proposed for ring B of colchicine.

VII.

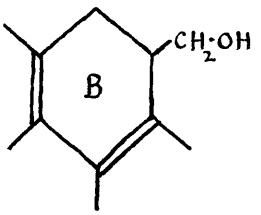
There are a number of objections to this structure for ring B. Thus it might be expected to give, after deamination and oxidation, not only terephthalic and trimellitic acids (p. 14), but also benzene tetra- and even penta-carboxylic acids, yet it is not recorded that such acids were obtained. This cannot be regarded as a very

serious objection however; the isolation of these acids from the complex mixture formed on oxidation would probably be difficult, and loss of carbon dioxide might well occur during the oxidation or later.

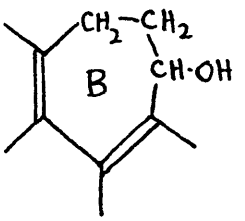
More cogent objections were stated by Cohen, Cook and Roe[20]. Colchinol methyl ether on the basis of Windaus's proposals should have the structure (XXIII), which represents a derivative of 9-amino-9:10-dihydrophenanthrene. This should readily lose ammonia and pass to the completely aromatic state (compare Windaus et al[21]), but no such behaviour is found in practice. Similarly, a carbinol which was obtained from colchinol methyl ether by the action of nitrous acid showed a stability not to be expected from a tertiary carbinol related to 9:10-dihydrophenanthrene.



(XXIII)



(XXIV)



(XXV)

Examination of the ultra violet absorption curves of N-acetylcolchinol methyl ether and the carbinol from colchinol methyl ether showed that the former gives a curve similar to that recorded for 9:10-dihydrophenanthrene, but

the curve of the latter, whilst it has much the same intensity, is considerably displaced towards the visible region, indicating that the carbinol is not a phenanthrene derivative. Moreover, spectroscopic examination of a mixture of the carbinol and a higher-melting substance formed during its preparation also failed to reveal the presence of a phenanthrene derivative.

The authors suggest that the carbinol may have one of the structures (XXIV) and (XXV), but point out that (XXIV) is difficult to reconcile with the resistance to dehydrogenation shown by N-acetylcolchinol methyl ether, since on this basis the substance would be a 9:10-dihydrophenanthrene derivative with unsubstituted hydrogen atoms at positions 9 and 10.

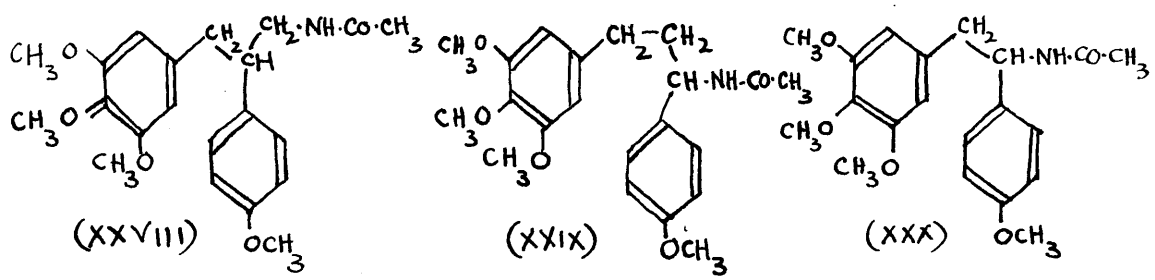
Lettré[22] recalls the fact that benzyl phenyl carbinol (XXVI) readily loses water, but benzyl phenyl methyl carbinol (XXVII) does so with difficulty[23], and considers

$Ph \cdot CH_2 \cdot CH(OH) \cdot Ph$ (XXVI)

$Ph \cdot CH_2 \cdot C(CH_3)(OH) \cdot Ph$ (XXVII)

that this invalidates the above objection to Windaus's structure, especially in view of the fact that rearrangement may occur during the formation of the carbinol. He objects to the structure (XXIV) because it does not agree with the formation of 4-methoxyphthalimide (p. 18), and to both (XXIV) and (XXV) because simple analogues of them, (XXVIII)

and (XXIX), did not show mitosis-poisoning effects on

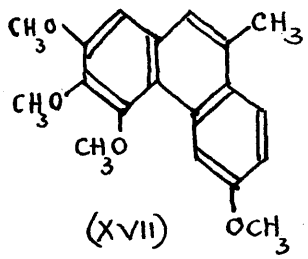


tissue-cultures, whilst an analogue of Windaus's structure (XXX) did show this effect.

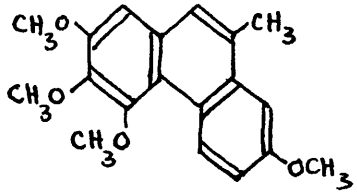
A significant contribution to the solution of the problem of the structure of ring B has recently been published from these laboratories. Details will be found in a paper published in the Journal of the Chemical Society[24], but the information is summarised here.

VIII.

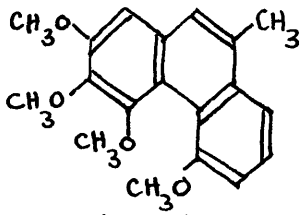
It was clear that the synthesis of the compounds 2:3:4:6- and 2:3:4:7-tetramethoxy-9-methylphenanthrene ((XVII) and (XVIII) respectively), which is not recorded by Windaus, would be of great interest and importance, since the identification of one of them with deaminocolchinol methyl ether would provide strong confirmation of Windaus's structure for ring B, and would remove the uncertainty which exists concerning the exact positions of the substituents of



(XVII)



(XVIII)



(XXXI)

ring C in colchicine itself. Buchanan, Cook and Loudon synthesized these two compounds, and they are described in the above-mentioned paper. (XVII) was prepared by an unambiguous route, but at one point in the synthesis of the 2:3:4:7-tetramethoxy compound (XVIII) the corresponding 2:3:4:5-tetramethoxy compound was simultaneously formed. The isomers were not differentiated, but both the 2:3:4:7- and the 2:3:4:5-tetramethoxy-9-methylphenanthrenes ((XVIII) and (XXXI)) were prepared. However, all three compounds were distinct from deaminocolchinol methyl ether, and Windaus's formulation of this compound must therefore be abandoned.

Subsequently Dr. J.D. Loudon showed that deaminocolchinol methyl ether differs from these synthetic compounds in some important particulars. Thus it does not appear to form a picrate, whereas the synthetic compounds readily give orange precipitates when a solution of picric acid in methanol is added. It is readily hydrogenated to a dihydride

using a palladium catalyst, whilst the synthetic compounds under the same conditions are unchanged. Moreover this dihydride differs from 9:10-dihydrophenanthrene in that the latter is readily dehydrogenated with palladium, but the dihydride of deaminocolchinol methyl ether resists dehydrogenation with palladium.

It was also discovered that deaminocolchinol methyl ether can be prepared by dehydration of the carbinol referred to on page 19, and that there is formed at the same time an isomer, termed iso deaminocolchinol methyl ether. iso Deaminocolchinol methyl ether hydrogenates to give the same dihydride as is formed from deaminocolchinol methyl ether.

Lastly, deaminocolchinol methyl ether was oxidised with sodium dichromate in acetic acid, and from the reaction products was isolated a quinone, characterized by the diazine produced by reaction with ortho phenylene diamine, and a further substance which was probably an unsaturated ketone.

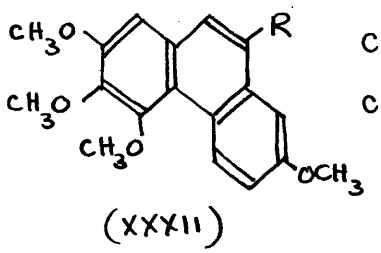
These important investigations will be referred to again later (page 31 , page 37 et seq.). Towards the end of them the present writer began the studies which are described in the following pages. His indebtedness to previous workers is here placed on record.

PART II. RELATIONSHIPS WITH SYNTHETIC PHENANTHRENE DERIVATIVES.

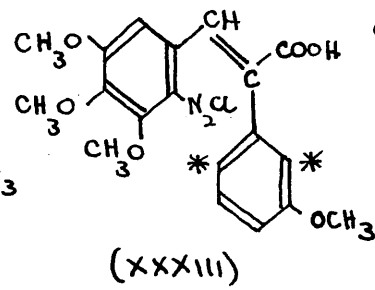
I.

The writer's researches began with an investigation into the problem of the differentiation of the 2:3:4:5- and 2:3:4:7-tetramethoxyphenanthrene derivatives described by Buchanan, Cook, and Loudon (see page 22). The object was twofold: in the first place to complete this part of the work of Buchanan, Cook, and Loudon, and in the second place to provide an introduction to a field of chemistry likely to be encountered later, when the structure of deaminocolchinol methyl ether came to be more closely investigated.

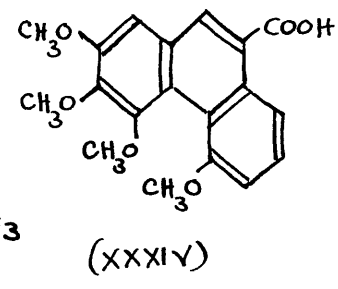
As an intermediate in the synthesis of 2:3:4:7-tetramethoxy-9-methylphenanthrene (XXXII, R = CH_3), the corresponding carboxylic acid (XXXII, R = COOH) had been prepared[24]. It was prepared by a Pschorr synthesis, the last stage of which involved ring-closure of diazotised 2-amino-3:4:5-trimethoxy-α-(metamethoxyphenyl) cinnamic acid (XXXIII). But ring-closure could occur at either of the positions marked with an asterisk in (XXXIII), and in fact the reaction product was found to be a mixture of the 2:3:4:7-tetramethoxy acid (XXXII, R = COOH) and the



(XXXII)



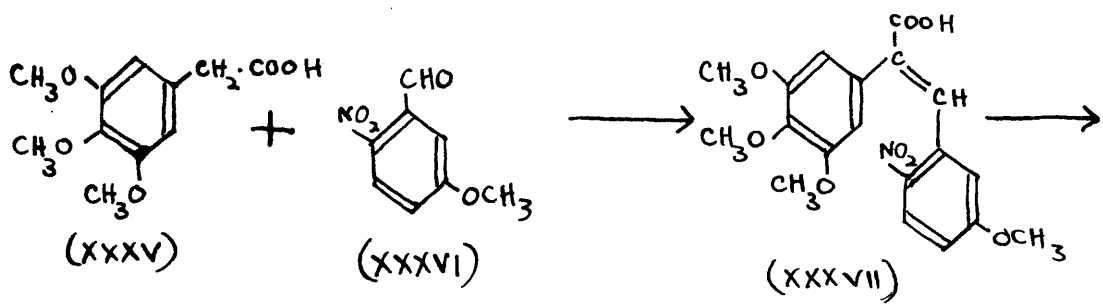
(XXXIII)



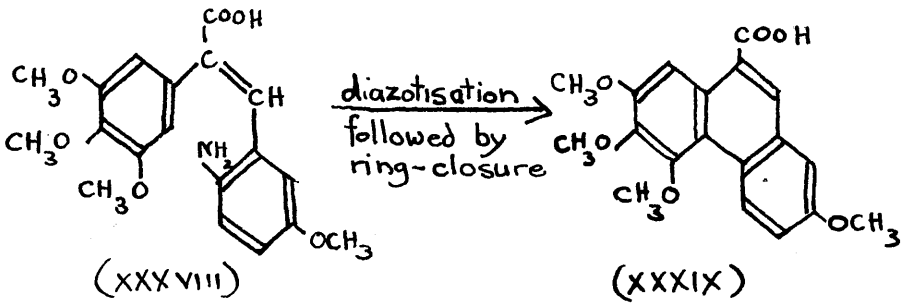
(XXXIV)

2:3:4:5-tetramethoxy acid (XXXIV). The acids were separated by fractional crystallization from glacial acetic acid, and they and their derivatives were distinguished by the terms "A series" and "B series".

In order to differentiate between the two acids a synthesis was required in which either a 2:3:4:5- or a 2:3:4:7-tetramethoxyphenanthrene derivative, but not both, would be formed. One way of ensuring this was to prepare a diazo-compound in which the diazo-amino group was already attached to the monomethoxylated nucleus, instead of to the trimethoxylated nucleus as in(XXXIII), and then to ring-close this as before. This was actually done by the following series of reactions:-



(XXXV) (XXXVI) (XXXVII)

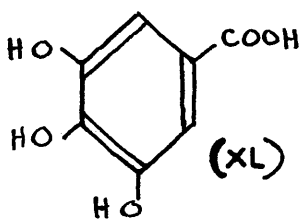


(XXXVIII) (XXXIX)

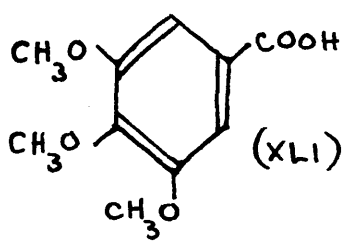
The ring-closure of (XXXVIII) provides no opportunity for the simultaneous production of isomers, and it follows that the product will be a 2:3:4:7-tetramethoxyphenanthrene derivative.

The way in which this substance (XXXIX) was subsequently used to differentiate between the A and B series will be explained presently, but first its synthesis will be treated in greater detail.

The first component used, 3:4:5-trimethoxyphenylacetic acid (XXXV) was prepared from gallic acid (XL) by methylation to 3:4:5-trimethoxybenzoic acid (XLI), followed



(XL)

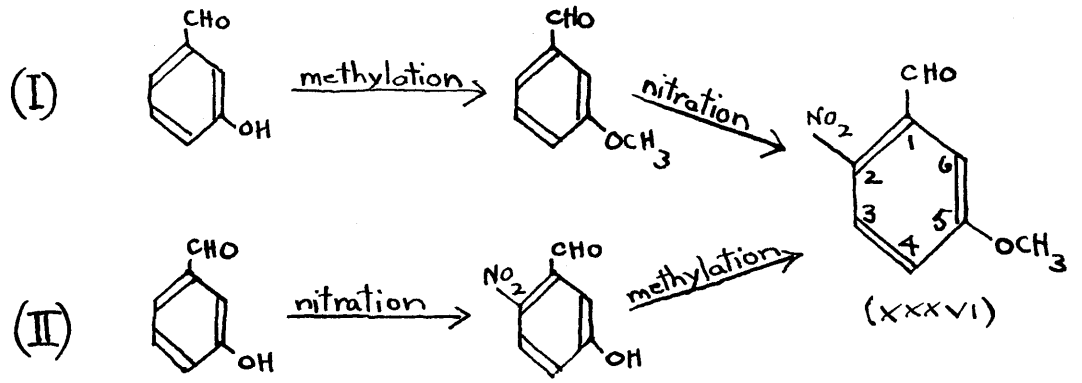


(XLI)

by homologisation using the method of Arndt and Eistert[25].

In the present case this involved preparation of the acid chloride, treatment with diazomethane to form the diazoketone, conversion of this to the homo-amide by the action of silver nitrate and ammonia, and hydrolysis of the amide by boiling with alkali.

Examination of the literature showed that the other component, 2-nitro-5-methoxybenzaldehyde (XXXVI), has been prepared by at least two routes:-



Route (I), however, appears to lead to a mixture of isomers in which the 6-nitro compound preponderates. Route (II) likewise leads to a mixture, but this difficulty can be neatly avoided[26] by nitrating not <u>meta</u> hydroxybenzaldehyde itself but the carbonate derived from it. This method was chosen, and gave good results.

The Perkin condensation between (XXXV) and (XXXVI) gave not only the expected product (XXXVII), but in addition two other compounds, giving quite distinct

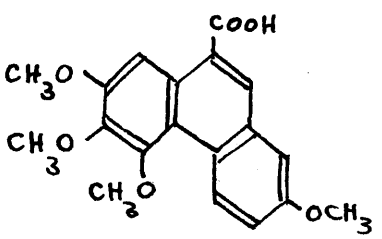
analytical figures, to which no constitution has been assigned. It was here too that the phenomenon of spontaneously changing melting points was first encountered. In one case a melting point was found to have risen by as much as 37° when redetermined some days later.

Reduction of the nitro-compound (XXXVII) was easily accomplished by the action of ferrous sulphate and ammonia, and the amino-compound (XXXVIII) was obtained in good yield. The ring-closure of this compound, however, proved to be more difficult than the preceding stages. After diazotisation, the resulting solution was treated with sodium carbonate and warmed. From the tar which was precipitated the required 2:3:4:7-tetramethoxyphenanthrene-10-carboxylic acid (XXXIX) was obtained in low yield. A subsidiary product was also isolated, and its separation is described in the Experimental section. Both in appearance and general properties it resembled a by-product first mentioned by Sharp[27] and later encountered by Buchanan, Cook, and Loudon in the preparation of the isomeric 2:3:4:6-tetramethoxyphenanthrene-9-carboxylic acid. The two compounds are isomeric, and though no structures can be assigned to them, it seems likely that they are of the same type.

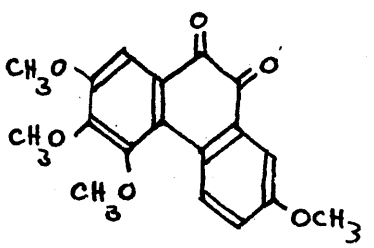
It had originally been the intention to decarboxylate

the acid (XXXIX) to obtain the parent tetramethoxyphenanthrene, for this same tetramethoxy compound should be obtained from either acid A or acid B on decarboxylation. It was fortunate, in view of the relatively small quantity of the acid (XXXIX) available, that a model experiment was first tried with 2:3:4:6-tetramethoxyphenanthrene-9-carboxylic acid, because distillation of this substance in the presence of copper in a high vacuum caused it to be converted into its methyl ester. A similar failure to decarboxylate a methoxylated phenanthrene acid was later found in the literature[28]. Consequently another method of orientation had to be devised. It was found that the phenanthrene 9- and 10-carboxylic acids could be readily converted to phenanthraquinones by oxidation with sodium dichromate and acetic acid, and this circumstance enabled the isomeric acids to be rigidly differentiated.

The new acid (XXXIX) under these conditions



(XXXIX)



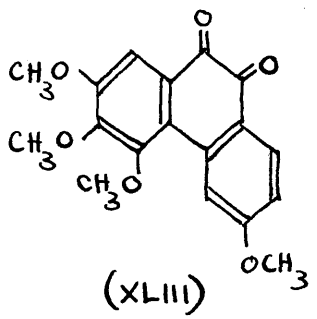
(XLII)

gave 2:3:4:7-tetramethoxyphenanthraquinone (XLII), characterized by the quinoxaline prepared by reaction with ortho phenylene diamine. When acid A was similarly oxidised the same quinone was obtained, and from it was prepared the same quinoxaline. The quinone was remarkable in that two distinct interconvertible crystalline forms crystallized simultaneously from benzene/ligroin, a circumstance which, since it was observed in both oxidations, provided evidence of identity additional to the normal mixed melting point determination. The quinoxaline as prepared from the acid A oxidation product was also obtained in two interconvertible forms, but only one of these forms was obtained in the case of the oxidation product of the acid (XXXIX).

Acid B gave a distinctly different product on oxidation. It was crystallized only with extreme difficulty, whereas the product from acid A was easily crystallized, and the crystals when finally obtained were distinct in colour and crystalline form from those previously encountered, and a mixed melting point showed a depression. A quinoxaline was prepared, which like its parent proved to be reluctant to crystallize. It was eventually obtained as crystals which differed in appearance from the "A" diazine, and which caused a melting point depression when the two were mixed.

The differentiation between the two series of compounds was thus completed. The A series must have the 2:3:4:7-tetramethoxyphenanthrene structure, since the phenanthraquinone of this series is identical with that prepared from 2:3:4:7-tetramethoxyphenanthrene-10-carboxylic acid (XXXIX). It follows that the B series is derived from 2:3:4:5-tetramethoxyphenanthrene.

The isomeric acid 2:3:4:6-tetramethoxyphenanthrene-9-carboxylic acid was also oxidised, so as to obtain a sample of 2:3:4:6-tetramethoxyphenanthraquinone (XLIII). Like the 2:3:4:7 compound, this quinone was obtained in two distinct crystalline forms. A quinoxaline was prepared from it in the usual way.



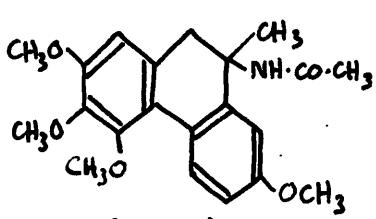
(XLIII)

II.

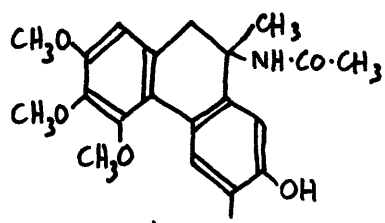
The three synthetic phenanthraquinones thus made available were now compared with the quinone obtained from the oxidation products of deaminocolchinol methyl ether (page 23). Mixed melting point determinations showed that this substance was identical with the synthetic

2:3:4:7-tetramethoxyphenanthraquinone (XLII), and quite distinct from both the 2:3:4:6- (XLIII) and the 2:3:4:5-tetramethoxyphenanthraquinones. This identity was confirmed by comparison of the derived quinoxaline derivatives.

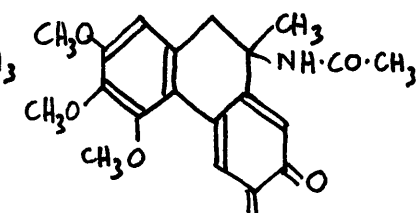
This result is of some importance. It establishes the methoxylation pattern of deaminocolchinol methyl ether, and consequently of N-acetylcolchinol methyl ether, from which the former can be directly prepared. Consequently the position of the phenolic group in ring C of N-acetylcolchinol, and indeed of all those colchicine derivatives in which this ring is aromatic, is defined. This removes the uncertainty expressed by Windaus concerning the positions of the substituents of ring C in colchicine itself. It also confirms the arrangement of methoxyl groups proposed by Windaus for ring A of colchicine, and provides fresh confirmation of the close relationship of colchicine and its derivatives to phenanthrene. On the basis of Windaus's proposals N-acetylcolchinol methyl ether can now be formulated as (XLIV), N-acetyliodocolchinol as (XLV), and colchicine itself as (XLVI).



(XLIV)



(XLV) I



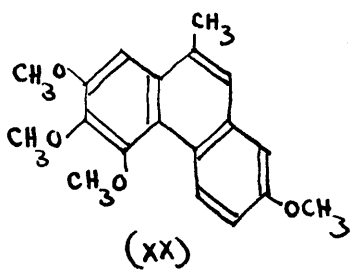
(XLVI)

PART III. THE STRUCTURE OF DEAMINOCOLCHINOL METHYL ETHER.

I.

A renewed attempt to elucidate the structure of deaminocolchinol methyl ether was stimulated by the results recorded above. For a fresh problem had now arisen, that of reconciling two conflicting lines of evidence with regard to deaminocolchinol methyl ether. T his compound has been shown not to be 2:3:4:7-tetramethoxy-9-methylphenanthrene, yet it is also known to oxidise, with loss of one carbon atom, to a phenanthrene derivative - 2:3:4:7-tetramethoxyphenanthraquinone.

The possibility that deaminocolchinol methyl ether might be not the 9- but the 10-methyl tetramethoxyphenanthrene (XX) is immediately suggested. However, its behaviour would seem to exclude a phenanthrene type of structure altogether.

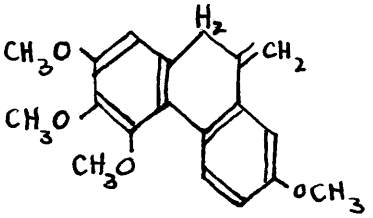


(XX)

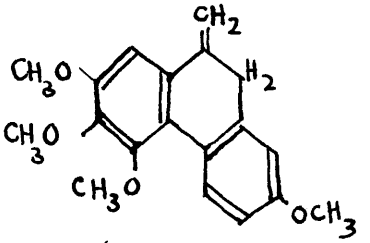
Attempts to hydrogenate synthetic 2:3:4:7-tetramethoxy-9-methylphenanthrene with palladium failed, yet deaminocolchinol methyl ether smoothly hydrogenates and gives a crystalline dihydride (page 22) which differs from 9:10-dihydrophenanthrene in its resistance to dehydrogenation. The failure of deaminocolchinol methyl ether to form a

picrate, in contrast with the synthetic methylphenanthrenes (page 22) also militates against its formulation as a phenanthrene derivative.

There are, however, two other relevant structures which have a phenanthrene arrangement of carbon atoms, but which differ from phenanthrene in some respects. They are 2:3:4:7-tetramethoxy-9-, and 2:3:4:7-tetramethoxy-10-methylene-9:10-dihydrophenanthrene (XLVII and XLVIII).



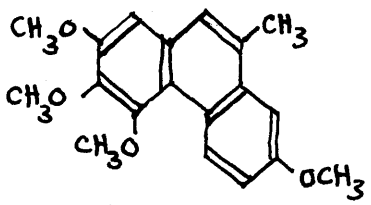
(XLVII)



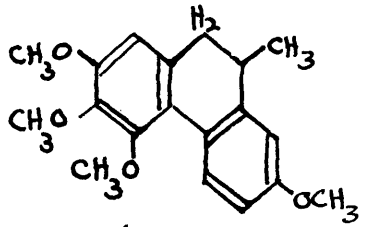
(XLVIII)

Hydrogenation of the exocyclic double bond would here account for the hydrogenation of deaminocolchinol methyl ether over palladium.

Direct confirmation of the structure (XLVII) was sought by attempting the partial hydrogenation of 2:3:4:7-tetramethoxy-9-methylphenanthrene (XVIII). For if this compound could be hydrogenated at the 9:10 positions only, the product, (XLIX), would be also the dihydride of (XLVII). But an attempt to effect this partial hydrogenation with platinum gave no conclusive result, since no crystalline



(XVIII)



(XLIX)

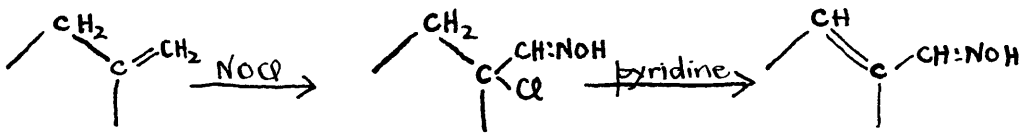
product could be obtained. The results indicated that this approach was impracticable.

Attention was therefore turned to another aspect of the structure under consideration. It would be expected that a 9- or 10-methylene-9:10-dihydrophenanthrene would readily rearrange to the more usual aromatic form ((XVIII) or (XX)). But deaminocolchinol methyl ether was recovered unchanged after three hours' boiling with sodium methoxide; indeed it survives fairly intense conditions of heat and alkalinity in the course of its preparation. It was also recovered, although in small yield, after boiling with a mixture of concentrated hydrochloric acid and glacial acetic acid.

Renewed attempts to effect dehydrogenation of the dihydride of deaminocolchinol methyl ether were then made. Yet the compound was recovered unchanged after heating under varying conditions with selenium, a treatment considerably

more severe than that which sufficed to convert 9:10-dihydrophenanthrene to phenanthrene.

Still considering a methylene dihydrophenanthrene structure, a series of reactions involving addition of nitrosyl chloride to the exocyclic double bond attached to the methylene group was envisaged thus:-



It was found that deaminocolchinol methyl ether did not react when treated with amyl nitrite and hydrochloric acid in glacial acetic acid at low temperatures, but reaction did take place when it was treated with excess nitrosyl chloride in ethereal solution. However, besides possible addition to the double bond, chlorination appeared to have taken place[x], and although a well-formed crystalline product was obtained, no constitution could be assigned to it. Consequently no direct comparison with the oxime of 2:3:4:7-tetramethoxy-9-phenanthraldehyde, which had been prepared for this purpose, was possible.

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[x] Cf. Tilden and Forster[29], who found that when nitrosyl chloride was passed through phenanthrene in benzene a product was obtained which they considered to be dichlorphenanthraquinone.

II.

The accumulated evidence now suggested that the methylene dihydrophenanthrene structures were incorrect. It was at this point that the discovery was made (page 23) that not only deaminocolchinol methyl ether but also iso deaminocolchinol methyl ether is formed during the dehydration of the carbinol obtained from colchinol methyl ether. Before discussing the significance of this observation, there is a point in connection with it which must be mentioned.

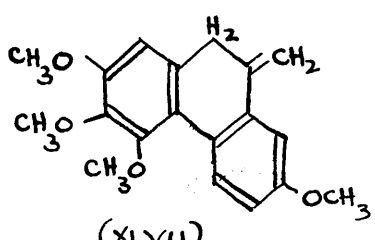
It was of some interest to know whether iso deaminocolchinol methyl ether was also formed when deaminocolchinol methyl ether was prepared by the original methods. The Hofmann degradation of colchinol methyl ether had been done in these laboratories on a small scale only, and colchinol methyl ether was not available in sufficient quantities to justify its repetition, so it was not possible to investigate this case. However, mother liquors from the crystallization of deaminocolchinol methyl ether were collected from various preparations in which Dr. Graham's method, the action of phosphorus pentoxide on N-acetylcolchinol methyl ether, had been used. It was expected that these mother liquors would be comparatively rich in iso deaminocolchinol methyl ether. They were evaporated, the residue was distilled, and the distillate gave deaminocolchinol methyl ether on

crystallization. The mother liquors from this crystallization, after standing for some time, yielded a few crystals which were distinct in crystalline form from those of deaminocolchinol methyl ether. They were carefully separated, and proved to be <u>iso</u> deaminocolchinol methyl ether.

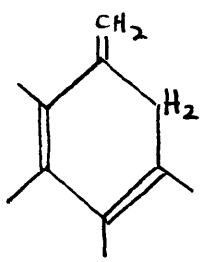
This result suggests that the <u>iso</u> compound is a normal product in the formation of deaminocolchinol methyl ether, for it is reasonable to suppose that the compound is also formed in the Hofmann degradation of N-acetylcolchinol methyl ether, but has escaped detection.

III.

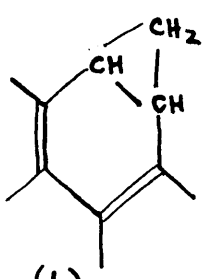
Both deaminocolchinol methyl ether and its isomer give the same dihydride on hydrogenation (page 23). Their properties exclude aromatic structures, so the hydrogenation result can only be interpreted on the basis of a six-membered middle ring by assuming that one of the isomerides has the methylene dihydrophenanthrene structure ((XLVII) or (XLVIII)), which has been shown to be unlikely, and the other isomeride the structure (L). But when the conditions under which the



(XLVII)

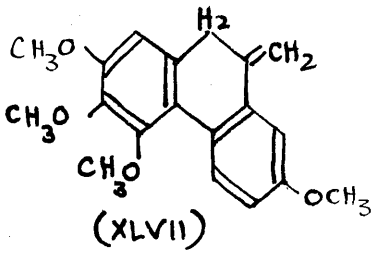


(XLVIII)

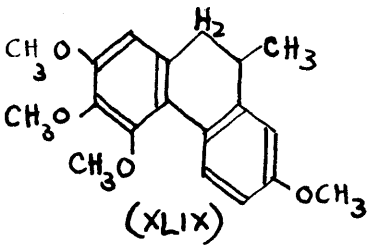


(L)

isomerides are formed are considered, this interpretation seems extremely improbable, and it would appear to be ruled out altogether by the difficulty of explaining the reduction of (L) to the dihydride of (XLVII) or of (XLVIII) (for example (XLIX), which is the dihydride of (XLVII)).

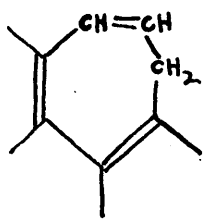


(XLVII)

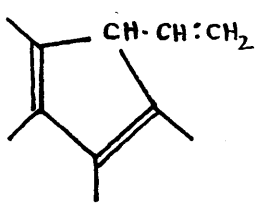


(XLIX)

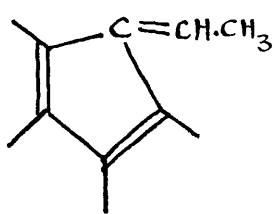
The two remaining possibilities were that deaminocolchinol methyl ether has either a five- or a seven-membered middle ring. On either basis the mechanism of its oxidation to a phenanthraquinone is obscure. Yet the simultaneous formation, in this oxidation, of an $\alpha\beta$ -unsaturated ketone (page 23) makes the seven-membered ring structure more acceptable. Such a product might reasonably be expected from the oxidation of a dibenz cycloheptatriene derivative (e.g., (LI)), though not from a dibenz cyclo-



(LI)



(LII)



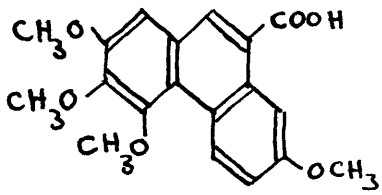
(LIII)

pentadiene derivative (e.g., (LII), (LIII)).

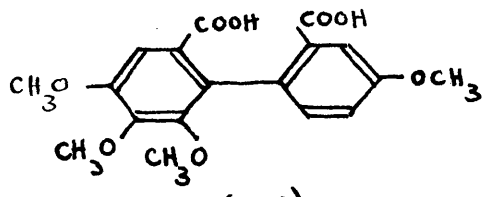
IV.

While these considerations were being developed, further attempts to clarify the position were made in the laboratory by re-examination of some acidic by-products which had been isolated during the above oxidations of the acids to phenanthraquinones.

The carbinol derived from colchinol methyl ether had given on oxidation an acidic substance (obtained by Professor Cook). 2:3:4:7-Tetramethoxyphenanthrene-9-carboxylic acid (LIV) (acid A) was oxidised with sodium dichromate and acetic acid (page 30) and gave, in addition to the phenanthraquinone, an acidic by-product which on sublimation yielded a crystalline acid. This was found to be identical with the



(LIV)



(LV)

acid obtained from the colchicine carbinol. The corresponding by-product obtained when the 2:3:4:5-tetramethoxy acid is oxidised has been shown to be probably a diphenic acid, so it seemed desirable to prepare the diphenic acid (LV) to be expected from direct oxidation of 2:3:4:7-tetramethoxy-

phenanthraquinone, in order to compare it with the acid described above.

The oxidation of phenanthraquinone to diphenic acid in fair yield by hydrogen peroxide and glacial acetic acid is described in the literature[30], but in view of the very small quantities of tetramethoxyphenanthraquinone available it was decided to investigate the oxidation under alkaline conditions in the hope of improving the yield of diphenic acid. Investigation showed that the use of sodium hydroxide and hydrogen peroxide gave diphenic acid in 95% yield from phenanthraquinone, so this method was used with the tetramethoxyphenanthraquinone. The acid was obtained as colourless prisms which sublimed unchanged, and analysed as 4:5:6:4'-tetramethoxydiphenic acid (LV). This substance, however, was not identical with the acid obtained from the colchicine derivative and from 2:3:4:7-tetramethoxyphenanthrene-9-carboxylic acid. Further, when the oxidation of the latter was repeated, the by-product obtained, though acidic, was distinct both from the acidic by-product previously obtained, and from the corresponding diphenic acid. Since only a few milligrams of material were obtained, and the stock of the parent acid was limited, this investigation was discontinued, especially since in the meantime a more successful approach to the constitution of deaminocolchinol methyl ether had been discovered.

V.

It had become clear that the experimental evidence available was not sufficient to enable the exact structure of deaminocolchinol methyl ether to be defined. To obtain more information it was decided to investigate the oxidation of the olefinic double bond. An oxidation in two distinct stages was proposed, first hydroxylating the double bond, and then cleaving the resulting glycol.

Milas and Sussmann[31] have developed a convenient method for hydroxylation of olefins which uses hydrogen peroxide in tertiary butanol with osmium tetroxide as catalyst. It would appear from examination of the literature, however, that this method has only been used successfully for olefinic substances of low molecular weight, and in this particular case the reagents were found to have little or no effect on deaminocolchinol methyl ether[x]. Criegee's method[32], that of the direct action of osmium tetroxide in ether, was more successful, and from deaminocolchinol methyl ether ($C_{19}H_{20}O_4$) a glycol whose empirical formula was found to be $C_{19}H_{22}O_6$ was readily obtained by its use.

In order to oxidise the glycol, it was treated with

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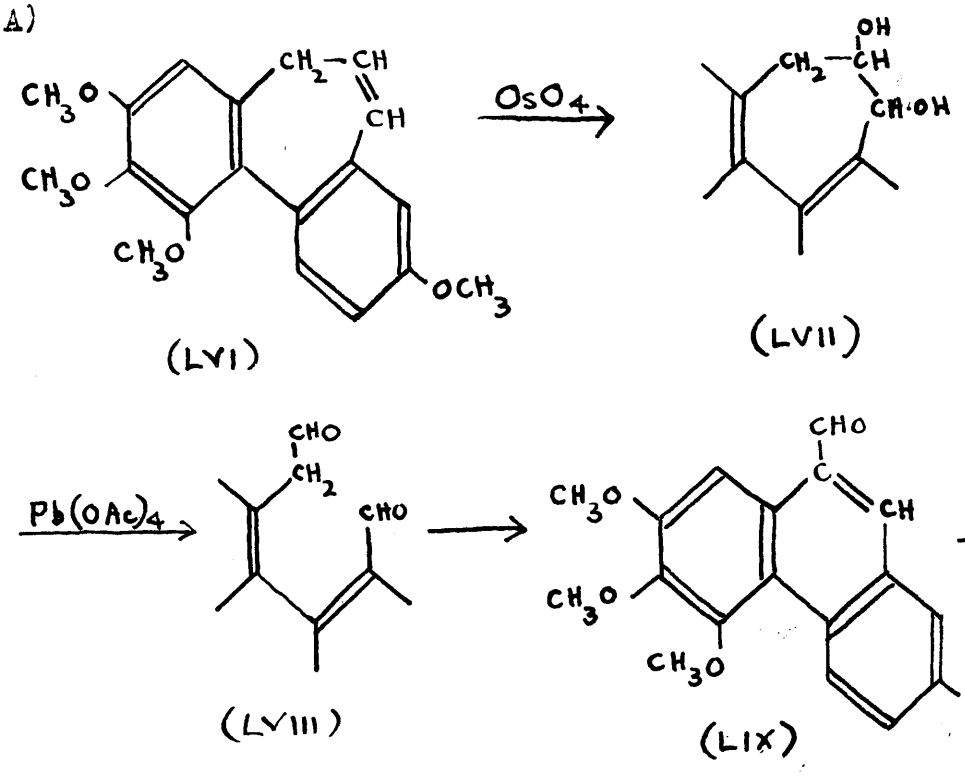
[x] Cf. Dr. N.A. McGinnis, who found that the Milas & Sussmann method failed with a compound of molecular formula $C_{15}H_{20}O_5$ (private communication).

lead tetra-acetate in benzene[33]. From this experiment a gummy product was obtained which slowly gave a few crystals when its methanol solution was allowed to stand. Here a remarkable observation, the significance of which will be appreciated presently, was made. If to a hot methanol solution of this gummy product was added a trace of sodium carbonate, a large crop of beautiful crystals was immediately obtained. This suggested that alkali was acting as a reaction catalyst, probably being supplied by the glass reaction vessel in those experiments in which sodium carbonate was not added. The crystalline product was shown to be an aldehyde of empirical formula $C_{19}H_{18}O_5$; that is, it is formed from the glycol by loss of two hydrogen atoms and one molecule of water, and retains all the carbon atoms of the original glycol.

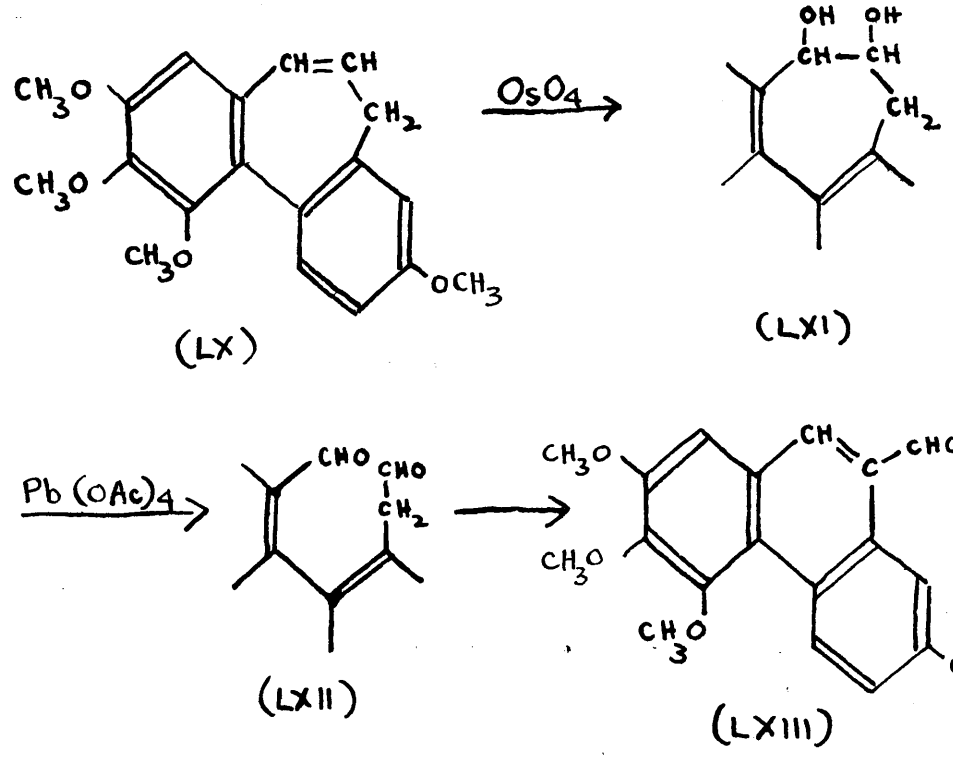
This result eliminated any structure for deaminocolchinol methyl ether containing a five-membered middle ring. Such structures must have an exocyclic double bond (see page 39), therefore after glycol cleavage one or two carbon atoms would be lost, and this is contrary to what was found in practice.

There remained, then, only the two dibenz <u>cyclo</u>-heptatriene structures (LVI) and (LX), and the oxidations must be interpreted in one of the two following ways:-

(A)


CH3O
CH3O
CH3O
OCH3
CH2—CH
CH
OsO4
OH
CH2—CH
CH·OH
(LVI)
(LVII)
Pb(OAc)4
CHO
CH2
CHO
(LVIII)
CHO
C
CH
CH3O
CH3O
CH3O
OCH3
+ H2O
(LIX)

(B)


CH3O
CH3O
CH3O
OCH3
CH=CH
CH2
OsO4
OH OH
CH—CH
CH2
(LX)
(LXI)
Pb(OAc)4
CHO CHO
CH2
(LXII)
CH3O
CH3O
CH3O
OCH3
CH
C—CHO
+ H2O
(LXIII)

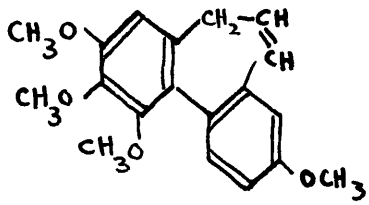
On oxidation of the glycol a mono-aldehyde was obtained, accompanied by the loss of one molecule of water. The inference is that the mono-aldehyde was formed from the di-aldehyde (LVIII) or (LXII) by intramolecular condensation as shown. This mechanism is supported by the fact that the crystalline aldehydic product of the oxidation is rapidly formed from the gummy reaction-product (which probably contains the dialdehyde) on adding a trace of alkali.

Both (LIX) and (LXIII) are phenanthrene aldehydes, and the product obtained from the oxidations did in fact show a striking resemblance to 2:3:4:7-tetramethoxy-9-phenanthraldehyde (LXIII). It had the same colour, and practically the same crystalline form; its melting point was only three degrees below that of the synthetic phenanthrene aldehyde, and the melting points of the derived oximes were exactly the same. Yet on mixing the substances, the melting points of both aldehydes and oximes were markedly depressed. The oxidation product was therefore not 2:3:4:7-tetramethoxy-9-phenanthraldehyde (LXIII).

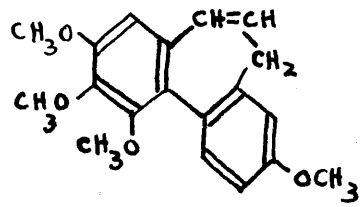
If the above argument is correct, the other possibility is that the monoaldehyde is 2:3:4:7-tetramethoxy-10-phenanthraldehyde (LIX). Unfortunately this substance was not available for comparison, although the corresponding carboxylic acid had been prepared (page 28). It seemed

at first sight simpler to oxidise the reaction product further, and compare the acid to be expected with the synthetic acid, than to embark on a synthesis of the 10-phenanthraldehyde. Yet there was a difficulty here, because of the small quantity of the aldehydic product available (18 milligrams). However, the oxidation was attempted and proved successful, for not only was an acid obtained and compared with the synthetic acid, but also the methyl ester was prepared and compared with the synthetic ester. These comparisons showed that the product obtained on oxidising the mono-aldehyde was indeed 2:3:4:7-tetramethoxyphenanthrene-10-carboxylic acid, and hence, by inference, that the product of the glycol cleavage was 2:3:4:7-tetramethoxy-10-phenanthraldehyde (LIX). It follows that the series (A), (LVI) to (LIX), represents the oxidation of deaminocolchinol methyl ether.

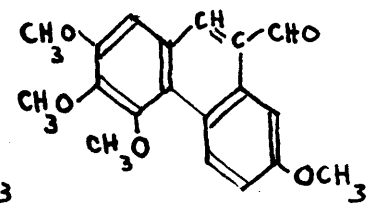
Now there lay to hand a clear and decisive check on the validity of this reasoning. If deaminocolchinol methyl ether has in fact the structure (LVI), to <u>iso</u> deaminocolchinol methyl ether must be attributed the structure (LX) (which differs only in the position of the olefinic double bond), and the oxidation series applied to this latter compound should give 2:3:4:7-tetramethoxy-9-phenanthraldehyde (LXIII).



(LVI)



(LX)



(LXIII)

To carry out the oxidations with iso deaminocolchinol methyl ether and test the argument was naturally a very attractive proposition, and since no supply of the pure iso compound was available, an attempt was made to obtain the compound from a mixture of the two isomers which had been left over from a previous preparation of iso deaminocolchinol methyl ether. By careful fractional crystallization a small quantity, some 34 milligrams, of slightly impure iso compound was eventually obtained[x]. Treatment with osmium tetroxide as before gave a compound which was presumed to be a glycol. There was not enough of it to permit complete characterisation, but it was shown to be distinct from the glycol obtained

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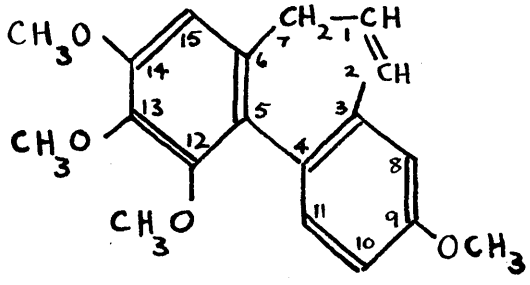
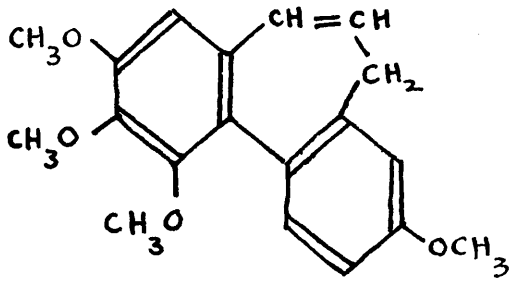
[x] In addition a few crystals of a substance of micro melting point 167-169° were isolated. The quantity did not permit analysis or further investigation. It is likely that this substance was the cause of the cloudiness observed during melting point observations on some of the intermediate fractions in the fractional crystallization.

from deaminocolchinol methyl ether. When this substance was in turn treated with lead tetra-acetate an aldehyde was obtained. It was found to be indeed identical with 2:3:4:7-tetramethoxy-9-phenanthraldehyde (LXIII), and this identity was confirmed by comparison of the oximes prepared from the natural and synthetic products.

The conclusions reached earlier were thus fully justified, and deaminocolchinol methyl ether and iso deaminocolchinol methyl ether can now be formulated[x] 9:12:13:14-tetramethoxy-3:4:5:6-dibenz-$\Delta^{1:3:5}$- and $\Delta^{3:5:7}$-cycloheptatriene respectively.



Deaminocolchinol methyl ether.



iso Deaminocolchinol methyl ether.

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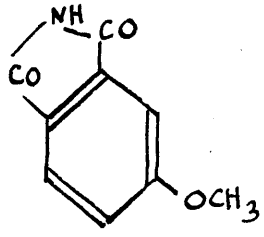
[x] The system of numbering used is that of Kenner and Turner[35].

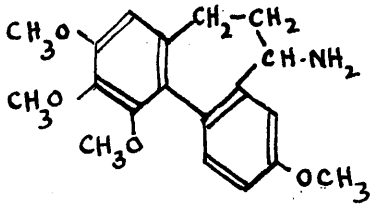
PART IV. A SYNTHETIC APPROACH TO DEAMINOCOLCHINOL METHYL ETHER.

I.

In order to confirm the conclusions concerning the structure of deaminocolchinol methyl ether and its isomer which had been reached by degradative reactions, the synthesis of deaminocolchinol methyl ether was undertaken. It was hoped, too, that a synthetic route might be devised which would provide information concerning the structure of colchinol methyl ether. The formation of 4-methoxyphthalimide (XXI) from N-acetylcolchinol methyl ether (Part I, page 17) suggests that the amino group of colchinol methyl



(XXI)



(LXIV)

ether is separated from the monomethoxylated nucleus (i.e., ring C) by only one carbon atom. That is to say, assuming that the conversion of colchinol methyl ether to deaminocolchinol methyl ether by Hofmann degradation does not involve rearrangement of the carbon skeleton[x], the structure

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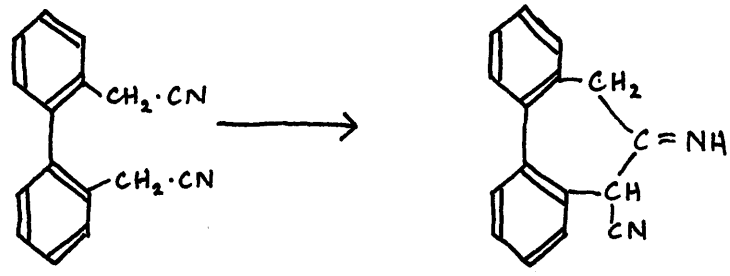
[x] This is a reasonable assumption - cf. Stevens and Richmond[34].

(LXIV), containing a seven-membered middle ring, is indicated for colchinol methyl ether. The possibility of preparing and suitably resolving a compound of this structure was therefore borne in mind when the synthetic approach was being considered.

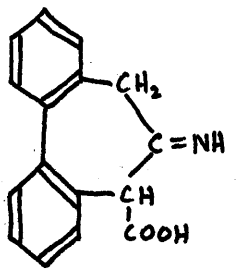
The literature contains few references to the synthesis of dibenz cyclohepta-diene and -triene derivatives. The following survey does not claim to be exhaustive. The most important papers are those of Kenner[35),36)] which describe three methods for the preparation of dibenz cyclo-heptadienes.

First[35)], ω ω'-dicyano-2:2'-ditolyl (LXV) with sodium ethoxide gives 1-imino-2-cyano-3:4:5:6-dibenz-$\Delta^{3:5}$-cycloheptadiene (LXVI)[35)] (Thorpe's reaction). From (LXVI)

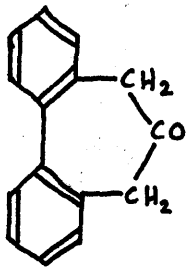


(LXV) (LXVI)

the acid (LXVII) and the ketone (LXVIII) can be prepared by the action of sulphuric acid.

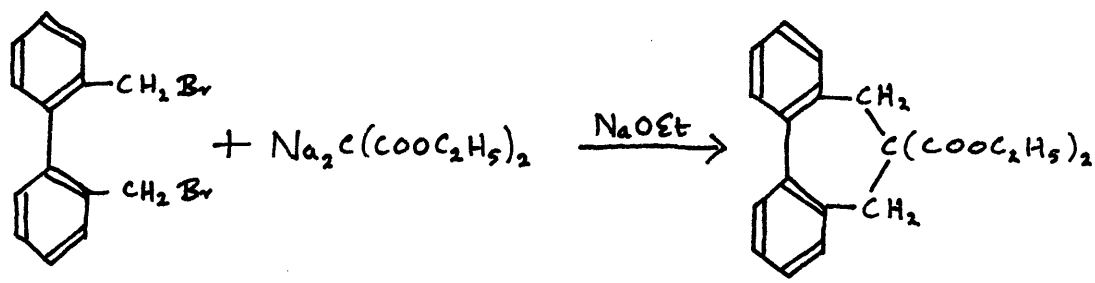


(LXVII)



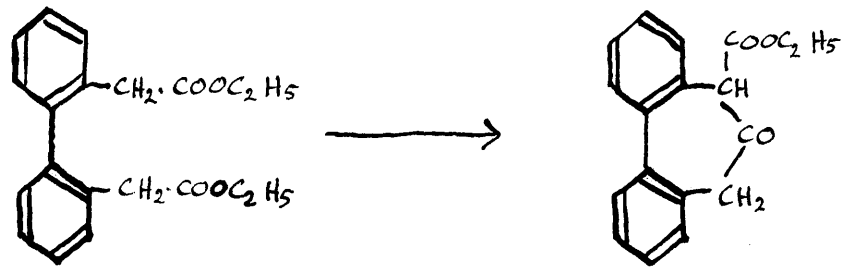
(LXVIII)

The other two methods are as follows[36]. ωω'-Dibromo-2:2'-ditolyl (LXIX) is condensed with ethyl malonate in the presence of sodium ethoxide to give diethyl-3:5-dibenz-$\Delta^{3:5}$-cycloheptadiene-1:1-dicarboxylate (LXX), and diethyl-2:2'-ditolyl-ωω'-dicarboxylate (LXXI) on heating



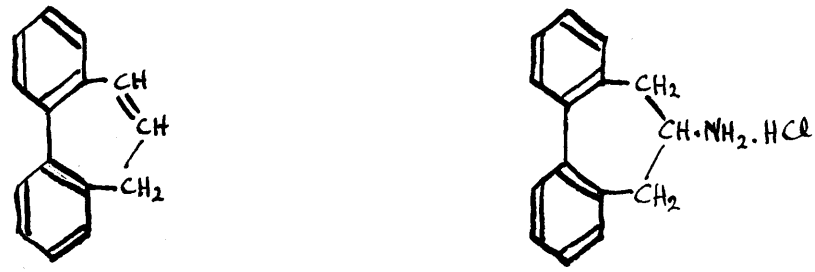
(LXIX) (LXX)

with sodium in benzene (Dieckmann) gives ethyl-3:5-dibenz-$\Delta^{3:5}$-cycloheptadiene-1-one-2-carboxylate (LXXII).



(LXXI) (LXXII)

From these two products Kenner prepared a number of derivatives, including dibenz cycloheptatriene itself (LXXIII). This was obtained, as an oil from which a crystalline picrate was isolated, by heating the amine hydrochloride (LXXIV), itself obtained either from (LXX) or (LXVIII).



(LXXIII) (LXXIV)

Other interesting but less important examples of the preparation of dibenz cyclohepta-dienes and -trienes have been reported by Weitzenböck[37] and by Borsche and Herbert[38].

The initial reactions on which the above methods are based are normal Ullmann reactions, which only give unsubstituted or symmetrically substituted diphenyls. Consequently the methods as they stand are unsuitable for

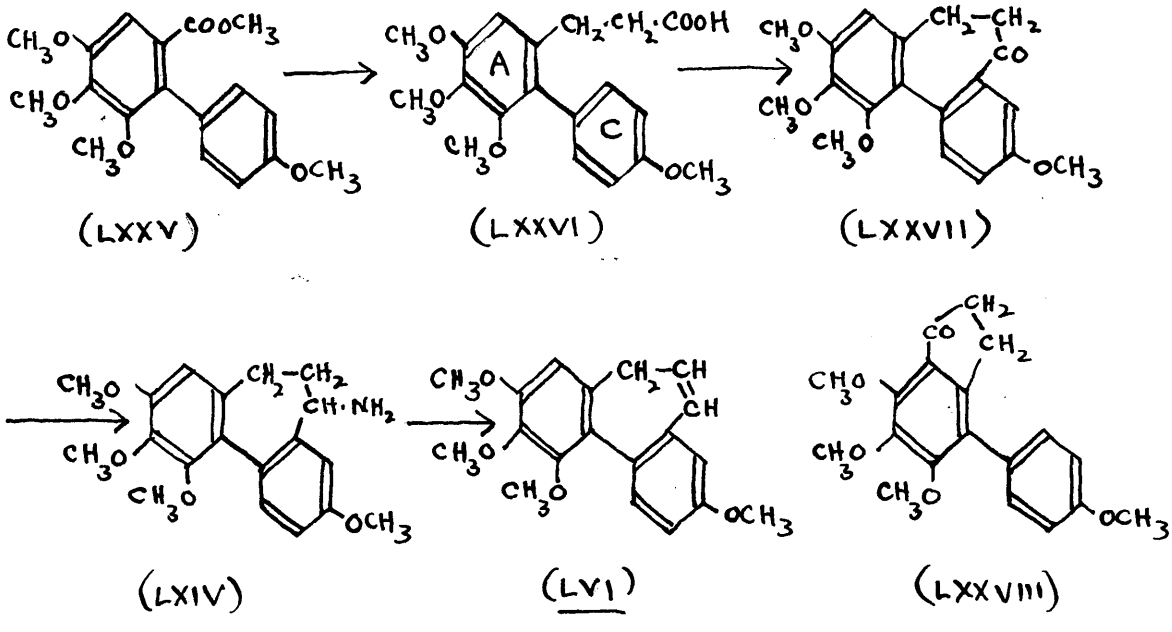
the preparation of unsymmetrically substituted dibenz cycloheptatrienes, into which class deaminocolchinol methyl ether falls.

There are of course examples[39) to 47)] of the preparation of seven-membered carbon ring compounds, such as benzsuberone, which are not dibenz cycloheptadienes and -trienes.

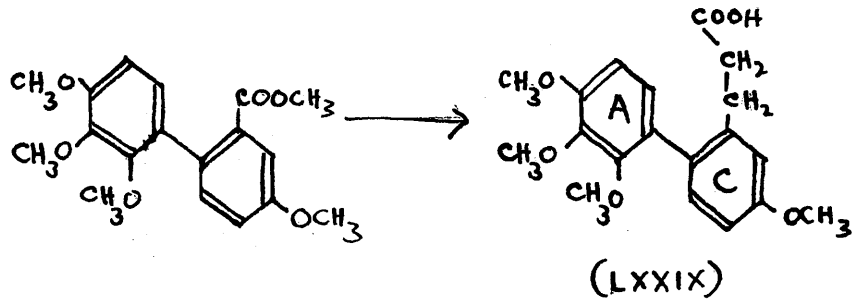
II.

For a variety of reasons synthetic methods involving intramolecular ring-closure of an acyl halide were thought to be most worthy of attention as possible routes to deaminocolchinol methyl ether.

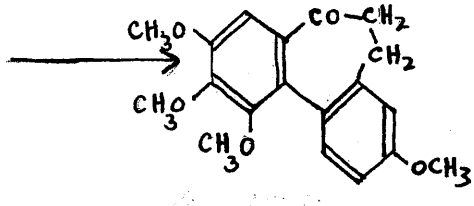
Eventually a synthesis was projected whose essential stages were as follows:-



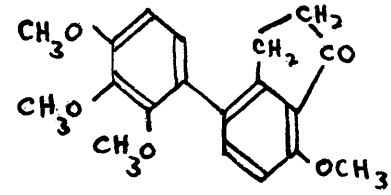
It was realised that the acid (LXXVI) might be expected to give the ketone (LXXVIII) in preference to (LXXVII). For not only are five-membered ring compounds formed more readily than seven-membered ring compounds (see later, page 62), but the free position in the trimethoxylated nucleus (ring A) is strongly activated since it is ortho to one methoxyl group and para to another. As a possible means of overcoming this difficulty an alternative synthesis was considered:-



(LXXIX)



(LXXX)



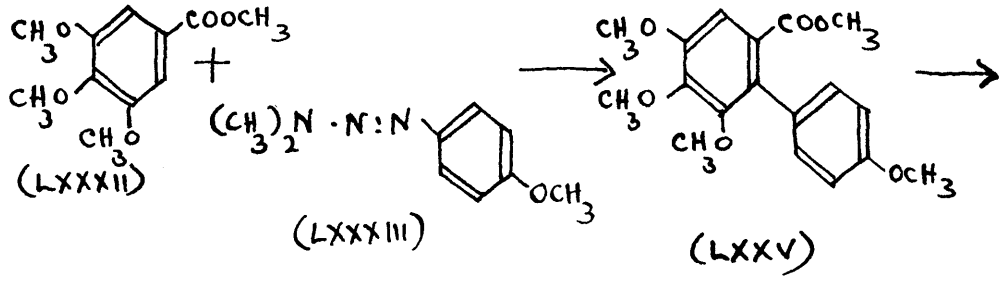
(LXXXI)

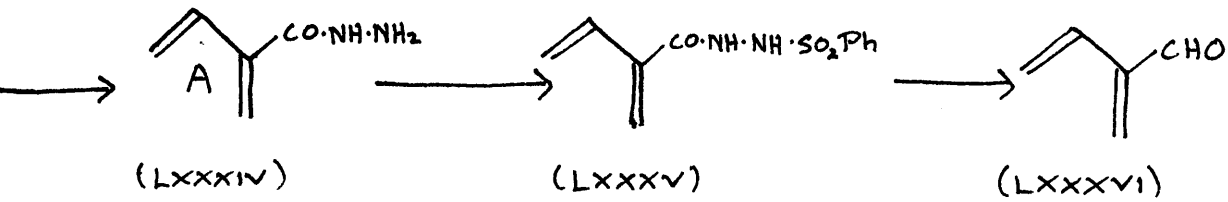
But even here, though the free position in the trimethoxylated nucleus (ring A) should be activated more strongly than that in the monomethoxylated nucleus (ring C), this factor might be outweighed by the tendency to prefer the formation of five- over seven-membered rings, giving (LXXXI) rather than (LXXX).

Moreover, the original project includes the preparation of the amine (LXIV), which would be an important contribution to the study of the structure of colchinol methyl ether, as has already been explained (page 49). This factor turned the scale in favour of the first route.

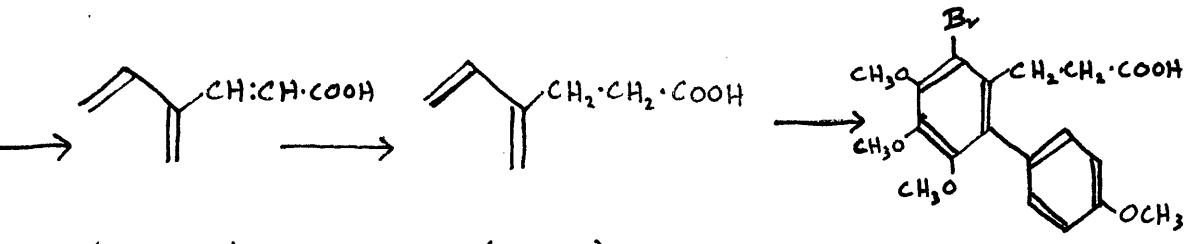
But the problem of avoiding the formation of the five-membered ring compound (LXXVIII) had still to be solved. The greater reactivity to be expected in ring A, however, itself offered hope of a solution. If the free position in ring A were first blocked by substitution, ring-closure could only occur in the sense (LXXVI) ⟶ (LXXVII), and the blocking substituent could be removed after ring-closure.

The final project, then, now given in greater detail, stood as follows:-

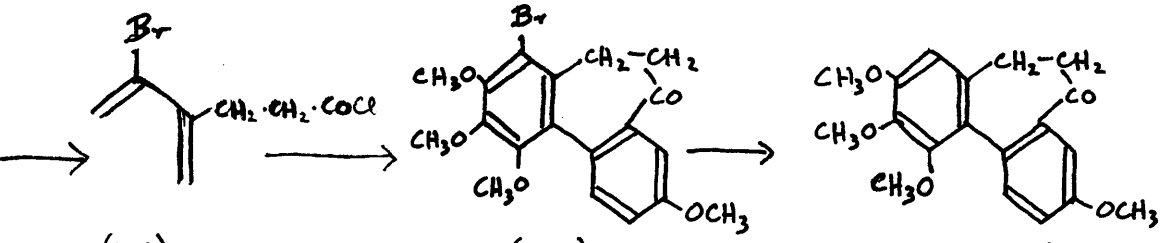




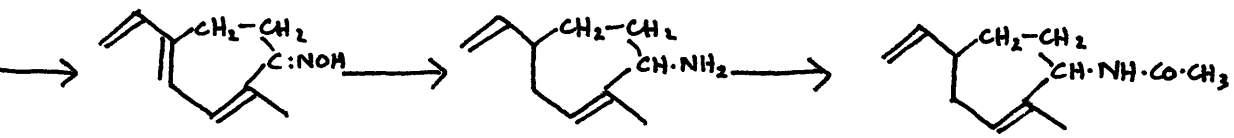
(LXXXIV) (LXXXV) (LXXXVI)



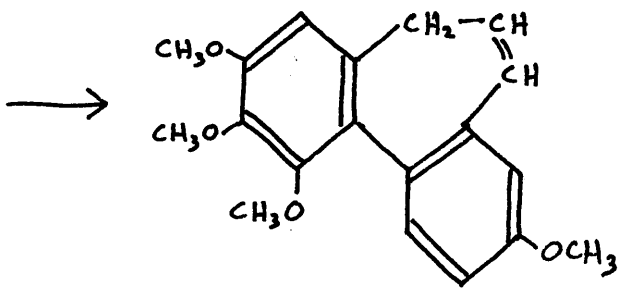
(LXXXVII) (LXXVI) (LXXXIX)



(XC) (XCI) (LXXVII)



(XCII) (LXIV) (XCIII)

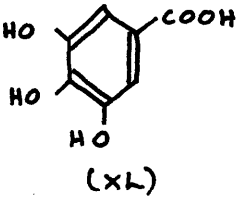


Deaminocolchinol methyl ether

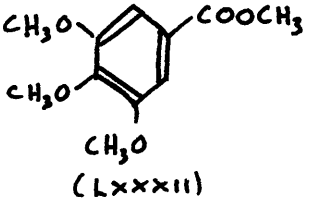
These steps will now be discussed individually.

III.

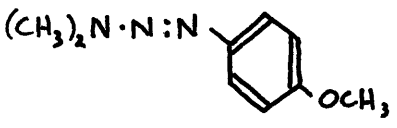
The synthesis began with the preparation of methyl-3:4:5-trimethoxybenzoate (LXXXII) by normal methylation and esterification methods from gallic acid (XL). This was used to prepare methyl-2-(p-methoxyphenyl)-3:4:5-trimethoxybenzoate (LXXV) by reacting it with 1-p-methoxyphenyl-3:3-dimethyltriazen (LXXXIII) by the method of Elks and Hey[48].



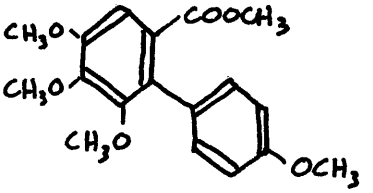
(XL)



(LXXXII)



(LXXXIII)

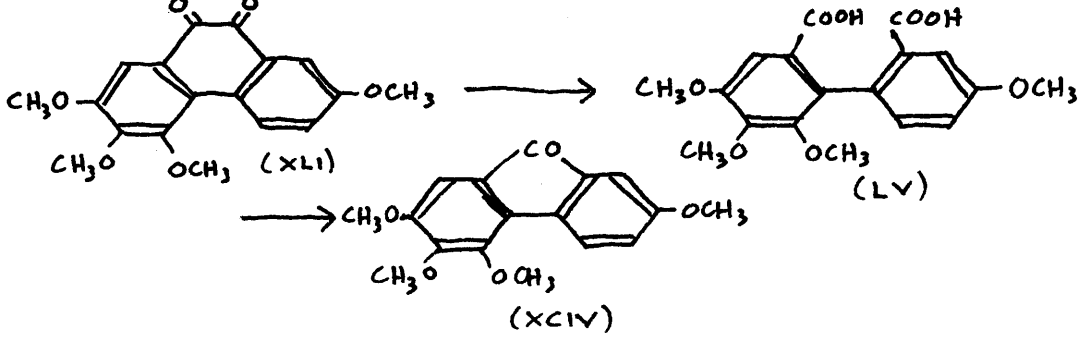


(LXXV)

1-Aryl-3:3-dimethyltriazens are easily prepared compounds, the present example (LXXXIII) being obtained from diazotised p-anisidine and dimethylamine. They are surprisingly stable in the free state, and in neutral or alkaline solution. In acidic media they regenerate the diazo-

compounds from which they are prepared, but if a second aryl component having a suitable unsubstituted position is present, a bi-aryl is formed. In the present case the reaction proved to be satisfactory, if somewhat tedious on account of the low yields, which necessitated the recovery and further treatment of unreacted methyl trimethoxybenzoate.

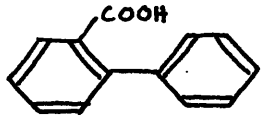
The constitution (LXXV) assigned to the main product of the reaction was confirmed by a simple but conclusive experiment. The acid obtained by hydrolysis of the ester (LXXV) was treated with thionyl chloride, and the acid chloride formed readily lost hydrochloric acid on warming in thionyl chloride. A red substance was formed, having ketonic properties, and its analytical figures were in agreement with its formulation as a fluorenone. Huntress and his collaborators have shown[49] that diphenic acid on heating is readily converted to fluorenone. A small quantity of 4:5:6:4'-tetramethoxydiphenic acid (LV), obtained by oxidation of synthetic 2:3:4:7-tetramethoxyphenanthraquinone (page 30) (XLI), was now heated, and a red gum was obtained. This on purification gave a red solid which by analogy with the behaviour of diphenic acid (Huntress) is designated 2:3:4:7-tetramethoxyfluorenone (XCIV).



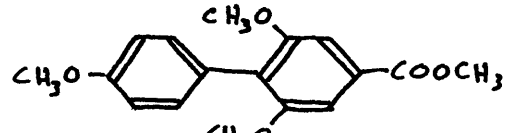
This substance proved to be identical with the ketonic substance obtained from the main reaction product via the acid chloride. This acid chloride must therefore be an ortho-phenylbenzoyl chloride derivative, and the constitution (LXXV) assigned to the parent ester is confirmed.

Besides the main product, a smaller quantity of a by-product, which proved to be of some interest, was isolated. Analysis, for carbon, hydrogen, and methoxyl, of the acid formed from the by-product on hydrolysis, gave figures which suggested that demethoxylation had occurred. Analysis figures consistent with those for the parent acid were obtained for the amide, which had been prepared from the acid chloride. The fact that the acid chloride, unlike that prepared above, can be isolated under the conditions used, and can be converted to the amide, would appear to exclude a structure based on ortho-phenylbenzoic acid (XCV).

The constitution (XCVI) is tentatively put forward



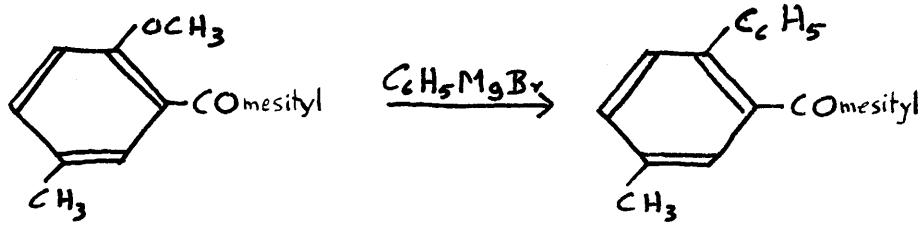
(XCV)



(XCVI)

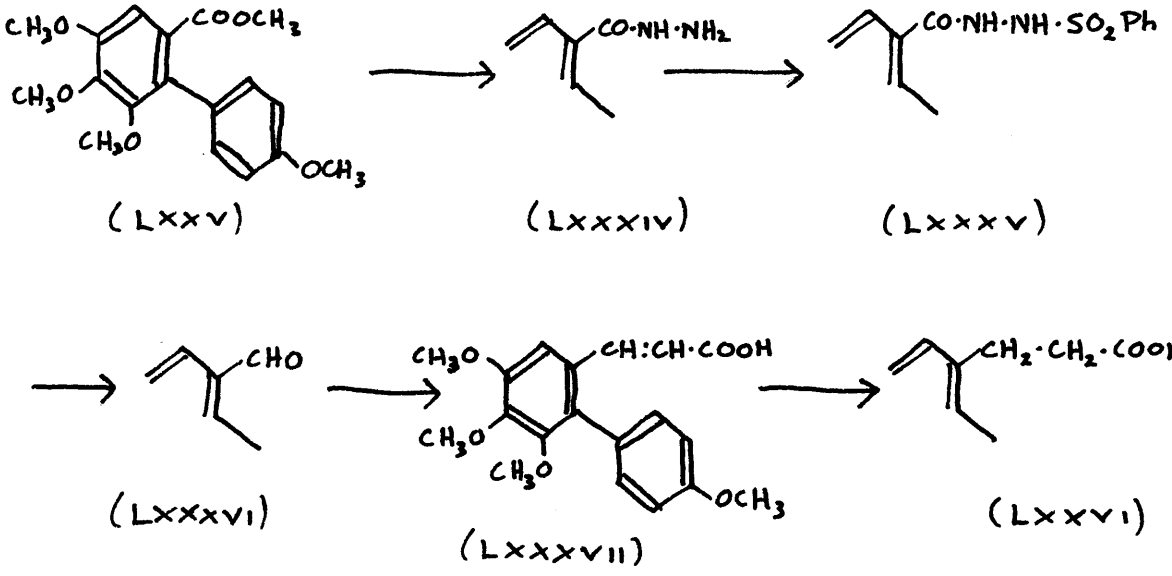
for the by-product, in which the para-methoxyphenyl residue has displaced one of the methoxyl groups of the original trimethoxybenzoic acid. In this connection may be mentioned the fact that Fuson and Speck[50] were able to replace a

methoxyl group by an alkyl or an aryl residue when compounds of the type (XCVII) were treated with alkyl or aryl magnesium bromides.



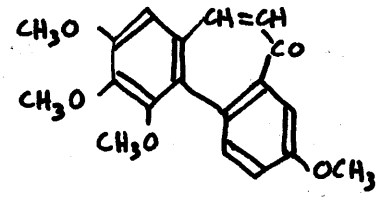
(XCVII) (XCVIII)

The conversion of (LXXV) to the aldehyde (LXXXVI) was effected by the McFadyen-Stevens method[51]. This involved preparation of the hydrazide (LXXXIV), and from this the benzenesulphonhydrazide (LXXXV), which with sodium carbonate in ethylene glycol at 160° gave the desired aldehyde.



(LXXV) (LXXXIV) (LXXXV)

(LXXXVI) (LXXXVII) (LXXVI)



(XCIX)

Doebner's modification of the Knoevenagel reaction proved to be eminently satisfactory for the formation of the substituted cinnamic acid (LXXXVII).

It was realised that stereochemical considerations might favour ring-closure of (LXXXVII) to give the unsaturated ketone (XCIX). However, an attempt to effect such a ring-closure with liquid hydrogen fluoride[x] failed, for a negligible quantity of neutral material was obtained, and 80% of the acid was recovered unchanged.

Consequently(LXXXVII) was converted into (LXXVI) by catalytic hydrogenation.

IV.

At this point the possibility of (LXXVI) giving on cyclization not (LXXVII) but the five-membered ring compound (LXXVIII) had to be considered.

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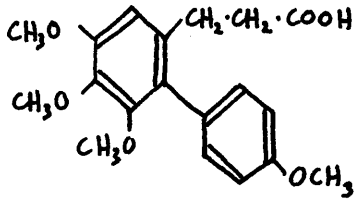
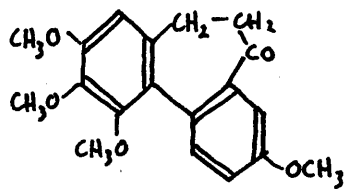
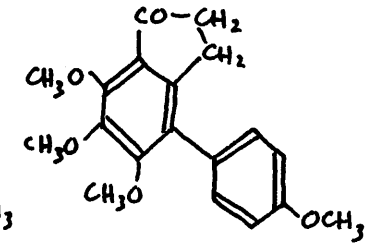
[x] Cf. Fieser and Hershberg[52].



(LXXVI)



(LXXVII)

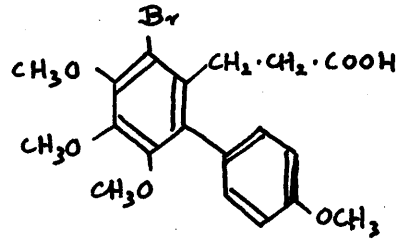


(LXXVIII)

The work of von Braun and his collaborators[53] has shown that in competitive Friedel-Crafts reaction formation of a five- takes preference over formation of a seven-membered ring. In addition, there is clear evidence that cyclization is facilitated when a position is activated by ortho and para directing groups. In this particular case the free position in the trimethoxylated nucleus is ortho to one methoxyl group, and para to another, hence strong activation is to be expected. Furthermore, the point of ring-closure involved in the formation of the seven-membered ring of (LXXVII) is meta to a methoxyl group, a circumstance observed to be unfavourable to ring-closure (see later, page 64).

All factors therefore conspired to facilitate the formation of (LXXVIII), and (LXXVI) was treated with hydrogen fluoride in the full expectation that this would occur. The acid was converted by this reagent to a neutral product having carbonyl properties, which was held for reference.

In order to block the highly reactive position in the trimethoxylated nucleus, and hence prevent closure to a five-membered ring, the acid (LXXVI) was brominated. A good yield of a monobromo compound, assumed to be (LXXXIX) was then obtained.



(LXXXIX)

Anticipating a little, it may be said that after ring-closure of this mono-bromo compound, and removal of the bromine, a ketonic product was obtained which was quite distinct from that formed by ring-closure of the unbrominated acid (LXXVI). This was exactly what had been predicted, and was considered to support the supposition that the ketonic product obtained from the unbrominated acid contains a five-membered ring, whilst the product from the brominated acid contains a seven-membered ring.

V.

Now that the most easily substituted position was blocked, some difficulty was to be expected in effecting ring-

closure. In the first place the known order of ease of cyclization - six-carbon ring > five > seven[x] - was not encouraging, and in the second place it is clear from empirical observation that a position meta to an ortho-para directing group such as methoxyl is deactivated with respect to ring-closure[xx]. This is in surprising conflict with the conclusions of the electronic theory, which asserts that electron repelling groups activate the whole nucleus, and that their ability to function as ortho and para directors rests simply on the fact that these positions are activated more strongly than the meta positions.

Ring-closures meta to ortho-para directors have been carried out, however[xxx], though no example of the formation

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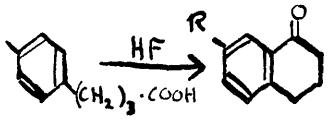
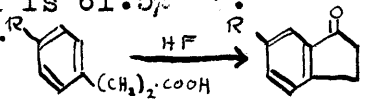
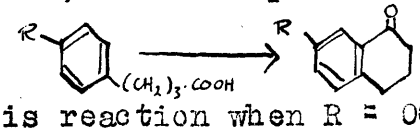
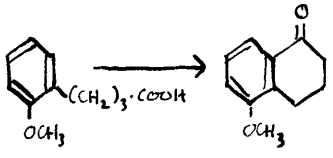
[x] See page 62

[xx] For example, in the reaction :— 

when R = H the yield is 92%[52], when R = OCH_3 the yield is 61.5%[56].
Similarly, in :— 

when R = H the yield is 73%[52], when R = OCH_3 the yield is 3% (Johnson and Shelberg, quoted in Organic Reactions Vol.II, page 120).

[xxx] In addition to the examples cited in the previous foot-note, see Krollpfeiffer and Schäfer[57] :-


when R = CH_3, C_2H_5, OCH_3.
Also Haworth and Sheldrick[58] for this reaction when R = OCH_3.
Lockett and Short[59] :-


of a seven-membered ring in this way has been found in the literature. In view of all these considerations, it was decided to concentrate attention on what appears to be one of the most powerful cyclizing agents - viz., aluminium chloride.

Of other agents tried later, phosphorus pentoxide in xylene gave a non-ketonic product, neither hydrogen fluoride nor concentrated sulphuric acid were of any value, and phosphorus pentoxide-syrupy phosphoric acid was inferior to the best of the aluminium chloride cases. In a single experiment aluminium bromide was found to be no better than aluminium chloride, and although its use was attractive in so far as it is known not to debrominate[54], yet its known tendency to cause demethylation[55] decided against further exploration of its value in this particular case.

Anticipations of difficulty were more than substantiated! This cyclization did in fact prove to be extremely troublesome. Furthermore, the results were very difficult to interpret, the more so because they were not always reproducible; conditions which at one time gave good results, later led to almost total failure.

It was possible to recover the unreacted acid, but the quality of this varied so much that it was not easy to assess its significance when estimating the value of any given set of reaction conditions. Moreover, it was not until

many experiments had been done that the presence of demethylated material (having very feeble acidity) was definitely established, so that the extent to which it occurred in the earlier experiments is not known. These two factors are discussed in more detail below. Finally, in spite of one trial experiment which seemed to indicate that it was not so, there is some ground for suspecting that serious loss of material occurred if the product was distilled, as it frequently was, from the crude reaction mixture. In later experiments, however, the distillation was eliminated, and the crude product was purified by chromatography. The material thus obtained could be satisfactorily debrominated without further purification.

Of the many experiments performed in the investigation of this one reaction, the results of only a selection are given in the Experimental section.

On three points only, namely, the nature of the solvent, and the quality and quantity of the condensing agent, was it possible to draw conclusions with any confidence. Carefully purified carbon disulphide, and aluminium chloride from a newly-opened bottle, were almost certainly advantageous. When the aluminium chloride was purified by sublimation, on the other hand, the main reaction was not improved, and side-reactions probably occurred to a greater extent. Similarly, the use of nitro benzene instead of

carbon disulphide increased the yield of unwanted phenolic material, and gave greater quantities than hitherto of a high-melting substance to which no constitution could be assigned. A fairly high proportion of aluminium chloride was favourable, 2.0 or 2.5 molecular proportions as against 1.0 molecular proportion led to an improvement in the quality, and to some extent in the quantity, of the ketonic product.

Refluxing the reaction mixture (when carbon disulphide was used) was probably detrimental, for when this was done the products almost invariably would not crystallize. When the reaction was carried out by allowing the mixture to stand in the refrigerator or in ice, the duration of the reaction, which varied from 18 to 92 hours, did not appear to be significant.

It has already been stated that the quantity of unreacted acid recovered was sometimes misleading, since its quality was not easily ascertained. In some cases straightforward crystallization gave material of a quality sufficiently high to permit its use in further cyclizations, whilst in others, more numerous, it was necessary to esterify, distil and crystallize the ester, which then gave good quality acid on hydrolysis and further crystallization. Sublimation of the acid itself was possible, but led to an unsatisfactory product, and was attended by some losses.

The presence of demethylated material in the product was a more serious hindrance. The occurrence of an impurity had been suspected for some time before it was confirmed, since the melting point of the ketone obtained was always wide after one crystallization, and further purification was wasteful. Yet the presence of phenolic material was thought to be unlikely, since the crude product was usually extracted with chloroform and then washed with caustic soda solution, a procedure which was expected to remove phenolic material. It was only when ether was used as the extracting solvent that the presence of a second component was definitely established; for this second component, readily soluble in chloroform, was sparingly soluble in ether, and remained as suspended matter during the extraction. It was isolated by virtue of its chloroform solubility, and was obtained as a crystalline material with physical properties similar to those of the main reaction product. Analysis indicated that demethylation of one methoxyl group had occurred, and this was at once confirmed by the ferric chloride test, which was negative for the fully methylated ketone. It is not known which methoxyl group had suffered demethylation. Because of its feeble acidity, the substance may be said to be a crypto- or pseudo-phenol[60]. Subsequently it was found possible to separate it easily from the main product by chromatography. On methylation it gave, in low yield, a

product identical with the fully methylated ketone.

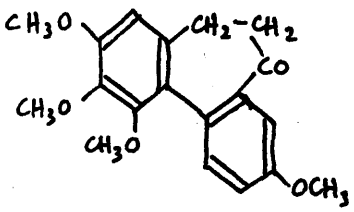
Eventually the poor yields and other difficulties had to be tolerated, and the bromo-ketone slowly amassed by laborious repetition.

VI.

Removal of bromine from the bromo-ketone presented no difficulty, even when impure bromo-ketone was used. Busch and Stöve[61] describe the quantitative removal of halogen from aromatic compounds by the action of hydrogen in the presence of palladised calcium carbonate, the reaction being carried out in alcoholic caustic potash. In this case, since a convenient supply was to hand, palladised strontium carbonate was used as the catalyst, and the presence of potassium hydroxide was found to be unnecessary.

Some complications which arose in the early experiments were later seen to be due to the presence of a high proportion of phenolic material in the bromo-ketone. A debromination product which gave a deep violet colour with ferric chloride was obtained from one of these early experiments. Its analysis figures agreed with those calculated for a mono-demethylated ketone.

Pure ketone, assumed to have the structure (LXXVII), was readily obtained when the starting material was freed



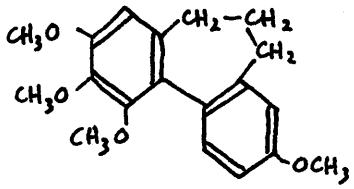
(LXXVII)

from phenolic impurities by chromatography. It was not necessary to crystallize the chromatogram product before debrominating.

VII.

Now that bromine-free ketone was available, two important reactions which lay off the main line of the synthesis of deaminocolchinol methyl ether, but which nevertheless were of great importance, could be attempted.

The first of these offered an immediate link with the natural products, for if the ketone is correctly represented by (LXXVII), reduction of the ketonic group to a methylene group would give (C), which is the dihydride of deaminocolchinol methyl ether.



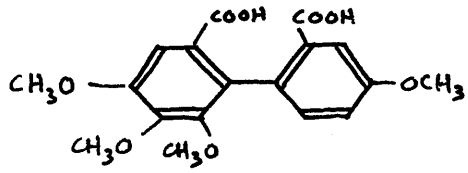
(C)

Accordingly a small sample of the ketone was treated with hydrazine hydrate in ethanol with a view to preparing

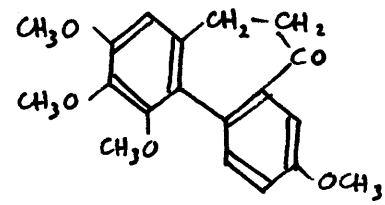
the hydrazone for use in a Kishner reduction[67]. The product, however, proved to be unsuitable for this, since it did not melt below 210°, and consequently no homogeneous melt was obtained with potassium hydroxide at 120°. Melting did not occur until the mixture was heated to 200°, but this high temperature caused resinification, and no crystalline product could be obtained.

It is possible that the original material was not a hydrazone but a ketazine ($R_2C{:}N.N{:}CR_2$)[68]. An impure sample of it heated with hydrazine hydrate in a sealed tube at 200° however failed to yield a crystalline product, whereas ketazines are said[68] to be reduced under these conditions to hydrocarbons ($R.CH_2.R$). This experiment had to be abandoned in view of the small amount of ketone available.

The other reaction mentioned above was an oxidation, by means of which it was hoped that information regarding the direction of ring-closure of the bromo-acid might be obtained. If the diphenic acid (LV) (which had been synthesized earlier)



(LV)



(LXXVII)

could be isolated on oxidation of the ketone, this would provide clear support for the supposition that the ring-closure had taken place in such a way as to give the desired seven-membered ring ketone (LXXVII).

6-Nitro-1-hydrindone (CI) is known to give a homophthallic acid on oxidation with chromic acid[69], but yields 4-nitrophthallic acid with alkaline potassium permanganate. The oxidation of the ketone was therefore undertaken with alkaline potassium permanganate in the hope that it would proceed to the diphenic acid stage. Some difficulty was encountered owing to the very low yield of acidic material obtained, but eventually the oxidation product, though not obtained completely pure, was shown to be quite distinct from the diphenic acid (LV). Of the acids encountered in this synthetic work the one which lay nearest to the new product in melting point was 2-(p-methoxyphenyl)-3:4:5-trimethoxybenzoic acid (CII), but a mixed melting-point determination showed that the new acid was not (CII). Its constitution remains unknown. This result does not prove that the ketone in question does not have the structure (LXXVII), but as a consequence of it the main synthesis had to be resumed lacking the hoped-for confirmation of the structure assigned to the ketone.

VIII.

A ketoxime was readily prepared from pure ketone by the usual method. It was a crystalline solid of melting-point 218-219°. When impure ketone which had its origin in remethylated phenolic bromo-ketone was used a second product was also obtained. This had a different crystalline form, and a melting point of 59°. Both products analysed correctly (carbon and hydrogen) for the required ketoxime. It is possible that they are syn and anti forms of the same oxime, but time did not permit inquiry into this. The ethanolic mother-liquors left after isolation of the above two substances were boiled with a drop of concentrated hydrochloric acid to see whether any low-melting material remaining in them would be converted into the high-melting substance. After standing for several days a good crop of a third product, melting point 95°, was obtained. This was not ketonic, and did not contain nitrogen. At the moment of writing no other analytical figures are available, and the constitution of this substance remains unknown.×

For the reduction of the oxime to an amine the method of Paul[70] was employed. This consists of a catalytic hydrogenation using Raney nickel at approximately 80° and a pressure of 50 atmospheres of hydrogen. It is claimed that

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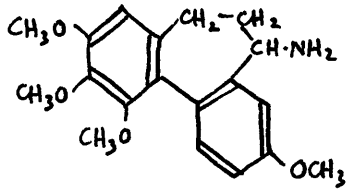
× It was later shown to be the methyl ether ester of 2-(p-methoxyphenyl)-3:4:5-trimethoxyhydrocinnamic acid (LXXVI).

under these conditions secondary amine formation is negligible.

In this case the high-melting oxime was dissolved in ethanol for the hydrogenation. The product yielded a picrate of sharp melting point, and analysis of the picrate (for nitrogen) was in fair agreement with the supposition that one molecule of base was combined with two molecules of picric acid. The base was liberated from the picrate, and an attempt was made to prepare an acetyl derivative, but only an uncrystallizable gum was obtained.

It was then discovered that the autoclave which had been used for the hydrogenation was contaminated with catalyst from a previous experiment, and possibly with organic material. This experiment was consequently considered to be of doubtful value, and the hydrogenation was repeated on a further sample of oxime. The picrate which was obtained this time was darker than that previously obtained. Its melting point was vague, but on the whole higher than formerly

If the base formed by hydrogenation of the oxime has the structure (LXIV), it should be comparable with colchinol methyl ether. This point has already been discussed (page 49 et seq.). Whilst a rigid comparison could only be made after resolution of the synthetic product, it was considered to be of interest to compare the melting



(LXIV)

points of the natural products and the unresolved synthetic products. For if the synthetic compounds were dl-mixtures, as distinct from racemic compounds, their melting points should be raised by admixture with the natural optically active compounds. A depression of the melting point would indicate either that the synthetic substance was a racemic compound of the same structure as the natural product, or that the two compounds had different structures.

The picrate of colchinol methyl ether was prepared for comparison with the synthetic picrate. There appeared to be a slight depression of the melting point on mixing, but this was not very definite owing to the indistinct melting range of the synthetic picrate.

A hydrochloride of sharp melting point was easily prepared from base which had been recovered from the crystallized picrate. The only sample of colchinol methyl ether hydrochloride available had a wide and rather low melting point; a mixture of the two hydrochlorides showed a distinct melting point depression.

Moderately pure hydrochloride was basified, and the amine thus obtained readily gave a solid acetyl derivative by the usual method. It was distinct in crystalline form from N-acetylcolchinol methyl ether, and its melting point was 20° lower than that of the natural material. A distinct melting point depression was obtained on mixing the two substances.

Thus no definite conclusions could be drawn from the melting point observations. Yet the closeness of the melting points of the synthetic and the natural products was not without interest.

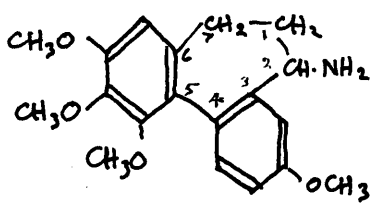
IX.

The final step in the synthetic scheme was deamination of the amine formed by hydrogenation of the oxime and assumed to have the structure (LXIV). The phosphorus pentoxide method (elimination of acetamide from the N-acetyl derivative; see page 15, footnote) was applied to the acetyl derivative of the amine, but it gave a product which differed from deaminocolchinol methyl ether. It was considerably less soluble in methanol, and separated as an oil which unlike deaminocolchinol methyl ether was very difficult to crystallize. Chromatography separated the product into two fractions, but both were still resistant to crystallization. The larger fraction was distilled, yielding a product which with some difficulty gave well-formed crystals, accompanied by much oily material, from methanol. The crystals, however, had a micro melting-point at least 20° below the melting points of deaminocolchinol methyl ether and its isomer, and about 10° lower than the lowest melting point observed for a mixture of the two natural products. In addition, the micro melting point of a slightly impure sample was depressed about 4° by admixture with deaminocolchinol methyl ether. It therefore seems fairly

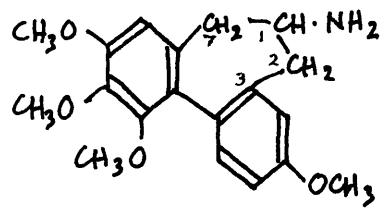
certain that the product is not deaminocolchinol methyl ether or its isomer.

A sample of the product showed no sign of picrate formation in methanol, indicating that no rearrangement to a phenanthrene derivative had occurred. Analyses of the hydrogenation products are to be carried out later, but further examination of the reaction product has not been possible since the author has had to cease work on this subject.

It is only possible at present to speculate on the reasons for this result. There are of course a number of uncertainties in the synthesis - for example, the structure of the bromo-acid (assumed to be (LXXXIX)) has not been rigidly established, nor is there proof that the cyclization of this acid gives a seven-membered ring. Furthermore, colchinol methyl ether may be (CIII), and not (LXIV), in which case the



(LXIV)



(CIII)

greater reactivity to be expected of a hydrogen atom at position 2 might lead to easy elimination of acetamide, whereas in the synthetic compound (LXIV) this elimination might be difficult or impossible.

PART V. CONCLUSION.

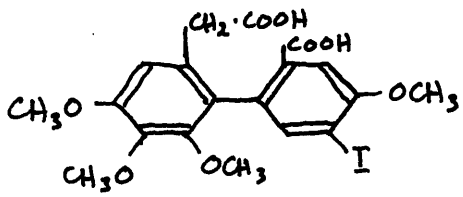
I.

To sum up: the methoxylation pattern of some degradation products of colchicine has been determined, and the structures of deaminocolchinol methyl ether and its isomer have been elucidated by degradative reactions. Although these structures have not been confirmed by synthesis, considerable progress towards this end has been made.

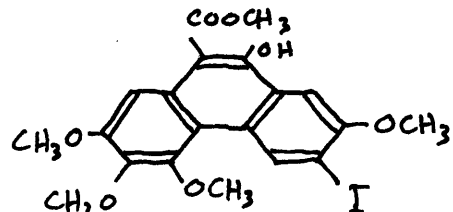
The seven-membered ring-structure proposed for deaminocolchinol methyl ether is not necessarily at variance with the isolation by Windaus of 9-methylphenanthrene after treatment of deaminocolchinol methyl ether with hydriodic acid followed by zinc dust distillation. Under these rather drastic conditions contraction of a seven- to a six-membered ring is conceivable.

II.

Unexpected confirmation of the structure proposed for deaminocolchinol methyl ether, in the form of a paper[71] published in America, has been received as this thesis is being prepared. The authors, working with deaminoiodocolchinol methyl ether, showed that oxidation of this compound with potassium permanganate in acetone gave an acid to which the homodiphenic acid structure (CIV) was assigned. The structure is supported by the isolation from the acid on



(CIV)



(CV)

esterification and treatment with sodium methoxide of an ester claimed to be (CV), the methyl ester of a phenanthrol acid. The authors consider that the homodiphenic acid (CIV) must arise from a cycloheptane structure.

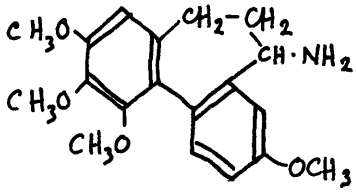
III.

It is interesting to consider whether colchicine itself has a seven-membered middle-ring, and if it has not, to ask at what point in its degradation to deaminocolchinol methyl ether is such a ring formed. It is true that the oxidation of colchicine and some of its degradation products to succinic acid[9], difficult to reconcile with Windaus's structure for colchicine, is readily explained if it is assumed that a cycloheptane ring system is present in colchicine itself. Beyond this, however, little is known at present, and the problem of the structure of colchicine itself remains to be solved.

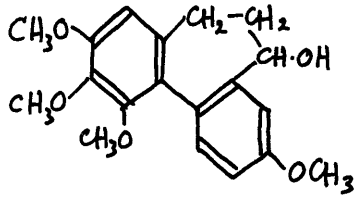
APPENDIX I.

An attempt to locate the position of the amino-group in colchinol methyl ether.

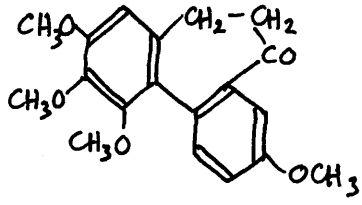
When the ketone (LXXVII) was first obtained, it was realised that it had value as a reference compound by which the exact position of the amino-group in colchinol methyl ether might be located, if the assumption is made that colchinol methyl ether has a seven-membered middle ring (see page 49). For in addition to making possible a synthesis of the structure (LXIV), which may represent



(LXIV)



(XXV)

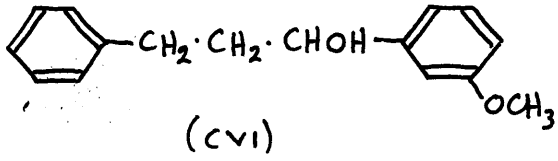


(LXXVII)

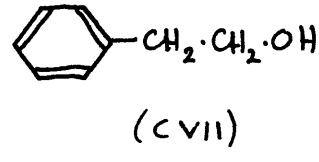
colchinol methyl ether, this ketone may be used in conjunction with the carbinol derived from colchinol methyl ether. If colchinol methyl ether has the structure (LXIV), the carbinol derived from it should be (XXV), and this when suitably oxidised would give the ketone (LXXVII). If the synthetic ketone and that derived from the natural product were found to be identical, the position of the ketonic group, and hence of the hydroxyl group in the carbinol, and the amino group

in colchinol methyl ether, would be located.

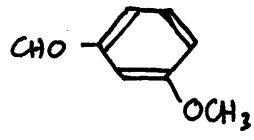
The carbinol, however, was only available in very limited quantities, and it was thought to be desirable to make preliminary trial oxidations with a more plentiful substance, before embarking on the oxidation of the carbinol itself. For this purpose the substance 1-(meta-methoxyphenyl)-3-phenylpropanol (CVI) was chosen. For the synthesis of this compound 2-phenylethanol (CVII) was converted to the corresponding chloride, and the Grignard



(CVI)



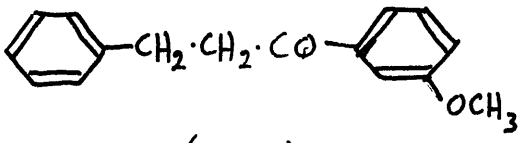
(CVII)



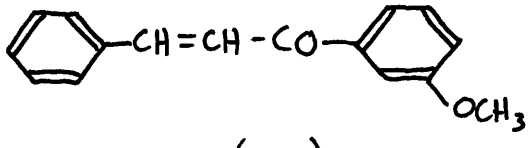
(CVIII)

compound from this was reacted with meta methoxybenzaldehyde (CVIII). The carbinol was obtained as an oil, from which it was not found possible to prepare crystalline derivatives. When treated with aluminium isopropoxide and cyclohexanone (Oppenauer reaction[66]) two products were obtained, a colourless liquid and a bright yellow solid. The colourless liquid analyses correctly as, and is therefore assumed to be,

the expected ketone (CIX). Analysis of the semicarbazone prepared from it supports this. The yellow product is



(CIX)



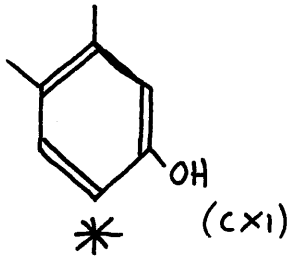
(CX)

apparently isomeric with the oil, but the analysis figures would not seriously conflict with the structure (CX) which might be expected to be yellow. Yet the production of such a chalkone in this reaction would be surprising, and this particular compound is described in the literature[62] as having a melting point distinct from that of the compound actually in question. Nevertheless this structure has not been entirely eliminated, and it was originally intended to investigate the matter further. However, the whole project had to be abandoned since the time available came to an end, and the constitution of the yellow compound remains unknown. Time did not permit the application of the Oppenauer oxidation conditions to the carbinol from colchinol methyl ether.

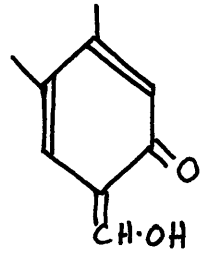
APPENDIX II

Attempts to introduce an ortho-aldehyde group into N-acetylcolchinol.

Ring C of N-acetylcolchinol has the phenolic structure (CXI). If an aldehyde group could be introduced at the position marked with an asterisk, the product should be



(CXI)

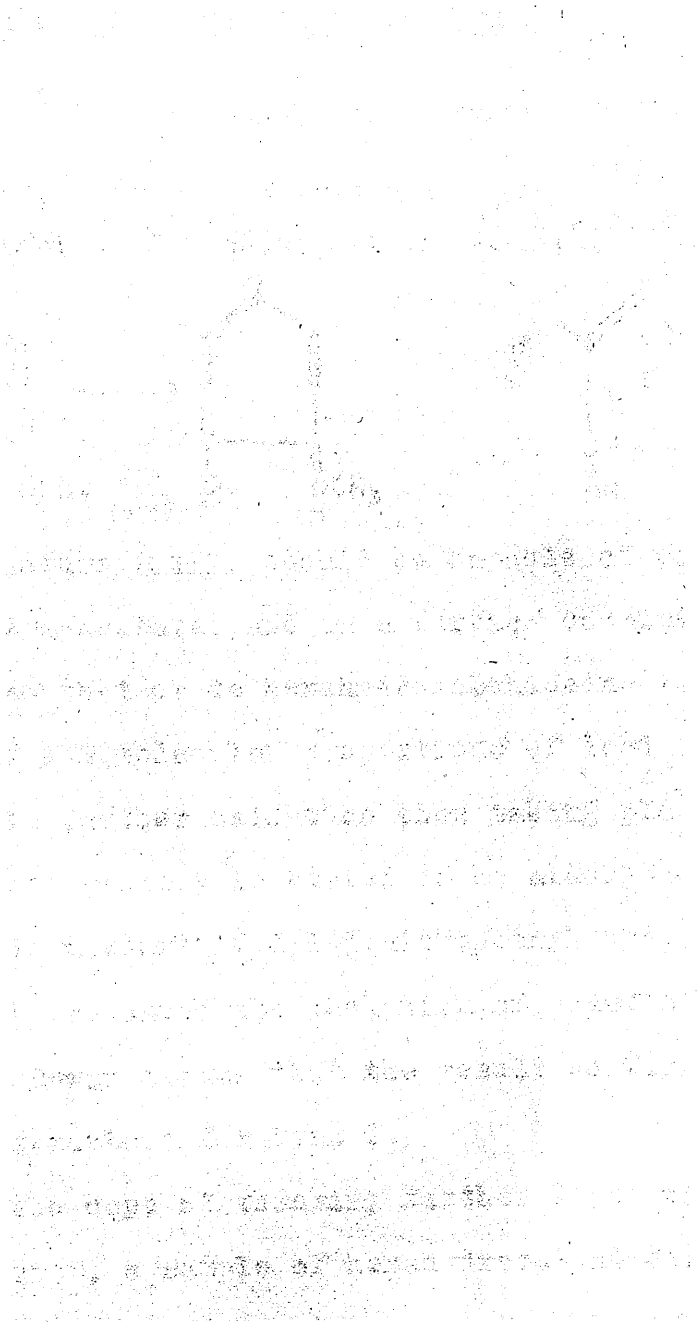


(III)

directly comparable with the structure (III) proposed by Windaus for colchiceine.

A first attempt to introduce an ortho aldehyde group was made using the Adams modification of the Gattermann reaction[63], but this was unsuccessful; most of the phenol was recovered unchanged, and no evidence of the production of a hydroxy aldehyde was obtained. The original Gattermann conditions also gave mostly unchanged phenol, but there was evidence of formation of a hydroxy aldehyde grouping, for the mother liquors gave a yellow colour with aqueous caustic potash. Reimer-Tiemann conditions gave a deeply coloured product which could not be crystallized. Chromatography failed to remove the colour, and alkali extraction, while it gave a lighter coloured product, did not yield any material

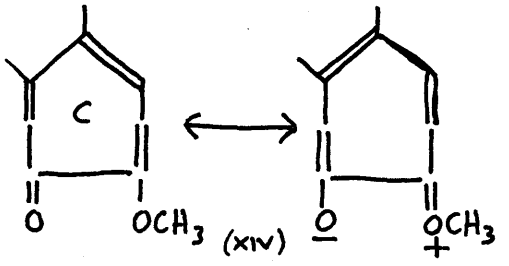
which, after acidification, could be crystallized. The project was therefore abandoned.

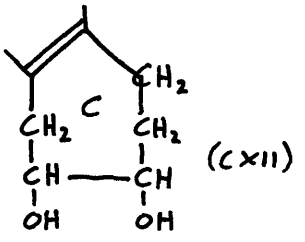


APPENDIX III.

Oxidation of hexahydrocolchiceine.

Dewar[64)18)] proposed the structure (XIV) for ring C of colchicine (see above, page 13). On this basis hexahydrocolchiceine[9)16)] should be an α-glycol (CXII)





Such a structure (CXII) should be capable of oxidation, e.g., by lead tetra-acetate, and in a further communication[65)] Dewar states that crude hexahydrocolchiceine rapidly consumes about 0.6 molecular proportions of lead tetra-acetate, considerable further oxidation then taking place more slowly. The oxidation product is stated to be aldehydic, and to give an amorphous mixture of 2:4-dinitrophenyl hydrazones. Lack of material prevented the isolation of a definite oxidation product. Dewar claims that the result confirms his suggested structure for ring C.

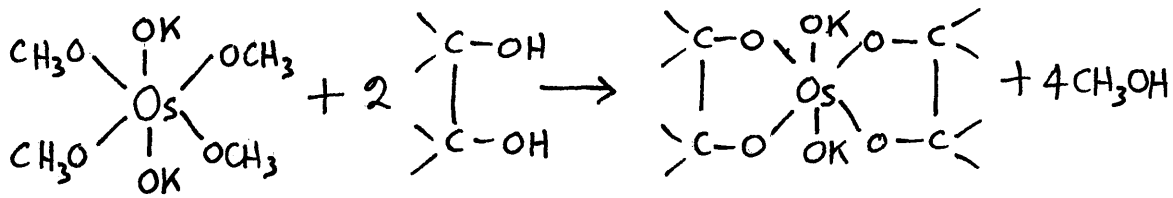
In the hope of throwing further light on this important conclusion, a sample of hexahydrocolchiceine was here oxidised by lead tetra-acetate in tetrachloroethane. As in Dewar's experiment, a carbonyl compound (or compounds) was formed, which could not be crystallized, nor could the

dinitrophenyl hydrazone prepared from it be crystallized. Some evidence was obtained by chromatography that the dinitrophenyl hydrazone was a mixture, but the quantities were too small to enable a definite result to be obtained. It was considered that the evidence available was not sufficient to prove that the oxidation products were aldehydic.

APPENDIX IV

Application of the potassium methyl osmiate test for α-glycols to hexahydrocolchiceine.

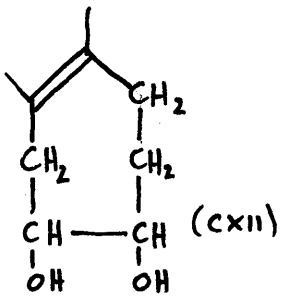
The potassium methyl osmiate test for α-glycols[72] depends on the fact that when an α-glycol is added to a methanol solution of the osmiate (CXIII) esterification occurs:-



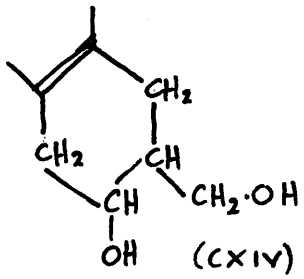
(CXIII)

This esterification takes place readily in the cold, and is accompanied by a colour change in the original blue-green solution. The colour change forms a simple indication that esterification has occurred.

When hexahydrocolchiceine was added to a solution of potassium methyl osmiate in methanol, there was an immediate colour change to green, comparable with that observed with known α-glycols. At first sight this indicates that hexahydrocolchiceine is an α-glycol, and supports Dewar's formula for colchicine, on which basis hexahydrocolchiceine is (CXII) (Appendix III).



(CXII)



(CXIV)

On the basis of Windaus's structure for colchicine, however, the substance is a 1:3-glycol (CXIV) and ought not to give a di-ester with potassium methyl osmiate.

On the other hand it is not certain that di-esters are not formed with 1:3-glycols if the hydroxyl groups are favourably placed for ring-closure. Certainly di-esters are not formed if the hydroxyl groups are not suitably placed, e.g., in trans-diols. For steric reasons a 1:3-glycol such as (CXIV) might form a di-ester. Unfortunately no pure 1:3-glycols were available when the test was carried out, and time did not permit the preparation of any for purposes of comparison.

To sum up; the result of the test appears to support Dewar's rather than Windaus's formula for colchicine, but this support may be fortuitous.

EXPERIMENTAL.

3:4:5-Trimethoxybenzoic acid (XLI). (Org.Synth., 6, 96).

Caustic soda (320 gr.) was dissolved in water (2000 cc.) and allowed to cool. The solution was placed in a three-neck flask and gallic acid (200 gr.) was added. The flask was immediately corked and the contents stirred mechanically till all the acid was dissolved. Dimethyl sulphate (268 cc. ; 356 gr.) was added all at once and stirred for twenty minutes, controlling the mild temperature rise (to 35°) by an ice bath. (Pressure was released by a Bunsen valve). Then more dimethyl sulphate (268 cc.) was added and stirred for ten minutes, keeping the temperature below 45°.

The water bath was then raised to the boil and held there for 2 hours, stirring the contents of the flask under reflux. Then caustic soda (80 gr.) dissolved in water (120 cc.) was added, and stirring and refluxing continued for a further 2 hours to hydrolyse any ester. The solution was cooled and acidified with hydrochloric acid. The pale brown precipitate, after standing for 2 hours, was filtered off and washed with cold water till free from mineral acid. It was crystallized from water (c. 10 litres), charcoaling. The white needles thus obtained were dried at 60 - 70°. 130 gr. (52% yield). M.p. 166 - 167°, with softening at 165°.

3:4:5-Trimethoxybenzoyl chloride.

Trimethoxybenzoic acid (160 gr.), and thionyl chloride (91 cc.) were refluxed for 2 hours (calcium chloride protection). The mixture slowly became mobile, and HCl was evolved. After 2 hours, excess thionyl chloride was removed in vacuo. The residual acid chloride was then distilled, b.p. 172-4/10 mm. The distillate crystallized readily on cooling. M.p. 79 - 80°. 153 gr. (88% yield).

ω -Diazo-3:4:5-trimethoxyacetophenone.

Anaesthetic ether (900 cc.), and 50% potassium hydroxide solution (270 cc.) were cooled to 5° and stirred mechanically. Nitrosomethyl urea (90 gr.) (prepared as Org. Synth., 15, 48) was added portionwise over ¾ hour. The mixture was stirred for ¼ hour, then the ether layer was decanted off, and dried over pellets of potassium hydroxide.

The ethereal solution was filtered by gravity and stirred mechanically, ice-cooling, while the above acid chloride (45 gr.) was added portionwise over 6 or 7 minutes. After stirring for 1 hour in ice, then for 2 hours at room temperature, the solid matter was filtered off and dried in an evacuated desiccator.

35.7 gr. (77.5% yield). Softens 100°, m.p. 101.5 - 102.5°.

3:4:5-Trimethoxyphenylacetamide.

Diazoketone (45 gr.) was added portionwise to 20% ammonia solution (600 cc.), stirring at room temperature. 10% silver nitrate solution (60 cc.) was added and warmed to 50 - 60°. The mixture was stirred at 50 - 60° (no higher) for 3 hours. Water (300 cc.) was added, and the liquid brought to the boil, refluxing for 1 hour. The liquid was then treated with charcoal. From the filtrate on standing in the refrigerator overnight there crystallized long, silky, colourless needles. These were filtered off and dried at 50° for 6 hours. 28.5 gr. (66.4% yield). Recrystallization from water, charcoaling, gave 23.2 gr. (54% yield). Slight softening 116°, m.p. 123 - 124.5°.

A further 26% of the theoretical yield was obtained from the aqueous filtrate and the crystallization mother-liquors by saturating with sodium sulphate at 35°, cooling to 32 - 33° (temperature of maximum solubility of sodium sulphate) and quickly filtering at this temperature. The residue was then crystallized from water, charcoaling.

All aqueous liquids were combined and made acid to Congo Red by dilute nitric acid. The precipitate was extracted with chloroform, the chloroform dried with sodium sulphate, then evaporated. After several crystallizations from benzene/60-80 pet. ether, and finally from absolute

alcohol, a 1% yield of 3:4:5-trimethoxyphenylacetic acid was obtained. M.p. 117.5 - 118.5° with slight softening at 115°.

3:4:5-Trimethoxyphenylacetic acid (XXXV).

The amide (22.1 gr.) and 10 N caustic soda solution (221 cc.) were refluxed for 6 hours. After cooling and neutralizing most of the excess alkali by concentrated hydrochloric acid, the solution was made acid to Congo Red by dilute hydrochloric acid. There was a crystalline precipitate which was filtered off after ice-cooling, and exposed overnight to dry. It was ground and stirred well with chloroform, then filtered from some insoluble matter (1.9 gr.)[x]. The aqueous mother-liquors were extracted well with chloroform, and the two chloroform solutions combined and dried over sodium sulphate. The chloroform was removed, leaving 20 gr. (90.5%) of residue. Crystallization from benzene/60-80 pet. ether gave 18.9 gr. (85.5% yield) of solid. Softens 117°, m.p. 118.5 - 119.5°.

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[x] An analysis, kindly carried out by Dr. Mair, indicated that this material was mainly organic acid with SiO_2 (c. 53%) and sodium salts, either adsorbed or combined.

2-Nitro-5-methoxybenzaldehyde (XXXVI).

a) m-Aldehydophenyl carbonate. (Mason, J.C.S., 1925,127,1195)

m-Hydroxybenzaldehyde (50 gr. ; 97.2% pure) was dissolved in a solution of caustic soda (17 gr.) in water (500 cc.), and saturated sodium carbonate solution (200 cc.) was added. The solution was then saturated with sodium chloride (c. 550 gr.), crushed ice (200 gr.) was added, and the whole divided between two wash-bottles connected in series. Phosgene was passed through the bottles for 1 hour; the bottles were then interchanged and phosgene passed for a further ½ hour, followed by a further ½ hour during which the phosgene was passed more rapidly, the bottles being occasionally shaken.

The brown precipitate was filtered off and washed with cold water till free from sodium chloride. Crystallization from glacial acetic acid gave 42.0 gr. (76% yield) of carbonate, m.p. 130 - 131°.

b) 4-Nitro-3-aldehydophenyl carbonate. (Mason, loc.cit.).

The carbonate (10.8 gr.) was added slowly to concentrated sulphuric acid (120 cc.), stirring well in ice and salt, at 0°. A mixture of concentrated sulphuric acid (20 cc.) and fuming nitric acid (4 cc.) was then added dropwise at 0° - 5° over 15 minutes. The liquid was stirred at 0 - 5° for ¾ hour, then poured on to crushed ice (500 gr.). After

standing for 24 hours the white solid was filtered off and washed till acid-free with cold water. It was dried in an evacuated desiccator over sulphuric acid. 14.2 gr. (98.6% yield). Crystallization from glacial acetic acid, charcoaling, gave 10.25 gr. (71.2% yield) of lemon-yellow solid, which discoloured and softened at 194°, m.p. 200° with decomposition.

On a larger scale the yield dropped to 64.3%. This was found to be due to partial hydrolysis during the crystallization from acetic acid; 2-nitro-5-hydroxybenzaldehyde was precipitated from the mother liquors by addition of water.

c) 2-Nitro-5-hydroxybenzaldehyde. (Mason, loc.cit.).

4% Caustic soda solution (400 cc.) was stirred vigorously in a bath of boiling water, and the nitro-carbonate (34.5 gr.) was added portionwise over 5 minutes. After stirring at 100° for a further 5 minutes, the mixture was cooled to 20° and filtered from a little undissolved material (1.1 gr.). This was shown to be unhydrolysed nitro-carbonate. The filtrate was made just acid to litmus by addition of glacial acetic acid, when yellow plates were precipitated. These were filtered off after the suspension had been allowed to stand in the refrigerator for 2 hours. The solid was dried in an evacuated desiccator over caustic soda. 29.8 gr. (93.1% yield). Softens at 120° and 140°, m.p. 145 - c 160°. (The wide melting point was probably due to the presence of sodium acetate).

d) 2-Nitro-5-methoxybenzaldehyde.

The hydroxy compound (28.8 gr.) was dissolved in caustic soda solution (124 cc. ; concentration 30 gr. NaOH in 350 cc. water). Dimethyl sulphate (31 cc.) was added dropwise over ¼ hour at 40° with stirring. More alkali, at the above concentration, was added as required to maintain alkalinity to Clayton Yellow, and this process was continued until alkalinity persisted. After standing in the refrigerator for 2 hours, the solid which had precipitated was filtered off and washed with a little cold water, then dried in an evacuated desiccator over calcium chloride. Crystallization from rectified spirits, charcoaling, gave 13.5 gr. (43.4% yield) of lemon-yellow needles. Softening 82.5°, m.p. 83 - 84°.

Repeated further methylation of the aqueous mother-liquors and washings gave in all a further 5.7 gr. (18.3%). Total:- 19.2 gr. (61.7% yield).

2-Nitro-5-methoxy-α-(3':4':5'-trimethoxyphenyl)cinnamic acid (XXXVII).

Sodium (2.3 gr.) was dissolved in absolute ethanol (40 cc.). To the hot solution was added 3:4:5-trimethoxy-phenylacetic acid (22.6 gr.). The liquid was cooled in the refrigerator, then sodium-dried ether (2 volumes) was added, precipitating a sticky solid which crystallized on scratching.

This solid was filtered off and, after grinding, dried in an evacuated desiccator over potassium hydroxide, then in an oven at 120 - 130° for 2½ hours. 24 gr. It was stored over potassium hydroxide.

This sodium salt (19.1 gr.), 2-nitro-5-methoxybenzaldehyde (13.9 gr.), and acetic anhydride (190 cc.) were heated in an oil bath at 125 - 130° for 8 hours (protected by calcium chloride). Water (150 cc.) was added, and the whole heated cautiously to 100°. When cool, the liquid was extracted with ether, adding water until separation occurred. During the extraction a brown solid separated; it was filtered off and later combined with the remainder of the product, which was recovered from the ethereal extract by shaking with sodium carbonate solution in 50 cc. portions, followed by acidification with hydrochloric acid.

The crude product was crystallized from methanol. 16.0 gr. (53.4% yield) - Product A, m.p. 119 - 122°, later rising spontaneously to 157 - 158°.

In an earlier experiment the crude product was crystallized from dilute ethanol. From the mother liquors was obtained another acidic substance, product C, which after several crystallizations from methanol was obtained as colourless prisms, m.p. 212° with decomposition. The product which had crystallized from dilute ethanol was separated by fractional crystallization from methanol into two distinct acidic

substances, one of which, of m.p. 137°, later changing spontaneously to 158 - 159°, was identical with product A above. The other was crystallized several times from methanol, and was then obtained as lemon-yellow needles, m.p. 193° - product B.

Product A, crystallized from methanol for analysis, was obtained as yellow needles, m.p. 158 - 159°.
Found C, 58.84; H, 4.69%. $C_{19}H_{19}O_8N$ requires C, 58.61; H, 4.88%.

Product B, m.p. 193°.
Found C, 53.31; H, 5.04; N, 4.28%.

Product C, m.p. 212° with decomposition.
Found C, 63.08; H, 5.45; N, 2.74%.

No constitution has been assigned to products B and C.

2-Amino-5-methoxy-α-(3':4':5'-trimethoxyphenyl)cinnamic acid (XXXVIII).

To ferrous sulphate ($FeSO_4.7H_2O$) (110 gr.) in water (340 cc.) was added 0.880 ammonia (285 cc.). The liquid was warmed to 70° with stirring, and the nitro-compound (15.9 gr.), dissolved in 0.880 ammonia (64 cc.) and water (250 cc.), was added and stirred at 70° for 2 hours. The hot liquid was decanted through a filter funnel, and the residue washed with hot water. The filtrate was cooled and made just acid to

Congo Red by dilute hydrochloric acid. The precipitate was filtered off and washed with water. It was then dissolved in sodium carbonate solution and filtered to remove a very small quantity of undissolved material. The solution was made just acid to Congo Red, and the precipitate filtered off and dried in an evacuated desiccator over potassium hydroxide. 11.3 gr. (77% yield).

A sample prepared for analysis by crystallization from ethanol had m.p. 189 - 190° with some preliminary darkening. It formed white masses of small colourless needles, which became yellow when pressed on to porous plate, and gave yellow alcoholic solutions.

Found C, 63.62; H, 5.97%. $C_{19}H_{21}O_6N$ requires C, 63.51; H, 5.85%.

2:3:4:7-Tetramethoxyphenanthrene-10-carboxylic acid (XXXIX).

(cf. Rapson and Robinson, J.C.S., 1935, 1541).

The amino-acid (11.3 gr.) was dissolved in 2.5 N sulphuric acid (113 cc.) and glacial acetic acid (170 cc.) by warming. (If the warming had been done earlier, it is likely that less acetic acid would have sufficed to give a clear solution). The solution was cooled to 5°, and N sodium nitrite solution (34 cc.) added dropwise with stirring at 0° - 5° over 10 minutes. The solution was stirred for 20 minutes at 0 - 5°, then diluted with cold water (400 cc.) and

neutralized with solid sodium carbonate (c̄ 250 gr.) to methyl red (external). It was warmed to 50° and stirred for 20 minutes, after which time a test portion no longer coupled with alkaline β-naphthol. A tar which had separated was freed from the watery layer by decantation, and then redissolved in water by addition of a little caustic soda. The solution was acidified by dilute hydrochloric acid, and the precipitate filtered off.

More solid was obtained by acidification of the original decanted aqueous portion; it was combined with that already obtained. The combined material was purified by crystallization from dilute ethanol.

Further small quantities were obtained by dilution of the alcoholic mother liquors, extraction with chloroform, and extraction of the chloroform solution with sodium carbonate solution.

Total yield 1.1 gr. (10%). M.p.:- c̄ 186 - 199°. (The low yield may be due to the large amount of acetic acid employed in the diazotisation).

To purify the acid it was esterified by dissolving it in an ethereal solution of diazomethane. Distillation, after the ether had been removed, gave two fractions which were methanically separated:-

Fraction (1). 240-250°/0.2 mm. A clear yellow oil which on crystallization from methanol gave colourless prisms.

M.p. 103 - 104° with softening at 102°.
Found C, 67.51; H, 5.55%. $C_{20}H_{20}O_6$ requires C, 67.42; H, 5.62%.

The pure ester (0.50 gr.) was hydrolysed by refluxing with 5% methanolic caustic potash (5 cc.) for 1 hour. Most of the alcohol was then boiled off, and the residual liquid acidified with hydrochloric acid. The precipitate was filtered off and recrystallized from dilute ethanol. 0.44 gr.

This pure acid was obtained as pale lemon-yellow leaflets, m.p. 200° with softening at 199°.
Found C, 66.58; H, 5.32%. $C_{19}H_{18}O_6$ requires C, 66.67; H, 5.26%.

Fraction (2). 250 - 290°/0.2 mm. A brown solid which on repeated crystallization from methanol gave brown plates, m.p. 210.5 - 211° with shrinking at 209°. This substance was also obtained from the chloroform extract of the crude product, from which the phenanthrene carboxylic acid had been removed by sodium carbonate extraction (see above), by extraction with caustic soda solution followed by acidification.

It was insoluble in sodium bicarbonate solution, soluble in caustic soda to a yellow solution. An alcoholic solution gave no colouration with ferric chloride solution. The substance was unaffected by boiling alcoholic potash. Found C, 63.66; H, 5.45; N, 8.31%. The constitution is unknown.

2:3:4:7-Tetramethoxyphenanthraquinone (XLII) from 2:3:4:7-tetramethoxyphenanthrene-10-carboxylic acid

The acid (0.3 gr.) was dissolved in glacial acetic acid (3 cc.) (distilled over chromium trioxide) at the boil. To the hot solution was added over a period of five minutes a solution of sodium dichromate (0.6 gr.) in water (0.3 cc.) and glacial acetic acid (0.6 cc.). The liquid was refluxed for $\frac{1}{2}$ hour, allowed to cool, then diluted with water (25 cc.). The mixture was then extracted with chloroform, and the chloroform extract washed with dilute sulphuric acid, then twice with concentrated sodium carbonate solution (see below).

The chloroform solution was dried with sodium sulphate, then evaporated to dryness. A solution of the residue in benzene-ligroin (2:1) was passed through a column of alumina, and elution with benzene gave a dark red solution. Concentration of the benzene solution and dilution with ligroin gave crystals when the liquid had stood for a short time. The crystals were of two types - red-violet rods and deep violet prisms; the proportion of prisms increased on standing. M.p.:- 191.5 - 192.5° with some preliminary softening.

A quinoxaline derivative was prepared by adding to a solution of the quinone in hot glacial acetic acid a solution of o-phenylenediamine in warm methanol. The colour was immediately discharged, and presently lemon-yellow crystals formed. The product was recrystallized from methanol.

M.p. 174 - 175° with darkening at 172°. For analysis see next experiment.

The sodium carbonate extract was acidified, and the resulting precipitate crystallized from dilute ethanol. The solid obtained was soluble in sodium bicarbonate solution, and readily soluble in 2N sodium carbonate solution. It softened slightly from 180° onwards, and partially melted at ~ 190°, but did not melt completely until 280°. When the m.p. bath was held at 210° for a few minutes, cooled, and reheated, there was no softening or melting until softening occurred at ~ 250°.

Oxidation of acid A.

Acid A (0.3 gr.) was dissolved in pure glacial acetic acid (7 cc.) and oxidised with sodium dichromate (0.6 gr.) as in the previous experiment.

The product crystallized from benzene-ligroin in two forms as before.

M.p. of prisms:- 192 - 193° with softening at 176° and 186°.

M.p. of rods:- 191.5° with softening at 189°.

A quinoxaline derivative was prepared as before. In this case recrystallization from methanol gave orange needles, and from the mother liquors on concentration lemon-yellow needles were obtained.

M.p. of orange form:- 185 - 186° with softening at 184°.

M.p. of yellow form:- 175 - 177° with softening at 174°.

The yellow form when melted, cooled, and remelted had m.p. 184.5 - 186°.

Mixed m.p. of orange and yellow forms:- 184.5 - 185.5° with softening at 184°.

Samples of both orange and yellow forms were dissolved in hot methanol and allowed to stand. The crystals obtained were intermediate in colour, and had m.p. 184 - 186° with shrinking at 178°.

Found C, 71.98; H, 4.82%. $C_{24}H_{20}O_4N_2$ requires C, 71.99; H, 5.00%.

The sodium carbonate extract was acidified. The product when crystallized from methanol, dilute methanol, dilute ethanol, or benzene-ligroin was invariably contaminated with a red substance. It was therefore sublimed at 190-200°/0.7 mm.

Yellow needles were obtained, which were soluble in sodium bicarbonate solution. With 2N sodium carbonate solution the yellow colour disappeared, but the solid did not dissolve until the liquid was diluted.

Micro m.p. 229 - 232°, with slight softening at ~ 213°.

Mixed micro m.p. with the acidic product from the oxidation of 2:3:4:7-tetramethoxyphenanthrene-10-carboxylic acid:- Marked softening ~ 162°, further marked change at 170°.

Mixed micro m.p. with the acid obtained from the naturally-derived carbinol (of micro m.p. 241 - 246°):- 241 - 246°.

The same oxidation when repeated gave an acidic by-product which was sublimed as before. Crystallization from dilute ethanol gave yellow crystals of micro m.p. 224 - 234° with some preliminary loss of liquid.

Mixed micro m.p. of this product with the acidic by-product of the first oxidation:- 207-235° with much preliminary loss of liquid.

Oxidation of acid B.

"Acid B" (0.3 gr.) was dissolved in pure glacial acetic acid (3 cc.) at the boil. A solution of sodium dichromate (0.9 gr.) (a little more than three times the theoretical quantity required) in water (0.4 cc.) and pure acetic acid (0.9 cc.) was added to the hot solution over 10 minutes. The liquid was refluxed for ¾ hour, then worked up as usual. Previous experiments had indicated that passage through alumina was attended by considerable losses, so this purification procedure was omitted. It is also possible that light has a detrimental effect on the substance, and all crystallizations were kept in the dark.

The material was purified by dissolving in benzene, adding 60 - 80 petrol-ether till a considerable brown

precipitate had formed, filtering this off and allowing the filtrate to stand in an open vessel. Fan-shaped clusters of red rods crystallized. M.p. 120 - 122° with softening at 118°.

Found: C, 66.05; H, 5.00%. $C_{18}H_{16}O_6$ requires C, 65.86; H, 4.88%.

A quinoxaline derivative was prepared by mixing warm solutions of the quinone in acetic acid, and o-phenylene diamine either in acetic acid or alcohol. A brown solid was precipitated by addition of water and filtered off. It was dissolved in benzene, dried over sodium sulphate, and passed through a short column of alumina. Elution with benzene gave a yellow solution, leaving a narrow orange band at the top of the column. The benzene was boiled off and the residue crystallised by allowing it to stand for some time in methanol. Tiny orange prisms. Softening 139°, m.p. 143 - 143.5° (micro m.p. uncorr.).

Found: N, 7.00%. $C_{24}H_{20}O_4N_2$ requires N, 7.00%.

Product obtained by sodium carbonate extraction.

In this case only a very small quantity was obtained (less than 10 mg.). 70 mg. available from other preparations was recrystallised several times from dilute methanol, charcoaling, and the material was obtained as clusters of small yellowish-green prisms. M.p.:- sinters c 200°, m.p. 214 -

216° with decomposition.

Found: C, 59.79; H, 4.85%.

4:5:6:6'-tetramethoxy-diphenic acid, $C_{18}H_{18}O_8$ requires C, 59.68; H, 4.97%.

2:3:4:6-Tetramethoxyphenanthraquinone (XLIII).

2:3:4:6-Tetramethoxyphenanthrene-9-carboxylic acid (0.3 gm.) was oxidised with sodium dichromate-acetic acid as usual. The quinone crystallized in two forms - long orange needles, and red spindle-shaped rods. The two forms were interconvertible and a mixed m.p. did not show any depression.

M.p. of needles:- shrinking 185°, m.p. 188° (micro m.p.); in a capillary tube:- softening c 183°, m.p. 184°.

M.p. of rods:- softening 192°, m.p. 193° (micro m.p.).

Total yield of quinone - 61 mg. (21.2%).

Found: C, 65.86; H, 4.88%. $C_{18}H_{16}O_6$ requires C, 65.86; H; 4.88%.

A quinoxaline derivative was prepared from the quinone as before. Recrystallized from ethanol it gave very small, pale lemon yellow crystals, micro m.p. 187 - 189°.

M.p. in capillary tube:- 180 - 181° with slight preliminary shrinking.

Found: N, 7.71, 7.69%. $C_{24}H_{20}O_4N_2$ requires N, 7.00%.

The sodium carbonate extract gave 11 mg. of material on acidification. It was not examined in view of the small quantity available.

Comparison of synthetic quinones.

Quinone from 2:3:4:7-tetramethoxyphenanthrene-10-carboxylic acid:- m.p. 191.5 - 192.5° with some preliminary softening.

Quinoxaline derived from this quinone:- m.p. 174 - 175° with darkening at 172°.

Quinone from acid A:- m.p. 192 - 193° with softening at 176° and 186°.

Quinoxaline derived from this quinone:- m.p. 175 - 177° or 185 - 186°.

Quinone from acid B:- m.p. 120 - 122° with softening c̄ 118°.

Quinoxaline derived from this quinone:- m.p. 143 - 143.5° with softening at 139°.

Mixed m.p. of quinone from acid A and quinone from acid B:- softening c̄ 120°, m.p. 158 - 170 - 180°.

Mixed m.p. of corresponding quinoxalines:- m.p. 125 - 140°.

Mixed m.p. of quinone from acid A and quinone from 2:3:4:7-tetramethoxyphenanthrene-10-carboxylic acid:- m.p. 192.5° with slight softening c̄ 170° and 190°.

Owing to the small quantities available, a mixed m.p. of the corresponding quinoxalines was not taken.

Comparison of natural and synthetic quinones.

Quinone derived from deaminocolchinol methyl ether:- m.p. 193.5° with sintering at 192°.

Quinoxaline derived from this quinone:- m.p. 174 - 176° with softening at 174°. (When melted, allowed to cool, then remelted, found m.p. 184.5 - 186°).

Mixed m.p. of natural quinone and 2:3:4:7-tetramethoxy-phenanthraquinone (of m.p. 192 - 193°):- m.p. 193.5° with sintering at 192°.

Mixed m.p. of corresponding quinoxaline (of m.p. 175 - 177° with softening at 174°) and natural quinoxaline:- m.p. 175 - 186° with softening at 174°.

Mixed m.p. of natural quinone and 2:3:4:6-tetramethoxy-phenanthraquinone (of m.p. 184°):- softens 160°, then much shrinking, leading to m.p. 180 - 188°.

Mixed micro m.p. of corresponding quinoxaline (of micro m.p. 187 - 189°) and natural quinoxaline:- m.p. 147 - 152°.

Hydrogenation of 2:3:4:7-tetramethoxy-9-methylphenanthrene

The methylphenanthrene (5.63 mg.) was dissolved in glacial acetic acid (2 cc.) and treated with hydrogen with shaking at room temperature over platinic oxide.

Hydrogenation was stopped when 0.490 cc. of hydrogen, equivalent to hydrogenation of 1.13 double bonds, had been

absorbed (40 minutes). The liquid was filtered from catalyst, and the acetic acid removed in vacuo at 90 - 100°. The residue failed to crystallize from methanol, dilute methanol, benzene-ligroin, methanol-ligroin, or ether.

Effect of alkali and acid on deaminocolchinol methyl ether.

1). Alkali.

Deaminocolchinol methyl ether (60 mg.) was refluxed for 3 hours with sodium (0.1 gr.) dissolved in methanol (3 cc.). The liquid was allowed to cool, water (5 cc.) was added, and stood overnight. The crystalline solid which had been formed was filtered off, washed with cold water, then with a little dilute hydrochloric acid, then with more cold water. It was recrystallized from methanol, and obtained as silky glistening leaflets. Sinters 110°, m.p. 110.5 - 112°.

M.p. of deaminocolchinol methyl ether:- sinters 108°, m.p. 110.5 - 111°.

Mixed m.p. of the above product and deaminocolchinol methyl ether:- sinters 109° m.p. 110 - 110.5°.

30 mg. remained after the above m.p. and mixed m.p. The methanol mother liquors were concentrated and allowed to stand. A further 20 mg. were obtained:- softens 108° m.p. 109 - 110°.

Mixed m.p. with deaminocolchinol methyl ether:- softens 108° m.p. 110 - 111°.

The mother liquors were tested by addition of excess picric acid in methanol; there was no formation of picrate.

2). Acid.

Deaminocolchinol methyl ether (50 mg.), glacial acetic acid (10 cc.) and concentrated HCl (0.5 cc.) were refluxed for 2½ hours, when a slight brown colour had developed. The liquid was allowed to cool and diluted with water; a grey-violet solid was precipitated. The whole was made just alkaline to Brilliant Yellow with dilute caustic soda solution and extracted with ether. The ethereal solution was washed twice with dilute caustic soda solution, then with water; the aqueous layers were coloured golden brown. The ethereal solution was dried over sodium sulphate, then evaporated to dryness. The residue was brown, and this colour was only lost after three crystallizations from methanol. The solid obtained was not satisfactorily crystalline, nor was it improved by two further crystallizations from methanol.

A sample tested with excess picric acid in methanol did not form a picrate.

Attempted dehydrogenation of the dihydride of deaminocolchinol methyl ether.

1). The dihydride (50 mg.), and selenium powder (50 mg.) were heated in a metal bath at 280 - 300°. Hydrogen selenide was detected, but its evolution had ceased when heating was discontinued after 7 hours.

The dark product was dissolved in chloroform/benzene, and passed through a column of alumina. Elution with benzene

gave a yellow band, but after removal of the benzene the product could not be crystallized.

Distillation in a high vacuum (air-bath temperature 160°) gave a product which could not be crystallized.

2). The dihydride (100 mg.) and selenium (26 mg.) were heated in an evacuated sealed tube at 280 - 285° for 12 hours. Much charring occurred, and when the tube was opened hydrogen selenide and methyl hydrogen selenide were detected. The product was ground under chloroform, and the whole filtered. The filtrate was washed with dilute caustic soda solution, then with water, then dried over sodium sulphate.

Distillation at 140 - 165°/0.4 mm. gave a yellow liquid. Crystallization from methanol yielded a few crystals of micro m.p. 94 - 97°. Mixed micro m.p. with the starting material (micro m.p. 95 - 96°):- m.p. 96 - 99°.

3). The dihydride (80 mg.) and selenium (21 mg.) were heated in an evacuated sealed tube at 260 ±2° for 18 hours.

The product was dissolved in chloroform and filtered through charcoal. After diluting with benzene the solution was passed through a column of alumina, eluting with benzene.

The product thus obtained was crystallized from methanol. Gave 56 mg. of crystalline solid.
Micro m.p. 96 - 99°. Mixed micro m.p. with the starting material:- 96 - 99°.

Action of nitrosyl chloride on deaminocolchinol methyl ether.

When deaminocolchinol methyl ether was treated with amyl nitrite and hydrogen chloride in acetic acid cooled in ice-salt, it did not react and was recovered. Reaction took place when a 5 - 6% solution of nitrosyl chloride in ether (2 cc.) was added slowly to an ethereal solution of the unsaturated compound (100 mg.) cooled in ice-salt.

The crystalline product separated from methanol as a yellow powder, micro m.p. 136 - 143°. This was analysed without further purification. Found: C, 52.9; H, 4.4%.

This substance was heated with pyridine (0.2 cc.) at 100° for 3 hours. Water was added, and the liquid acidified with dilute sulphuric acid. The precipitated oil was extracted with chloroform. The product distilled in high vacuum, bath temperature 180 - 210°/0.2 mm. The distillate gave deep yellow prisms from methanol, m.p. 174 - 175°. The substance appeared to be completely insoluble in caustic soda solution.

Found: C, 58.90; H, 5.11; N, 3.92; Cl, 9.64%.

Under the microscope a few apparently colourless crystals were seen. When the stage was revolved through 180°, however, these crystals became yellow, and some of the yellow crystals became colourless.

Isolation of iso deaminocolchinol methyl ether from N-acetylcolchinol methyl ether.

N-acetylcolchinol methyl ether was treated with phosphorus pentoxide in xylene as recorded by Cook, Graham et al (J.C.S., 1944, 322). Deaminocolchinol methyl ether was obtained when the product was crystallized from methanol. The methanol mother liquors were combined and distilled at 180°/0.2 mm. The distillate was crystallized twice from methanol, and in this way more deaminocolchinol methyl ether, of m.p. 108 - 110°, was obtained. The mother liquors from the first crystallization were allowed to stand, and a few crystals appeared. These were carefully isolated and recrystallized from methanol. Approximately cubic crystals formed. They were lifted out of the mother liquors and dried.
Micro m.p.:- 97 - 100° with softening at 96°.
Mixed micro m.p. with deaminocolchinol methyl ether:- 81 - 95°.
Mixed micro m.p. with iso deaminocolchinol methyl ether (of micro m.p. 96 - 100 - 124°):- 98 - 100 - 105°.

Diphenic acid.

Phenanthraquinone (1.04 gr.) was suspended in methanol (10 cc.) and 100 vol. hydrogen peroxide (3.4 cc., 6 molecular proportions) was added, followed by 2N caustic soda solution (5.25 cc., 2.1 molecular proportions) added dropwise with shaking over 10 minutes. Heat developed, and at the end of

addition practically all the solid had gone into solution. Further hydrogen peroxide (1.7 cc.) was added and stood overnight, but there was no apparent change. The undissolved solid was ground with a glass rod, more peroxide (1.7 cc.) added, and the whole gently warmed. The solid had completely dissolved after ¼ hour, giving a pale yellow solution. The alcohol was boiled off on the steam bath, and the residue diluted with water. Since the liquid was slightly hazy it was filtered through a bed of kieselguhr. The clear filtrate was acidified with concentrated hydrochloric acid, and the white precipitate filtered off and dried in an evacuated desiccator over potassium hydroxide, then at 60° for 2 hours. 1.05 gr. (86.78%) m.p. 225 - 228° with some shrinking from 200°. The aqueous mother liquors gave a further 0.10 gr. (8.26%) on extraction with chloroform. M.p. as before.

Crystallization of these two crops from c 25% ethanol gave respectively colourless plates (0.98 gr., 80.98%) m.p. 227.5 - 230.5° with very slight softening at 200°, and colourless needles (0.08 gr., 6.61%) m.p. 227 - 230° with very slight softening at 200°.

4:5:6:4'-Tetramethoxydiphenic acid (LV).

2:3:4:7-Tetramethoxyphenanthraquinone (56 mg.) was suspended in methanol (1 cc.) and treated with 100 volume hydrogen peroxide (0.12 cc.; 6 molecular proportions) followed by 2N caustic soda solution (0.18 cc.; 2.1 molecular proportions) added dropwise with shaking over 10 minutes. Subsequently two further portions of hydrogen peroxide (0.06cc.) were added, and the undissolved solid was ground with a glass rod. After standing for a time until all the solid was dissolved, the alcohol was boiled off and the residue diluted with water. The hazy liquid was filtered through kieselguhr, and the clear filtrate acidified with concentrated hydrochloric acid. The gummy solid which was precipitated was extracted with chloroform. After drying with sodium sulphate 50 mg. of crude product (80.9% yield) were obtained. Crystallization from dilute ethanol gave colourless prisms (28 mg.). Micro m.p. 238 - 240° with softening from ca. 230°.

Sublimation (210 - 220°/0.3 mm.) gave an almost quantitative yield of colourless prisms. Micro m.p. 239 - 242° with softening from ca. 235°. Capillary m.p. 240 - 241° with shrinking at 231°.

Found: C, 59.67; H, 4.95%. $C_{18}H_{18}O_8$ requires C, 59.68; H, 4.97%.

Mixed m.p. with acid obtained during first oxidation of acid A:- micro m.p. 210 - 225 - 235° with softening at 200°.

Mixed m.p. with acid obtained during second oxidation of acid A:- micro m.p. 210 - 220 - 228° with preliminary softening.

Attempted hydroxylation of deaminocolchinol methyl ether. (Cf. Milas and Sussman[31]).

Deaminocolchinol methyl ether (0.10 gr.) was dissolved in a little distilled tertiary butanol. A 4.96% solution of hydrogen peroxide in tertiary butanol (0.23 cc.; one molecular proportion plus a small excess) was added at room temperature, followed by two drops of a 0.5% solution of osmium tetroxide in tertiary butanol. A brown colour began to develop, and much crystalline solid was deposited. After standing for five days the colour had changed to orange.

The butanol was now removed in vacuo, and the residue crystallized from methanol. The product had micro m.p. 105 - 107°. Mixed micro m.p. with the starting material:- 106-109°.

Preparation of a glycol from deaminocolchinol methyl ether.

Deaminocolchinol methyl ether (100 mg.) was dissolved in sodium-dried ether (5 cc.), and to the solution added osmium tetroxide (90 mg.) dissolved in dry ether (5 cc.). There was an immediate development of a brown colour, presently followed by the appearance of a brown sediment. The mixture was allowed to stand for four days, adding dry ether as required. On evaporation of the ether a uniform black powder was left.

Sodium sulphite ($Na_2SO_3 7H_2O$) (0.9 gr.) in water (10 cc.) and methanol (20 cc.) were added, and refluxed for 2½ hours. The black insoluble powder was filtered off; it was extracted twice with boiling methanol. The combined filtrates were treated with charcoal, then evaporated to dryness in vacuo. Water was added to the residue, and the undissolved solid extracted with ether. T he ether solution was washed with water, the ether boiled off, and the residue crystallized from dilute methanol, charcoaling. 60 mg., plus a further 28 mg. from the mother liquors (80% yield).

A sample recrystallized from dilute methanol for analysis was obtained as colourless slender rods m.p.:- 165 - 166°.

Found: C, 66.04; H, 5.92%. $C_{19}H_{22}O_6$ requires C, 65.89; H, 6.36%.

Cleavage of the glycol from deaminocolchinol methyl ether.

The glycol (60 mg.) was dissolved in pure dry benzene (12 cc.), and lead tetra-acetate (80 mg.) was added portionwise with shaking and exclusion of moisture at 40° over 5 minutes. The liquid was brought to the boil, then stood at room temperature for 1 hour. It was filtered from undissolved solid, washing with benzene. The benzene solution was washed with water, then dried over sodium sulphate. After removal of the benzene, the residue was crystallized from

methanol. Only a few crystals appeared on standing for two days, and when the methanol was evaporated a gum was obtained which could not be crystallized. It was dissolved in methanol, a trace of sodium carbonate added, and brought to the boil. On cooling a mass of bright yellow rods crystallized. 41 mg. (72.5% yield).

A sample recrystallized from methanol for analysis had m.p. 130 - 131°; micro m.p. 132 - 133°.

Mixed micro m.p. with 2:3:4:7-tetramethoxy-9-phenanthraldehyde (of micro m.p. 134°):- 100 - 120°.
Found: C, 69.66; H, 5.91%. $C_{19}H_{18}O_5$ requires C, 69.9; H, 5.5%.

The product gave a pale orange-yellow precipitate when an alcoholic solution was treated with 2:4-dinitrophenyl hydrazine in alcohol acidified with sulphuric acid.

It gave an oxime which crystallized from methanol as pale mauve rods, m.p.:- 169 - 170°; micro m.p.:- 160 - 164°.

Mixed micro m.p. with the oxime of 2:3:4:7-tetramethoxy-9-phenanthraldehyde (of m.p. 169 - 170°):- 140 - 163°.
Found: C, 66.77; H, 5.32; N, 4.61%. $C_{19}H_{19}O_5N$ requires C, 66.85; H, 5.57; N, 4.11%.

Oxidation of the aldehydic product.

The above aldehyde (18 mg.) was dissolved in purified A.R. acetone (1 cc.), and a 6% solution of potassium permanganate in pure acetone (0.1 cc.) was added dropwise over 20 minutes at 55 - 60°. The mixture was allowed to stand overnight, then sulphurous acid was added till the brown colour disappeared. The pale yellow solid left was extracted with chloroform, and the chloroform solution extracted with sodium carbonate solution. (Subsequently 12 mg. of the starting material were recovered from the residual chloroform solution).

The sodium carbonate solution on acidification with dilute hydrochloric acid gave a precipitate which after crystallization from dilute ethanol was obtained as pale yellow needles, micro m.p.:- 198 - 201°.

Micro m.p. of 2:3:4:7-tetramethoxy phenanthrene-10-carboxylic acid:- 203 - 207°.

Mixed (micro) m.p. of 2:3:4:7-tetramethoxy phenanthrene-10-carboxylic acid and this product:- 197 - 204°.

Esterification of the oxidation product.

The whole of the acidic product was esterified with diazomethane in ether. On crystallization from methanol the product gave colourless prisms, micro m.p. 100 - 102°.

Micro m.p. of synthetic 10-ester:- 103 - 105°.

Mixed (micro) m.p. of synthetic 10-ester and this ester:- 101 - 103°.

Oxidation of iso-deaminocolchinol methyl ether.

A slightly impure specimen of the iso-compound (m.p. 93 - 99°) (34 mg.) was hydroxylated with osmium tetroxide as described above for deaminocolchinol methyl ether. The crude product was crystallized from methanol, and a crystal examined had micro m.p. 162 - 168°. Mixed with the glycol from the previous oxidation, gave m.p. 140 - 160°.

The crystallized product together with that recovered from the crystallization mother-liquors was oxidised in benzene with lead tetra-acetate. The product crystallized from methanol in the presence of a trace of sodium carbonate. Micro m.p. 129 - 133°. Mixed with synthetic 9-aldehyde (of m.p. 134°):- micro m.p. 130 - 134°. Mixed with synthetic 10-aldehyde:- micro m.p. 112 - 126°.

It gave an oxime which was crystallized from methanol. Micro m.p. 166 - 169°. Mixed with oxime from synthetic 9-aldehyde (m.p. 169 - 170°):- micro m.p. 166 - 170°.

Preparation of the oxime of 2:3:4:7-tetramethoxy phenanthrene-9-aldehyde.

The aldehyde (0.11 gr.) was dissolved in methanol (6 cc.), then hydroxylamine hydrochloride (0.04 gr.) and anhydrous sodium acetate (0.06 gr.) were added. The mixture was refluxed for 3½ hours, then stood overnight. Large brown diamond-shaped crystals and small prisms appeared.

The mother liquors were decanted off and the residue washed with cold water by decantation. Crystallization from methanol gave large brown prisms (72 mg.).
M.p. - softening 167°, m.p. 169 - 170° (in capillary tube).
Found: C, 67.14, 67.06; H, 5.30, 5.39; N, 4.63, 4.49%.
$C_{19}H_{19}O_5N$ requires C, 66.85; H, 5.57; N, 4.11%.

Methyl-3:4:5-trimethoxybenzoate (LXXXII).

3:4:5-Trimethoxybenzoic acid (300 gr.), and methanol (1500 cc.) containing concentrated sulphuric acid (150 cc.) were refluxed for 6 hours. The methanol was then distilled off until the residue was a concentrated solution, and the whole then cooled with shaking. A solid crystallized, and was filtered off and dried by exposure. It was dissolved in ether. The mother liquors were diluted with water (4 volumes), and extracted twice with ether. The combined ethereal extracts were now washed with 3N caustic soda solution, then with water.

The ether was dried over sodium sulphate, and then evaporated. The residue on crystallization from methanol gave 270 gr. of solid. M.p. 84°.

Unesterified acid was recovered from the caustic soda extract by acidification with concentrated hydrochloric acid. The precipitate thus formed was recrystallized from water. 9 gr. M.p. 165 - 167°.

1-(p-Methoxyphenyl)-3:3-dimethyl triazen (LXXIII).

p-Anisidine (25 gr.) was diazotised, and the cold solution added to dimethylamine (70 gr.; 25% solution) and 30% sodium carbonate solution (100 gr.) with stirring and ice-cooling. After stirring for 30 minutes the solution was extracted with benzene. The benzene extract was dried over potassium hydroxide, then the benzene was distilled off and the residue distilled in vacuo at 155 - 157°/10 - 12 mm.

Analysis (L.C. 41) found N, 23.2%. $C_9H_{13}ON_3$ requires N, 23.5%.

Methyl-2-(p-methoxyphenyl)-3:4:5-trimethoxybenzoate (LXXV).

Methyl trimethoxy benzoate (75 g.), and 1-(p-methoxyphenyl)-3:3-dimethyl triazen (14 g.) were heated on the steam bath. Glacial acetic acid (18 g.) was added dropwise over 10 minutes, when mild effervescence occurred. Heating was continued overnight.

The liquid was then extracted with chloroform, and the chloroform washed five times with dilute hydrochloric acid, once with water, once with dilute caustic soda, then again with water. After drying with sodium sulphate the product was distilled in vacuo. The fraction of b.p. 166 - 178°/10 mm. (63 g.) was unchanged methyl trimethoxy benzoate, which was used again without further purification.

In this way a quantity of higher boiling material was

collected; it was subsequently distilled, the main fraction being collected 170 - 230°/8 mm. This was redistilled, giving two fractions of equal weight, 1) 170 - 225°/2.5 mm., 2) 225 - 226°/2.5 mm. The first fraction was impure, but on crystallization from methanol the pure product was obtained, m.p. 71 - 73° or 80 - 81°. The second fraction gave a good yield of the same substance on crystallization from methanol. A sample purified for analysis had m.p. 74°.
Analysis L.C.44Found; C, 64.9; H, 5.85%. $C_{18}H_{20}O_6$ requires C, 65.1; H, 6.0%.

Various impure samples of the ester were combined and hydrolysed by methyl-alcoholic potassium hydroxide in the usual way. Fractional crystallization from methanol gave the corresponding acid as stout prisms, m.p. 168 - 170°. In addition another acid was obtained as long needles, m.p. 225 - 228°.

The first acid was re-esterified with ethereal diazomethane and the product added to the main bulk.

From 55.3 g. of triazen, 17.9 g. of ester were obtained (17.5%). (24 gr. of methyl trimethoxybenzoate were ultimately recovered unchanged).

Action of thionyl chloride on the acid of m.p. 168 - 170°. The acid (2.5 gr.) (dried at 110°), and thionyl chloride (7 cc.) were mixed, and the acid dissolved by gentle warming. Excess thionyl chloride was removed in vacuo. A red powder was left which was crystallized from methanol. M.p. 114 - 115°. Gives a 2:4-dinitrophenyl hydrazone in methanol.

Analysis (L.C. 46) found C, 67.8; H, 5.3%.

Tetramethoxyfluorenone, $C_{17}H_{16}O_5$, requires C, 68.0; H, 5.3%.

Mixed m.p. with 2:3:4:7-tetramethoxyfluorenone (below):- m.p. 110 - 111° with some preliminary shrinking.

2:3:4:7-Tetramethoxyfluorenone (XCIV).

A small quantity of tetramethoxydiphenic acid (m.p. 236 - 238°) was heated in a Pyrex tube in a metal bath. At 300° gas was evolved and the solid became red. The bath temperature was raised to 350 - 360°, when a red liquid distilled. Heating was continued for 10 minutes. The tube was cut, and the red distillate dissolved in benzene. This benzene solution was washed with sodium carbonate solution and water, then dried over sodium sulphate. After evaporation, the residual gum was crystallized from methanol. A red solid was obtained, m.p. 108 - 110° with softening at 106°.

Examination of the by-product (acid, m.p. 225 - 228°).

The acid of m.p. 225 - 228° was crystallized repeatedly from methanol. It was obtained as long colourless needles, m.p. 227-228°.

Found: C, 66.40; H, 5.61%. Methoxyl, 30.56, 30.87%. $C_{16}H_{16}O_5$ (acid corresponding to XCVI) requires C, 66.67; H, 5.56%. Methoxyl, 32.29%.

Preparation of the acid amide. The acid (80 mg.) was treated with pure thionyl chloride (3 vols.) and gently warmed on the steam bath (calcium chloride protection). There was immediate reaction, and the solid dissolved. After warming for a few minutes, during which time no red colour developed, the excess thionyl chloride was removed in vacuo on the steam bath. The residue was cooled, and excess 0.880 ammonia added. A white solid formed immediately. After standing overnight water was added, and the solid was filtered off.

It was crystallized repeatedly from absolute ethanol for analysis. Tiny colourless needles, m.p. 232°.

Found: C, 66.62; H, 5.64%. $C_{16}H_{17}O_4N$ (amide of XCVI) requires C, 66.89; H, 5.92%.

2-(p-Methoxyphenyl)-3:4:5-trimethoxybenzoyl hydrazide (LXXXIV).

Methyl-2-(p-methoxyphenyl)-3:4:5-trimethoxybenzoate (14.6 gr.) was dissolved in methanol (30 cc.), and 99% hydrazine hydrate (30 cc.) was added. The liquid was refluxed for 7½ hours, treated with charcoal, and allowed to crystallize. The product was washed well with water, then dried at 100°. 10.5 g. of solid were obtained. Mother-liquors gave a further 2.5 g. Total yield 89%.

A sample crystallized from methanol for analysis had m.p. 154-155°, and was obtained in clusters of long colourless rods.

Found: C, 61.53; H, 5.98%. $C_{17}H_{20}O_5N_2$ requires C, 61.45; H, 6.02%.

Benzenesulphon-(2-p-methoxyphenyl)-3:4:5-trimethoxybenzoyl hydrazide (LXXXV).

The above hydrazide (14.0 g.) was dissolved in dry pyridine (82 cc.) and distilled benzene sulphonyl chloride (8.2 g.) was added with stirring and ice-cooling. T he solution was allowed to stand in ice for 2 hours, followed by 1 hour at room temperature. The liquid was then poured on to crushed ice and hydrochloric acid, when a sticky yellow solid was precipitated. This slowly hardened and was then filtered off and exposed overnight. Crystallization from methanol gave 14.1 g. of solid, followed by a further 3.4 g. on concentrating the mother liquors.

Total yield 88%.

A sample crystallized from methanol for analysis had m.p. 177.5 - 178.5°. Colourless prisms.

Found: C, 58.24; H, 5.31%. $C_{23}H_{24}O_7N_2S$ requires C, 58.48; H, 5.09%.

2-(p-Methoxyphenyl)-3:4:5-trimethoxybenzaldehyde (LXXXVI).

41.3 gr. of sulphonhydrazide were converted to aldehyde in three batches, each of approximately 14 gr.

The sulphonhydrazide (14 gr.) was dissolved in hot ethylene glycol (140 cc.), cooled to 160°, and stirred vigorously in an oil-bath at that temperature. Ground A.R. sodium carbonate (8.4 gr.) was then added, and stirring and heating continued for 2 minutes 10 seconds. The oil-bath was removed and the reaction quenched by the addition of hot water (140 cc.). The mixture was cooled and extracted with chloroform.

The chloroform solutions from the three batches were combined and washed twice with 2N caustic soda solution, then with water. The chloroform was dried over sodium sulphate, then evaporated. The crude oily product (26 gr.; 98.4%) was crystallized from methanol. 19.2 gr. (72.6%) of aldehyde, m.p. 61 - 63°. More material was obtained from the mother liquors on concentrating. It was combined with similar material from other preparations and purified via the bisulphite compound.

A sample was repeatedly crystallized from methanol for analysis. It was obtained as colourless prisms, m.p. 62 - 63°.

Found: C, 67.40; H, 6.04%. $C_{17}H_{18}O_5$ requires C, 67.54; H, 5.96%.

2-(p-Methoxyphenyl)-3:4:5-trimethoxycinnamic acid (LXXXVII).

The aldehyde (3 g.) was dissolved in dry pyridine (6 cc.) and a few drops of dry piperidine were added, followed by malonic acid (2.0 g.; 1.9 molecular proportions), and the whole heated on a steam bath (calcium chloride protected) for 1 hour. Carbon dioxide evolution had then ceased. The liquid was refluxed for ¼ hour, then poured on to ice and concentrated hydrochloric acid. A sticky solid was precipitated, which became granular after a time and was filtered off. It was crystallized from dilute methanol, giving 2.9 g. of material.

Yield 85%.

Repeated crystallization from dilute methanol gave colourless prisms of m.p. 187 - 188°.

Found: C, 66.48; H, 6.21%. $C_{19}H_{20}O_6$ requires C, 66.27; H, 5.81%.

2-(p-Methoxyphenyl)-3:4:5-trimethoxyhydrocinnamic acid (LXXVI).

Palladium-black (0.17 g.) in glacial acetic acid (50 cc.) was saturated with hydrogen. The unsaturated acid

(2.8 g.) dissolved in glacial acetic acid (30 cc.) was then added, and saturated with hydrogen at 20°C with shaking. The palladium was filtered off and the filtrate evaporated to dryness in vacuo. Crystallization from methanol gave 2.67 g. of the saturated acid (95% yield).

A sample recrystallized from methanol several times was obtained as colourless prisms, m.p. 103°.
Found: C, 65.75; H, 6.32%. $C_{19}H_{22}O_6$ requires C, 65.89; H, 6.36%.

Action of hydrogen fluoride on 2-(p-methoxyphenyl)3:4:5-trimethoxyhydrocinnamic acid

The acid (0.20 gr.) was finely ground and added to liquid hydrogen fluoride (ĉ 4 cc.) in a platinum crucible. It dissolved readily when stirred with a copper wire. The liquid was allowed to stand overnight in a bell-jar, protected from moisture by calcium chloride. During this period the hydrogen fluoride evaporated, and a red gum was left. It was dissolved in chloroform, and the chloroform extracted with sodium carbonate solution.

Acidification of the sodium carbonate solution, followed by extraction of the precipitate with chloroform, gave 0.10 gr. of crude acid. This was crystallized from dilute methanol and then had m.p. 100 - 102°. Mixed m.p. with the starting material:- 101 - 102°. 77 mg.

The chloroform solution, dried with sodium sulphate and then evaporated, gave 0.10 gr. of a golden-brown gum. It was crystallized from dilute methanol, then from cyclohexanone, and again from dilute methanol. Pale brown prisms, m.p. 73 - 74°. A methanol solution gave a 2:4-dinitrophenyl hydrazone.

Found: C, 69.16; H, 6.14%. $C_{19}H_{20}O_5$ requires C, 69.5; H, 6.10%.

Note:- Structures of synthetic compounds from here to p.150 rest solely on analyses figures

2-(p-Methoxyphenyl)-6-bromo-3:4:5-trimethoxyhydrocinnamic acid (LXXXIX).

2-(p-Methoxyphenyl)3:4:5-trimethoxyhydrocinnamic acid (2.47 gr.) was dissolved in dry chloroform (50 cc.). Bromine (0.40 cc.; a slight excess over two atoms) dissolved in dry chloroform (10 cc.) was then added, and the liquid allowed to stand, protected by calcium chloride, for 2 hours. Hydrogen bromide was evolved.

The chloroform solution was then washed with water until free from mineral acid, and the chloroform then distilled off in vacuo. The residue was crystallized from benzene-ligroin. 2.90 gr. Softens 160°, m.p. 167 - 168°.

A sample was prepared for analysis by dissolving the acid in ether, extracting with dilute sodium carbonate solution, and precipitating the acid by acidification with hydrochloric acid. Crystallization from methanol gave colourless prisms, m.p. 169 - 170°.

Found: C, 53.30; H, 4.96%. $C_{19}H_{21}O_6Br$ requires C, 53.64; H, 4.94%. The acid could be sublimed at c 150° (air-bath temp.)/0.1 mm.

The methyl ester was easily prepared in the usual way by refluxing the acid with methanol containing a little concentrated sulphuric acid. It distils at 180 - 210° (air-bath temperature)/0.2 mm., and crystallizes from methanol as clusters of needles, m.p. 90 - 91°, with softening at 89°.

Found: C, 54.63; H, 5.25%. $C_{20}H_{23}O_6Br$ requires C, 54.67; H, 5.24%.

9:12:13:14-Tetramethoxy-15-bromo-3:4:5:6-dibenz-$\Delta^{3:5}$-cycloheptadiene-2-one (XCI).

The following is a general account of the procedure employed.

The bromo-acid (LXXXIX) was added to pure dry benzene (10 volumes) in which was suspended phosphorus pentachloride (1.1 molecular proportions). The mixture was kept at room temperature (protected by calcium chloride), shaking occasionally until all the solid had dissolved ($\frac{3}{4}$ hour). Volatile matter was then removed in vacuo at 60°, evacuation at 60° was continued for a further $\frac{1}{4}$ hour, followed by evacuation at room temperature for a further $\frac{3}{4}$ hour, by which time the acid chloride was usually crystalline.

The acid chloride was normally used without further purification, but it could be crystallized from dried ligroin. It was then obtained as prisms, slightly discoloured, of micro m.p. 91-93°.

The acid chloride was dissolved in the solvent to be used (e.g., two volumes of carbon disulphide), and finely-ground aluminium chloride (taken for preference from a previously unopened bottle) was added. The mixture was then either heated or stood in a desiccator over potassium hydroxide at room temperature or in the refrigerator.

Water and a little hydrochloric acid were added, and the solvent removed by steam distillation, which also served to hydrolyse any unreacted acid chloride. In the later experiments two main methods were then used to work up this product:-

A. Organic material was extracted with chloroform. The chloroform solution was washed with dilute sodium carbonate solution, then with caustic soda solution. These alkali washings removed unchanged acid, but apparently did not extract monodemethylated material, since this could actually be isolated from a chloroform solution which had been washed with caustic soda solution (see B below). Some phenolic material however was extracted by the caustic soda solution; it presumably had suffered demethylation to a greater extent.

The unreacted acid was recovered from the alkali

extracts by acidification followed by extraction with chloroform. It was of varying quality, and was best purified through the methyl ester.

The residual chloroform solution was dried over sodium sulphate, evaporated, and the product distilled in a high vacuum, air-bath temperature 180-200°/0.4 mm. The quantity of distillate was never more than about 50% of the original quantity to be distilled. The distillate contained phenolic material, since a methanol solution gave a violet colour with ferric chloride solution. It could be freed from this by chromatography (see below), or by repeated crystallization from methanol, when it was obtained as rosettes of pale lemon-yellow rods, m.p. 134-136°. If crystallized from benzene/ligroin, the material had the same crystalline form as before, but its m.p. was 143-143.5° with softening at 140°. Found: C, 56.21; H, 4.79%. $C_{19}H_{19}O_5Br$ (XCI) requires C, 56.02; H, 4.67%.

B. Alternatively the organic material was extracted with ether. The ethereal solution was washed with sodium carbonate solution and caustic soda solution as before. It was dried with sodium sulphate and evaporated. The residue did not give a violet colour in methanol when ferric chloride solution was added. It was dissolved in dry benzene and passed through a column of alumina, eluting with benzene. The product, after evaporation of the benzene, was obtained as a pink glass, which could be debrominated without further

purification, giving results as good as those obtained with crystallized bromo-ketone.

The original aqueous liquid, which contained suspended solid matter, was extracted with chloroform, which dissolved the suspended solid. This chloroform was shaken with the above sodium carbonate solution, and then with the caustic soda solution. The process was repeated, and the combined chloroform extracts dried over sodium sulphate. When the chloroform was removed, a methanol solution of the residue gave a deep violet colour with ferric chloride solution.

This material was methylated by dissolving in dry benzene (20 volumes), and refluxing for 7 hours with dimethyl sulphate (4 molecular proportions) and potassium carbonate (5 molecular proportions). Water and a little dilute sulphuric acid were then added, and after boiling for ½ hour the benzene layer was separated and dried over sodium sulphate. When the benzene was removed, the product no longer gave a violet colour with ferric chloride solution. It was best purified by passing it in benzene solution through a column of alumina, eluting with benzene. The product was crystallized only with great difficulty, and was not obtained in a satisfactory crystalline state. It could however be used directly for debromination. The yields obtained in the methylation were poor, and there appeared to be material other than the fully-methylated ketone present in the product.

The total yield of the desired ketone was not much augmented by the methylation procedure.

Method B offers advantages of manipulation over A, but it is doubtful whether the yield is much improved by using it.

The cryptophenolic material could be obtained pure either by distillation followed by crystallization, or, better, by chromatography. Elution with benzene caused any fully-methylated material present to pass down the column, while the demethylated material was retained. Addition of a few drops of methanol to the benzene enabled the demethylated material to be recovered. A sample of this crystallized repeatedly from methanol was obtained as pale lemon-yellow prisms, m.p. 149-150°, with softening at 148°. Admixture with the fully-methylated ketone depressed the melting point (micro) by 15°. The phenolic material appears to be insoluble in aqueous caustic soda at all concentrations and temperatures, but it has some solubility in aqueous-alcoholic caustic soda or potash.

Found: C, 54.9; 54.7; H, 4.5, 4.55%. $C_{18}H_{17}O_5Br$ requires C, 54.96; H, 4.32%.

The table which follows summarises a number of the cyclisation experiments performed with aluminium chloride as the condensing agent.

Experiment number	Solvent	Molecular proportions of aluminium chloride	Conditions	% Yield of crude Ketone (Not taking acid recovery into account)	% Yield of recovered acid after purification	% Yield of crude acid recovered	% Yield of purified Ketone.
5	$C_6H_5.NO_2$	1.1	0° overnight	42[2]	19.0	33.3	15% after distillation[1]. Yield after crystallizn. not recorded.
9	CS_2	1.1	Refluxed 1¼ hrs., then room temp. 18 hrs.	50-55	Unsatisfactory crystallization.	25-30	25-28% after distn.[1] Not satisfactorily crystallized.
10	CS_2	1.25	Refluxed 2 hrs., then room temp. 18 hrs.	58	10%, of poor quality	35	15.7% after distn.[1] Would not crystallize.
12	CS_2	2.0	41 hrs. at 0°	65	-	29	36.6% after distn. 15.7% after crystn.[1]
14	CS_2	2.0	67 hrs. at 0°	25[2]	65	75	8.9% after distn.[1] Would not crystallize.
15	CS_2	2.0[3]	68 hrs. at 0°	20[2]	28	76	8.3% after distn.[1] 5.3% after crystn.[1] (Wide m.p.)

Expt. no.	Solvent	Mol. props. of $AlCl_3$	Conditions	% Yield of crude acid recovered	% Yield of recovered acid after purification	% Yield of crude Ketone	% Yield of purified Ketone
16	CS_2 (4)	2.5	92 hrs. at 0°	36	-	37	18.8% after distill^{n}. 16.7% after crystallization.
17	$C_6H_5.NO_2$	1.1	48 hrs. at 0°	7	-	37% extracted by ether → plus 42% extracted by chloroform →	11.5% after distill^{n}. 9.6% after crystallization (phenol-free) 10.4% after distill^{n}. 6.3% after crystallization (Phenolic).
19	CS_2 (4) (very dilute)	2.5	73 hrs. at 0°	75	54	27	12% after chromatogram. Not satisfactorily crystallized.
21 and 22	CS_2 (4)	2.5	48 hrs. at 0°	20	-	24% extracted by ether → plus 4.5% extracted by chloroform →	20% after chromatogram. 12% after crystall^{n}. (poor quality) Methylation, followed by chromatogram gave 32%(crude)(5).
(Results given are average for two experiments).							

Notes.

(1). This contained phenolic material.

(2). In this experiment a high-melting substance was detected. It was revealed by its insolubility when the crude reaction product was dissolved in benzene in order to transfer it to a distillation flask. Crystallization from nitrobenzene/benzene gave colourless prisms m.p. 348-350° with slight decomposition.

Found: C, 55.34; H, 4.88%. No constitution has been assigned to this substance.

(3). Aluminium chloride purified by sublimation.

(4) Carbon disulphide purified by drying over calcium chloride, distilling over mercuric chloride, and storing over calcium chloride.

(5). Debromination of this material, and preparation of the oxime showed that of this 32% yield not more, and probably rather less than one sixth was of satisfactory quality - i.e., the true yield should be $\leq$ 5% at most.

Cyclisation of the bromo-acid (LXXXIX) using other condensing agents.

1). Phosphorus pentoxide. The acid was refluxed for 1½ hours with phosphorus pentoxide in dry xylene. The product was obtained as colourless diamond-shaped crystals, micro m.p. 110-111°. It did not give a dinitrophenyl hydrazone in methanol.
Found: C, 62.92; H, 3.90%. No constitution has been assigned to this product.

2). Hydrogen fluoride. This had little or no effect on the acid, and 80% of it was recovered unchanged.

3). Concentrated sulphuric acid. The bromo-acid was dissolved in cold concentrated sulphuric acid and allowed to stand for 24 hours. No ketonic product was obtained, but the starting material could not be recovered. Sulphonation had probably occurred.

4). Phosphorus pentoxide/syrupy phosphoric acid. The bromo-acid was heated with these reagents at 140-145° for 3 minutes. An 8% yield of crystalline ketone of moderately good quality was obtained.

5). Aluminium bromide. The acid chloride dissolved in carbon disulphide was treated with aluminium bromide and worked up as in the aluminium chloride experiments. 45% of the acid was recovered unchanged. A 48% yield of impure

(crude) ketonic material was obtained. It was not worked up independently.

9:12:13:14-Tetramethoxy-3:4:5:6-dibenz- $\Delta^{3:5}$ -cycloheptadiene -2-one (LXXVII).

The bromo-ketone (1 part) was dissolved in methanol (100-350 volumes), 2% palladised strontium carbonate (6 parts) was added, and the mixture was shaken in an atmosphere of hydrogen for 3-4 hours. The catalyst was filtered off, and the filtrate evaporated to dryness. The residue was dissolved in chloroform and water, and the two layers allowed to separate. The chloroform solution was dried over sodium sulphate, and the product after isolation was distilled in a high vacuum, air-bath temperature 160-175°/0.2 mm. The distillate crystallized from methanol. Yield 55%.

When phenol-free bromo-ketone had been used the product gave no colour with ferric chloride solution in methanol. Repeated crystallization from methanol then gave colourless prisms, m.p. 82.5-85° with softening at 81°. Crystallization from benzene raised the m.p. to 84.5-85°.

Found: C, 69.40; H, 5.98%. $C_{19}H_{20}O_5$ (LXXVII) requires C,69.50; H,6.10%. Bromo-ketone which contained much phenolic material gave a product which crystallized from methanol as long, colourless prisms. Ferric chloride solution gave a deep violet colour. Repeated crystallization gave a product of

m.p. 122-123°.

Found: C, 68.39; H, 5.84%. $C_{18}H_{18}O_5$ requires C, 68.80; H, 5.73%.

In one particular debromination bromo-ketone which had been obtained by methylation of phenolic material from the ring closure, and which was not satisfactorily crystallized, was used. It gave an oil which could not be crystallized, but was used directly for oxime preparation (see below).

9:12:13:14-Tetramethoxy-3:4:5:6-dibenz-$\Delta^{3:5}$-cycloheptadiene-2-one oxime (XCII).

The ketone (LXXVII) (200 mg.) was dissolved in methanol (2 cc.). Hydroxylamine hydrochloride (67 mg.) was added, followed by fused sodium acetate (100 mg.), and the whole refluxed for 3 hours.

The mixture was cooled, diluted with water, and the precipitate either filtered off or extracted with chloroform.

Crystallization from ethanol gave colourless needles (196 mg. 94%). Repeated crystallization from ethanol gave silky needles, m.p. 218-219°. The product was insoluble or very sparingly soluble in caustic soda at all concentrations. It was insoluble in 2N hydrochloric acid, but readily dissolved on addition of a little concentrated hydrochloric acid. It was not reprecipitated on dilution.

Found: C, 66.57; H, 6.17%. $C_{19}H_{21}O_5N$ (XCII) requires C, 66.46; H, 6.12%.

When ketone which had been obtained originally from

re-methylated phenolic material was used (see page 142), a second product was isolated in addition to the oxime of m.p. 218-219°. This material was obtained from methanol as colourless diamond-shaped crystals of m.p. 58.5-59° with softening at 57°.

Found: C, 66.38; H, 6.02%. $C_{19}H_{21}O_5N$ (e.g. XCII) requires C, 66.46; H, 6.12%.

The two products may be the syn and anti forms of the oxime.

In an investigation into the possibility of converting the one form to the other, ethanol mother-liquors which remained after the isolation of the low-melting material were boiled for a few minutes with two or three drops of concentrated hydrochloric acid. After standing for several days a good crop of silky crystals was obtained. Repeated crystallization from methanol gave colourless silky needles, m.p. 94.5-95° with softening at 93°.

The material does not contain nitrogen, and does not give a 2:4-dinitrophenyl hydrazone in methanol.

Found: C, 67.19 ; H, 6.48% Methyl ester of (LXXVI), $C_{20}H_{24}O_6$, reqs. C, 66.6; H, 6.7%. Ethyl ester of (LXXVI), $C_{21}H_{26}O_6$, reqs. C, 67.4; H, 6.95%

~~No constitution has been assigned to the substance~~.

The material was refluxed with methanolic KOH for 3 hours, the alcohol allowed to boil off, and water added to the residue. The resulting clear solution was acidified, and a white precipitate was obtained. Crystallization of this from benzene/ligroin gave an acid of m.p. 102-103°. Mixed m.p. with (LXXVI):- 102-103°.

9:12:13:14-Tetramethoxy-2-amino-3:4:5:6-dibenz-$\Delta^{3:5}$-cyclo-heptadiene (LXIV).

The oxime (XCII) (200 mg.) was dissolved in absolute ethanol (70-80 cc.), and hydrogenated over Raney nickel (c 200 mg.) at 80-90°/60-65 atmospheres for 4 hours. After filtering from catalyst the solvent was boiled off and the residue dissolved in ether. The solution was filtered to remove a small amount of insoluble matter, then to the concentrated solution was added a saturated solution of picric acid in ether. A picrate was precipitated, which after standing for a time was freed from ether by decantation, washed with a little ether, then crystallized from methanol.

A further crystallization from methanol gave yellow-brown prisms of vague melting-point:- softening at c 170° led to melting at 216°, ending at c 220°. Considerable darkening occurred during the melting.

A mixed melting point with the picrate from colchinol methyl ether (see later, page 147) (of m.p. 223-225°) showed softening at c 180°, leading to melting at 212-216°.

The material was washed with hot benzene and crystallized twice more from dilute methanol. It was then obtained as stout yellow-brown needles with an even wider m.p.:- 178°- 200°- c 220° with much darkening.

Mixed melting point with picrate of colchinol methyl ether:- softening c 178°, m.p. 187 - 208 - c 220°.

Found: C, 53·67 ; H, 4·59 ; N, %.

$C_{19}H_{23}O_4N$. $C_6H_3O_7N$ requires C, 53·8 ; H, 4·59 ; N, 10·0 %.

Amine hydrochloride.

All the mother liquors, except those of the first methanol crystallization, from the above picrate crystallizations were combined and evaporated to dryness. The residue was dissolved in a large volume of ether and shaken vigorously with 5N caustic soda solution until both aqueous and ethereal layers were completely free from colour. The ether was then washed twice with water. The product was isolated from the ethereal solution, and a few drops of concentrated hydrochloric acid were added. A solid crystallized on stirring the solution. After standing overnight it was filtered off and crystallized from moderately concentrated hydrochloric acid, charcoaling.

Further crystallization from hydrochloric acid gave white clusters of fine rods. They were dried in an evacuated desiccator over potassium hydroxide.

M.p. 211-212° with preliminary shrinking.

Micro m.p.:- softens c 215°, m.p. 217-218°.

Mixed micro m.p. with colchinol methyl ether hydrochloride

(micro m.p. 230-234° with considerable softening from 215°):- softens c 200°, m.p. 205-234°.

Found: C, 62·27; H, 6·43%.

$C_{19}H_{23}O_4N.HCl$ requires C, 62·37; H, 6·57%.

Acetylation of the amine.

The mother liquors from the hydrochloric acid crystallizations of the hydrochloride were basified by concentrated caustic soda solution, and the white precipitate was extracted with ether. After drying with sodium sulphate the base was isolated as a brown gum. A little A.R. acetic anhydride was added, and the mixture allowed to stand for ½ hour. 2N Caustic soda solution was then added and the whole shaken with ice-cooling. A solid was precipitated after a short time. It was filtered off, washing well with cold water, then dried in an evacuated desiccator over potassium hydroxide.

Crystallization from methanol for analysis gave colourless prisms, m.p. 180-180.5° with softening at 179°.

Mixed m.p. with N-acetylcolchinol methyl ether (of m.p. 203-204°):- m.p. 163 - c 200°.

Found: C, 68·00; H, 6·81; N, %.

$C_{21}H_{25}O_5N$ requires C, 67·9; H, 6·75; N, 3·8%.

A preliminary hydrogenation had given a picrate which differs from the above picrate. It crystallized from methanol as bright yellow prisms, m.p. 189-190°, with softening at 186°.

Found: N, 12.03, 12.08%. $C_{19}H_{21}O_4.NH_2.2\left[C_6H_3O_7N_3\right]$ requires N, 12.46%.

An attempt to prepare a solid acetyl derivative by the usual method failed. The hydrogenation, however, had been carried out in an autoclave which was later shown to be contaminated with catalyst from a previous experiment, and possibly also with organic material. Consequently the above preparation could not be regarded as satisfactory, and it was not pursued further.

Picrate of colchinol methyl ether.

To a concentrated ethereal solution of colchinol methyl ether, prepared by hydrolysis of N-acetylcolchinol methyl ether, was added a saturated solution of picric acid in ether. The supernatant liquid was decanted from the yellow picrate which formed, and the precipitate recrystallized from methanol for analysis. It was obtained as bright yellow prisms, m.p. 223-225°, discolouring at 210°.

Found: C, 54.12 ; H, 4.60 ; N, %.

$C_{19}H_{23}O_4N.C_6H_3O_7N_3$ requires C, 53.8; H, 4.7; N, 10.0 %.

Action of phosphorus pentoxide on the acetyl derivative of the amine.

The methanol mother-liquors from the crystallization of the acetyl derivative (page 146) were evaporated to dryness, and to the residue (20 mg.) dissolved in dry xylene (1 cc.) phosphorus pentoxide (c 40 mg.) was added. The mixture was refluxed for 20 minutes in an oil-bath.

The liquid was then allowed to cool and decanted from the solid matter, the solid being subsequently washed well with hot xylene. The combined xylene solutions were filtered through a bed of charcoal and evaporated to dryness on the steam bath. A brown gum was obtained which was dissolved in hot methanol. On cooling an oil separated which would not solidify.

A sample in methanol showed no sign of picrate formation when picric acid in methanol was added.

The methanol was then removed, and the material dissolved in dry benzene and passed through a column of alumina. Elution with benzene gave fraction (1). Addition of a little methanol to the benzene gave fraction (2), which was isolated as a brown oil sparingly soluble in methanol, and separating therefrom as an oil which would not solidify.

Fraction (1) on isolation yielded a brown gum which would not crystallize from methanol or from benzene/ligroin.

It was distilled in a high vacuum, collecting a fraction of b.p. 140-145°/0.2 mm. From methanol colourless crystals

slowly appeared, accompanied by much oil. The crystals, washed with methanol, had micro m.p.:- softening at 60°, m.p. 64-70°. Mixed with deaminocolchinol methyl ether:- micro m.p. 64-95°. Crystallization from 60-80° pet. ether gave crystals (diamonds and cubes) of micro m.p. 70-72° with some preliminary softening. No picrate was formed in methanol.

Oxidation of 9:12:13:14-tetramethoxy-3:4:5:6-dibenz-$\Delta^{3:5}$-cyclo-heptadiene-2-one.

The ketone (50 mg.) was suspended in 2N caustic soda solution (1 cc.), and a 3% aqueous potassium permanganate solution was added dropwise, with shaking, as fast as the pink colour disappeared. After adding 2.66 cc. (≡ rather more than 5 atoms of oxygen) the pink colour was no longer discharged. The mixture was allowed to stand overnight, filtered, and the green filtrate acidified with dilute sulphuric acid. A chocolate-brown precipitate was formed, which became white when a few drops of sulphurous acid were added. The precipitate was then extracted with chloroform, and acidic material recovered from this by shaking with sodium carbonate solution followed by caustic soda solution. Acidification of the combined alkali extracts gave material which did not crystallize satisfactorily. It was redissolved in chloroform, and the chloroform solution shaken with sodium carbonate solution. This solution was then treated with charcoal before the acidic material was liberated by acidification with hydrochloric acid. The acidic product, extracted by chloroform, gave crystals from methanol which were slightly tainted by a yellow substance.

No colour developed when ferric chloride was added to a methanol solution.

Micro m.p.:- softens 130°, m.p. 139-143-162°.

Mixed micro m.p. with (CII):- considerable softening from ~ 110°, m.p. 125-140°.

2-Phenylethyl chloride.

Cf. Darzens, C.r., 1911, 152, 1314.

Purified thionyl chloride (42 cc.) was added dropwise over 1 hour, stirring and ice-cooling, to a mixture of distilled 2-phenylethanol (65 gr.) and distilled dimethyl aniline (65 gr.). After standing in ice for 2 hours, the mixture was heated in an oil bath at 120° until reaction had subsided (½ hour).

The liquid was then allowed to cool, poured into water, and the precipitated oil was extracted with ether. The ethereal solution was washed with water, sodium carbonate solution, and again with water. After drying over sodium sulphate the product was isolated and distilled 86 - 87°/ 11 mm. 67 gr. of colourless oil.

1-(m-methoxyphenyl)-3-phenylpropanol (CVI).

A Grignard solution was prepared by gradual addition of a solution of 2-phenylethyl chloride (66 gr.) in dry ether (430 cc.) to magnesium turnings (11.2 gr.). Refluxing was continued for 4½ hours after the addition was complete.

The mixture was cooled in ice, and distilled m-methoxy benzaldehyde (58.3 gr.) was added dropwise with shaking over ½ hour. The mixture was then stood in the refrigerator overnight. In the morning it was poured on to crushed ice, and moderately concentrated hydrochloric acid was added until all the precipitate was dissolved. The ethereal layer was separated, and the aqueous layer extracted with ether. Both ethereal solutions were combined and dried over calcium chloride. The product was isolated and distilled:-

Fraction 1,	125°/20 mm.	
Fraction 2,	170°/0.4 mm.	15 gr.
Fraction 3,	167-169°/0.4 mm.	31.2 gr.
Fraction 4,	200°/1 mm.	17.5 gr.

Fractions 3 and 4 were colourless oils which reacted with sodium in dry ether.

Attempts to prepare a crystalline 3:5-dinitrobenzoate and a crystalline anthraquinone-β-carboxylate from fraction 3 failed.

A sample of fraction 3 was redistilled for analysis,

collecting the fraction of b.p. 175-177°/0.2 mm.

Found: C, 79.25; H, 7.25%. $C_{16}H_{18}O_2$ requires C, 79.34; H, 7.44%.

Oppenauer oxidation of 1-(m-methoxyphenyl)-3-phenylpropanol.

The carbinol (fraction 3 above) (2.40 gr.), aluminium iso propoxide (freshly prepared. Org.Reactions, II, 198) (2.04 gr.; 1 molecular proportion), dried and distilled cyclohexanone (30 cc.; 30 molecular proportions), and dried benzene (165 cc.) were refluxed in an oil bath at 110° protected by calcium chloride, for 3 hours, then allowed to stand overnight.

The liquid was washed twice with dilute sulphuric acid, then once with water. After drying over sodium sulphate the benzene was distilled off, followed by the cyclohexanone (in vacuo). Distillation was then continued until the temperature reached 150°/12 mm. (fraction 1). The remainder distilled at 140-162°/0.4 mm. (fraction 2) (2.5 gr.).

Fraction 1:- This was shown to be cyclohexylidene cyclohexanone (literature b.p. 136-138°/10 mm.; 143-144°/15 mm.) by preparation of its semicarbazone. This on crystallization from ethanol had m.p. 176-179°. Literature m.p.:- 175-177°; 179-181°.

Fraction 2:- This was separated into two fractions, A and B, by treatment with Girard's reagent T.

Fraction A, which had reacted with the reagent, was recovered in the usual way as a thin brown oil. It was distilled in vacuo at 140°/0.2 mm. and then obtained as a clear colourless oil.

Found: C, 79.8; H, 6.75%. $C_{16}H_{16}O_2$ (CIX) requires C, 80.00; H, 6.67%.

A semicarbazone was prepared, and crystallized from methanol for analysis. It was obtained as beautiful colourless plates, m.p. 160-160.5°.
Found: C, 68.69; H, 6.38%. $C_{17}H_{19}O_2N_3$ requires C, 68.68; H, 6.40%.

Fraction B had not reacted with Girard's reagent, nevertheless it gave a 2:4-dinitrophenyl hydrazone in methanol. It crystallized readily from methanol as bright yellow needles. A sample prepared for analysis had m.p. 83-84°. Found: C, 80.35; H, 6.6%. No constitution has been assigned to this substance. It gives an orange solution, deeper in colour than the original solid, in concentrated sulphuric acid. This supports the chalkone structure (CX).

Oxidation of hexahydrocolchiceine by lead tetra-acetate.

Hexahydrocolchiceine (0.20 gr.) was dissolved in distilled and dried tetrachloroethane (2 cc.), warmed to 40-45°, and lead tetra-acetate (0.25 gr.) added portionwise with shaking, protecting the reaction mixture with calcium chloride. When the addition was complete the mixture was shaken in a boiling water bath for 2-3 minutes, then stood at room temperature for five days. It was filtered from a fine white solid (probably lead diacetate), the filtrate was steam distilled, and the residue extracted with chloroform. The product was isolated after drying as a dark viscous oil (160 mg.). It gave a 2:4-dinitrophenyl hydrazone in methanol. Attempts to purify the oil by crystallization and by chromatography failed. A sample of the dinitrophenyl hydrazone was passed through a column of alumina in benzene solution. A dark band was retained, whilst an orange coloured substance slowly diffused through the lower part of the column. It was preceded and followed by yellow bands, but it was not possible to separate them. Attempted crystallization of the product (from methanol, from benzene/ligroin) was unsuccessful.

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Note:- Structures of synthetic compounds from here to page 150 rest solely on analysis figures .

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