COLCHICINE AND RELATED COMPOUNDS.

A

THESIS

for the degree of

DOCTOR OF PHILOSOPHY

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by

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Contents.

Summary.

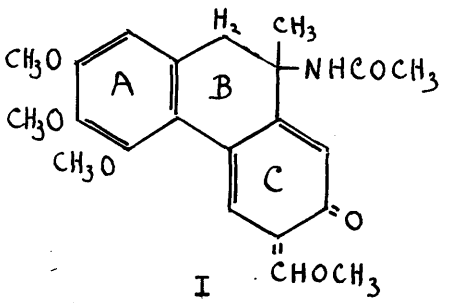
A new synthesis of dibenzcycloheptatrienes has been developed. The method provides a route to derivatives unsymmetrically substituted in the lateral nuclei and is based upon the stepwise oxidation of the appropriate 9- or 10-methyl phenanthrenes. Thus 2:3:4:7-tetramethoxy-10-methyl phenanthrene has been oxidised to 9:12:13:14-tetramethoxy-3:4:5:6-dibenzcyclohepta-1:3:5-trien-7-one which has been shown, by direct comparison, to be identical with a degradation product of colchicine, isolated by Barton, Cook and Loudon. Accordingly the dibenzcycloheptatriene structure of certain colchicine degradation products has been synthetically established.

In an attempt to elucidate the aromatisation of colchiceine, the bromination of this primary hydrolysis product has been re-investigated. A weakly acidic bromo-derivative obtained in this manner is isomeric with tribromo-colchiceine and apparently distinct from the tribromo-carboxylic acid described by Windaus. Methylation of this compound has afforded a methyl ether (or ester), isomeric with tribromo-colchicine.

Part I - Introduction.

I. Colchicine is the alkaloid of colchicum autumnale Linn. Extraction of the dried tissues of this plant with ethanol affords a crude infusion of the alkaloid whose purification will be discussed in a later section.

The chemical constitution of colchicine is still unknown although its elucidation is desirable in view of the widespread interest aroused by the physiological properties of the alkaloid. The first sustained work in this direction was carried out by Zeisel. He was followed by Windaus[1] who, after an extensive degradative study, proposed the formula (I) for colchicine.

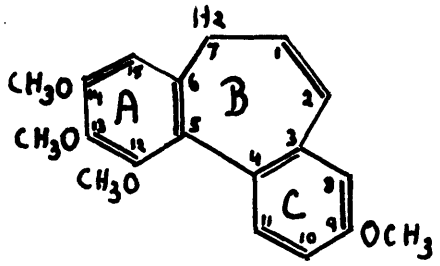


I

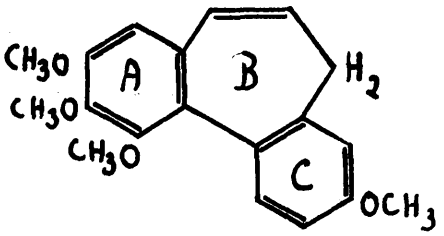
While subsequent investigations have confirmed Windaus's conclusions on the vicinal trimethoxy phenylene structure of ring A and its orientation with respect to ring B, it has become apparent that the structure I is unsatisfactory in several respects. Since ring C will be

considered in detail later, the discussion in the following section will be confined to the structure of ring B as it appears in certain degradation products of colchicine, particularly deaminocolchinol methyl ether.

II.



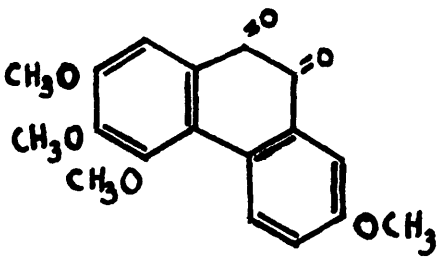
II



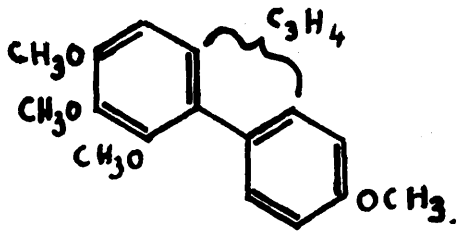
III

It has recently been demonstrated by Barton, Cook and Loudon[2] that deaminocolchinol methyl ether and iso-deaminocolchinol methyl ether, two important degradation products of colchicine, possess the structures (II) and (III) respectively, wherein ring B is seven-membered. The evidence[2] upon which these structures are based may be summarised as follows:-

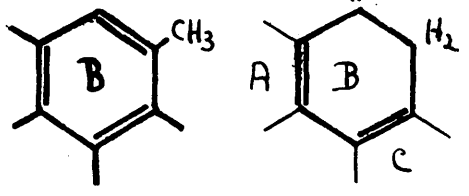
Deaminocolchinol methyl ether, on oxidation with sodium dichromate, yielded two products, one having the properties of an $\alpha:\beta$ -unsaturated ketone and the other being the known 2:3:4:7-tetramethoxy phenanthraquinone (IV). The production of (IV) in this way established the presence of the tetramethoxylated diphenyl residue (V) in deaminocolchinol methyl ether, leaving the nature of the central ring to be determined.



IV

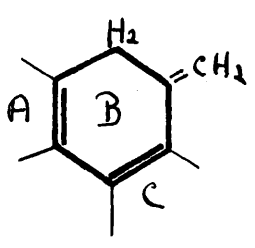


V

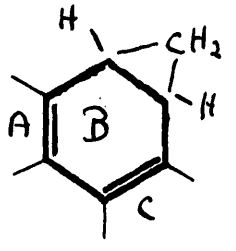


VI

VII



VIII



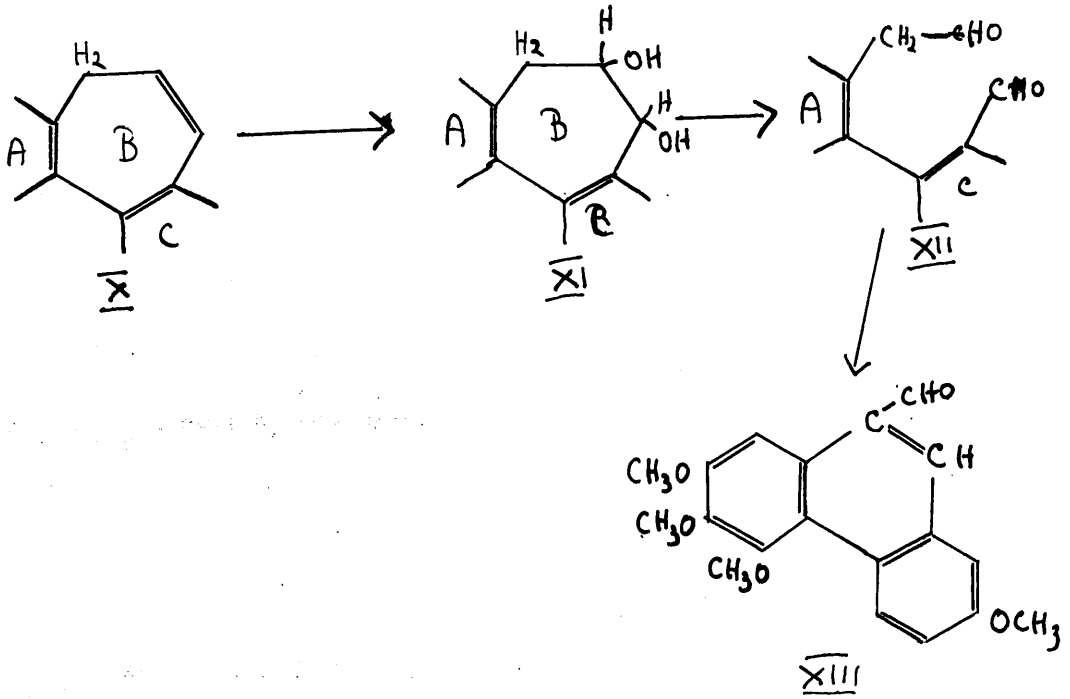
IX

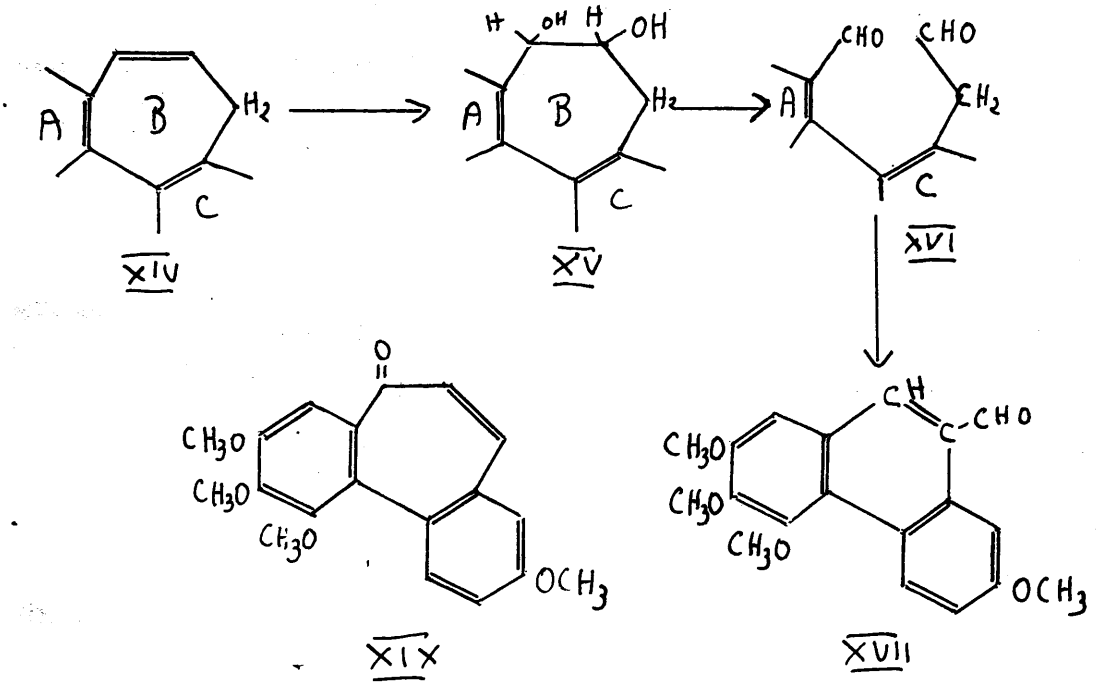
Of the possible arrangements of the three carbon atoms bridging the diphenyl nucleus, aromatic structures such as (VI) were eliminated by the ready hydrogenation of deaminocolchinol methyl ether to a dihydride. Moreover the inability of deaminocolchinol methyl ether to isomerise to a phenanthrene derivative and the failure of its dihydride to undergo dehydrogenation ruled out the possible structures (VII) and (VIII). Finally disregarding the improbable structure (IX), Barton, Cook and Loudon excluded the possibility of a central six-membered ring on the following evidence.

In the preparation of deaminocolchinol methyl ether by the de-acetamidation of N-acetyl colchinol methyl ether[3],

these authors isolated the isomeric compound, iso-deaminocolchinol methyl ether (III). This isomeride was smoothly hydrogenated to a dihydride identical with the dihydride of deaminocolchinol methyl ether. Such isomerism, inexplicable on the basis of a central six-membered ring since the structures (VII) and (VIII) had been abandoned on other evidence, prompted Barton, Cook and Loudon to inquire into the more accommodating possibilities of a seven-membered ring.

On this point, decisive information was obtained from the stepwise oxidation of the double bond in deaminocolchinol methyl ether, first by the method of Criegee using osmium tetroxide in ether, to a glycol. The latter, by cleavage with lead tetra-acetate, yielded a mono-aldehyde which was identified as 2:3:4:7-tetramethoxy-10-phenanthraldehyde (XIII) by oxidation to the corresponding known phenanthrene-10-carboxylic acid. The production of (XIII) by these methods was presumed to occur through the intermediate formation of the di-aldehyde (XII) which, in turn, had arisen from the seven-membered ring B structure (X), by way of the diol (XI).


H2
A
B
C
X
H
OH
XI
CH2—CHO
CHO
XII
CHO
CH
CH3O
CH3O
CH3O
OCH3
XIII


A
B
H2
C
XIV
H
OH
XV
CHO
CHO
CH2
XVI
O
CH3O
CH3O
CH3O
OCH3
XIX
CH
CHO
XVII

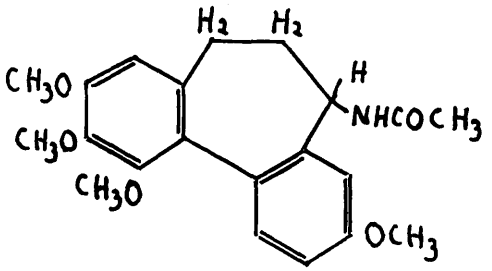
Confirmation of these views resulted from the similar oxidation of iso-deaminocolchinol methyl ether from which, by the steps indicated (XIV ⟶ XVII) 2:3:4:7-tetramethoxy-9-phenanthraldehyde (XVII) was obtained and identified by synthesis.

From these results, Barton, Cook and Loudon concluded that deaminocolchinol methyl ether is 9:12:13:14-tetramethoxy-3:4:5:6-dibenzcyclohepta-1:3:5-triene (II) and that iso-deaminocolchinol methyl ether is the isomeric 9:12:13:14-tetramethoxy-3:4:5:6-dibenzcyclohepta-3:5:7-triene (III).

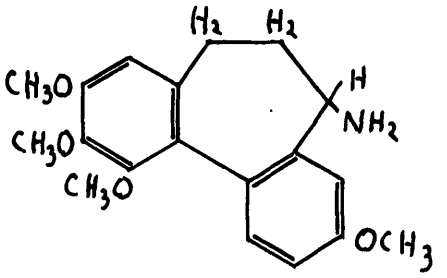
To the $\alpha:\beta$-unsaturated ketone, formed simultaneously with 2:3:4:7-tetramethoxyphenanthraquinone in the oxidation of deaminocolchinol methyl ether, these authors tentatively assigned the structure (XIX), ascribing its formation to the oxidation of the methylene group at position 7 to a carbonyl group.

Assuming Hoffmann degradation does not involve rearrangement of the carbon skeleton (compare Stevens and Richmond[4]), it may be further concluded that the immediate degradation precursors of (II), N-acetyl colchinol methyl ether and colchinol methyl ether possess the structures (XX) and (XXI) respectively although the

precise position of the amino-substituent is uncertain and requires further investigation



XX

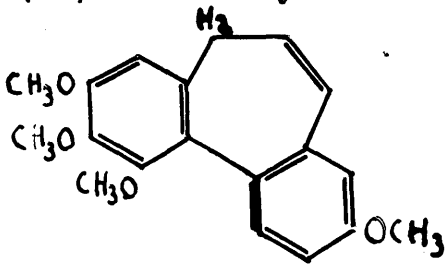


XXI

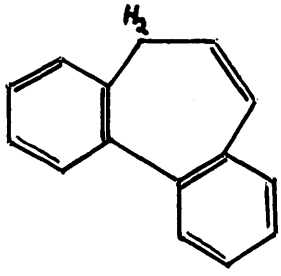
While it still remains to be determined whether the central seven-membered ring structure of (XX) is present in colchicine itself, such a structure (formulated later on p. 48) is not inconsistent with the known chemical behaviour of the alkaloid.

Part I - Discussion.

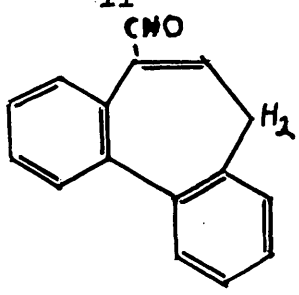
In view of the structure assigned to deamino-colchinol methyl ether by Barton, Cook and Loudon, the synthesis of the tetramethoxy dibenzcycloheptatriene (II) is clearly desirable



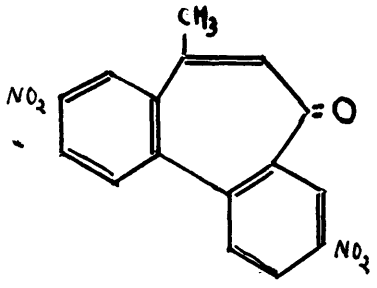
II



XXII



XXIII



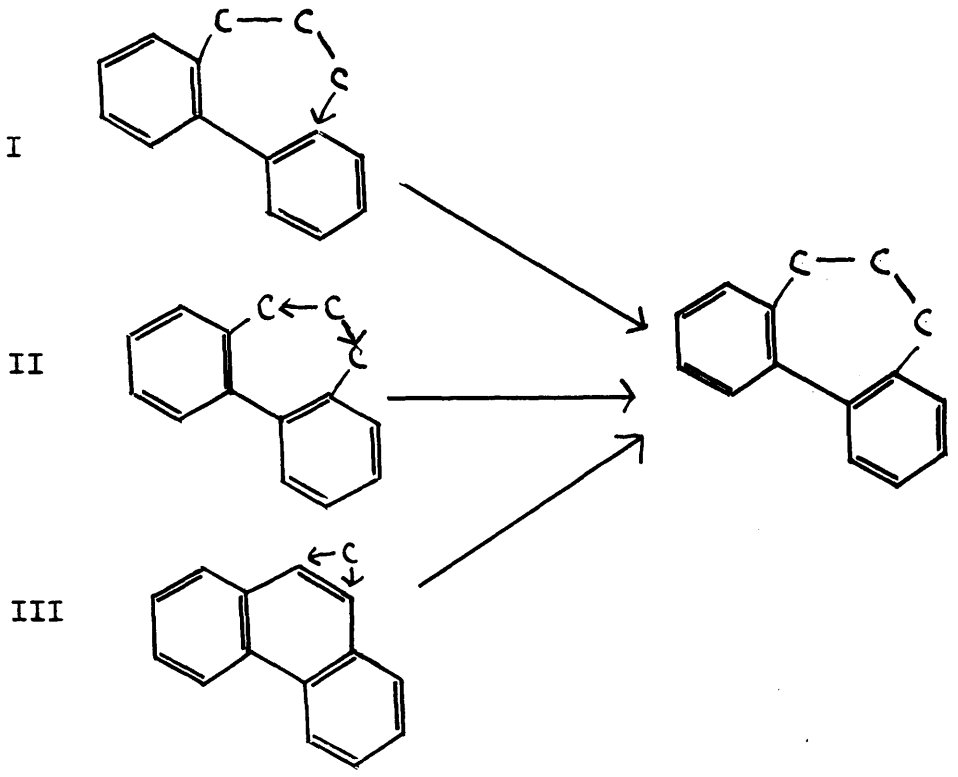
XXIV

Comparatively little is known of the chemistry of dibenzcycloheptatriene (XXII) and its derivatives. The synthesis of a few compounds of this type are, however, described in the literature. Kenner[5], for example, has prepared a number of derivatives of (XXII) from ω -ω'-dibromo-ditolyl (compare Kenner and Turner[6];

also Cook, Dickson and Loudon[7]). In addition, Weitzenböck[8] has described the preparation of (XXIII) from the bisacetal of diphenyl-o,o'-diacetaldehyde, while Borche and Herbet[9] have reported the direct formation of (XXIV) by heating 2-bromo-5-nitroacetophenone with copper. These known syntheses, however, are either based on, or proceed through, symmetrically substituted diphenyls and accordingly they are unsuited for the preparation of structures such as (II) which are unsymmetrically substituted in the lateral nuclei.

The investigations to be described here form part of a general inquiry into the chemistry of colchicine, at present under way in these laboratories. They comprise a study of the chemistry of dibenzcycloheptatrienes with special reference to the development of a synthesis of the unsymmetrical types.

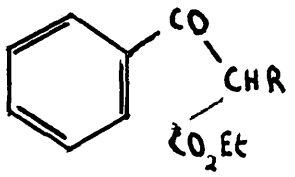
Three particular approaches to this study - the appropriate bridging of preformed diphenyl nuclei - were investigated. The first depends upon the seven-membered ring closure of suitable diphenyl-ō-propane derivatives. The second requires the appropriate introduction of one carbon atom into a suitable o,o'-disubstituted diphenyl. The third is based upon the ring expansion of appropriate phenanthrene derivatives.



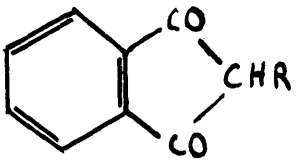
I. Cyclisation of diphenyl-o-propane derivatives.

In this approach information was required concerning the nature and direction of cyclisation in the two following cases:-

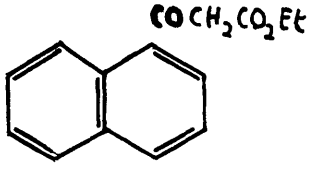
A.(i). Wöjack[10] has shown that although, with concentrated sulphuric acid, ethyl benzoyl acetate is simply hydrolysed to acetophenone and benzoic acid, its C-alkyl derivatives (XXV) and β-naphthoyl acetic ester yield indane derivatives of the type (XXVI).



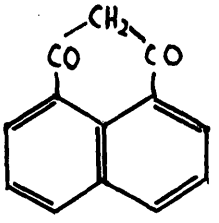
XXV



XXVI

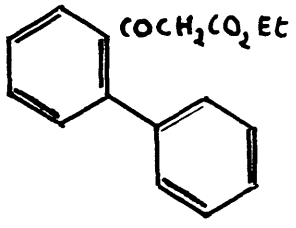


XXVII

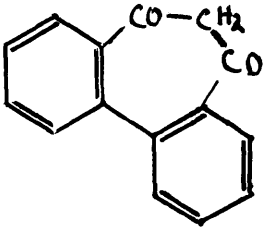


XXVIII

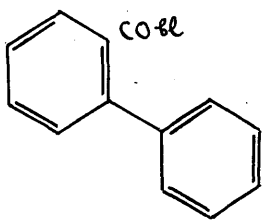
On the other hand, ∝ -naphthoyl acetic ester (XXVII) cyclises at the peri-position, affording peri-naphthane-1:3-dione (XXVIII) and not an indane derivative. The possibility of producing the seven-membered ring compound (XXX) from o-phenyl benzoyl acetic ester (XXIX) was, therefore, worth investigating, the more so since from evidence of other types of ring closure, Kenner[5] has concluded that the central seven-membered ring of (XXX) finds its steric analogue in the five-membered ring of indane.



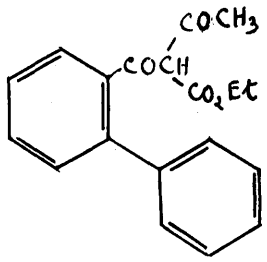
XXIX



XXX



XXXI



XXXII

o-Phenyl benzoyl chloride (XXXI), an intermediate in the formation of o-phenyl benzoyl acetic ester (XXIX), is readily converted into fluorenone (compare p.19), and accordingly its preparation presented some difficulty. The more elegant thionyl chloride method of preparation was preferred to that of Graebe[37], who obtained the acid chloride by grinding equi-molecular quantities of the acid and phosphorous pentachloride, observing no fluorenone formation below 50°C. Although Schönberg and Warren[11] had reported low yields with thionyl chloride at 40°C and 45°C, it was found here, after some experimenting, that this reagent at ordinary temperatures gave the acid chloride in good yield as evidenced by the yield of pure o-phenyl benzoyl acetophenone subsequently realised from it (compare Experimental).

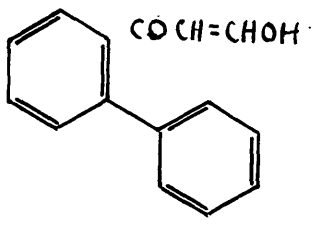
Condensation of this crude acid chloride with the sodium salt of aceto-acetic ester yielded o-phenyl benzoyl aceto-acetic ester (XXXII) which, on removal of the

acetyl group by hydrolysis, afforded the desired o-phenyl benzoyl acetic ester (XXIX).

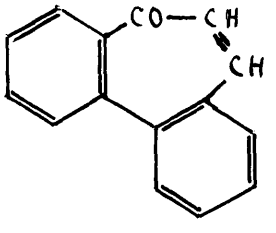
Attempted cyclisation of this ester with phosphorous oxychloride resulted in the production of amorphous material, while treatment with concentrated sulphuric acid, for varying lengths of time and at various temperatures, caused sulphonation. With more dilute sulphuric acid (80%), however, heating at 50°C. for three minutes afforded an acidic compound. The presence of a five-membered ring in this product was demonstrated by oxidation with sodium dichromate to fluorenone. This fact, together with the observed physical properties, suggested that the acid was 9-fluoryl&dine.acetic acid - a conclusion which was later confirmed by mixed melting point with an authentic sample of the acid. Since the crude product exhibited no enolic character, the presence of 2:7-diketo-dibenzcycloheptadiene (XXX) can be precluded.

Apparently cyclisation has taken place through the enolic modification of o-phenyl benzoyl acetic ester, accompanied by hydrolysis of the ester grouping. This result recalls the observation of v. Braun and Manz[12] that, ceteris paribus, in a competitive Friedal-Crafts' reaction, a five-membered ring is formed in preference to a seven-membered one.

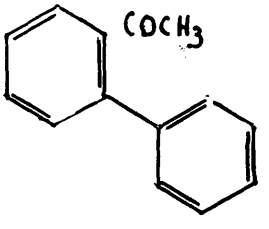
A.(ii). In o-phenyl benzoyl acetic ester, the essential factor in promoting cyclisation was the carbonyl reactivity. Therefore the behaviour of the hydroxymethylene derivative (XXXIII) of o-phenyl acetophenone, towards dehydrating agents, was investigated in the hope that greater carbonyl reactivity in the potential aldehydic grouping of the hydroxymethylene ketone would induce ring closure to the $\alpha:\beta$-unsaturated ketone (XXXIV). Cyclisations of this type have not been described.



XXXIII



XXXIV



XXXV

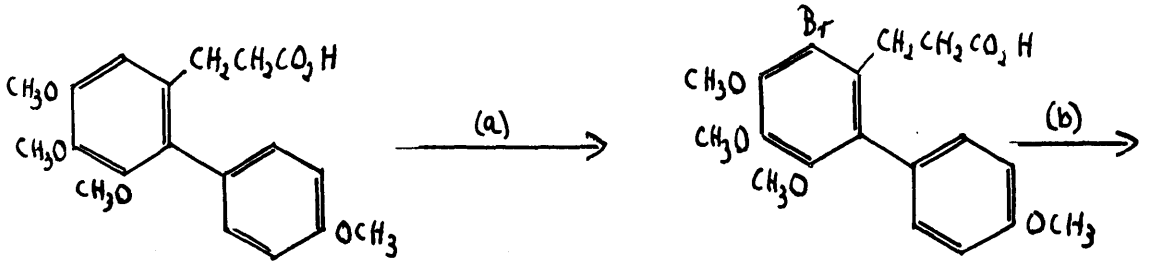
o-Phenyl acetophenone (XXXV), formed by ketonic hydrolysis of o-phenyl benzoyl acetic ester, was converted into the sodium salt of the hydroxymethylene ketone (XXXIII) by condensation with ethyl formate in the presence of sodium ethoxide.

The action of phosphorous oxychloride on the free hydroxymethylene ketone and of both anhydrous hydrogen fluoride and concentrated sulphuric acid on the sodium

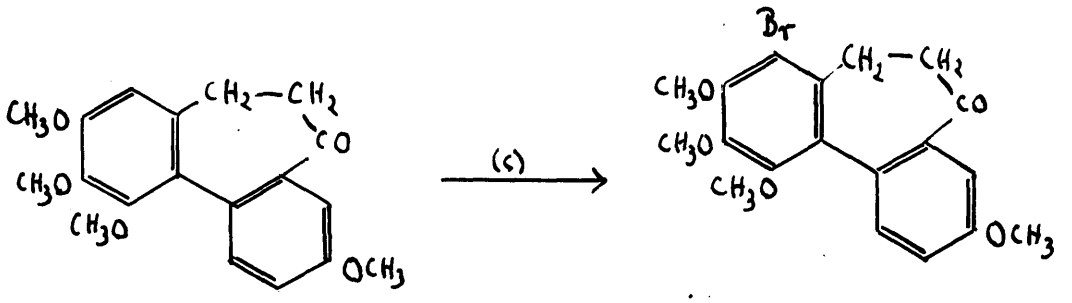
salt, afforded only amorphous material. With the last mentioned reagent, however, the production of some ketonic material was shown by the isolation of a crystalline dinitrophenyl hydrazone. This ketonic derivative was definitely distinct from the dinitrophenyl hydrazone of the unsaturated ketone (XXXIV) which has been independently synthesised (Cook, Dickson and Loudon[7]) and also from the dinitrophenyl hydrazone of o-phenyl acetophenone (XXXV). Its constitution is not known.

Therefore while attempts to effect cyclisation of the hydroxymethylene ketone (XXXIII) have led to inconclusive results, it has been demonstrated that the ring-closure of o-phenyl benzoyl acetic ester does not occur in the desired direction.

I.B. The work in this section was designed to supplement investigations carried out by Dr. N. Barton[13] on a projected synthesis of deaminocolchinol methyl ether. This project involved the following critical stages.

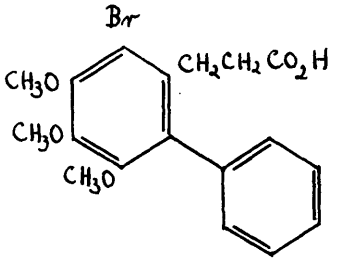


XXXVI XXXVII

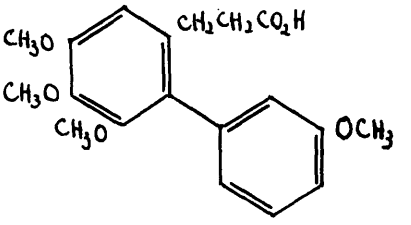


XXXVIII XXXIX

The introduction of the bromo-substituent at stage (a) was intended to preclude cyclisation of (XXXVI) to a hydrindone. The subsequent cyclisation, expected to yield (XXXVIII), had however proved to be extremely troublesome and it was concluded that the unfavourable orienting influence of the methoxyl group in the second phenyl nucleus might in part be responsible. To test this view, two analogues of (XXXVII) were required for comparative cyclisations. In one of these (viz. XL), the methoxyl group was omitted and in the other (viz. XLI) the methoxyl group was placed in a position more favourable to the desired cyclisation.



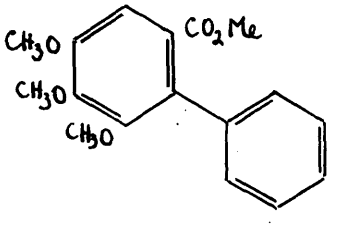
XL



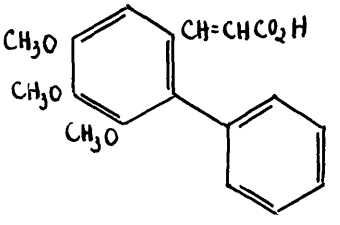
XLI

The synthesis of the two unbrominated parent acids has been achieved in the following manner:-

(i) Synthesis of 2-phenyl-3:4:5-trimethoxy dihydrocinnamic acid.



XLII



XLIII

Methyl 2-phenyl-3:4:5-trimethoxy benzoate (XLII)* was converted into the corresponding aldehyde by the method of McFadyen and Stevens[14], viz:-

$$RCO_2Me \longrightarrow RCONHNH_2 \longrightarrow RCONHNSO_2Ph \longrightarrow RCHO$$

This aldehyde was condensed with malonic acid to give 2-phenyl-3:4:5-trimethoxy cinnamic acid (XLIII) which, on catalytic hydrogenation, yielded the desired 2-phenyl-3:4:5-trimethoxy dihydrocinnamic acid (XLIV)

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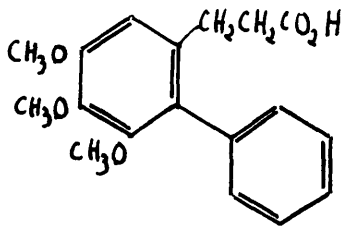
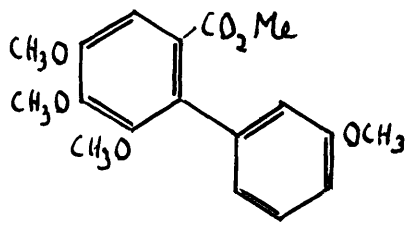
* This intermediate was kindly prepared for this work by Mr. J. McKeown, B.Sc.



XLIV



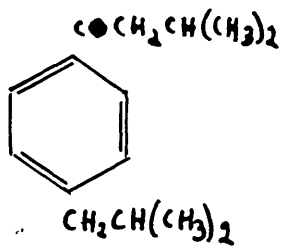
XLV

(ii). Synthesis of 2-(m-methoxyphenyl)-3:4:5-trimethoxy dihydrocinnamic acid.

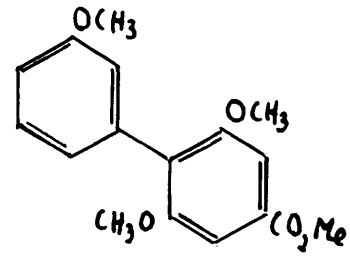
Methyl 2-(m-methoxyphenyl)-3:4:5-trimethoxy benzoate (XLV) was prepared by the condensation of methyl trimethyl gallate with 1-m-methoxyphenyl-3:3-dimethyl triazen, in glacial acetic acid, in the manner of Elks and Hey[15]. This ester, a colourless oil, was obtained pure only after hydrolysis to the corresponding acid and re-esterification of the purified acid.

There was isolated, in addition, a second ester whose percentage composition indicated that the removal of a methoxyl group had accompanied the formation of the diphenyl linkage. Now, the reactivity of the middle methoxyl group in trimethyl pyrogallol and its derivatives is well-known and is evidenced by its replacement with hydrogen[16] and its hydrolysis with sulphuric acid[17]. Moreover, Haller and Schaffer[18] have reported that the reaction of 3:4:5-trimethoxy benzonitrile with isobutyl

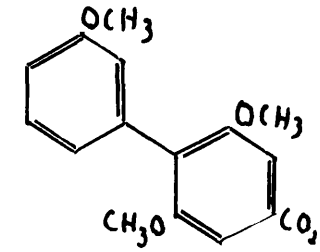
magnesium bromide afford, inter alia, a neutral ketone to which they assigned the structure (XLVI) where the middle methoxyl group has been replaced by the alkyl group of the Grignard reagent. From these considerations, the structures (XLVII) and (XLVIII) are tentatively suggested for the second ester and its parent acid.



XLVI

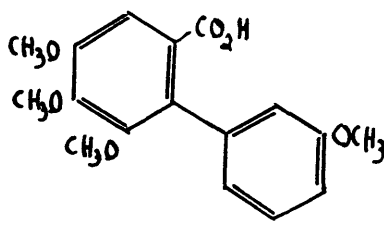


XLVII

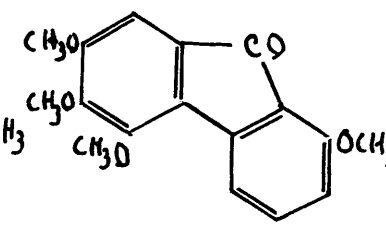


XLVIII

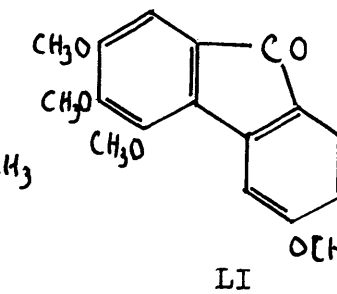
The ready conversion of o-carboxy diphenyl, through its acid chloride, into fluorenone has already been noted (p. 12). This cyclisation, conveniently effected by thionyl chloride, is common to all o-carboxy diphenyls with appropriate free ortho-position and is diagnostic of such a structure.



XLIX



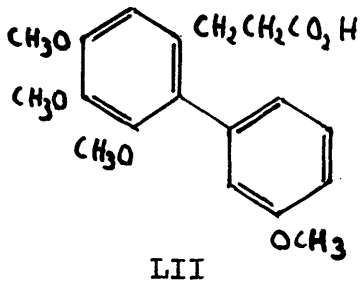
L



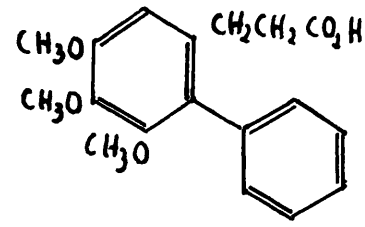
LI

The acid (XLVIII), as expected from the assigned structure, did not give a fluorenone on refluxing with thionyl chloride, while the structure (XLIX) for the parent acid of the main ester product was confirmed by its conversion into the two theoretically possible fluorenones (L) and (LI). These ketones which were separated by fractional crystallisation, have not been individually oriented.

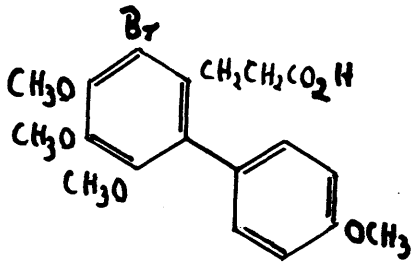
Methyl 2-(m-methoxyphenyl)-3:4:5-trimethoxy benzoate (XLV) was converted into the corresponding dihydrocinnamic acid (LII) by the route already described for methyl-2-phenyl-3:4:5-trimethoxy benzoate (XLIV)



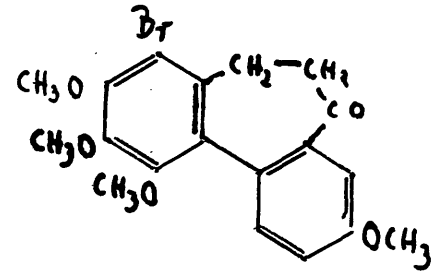
LII



XLIV

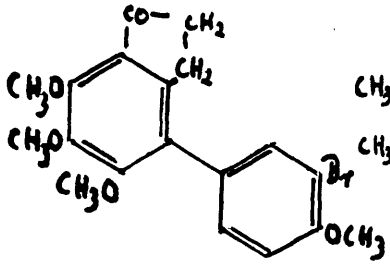


XXXVII

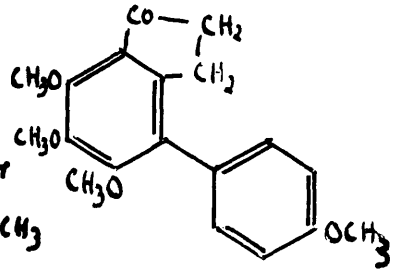


XXXVIII

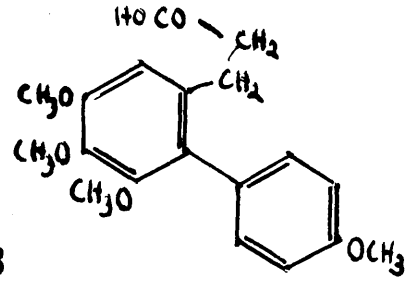
At this stage it had become apparent that cyclisation of Barton's bromo-acid (XXXVII) did not in fact lead to the desired seven-membered ring product (XXXVIII). Recent work by Frank, Fanta and Tarbell[19] points to the same conclusion and it may be added here that Barton, Cook and Loudon[20] in a forthcoming publication show that, on cyclisation, the acid (XXXVII) affords a product which is probably (LIII) since it is debrominated to the hydrindone (LIV), obtained in the cyclisation of (XXXVI).



LIII



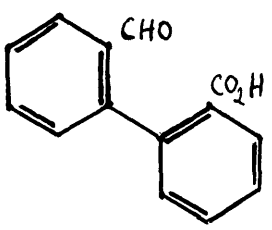
LIV



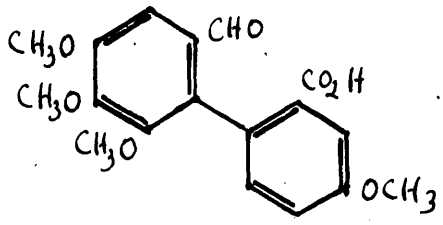
XXXVI

In consequence, although the nature of the cyclisation products from the synthetic propionic acids (LII) and (XLIV) and from their brominated derivatives is still a matter of independent interest, its investigation was suspended meantime in favour of the more immediate problem of finding a synthesis of dibenzcycloheptatrienes, applicable to degradation products of colchicine.

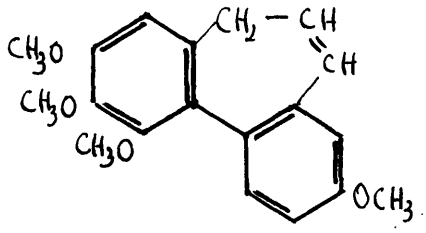
II. Syntheses based upon o,o'-disubstituted diphenyls.



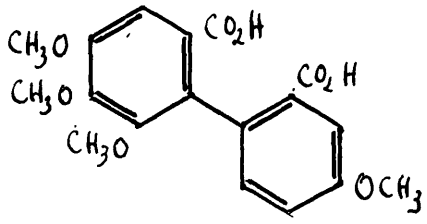
LV



LVI



II

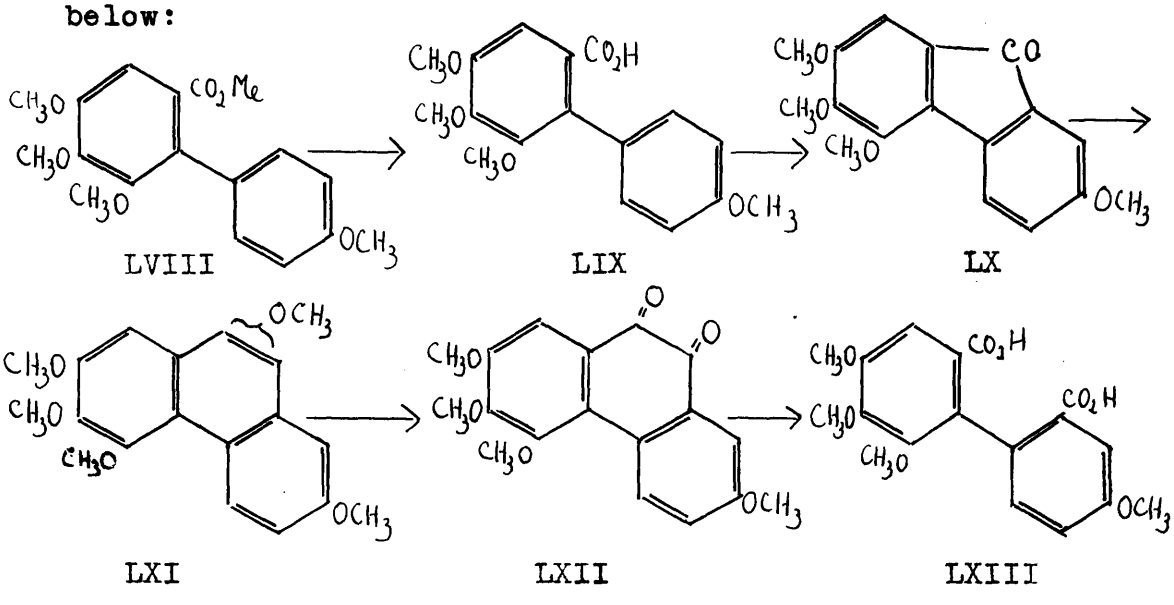


LVII

Since, from preliminary investigations carried out in these laboratories, the most hopeful o,o'-disubstituted diphenyl appeared to be the aldehydo-acid (LV), the synthesis was undertaken of the tetramethoxylated analogue (LVI), a potential intermediate in the synthesis of deaminocolchinol methyl ether (II). The investigations carried out in this connexion may be conveniently discussed under two headings - (A) the synthesis of 4:5:6:4'-tetramethoxydiphenic acid (LVII), and (B) the project of converting the latter into the required aldehydo-acid (LVI).

(A) Synthesis of 4:5:6:4'-tetramethoxy diphenic acid.

The route employed in this synthesis is outlined below:

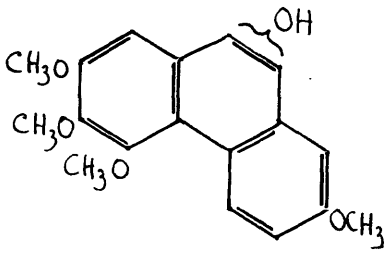


The preparation of 2:3:4:7-tetramethoxy fluorenone (LX) was a repetition of work carried out by Dr. Barton[13], and involved the preparation of (LVIII) and its cyclisation to (LX) essentially as described (p. 18) for the isomeric acid (XLV).

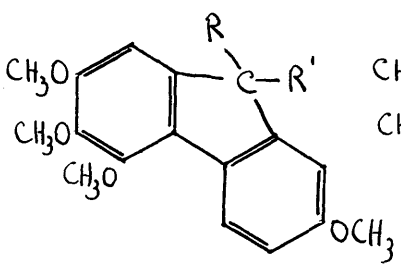
When fluorenone is treated with diazomethane in ether-methanol, ring enlargement occurs and a mixture of phenanthrene derivatives is obtained[21]. With the tetra-methoxy fluorenone (LX), there should be produced a mixture of tetra-methoxy phenanthrene derivatives which, without further purification, should oxidise to 2:3:4:7-

tetramethoxy phenanthraquinone (LXII). In a pilot experiment, it was found that the tetramethoxyfluorenone (LX), with excess diazomethane, afforded a red gum which consisted of (i) a small gummy acidic fraction and (ii) a neutral fraction which, by means of chromatography, was further separated into (iii) a neutral gum, (iv) unchanged tetramethoxy fluorenone and (v) a crystalline material, the main product.

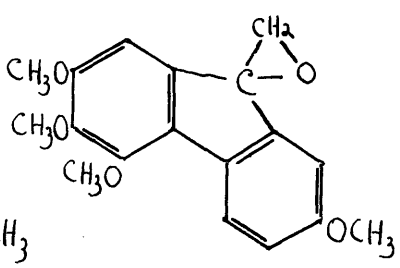
Fraction (i), on oxidation with sodium dichromate, yielded a small amount of the tetramethoxy phenanthraquinone (LXII) and mainly the tetramethoxy fluorenone (LX). This information suggests that fraction (i) consists of 9- (or 10-)-hydroxy-2:3:4:7-tetramethoxy phenanthrene (LXIV) and a 9-derivative of 2:3:4:7-tetramethoxy fluorene (LXV) where R or R' = acidic radical), the nature of which is unknown.



LXIV



LXV

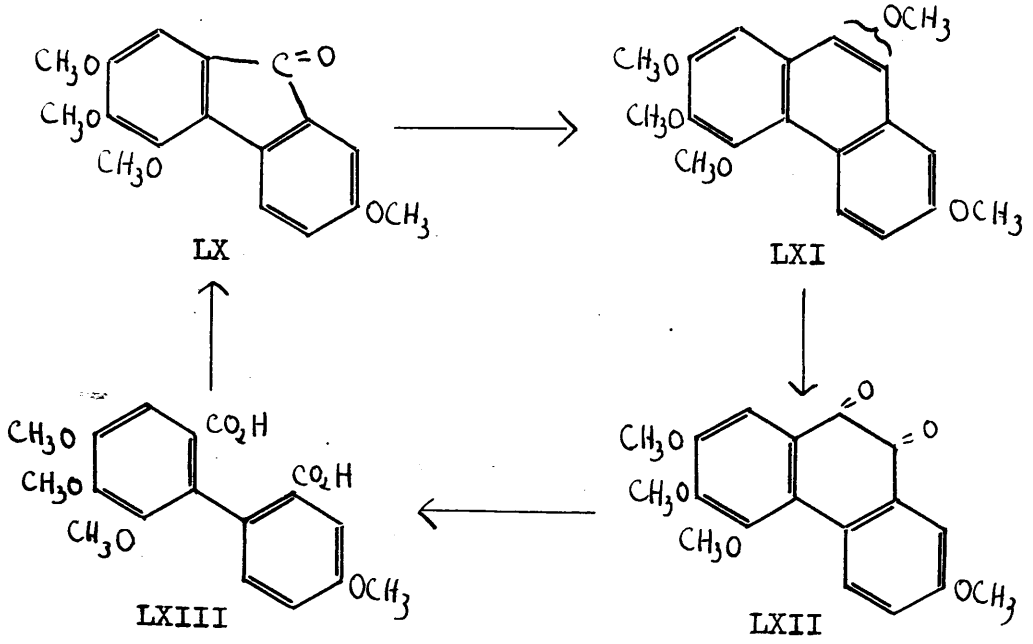


LXVI

Fraction (iii) afforded the tetramethoxy fluorenone on oxidation and presumably consists of the ethylenic oxide (LXVI). The formation of such oxides by the action of

diazomethane on ketones is well known[22].

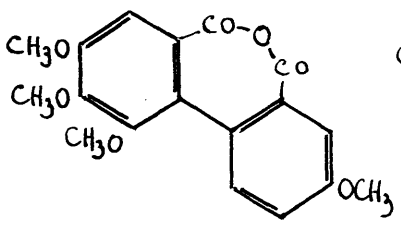
The main fraction (v) analysed correctly for 2:3:4:7-9 (or 10)-pentamethoxy phenanthrene (LXI) and is presumably formed by methylation of the intermediate 9 (or 10)-phenanthrol (LXIV) (compare Cook and Schoental[23]). Oxidation of the pentamethoxy phenanthrene (LXI), with sodium dichromate, afforded 2:3:4:7-tetramethoxy phenanthraquinone (LXII). The conversion of this quinone into the corresponding diphenic acid and anhydride has already been described by Barton[13]. Subsequent investigations revealed that the crude gum obtained from the ring enlargement of the fluorenone (LX) can be oxidised directly to the quinone (LXII) and original reactant.



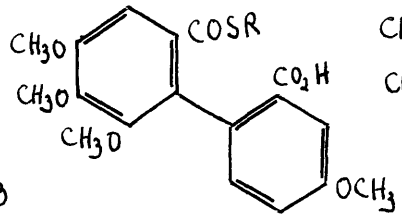
The ring enlargement of (LX), therefore, provides a route to the quinone (LXII) and the corresponding diphenic acid, these being two degradation products of colchicine, already synthesised by Barton, Cook and Loudon[2] and now made available from more accessible materials by the present alternative method. Since the reverse process - the ring contraction of the quinone (LXII) to the fluorenone (LX) - has already been accomplished[13] by oxidation to the corresponding diphenic acid (LXIII) and heat treatment of the latter, a complete cycle of ring enlargement and ring contraction (LX ⟶ LXI ⟶ LXII ⟶ LXIII ⟶ LX) has thus been accomplished.

II. B. Investigations in the synthesis of o-carboxy-o'-aldehydodiphenyls.

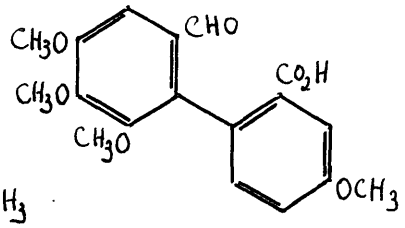
Simultaneously with the work described above, a series of model experiments was carried out to ascertain the best means of applying 4:5:6:4'-tetramethoxy diphenic acid to the required type of synthesis.



LXVII

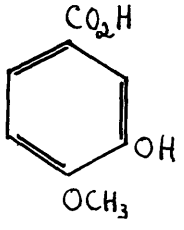


LXVIII

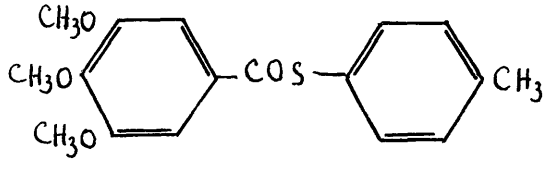


LXIX.

One of the methods which suggests itself is the preparation of a mono-thio ester such as (LXVIII) from the corresponding anhydride (LXVII) followed by catalytic desulphurisation with Raney nickel[24] to the synthetically interesting aldehydo-acid (LXIX). The application of these methods however is complicated by lack of symmetry in the anhydride and also by the susceptibility of the vicinal trimethoxy structure towards hydrogenolysis. In the latter connexion, Schwenk and co-workers[25] have shown that, in the reduction of isovanillic acid (LXX) and p-methoxy acetophenone, elimination of the methoxyl group occurs. Consequently, before investigations in the highly inaccessible tetramethoxy diphenic acid series were undertaken, information was sought concerning the stability of the vicinal trimethoxy benzoyl system towards the desulphurisation conditions to be employed.



LXX



LXXI

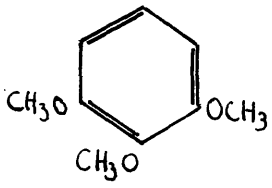
In choosing, p-thio cresyl 3:4:5-trimethoxy benzoate (LXXI) as the model thio-ester, it was decided to investigate the use of the convenient and readily

accessible p-thio cresol in this type of reaction as an alternative to the noxious and less accessible ethyl mercaptan employed by Wolfrom and Karabinos[24] in the original method.

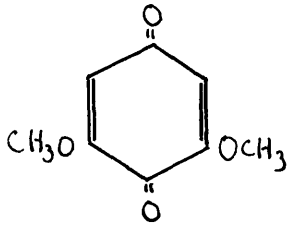
3:4:5-Trimethoxy benzoyl chloride, prepared by the action of thionyl chloride on the corresponding acid[26], was found to be surprisingly unreactive towards p-thiocresol. Esterification would not take place in pyridine at ordinary temperatures and the acid chloride was recovered unchanged under Schotten-Baumann conditions. After some experimenting, it was found that the thio-ester (LXXI) was formed in high yield when the acid chloride and excess p-thiocresol were heated together in pyridine at 80°C.

Hydrogenolysis of p-thiocresyl-3:4:5-trimethoxy benzoate, employing both Adkin's very active Raney nickel[27] and the less active catalyst of Mozingo[28], did not afford 3:4:5-trimethoxy benzaldehyde but a non-ketonic gum which, on fractional distillation, was separated into a low melting solid and 3:4:5-trimethoxy benzyl alcohol, the latter being identified by direct comparison of its analysed 3:5-dinitrobenzoate with an authentic sample (Cook and Graham[3]). It was at first considered possible that the solid, from its mode of formation, from its boiling point and from its ready picrate formation, was 3:4:5-trimethoxy toluene - a possibility eliminated by direct comparison with 3:4:5-

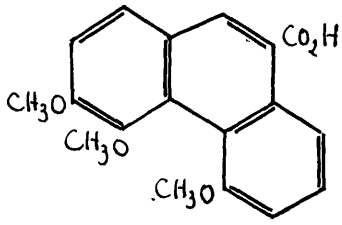
trimethoxy toluene[29], an oil which gave a picrate quite distinct from the picrate of the above crystalline product.



LXXII



LXXIII



LXXIV

Although the carbon analyses of the crystalline hydrogenolysis product were consistently low (see Experimental), the percentage composition of the picrate indicated that the product was 1:2:3-trimethoxy benzene (LXXII). This was supported by oxidation of the compound with dilute nitric acid to 2:6-dimethoxy p-benzoquinone (cf. Baker[30]) and was confirmed by direct comparison of the product (and its picrate) with 1:2:3-trimethoxy benzene (and picrate), prepared by methylation of pyrogallol[30]. The production of (LXXII) in this way is rather surprising although complete removal of the aldehydic and carboxyl groups in the nitration of 3:4:5-trimethoxy benzaldehyde and 3:4:5-trimethoxy benzoic acid has been observed by several workers[31],[32]. A similar reductive cleavage has been encountered in the Rosenmund reduction of 3:4:5-trimethoxy benzoyl chloride and is discussed later (p. 45).

In the course of the work just described, an attempt was made to obtain 1:2:3-trimethoxy benzene from the available

3:4:5-trimethoxy benzoic acid by decarboxylation. However, when refluxed with copper bronze in quinoline or distilled in vacuo from either soda lime or copper chromite, this acid yielded the corresponding ester, methyl 3:4:5-trimethoxy benzoate. Internal methylations of this type have been observed by several workers. Thus Pollack[33] found that dry distillation of 3:4:5-trimethoxy benzoic acid led to the formation of a small amount of the corresponding methyl ester while similar results were obtained by Pschorr[34] in the attempted decarboxylation of 3:4:5-trimethoxy phenanthrene 9-carboxylic acid (LXXIV). This esterification which is presumably accompanied by demethylation at the vicinal methoxyl centre, affords yet another example of the extreme reactivity of such a system.

Accordingly the results show that under the hydrogenolysis conditions employed, p-thiocresyl 3:4:5-trimethoxy benzoate affords a mixture of 1:2:3-trimethoxy benzene and 3:4:5-trimethoxy benzyl alcohol. While, therefore, the vicinal trimethoxyl groups survive, the thio ester grouping is either reduced beyond the aldehyde stage or completely split off. To decide whether these results are due to the inherent sensitivity of this particular molecule or to the use of the p-thiocresyl in place of the ethyl thio ester and also to obtain more

precise information on the desulphurisation technique of Wolfrom and Karabinos, the hydrogenolysis of p-thiocresyl benzoate was studied and the results compared with those obtained by Wolfrom and Karabinos in the desulphurisation of ethyl thio benzoate. p-Thiocresyl benzoate, prepared by heating benzoyl chloride with an excess of p-thiocresol in pyridine, when treated with both Adkin's and Mozingo's Raney nickel afforded not only benzaldehyde in small yield (10%) but also benzyl alcohol (23%). Since Wolfrom and Karabinos report a 60% yield of benzaldehyde from ethyl benzoate, it appeared possible that the use of different thio-esters might influence the course of hydrogenolysis.

Information on this point was sought by a study of the desulphurisation of ethyl thio 3:4:5-trimethoxy benzoate and ethyl thio benzoate which were prepared by treating the corresponding acyl chloride with a large excess of ethyl mercaptan in pyridine. The former ester in complete agreement with the corresponding p-thiocresyl-3:4:5-trimethoxy benzoate, afforded, with Mozingo's Raney nickel, 3:4:5-trimethoxy benzyl alcohol (40%) and 1:2:3-trimethoxy benzene (20%) - a result which indicates that the course of reduction in the trimethoxy benzoyl series at least is independent of the thio ester employed.

Hydrogenolysis of ethyl thio benzoate, however, gave

rather surprising results. Treatment of this ester with Adkin's Raney nickel afforded a volatile product whose separation from the ethanol, used as solvent, presented some difficulty. After fractional distillation had failed to effect a separation, the mixture was cautiously treated with concentrated nitric acid and the aromatic product isolated as a nitro compound which, on catalytic reduction, yielded an amine characterised as aniline by means of its tribromo- and acetyl- derivatives. In this way, it was shown that catalytic desulphurisation as here carried out and in contrast to the findings of Wolfrom and Karabinos[24], affords benzene* in 60% yield. This result suggests that the elimination of the -COSR grouping previously observed in the case of the ethyl thio and p-thiocresyl-3:4:5-trimethoxy benzoates is not a unique property of the vicinally substituted trimethoxy benzene nucleus and that such behaviour, hitherto unobserved, may also be exhibited by the thio esters of other aromatic acids.

While the complete removal of the -COSR grouping in the hydrogenolysis of these thioesters is surprising, the production of the corresponding alcohol finds some

---

* The production of benzene in the hydrogenolysis of p-thiocresyl benzoate, although not encountered, would not be significant in view of the thio ester used.

analogy in recent work by Prelog[35]. This author has shown that thio-esters, when shaken with Raney nickel in a suitable solvent, afford the corresponding alcohol in high yield. When this procedure of Prelog was applied to the present case, p-thiocresyl 3:4:5-trimethoxy benzoate gave 3:4:5-trimethoxy benzyl alcohol (40%) and 1:2:3-trimethoxy benzene (30%). Both experimental techniques in our hands have therefore given essentially the same results.

The failure of thio-esters to yield aldehydes under Wolfrom and Karabinos conditions has been noted very recently by other workers. Thus Frank, Fonta and Tarbell[19] found that iso-propyl thio-3:4:5-trimethoxy benzoate afforded a non-ketonic gum from which they could only isolate 3:4:5-trimethoxy benzyl alcohol as its 3:5-dinitrobenzoate in very low yield. Similarly Spero, McIntosh and Levin[36] report that the ethyl thio ester of a cholanic acid derivative was reduced to the corresponding alcohol. These latter authors, however, were finally able to prepare the required aldehyde in consistently good yield by a standard poisoning of the Raney nickel.

From the diverse results described in the literature together with the present findings, it would appear that the course of catalytic reductive desulphurisation of thio

esters with Raney nickel is dependent upon the activity of the catalyst used.

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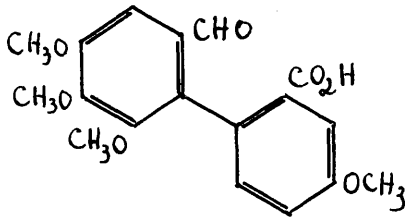
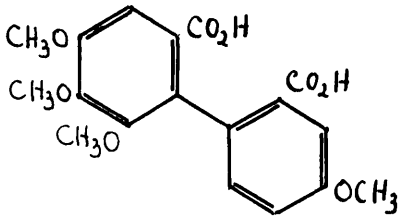


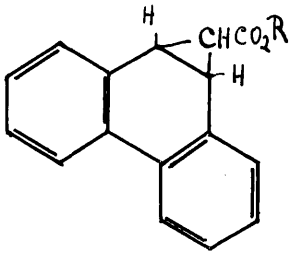
LXIX



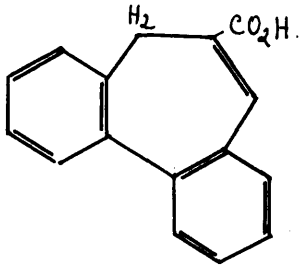
LXIII

These results therefore precluded the preparation of the aldehydo-acid (LXIX) from the corresponding mono-thioester and since a study of alternative routes to (LXIX) from the diphenic acid (LXIII) had been undertaken by others working in these laboratories, this line of investigations was discontinued.

III. Synthesis of Dibenzcycloheptatrienes from Phenanthrene Derivatives.



LXXV

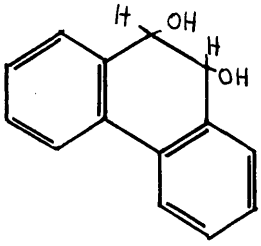


LXXVI

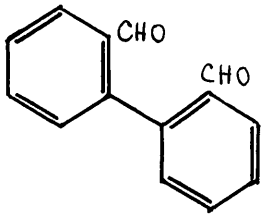
The possibility of utilising the well known reactivity of the 9:10-double bond of phenanthrenes in the synthesis of dibenzcycloheptatriene derivatives was first explored by Drake and Sweeney[38] who attempted to isomerise the norcardiene carboxylate (LXXV) (where R = Et), obtained by the action of diazo-acetic ester on phenanthrene, to the dibenzcycloheptatriene carboxylic acid (LXXVI). Although this preliminary work was unsuccessful due to the stability of the free acid (LXXV) (where R = H) (compare Cook, Dickson and Loudon[7]), it was here decided to extend these investigations in the hope that other olefinic reagents, particularly osmium tetroxide, might effect an expansion of the central ring in the phenanthrene nucleus.

Criegee[39] has shown that phenanthrene on treatment with osmium tetroxide in benzene, affords cis-9:10-dihydrophenanthrene-9:10-diol (LXXVII) which, with lead tetra-

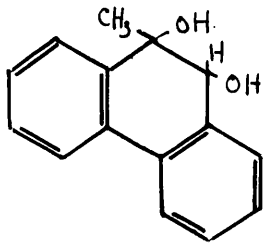
acetate, is oxidised to diphenyl-o,o'-dialdehyde (LXXVIII).



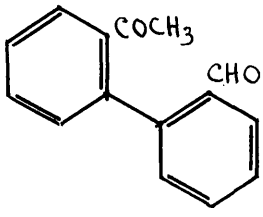
LXXVII



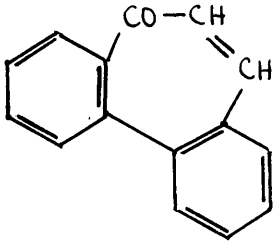
LXXVIII



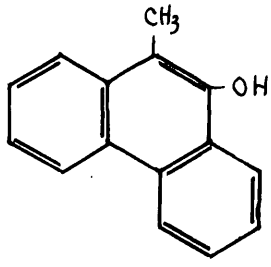
LXXIX



LXXX



LXXXI



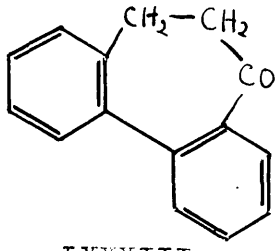
LXXXII

Mr. G. Buchanan, B.Sc., in connexion with the present general inquiry, has successfully applied the same process to 9-methyl phenanthrene. The latter yielded a crude diol (LXXIX) which, by cleavage with lead tetra-acetate and renewed cyclisation, afforded the known unsaturated ketone (LXXXI) (Cook, Dickson and Loudon[7]).

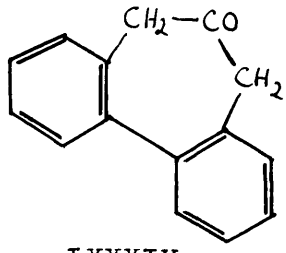
As a preliminary to investigating the reaction in the tetramethoxy phenanthrene series, Buchanan's work was here repeated. The diol (LXXIX) was obtained analytically pure and was characterised by dehydration to the pure phenanthrol (LXXXII). The subsequent stages of cleavage

(presumably to (LXXX)) and cyclisation were also confirmed.

It was a point of considerable interest and value to ascertain the behaviour of the dibenzcycloheptatrienone (LXXXI) on oxidation with sodium dichromate. Saturated ketones of this type (viz. (LXXXIII) and (LXXXIV)) are oxidised to phenanthraquinone under these conditions(7). The question, therefore, arises whether or not the modification introduced by the unsaturated centre in (LXXXI) influences this result. Oxidation of the unsaturated ketone did in fact lead to the formation of phenanthraquinone.

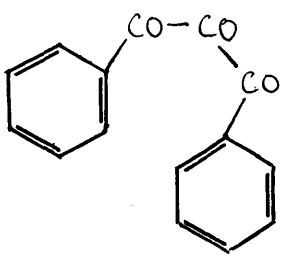


LXXXIII

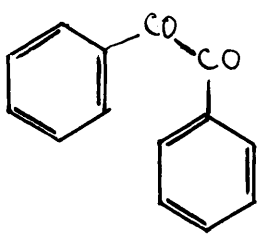


LXXXIV

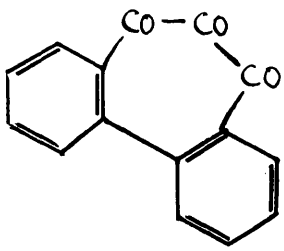
The mechanism of this oxidative degradation is not apparent although the observation of Schönberg and Azzam(40) that diphenyl triketone (LXXXV) yields benzil (LXXXVI) under acid conditions suggests a possible route involving the intermediate formation of the triketone (LXXXVII). The same intermediate could be involved in the oxidation of the saturated ketones (LXXXIII) and (LXXXIV).



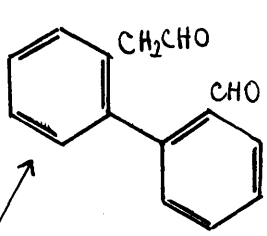
LXXXV



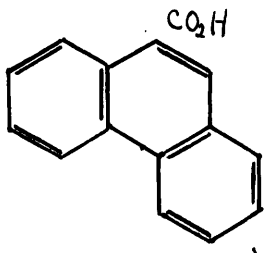
LXXXVI



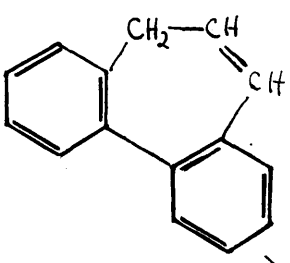
LXXXVII



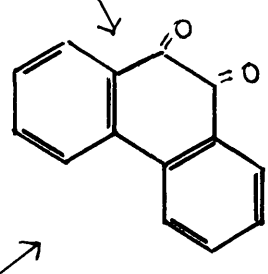
LXXXIX



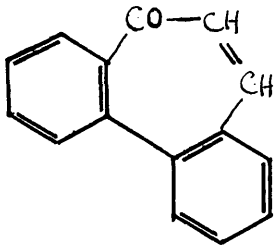
XC



LXXXVIII



XCI



LXXXI

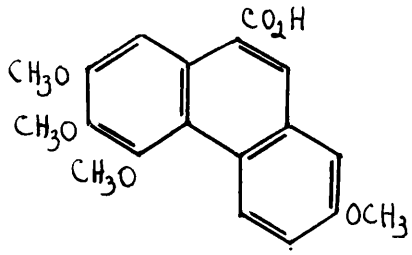
This result provided additional information on the oxidation of dibenzcycloheptatriene (LXXXVIII). From this oxidation, Cook, Dickson and Loudon[7] obtained, in addition to phenanthraquinone, the unsaturated ketone

(LXXXI) and phenanthrene-9-carboxylic acid (XC). The isolation of the latter indicates one possible route to phenanthraquinone (LXXXVIII ⟶ LXXXIX ⟶ XC ⟶ XCI), involving cleavage at the double bond followed by renewed cyclisation. It is now evident that the unsaturated ketone (LXXXI) is an intermediate in an alternative route (LXXXVIII ⟶ LXXXI ⟶ XCI) in which scission of the double bond is unlikely.

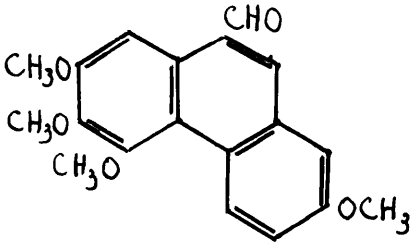
Finally this result demonstrates the ease with which dibenzcycloheptatrienes furnish phenanthraquinones on sodium dichromate oxidation. Consequently this property which now appears to be common to all dibenzcycloheptatrienes promises to be of considerable diagnostic value in this field.

Synthesis of 9:12:13:14-tetramethoxy-3:4:5:6-dibenzcyclohepta-1:3:5-trien-7-one.

In view of the success attending the preliminary investigations described above, the oxidation of 9 (or 10)-methyl phenanthrenes appeared to provide a route to dibenzcycloheptatrienes of requisite adaptability. Accordingly attention was directed to the controlled oxidation of 2:3:4:7-tetramethoxy-10-methyl phenanthrene which was synthesised as follows:-

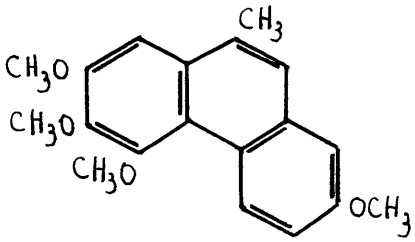


XCII

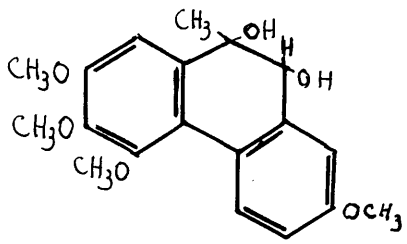


XCIII

The methyl ester of 2:3:4:7-tetramethoxyphenanthrene-10-carboxylic acid (XCII), previously synthesised by Barton, Cook and Loudon[2], was converted into the corresponding aldehyde (XCIII), by the method of McFadyen and Stevens[14]. This aldehyde (and its oxime) were found to be identical with the aldehyde (and oxime) obtained by Barton, Cook and Loudon in the stepwise oxidation of deaminocolchinol methyl ether (compare p. 4) and identified by them through its oxidation product, viz., the synthetic acid (XCII). Kischner[41] reduction of the aldehyde (XCIII) afforded the required 2:3:4:7-tetramethoxy-10-methylphenanthrene (XCIV)



XCIV

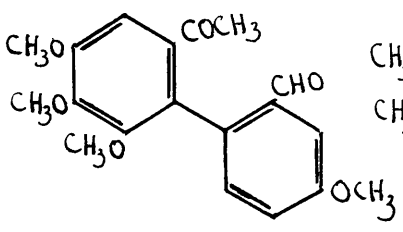


XCV

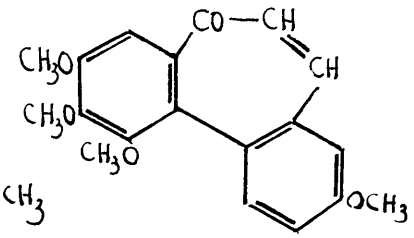
Oxidation of (XCIV), in the manner of Criegee[39] using osmium tetroxide in benzene, gave cis-2:3:4:7-

tetramethoxy-10-methyl-9:10-dihydrophenanthrene-9:10-diol (XCV). It may be mentioned here that dehydration of this diol (XCV) to the corresponding phenanthrol appears to be subject to complication. For instance, attempted dehydration of (XCV) with hydrochloric acid in acetic acid afforded a neutral compound with an unaccountably high carbon content (see Experimental). The use of iodine in toluene similarly led to inconclusive results.

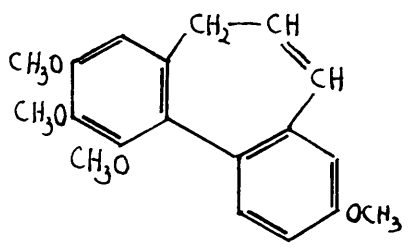
The diol (XCV), on cleavage with lead tetra-acetate in benzene, afforded a gum. The methanolic solution of the latter, presumably (XCVI), in the presence first of dilute sodium bicarbonate and then of dilute sodium hydroxide all in an atmosphere of nitrogen, slowly deposited a gum from which there was isolated, by chromatography, 9:12:13:14-dibenzcycloheptatriene-7-one (XCVII). This $\alpha:\beta$-unsaturated ketone was identified by micro-melting point and mixed micro-melting point as the unsaturated ketone obtained by Barton, Cook and Loudon[2] as part-product of the oxidation of deaminocolchinol methyl ether (compare p. 6).



XCVI



XCVII

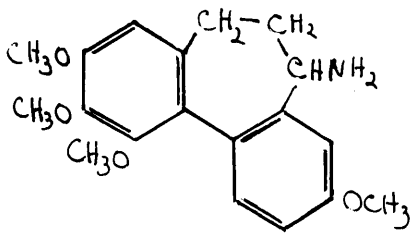


II

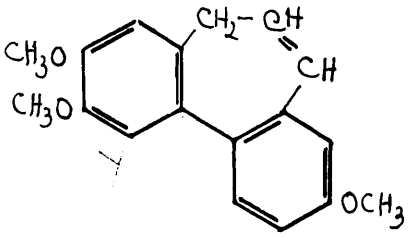
The unsaturated ketone (XCVII) is therefore the first compound wherein the presence of the central seven-membered ring is synthetically established for this series of colchicine degradation products. In addition the location of the double bond in deaminocolchinol methyl ether (II), determined by Barton, Cook and Loudon on degradative evidence, is synthetically confirmed. Finally the success of the method encourages the hope that the process may be applied to the synthesis, from 2:3:4:7-tetramethoxy-9-methyl phenanthrene of the isomeric ketone which would be a useful intermediate for the ultimate synthesis of deaminocolchinol methyl ether.

In addition to the unsaturated ketone (XCVII), there was isolated, from the crude condensate from (XCVI), a high melting, neutral material which was non-ketonic and which oxidised to 2:3:4:7-tetramethoxy phenanthraquinone. This product, from its percentage composition and micro-Rast molecular weight determinations, appears to possess the molecular formula $C_{38}H_{40}O_{10}$ and was shown by micro-hydrogenation to contain one double bond per nineteen carbon atoms. The nature of this compound is unknown.

Projected Synthesis of Deaminocolchinol methyl ether.

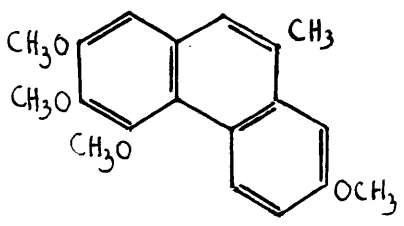


XXI

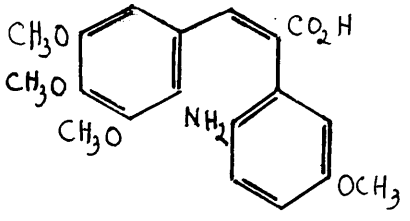


II

For the synthesis of colchinol methyl ether (XXI) and deaminocolchinol methyl ether (II) by the above methods, 2:3:4:7-tetramethoxy-9-methylphenanthrene (XCVIII) is required as an intermediate. Although this methyl phenanthrene has been synthesised previously by Buchanan, Cook and Loudon[42], not only does the route employed by them require the highly inaccessible 2-nitro-3:4:5-trimethoxy benzaldehyde but it also involves the production of isomers in the cyclisation of the Pschorr acid (XCIX).



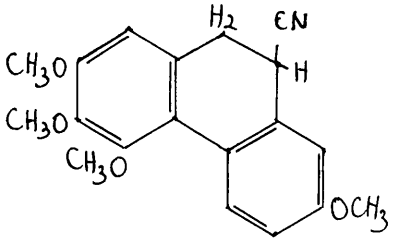
XCVIII



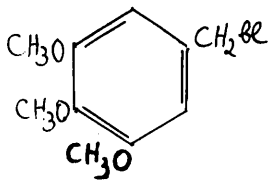
XCIX

Since the synthesis of 2:3:4:7-tetramethoxy-9:10-dihydrophenanthrene-9-nitrile (C) has already been accomplished in these laboratories by D. Ellis[43], the

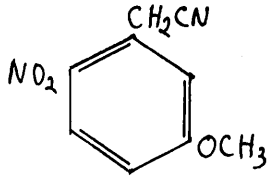
conversion of this cyano-compound (C) into the required 2:3:4:7-tetramethoxy-9-methyl phenanthrene (XCVIII) appeared to offer a more attractive route.



C

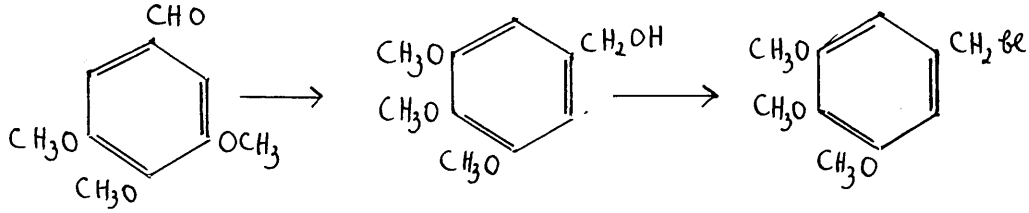


CI



CII

Consequently the synthesis of 2:3:4:7-tetramethoxy-9:10-dihydrophenanthrene-9-nitrile (C) was undertaken employing the methods of the aforementioned author. Of the two primary components required for this synthesis - 3:4:5-trimethoxy benzyl chloride (CI) and 2-nitro-5-methoxy benzyl cyanide (CII) - the latter (CII) was kindly prepared for this work by Dr. Dickson. The former (CI) was secured by the route, described by Cook and Graham[3], viz:-



CIII CIV CV

In this connexion several points have arisen which merit discussion.

3:4:5-Trimethoxy benzaldehyde (CIII). During attempts to standardise the Rosenmund reduction of 3:4:5-trimethoxy benzoyl chloride, it was found that this acid chloride when refluxed in decalin with palladised barium sulphate, afforded 1:2:3-trimethoxy benzene in 40% yield. The removal of the -COCl group in this particular molecule has already been observed by Späth[44]. Rosenmund and Heise[45], who obtained similar results in the case of p-anisoyl chloride, considered that the formation of 1:2:3-trimethoxy benzene and anisole in this way occurred through the reductive cleavage of the intermediate ester $RCOCH_2R$ in the following manner:-

$$RCO_2\ CH_2\ R \longrightarrow RCO_2H + CH_4 + RH$$

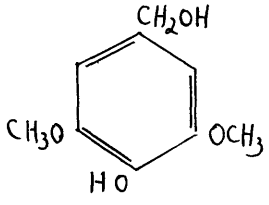
(where R = p-anisoyl or 3:4:5-trimethoxybenzoyl).

A similar cleavage may also operate in the elimination of the -COSR grouping in the hydrogenolysis experiments already described (pp.28-34).

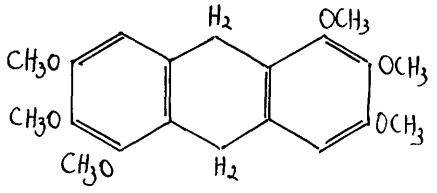
3:4:5-Trimethoxybenzaldehyde was finally secured in the large quantities required for the present investigations by Sönn-Muller reduction of the corresponding acid chloride - the process used by Cook and Graham.

3:4:5-Trimethoxy benzyl alcohol. Catalytic reduction of 3:4:5-trimethoxy benzaldehyde to the corresponding alcohol proceeded smoothly except in one case where

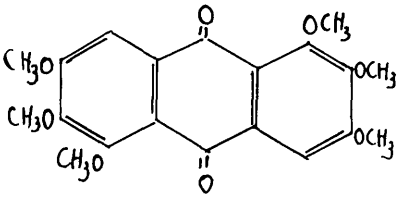
incomplete hydrogen absorption occurred. In this case, two crystalline by-products were isolated in addition to the expected alcohol. One of these products was identified by direct comparison as the compound which Cook and Graham[3] obtained from the attempted methylation of syringic alcohol (CVI) with methyl-p-toluene sulphonate and which they suggested might be the hexamethoxy-dihydroanthracene (CVII). That the tentative formula (CVII) for this compound was apparently correct, has now been demonstrated by oxidation to the known hexamethoxy anthraquinone (CVIII)[46]. The other product obtained in this reduction has not been identified.



CVI



CVII



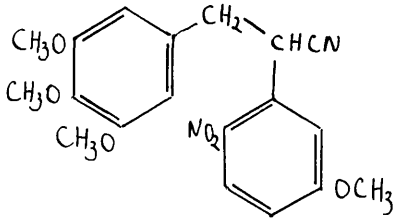
CVIII

It may be mentioned here that reduction of 3:4:5-trimethoxybenzaldehyde by a crossed Cannizzaro reaction afforded the alcohol in low yield

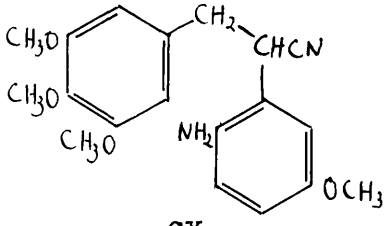
3:4:5-Trimethoxy benzyl chloride (CI) was obtained from the above alcohol in improved yield using a modification of the procedure described by Cook and Graham.

- - - - -

The condensation of 3:4:5-trimethoxy benzyl chloride (CI) with 2-nitro-5-methoxy-benzyl cyanide (CII) afforded ∝-(3':4':5'-trimethoxy benzyl)-2-nitro-5-methoxy benzyl cyanide (CIX) which was catalytically reduced to the corresponding amine (CX).



CIX

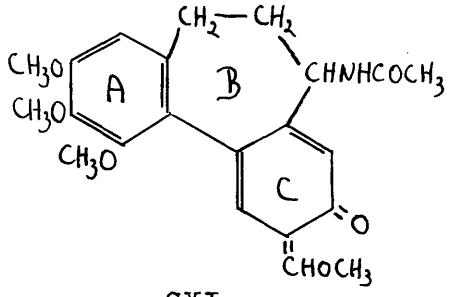


CX

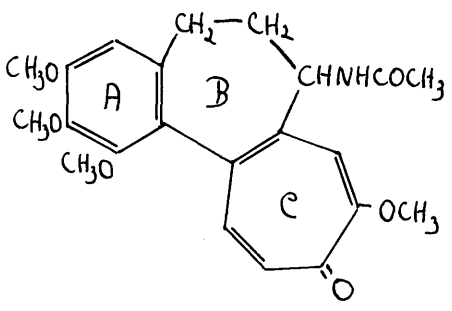
At the time of writing, the Pschorr ring closure of the amine (CX) is under investigation. Preliminary investigations indicate that this cyclisation, in our hands, affords the required dihydrophenanthrene-9-nitrile in variable yields which are, in general, considerably lower than those obtained by Ellis[43].

Part II - Introduction

In Part I, it has been shown that certain degradation products of colchicine possess a tetramethoxylated dibenzcycloheptatriene structure and that a central seven-membered ring may be present in the alkaloid itself (see p. 7). Making this probable assumption, colchicine may now be represented by the two rival formulae (CXI) and (CXII), the former containing the methoxy-methylene ring C structure proposed by Windaus[1] and the latter the cycloheptatrien-ol-one ring C structure proposed by Dewar[47].



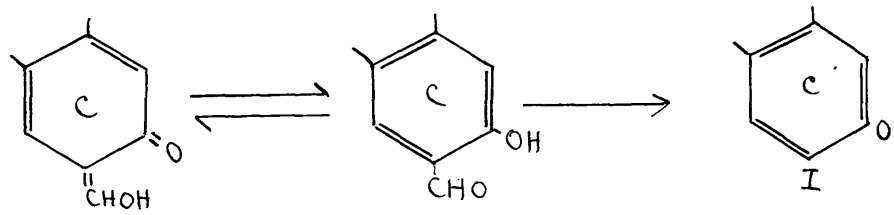
CXI



CXII

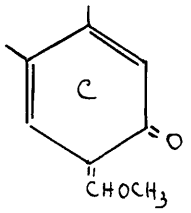
Windaus's arguments for the methoxy-methylene structure are as follows. Colchicine is readily hydrolysed to methanol and colchiceine which, unlike colchicine, is acidic and exhibits the ferric chloride colour reaction characteristic of enols. Further hydrolysis yields acetic acid and the amphoteric trimethyl

colchicinic acid. The latter gives rise to two isomeric dibenzene sulphonyl derivatives which are partially hydrolysed to the same mono-N-benzene sulphonyl derivative. Isomerism must therefore be centred in the o-benzene sulphonyl grouping and Windaus concluded that the isomers were cis- and trans-isomers about the double bond of a hydroxy-methylene group. Finally from the conversion of colchiceine into N-acetyl iodo colchinol (CXV), by treatment of the former with sodium hydroxide and iodine, Windaus proposed the hydroxy-methylene structure (CXIII) for ring C in colchiceine, considering that formation of (CXV) occurred through the replacement of the aldehydic group in the tautomer (CXIV) by an iodine atom. Analogous replacements have been observed in the other o-hydroxy aromatic aldehydes[48] which closely resemble colchiceine in their colour reactions with acids and alkalis[1]. Moreover the structure of the iodo phenolic ring (CXV) is shown by oxidation of the derived methyl ether to 4-iodo-5-methoxy-1:2-phthalic acid which has been synthesised by Grewe[49].

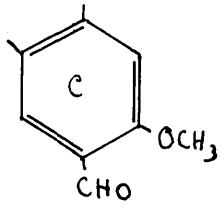


CXIII CXIV CXV

On this basis, Windaus concluded that the tribromo-carboxylic acid[50] which he obtained in the bromination of colchiceine, had arisen through oxidation of the aldehydic grouping in the tautomer (CXIV)

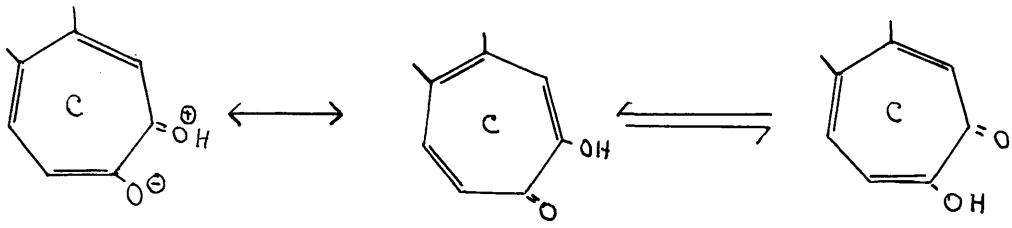


CXVI



CXVII

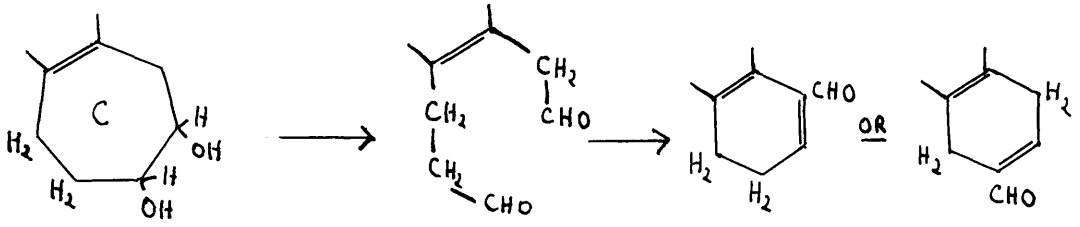
The structure (CXIII) however invites a closer inspection, it implies a facile tautomerisation to the aromatic structure (CXIV) which is not found in practice. For example, methylation of colchiceine with ethereal diazomethane affords colchicine and an isomeric compound, iso-colchicine[51] to neither of which can be assigned the structure (XCVII) in view of their extreme ease of hydrolysis to colchiceine (compare structure (CXVI)). Accordingly, in its behaviour towards diazomethane, colchiceine does not appear capable of the tautomeric equilibrium (CXIII $\rightleftharpoons$ CXIV). The similarity of the absorption spectra of colchiceine and colchicine and the distinct absorption spectrum of the more aromatic N-acetyl iodocolchinol (CXV) point to the same conclusion. Moreover, the structures (CXIII) and (CXVI) do not explain the inertness of colchiceine and colchicine towards carbonyl and olefinic reagents.



CXIX CXVIII CXX

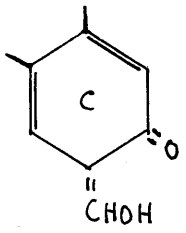
On the other hand, the alternative cycloheptatrien-ol-one or "tropolone" structure (CXVIII), recently postulated by Dewar on theoretical grounds, appears capable of accommodating most of the known facts. Here, resonance with the possible ionic structure (CXIX) may account for the stability of the system at the same time explaining the non-carbonyl and non-olefinic nature of colchiceine. In addition, the existence of isomers is readily explicable in terms of the tautomeric equilibrium (CXVIII $\rightleftharpoons$ CXX). Dewar considered that aromatisation of the structure (CXVIII) was due to benzilic acid re-arrangement. This mechanism provides an elegant explanation of the formation of trimellitic acid when colchicine is first fused with potassium hydroxide and then oxidised with potassium permanganate. Similarly, the alkaline hydrolysis of colchicine to a carboxylic acid, isomeric with colchiceine is readily interpreted on this basis. Facile aromatisation at ring C by benzilic acid rearrangement may also be implicit in the isolation of a supposed tribromocarboxylic acid as a bromination product of

colchiceine (vide supra). On the other hand, such a mechanism does not readily explain the conversion of colchiceine into N-acetyl iodo colchinol.

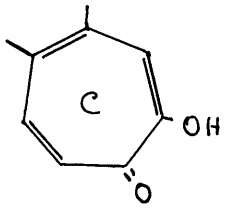


CXXI CXXII CXXIII

In a very recent publication, Tarbell et al[52] have furnished evidence which apparently excludes the hydroxy-methylene structure for ring C and favours the tropolone structure. From the periodic oxidation of hexahydrocolchiceine[53], these authors obtained a crude mono-aldehyde. The latter gave a dinitrophenylhydrazone whose percentage composition approximated to that required for the dinitrophenylhydrazone of the aldehyde (CXXIII). These results strongly suggest that hexahydrocolchiceine is a 1:2 diol (probably (CXXI)) and that formation of (CXXIII) occurs through the series of reactions (CXXI $\longrightarrow$ CXXII $\longrightarrow$ CXXIII). In terms of the Windaus formulation, hexahydrocolchiceine would be a 1:3 diol and therefore incapable of oxidation to (CXXIII).



CXIII



CXVIII

Consequently the considerable body of unfavourable evidence must lead to the abandonment of the hydroxmethylene structure (CXIII) for ring C in colchiceine. On the other hand, the tropolone structure (CXVIII) is more accommodating and accounts for most of the known facts. However, conclusive proof of the structure (CXVIII) is still lacking. Moreover, a discussion of the ultimate structure of ring C must necessarily be incomplete without a fuller knowledge of how this ring becomes aromatic. In particular, more precise information is required concerning the transformations undergone in the halogenation of colchiceine.

Part II - Discussion.

In connexion with the interest in the aromatisation of ring C in colchiceine, it was decided to re-investigate the complete bromination of colchiceine as described by Windaus and to examine the nature of the resulting tribromocarboxylic acid.

Extraction of colchicine.

As a preliminary to the contemplated degradative study of colchiceine, pure colchicine was extracted in some quantity from a crude Extract of Colchicum, supplied by Messrs. Ramson of Hitchin, Herts. After some experimenting the following method was devised in which separation of the alkaloid from unwanted contaminants depends upon its solubility first in water and then in chloroform.

The crude extract, diluted with water, was thoroughly extracted with hot paraffin wax to remove waxy materials which otherwise tend to retard, or escape removal in, the subsequent filtration from insoluble tars. This filtration, although still tedious, is accelerated by the use of large quantities of paper pulp. Exhaustive extraction of the aqueous alkaloid filtrate with chloroform (acid-free; cf. Zeisel[54]) afforded crude colchicine

which was further purified by chromatography[55]. The initial chromatogram effected a satisfactory separation from the more strongly adsorbed impurities, but the colchicine was contaminated by an intensely green coloured, non-adsorbed impurity (cf. Experimental). Further chromatographic purification, with newly activated alumina and using a weaker solvent, afforded almost colourless colchicine, crystallisable as the chloroform addition complex. Removal of the last traces of chloroform - a removal necessitated by the ready formation of the above addition complex - was effected by evaporation with methanol[56]. The colchicine, thus purified, crystallised in fine colourless needles from ethyl acetate[57].

Bromination of Colchiceine.

The bromination of colchiceine was first described by Zeisel and v. Stockert[58], who obtained an amorphous yellow compound. On the basis of analysis results these authors considered that this product was tribromocolchiceine with one molecule of water of crystallisation $C_{21}H_{20}O_6NBr_3 \cdot H_2O$ (A). They recorded no melting point.

Later, Windaus and Schiele[50] described rather different results. When they treated colchiceine, in glacial acetic acid, with an excess of bromine, they

obtained a crystalline derivative (B) which, on rapid heating, sintered at 240°C and melted at 268°C. This product which was acidic did not give a ferric chloride colour reaction. Since it lost carbon monoxide at 230-240°C. on slow heating, Windaus considered that the compound was a carboxylic acid. Methylation with diazomethane in acetone, however, did not afford a crystalline methyl ester. Analysis results indicated the molecular formula $C_{21}H_{20}O_7NBr_3$ (compare A). From these facts Windaus concluded that tribromination had been accompanied by the oxidation of an aldehydic group to a carboxylic group (see p. 50), viz:-

$$(C_{20}H_{22}O_5N)(CHO) + O + 3Br_2 \longrightarrow (C_{20}H_{19}O_5Br_3N)(CO_2H) + 3HBr$$

It was found here, however, that Windaus's results could not be substantiated. Colchiceine, in glacial acetic acid, was slowly treated with a considerable excess of bromine, in the manner described by Windaus. After the addition of about one quarter of the bromine, a heavy yellow precipitate was obtained which, on the addition of more bromine, became oily and finally redissolved. Possibly these changes indicate that bromination occurs in three distinct stages. The reaction mixture, after standing twenty-four hours at ordinary temperatures, yielded on dilution with water an amorphous solid which

crystallised from methanol. Further dilution of the mother liquors afforded only amorphous material which could not be obtained crystalline. The yield of crystalline product is low (10-30%), varying considerably with the quality of colchiceine employed. All the colchiceine appears to react since the mother liquors at the end of the reaction do not give a ferric chloride colour test.

This bromination product (C) has somewhat different properties from those of Widaus's carboxylic acid (B). It crystallises in a thick mat of colourless needles which, before and after drying at 100°C for two hours in vacuo, char at 218-230°C on slow heating and at 224-244°C on rapid heating. There was no evidence of evolution of gas. The compound (C) is insoluble in dilute sodium bicarbonate; insoluble in cold, and only slightly soluble in warm, dilute sodium carbonate; and almost insoluble in cold, but completely soluble in warm, dilute sodium hydroxide. It may be re-precipitated unchanged from the cooled sodium carbonate and sodium hydroxide solutions with dilute mineral acids. Since there was no loss of weight when it was heated at 100° for two hours in vacuo, the product is unlikely to be a hydrate. The analytical results which are compared in the following

table with the possible products of bromination, seem to indicate that simple tribromination of colchiceine has occurred.

Zeisel's Hydrate (A) ($C_{21}H_{20}O_7Br_3N$)	Windaus's Acid (B) ($C_{21}H_{22}Br_3O_7N$)	Tribromocolchiceine ($C_{21}H_{20}Br_3O_6N$)	Product (C)
requires	requires	requires	Found
C = 39.5	C = 39.4	C = 40.5	C = 40.7%
H = 3.1	H = 3.5	H = 3.2	H = 3.5%
Br= 37.7	Br= 37.5	Br= 38.6	Br= 38.8%.

On the other hand, in sharp contrast with colchiceine, the present bromination product is only feebly acidic - a fact which suggests the presence of an enolic grouping although the compound does not give a ferric chloride colour reaction or yield a p-toluene sulphonyl derivative.

Although Windaus did not obtain a crystalline methyl ester of his carboxylic acid, methylation of the present compound with diazomethane in ether-acetone afforded a crystalline product (D) which melts at 131°C and which analyses as a tribromocolchicine. Now Zeisel and v. Stockert[58] obtained, from the bromination of colchicine in methanol, an amorphous solid melting at 131°C. On analytical data, these authors considered that this compound was tribromocolchicine. A comparison, therefore,

of the methyl ether (D) with tribromocolchicine would decide whether the present bromination product is simply a tribromo-derivative of colchiceine. However, when the bromination of colchicine was carried out in methanol, under Zeisel's conditions, only amorphous products of no definite melting point were obtained. Purification of these crude products by chromatography proved ineffectual and acid hydrolysis did not yield crystalline material. When bromination of colchicine was conducted in chloroform, there was isolated a crystalline compound (E) melting at 146-150°C. This product, it became evident, when adsorbed on B.D.H. alumina, is partially hydrolysed with formation of an aluminium complex (cf. Experimental). Consequently succeeding chromatograms were conducted with alkali-free alumina[59]. After chromatographic purification, the product (E) melted at 147-150°C. Analyses results which are compared in the following table with mono- and di-bromo-colchicine, with and without one molecule of methanol of crystallisation, indicate that this compound is a mixture of mono- and di-bromo colchicine.

Monobromocolchicine	Dibromocolchicine	Compound (E)
with methanol of crystallisation	with methanol of crystallisation	before rigorous drying
m.p. 151-153°C*	m.p. -----**	m.p. 147-150°C
requires	requires	found
C = 52.2	C = 48.9	C = 51.3%
H = 5.3	H = 4.6	H = 5.6%.

Monobromocolchicine	Dibromocolchicine	Compound (E)
m.p. ----- **	m.p. 146-150°C*	after drying at 100°C in vacuo
requires	requires	found
C = 55.2	C = 47.4	C = 52.8%
H = 5.0	H = 4.1	H = 5.6%
Br=18.5	Br= 28.1	Br= 22.6%.

These results therefore precluded the direct comparison of the methyl ether (E) with tribromocolchicine. In addition attempts to characterise the bromination product of colchiceine by catalytic debromination led only to intractable gums.

Therefore, while analytical evidence favours the view that colchiceine, on bromination, merely undergoes simple substitution, the nature of the product, obtained

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* Described by Zeisel and v. Stockert[58]

** Unknown.

here, and its methyl ether still remains to be determined. At the moment no significance can be attached to the sharp decrease in acidity which accompanies bromination. It seems certain, however, that the present compound is distinct from the carboxylic acid described by Windaus. In connexion with Windaus's conclusions, it is interesting to note that when salicylaldehyde was brominated under identical conditions, oxidation of the aldehydic group did not occur and 3:5-dibromosalicylaldehyde was obtained in excellent yield.

Together with a study of the bromination of colchiceine, a number of small scale experiments were carried out. These experiments were designed principally to obtain information concerning the functional groups in colchicine and colchiceine with particular respect to ring C.

Colchicine, on chromic acid oxidation, affords oxy-colchicine in which a methylene group has been converted into a carbonyl group[60]. It was considered that selenium dioxide might provide a more elegant route to this compound and the unknown but presumably analogous oxycolchiceine. It was found, however, that colchicine when heated with selenium dioxide in acetic anhydride

was mainly recovered as colchiceine; hydrolysis may have been incidental to the method of working up. The neutral product which represented a very small fraction of the original reactant could not be obtained crystalline. Colchicine and colchiceine when treated with freshly prepared selenium dioxide in dioxan-water according to the technique of Kaplan[61] were recovered unchanged. Colchiceine, in acetic anhydride with freshly prepared selenium dioxide, failed to afford a crystalline product. An alternative oxidising agent for reactive methylene groups is lead-tetra-acetate. With this reagent, however, colchicine gave an intractable gum.

Ring C on the Windaus formulation possesses a conjugated double bond system which should be detectable by means of a Diels-Alder addition reaction with maleic anhydride. Bursian[53] has shown that both colchicine and colchiceine do not add maleic anhydride in boiling benzene or at 130°C. In addition to possessing a conjugated double bond system, ring C on this basis is also o-quinoid and should therefore add butadiene and its derivatives. No such addition was observed, however, when colchicine and the less reactive but easily accessible butadiene - diphenyl butadiene - were refluxed together in xylene for eight hours or when they were fused at 145°C for three hours.

E X P E R I M E N T A L

(All m.p.s are uncorrected).

Part I.

o-Phenyl benzoyl Chloride (XXXI).

Finely powdered, dry o-phenyl benzoic acid (20 g.), prepared by caustic potash fusion from fluorenone[37] was dissolved in pure, dry benzene (20 ml.). Excess thionyl chloride (20 ml.) was then added ahd the solution allowed to stand overnight. The benzene and excess thionyl chloride were removed by evaporation under reduced pressure. The acid chloride was evaporated twice more with dry benzene to ensure complete removal of all excess thionyl chloride. The crude product was used directly for the next stage.

o-Phenyl benzamide m.p. 174°C (literature 177°C., corr.) characterised the product.

Ethyl o-phenyl benzoyl acetate (XXIX).

Sodium (4.6 g.; 2.0 mole.) was dissolved in ethanol (65 ml.) and, to half of this solution, aceto-acetic ester (25.7 g.; 2.0 mole.) was added. The mixture was cooled to 5°C and half the total quantity of o-phenyl benzoyl chloride, namely, 25 g. (0.75 mole.), in dry ether (75 ml.), was added, slowly and with stirring, keeping the temperature below 12°C. To the reaction mixture, half the remaining ethanolic solution of sodium ethoxide was

added, followed by the addition of half the remaining solution of the acid chloride and this process of alternate treatment was repeated so as to complete the addition in four successive stages. Since, on standing in the refrigerator for several days, the sodium salt of the required product did not separate, the solution was extracted with water (220 ml.), the aqueous extract being washed twice with ether to remove organic materials. This aqueous solution of sodium salts was heated for six hours at 40-50°C with ammonium chloride (18.2 g.) and concentrated ammonia (23 ml.). A red oil separated out which, after cooling, was run off, washed with dilute sulphuric acid (colour change to light yellow), then with water and dried ($CaCl_2$).

The oil decomposed before distillation at 11 mm. and 1 mm. Therefore an analysis specimen could not be prepared. However, ketonic hydrolysis to o-phenyl acetophenone serves to characterise the product.

9-Fluorylidene acetic acid.

Ethyl o-phenyl benzoyl acetate (500 mg.) was rapidly heated, in 85% sulphuric acid (1.5 gm.), to 50°C and maintained at that temperature for three minutes. The solution was cooled and poured over crushed ice. The yellow solid which was precipitated was dissolved in dilute sodium hydroxide, filtered, re-precipitated with concentrated hydrochloric acid and crystallised from benzene in small yellow needles. M.P. and mixed m.p. with 9-fluorylidene acetic acid, 223-224°C.

Oxidation of 9-fluorylidene acetic acid.

9-Fluorylidene acetic acid (100 mg.), in warm glacial acetic acid, was treated with a solution of sodium dichromate (200 mg.; one-third excess) in glacial acetic acid (0.25 ml.) and water (0.53 ml.). After the addition of the oxidising solution was complete, the solution was refluxed for 45 minutes. Water (3 ml.) was then added and the solution extracted with benzene. The extract was washed with sodium carbonate, then water, dried (Na_2SO_4) and evaporated to dryness in vacuo. A gum which would not crystallise was obtained. It was then adsorbed on a short column of activated (300°C for one hour) alumina from 40 ml. benzene/petroleum ether (60-80°) (1:1) as a yellow band of general adsorption which was eluted rapidly with benzene. Evaporation of the eluate to dryness, in vacuo, yielded a gummy solid which crystallised from benzene/petroleum ether (40-60°) in yellow needles.

After recrystallisation, micro m.p. and mixed micro m.p. with fluorenone (80-81.5°C) identified the product.

o-Phenyl acetophenone (XXXV).

The crude moist yellow oil of o-phenyl benzoyl acetate (20 g.), water (780 ml.) and concentrated sulphuric acid (20 ml.) were refluxed for 16 hours, thus ensuring

all the carbon dioxide had been evolved. The ketone was extracted with ether, the ethereal extract shaken with 10% caustic potash solution, then water and dried ($CaCl_2$). The ketone distilled in vacuo as a greenish, almost colourless, liquid b.p. 160-162°/13 mm.
(Found: C, 85.9; H, 6.1; $C_{14}H_{12}O$ requires C, 85.7; H, 6.3%).

o-Phenyl acetophenone 2:4-dinitrophenylhydrazone crystallised from acetic anhydride in red needles, m.p. 139°C. (Found: C, 63.6; H, 4.0. $C_{20}H_{16}O_4N_4$ requires C, 63.8; H, 4.2%).

Yield of ketone, based on o-phenyl benzoic acid is 45%.

Hydroxymethylene derivative of o-phenyl acetophenone (XXXIII).

To a suspension of sodium ethoxide (1.8 g.) in dry ether (100 ml.), there was added, slowly and with cooling, a mixture of o-phenyl acetophenone (5 g.) and ethyl formate (2.1 g.). The reaction mixture, on standing in the refrigerator overnight, deposited the sodium salt of the oxymethylene ketone which was filtered off and washed with dry ether. Yield of sodium salt admixed with some sodium formate, 5.5 g.

This sodium salt decomposed rapidly on exposure to the atmosphere and had to be stored in vacuo.

The sodium salt (0.5 g.) was dissolved in water and acidified with dilute sulphuric acid. The resulting oil was extracted with ether, dried (Na_2SO_4) and, after removal of the ether, distilled at 97-100°C/0.15 mm. (air bath temperature) as a viscous greenish liquid.
(Found: (a) C, 76.3; H, 5.7: (b) C, 77.0; H, 5.9. $C_{15}H_{12}O_2$ requires C, 80.4; H, 5.4%).

The low carbon content found cannot be explained.

Treatment of the hydroxymethylene derivative of o-phenyl acetophenone (sodium salt) with concentrated sulphuric acid.

The sodium salt of the oxymethylene ketone (0.5 g.) was treated with enough concentrated sulphuric acid to ensure complete solution. After standing in the refrigerator for two days, the solution, on pouring over crushed ice, afforded a brown solid which was amorphous but which yielded a 2:4 dinitrophenylhydrazone, crystallising in yellow-red needles from rectified spirits, m.p. 121-122°C.
(Found: C, 45.2; H, 4.1; N, 23.2%). This corresponds to the empirical formula $C_9H_{10}O_4N_4$ which requires C, 45.3; H, 4.2; N, 23.5%).

2-Phenyl-3:4:5-trimethoxy benzoic acid hydrazide.

Methyl 2-phenyl-3:4:5-trimethoxy benzoate (16.7 g.) was dissolved in methanol (60 ml.) and 90% hydrazine

hydrate (31 ml.) was added. The mixture was refluxed for eight hours. On cooling the hydrazide crystallised out, was filtered, washed with a little water and dried at 110°C. The filtrate, on concentration, yielded more hydrazide. Yield, 14.4 g. (86%).

An analysis sample was recrystallised from methanol in colourless needles m.p. 156°C. (Found: C, 63.7; H, 5.9; $C_{16}H_{18}O_4N_2$ requires, C, 63.8; H, 6.0%).

2-Phenyl-3:4:5-trimethoxy benzoic acid phenyl sulphonyl hydrazide.

The above hydrazide was dissolved in pyridine (84 ml.) and the solution cooled in ice. Freshly distilled benzene sulphonyl chloride was added, dropwise and with shaking, into this solution which was then allowed to stand for two hours in ice and for a further hour at room temperature. On pouring the pyridine solution into a mixture of ice and concentrated hydrochloric acid, slowly and with stirring, a yellowish powder was precipitated which was filtered off, washed with dilute hydrochloric acid followed by water, recrystallised from methanol in colourless prisms m.p. 161-163°C and dried at 120°C. Yield, 18.7 g. (91%). (Found: C, 59.4; H, 4.9: $C_{22}H_{22}O_6N_2S$ requires, C, 59.7; H, 5.0%).

2-Phenyl-3:4:5-trimethoxy benzaldehyde.

The above phenyl sulphonyl hydrazide (18.5 g.) was dissolved in hot ethylene glycol (150 ml.) and heated to 160°C. Powdered anhydrous sodium carbonate (20 g.) was added, in one portion, and the reaction mixture was vigorously stirred at 160°C. for 100 seconds. Warm water (150 ml.) was then added to terminate the reaction. When the solution was allowed to cool, the aldehyde crystallised out, was filtered off and washed with water. The mother liquors were extracted, exhaustively, with ether. The ethereal extract was washed with 2N sodium hydroxide, dried (Na_2SO_4) and, on evaporation, gave a small amount of aldehyde which was crystallised, along with the main bulk of aldehyde, from methanol in yellowish almost colourless plates, m.p. 92-93°C. Boiling with charcoal failed to remove the residual colour. Yield, 9.4 g. (83%). (Found: C, 70.6; H, 5.7: $C_{16}H_{16}O_4$ requires C, 70.6; H, 5.9%).

The alkaline washings of the ethereal extract, on saturation with carbon dioxide, yielded a small amount of phenyl sulphonyl hydrazide of the acid.

2-Phenyl-3:4:5-trimethoxy cinnamic acid (XLIII).

The above aldehyde (9.3 g.) was dissolved in dry pyridine (20 ml.) and a few drops of piperidine were added, followed by malonic acid (7.43 g.; 2.09 mole.). The

solution was heated on a water bath ($CaCl_2$ guard) until evolution of carbon dioxide had ceased (about four hours) and was then refluxed for 15 minutes. On pouring the cooled solution on a mixture of ice and concentrated hydrochloric acid, with stirring, a sticky yellow solid separated which soon became granular. It was filtered off, dissolved in ether and the resulting ethereal solution extracted with sodium hydroxide. The alkaline extract, on acidification with concentrated hydrochloric acid, precipitated the acid which was filtered off, and crystallised from glacial acetic acid/water (2:1) in small colourless needles, m.p. 165°C. Yield, 9.7 g. (91%). (Found: C, 68.7; H, 5.6. $C_{18}H_{18}O_5$ requires C, 68.8; H, 5.8%).

The ethereal solution, after drying (Na_2SO_4), on concentration yielded 200 mg. of a yellow oil which, on retreatment with malonic acid, afforded no substituted cinnamic acid.

2-Phenyl-3:4:5-trimethoxy dihydrocinnamic acid (XLIV).

The above unsaturated acid (9.6 g.) was dissolved in glacial acetic acid (330 ml.) and hydrogenated by shaking with palladium black (0.6 g.) in an atmosphere of hydrogen at room temperature. The solution, filtered from palladium, was evaporated almost to dryness in vacuo

and the residue crystallised from acetic acid/water (1:1) in colourless plates, m.p. 121-122°C. (Found: C, 68.7; H, 6.3. $C_{18}H_{20}O_5$ requires C, 68.7; H, 6.3%).

1-(m-methoxyphenyl)-3:3-dimethyltriazen.

A diazo-solution, from m-anisidine (100 g.), concentrated hydrochloric acid (288 ml.), water (200 ml.) and sodium nitrite (56 g.), was added, with stirring, to a mixture of 25% dimethylamine (280 g.) and 30% sodium carbonate solution (800 ml.) maintained at 0°C. Stirring was continued for 30 minutes following the addition and the product was extracted with benzene and recovered from the dried solution. It distils as a yellow liquid, b.p. 161°C/15 mm. Yield, 114 g. (Found: C, 60.4; H, 6.9. $C_9H_{13}ON_3$ requires C, 60.3; H, 7.25%).

Methyl 2-(m-methoxyphenyl)-3:4:5-trimethoxy benzoate (XLV).

Methyl trimethyl gallate (165 g.) and 1-m-methoxyphenyl-3:3-dimethyl triazen (32 g.) were slowly treated with glacial acetic acid (43 ml.) at 100°C and the whole heated for 16 hours on a water bath. The resulting dark liquid was dissolved in chloroform and the solution thoroughly washed with dilute hydrochloric acid, water, dilute sodium hydroxide and again with water. After drying, recovery distillation gave the unchanged ester (149 g.), which was used directly for renewed action

with the triazen, and also a residue.

This procedure was repeated three times:-

(a) 149 g. ester treated with 30 g. triazen,

(b) 125 g. ester recovered and treated with 25.5 g. triazen,

(c) 110 g. ester recovered and treated with 27 g. triazen.

Finally, 94 g. ester was recovered.

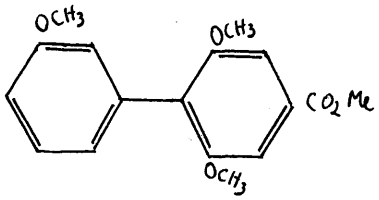
The combined residues from all these runs gave on fractionation -

(I) Small fraction, b.p. 174-185°C/8 mm. - unchanged starting material,

(II) Medium fraction, b.p. 185-215°C/8 mm. Since charring then began, distillation was continued under high vacuum,

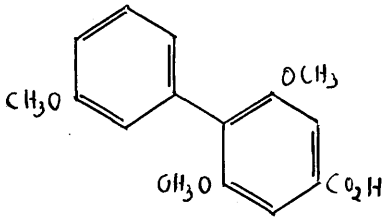
(III) Large fraction, b.p. 203-220°C/0.5 mm.

On rubbing fractions (II) and (III) with half their volume of methanol and allowing them to stand for several days in the refrigerator, there separated a colourless solid which was filtered off and well washed with methanol. All the washings were combined with the methanolic mother liquors. The solid crystallised from glacial acetic acid in small prisms, m.p. 154-156°C. Yield, ca. 1.5 g. (Found: C, 67.5; H, 5.7. $C_{17}H_{18}O_5$ requires C, 67.55; H, 5.7%). The proposed structure for this ester is



This ester (600 mg.) was hydrolysed to its parent acid by refluxing it for one hour with excess 50% potassium hydroxide (1 ml.) and sufficient methanol to keep most of it in solution. After removal of the methanol, the diluted residue, on acidification, gave a white precipitate which crystallised from glacial acetic acid in small colourless needles, m.p. 215°C. (Found: C, 65.9; H, 5.6; after drying in vacuo at 100°C; C, 66.4; H, 5.2. $C_{16}H_{16}O_5$ requires C, 66.7; H, 5.55%).

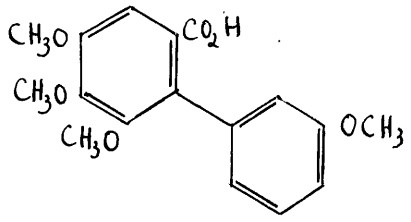
The proposed structure for this acid is



This acid, on esterification with diazo-methane, afforded the original ester, m.p. 155-157°C, which rehydrolysed to the acid, m.p. 215°C.

However, the main constituent ester of the methanolic mother liquors could not be isolated pure. The crude gummy ester (44 g.) obtained by concentration of the methanol solution, was hydrolysed by refluxing it for three hours with excess 50% potassium hydroxide (66 ml.) in

sufficient methanol to keep the mixture homogeneous. After removal of the methanol, a small amount of unsaponified oil was extracted with chloroform and ignored. Acidification of the diluted residue with concentrated sulphuric acid precipitated an oil which became gummy overnight in the refrigerator. This gum solidified on rubbing with methanol (1 ml.) and the solid filtered. It crystallised from methanol/water (1:1) in colourless prisms, m.p. 134-135°C. Yield, 19 g. (Found: C, 64.2; H, 5.8. $C_{17}H_{18}O_6$ requires C, 64.1; H, 5.7%). This is the required acid of formula:-



2:3:4:6- and 2:3:4:8-Tetra-methoxy fluorenones (L and LI).

2-(m-Methoxyphenyl)-3:4:5-trimethoxy benzoic acid (1 g.) was refluxed with an excess of thionyl chloride (10 ml.) for a few minutes. The excess thionyl chloride was distilled off and the last traces removed by evaporation twice with benzene in vacuo. The resulting solid was recrystallised from methanol and the melting point indicated a mixture of compounds.

Fractional crystallisation from methanol first yielded small lemon-yellow needles (fluorenone I) and subsequently a mixture of these yellow needles and heavier stout golden needles (fluorenone II). By shaking and decantation, the mother liquors removed the lighter needles of fluorenone I, leaving the heavier needles of fluorenone II. Repetition of this procedure effected a separation.

Fluorenone I - formed in predominant amount, yellow needles from methanol, m.p. 122°C. (Found: C, 68.1; H, 5.45. $C_{17}H_{16}O_5$ requires C, 68.0; H, 5.3%). Its dinitrophenylhydrazone crystallises in small deep red needles from acetic acid, m.p. 236°C. (Found: C, 57.6; H, 4.1. $C_{23}H_{22}O_8N_4$ requires C, 57.5; H, 4.2%).

Fluorenone II - formed in very small amount, less soluble than fluorenone I, stout golden needles from methanol, m.p. 152-153°C. (Found: C, 68.2; H, 5.2. $C_{17}H_{16}O_5$ requires C, 68.0; H, 5.3%).

Its dinitrophenylhydrazone crystallises in small red needles from acetic acid, m.p. 237°C. (Found: C, 57.8; H, 3.7. $C_{23}H_{22}O_8N_4$ requires C, 57.5; H, 4.2%).

Methyl 2-(m-methoxyphenyl)-3:4:5-trimethoxy benzoate (XLV).

2-(m-Methoxyphenyl)-3:4:5-trimethoxy benzoic acid (18 g.) was esterified by means of diazo-methane in ether.

On evaporation of the ether solution, the ester was obtained as a colourless oil, b.p. 195-196°C/0.5 mm., which was not analysed. Yield, 17.3 g.

2-(m-Methoxyphenyl)-3:4:5-trimethoxy benzoic acid hydrazide.

Methyl 2-(m-methoxyphenyl)-3:4:5-trimethoxy benzoate (15.6 g.) was treated with an excess of 90% hydrazine hydrate (30 ml.) and sufficient methanol to keep the heated mixture homogeneous. After refluxing the mixture for nine hours on a water bath, approximately half the methanol was removed. There then crystallised, on standing, the hydrazide which was filtered off and dried. A further small amount of product was obtained by extraction of the water-diluted methanolic mother liquors. Yield (crude), 15.2 g. (98%).

An analysis specimen recrystallised from methanol in small colourless prisms, m.p. 137-138°C. (Found: C, 61.6; H, 6.0. $C_{17}H_{20}O_5N_2$ requires C, 61.45; H, 6.0%).

2-(m-Methoxyphenyl)-3:4:5-trimethoxy benzoic acid phenyl sulphonyl hydrazide.

The above hydrazide (15 g.) dissolved in dry pyridine (88 ml.) was treated with freshly distilled benzene sulphonyl chloride (8.8 g.) in the same manner as 2-phenyl-3:4:5-trimethoxy benzoic acid hydrazide. The product crystallised from methanol in colourless prisms, m.p. 182-

183°C. Yield, 18.8 g. (89%). (Found: C, 58.5; H, 5.0. $C_{23}H_{24}O_7N_2S$ requires C, 58.7; H, 5.1%).

2-(m-Methoxyphenyl)-3:4:5-trimethoxy benzaldehyde.

The above phenyl sulphonyl hydrazide (19.1 g.) was dissolved in hot ethylene glycol (155 ml.) and heated to 160°C in an oil bath. Powdered anhydrous sodium carbonate was added in one portion, and the well stirred reaction mixture held at 160°C for 100 seconds. Then warm water (155 ml.) was added to terminate the reaction. The cooled solution was thoroughly extracted with chloroform. The chloroform extract was washed with 2N sodium hydroxide, dried (Na_2SO_4) and evaporated to give 5.8 g. of gummy aldehyde.

The alkaline washings of the chloroform extract on saturation with carbon monoxide precipitated 8.1 g. starting material. Retreatment of recovered phenyl sulphonyl hydrazide - decomposition this time being carried out at 160°C for 120 seconds - yielded 4.4 g. gummy aldehyde which, together with the main bulk of aldehyde, crystallised on standing. Yield, 10.2 g. (84%).

An analysis specimen crystallised from moist methanol in small colourless plates, m.p. 60-61°C. (Found: C, 67.4; H, 5.8. $C_{17}H_{18}O_5$ requires C, 67.5; H, 6.0%). Its dinitrophenylhydrazone crystallised in rosettes of small

orange needles, m.p. 192°C. (Found: C, 57.4; H, 4.7. $C_{23}H_{22}O_8N_4$ requires C, 57.3; H, 4.6%).

2-(m-Methoxyphenyl)-3:4:5-trimethoxy cinnamic acid.

The above crude aldehyde (10.0 g.) was dissolved in dry pyridine (20 ml.) and a few drops of piperidine were added, followed by malonic acid (7.2 g.; 2.09 mole.). The solution was heated on a water bath (Ca.Cl_2 - guard) until carbon monoxide evolution had ceased (about two hours), refluxed for 15 minutes and then worked up in the same manner as 2-phenyl-3:4:5-trimethoxy cinnamic acid except that benzene and not ether was used as the solvent for crude acid. The required acid crystallised in colourless needles from glacial acetic acid/water (1:1), m.p. 150-151°C.

The benzene extract, on evaporation, afforded 900 mg. of gum which failed to react with malonic acid, but which gave the same dinitrophenyl hydrazone as the original aldehyde. On attempted purification of this gum by distillation at 0.15 mm., it decomposed.

Yield of aldehyde, allowing for 900 mg. gum recovered, 8.9 g. (86%). (Found: C, 66.2; H, 5.8. $C_{19}H_{20}O_6$ requires C, 66.3; H, 5.8%).

2-(m-Methoxyphenyl)-3:4:5-trimethoxy dihydrocinnamic acid (LII)

The above unsaturated acid (8.8 g.) was dissolved in glacial acetic acid (300 ml.) and hydrogenated by shaking with palladium black (0.5 g.) in an atmosphere of hydrogen at room temperature. The solution, filtered from palladium, was evaporated almost to dryness and the residue crystallised from dilute acetic acid in colourless prisms, m.p. 89-91°C. Yield, 8.4 g. (96%). (Found: C, 65.7; H, 6.2. $C_{19}H_{22}O_6$ requires C, 65.9; H, 6.4%).

2-(p-Methoxyphenyl)-3:4:5-trimethoxy benzoic acid (LVIII).

Methyl trimethyl gallate (318 g.) and 1-(p-methoxyphenyl)-3:3-dimethyl triazen (265 g.) were condensed, in the manner described by Barton[13], to give methyl 2-(p-methoxyphenyl)-3:4:5-trimethoxy benzoate (59 g.) which was hydrolysed to the required acid (55 g.), m.p. 168-170°C.

2:3:4:7-Tetramethoxy fluorenone (LX)[13].

The above acid (5 g.) with thionyl chloride yielded the required fluorenone (3.5 g.), m.p. 113-115°C.

Ring Enlargement of 2:3:4:7-tetramethoxy fluorenone.

A cooled solution of the above fluorenone (500 mg.), in ether (20 ml.) and methanol (40 ml.), was slowly treated with a large excess of diazomethane in ether. After standing two hours in ice, the solution was left overnight

at room temperature. There was a considerable fading of colour in the reaction mixture which after removal of excess diazomethane and evaporation, yielded a dark red gum (500 mg.). This gum dissolved in ether was extracted with sodium hydroxide.

The sodium hydroxide extract, after acidification, was extracted with chloroform. The dried chloroform solution, on evaporation, afforded 50 mg. gum - Fraction (i).

The ether solution which had been extracted with alkali was washed with water, dried and, on evaporation, gave 490 mg. of gummy material - Fraction (ii).

Fraction (ii) was adsorbed on a column of B.D.H. alumina, previously activated at 300°C for 1 hour, from 100 ml. of benzene:petroleum ether (1:1). On development with the same solvent, the column was observed to consist of the following bands (from bottom to top):-

(a) Broad colourless band fluorescing pale blue in U.V.,

(b) Broad pink band fluorescing scarlet in U.V.,

(c) Broad colourless band fluorescing pale yellow in U.V.

Band (a) was eluted with benzene. The concentrated eluate yielded 240 mg. of a colourless gum which crystallised from methanol in colourless needles of 2:3:4:7:9 (or 10)-pentamethoxy phenanthrene, m.p. 115-117°C. (Found: C, 69.6; H, 6.1; OCH_3, 47.75. $C_{19}H_{20}O_5$ requires C, 69.5; H, 6.1; OCH_3, 47.25%) - Fraction (v).

Band (b) was eluted with benzene:ether (1:1) and the eluate, after concentration, afforded a solid which crystallised from methanol in crimson needles, micro-melting point and mixed micro-melting point with 2:3:4:7-tetramethoxy fluorenone, 110-113°C. Yield, 45 mg. - Fraction (iv).

Band (c) was eluted with benzene:ether (1:1) and the concentrated eluate yielded 200 mg. of gum - Fraction (iii).

Oxidation of the various fractions of ring enlargement.

Fraction (i) - The acidic gum (50 mg.), in warm glacial acetic acid (0.1 ml.), was treated with a solution of sodium dichromate (100 mg.), in glacial acetic acid (0.15 ml.) and water (0.25 ml.), and the solution refluxed for 45 minutes. Dilution of the cooled, deep-green coloured solution and extraction with benzene afforded a gum which was dissolved in benzene:petroleum ether (3:2) and passed through a column of activated B.D.H. alumina. There developed with benzene:petroleum ether (3:2) a lower pink band of general adsorption and an upper narrow dark brown band, both of which were eluted with benzene, the former giving eluate (a) and the latter eluate (b).

Eluate (a), on concentration, afforded 24 mg. of a solid which crystallised from methanol in crimson needles, micro-melting point and mixed micro-melting point with 2:3:4:7-tetramethoxy fluorenone, 111-113°C.

Eluate (b), on concentration, yielded a few mg. of a violet coloured gum which crystallised from benzene: petroleum ether in violet prisms and red-violet needles, micro-melting point and mixed micro-melting point with 2:3:4:7-tetramethoxy phenanthraquinone, 192-194°.

Fraction (iii) - The neutral gum (200 mg.) was oxidised with sodium dichromate (400 mg.) in the manner described above for fraction (i). The crude oxidation product, in benzene, was passed through a column of B.D.H. alumina and there developed, with benzene, a pink band of general adsorption which, on elution with benzene and concentration, afforded a solid. This solid crystallised from methanol in crimson needles, micro-melting point and mixed micro-melting point with 2:3:4:7-tetramethoxy fluorenone, 113-114°C.

Fraction (v) - 2:3:4:7:9 (or 10)-Pentamethoxy phenanthrene (100 mg.) was oxidised in the manner described above. The crude oxidation product was adsorbed on a column of alumina from its solution in benzene:petroleum ether (3:2) with the development of the following bands:-

(a) Upper brown band eluted with methanol - eluate (1)

(b) Lower deep violet-brown band, eluted with benzene - eluate (2).

Eluate (1), on concentration, yielded a brown amorphous solid (32 mg.) which was not further examined.

Eluate (2), on concentration, yielded a deep violet gum which crystallised from benzene:petroleum ether in deep violet prisms and violet red needles, micro-melting point and mixed micro-melting point with 2:3:4:7-tetramethoxy phenanthraquinone, 192-194°C. Yield, 31 mg.

Corresponding diazine crystallised from methanol in lemon coloured needles, m.p. and mixed m.p. with 2:3:4:7-tetramethoxy phenanthrazine, 176-177°C.

Oxidation of the crude reaction product of the ring enlargement.

The crude red gum (1 g.), obtained from the action of excess diazomethane on 2:3:4:7-tetramethoxy fluorenone (1 g.) was oxidised with sodium dichromate (2.9 g.) in the above manner. The crude oxidation product, in benzene: petroleum ether (3:2) was passed through a column of B.D.H. alumina and there developed the following bands (from bottom to top):-

(a) Broad orange band of general adsorption which was eluted with benzene - eluate (1)

(b) Broad violet-red band, eluted with benzene - eluate (2)

(c) Upper dark brown band, eluted with methanol - eluate (3)

Eluate (1), on concentration, yielded 2:3:4:7-tetramethoxy fluorenone. Yield, 385 mg. (38.5% recovery).

Eluate (2), on concentration, yielded 2:3:4:7-tetramethoxy phenanthraquinone, micro-melting point, 193-194°C.

Yield, 285 mg. which corresponds to 43% yield on the fluorenone consumed.

The corresponding diazine had m.p. of 176-177°C, undepressed on admixture with 2:3:4:7-tetramethoxy phenanthrazine.

Eluate (3), on concentration, afforded 120 mg. of amorphous material which was retained.

3:4:5-Trimethoxy benzoyl chloride[26].

The required acid chloride distilled at 180°C/17 mm., m.p. 77°C. Yield, 86%.

p-Thio-cresyl 3:4:5-trimethoxy benzoate (LXXI).

p-Thio-cresol (2.6 g.; 2.5 mole.), in dry pyridine (14 ml.), was treated with finely powdered 3:4:5-trimethoxy benzoyl chloride (2 g.) and the reaction mixture heated at 80°C. for one hour. The cooled reaction mixture was poured, with stirring, on a mixture of ice and dilute hydrochloric acid and the resulting solid was extracted with benzene. The dry benzene solution, after washing with dilute acid, water, dilute sodium hydroxide and finally water, was concentrated, yielding a solid which crystallised from methanol in large colourless plates, m.p. 102°C. Yield, 2.35 g. (88%). (Found: C, 64.2; H, 5.4. $C_{17}H_{14}O_4S$ requires C, 64.35; H, 5.4%).

Hydrogenolysis of p-thio cresyl 3:4:5-trimethoxy benzoate. (According to the procedure of Wolfrom and Karabinos[24]).

The above thio-ester (2.25 g.), in 70% ethanol (50 ml.) was refluxed with Raney nickel (12 g.) for six hours. After filtration from catalyst the ethanol was removed on a water bath. The non-ketonic residual oil gave the following fractions:-

(a) First fraction distilled at 80°C/0.5 mm. as a colourless oil which crystallised from petroleum ether (40-60°) in colourless needles, m.p. and mixed m.p. with 1:2:3-trimethoxy benzene, 42-43°C. Yield, 240 mg. (20%).

The corresponding picrate crystallised in small golden needles, m.p. and mixed m.p. with 1:2:3-trimethoxy benzene picrate, 79-80°C. (Found: C, 45.8; H, 3.8; N, 10.4. $C_{15}H_{15}O_{10}N_3$ requires C, 45.4; H, 3.8; N, 10.6%).

Oxidation of this fraction with dilute nitric acid yielded 2:6-dimethoxy benzoquinone, which crystallised in yellow needles from acetic acid, m.p. 246-248°C. (Found: C, 56.9; H, 5.0. $C_8H_8O_4$ requires C, 57.1; H, 4.8%).

Analysis of 1:2:3-trimethoxybenzene

Found: (a) C, 63.3; H, 6.6%,

(b) C, 63.2; H, 6.3% (After purification via picrate)

(c) C, 63.65; H, 6.7% (Specimen prepared by Mr. Cameron).

$C_9H_{12}O_3$ requires C, 64.3; H, 7.1%.

(b) Second fraction distilled at 152-154°C/0.5 mm. as a

viscous oil. Yield, 620 mg. (40%).

3:5-Dinitrobenzoate crystallised from ethanol in yellow leaflets, m.p. and mixed m.p. with 3:4:5-trimethoxy benzyl 3:5-dinitrobenzoate[3], 147-148°C. (Found: C, 52.3; H, 4.15. $C_{17}H_{15}O_9N_2$ requires C, 52.2; H, 3.85%).

Hydrogenolysis of p-thio cresyl-3:4:5-trimethoxy benzoate. (According to the procedure of Prelog et al.[35]).

To p-thiocresyl-3:4:5-trimethoxy benzoate (4 g.) in dioxan (40 ml.) there was added Raney nickel (32 g.), suspended in dioxan (40 ml.). Considerable heat was developed and the reaction was completed by shaking for one hour. After filtration from catalyst and removal of dioxan, the resulting neutral oil was distilled and the following fractions were obtained:

Fraction (1) distilled as a colourless oil, b.p. 95°C/1 mm., which crystallised in needles from petroleum ether, m.p. and mixed m.p. with 1:2:3-trimethoxy benzene, 42-43°C. Yield, 0.705 g. (30%).

Fraction (2) distilled as a colourless viscous oil, b.p. 163-165°C/2 mm., which afforded a 3:5-dinitrobenzoate, m.p. and mixed m.p. with 3:4:5-methoxy-3:5-dinitrobenzoate, 147°C. Yield of 3:4:5-trimethoxy benzyl alcohol, 1.05 g. (40%).

p-Thiocresyl benzoate, cf. Schiller and Otto[62].

Benzoyl chloride (2 g.), in pyridine (15 ml.) was treated with p-thiocresol (3 g.) and the reaction mixture heated at 70°C for one hour. When the cooled pyridine solution was poured over a mixture of ice and dilute hydrochloric acid, there was precipitated a colourless solid which, after working up in a manner similar to p-thiocresyl 3:4:5-trimethoxy benzoate, crystallised from methanol in small, colourless needles, m.p. 73-74°C. Yield, 3 g. (93%).

Hydrogenolysis of p-thiocresyl benzoate.

The above ester (2 g.), in 70% ethanol (40 ml.), was refluxed with Raney nickel (10 g.) for 6 hours. After filtering from catalyst, the ethanol was removed on a water bath. The distillate, on treatment with 2:4-dinitrophenyl hydrazine, afforded benzaldehyde-2:4-dinitrophenyl hydrazone, m.p. and mixed m.p., 235°C. Yield, 250 mg., which corresponds to 10% benzaldehyde.

The residual gum, obtained after removal of solvent, distilled as a colourless oil, b.p. 178°/24 mm. Yield, 250 mg. The 3:5-dinitrobenzoate crystallised in colourless needles from ethanol, m.p. and mixed m.p. with benzyl 3:5-dinitrobenzoate, 110-112°C.

Ethyl thio-3:4:5-trimethoxy benzoate.

s-Ethyl iso thiourea sulphate (45 g.), prepared by the ethylation of thiourea[63] was decomposed by an equivalent volume of 5N-sodium hydroxide and the resulting dried ethyl mercaptan bubbled into dry pyridine (20 ml.). To this solution of ethyl mercaptan, cooled in ice, there was added 3:4:5-trimethoxy benzoyl chloride (9.5 g.) and the resulting solution, after standing overnight, was poured over ice and dilute hydrochloric acid. The benzene solution of the precipitated oil was washed in turn with dilute hydrochloric acid, water, dilute sodium hydroxide and finally water, dried and concentrated. The residual oil distilled at 185°C/0.3 mm. and was crystallised in colourless needles from petroleum ether (40-60°), m.p. 35-36°C. Yield, 90%.

Hydrogenolysis of ethyl thio-3:4:5-trimethoxy benzoate.

The above thio-ester (7 g.) in 70% ethanol (140 ml.) was refluxed with Raney nickel (35 g.) for two hours. Concentration of the ethanolic solution, after removal of catalyst, afforded a neutral gum which distilled in the following fractions:-

(1) First fraction, b.p. 96°C/1 mm. which crystallised from petroleum ether in colourless needles, m.p. and mixed m.p. with 1:2:3-trimethoxy benzene, 42-43°C. Yield, 1.1 g. (20%).

(2) Second fraction, b.p. 154°C/1 mm., which consisted of 3:4:5-trimethoxy benzyl alcohol, characterised as its 3:5-dinitrobenzoate. Yield, 2.1 g. (40%).

Ethyl thio benzoate.

To a cooled solution of ethyl mercaptan in pyridine (30 ml.) (prepared from s-ethyl iso thiourea sulphate (45 g.) in the manner described above) there was added benzoyl chloride. The reaction mixture after standing overnight was worked up by the method described for ethyl thio 3:4:5-trimethoxybenzoate. The required ester distilled as a colourless oil, b.p. 124°C/15 mm. Yield, 10 g. (80%).

Hydrogenolysis of ethyl thio benzoate.

The above thio ester (9.5 g.) in 70% ethanol (180 ml.) was refluxed with Raney nickel (54 g.) for two hours. After removal of catalyst, the diluted reaction mixture was extracted with ether. The dried ether extract was concentrated employing an eighteen inch glass bead fractionating column and the resulting mixture of ethanol and aromatic product was cautiously treated with an excess of concentrated nitric acid, nitration being completed by refluxing for one hour. The nitro-compound thus obtained distilled as a yellow liquid, b.p. 208-210°C.,

which, with Raney nickel, was rapidly reduced to an amine, b.p. 180-182°C. Acetyl derivative, m.p. and mixed m.p. with acetanilide, 115°C. Tribromo derivative, m.p. and mixed m.p. with tribromaniline, 118°C. Yield of benzene, based on aniline isolated, is 60%.

Cis-9:10-dihydro-9-methyl phenanthrene-9:10-diol (LXXIX).

9-Methyl phenanthrene (2 g.), in thiophene-free sodium-dried benzene (15 ml.), was treated with osmium tetroxide (3 g.) and pyridine (2.4 ml.). After seven days, the dark-brown crystals which separated were filtered off, dissolved in chloroform and shaken with a solution of mannitol (50 g.) and potassium hydroxide (2 g.) in water (200 ml.) for 2 hours. The dried yellow coloured chloroform layer, on evaporation in vacuo at room temperature, yielded a gum which crystallised from aqueous methanol in colourless prisms, m.p. 130-131°C (softening at 115°C). Yield, 1.75 g. (80%).
(Found: (a) C, 74.1; H, 6.8. $C_{15}H_{14}O_2 \cdot H_2O$ requires C, 73.8; H, 6.6%: (b) After drying at 100°C for one hour in vacuo; C, 79.9; H, 6.1. $C_{15}H_{14}O_2$ requires C, 79.7; H, 6.2%).

9-Methyl-10-hydroxy phenanthrene (LXXXII).

The above diol (100 mg.) was refluxed with concentrated hydrochloric acid (0.2 ml.) in glacial acetic acid (2 ml.) for one minute. The cooled solution, on dilution, afforded almost colourless needles which were recrystallised from aqueous methanol, m.p. 125°C (softening at 122°C). (Found: C, 86.2; H, 5.7. $C_{15}H_{12}O$ requires C, 86.5; H, 5.7%).

3:4:5:6-Dibenzcycloheptatrien-7-one (LXXXI).

Cis-9-methyl-9:10-dihydrophenanthrene-9:10-diol (100 mg.) in sodium-dried benzene (20 ml.) was oxidised, in the manner employed by Mr. Buchanan, B.Sc., by treatment with lead tetra-acetate (210 mg.) and shaking vigorously for two hours. After the reaction mixture had then been refluxed for ½ hour, the cooled solution was filtered through a bed of charcoal, washed with water and concentrated in vacuo at 40°C. The resulting colourless gum, dissolved in methanol, was treated with a few drops of dilute sodium hydroxide (colour change to yellow) and water added to a permanent turbidity. After standing 48 hours in an atmosphere of nitrogen, the methanolic solution deposited a gum which, after chromatography, crystallised in colourless prisms from benzene:petroleum ether, m.p. 81-83°C. Yield, ca. 65%.

Oxidation of 3:4:5:6-dibenzcycloheptatrien-7-one.

The above ketone (60 mg.), in glacial acetic acid (0.5 ml.) was refluxed with sodium dichromate (250 mg.) in acetic acid (0.75 ml.) for ½ hour. The diluted solution was extracted with chloroform and the chloroform solution, after a thorough extraction with sodium bicarbonate, was dried and concentrated. The residual gum crystallised from benzene in orange-coloured plates, m.p. and mixed m.p. with phenanthraquinone, 200-202°C.

The corresponding diazine melted at 218-220°C and was undepressed on admixture with phenanthrazine.

Methyl 2:3:4:7-tetramethoxy phenanthrene-10-carboxylate.

2:3:4:7-Tetramethoxy phenanthrene-10-carboxylic acid (4.5 g.) suspended in methanol (65 ml.) containing concentrated sulphuric acid (5 ml.) was heated under reflux. After one hour a homogeneous solution was obtained and esterification was completed by further heating for four hours. Part of the solvent was distilled off and the required ester which separated was collected and combined with a small amount recovered from an alkali-washed ether extract of the diluted mother liquors. This ester was used directly for hydrazide formation. Yield (crude), 4.7 g., m.p. 101-102°C.

Hydrazide.

The methyl ester (5 g.), 90% hydrazine hydrate (10 ml.) and sufficient ethanol (ca. 30 ml.) to form a hot homogeneous solution were heated under reflux for four hours. On cooling, the methyl ester was recovered unchanged but this was probably due to the poor quality of the hydrazine hydrate since retreatment of the ester, with fresh reagent, for only two hours gave the hydrazide as colourless platelets, m.p. 216°C unchanged but sharper after crystallisation from ethanol. (Found: N, 8.0. $C_{19}H_{20}O_5N$ requires N, 7.8%).

Phenyl sulphonhydrazide.

The hydrazide (4.1 g.) in pyridine (50 ml.) was treated in the cold with benzene sulphonyl chloride (2.1 g.) and the resulting solution left stoppered at room temperature for 12 hours. On pouring the reaction mixture into iced hydrochloric acid, a yellow solid was precipitated which was filtered off, washed with dilute hydrochloric acid followed by water and crystallised from acetic acid, m.p. 230-231°C depressed below 200°C on admixture with the above hydrazide. (Found: N, 5.6. $C_{25}H_{24}O_7N_2S$ requires N, 5.6%).

2:3:4:7-Tetramethoxy-10-phenanthraldehyde (XCIII).

The crude (dried at 120°C) sulphonhydrazide (5.7 g.) in ethylene glycol (80 ml.) at 160°C was treated with anhydrous sodium carbonate (3.6 g.) and after 80 seconds the reaction was terminated by addition of boiling water (100 ml.). The aldehyde, recovered in ether, had m.p. (crude) 127-128°C, raised by crystallisation from methanol to 129-130°C and undepressed by the aldehyde of m.p. 130-131°C obtained from the stepwise oxidation of deaminocolchinol methyl ether[2].

This aldehyde gave an oxime of micro m.p. 164-166°C undepressed on admixture with the oxime (micro m.p. 165-166°C) of the degradation aldehyde. Yield, 2.3-2.5 g.

2:3:4:7-Tetramethoxy-10-methyl phenanthrene (XCIV).

The above aldehyde (1.1 g.) was heated with ethanol (40 ml.) and hydrazine hydrate (99%; 4 ml.) for two hours. Removal of the solvent afforded a yellow solid, m.p. 145-150°C., but this when intimately mixed with powdered potassium hydroxide (2 g.) at 120-125°C (oil bath) readily gave an effervescent melt. Heating at this temperature was maintained for 5-10 minutes when water was added. Extraction of the diluted reaction with chloroform gave a yellow solid which distilled at 160-170°C (air bath temperature) and

crystallised from benzene in slightly yellow prisms, m.p. 132-134°C depressed below 110°C by the above aldehyde and raised to 134-135°C on recrystallisation. Yield, 850 mg. (Found: C, 73.2; H, 6.4. $C_{19}H_{20}O_4$ requires C, 73.1; H, 6.4%).

Cis-2:3:4:7-tetramethoxy-10-methyl-9:10-dihydrophenanthrene-9:10-diol (XCV).

Osmium tetroxide (0.68 g.; 1 mole with 10% excess) in sodium dried thiophene-free benzene (25 ml.) became red-brown on addition of 2:3:4:7-tetramethoxy-10-methyl phenanthrene (750 mg.). On addition of pyridine (0.55 ml.) the colour lightened and the methyl phenanthrene rapidly dissolved. After standing at room temperature for 14 days, during which time three drops of pyridine were added on the 7th and 9th days, the reaction mixture deposited dark-brown crystals of the required complex. The methylene chloride solution of this osmium tetroxide-pyridine complex, after filtration from a small amount of insoluble material, was shaken with mannitol (10 g.) and potassium hydroxide (1 g.) in water (100 ml.) until the organic layer was colourless (about 1 hour). The methylene chloride solution was separated, washed with water, dried and concentrated in vacuo at room temperature. The residual gum crystallised from aqueous methanol in colourless prisms, m.p. 155-156°C.

Yield, 620 mg. (Found: C, 66.0; H, 6.4. $C_{19}H_{22}O_6$ requires C, 65.9; H, 6.4%).

Dehydration of diol: The diol (70 mg.) was refluxed for 1 minute with concentrated hydrochloric acid (0.2 ml.) in acetic acid (2 ml.). The cooled solution, diluted with water, deposited colourless crystals which were recrystallised from methanol in plates, m.p. 135°C.

(Found: (a) C, 72.2; H, 6.4. (b) C, 72.3; H, 6.5%).

This product is insoluble in sodium hydroxide and does not give a ferric chloride colour reaction.

9:12:13:14-Tetramethoxy-3:4:5:6-dibenzcycloheptatrien-7-one (XCVII).

To the above diol (100 mg.) in sodium-dried, thiophene-free benzene (8 ml.) there was added lead tetra-acetate (80 mg.) and the mixture shaken vigorously for two hours at room temperature. The lead di-acetate which separated was removed by filtration through a bed of charcoal and, after being washed with water, the dried filtrate was concentrated in vacuo. A solution of the resulting colourless oil was treated with a little sodium bicarbonate and brought to a slight permanent turbidity by the addition of water. Since this reaction mixture on standing in an atmosphere of nitrogen for two days did not deposit any material, the solution was made alkaline to phenolphthalein

by addition of sodium hydroxide and left for three days, again in an atmosphere of nitrogen. The yellow gum which had separated partially solidified on rubbing with methanol. The yellow solid thus obtained was filtered off and worked up as described below. The methanolic mother liquors, on concentration, yielded a further small amount of this yellow solid and a gum which was combined with a further small amount of gum obtained from an alkali-washed chloroform extract of the diluted reaction mixture mother liquors. This gum, dissolved in benzene, was passed through a small column of B.D.H. alumina and there developed a yellow band of general adsorption which, on elution with benzene, afforded a slightly yellow gum. This gum, obtained from the chromatogram, crystallised in yellow sheaves from methanol, micro-m.p. and mixed micro m.p. with the $\alpha:\beta$ -unsaturated ketone obtained in the oxidation of deaminocolchinol methyl ether, 109-111°C.

The yellow solid, obtained in this reaction, crystallised from acetic acid in small cream-coloured needles of micro-m.p. 208-209°C which depressed the micro-m.p. of the $\alpha:\beta$ -unsaturated ketone obtained in the oxidation deaminocolchinol methyl ether to below 90°C (unchanged on cooling and remelting). This neutral and non-ketonic compound, on sodium dichromate oxidation, afforded 2:3:4:7-tetramethoxy

phenanthraquinone, micro-m.p. and mixed micro-m.p. 192-194°C. Diazine, micro-m.p. and mixed micro-m.p. with 2:3:4:7-tetramethoxy phenanthrazine, 175-176°C.
(Found: C, 69.65; H, 6.0. Molecular weight by Micro-Rast, 643 and 683; $C_{38}H_{40}O_{10}$ requires C, 69.5; H, 6.1%. Molecular weight, 656). Micro-hydrogenation, over palladium, indicated the presence of one double bond per nineteen carbon atoms.

Attempted Rosenmund Reduction of 3:4:5-trimethoxy benzoyl chloride.

Decalin (5.5 ml.), 3:4:5-trimethoxy benzoyl chloride (10 g.) and palladised barium sulphate (5 g.) were refluxed in a stream of hydrogen until the evolution of hydrogen chloride ceased (6 hours). After filtration from catalyst, the decalin solution, on cooling, deposited 3:4:5-trimethoxy benzoic anhydride (0.5 g.) which was filtered off and collected. The filtrate was washed with sodium bicarbonate (from which there was obtained 0.5 g. of 3:4:5-trimethoxy benzoic acid), dried and concentrated. After removal of the solvent, a colourless oil distilled at 124°C/12 mm. which crystallised from petroleum ether in colourless needles, m.p. and mixed m.p. with 1:2:3-trimethoxy benzene, 42-43°C. Yield, 3 g. (40%).

The corresponding picrate crystallised from methanol

in golden needles, m.p. and mixed m.p. with 1:2:3-trimethoxy benzene picrate, 79-80°C.

3:4:5-Trimethoxy benzaldehyde (CIII)[3,64].

Sönn-Muller reduction of 3:4:5-trimethoxy benzoic acid (325 g.) afforded the required aldehyde (88 g.), b.p. 140°C/1 mm., m.p. 75°C.

3:4:5-Trimethoxy benzyl alcohol (CIV)[3].

(a). The above aldehyde (70 g.) in ethanol (700 ml.) was hydrogenated by shaking with platinic oxide (2.5 g.) in an atmosphere of hydrogen at room temperature. The theoretical volume of hydrogen was absorbed in 20 hours and the required alcohol distilled as a colourless viscous oil at 152-154°C/0.5 mm. Yield, 70 g.

(b). 3:4:5-Trimethoxy benzaldehyde (15 g.), in ethanol (150 ml.) was hydrogenated in the manner described in (a) except that a trace of ferric chloride was added as a promoter. Only two thirds of the theoretical amount of hydrogen was absorbed. Distillation of the partially hydrogenated material afforded 3:4:5-trimethoxy benzyl alcohol, b.p. 152-155°C/1 mm. (5 g.) and also a residue which, on trituration with ether afforded a colourless solid. This product crystallised in prisms from acetic acid, m.p. 198-200°C, undepressed on admixture with the compound obtained by Cook and Graham[3] in the methylation of syringic alcohol (see p. 46).

This by-product, on oxidation with sodium dichromate, yielded the known[46] 1:2:3:5:6:7-hexamethoxy anthraquinone which crystallised in yellow needles from acetic acid, m.p. 250°C. (Found: C, 61.9; H, 5.2. $C_{20}H_{20}O_8$ requires C, 61.9; H, 5.2%).

The gummy filtrate from the above by-product, on standing several days over ether, deposited another distinct compound which formed long colourless needles from methanol, m.p. 83°C. (Found: C, 63.7; H, 6.8%).

3:4:5-Trimethoxy benzoyl chloride (CI)[3].

3:4:5-Trimethoxy benzyl alcohol (10 g.) in purified dimethyl aniline (88 ml.), was treated, dropwise and with shaking, with thionyl chloride (8.2 ml.), purified by the method of Fieser[65], the whole being kept below 0°C. The resultant dark orange mixture was allowed to stand below 0°C for 2 hours when excess thionyl chloride was destroyed by cautious addition of crushed ice (10 g.). After the addition of dilute hydrochloric acid (10 ml.) to remove dimethyl aniline, water (50 ml.) was added. The resultant 3:4:5-trimethoxy benzoyl chloride was filtered off, washed with dilute hydrochloric acid, dried and used directly for the next stage. Yield (crude), 9.6 g. m.p. 58°C.

In this way 57 g. of 3:4:5-trimethoxy benzyl alcohol yielded 53 g. of the required product.

<u>α-(3':4':5'-Trimethoxybenzyl)-2-nitro-5-methoxy benzyl cyanide (CIX)</u>[43].

Condensation of 3:4:5-trimethoxy benzyl chloride (53 g.) with 2-nitro-5-methoxy benzyl cyanide (47.5 g.) in ethyl alcohol in the presence of sodium ethoxide, afforded the required benzyl cyanide (70 g.), m.p. 162°C.

<u>α-(3':4':5'-Trimethoxy benzyl)-2-amino-5-methoxy benzyl cyanide (CX)</u>[43].

The above nitro-compound (10 g.) in peroxide-free dioxan (200 ml.) was hydrogenated in one hour with 2% palladised strontium carbonate (10 g.) and the crude amine used directly for Pschorr ring closure (see p. 47).

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Part II.

Extraction of Pure Colchicine.

After some experimenting the following procedure was adopted. A concentrated Extract of Colchicum (specified to contain 4.3% colchicine) was supplied by Messrs. Ramsom of Hitchin, Herts. The crude extract (426 g.), diluted with water (600 ml.), was extracted twice with hot paraffin wax (100 g.) which took up some green colour. The combined wax layers were washed with boiling water (1 litre in four lots) and, after admixture with paper pulp (70 g.), the aqueous solutions were filtered through a precoating of pulp (10 g.). The filter bed was well washed with water, churned up with boiling water and refiltered through a fresh precoating of pulp (10 g.). These washings were added to the clear, deep-brown filtrate which was exhaustively extracted with acid-free chloroform (5 litres in 20 lots). The chloroform extract, dried over potassium carbonate, was evaporated to a dark brown syrup which was dissolved in dry chloroform (150 ml.) and adsorbed on a column of B.D.H. alumina (23 cms. by 3½ cms.), saturated with benzene. On development with chloroform the column was observed to consist of the following bands (from bottom to top):-

(1) Bright green band accompanying the benzene-chloroform interface,

(2) Broad pale green band,

(3) Colourless band fluorescing pink in ultra-violet light,

(4) Broad bright yellow band,

(5) Crimson band,

(6) Brown band.

Since bands (1) and (2) could not be separated, they were eluted together with chloroform. Band (3) was eluted separately with chloroform.

After extrusion of the column, the remaining bands were eluted separately, (4) and (6) with methanol and (5) with methanolic ammonia.

The concentrated eluates of bands (3), (4), (5) and (6) were retained for future inspection.

The mixed eluate of bands (1) and (2) was evaporated to dryness. The residue, dissolved in the minimum of acid-free chloroform:peroxide-free ether (1:1), was re-chromatogramed using B.D.H. alumina (previously activated at 280°C/ 10 mm. for one hour), saturated with benzene. On development with chloroform:ether the almost colourless column was seen, in ultra-violet light, to consist of the following bands (from bottom to top):-

(1') Broad yellow-green band,

(2') Narrow pink band,

(3') Narrow yellow band.

Band (1') was eluted with chloroform:ether and finally with chloroform, until the eluate, on evaporation, gave no residue. The concentrated eluate was freed from last traces of chloroform by repeated evaporation with methanol. The product crystallised from ethyl acetate in fine colourless needles, m.p. 153-155°C. Yield, 13.28 g.

The lower half of the column still fluoresced faintly green in ultra-violet light and so the column was extruded. The separated bands (1'), (2') and (3') were then eluted with methanol.

The methanolic eluate of band (1'), on evaporation, afforded a yellow gum which, on crystallisation from ethyl acetate, yielded a further 1.79 g. of faintly yellow coloured colchicine, m.p. 153-155°C.

The ethyl acetate mother liquors from these crystallisations, on evaporation, yielded a non-crystallisable gum.

The concentrated eluates of bands (2') and (3') were retained, along with concentrated eluates of bands (3), (4), (5) and (6) of the earlier chromatogram, for future investigation.

Colchiceine.

Colchicine (2.05 g.) was boiled with very dilute hydrochloric acid (0.75 ml. concentrated acid in 150 ml. water) until colchiceine crystallised from the boiling solution (one hour). The product was filtered off and the filtrate, on boiling for a further hour, afforded more colchiceine. Yield, 1.68 g. (84.5%).

Chloroform extraction of the acid mother liquors yielded 105 mg. of poorer quality colchicine. Total yield, 1.785 g. (90%).

Bromination of Colchiceine.

Colchiceine (1 g.), in glacial acetic acid (20 ml.) was treated, slowly and with shaking, with bromine (1 ml.; ca 100% excess). After the addition of about 0.3 ml. bromine, a heavy yellow precipitate appeared which, on the addition of more bromine, became oily and finally redissolved. The acetic acid solution after standing for twenty-four hours at ordinary temperatures, was heated on a water bath and water was added to a permanent turbidity. There separated out, on cooling a red-brown solid which crystallised from methanol in a thick mat of colourless needles, decomp. pt., 218-230°C. Yield, 490 mg. (30%). (Found: C, 40.7; H, 3.5; Br. 38.8. $C_{22}H_{20}Br_3O_6N$ requires C, 40.5; H, 3.2; Br, 38.6%).

Methylation of Brominated Colchiceine.

To the brominated colchiceine (100 mg.), in Analar acetone (15 ml.) there was added an excess of diazomethane in peroxide-free ether (15 ml.). The methylation solution, after standing overnight at ordinary temperatures, afforded, on concentration, a yellow gum which, after extracting with dilute sodium hydroxide, was adsorbed on a column of alkali-free alumina[59] from dry benzene. On development with benzene, the column was observed to consist of an upper narrow brown band and a lower band pale blue band of general absorption. This lower band was eluted with benzene and the eluate, on concentration, yielded a gum which crystallised in small colourless needles from benzene, m.p. 131°C. Yield, 75 mg. (73%). (Found: C, 41.5; H, 3.5. $C_{22}H_{32}Br_3O_6N$ requires C, 41.9; H, 3.5%).

Bromination of Salicylaldehyde.

Salicylaldehyde (2.5 g.), in glacial acetic acid (30 ml.), was treated with bromine (5 ml.). The acetic acid solution, after standing twenty-four hours, was worked up in a manner similar to that described in the bromination of colchiceine and yielded in almost theoretical amount 3:5-dicromo salicylaldehyde, m.p. 83-84° (literature, m.p. 85°C).

Brominated Colchicine.

Colchicine (200 mg.), in dry chloroform, was treated,

slowly and with shaking, with bromine (0.12 ml.) in dry chloroform. After standing for two days in the dark (a blank experiment showed an uptake of bromine), the dried chloroform solution, after removal of the excess bromine by extraction with dilute sodium hydroxide, was evaporated and the resultant gum was adsorbed on a column of alkali-free alumina from benzene. On development with benzene, there was a separation into an upper narrow band, strongly absorbed, and a lower pale green band of general absorption which on elution with benzene/chloroform (2:1) afforded a gum which crystallised from dilute methanol, m.p. 147-150°C. (Analysis results appear in the text, p.60).

Note: When chromatography was carried out using B.D.H. alumina (previously activated at 300°C for one hour), on development with benzene, the column was observed to consist of:

(a) upper narrow yellow band, strongly absorbed, which was eluted with methanol - eluate (1),

(b) lower pale green band of general absorption which was eluted with chloroform - eluate (2).

Eluate (2), on concentration, yielded a gum which crystallised from dilute methanol, m.p. 147-150°C.

Eluate (2), on concentration, yielded a white powder, insoluble in most organic solvents, which crystallised from a

large volume of methanol in square plates, m.p. > 360°C, and which responded to the alizarin spot test for aluminium.

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