SYNTHESES IN THE COLCHICINE SERIES

T H E S I S

submitted by

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Preface.

The author wishes to express his thanks to Professor J. W. Cook, F.R.S. and to Dr. J. D. Loudon for much valuable advice and encouragement given during the course of the work reported here.

He is indebted to Mr. G. Doig for practical assistance in the preparation of certain starting materials, and also to Mr. J.M.L. Cameron and Miss R.H. Kennaway, who performed the micro-analyses. Finally the author would like to acknowledge his thanks to the Department of Scientific and Industrial Research for a maintenance grant during the tenure of which this work was carried out.

Contents.

INTRODUCTION.

The toxic principle Colchicine was isolated[1] in 1820 from the seeds and corms of the autumn crocus, Colchicum autumnale L. (Liliacae). Since then it has been obtained in small quantities from other Colchicum and numerous Liliaceous species. Recently Santavy and Reichstein[2] have isolated several other substances from various tissues of the Colchicum autumnale and have shown that some of them are related to colchicine.

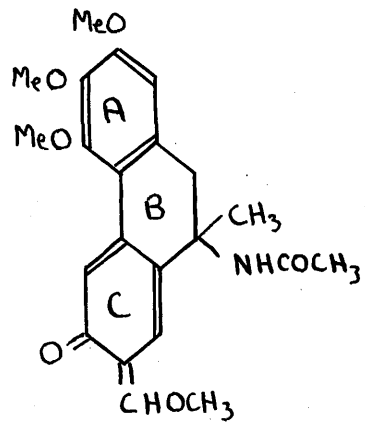
Like most other plant alkaloids colchicine exhibits marked physiological properties. For many years colchicine has been employed, generally as its salicylate, as standard treatment for gout but in recent years it has attracted much attention by reason of its remarkable effect on mitosis or cell-division. Various authors have observed that the latter process is arrested at the metaphase stage by the action of colchicine. Since cancer is the uncontrolled proliferation of cells, the latter result has obvious implications and in fact Amoroso[3] has observed that colchicine induces regression of mouse tumours and is effective in treating spontaneous tumours in dogs. However Ludford[4] has shown that this inhibition of cell-division is not specific for tumour cells and that the

quantity required to interfere efficiently with the growth of a transplanted tumour approaches the lethal dose for the host. It is therefore desirable to establish the structure of this important biological substance before seeking some analogue which may possibly be more specific in its action and less toxic.

There are several excellent reviews of the chemistry of colchicine[5,6] but a brief account of some of the structural features of the alkaloid will be given here in order to supply the necessary background.

Colchicine is not a typical alkaloid, e.g. it is non basic, and as far as is known is unlike any other member of this class of substances. The first structural work, by Zeisel[7], revealed the presence of a hydrolysable methoxyl group and an acetyl group. These were demonstrated by the mild acid hydrolysis of colchicine, $C_{22}H_{25}O_6N$, to colchiceine, $C_{21}H_{23}O_6N$, which was further hydrolysed with stronger acid to acetic acid and an amphoteric compound, $C_{19}H_{21}O_5N$, named trimethyl-colchicinic acid. The above three compounds were each shown by Zeisel to possess three normal methoxyl groups. Later Windaus[8], as the result of an intensive series of degradation studies, proposed the structure (I) for Colchicine, with the added proviso that the positions of

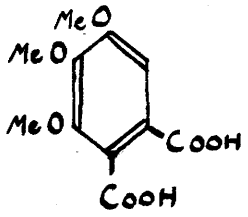
the methoxymethylene and carbonyl groups may be interchanged.



I

Whilst the structure above has been confirmed in respect of the vicinally tri-methoxylated ring A and its orientation to ring B, it has proved unsatisfactory in several other respects.

Windaus[9] found that colchicine and its two hydrolysis products, colchiceine and trimethylcolchicinic acid, afforded 3:4:5 - trimethoxyphthalic acid (II) on alkaline permanganate oxidation. This therefore represents ring A with its three vicinal methoxyl groups. Since the alkaloid was regarded as derived from a phenanthrene structure, the production of (II) indicated either a 1:2:3- or a 2:3:4- arrangement of the methoxyl groups as in the part-formula (III) or (IV).



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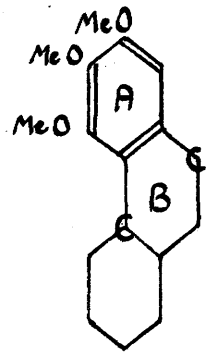

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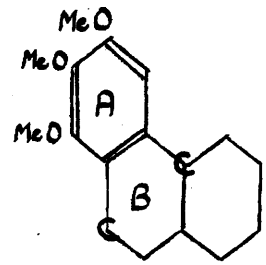
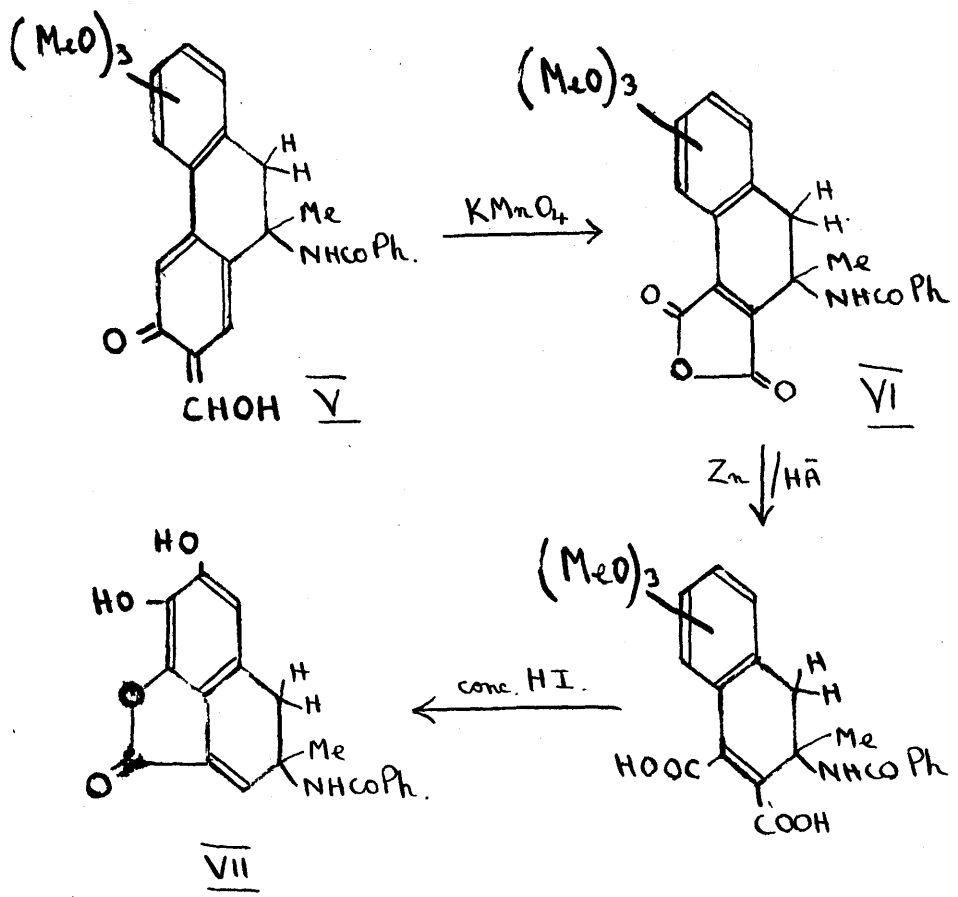


III

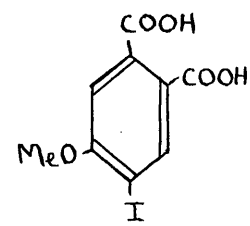
Arguing from the series of reactions which are shown diagramatically below, Windaus[8] favoured the latter pattern. N-benzoyltrimethylcolchicinic acid (V) on oxidation with potassium permanganate afforded an anhydride (VI) which was considered to be a partially hydrogenated naphthalene derivative. When the anhydride ring was opened and the methoxyl groups hydrolysed to hydroxyls, the resultant product readily formed a lactone (VII). The formation of the latter was interpreted as arising by interaction of peri-substituents.



The vicinal methoxyl groups in colchicine were therefore assigned the 2:3:4 positions.

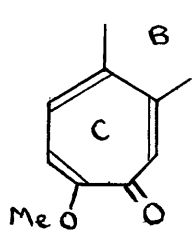
Colchiceine displays the properties of an enolone, e.g. it gives a deep green colouration with ferric chloride solution, but Windaus[10] found that these properties were lost on treatment with iodine and sodium hydroxide. The product, N-acetyliodocolchinol, exhibited the properties of a true phenol and hence it appeared that a second ring

of colchicine had been converted into aromatic form. The same author provided evidence in support of this assumption by isolating 4 - iodo - 5 - methoxyphthalic acid (VIII) from the oxidation of the transformation product's methyl ether[11]. The above substituted phthalic acid was later synthesised by Grewe.[12] More recently Bursian[13] has observed a marked difference in the character of the ultra-violet absorption spectra of colchiceine and N-acetyl-iodocolchinol whereas the former closely resembles colchicine in absorption characteristics. The difference in ultra-violet absorption spectrum was attributed to the aromatisation of ring C.



VIII

Windaus in proposing the structure shown in (I) for ring C, endeavoured to reconcile these results with the known replacement of the formyl group of o-hydroxy-benzaldehyde by iodine. As will be discussed later (p.66) the tropolone formula (IX) for ring C provides a more satisfactory picture but in the meantime consideration is confined to the question of structure in the colchinol series of degradation products.

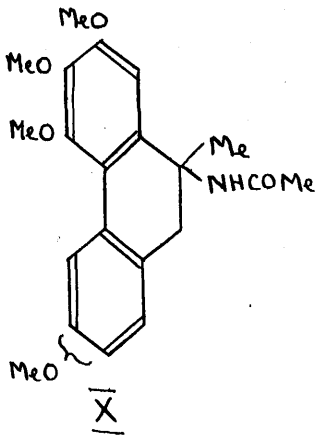


IX

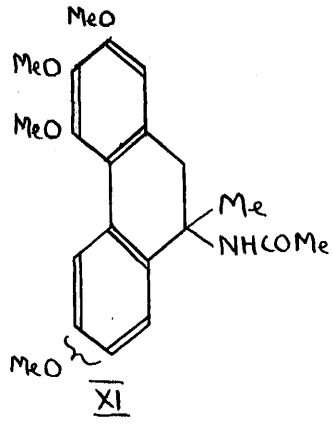
The further degradation of N-acetyliodocolchinol methyl ether has provided considerable insight into the general structure of the alkaloid and in particular into the nature of ring B. Dehalogenation[11] of the compound afforded N-acetylcolchinol methyl ether which was submitted to the standard Hofmann degradation[8]. By a one stage process Windaus obtained the nitrogen free compound, deaminocolchinol methyl ether. This deamination reaction was accompanied by the loss of optical activity which had characterised colchicine and this series of colchinol degradation products. The hydriodic acid hydrolysis of the four methoxyl groups of deaminocolchinol methyl ether followed by zinc dust distillation afforded 9-methylphenanthrene which was identified by synthesis[14]. Its isolation led Windaus to the conclusion that deaminocolchinol methyl ether was a tetramethoxy derivative of 9-methylphenanthrene.

Colchicine can be oxidised with chromium trioxide to a ketonic product, $C_{22}H_{23}O_7N$, named oxycolchicine[15], thereby revealing the presence of an active methylene group in the alkaloid's structure. Since the sequence of changes from colchicine to deaminocolchinol methyl ether was considered to have occurred without any structural rearrangement of ring B there were therefore two possible

structures for N-acetylcolchinol methyl ether (X) and (XI).



X

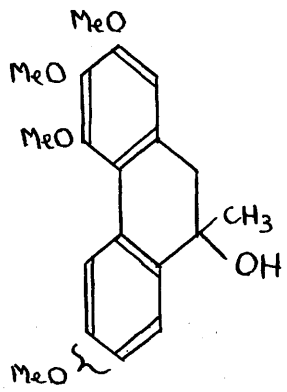


XI

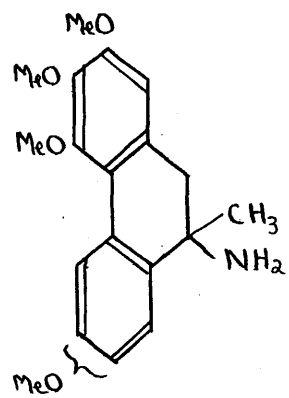
The latter seemed preferable on account of the isolation of 4 - methoxyphthalimide from the oxidation of colchinol methyl ether[11]. Thus in 1924 Windaus formulated N-acetyl-colchinol methyl ether as a tetramethoxy derivative of 9-acetylamino-9:10-dihydro-9-methylphenanthrene (XI).

This structure reamined unquestioned until 1940. In that year Cohen, Cook and Roe[16] pointed out that colchinol methyl ether, as pictured by the German author, should be capable of a facile loss of ammonia thereby reverting to a more stable phenanthrene structure. In practice there was no evidence of such instability. In this connection it is noteworthy that Windaus[17] observed such an instability in compounds of the 9-amino-9:10-dihydrophenanthrene type which he attempted to synthesise as model compounds. By the action of nitrous acid on colchinol methyl ether, the same authors[16] obtained a

carbinol which was definitely not tertiary in character as expected (XII) from Windaus' conception of colchinol methyl ether (XIII). The reactivity of this alcohol towards



XII

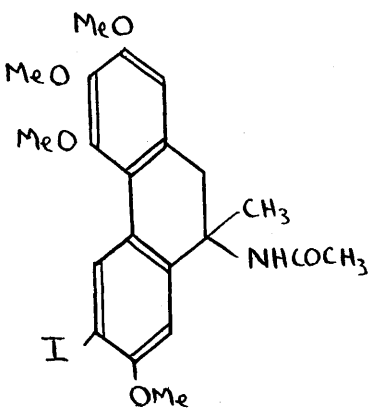


XIII

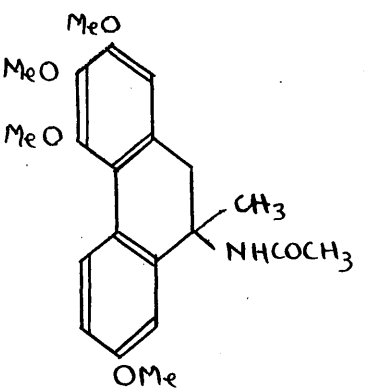
phthalic anhydride tended to suggest that this new degradation product was a secondary alcohol. Furthermore, the high stability of this product was not in harmony with such a structure as (XII). However dehydration could be effected by the action of phosphorus pentoxide in boiling xylene[19] with the formation of deaminocolchinol methyl ether. It was therefore obvious that deaminocolchinol methyl ether would provide the key to the structure of the colchinol series of degradation products.

Windaus had concluded that deaminocolchinol methyl ether was either 2:3:4:6- or 7-tetramethoxy-9-methyl-phenanthrene[8] but this conception was finally disproved by

the synthesis of these two compounds[18] which were found to be distinct from the degradation product. However, it was found that when the latter substance was oxidised with sodium dichromate in acetic acid there was produced a quinone which was identical with 2:3:4:7-tetramethoxy-phenanthraquinone formed by oxidising the corresponding phenanthrene-9-carboxylic acid. The methoxylation pattern was therefore established for N-acetylcolchinol methyl ether and accordingly in terms of the Windaus formulation N-acetyliodocolchinol methyl ether became (XIV) and the deiodo compound (XV).



XIV



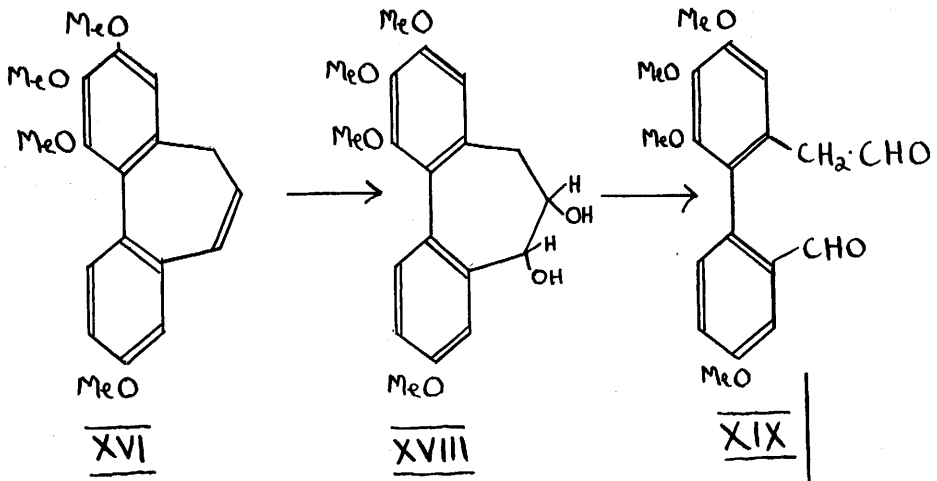
XV

The synthetic 2:3:4:7-tetramethoxy-9-methyl-phenanthrene differed markedly in chemical reactivity from deaminocolchinol methyl ether[19]. Firstly, the synthetic material afforded a crystalline molecular complex with picric acid whereas the degradation product showed no sign of picrate formation. Secondly, the latter product

readily absorbed one molecule of hydrogen, in contradistinction to the non-absorption of hydrogen by the synthetic substance. The failure of the resulting dihydrodeaminocolchinol methyl ether to lose a molecule of hydrogen with dehydrogenation catalysts seemed incompatible with a 9:10-dihydrophenanthrene structure for this product.

Deaminocolchinol methyl ether is formed by (a) Hofmann degradation of colchinol methyl ether or (b) dehydration of the carbinol as described above. Cook and Graham[20] showed that it was also produced, in improved yield, by the direct elimination of the elements of acetamide from N-acetylcolchinol methyl ether by the action of phosphorus pentoxide in boiling xylene. When prepared by either of the latter two methods deaminocolchinol methyl ether was accompanied by a small amount of an isomeric substance. This isomer, iso-deaminocolchinol methyl ether, was also found to be capable of ready hydrogenation to the same dihydro compound obtained from deaminocolchinol methyl ether. The two isomers therefore differed only in thelocation of an ethylenic double bond. On the basis of the above observations Barton, Cook and Loudon[19] considered that deaminocolchinol methyl ether and its bond isomer were best represented by

the formulae (XVI) and (XVII), although not necessarily respective. The presence of the two isomers was considered to be due to a triad type of tautomerism.



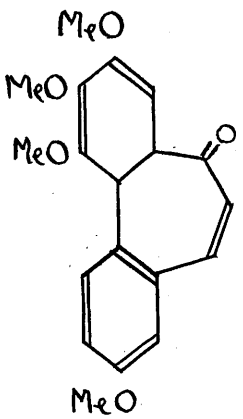
The same authors went on to prove conclusively that these degradation products of colchicine were indeed methoxylated derivatives of dibenzocycloheptatriene.

The Glasgow workers utilized the ethylenic character of deaminocolchinol methyl ether by reacting the

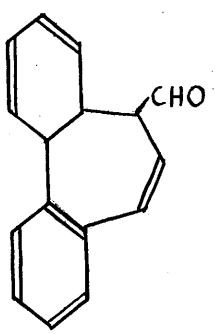
compound with osmium tetroxide. The resulting glycol (XVIII) was cleaved with lead tetraacetate to a gummy dialdehyde (XIX) which was cyclised to give 2:3:4:7-tetramethoxy-10-phenanthraldehyde (XX). The latter compound was oxidised to the corresponding 10-phenanthroic acid which was identified by synthesis.[19] Later the phenanthraldehyde was also synthesised[21]. Likewise iso-deaminocolchinol methyl ether was oxidised to the known 2:3:4:7-tetramethoxy-9-phenanthraldehyde. From these elegant oxidation experiments it was clear that deaminocolchinol methyl ether had the structure (XVI) and the iso-compound the structure (XVII). From the dichromate oxidation of the former it will be recalled that 2:3:4:7-tetramethoxyphenanthraquinone was obtained but this was not the sole product. Another substance, $C_{19}H_{18}O_5$, was isolated which displayed the properties of an $\alpha:\beta$ unsaturated ketone. The above structure for deaminocolchinol methyl ether accommodates the production of such a ketone by oxidation. Accordingly the $\alpha:\beta$ unsaturated ketone was represented by the structure (XXII). This was later verified by its synthesis[21,22] which incidentally provided the first synthetic proof of a seven membered structure for ring B in a degradation product of colchicine.

At first sight the conversion of such seven

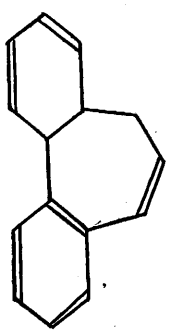
membered ring structures into derivatives of phenanthrene may not seem apparent, particularly the oxidation of deaminocolchinol methyl ether to the corresponding phenanthraquinone. This type of conversion, however,



XXII



XXIII

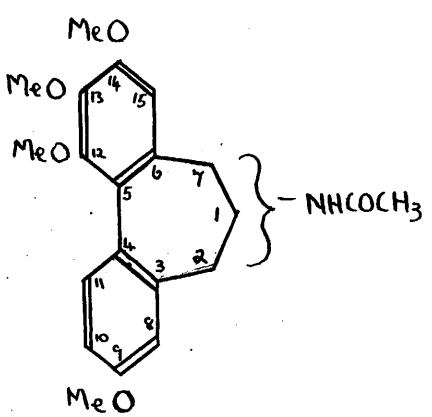


XXIV

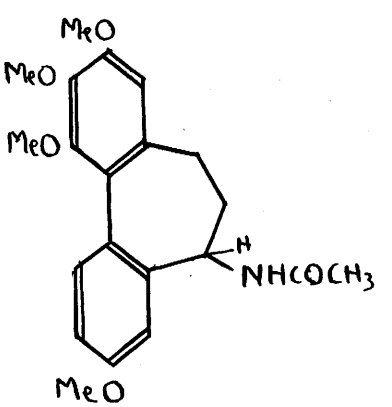
finds a precedent in the known oxidation of (XXIII) to phenanthraquinone[23]. In its simplest form this type of reaction is illustrated by the production of benzil from diphenyltriketone[24]. The isomerisation of (XVI) to the corresponding 9-methylphenanthrene under the drastic conditions of zinc dust distillation was paralleled by the conversion of dibenzocycloheptatriene (XXIV) into 9-methylphenanthrene[25]. The former compound was also shown by Cook, Dickson and Loudon[25] to be oxidisable to phenanthraquinone. Thus objections based on the production of phenanthrene derivatives from a structure

such as (XVI) are removed. This structure is supported by independent evidence supplied by Fanta, Frank and Tarbell[26]. These authors oxidised iododeaminocolchinol methyl ether, formed by deamination of N-acetyliodocolchinol methyl ether, to a dibasic acid which must be a homodiphenic acid, since its ester underwent the Dieckmann reaction to give a phenanthrol derivative.

Deaminocolchinol methyl ether is formed by eliminating the elements of acetamide from N-acetylcolchinol methyl ether and viewed in reverse this reaction leads to three possible structures for the N-acetyl compound (XXV).



XXV



XXVI

The structure wherein the acetylamino residue is attached to the central position (i.e. 1) of ring B must be discounted in order to accommodate Windaus' isolation of

succinic acid[10] from among the oxidation products of colchicine and its derivatives. Of the remaining alternatives in which the substituent in ring B is attached at positions 2- or 7-, the latter is more plausible in view of the isolation of 4-methoxyphthalimide from the oxidation of the free amine, colchinol methyl ether. Accordingly on the balance of evidence N-acetylcolchinol methyl ether appears to possess the structure (XXVI).

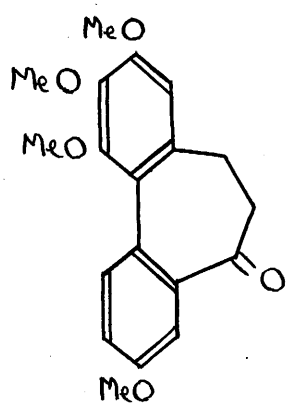
The immediate aim of the present work has been the synthesis of (XXVI) in order to provide the critical test of structure.

PART I

THE CYCLISATION OF SOME DIPHENYLYL PROPIONIC ACIDS.

DISCUSSION

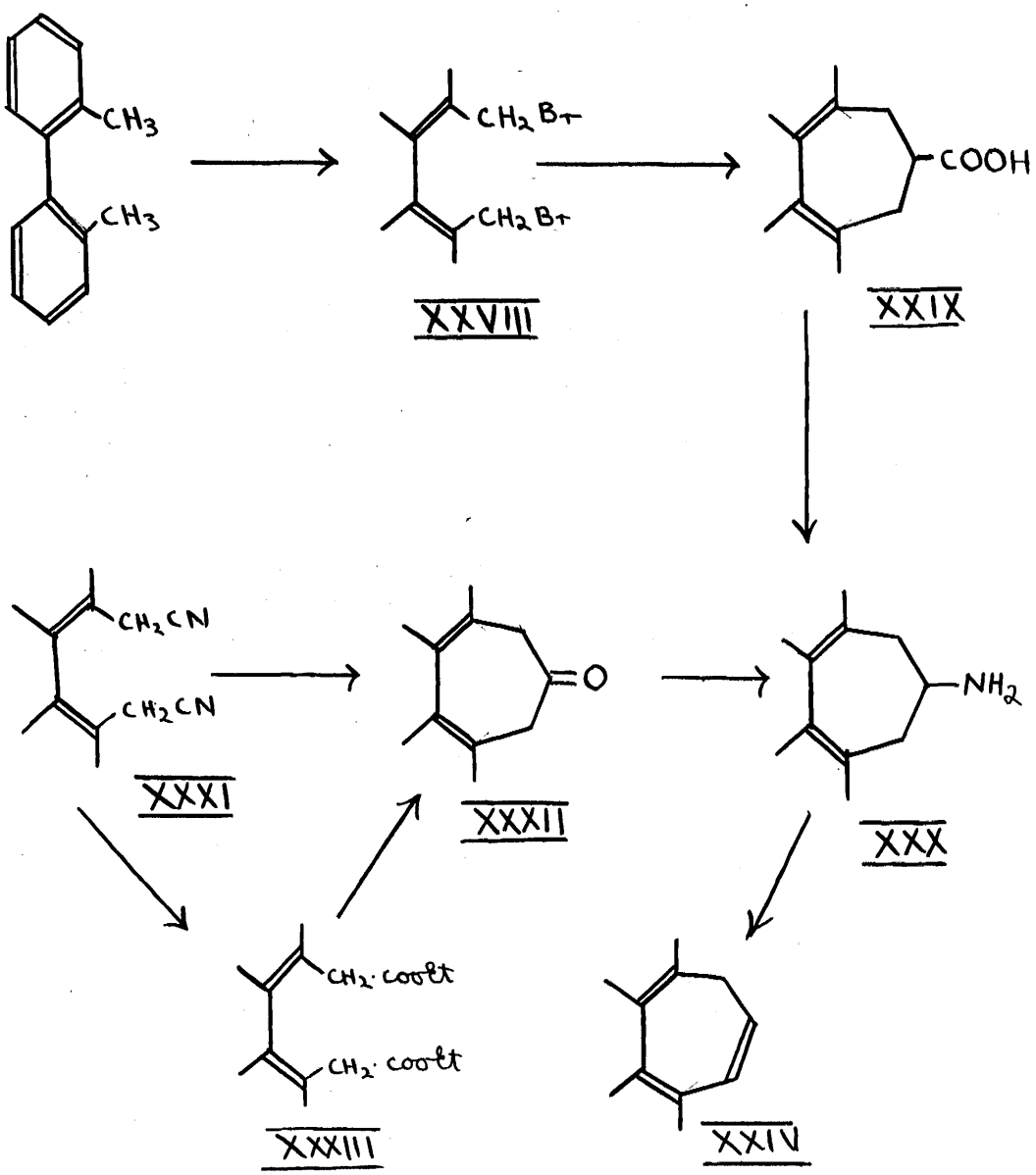
In the foregoing introduction it has been indicated that the most probable structure for N-acetyl-colchinol methyl ether is that represented by (XXVI). Any projected synthesis of (XXVI) would clearly involve the preparation of the ketone (XXVII) which could then be converted by standard procedure to the acetylamino compound.



XXVII

The limited investigations into the chemisty of dibenzocyclo-heptane derivatives may be gauged by the paucity of relevant literature.

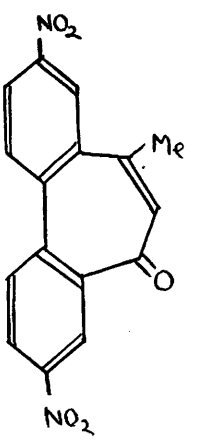
Kenner[27] (c.f. Kenner and Turner[28]) has recorded a synthesis of the related dibenzocycloheptatriene (XXIV), that is the parent hydrocarbon structure of deamino-colchinol methyl ether. His interest lay in the formation of six and seven membered ringed structures from derivatives of 2:2'-ditolyl.



The latter compound was brominated yielding the $\omega:\omega'$ dibromo derivative (XXVIII) which was then condensed with malonic ester. Hydrolysis and elimination of carbon dioxide from the resulting condensate afforded the carboxylic acid (XXIX) which was then converted into the

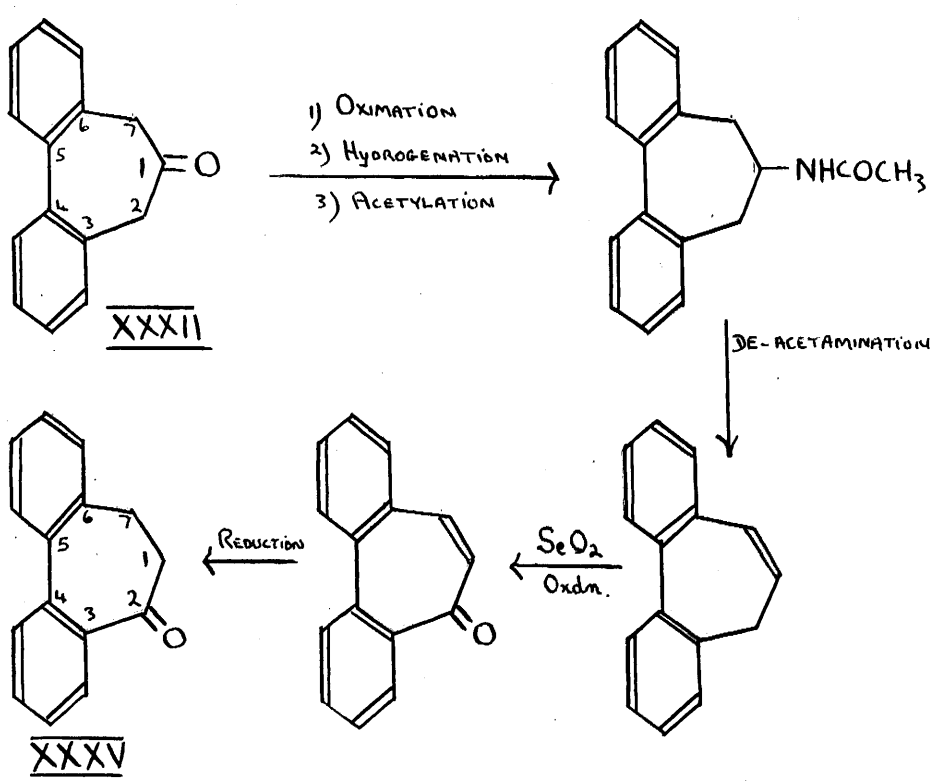
amine (XXX) by the Curtius reaction. The same amine was also produced by reducing the oxime of the ketone (XXXII) which was in turn formed by cyclisation of the dinitrile (XXXI) by the method of Thorpe. The intermediate ketone (XXXII) was also synthesised by the Dieckmann method from the di-ester (XXXIII). The triene (XXIV) was obtained from the hydrochloride of the amine (XXX) by thermal decomposition. This work has been repeated and improved by Cook, Dickson and Loudon[25] who found that the triene (XXIV) was more satisfactorily prepared by the action of phosphorus pentoxide in xylene on the acetylated base, following the procedure of Cook and Graham[20] for deacetylating N-acetylcolchinol methyl ether.

Another compound containing this tricyclic skeleton has been described by Weitzenbock[23] who obtained the aldehyde (XXIII) during the hydrolysis of the bis-acetal of diphenyl -o·o'- diacetaldehyde. The above preparative methods depend on the interaction between suitable o·o' side chains of symmetrically substituted diphenyls. Presumably the formation of the ketone (XXXIV) by heating 2-bromo-5-nitroacetophenone with copper powder[102] also proceeds by this method.



XXXIV

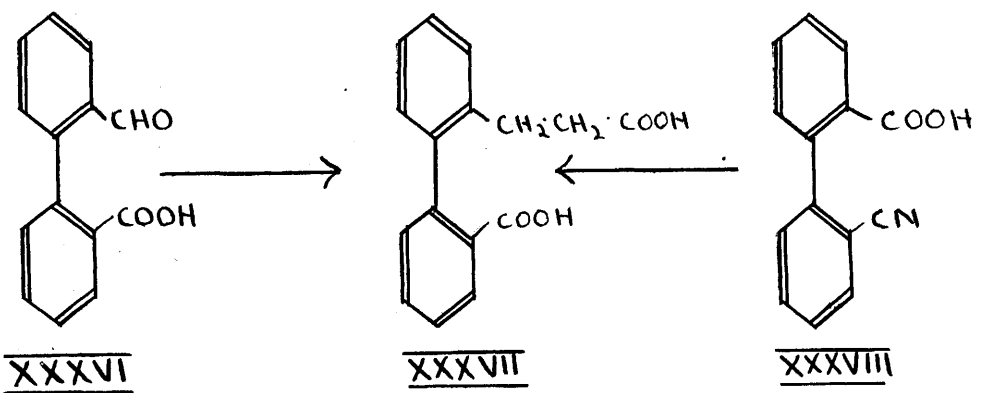
The above account represents the extent of the literature pertinent to the type of colchicine degradation product under consideration at present. It will be noted that the ketone grouping in the above described dibenzo-cycloheptadienone (XXXII) is located at position 1 whereas the desired intermediate (XXVII) is a 2 keto derivative. While the conversion of the former to the latter has been achieved[25] in the unmethoxylated series, as shown in the scheme below, the method is wasteful and obviously subject to orientation difficulties when an unsymmetrically substituted ketone is employed.



Thus it was desirable to find an alternative route to

ketone (XXVII).

Recent work[29] in this department has shown that the acid (XXXVII) can be prepared from diphenic anhydride via the aldehydo-acid (XXXVI). Cyclisation of this dicarboxylic acid by heating (a) the barium salt alone or (b) by treating the sodium salt with acetic anhydride yielded a gum which afforded the 2:4-dinitrophenylhydrazone of the required ketone (XXXV).

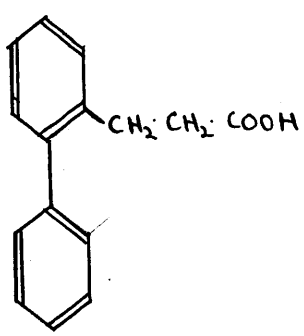


XXXVI XXXVII XXXVIII

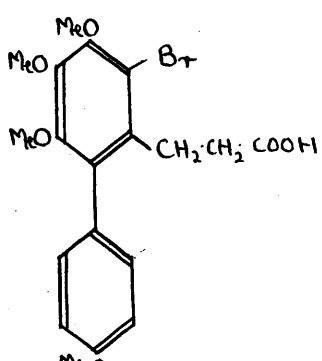
The extension of this approach to the appropriate tetramethoxylated diphenic acid was considered but rejected, partly due to the above result and also to the inaccessibility of the required starting acid. More recently Rapoport and Williams[30] have synthesised the acid (XXXVII) by a series of stages from the cyano acid (XXXVIII) obtained by the Beckmann rearrangement of phenanthraquinone

monoxime. In the hands of the latter authors ring closure of the acid (XXXVII) by means of Zeigler's procedure afforded the pure ketone (XXXV) in satisfactory yield. Attention was therefore transferred to the possibility of cyclising an acid of the type (XXXIX).

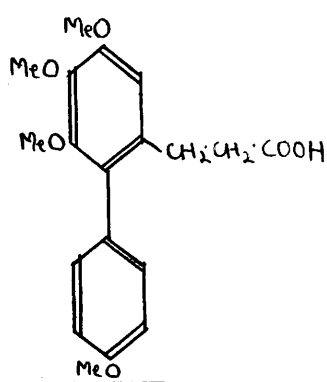
Barton, Cook and Loudon[31] had envisaged that the cyclisation of the acid (XL) would lead to the dibenzocyclo-heptadienone (XXVII). However ring closure of this acid by means of aluminium chloride afforded a bromo-ketone which could be debrominated to yield the same ketone as resulted from the cyclisation of the unbrominated acid (XLI). The



XXXIX



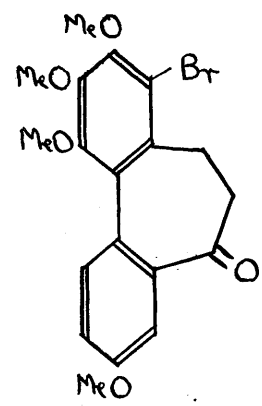
XL



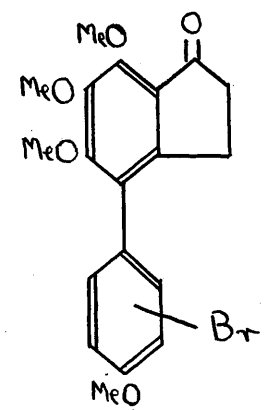
XLI

debromo-ketone was converted, via its oxime, into the corresponding amine which was characterised through its acetyl derivative. Deacetamination of the latter compound by the method of Cook and Graham gave a product which, although not characterised, was definitely shown to be

distinct from deaminocolchinol methyl ether. Furthermore, Cook, Dickson and Loudon[25] having shown that dibenzocyclo-heptadienones are easily oxidised to phenanthraquinones, the complete absence of a phenanthraquinone derivative on application of this test to the debromo- and bromo-ketones clearly excludes the required seven membered ring structure e.g. (XLII) for these compounds.



XLII

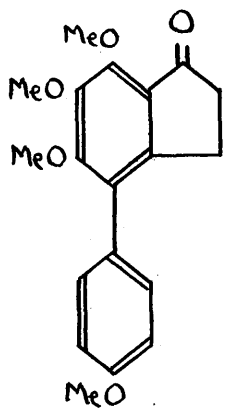


XLIII

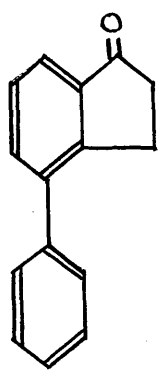
The bromo ketone was formulated as (XLIII). This same conclusion was also reached by Tarbell and his colleagues[32,33] who found that the ultra-violet absorption spectrum of the synthetic N-acetyl compound differed from that of N-acetyl-colchinol methyl ether.

As an alternative to the Friedel-Crafts type of cyclisation, the action of anhydrous hydrogen fluoride on the acid (XL) has now been examined. Cyclisation at room

temperature under anhydrous conditions led to a mixture of ketones, although Fanta, Frank and Tarbell[32] have since claimed that this acid was entirely unaffected under these conditions. The mixture of ketones was separated by crystallisation and shown to consist of the bromo-indanone (XLIII) and the bromine free indanone (XLIV). The presence of the latter compound may be due to some disproportionation of the starting material as displayed by 4-iodoresorcinol dimethyl ether under the influence of acidic reagents[34]. Thus the Friedel-Crafts and hydrogen fluoride methods afford essentially the same result but the latter method is superior as the product is more readily isolated in better yield and is free from kryptophenolic material which was encountered in the aluminium chloride technique.



XLIV



XLV

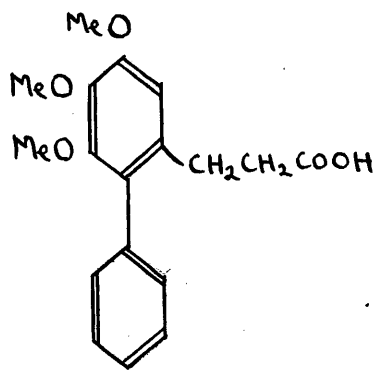
The unexpected course of the above cyclisation is probably due to a combination of adverse steric and orientating influences. The position of the methoxyl

group in the disubstituted nucleus is particularly unfavourable to the formation of a seven membered ring. By reason of the importance of dibenzocyclo-heptadienones in the chemistry of colchicine it was decided to investigate the direction of ring closure in several compounds related to (XL).

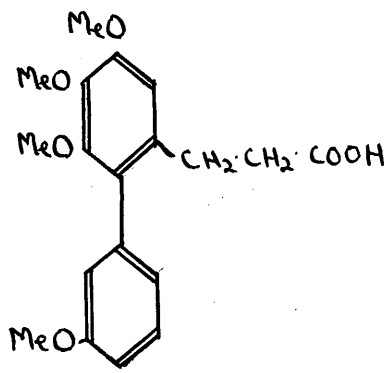
Von Braun and Manz[35] have reported that the indanone (XLV) is the sole product of a Friedel-Crafts cyclisation of the diphenylpropionic acid (XXXIX). Reinvestigation of the latter work by Cook, Dickson and Loundon,[29] however, led to the conclusion that although the indanone (XLV) was the major product, a small amount of an oil was also formed. Oxidation of this oil resulted in the formation of phenanthraquinone which indicated that the oil contained some dibenzocyclo-heptadienone. It has now been shown that hydrogen fluoride cyclisation of (XXXIX) leads to a similar result, the yield of the seven membered ketone, calculated from the amount of phenanthraquinone isolated, being approximately 10%.

In order to study the influence of the methoxyl group in the disubstituted nucleus the two acids (XLVI) and (XLVII) were prepared by previous workers in this department. It has now been found that both acids on

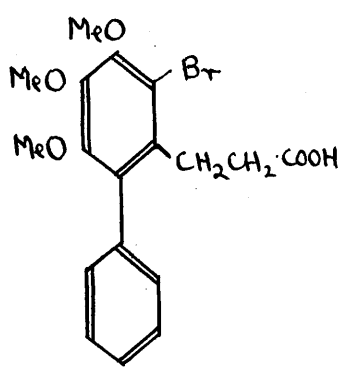
treatment with hydrogen fluoride were cyclised to the corresponding indanones. The failure of the oxidation test to give (coloured) phenanthraquinone derivatives indicated the absence of any seven membered ring formation. The corresponding bromo-acids (XLVIII) and (XLIX) were



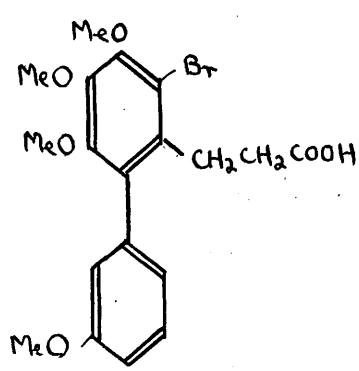
XLVI



XLVII



XLVIII



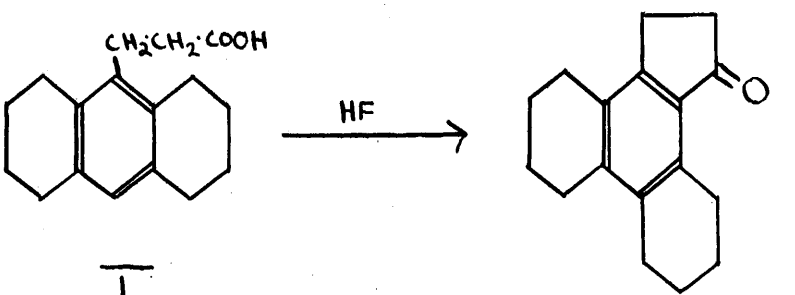
XLIX

prepared by direct bromination of the acids (XLVI) and (XLVII) respectively. The bromo-acids were assigned the structures shown by analogy with previous cases[32]. Cyclisation of (XLIX) gave a bromo-ketone which on

debromination, using hydrogen in the presence of palladised strontium carbonate, afforded the same indanone as obtained above by cyclisation of the acid (XLVII). Failure of the oxidation test again excluded any seven membered ring formation. The bromo-acid (XLVIII) on cyclisation by either the Friedel-Crafts or hydrogen fluoride methods gave a gummy product which was probably a mixture. Fanta, Frank and Tarbell[32] have found that treatment of the acid (XL) with phosphorous oxychloride in benzene or toluene causes intermolecular demethylation, affording the methyl ester of the starting acid. No such explanation is tenable here since treatment of the gummy cyclisation product with Girard's reagent T showed that it was entirely ketonic. Debromination of this gum failed to produce a solid and oxidation of the gum before and after debromination failed to give a phenanthraquinone derivative.

Thus it may be concluded that, in the case of (XLIX) at least, cyclisation is achieved by displacement and migration of bromine, and that in neither (XLIX) or (XLVIII) is there any tendency towards the formation of a seven membered ring. It may be noted that the displacement and migration of bromine, encountered in these cyclisation experiments, is not without precedent. Badger, Carruthers, Cook and Schoental[36] found that isomerisation to (LI)

accompanies the hydrogen fluoride cyclisation of (L).



L LI

These investigations sufficiently showed that the project of bridging the diphenyl system using intermediates of the diphenylpropionic acid type was not likely to yield practicable results. Accordingly a new approach was sought.

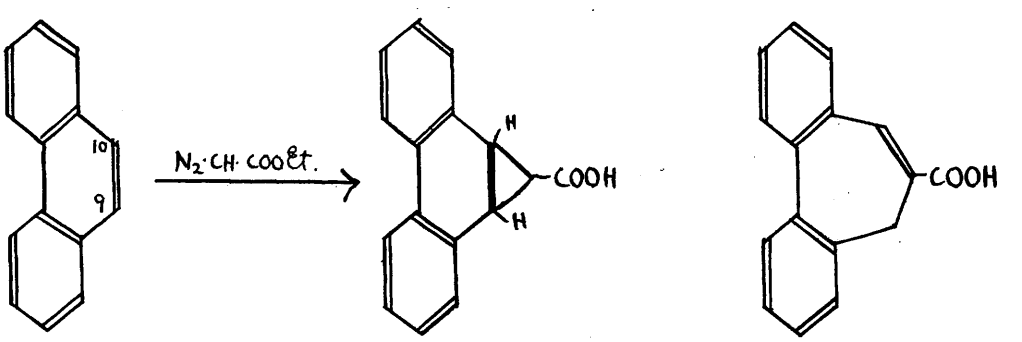
PART II.

THE SYNTHESIS OF N-ACETYLCOLCHINOL METHYL ETHER.

INTRODUCTION

The preceding approach having failed to yield the required dibenzocycloheptadienone (XXVII), attention was then focussed on the possibility of enlarging the central ring of an appropriately methoxylated phenanthrene.

It has been demonstrated, by workers in this department[25] and by Drake and Sweeney[34], that ethyl diazoacetate is capable of addition across the 9:10- bond of phenanthrene. This result is in keeping with the well known ethylenic character of this bond. Both groups of workers have, however, shown that the resulting adduct, after hydrolysis, was not the dibenzocycloheptatriene carboxylic acid (LIII) but the alkali stable norcaradiene carboxylic acid (LII).

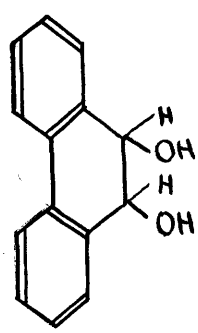


LII LIII

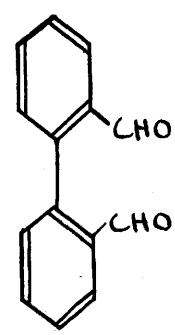
It is noteworthy that similar results have recently been obtained by Badger, Cook and Gibb[38] who have found that

diazoacetic ester is capable of forming alkali stable norcaradiene adducts with several other polycyclic aromatic hydrocarbons.

Still viewing the possibility of utilising the 9:10- double bond of phenanthrene, attention was turned to the work of Criegee, Marchand and Wannowius[39]. These authors found that their improved method for hydroxylating ethylenic double bonds was applicable to phenanthrene. The hydrocarbon was thus converted into cis-9:10-dihydro-9:10-dihydroxyphenanthrene (LIV). This process has been extended by Cook and Schoental[40] who have obtained similar diols from a number of polycyclic aromatic hydrocarbons. The German workers found that the diol from phenanthrene (LIV) underwent normal glycol fission by means of lead tetra-acetate with the formation of the dialdehyde (LV).



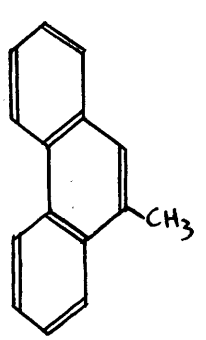
LIV



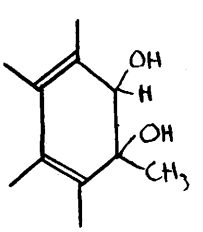
LV

Provided this process could be applied to 9-methylphenanthrene it would offer an elegant and flexible method of synthesising suitable diphenyl derivatives which could possibly be

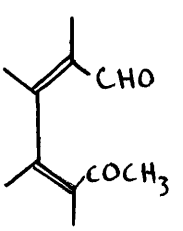
cyclised to the required type of compound. It was in fact shown by Buchanan, Cook, Loudon and MacMillan[22] that the diol (LVII) could be formed from 9-methylphenanthrene (LVI) by Criegee's method. The procedure consists in allowing the compound to be hydroxylated to react with osmium tetroxide in presence of pyridine and generally with benzene as solvent. Thereby the diol is gradually precipitated as a crystalline complex of the osmic ester with pyridine and is liberated by shaking the complex with mannitol in the presence of alkali. Cleavage of the diol was effected by means of lead tetra-acetate and the gummy product, presumably containing the keto-aldehyde (LVIII), on treatment with sodium hydroxide in methanol afforded the trienone (LIX). This product was identical with the compound prepared by the action of selenium dioxide on the parent dibenzocycloheptatriene (p.20).



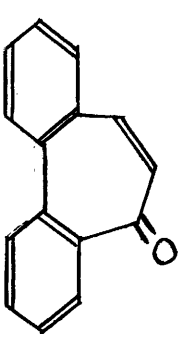
LVI



LVII



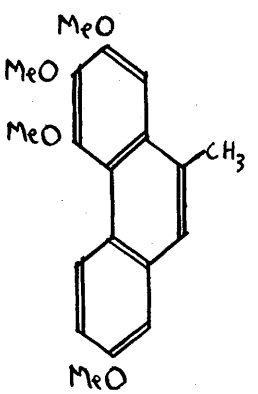
LVIII



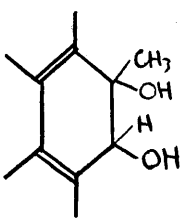
LIX

The yield of (LIX) from (LVIII), although somewhat variable,

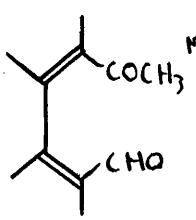
was occasionally very good and apparently warranted application of the same procedure to 2:3:4:7-tetramethoxy-10-methylphenanthrene (LX). The latter compound was



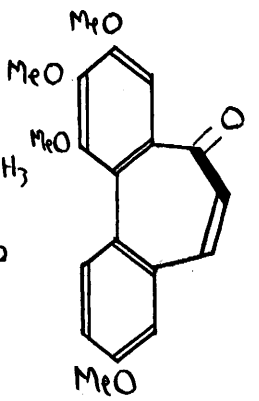
LX



LXI



LXII



LXIII

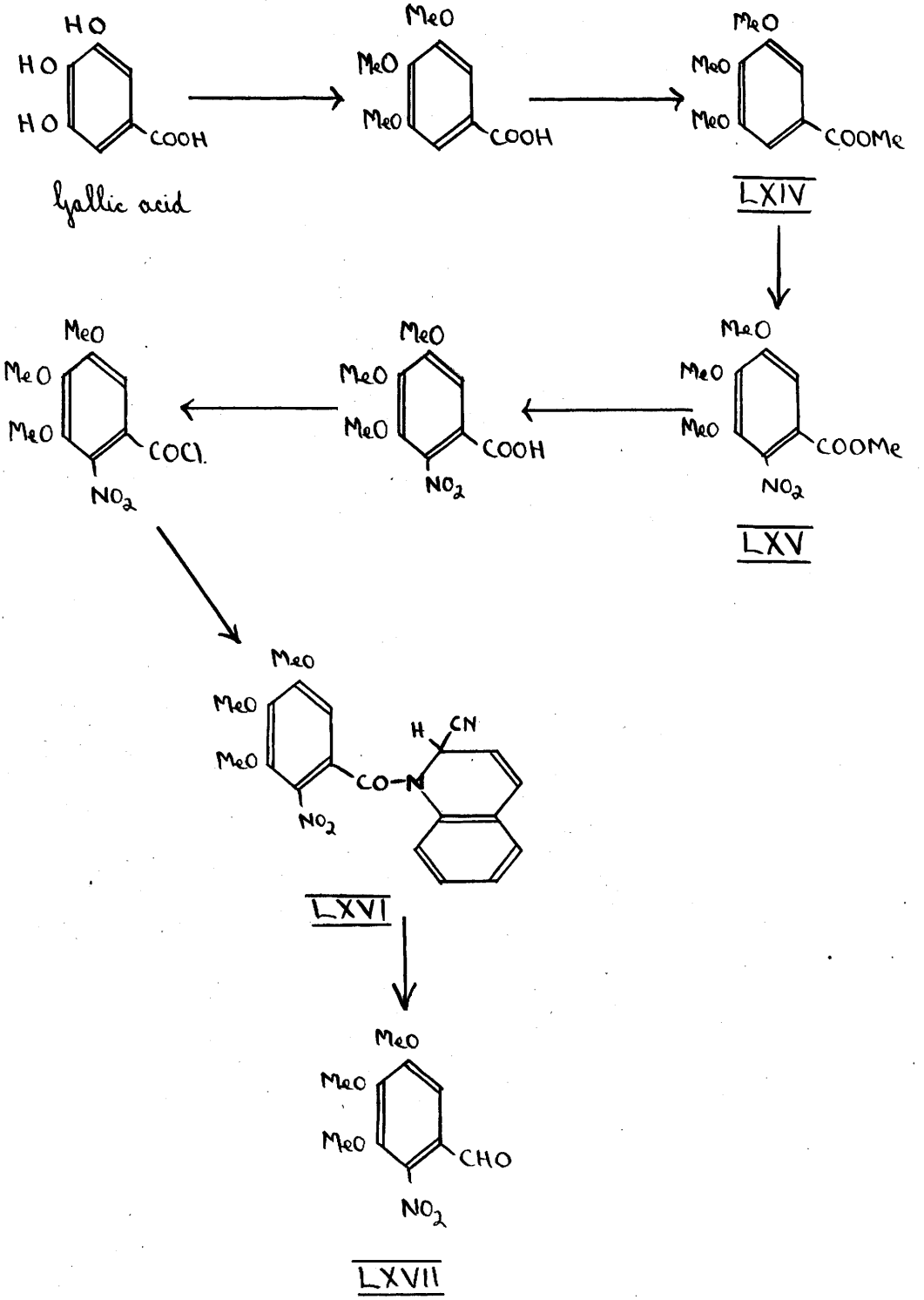
satisfactorily hydroxylated and the resulting diol (LXI) cleaved as before to give the keto-aldehyde (LXII) as a gum. Cyclisation, however, yielded a mixture of compounds which contained in addition to (LXIII), a large proportion of a high melting solid. While the precise nature of this solid was not ascertained, its properties indicated that it was a condensate formed ultimately from two moles of the intermediate (LXII) and therefore at the expense of the trienone (LXIII). The latter compound proved identical with the unsaturated ketonic by-product obtained from the chromic acid oxidation of deaminocolchinol methyl ether (p.13).

Despite the extremely poor yield of (LXIII) it was decided to investigate this method of approach to the synthesis of (XXVII). It was obvious that the critical cyclisation step would require to be re-examined and more favourable reaction conditions discovered before the method would prove of any value for the proposed synthesis.

DISCUSSION.

The requisite starting material, viz. 2:3:4:7-tetramethoxy-9-methylphenanthrene has been synthesised by Buchanan, Cook and Loudon[18]. Their method entails some sixteen stages from readily accessible materials but it has been shown (unpublished work of this department) that this method is at present the most practicable one. With the assistance of Mr. G. Doig it has been possible to accumulate some nine grams of the required material by this tedious and time consuming synthesis.

The initial stumbling block lies in the preparation of 2-nitro-3:4:5-trimethoxybenzaldehyde (LXVII) in adequate quantities. The inaccessibility of this compound has been noted by Cook and Graham[20] and has been subject of comment by various authors.[41] The route followed is shown overleaf in diagramatic form. Gallic acid was methylated by means of dimethylsulphate in alkali, followed by esterification to give methyl trimethylgallate (LXIV). The nitration of this ester to give methyl 2-nitro-3:4:5-trimethoxybenzoate (LXV) has been reported to give an 80% yield by Bogert[42] but Buchanan, Cook and Loudon[18] have been unable to obtain such a high yield, although many variations have been attempted. Bogert nitrated the ester, in acetic anhydride solution, with a mixture of concentrated nitric and

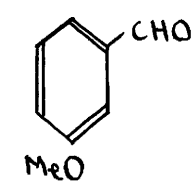

HO
HO
HO
COOH
gallic acid
MeO
MeO
MeO
COOH
MeO
MeO
MeO
COOMe
LXIV
MeO
MeO
MeO
COOMe
NO2
LXV
MeO
MeO
MeO
COOH
NO2
MeO
MeO
MeO
COCl
NO2
MeO
MeO
MeO
CO-N
H
CN
NO2
LXVI
MeO
MeO
MeO
CHO
NO2
LXVII

fuming nitric acids. Various interpretations of this nitrating mixture had been previously shown to give much poorer yields than recorded by Bogert. In the present work several variations have been applied but the yields never exceeded 35%. The following table summarises the nitration results.

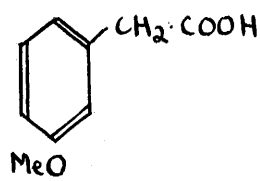
Ester media	Nitrating agent	Tempt.	% Yield
Acetic anhydride (1) Solution (2) Suspension	Fuming nitric acid (2.5 mols.)	In all cases 0-5°	30-35%
Suspension in acetic anhydride	Fuming nitric acid (1.5 mols.)		16%
Do.	Conc. nitric acid which had been distilled from conc. sulphuric acid		30-35%
Acetic anhydride (1) Solution (2) Suspension	Fuming nitric acid in acetic anhydride		

The nitro ester was then hydrolysed to the acid and converted to the acid chloride which gave the "Reissert compound" (LXVI) with anhydrous hydrogen cyanide and quinoline. Hydrolysis of (LXVI) by an improved method gave the required 2-nitro-3:4:5-trimethoxybenzaldehyde (LXVII).

The substituted phenylacetic acid (LXIX), required for a Pschorr type synthesis, was obtained as follows.



LXVIII

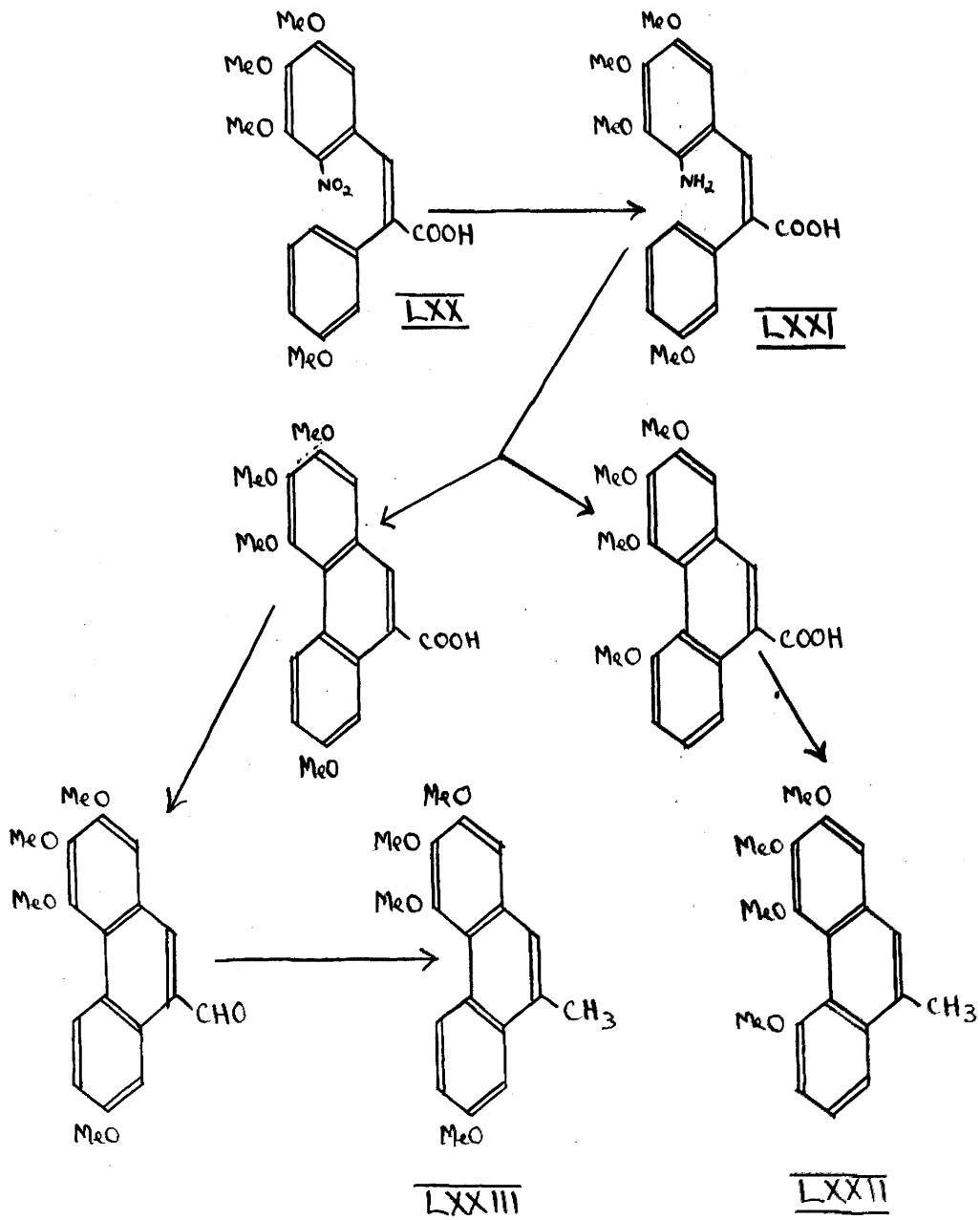


LXIX

m-Hydroxybenzaldehyde was methylated to give (LXVIII) which was converted to m-methoxyphenylacetic acid (LXIX) by means of Erlenmeyer's azlactone synthesis.

Condensation of (LXVII) and (LXIX) gave a mixture of stereoisomers (LXX) which was reduced, the cis-isomer yielding the amino-acid (LXXI), while the trans-isomer gave a carbostyril derivative which was separated by reason of its insolubility in aqueous sodium carbonate. Pschorr ring-closure of (LXXI) led to a mixture of 2:3:4:5- and

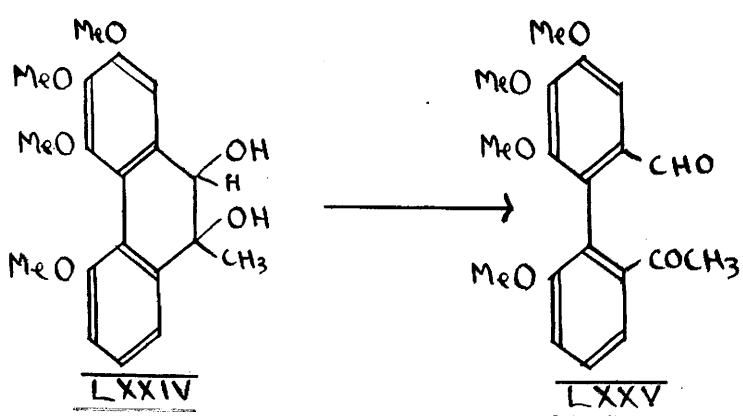
2:3:4:7- tetramethoxyphenanthrene-9-carboxylic acids which were separated by crystallisation. The acids were separately converted to the aldehydes by the method of McFadyen and Stevens i.e. via the methyl ester, hydrazide and benzenesulphonylhydrazide.



Kischner-Wolfe reduction in each case gave the isomeric 2:3:4:5- and 2:3:4:7- tetramethoxy-9-methylphenanthrenes (LXXII) and (LXXIII). In this series of reactions several additions and amendments were noted in respect of the former series of compounds as reported by Buchanan, Cook and Loudon.[18] These are recorded in the experimental section.

The ring enlargement of the 2:3:4:5-tetramethoxy -9-methylphenanthrene was studied first in order to obtain some experience and in an attempt to discover the optimum conditions for the cyclisation stage.

This methoxylated 9-methylphenanthrene (LXXII) reacted with osmium tetroxide and pyridine to give a benzene insoluble osmium-pyridine complex which was hydrolysed by means of potassium hydroxide and mannitol to yield the cis-diol (LXXIV). The latter compound when treated with lead tetra-acetate in benzene solution at room temperature afforded a crystalline product which was not immediately recognised as the keto-aldehyde (LXXV).



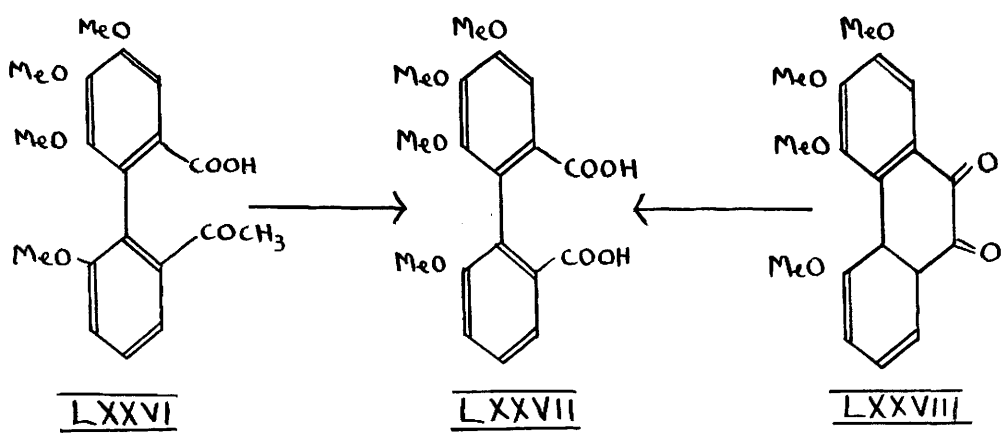
LXXIV LXXV

Its identity came into question partly because of misleading analytical data but mainly on account of its remarkable chemical stability. The scission product however formed a red 2:4-dinitrophenylhydrazone and a dioxime which was analysed. A positive Schiff test indicated the presence of an aldehydo group. When the process of cleavage was carried out in boiling benzene solution and the resulting product was distilled in vacuo the same compound as obtained in the cold was isolated. This remarkable stability is in sharp contrast to the ease of cyclisation displayed by the scission products of certain cyclohexane diols. These have been shown[43,44] to undergo cyclisation to the corresponding cyclopentene derivatives when submitted to the above treatment.

In a preliminary attempt at cyclisation the cleavage product was recovered unchanged after remaining for forty hours dissolved in a half saturated solution of dry hydrochloric acid gas in dry ether. Recovery of the keto-aldehyde was again effected after refluxing its solution in acetic anhydride with or without the addition of anhydrous sodium acetate. It was therefore thought advisable to seek confirmation of the keto-aldehyde structure assigned to the crystalline cleavage product of the diol (LXXIV).

Oxidation of the scission product by means of

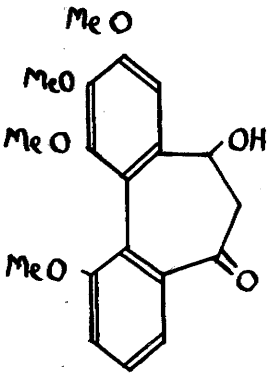
sodium dichromate in acetic acid led to the recovery of most of the starting material. A very small amount of acidic material was isolated but there was no evidence of phenanthraquinone formation. The latter result excludes any tricyclic structure for the scission product. The same acid as obtained above was more conveniently formed by oxidation with potassium permanganate in acetone at room temperature. This acid exhibited ketonic reactions e.g. formed a yellow 2:4-dinitrophenylhydrazone. The further oxidation of this keto-acid (LXXVI) by means of potassium hypobromite resulted in an acid which was identical with the diphenic acid (LXXVII), prepared for comparison purposes by hydrogen peroxide oxidation of the corresponding 2:3:4:5-tetramethoxyphenanthraquinone (LXXVIII). The keto-aldehyde structure (LXXV) for the product obtained by lead tetra-acetate cleavage of the diol (LXXIV) is therefore established as a result of the above graded oxidation experiments.



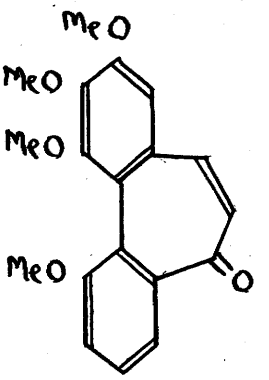
LXXVI LXXVII LXXVIII

When the phenanthraquinone (LXXVIII) was first prepared by dichromate oxidation of 2:3:4:5-tetramethoxy-9-phenanthroic acid[19] it was accompanied by an acidic by-product which from its analysis was presumed to be the diphenic acid (LXXVII). The presence of this acidic by-product of m.p. 216° has now been confirmed during the present work. But it has now been shown that this by-product is not identical with the true diphenic acid (LXXVII) of m.p. 249° now obtained by hydrogen peroxide oxidation of the phenanthraquinone (LXXVIII). Barton[45] found an analogous state of affairs in the related 2:3:4:7-tetramethoxy series of compounds. At present the structures of these acidic by-products remain unknown.

The crystalline keto-aldehyde (LXXV) facilitated a closer examination of the cyclisation stage. When treated with sodium hydroxide in methanol it afforded some high melting insoluble material together with a colourless product which from its analysis and oxidation to 2:3:4:5-tetramethoxyphenanthraquinone (LXXVIII) was regarded as the hydroxy-ketone (LXXIX).



LXXIX



LXXX

During the chromatographic separation of (LXXIX) the presence of a third substance was indicated by a small yellow band which fluoresced when observed under ultra-violet light. This new substance was probably the trienone (LXXX) but it was not obtained in sufficient quantity to allow its isolation in a solid state. Recently a similar type of condensation, although not intra-molecular, between 9-phenanthraldehyde and aqueous acetone in the presence of dilute sodium hydroxide has been shown to yield a mixture of three analogous products[46]. The hydroxy-ketone (LXXIX) was the sole product obtained by heating the keto-aldehyde with pyridine containing a few drops of piperidine i.e. the Doebner-Knoevenagel

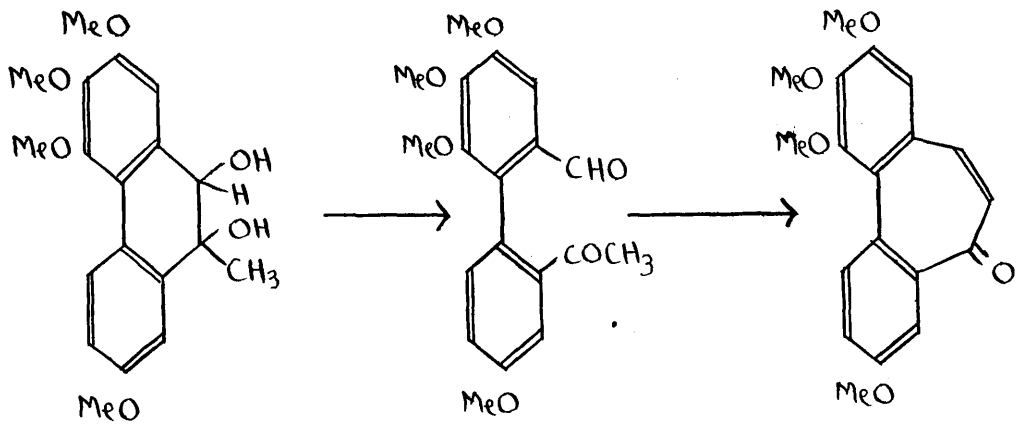
reaction. An attempt to prepare the diacetate of the keto-aldehyde (LXXV) resulted in an uncrystallisable gum which however on hydrolysis with dilute hydrochloric acid afforded the hydroxy-ketone (LXXIX).

When the hydroxy-ketone (LXXIX) was treated with acetic anhydride in pyridine a gum resulted which on distillation afforded the trienone (LXXX). The latter, although still accompanied by some of the hydroxy-ketone was best prepared by dissolving the keto-aldehyde (LXXV) in acetic acid saturated with hydrogen chloride. When the above acetic-hydrochloric acid method was applied to the gummy scission product of the diol (LXI) the trienone (LXIII) resulted in very good yield. In this case no hydroxy-ketone corresponding to (LXXIX) was encountered. The absence of high melting (dimeric) materials by this acetic-hydrochloric technique suggests that the resulting trienones are prevented from further condensation by oxonium salt formation. This proposal receives experimental support as the reaction solution is dark red in colour indicating oxonium salt formation.

It may conveniently be recorded here that the use of sodium methoxide as a condensing agent for the cyclisation of (LXII) results in the formation of the trienone (LXIII) in moderate yield. The latter method

however is inferior to the acid catalysed method. In view of the discovery of suitable cyclisation conditions the extension of this ring enlargement process to 2:3:4:7-tetramethoxy-9-methylphenanthrene was now undertaken.

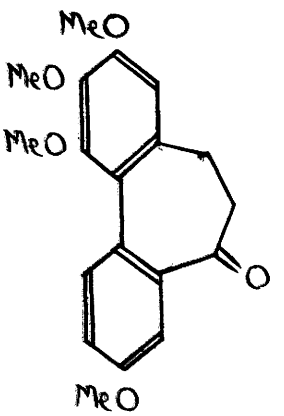
In striking contrast to the other 9- or 10-methylphenanthrenes investigated, the above mentioned isomer failed to form an insoluble precipitate when treated with osmium tetroxide in benzene-pyridine. In other respects, however, the reaction appeared to proceed normally and after a suitable interval the addition of pure n-hexane afforded an osmic ester from which the diol (LXXXI) was obtained without difficulty.



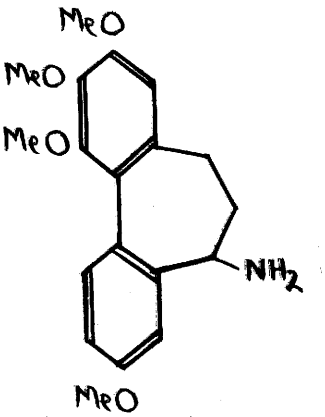
LXXXI LXXXII LXXXIII

Cleavage of (LXXXI) with lead tetra-acetate resulted in a gummy keto-aldehyde (LXXXII) which was characterised by the formation of a dioxime. A preliminary attempt to cyclise this keto-aldehyde with alkali gave only a high

melting solid which was not investigated. Cyclisation was effected by the acetic-hydrochloric method. The resulting trienone (LXXXIII) was isolated in good yield by means of chromatography. This substance was obtained as a yellow gum which only crystallised slowly on standing. Hydrogenation of the gummy trienone (LXXXIII) by means of a palladium on charcoal catalyst afforded the dienone (LXXXIV). This method of reduction was first found to



LXXXIV



LXXXV

be successful in the 2:3:4:5-tetramethoxy series, the trienone (LXXX) being smoothly hydrogenated to the corresponding saturated ketone. The overall yield of (LXXXIV) from 2:3:4:7-tetramethoxy-9-methylphenanthrene was ca. 60%.

The oxime of (LXXXIV) was readily formed by the usual hydroxylamine hydrochloride - sodium acetate method.

The reduction of this oxime to the corresponding amine proved particularly troublesome. Hydrogenation at atmospheric pressure in the presence of active Adam's catalyst, using methanol or methanol containing hydrogen chloride as solvent, only resulted in recovery of the oxime unchanged. When hydrogenation was attempted using the same catalyst but employing a mixture of acetic acid and acetic anhydride as solvent only a small amount of a non-basic material was isolated. This substance was probably the acetate of the starting oxime c.f.[47]. It was therefore found necessary to resort to more drastic hydrogenation conditions. The use of Raney Nickel at 65-75 atmospheres pressure and at 80-90° was found to result in the smooth reduction of the oxime to the amine (LXXXV). This amine and its immediate derivatives were, of course, optically inactive and the melting points found for them differed markedly from those of the optically active forms which are obtained by degradation of colchicine. Therefore, in order to establish the identity of the synthetic and degradation products it was necessary to resolve the former.

On account of the highly competitive nature of this work a preliminary note of the synthesis of the (±) amine was published[48]. Almost simultaneously with this

Rapoport, Williams and Cisney[49], in a communication to the editor of the Journal of American Chemical Society, announced an alternative synthesis of the same (±) amine. The N-acetyl derivative of the latter was shown to be identical with a specimen of (±) N-acetylcolchinol methyl ether. The racemisation was accomplished by heating the N-benzylidene derivative of colchinol methyl ether with methanolic benzyltrimethylammonium hydroxide. The ultra-violet and infra-red absorption spectra of the synthetic and degradation products were also shown to be identical.

This American work converged with the method described here at the dienone stage (LXXXIV). The melting behaviour of the latter compound and its oxime are in fair agreement with that found in the present work. In passing it may be noted that the American workers also appeared to experience difficulty in reducing the oxime of (LXXXIV) as shown by a recent full account of their work[50]. There the hydrogenation is described using a mixture of Adam's catalyst and palladium on charcoal under pressure. The reaction took four days to complete and then only a 39% yield was obtained. The resulting amine was not isolated but converted to the N-acetyl derivative. Again a corresponding melting point is noted.

Meanwhile the resolution of the (±) amine was being investigated. The latter bears some slight structural resemblance to α-phenylpropylamine which has been successfully resolved into its two optically active forms by means of (-)-malic and (+)-tartaric acids[51]. The synthetic (±) amine formed a crystalline salt with (-)-malic acid. After repeated crystallisation from various solvents no sign of resolution could be detected when the salt was decomposed and the recovered amine examined polarimetrically. Two distinct types of crystalline form were observed on crystallisation of this malate from methanol but these proved to be dimorphic forms which could be inter-converted by further crystallisation. Neither form afforded an optically active amine on decomposition. Likewise the crystalline salt obtained with (+)-tartaric acid could not be resolved by repeated crystallisation from the usual solvents.

Both (+)-α-bromocamphor-π-sulphonic and (+)-camphor-10-sulphonic acids failed to give crystalline salts with the synthetic amine, only gums being obtained in each case. Using the "half neutralisation" method of Pope and Peachy[52] (c.f. Pope and Rich[53]) both acids still afforded gummy salts. The gummy bromo-camphor sulphonate obtained by this method showed slight signs of resolution when fractionally precipitated, as the recovered amine

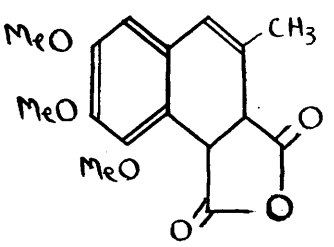
exhibited a very small positive rotation in chloroform solution. This method however was not practicable and was abandoned.

In view of the successful resolution of α-phenylethylamine by means of the (+) and (-) forms of 6,6'-dinitrodiphenic acid[54] and also the ready resolution of various alkaloids[55,56] it was decided to investigate its use in this instance. In the above successful applications of this reagent it has been found that both optically active forms of the bases could be obtained by the successive use of both enantiomorphic forms of the dinitrodiphenic acid. The drawback, however, lies in the inaccessibility of this resolving agent. A quantity of the (±)-acid was placed at the author's disposal. The resolution of this acid by means of brucine, as first described by Christie and Kenner[57], is not practicable when a supply of both enantiomorphs is required. However, Ingersoll and Little[54] have shown that both forms of dinitrodiphenic acid can be obtained in quantity by resolution with (+)- and (-)- α-phenylethylamine. The latter enantiomorphs are in turn obtained by resolution of the (±)-α-phenylethylamine with (-)-malic and (+)-tartaric acids[58].

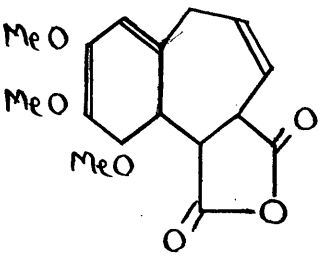
Properties favourable to the resolution of the synthetic amine (LXXXV) were found in its salt with (+)-6,6'-dinitrodiphenic acid. When this (+)-acid was combined with the (±)-amine (LXXXV) and the resulting acid salt was crystallised several times from methanol (-)-colchinol methyl ether (+)-6,6'-dinitrodiphenate was obtained. By direct comparison of melting points and optical rotations it was shown that the recovered (-)-amine, its salts and N-acetyl derivative were respectively identical with colchinol methyl ether, its salts and N-acetylcolchinol methyl ether as prepared from colchicine. Thus colchinol methyl ether is proved to possess the structure (LXXXV).

It may be noted that Rapoport, Williams and Cisney[50] failed to effect the resolution of the synthetic (±)-colchinol methyl ether although they also observed that (-)-malic and (+)-tartaric acids formed crystalline salts with the (±)-base. The same authors also failed to obtain crystalline derivatives with the two camphor sulphonic acids tried during the present work. A fifth acid, (+)-mandelic acid, was used by the American workers but again no crystalline salt could be obtained.

The question of whether colchicine itself has a central seven membered ring now arises. From the present proof of the seven membered ring B in colchinol methyl ether and the recent work of Cook, Johnston and Loudon[59] it would appear that colchicine also has ring B in seven membered form. The latter authors have shown conclusively that the compounds obtained by Windaus on oxidising N-benzoyltrimethylcolchicinic acid with potassium permanganate were not hydronaphthalene derivatives as he supposed (p.4). In particular it was shown that deamino-colchicinic anhydride, which becomes (LXXXVI) on the Windaus formulation, is not identical with synthetic 6:7:8-trimethoxy-3-methylnaphthalene-1:2-dicarboxylic acid anhydride (LXXXVI) and, therefore, like the colchinol series of degradation products, probably contains the seven membered ring B i.e. (LXXXVII). This conclusion has recently been substantiated by the synthesis of the dihydride of (LXXXVII) which was found to be identical with dihydrodeaminocolchicinic anhydride[60].



LXXXVI



LXXXVII

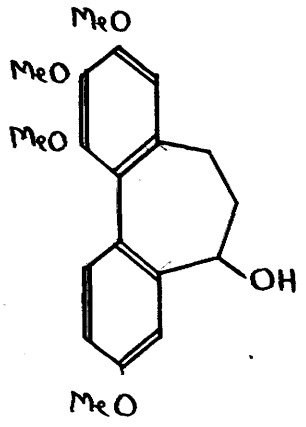
There is consequently good reason to believe that the seven membered ring B, now firmly established for both the colchinol and the colchicinic series of degradation products, also occurs in colchicine itself.

PART III.

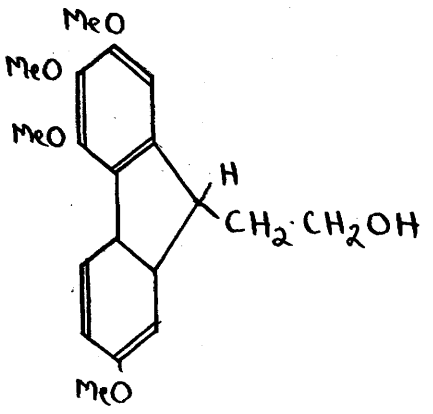
THE STRUCTURE OF THE CARBONOL FROM COLCHINOL METHYL ETHER.

It will be recalled that Cohen, Cook and Roe[16] obtained a laevoratory carbinol by the action of nitrous acid on colchinol methyl ether. Attempted dehydrogenation of this carbinol (A) by heating with isoamyl disulphide at 210° afforded a higher melting isomeric carbinol (B). The latter compound also appeared to accompany A when the nitrous acid reaction was heated for some time before working up the product. Since colchinol methyl ether has now been shown to have the structure (LXXXV), the resulting carbinol would be expected to possess the structure (LXXXVIII) provided the reaction were a simple replacement of the amino group by a hydroxyl group. The structure (LXXXVIII) for the degradation carbinol has, however, been the subject of criticism by Horning and Ullyot and their colleagues[61]. These authors have pointed out that the compound (LXXXVIII) should exhibit a similar ultra-violet absorption to that of dihydrodeaminocolchinol methyl ether whereas the carbinol (A) differed considerably in this respect. This reasonable suggestion followed from their observation that dihydrodeaminocolchinol methyl ether, colchinol methyl ether and its N-acetyl derivative all possessed very similar absorption curves, the amino and acetylamino groups having practically no effect on the ultra-violet absorption. No alternative structure was proposed for the carbinol (A) but it was shown that the

fluorene derivative (LXXXIX) possessed ultra-violet absorption characteristics resembling (A).



LXXXVIII

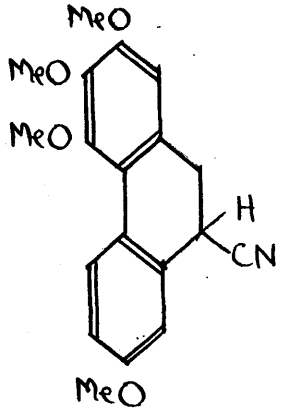


LXXXIX

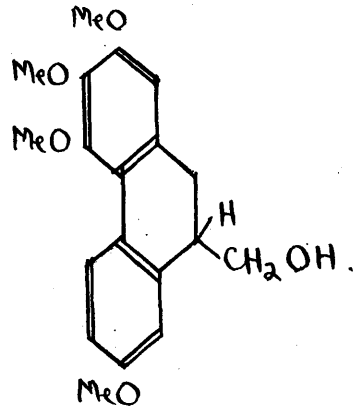
The alcohol (LXXXVIII) has now been synthesised by lithium aluminium hydride reduction of the corresponding ketone (LXXXIV). The synthetic, optically inactive, carbinol could not be directly compared with carbinol (A) and as the quantity available was small (ca. 100 mgms.) resolution was out of the question. Two tests, however, served to demonstrate that this synthetic product did not possess the same structure as the degradation carbinol. Firstly, the synthetic alcohol dissolved in concentrated sulphuric acid to give a red coloured solution whereas the degradation product afforded an apple-green coloured sulphuric acid solution. Secondly, the ultra-violet absorption spectrum of (LXXXVIII) was found to differ

markedly from the degradation carbinol (A). However, it was found that the absorption curve of the former compound closely resembles that of dihydrodeaminocolchinol methyl ether as predicted by the American workers.[61] The appropriate curves are shown on the accompanying graph. From these results it may now be concluded that the carbinol obtained by degradation of colchicine does not possess the seven membered ring B found in the colchinol series.

For comparison purposes the isomeric dihydrophenanthryl carbinol (XCI) has been prepared. For this purpose a small quantity of the cyano compound (XC) was



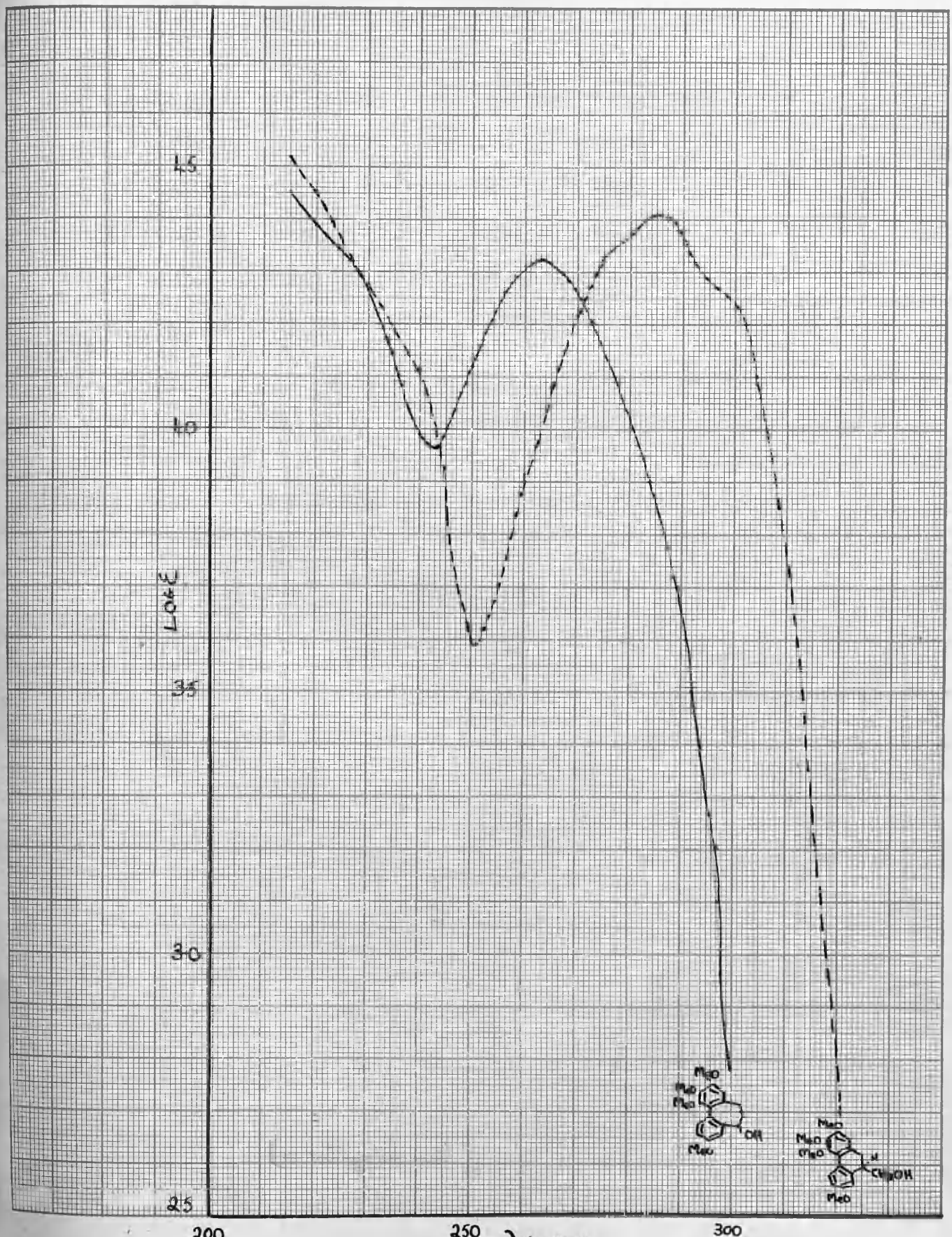
XC



XCI

available*. Prolonged hydrolysis of the latter compound afforded the corresponding acid, although some of the intermediate amide was isolated after extraction of the acid. The methyl ester of the above acid was smoothly

* J., 1949, 1044.


4.5
4.0
3.5
3.0
2.5
Log ε
200
250
300
λ in mμ.

reduced to the carbinol (XCI) by means of lithium aluminium hydride. Again, an optically inactive carbinol of higher melting point than the carbinol (A) was obtained. The striking coincidence in absorption characteristics of the two latter alcohols is illustrated by the following table. The absorption measurements of

Wavelength in mμ.		Carbinol A log. ε		(±) Carbinol (XCI) log. ε
300		4.225		4.22
295		4.27		4.27
290		4.34		4.34
286		4.39		4.39
285		4.40		4.40
284	Max.	4.40	Max.	4.40
283		4.39		4.39
282		4.385		4.39
280		4.365		4.36
270		4.215		4.22
265		4.09		4.08
260		3.91		3.91
255		3.71		3.70
252		3.62		3.62
251	Min.	3.61	Min.	3.60
250		3.615		3.61
249		3.63		3.63
240		4.10		4.11
230		4.27		4.28
220		4.45		4.45

both compounds were recorded on a modern "Unicam" quartz spectrophotometer. This may account for the absence of

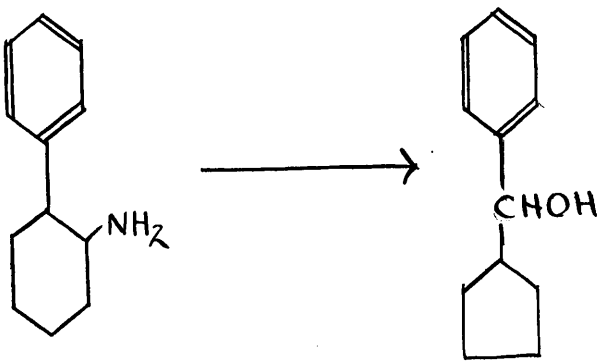
a slight inflexion at ca. 295 m.μ. reported originally for the carbinol (A) by Cohen, Cook and Roe[16], their measurements in 1940 presumably being recorded by a photographic method.

A further pointer to the equivalence of structure between (XCI) and the degradation carbinol was afforded by the action of concentrated sulphuric acid on these compounds. The synthetic alcohol dissolved in sulphuric acid to give an apple-green solution identical with that from carbinol (A). The isomeric carbinol (B) also afforded an apple-green coloured sulphuric acid solution. In all three cases this green colour changed to violet-purple on standing. Finally, the carbinol (B) was found to be identical with the synthetic (±)-carbinol (XCI), the melting behaviour being unaffected on mixing. A crude p-phenylbenzoate of m.p. 108-109° was originally obtained from (B) but a specimen of this was not available to carry out a mixed melting point determination with the p-phenylbenzoate of (XCI) obtained analytically pure and of m.p. 125°. Nevertheless comparison of the synthetic and (A) and (B) alcohols (see table overleaf) shows that a very close relationship exists between these three compounds and in particular shows that (B) is identical with the synthetic (±)-2:3:4:7-tetramethoxy-9:10-dihydro-

	Carbinol A	Carbinol B	Compound (XCI)	Compound (LXXXVIII)
m.p.	115-116°	157-160°	165-166°	148-150°
m.p. of p-phenyl-benzoyl derivative	146-147°	108-109°	125°	———
Optical activity	(-)	(±)	(±)	(±)
Colour with conc. H_2SO_4	apple-green	apple-green	apple-green	red
Absorption Spectrum	Max. 284 mμ. Min. 251 mμ. log ε = 4.4 and 3.6			Max. 263 mμ. Min. 242 mμ. log ε = 4.32 log ε = 3.96
Dehydration product	deamino-colchinol methyl ether	———	deamino-colchinol methyl ether	———
Mixed m.p. of carbinol B and carbinol (XCI) 164-166°				

9-phenanthyl carbinol (XCI). The carbinol (A) is regarded as the laevorotory form of the latter, (B) arising from (A) by racemisation during the attempted dehydrogenation. The action of nitrous acid on colchinol methyl ether therefore causes ring B to contract from seven to six membered form.

Demjanow[62] has stated that ring contraction may take place when an alicyclic amine reacts with nitrous acid, but examples in the literature appear mainly to be confined to contractions from four to three membered rings. Demjanow[63], himself, has described the reaction with cyclobutylamine and a group of German workers have shown[64] that cyclobutylamines derived from truxillic and truxinic acids also yield cyclopropane derivatives. Recently Nightingale and Maienthal[65] have shown that 2-phenylcyclohexylamine (XCII) reacts with nitrous acid to give phenylcyclopentyl carbinol (XCIII). This result is in contrast



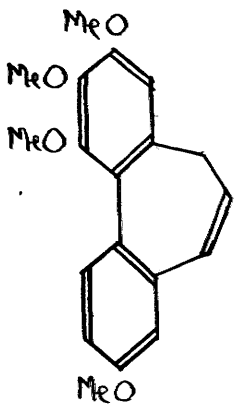
XCII XCIII

to the findings of several authors who have shown that cis-[66] and trans-[66,64] 2-methylcyclohexylamines, cyclohexylamine[64] and several amines derived from monocyclic terpenes[64] all react with nitrous acid without ring contraction occurring. The present example is therefore not unprecedented. The reaction may conveniently be termed the "reversed" Demjanow reaction.

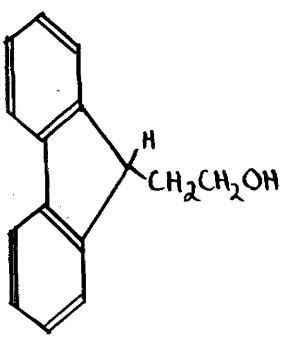
The carbinol (A) obtained from colchicine was shown to undergo dehydration with the production of deaminocolchinol methyl ether[19]. The latter product has been firmly established as the seven membered ring B structure (XVI)[19] and therefore dehydration of the carbinol (A) must be accompanied by ring enlargement. The behaviour of the synthetic (±)-carbinol (XCI) under the dehydration conditions parallels that of the carbinol (A) . The resulting gummy mixture of deaminocolchinol methyl ether and its iso-compound did not readily crystallise but hydrogenation over palladium on charcoal afforded dihydrodeaminocolchinol methyl ether. Ring contraction therefore occurs when nitrous acid reacts with colchinol methyl ether and the resulting carbinol is ring enlarged on dehydration with phosphorus pentoxide in xylene.

It may be noted here that the fluorene compound (LXXXIX) which Horning and Ullyot[61] showed to have a very

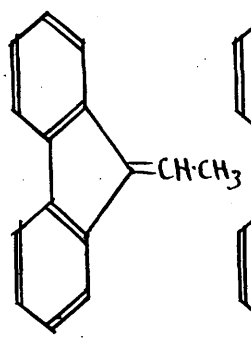
similar ultra-violet absorption spectrum to the carbinol (A) is not likely to undergo dehydration with the production of deaminocolchinol methyl ether. This follows from some recent work[68] in which the corresponding unmethoxylated fluorine derivative (XCIV) was found to lose the elements of water with the production of ethylidene-fluorene (XCV).



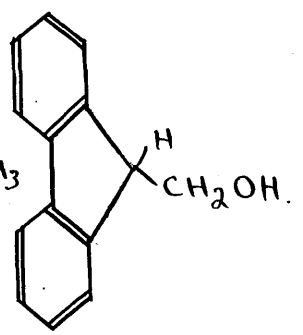
XVI



XCIV



XCV

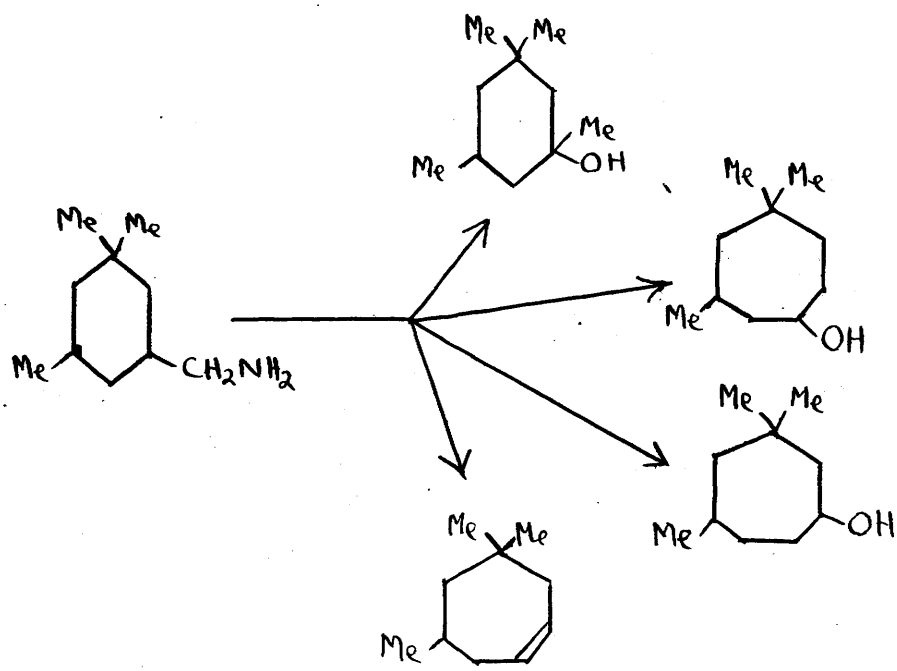


XCVI

The ring enlargement of the carbinol (XCI) is analogous to the formation of phenanthrene and 2:7-dibromophenanthrene by the reaction of phosphorus pentoxide in xylene on (XCVI)[69] and its 2:7-dibromo derivative[70] respectively.

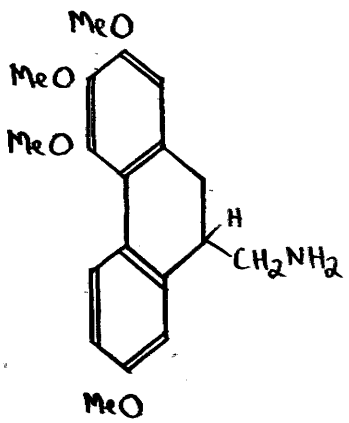
A reaction very similar in character to the above ring enlargement has also been investigated as an alternative route to dibenzocycloheptane derivatives. The

reaction, which is here termed the "direct" Demjanow reaction, involves the transformation, by the action of nitrous acid on an alicyclic methylamine, of a ring system into one with one more carbon atom. Thus C-cyclopentyl-methylamine on treatment with nitrous acid gives cyclo-hexanol[71]. By this reaction several bicyclodecane derivatives, required as intermediate in the synthesis of azulenes, have been prepared[72,73]. The complexity of the reaction mixture may be illustrated by the following example taken from the work of Babier[74].

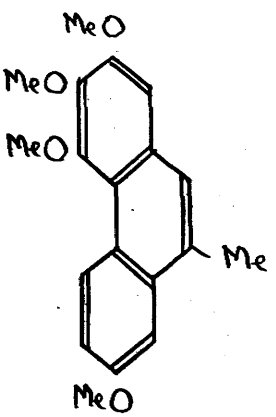


In the present investigation the amine (XCVII), obtained by hydrogenation of the cyano compound (XC) with the aid of Adam's catalyst, was treated with nitrous acid at 100°. From the resulting dark coloured gum three

products were isolated by the aid of chromotography. Firstly, a small amount of 2:3:4:7-tetramethoxy-9-methyl-phenanthrene (LXXIII) was obtained and identified by comparison with an authentic specimen. A later fraction



XCVII

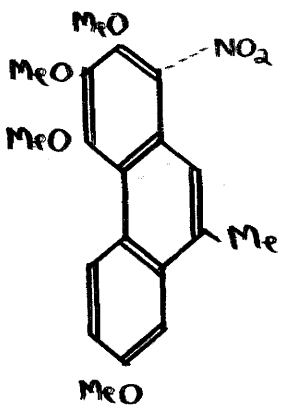


LXXIII

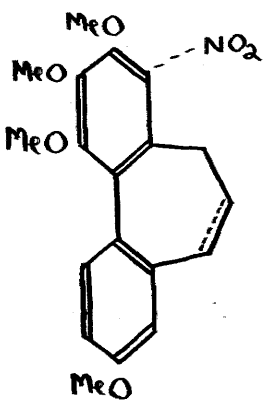
from the chromotogram yielded a gum which was ultimately obtained crystalline and proved to be identical with deaminocolchinol methyl ether. Iso-deaminocolchinol methyl ether may also have been present in the reaction mixture but was not isolated. A small amount of a third, yellow crystalline, product was also isolated. However, no evidence of alcolholic products could be found, the reaction gum having failed to form a p-phenylbenzoate. Several fractions, over and above the three already described, were obtained from the chromotogram but all proved to be intractable. The use of the Demjanow

for the synthesis of dibenzocycloheptane derivatives is therefore vastly inferior to the method employed for the synthesis of colchinol methyl ether.

The yellow by-product obtained during the above ring-enlargement analysed for the substance $C_{19}H_{19}O_6N$. These figures correspond to either a nitro derivative of a tetramethoxylated methylphenanthrene e.g. (XCIX) or a tetramethoxylated dibenzocycloheptatriene e.g. (C).



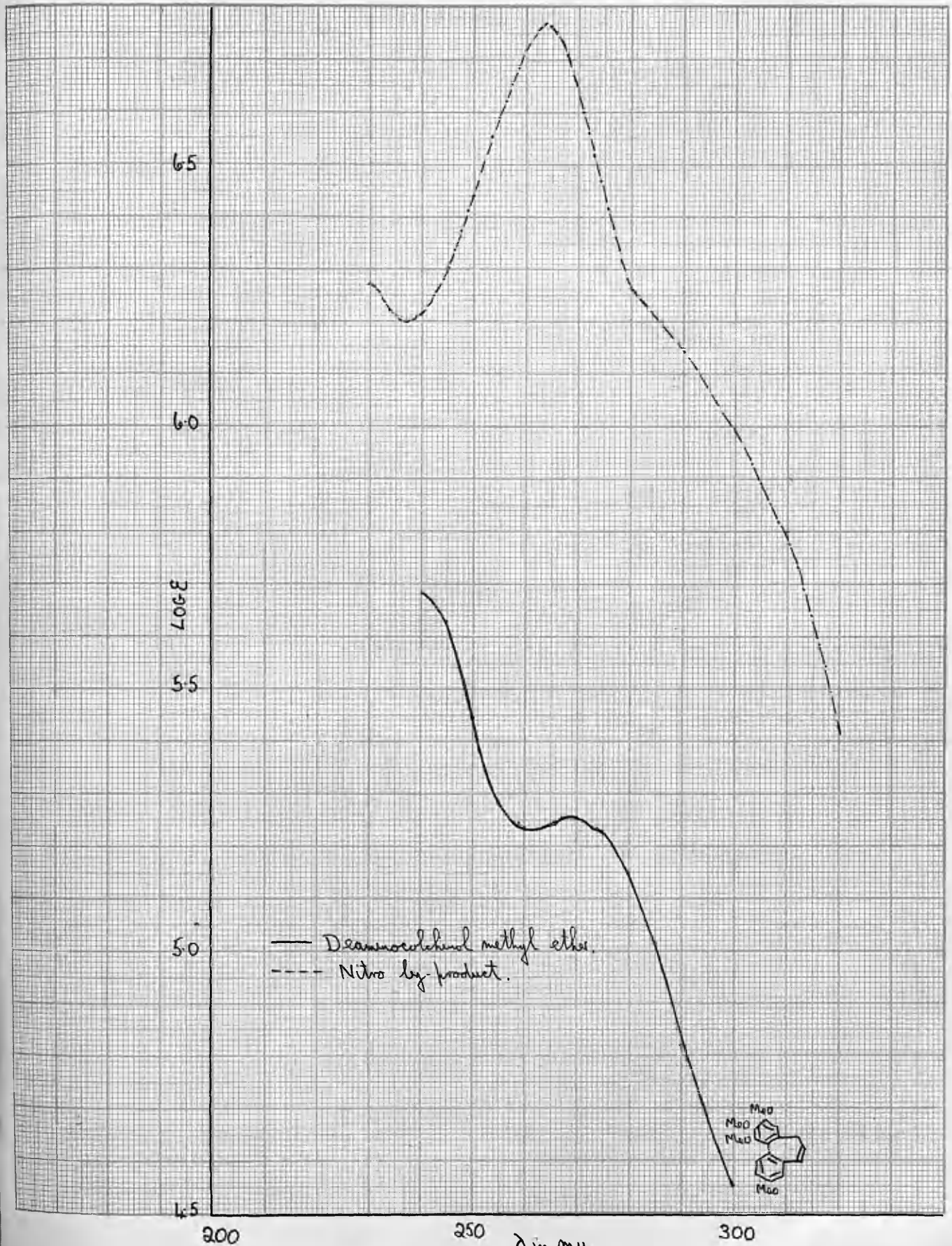
XCIX



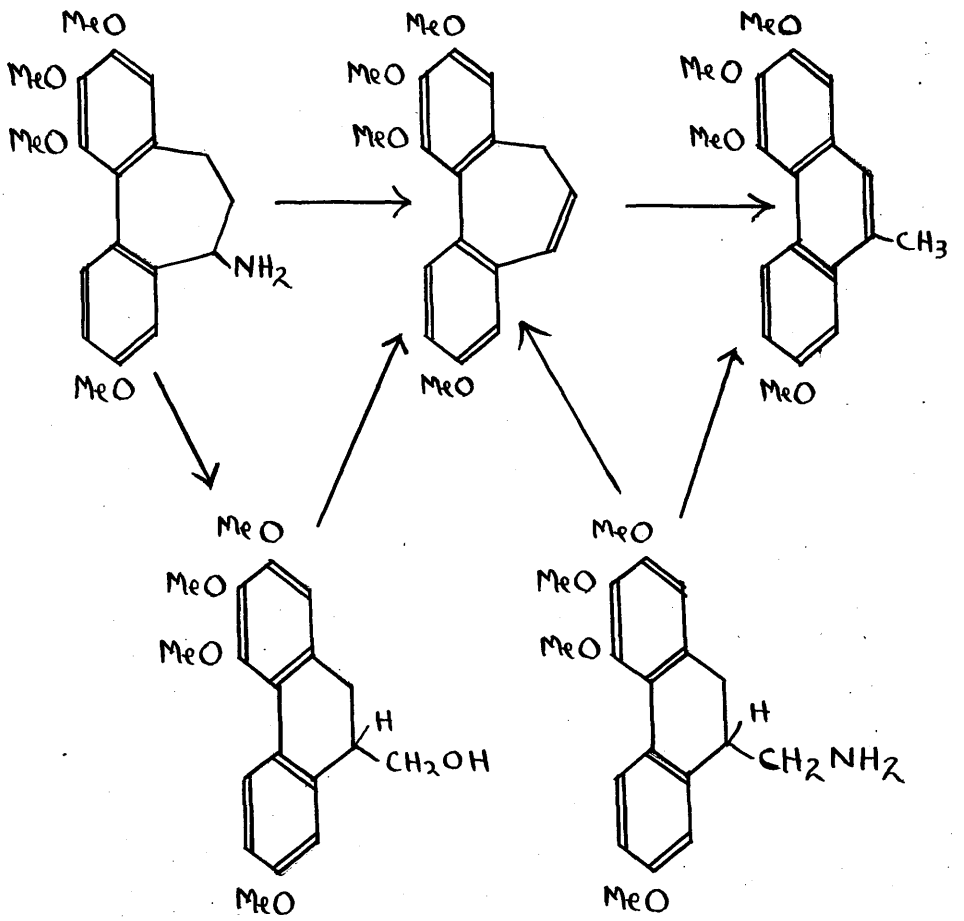
C

The absorption spectrum of this by-product is shown on the accompanying graph, from which it would appear that it is not a phenanthrene derivative. The absorption curve for deaminocolchinol methyl ether has been measured for comparison purposes.

The structural changes brought to light in the investigations just described are summarised in the diagram


6·5
6·0
5·5
5·0
4·5
log ε
200
250
300
λ in mμ.
—— Deaminocolchinol methyl ether.
---- Nitro by-product.
MeO
MeO
MeO
MeO

below. They elucidate a minor problem and provide another instance of those molecular rearrangements by which the structural chemistry of colchicine is so frequently beset.



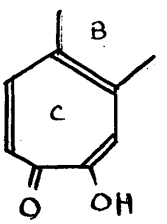
PART IV.

SOME PRELIMINARY EXPERIMENTS IN AN ATTEMPTED SYNTHESIS OF COLCHICINE

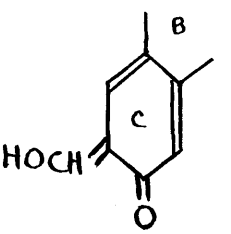
DISCUSSION

In this section it is proposed to give a brief summary of the structure of colchicine, with particular reference to ring C, before going on to consider a projected synthesis of the alkaloid.

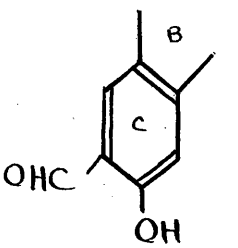
The tropolone concept for ring C of colchiceine (CI), proposed by Dewar[45], avoids the anomalous stability attributed to the hydroxy-methylene from (CII) over the more usual aromatic form (CIII). The structure of



CI

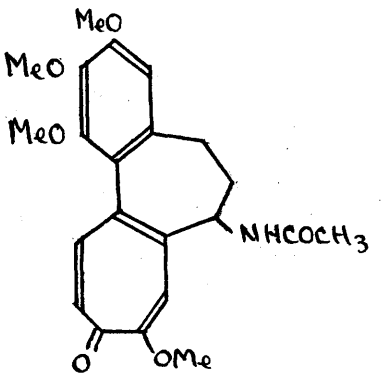


CII

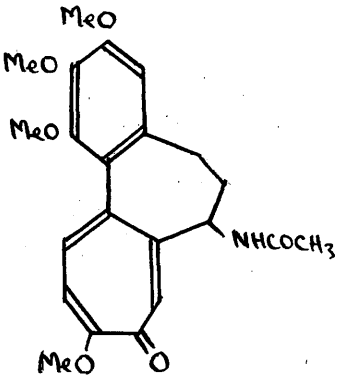


CIII

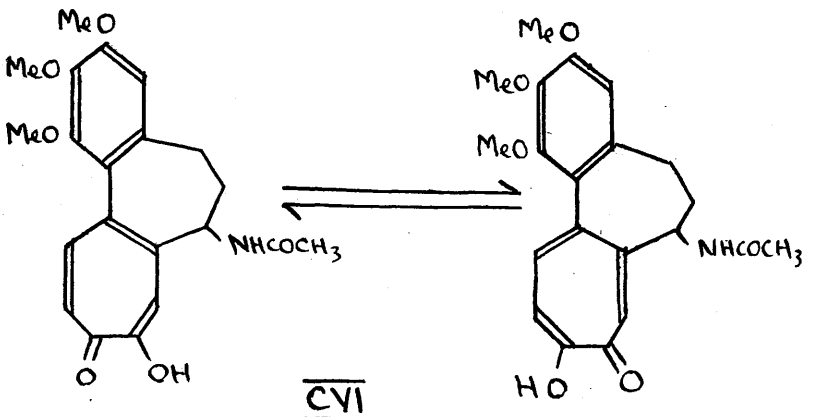
colchicine and iso-colchicine, both formed by methylation of colchiceine[46], accordingly became (CIV) and (CV), but not necessarily respective. Colchiceine is now represented by the tantomeric structure (CVI).



CIV



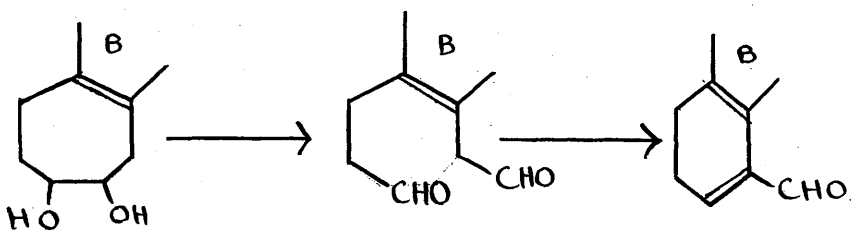
CV



CVI

Strong support for the above tropolone formulae for these products has been obtained by purely chemical and physical methods.

Hydrogenation of colchicine and colchiceine produces hexahydro-derivatives which retain one double bond as shown by the uptake of one atom of oxygen from perbenzoic[13] or monoperphthalic acids[44]. Hexa-hydro-colchiceine exhibits the properties of the expected $\alpha:\beta$-diol (CVII), showing evidence of cleavage with lead

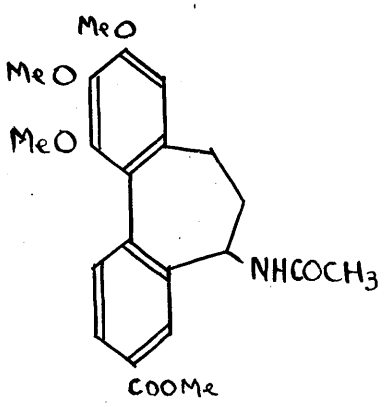


CVII CVIII CIX

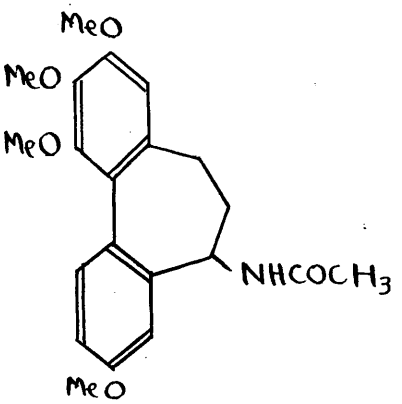
tetra-acetate or periodic acid. Although the scission products were not well defined, these from the latter reaction afforded an amorphous 2:4-dinitrophenylhydrazone which appeared to be derived from the mono-aldehyde (CIX), formed by internal condensation of the initial cleavage product (CVIII). Neither colchicine nor colchiceine display carbonyl activity but it is significant that tetrahydro-colchiceine, obtained by hydrogenating colchiceine under mild conditions, affords a 2:4-dinitrophenylhydrazone[44].

Recently strong support for the tropolone structure of colchicine has been obtained by comparison of its chemical reactivity with that of tropolone. Thus certain transformations of colchiceine to products of proven structure have been paralled by a rapidly increasing number of synthetic tropolone derivatives. Allo-colchicine, obtained by the action of sodium methoxide on

colchicine, has been shown to have the structure (CX). This was demonstrated by Fernholtz[48] who converted allo-colchicine by standard procedure into colchinol methyl



CX



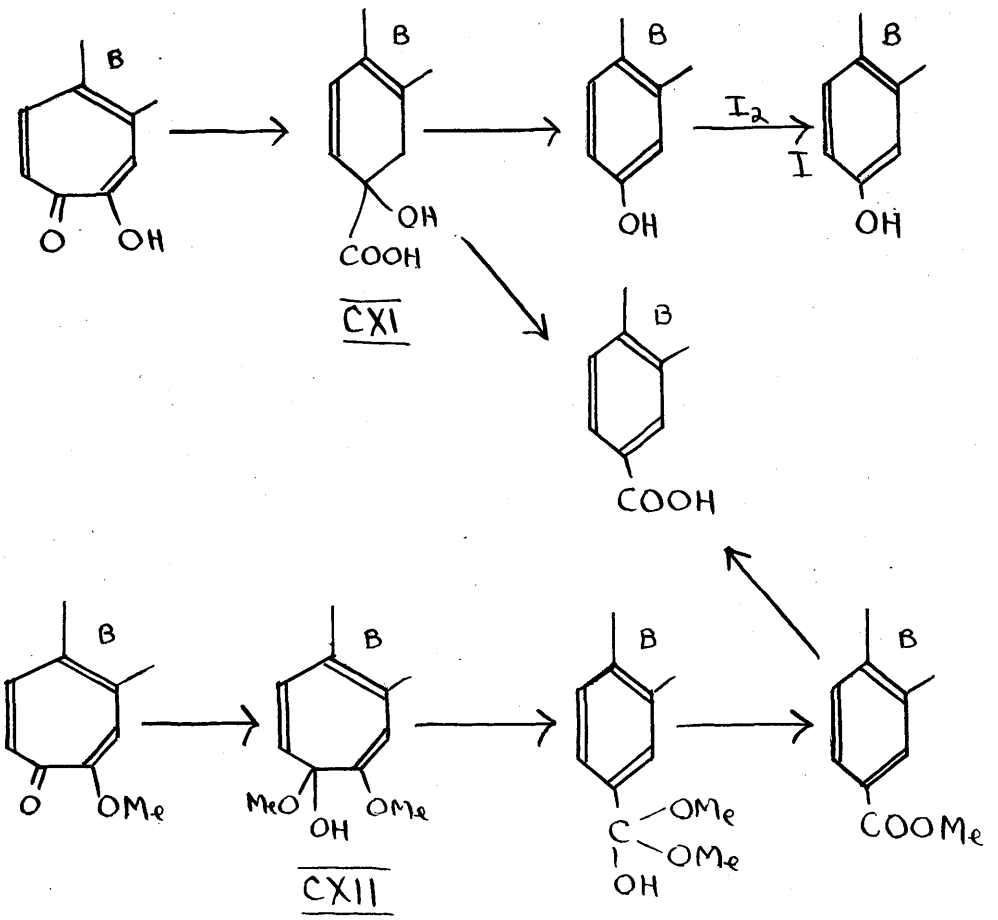
LXXXV

ether which has now been firmly established as (LXXXV). This type of transformation from tropolonoid to benzenoid form has been duplicated by tropolone methyl ether[49,80] and several of its halogen[80] and nitro[81] derivatives, substituted methyl benzoates resulting in all cases.

Again the production of N-acetyliodocolchinol from colchiceine finds a precedent in the ultimate conversion of tropolone into tri-iodophenol[79,80]. Thirdly, the fusion of colchiceine with alkali, followed by oxidation produces benzene 1:2:4-tricarboxylic acid[8]. This reaction finds an analogy in the production of benzoic acid from tropolone by sodium fusion[49,80].

These changes have been postulated[6] as occurring by a benzilic acid type of rearrangement, via the

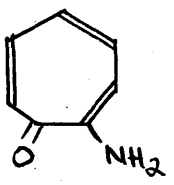
intermediates (CXI) and (CXII) as pictured below. The



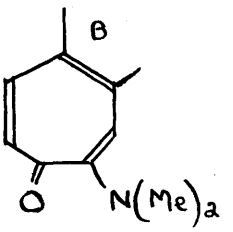
direct production of N-acetylcolchinol by alkaline hydrogen peroxide oxidation of colchiceine[82] could also occur through a benzilic acid rearrangement and oxidation of the intermediate (CXI).

Replacement of the methoxyl group in ring C of colchicine by ammonia and various amines[83] finds its counterpart in the tropolone series where 2-aminocyclo-

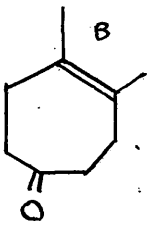
heptatrienone (CXIII) is formed by the reaction of tropolone methyl ether with ammonia[79]. Rapoport and Williams[84]



CXIII

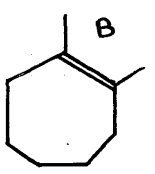


CXIV

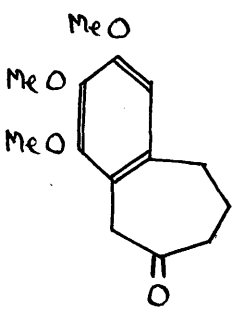


CXV

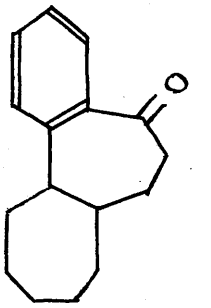
have recently hydrogenated the dimethylamino derivative of colchicine (CXIV) and obtained the ketone (CXV). Further reduction of (CXV) afforded the compound (CXVI). These findings have only been announced in a preliminary note wherein no evidence, other than analytical data, is proposed for the structures of these new degradation products of colchicine. The synthesis of the ketone



CXVI



CXVII



CXVIII

(CXVII) by the above authors[85] and also the synthesis of (CXVIII) by Gutsche[86], indicates possible routes to (CXVI)

or its dihydrodeamino derivative, also obtained by Rapoport and Williams[84].

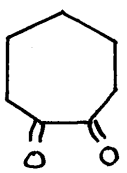
The physical chemist has added several contibutions in support of the topolone formula for colchicine. On the basis of polarographic[87] and infra-red[88] studies, close similarities have been observed between colchicine and several established tropolone compounds. Finally, Pepinski[89], using x-ray diffraction techniques, has very recently completed a Fourier analysis on colchicine. The resulting electron map shows that colchicine has the structure (CV) and consequently iso-colchicine is to be represented by (CIV). This work thus orientates the positions of the carbonyl and methoxyl groups in ring C.

In view of the strong evidence, admittedly indirect in character, which has accumulated in favour of the structure (CV) for colchicine, it seemed desirable to attempt its synthesis.

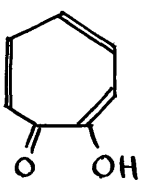
A short summary of the known methods for the synthesis of tropolone derivatives must necessary be presented here.

Essentially there are at present only two general methods of synthesising tropolone derivatives. The method of Cook et. al.[90,91] led to the first successful synthesis of

a tropolone derivative and has subsequently been used for the preparation of several topolones. The method consists of the dehydrogenation of a cycloheptane-1:2-dione. The dehydrogenation step has been carried out by means of a catalytic method but a bromination and dehydrobromination procedure has been shown to be more widely applicable. Thus tropolone (CXIX) itself has been synthesised by the bromination and dehydrobromination of cycloheptane-1:2-dione (CXX). The required diones can be satisfactorily



CXX

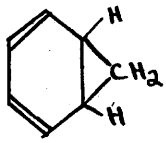


CXIX

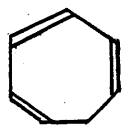
prepared by selenium dioxide oxidation of the corresponding ketones which are in turn obtained by ring enlargement of the appropriate cyclohexanone derivatives by means of diazomethane.

The second method is due to Doering and Knox[49] who found that benzene could be caused to react with diazomethane when irradiated with ultra-violet light. The resulting compound was either cycloheptatriene (CXXI) or

the norcaradiene (CXXII). When this compound was

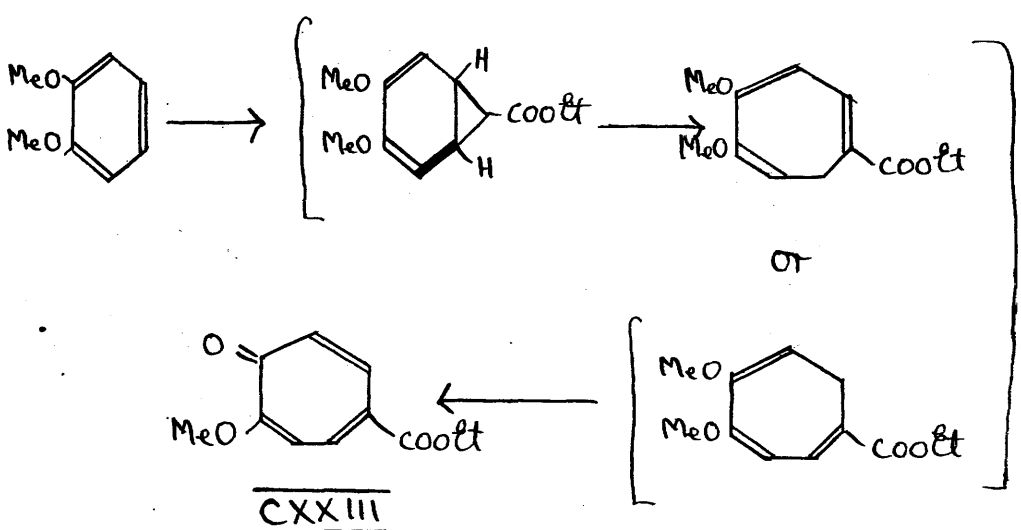


CXXII



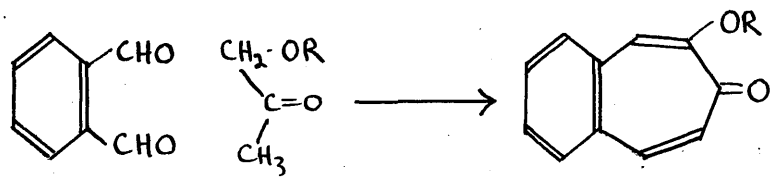
CXXI

oxidised with aqueous permanganate tropolone was formed in very low yield (ca. 1%). This method is obviously not a practicable route to tropolone compounds but a reaction very similar in character has been successfully used by Bartiels-Keith and Johnson[92]. These authors reacted veratrole with diozoacetic ester and by a bromination-dehydrobromination procedure obtained the tropolone-carboxylic ester (CXXIII) from the resulting adduct.



CXXIII

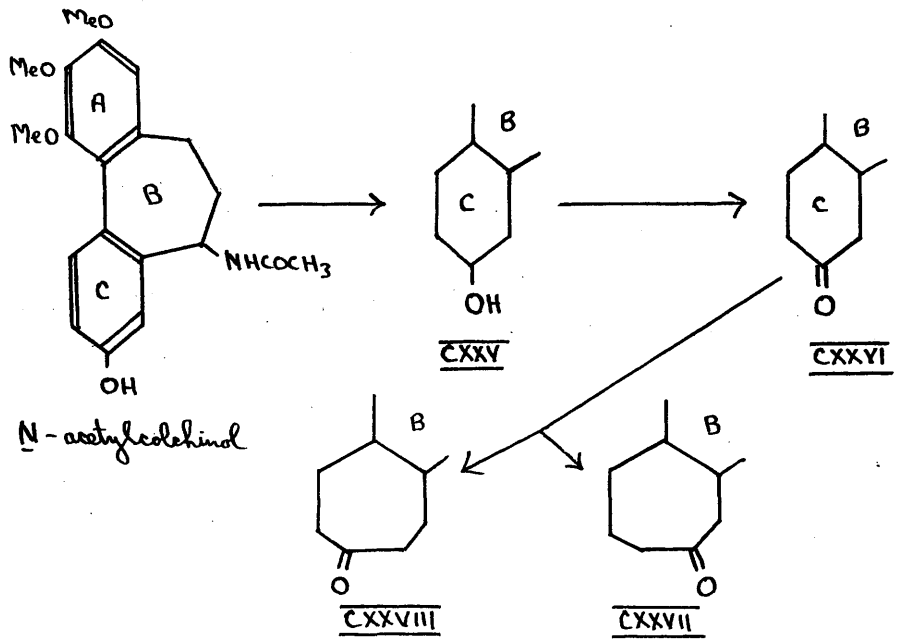
This method is however subject to poor yields. A third, elegant, synthesis of a tropolone has been reported by Tarbell, Scott and Kemp.[93] These authors have synthesised β:γ-benzotropolone (CXXIV) by a simple condensation reaction as shown below. This method, however, is restricted by the availability of appropriate dialdehyde derivatives. It was therefore decided in the remaining



CXXIV ;(R=H)

short time at the authors disposal to try and utilise the "dione" method of Cook et. al.[90,91]

The projected synthesis starts from N-acetylcolchinol or its methyl ether. For the expansion of ring C of N-acetylcolchinol into the required seven membered ketonic form (CXXVI) it was therefore necessary to discover a method of reducing N-acetylcolchinol to (CXXV). This alcohol could then be oxidised to the



ketone (CXXVI) which may be amenable to ring enlargement with the formation of either (CXXVII) or (CXXVIII).

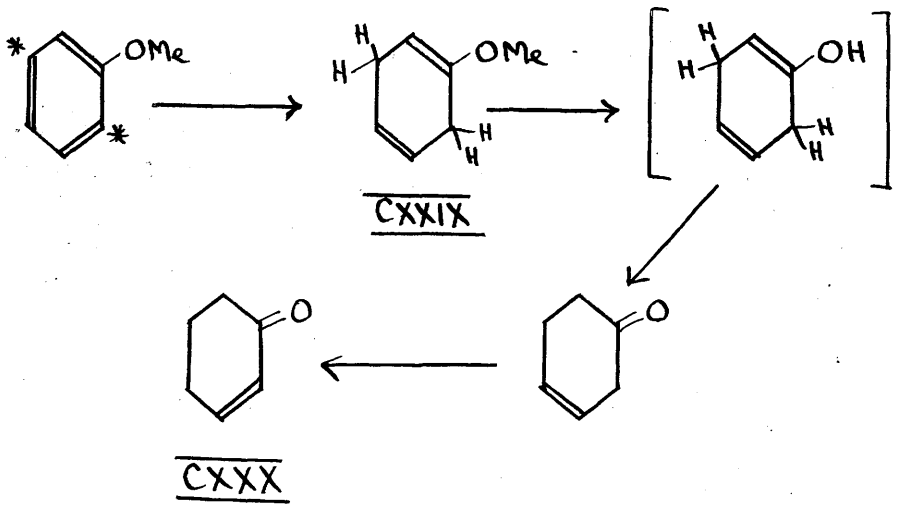
Hydrogenation of two separate samples of N-acetylcolchinol, on a quantitative micro-scale, by means of very active Adam's catalyst at ordinary temperature and pressure, did not result in the uptake of hydrogen.

A modification of the above catalytic method, due to Levine and Pendergass[94] was next used. The method consists of employing Adam's catalyst under a slight pressure (5-10 atmospheres) at room temperature and in the presence of a trace of alkali. This procedure has been found to be very successful for the reduction of certain phenols to the corresponding cyclohexanols. When applied to N-acetylcolchinol, this technique did not lead to reduction, the starting material being recovered even after hydrogenation for six hours.

The use of palladised strontium carbonate catalyst at elevated temperature and pressure has been advocated by Martin and Robinson[95] who have successfully exploited the method for the reduction of several phenols. This method was, however, not found to be of any use in the present attempted hydrogenation of N-acetylcolchinol, the latter being largely recovered unchanged.

These results clearly show that N-acetylcolchinol is suprisingly resistant to catalytic hydrogenation. The continued application of different catalytic methods of reduction was not further investigated, attention being turned to chemical methods of reduction.

One known disadvantage in the use of metal-alcohol techniques of reduction lies in the complete removal of the central methoxyl group in such vicinal trimethoxylated compounds[31]. Recently, Birch[96] has introduced the use of sodium and liquid ammonia-alcohol solutions as a reducing agent. He has found that methyl ethers of phenols with two free "para" positions are reduced by this method to the dihydro-compound e.g. anisole to (CXXIX).



CXXIX

CXXX

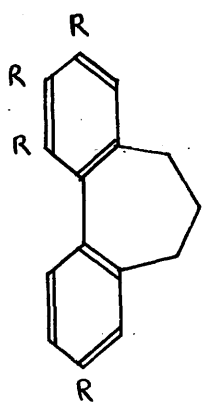
The resulting dihydro-enol ethers are readily hydrolysed to the $\beta:\gamma$-unsaturated ketones which can be rearranged to $\alpha:\beta$-unsaturated ketones. Thus anisole has been converted into Δ^2-cyclohexenone (CXXX). A slight amount in excess of the required two atoms of sodium is usually employed. When N-acetylcolchinol methyl ether was treated in liquid ammonia-alcohol solution with two atoms of sodium it was recovered unchanged on working up the reaction mixture. However, when a large excess of sodium was employed a gum was obtained which could not be crystallised. This gum afforded an orange-red coloured 2:4-dinitrophenyl-hydrazone which again could not be crystallised from the usual solvents. The reaction gum which may have contained some dihydro-enol ether, was treated with hydrochloric acid to effect hydrolysis of the enol ether. The resulting gum,

which still exhibited ketonic properties, could not be induced to afford a solid even after chromotography and high vacumn distillation.

Thus a preliminary examination of the reduction of N-acetylcolchinol and its methyl ether, as a first step in the proposed total synthesis of colchicine, has failed to yield the required reduction product.

APPENDIX.

It has been pointed out (p.14,23) that several dibenzocycloheptadiene, -triene and -trienone derivatives yield phenanthraquinones on dichromate oxidation. The compounds (CXXXId→h), with or without methoxyl groups, all yield the appropriate phenanthraquinones. Three more dibenzocycloheptadiene derivatives have now been oxidised in order to assess the value of this oxidation test for the detection of dibenzocycloheptane derivatives. All three unmethoxylated compounds examined (CXXXIa, b and c) failed to yield phenanthraquinone, the starting material being recovered in good yield. The failure of (CXXXIc) to give phenanthraquinone accords with the known failure of N-acetylcolchinol methyl ether to afford a phenanthraquinone on oxidation[94].



CXXXI

a) $-CH_2\ CH\ (COOH)\ CH_2-$; (R=H)

b) $-CH_2\ CH\ (NH_2)\ CH_2-$; (R=H)

c) $-CH_2\ CH\ (NHCOCH_3)\ CH_2-$; (R=H or OMe)

d) $-CH_2\ CO-\ CH_2-$; (R=H)

e) $-CH_2\ CH_2-\ CO-$; (R=H or OMe)

f) $-CH_2\ CH = CH-$; (R=H or OMe)

g) $-CH = CH\ CO-$; (R=H or OMe)

h) $-CH\ (OH)\ CH_2\ CO-$; (R=OMe)

This test thus appears only to be of diagnostic value for compounds carrying an unsaturated centre in the three carbon bridged diphenyl system.

SUMMARY.

In part I it has been shown that the ring closure of certain β-diphenylyl propionic acids does not lead to dibenzocycloheptadienone derivatives. These cyclisation products are indanone derivatives.

In part II the expansion of the central ring of several 9- and 10- methylphenanthrenes to dibenzocycloheptatrienone derivatives has been examined. Ring expansion can be achieved in three stages viz. (1) formation of a 9:10-diol (2) cleavage of the diol to a keto-aldehyde which is (3) cyclised to give the required type of product. Optimum conditions for the cyclisation stage have been found. When 2:3:4:7-tetramethoxy-9-methylphenanthrene was submitted to the above process 9:12:13:14-tetramethoxy-3:4-5:6-dibenzocyclohepta-3:5:7-trien-2-one was formed. Hydrogenation of the latter afforded 9:12:13:14-tetramethoxy-3:4-5:6-dibenzocyclohepta-3:5-dien-2-one. The oxime of the last named compound was hydrogenated to give (±)-2-amino-9:12:13:14-tetramethoxy-3:4-5:6-dibenzocyclohepta-3:5-diene (I) which was resolved by means of (+)-6:6'-dinitrodiphenic acid. The resulting laevorotatory form of (I) was shown to be identical with (-)-colchinol methyl ether obtained by degradation of colchicine. The structure of the last named product is thereby firmly established.

In part III (±)-2-hydroxy-9:12:13:14-tetramethoxy-3:4-5:6-dibenzocyclohepta-3:5-diene is described. It has been shown to be structurally distinct from the (-)-carbinol formed by the action of nitrous acid on colchinol methyl ether. The latter reaction involves a Demjanow rearrangement, accompanied by some racemisation, affording (-)- and (±)-9:10-dihydro-9-hydroxymethyl-2:3:4:7-tetramethoxyphenanthrene. The (±)- form of the latter has been synthesised and converted, by dehydration, to 9:12:13:14-tetramethoxy-3:4-5:6-dibenzocyclohepta-1:3:5-triene. The dihydro derivative of the latter proved identical with dihydrodeaminocolchinol methyl ether.

By the action of nitrous acid (±)-9:10-dihydro-9-aminomethyl-2:3:4:7-tetramethoxyphenanthrene has been converted to deaminocolchinol methyl ether.

In part IV a total synthesis of colchicine has been envisaged but the initial step viz. the hydrogenation of ring C of N-acetylcolchinol or its methyl ether, has not been realised.

Experimental to Part I.

Cyclisation of β-(5-bromo-2:3:4:4'-tetramethoxy-6-diphenylyl) propionic acid (XL).

The acid (1 g.) was dissolved in anhydrous hydrogen fluoride (ca. 10 c.c.) which was allowed to evaporate overnight in the absence of moisture. The residue, after treatment with ice cold dilute sodium hydroxide, was recovered in ether and on concentration yielded a neutral solid (0.38 g.) which was crystallised from light petroleum (b.p. 40-60°) and gave as first crop, warty nodules of the bromo-indanone (XLIII). These were recrystallised from methanol in fine colourless needles (0.08 g.), (micro-) m.p. and mixed m.p. 141.5°.

From the mother liquors of the bromo-indanone, 5:6:7-trimethoxy-4-p-methoxyphenylindan-1-one (XLIV) was obtained as colourless needles m.p. and mixed m.p. 84-86°. The sodium hydroxide extract yielded the unchanged starting material (0.5 g.)

Debromination of the bromo-indanone (XLIII)

The bromo-indanone (0.08 g.) was dissolved in methanol (ca. 20 c.c.) and shaken with 2% palladised strontium carbonate (ca. 0.7 g.) in an atmosphere of

hydrogen until absorption of hydrogen had ceased (2 hours). The filtered solution on concentration yielded 5:6:7-trimethoxy-4-p-methoxyphenylindan-1-one (XLIV), m.p. 84-86°. The oxime was obtained as colourless needles (micro-) m.p. and mixed m.p. 216-5°.

Cyclisation of β-2-Diphenylyl propionic acid (XXXIX)

The acid (0.84 g.) was treated with anhydrous hydrogen fluoride as described in the previous experiment. The neutral material, recovered from the ether extract, crystallised from ethanol yielding 4-phenylindanone (XLV) (79% yield) m.p. 86-87°. (Found: C, 86.5; H, 5.5. $C_{15}H_{12}O$ requires C, 86.5; H, 5.8%). The semicarbazone had a m.p. and mixed m.p. 230-6° (decomp.).

Detection of Dibenzcycloheptadienone

The mother liquors from the crystallisation of the above 4-phenylindanone gave a yellowish gum on concentration. This gum, dissolved in glacial acetic acid (0.7 c.c.), was refluxed for one hour with a solution of sodium dichromate (0.3 g.) in acetic acid (0.9 c.c.). The cooled solution was poured into water and extracted with chloroform. The chloroform extract was washed with sodium carbonate, water and finally dried. On concentration this extract gave an orange solid, which after sublimation 160-170°/14 m.m.

afforded phenanthraquinone m.p. and mixed m.p. 201-204°. The diazine from o-phenylenediamine formed lemon crystals from ethanol m.p. and mixed m.p. 216-217°.

5:6:7-Trimethoxy-4-m-methoxyphenylindan-1-one was obtained by treatment of the acid (XLVII) (1 g.) with anhydrous hydrogen fluoride. It formed thick colourless plates m.p. 141-142° from methanol (Found: C, 69.25; H, 6.1. $C_{19}H_{20}O_5$ requires C, 69.5; H, 6.1%). The oxidation test applied to the cyclised material gave no evidence of phenanthraquinone derivatives.

β-(5-Bromo-2:3:4:3'-tetramethoxy-6-diphenylyl) propionic acid (XLIX)

A solution of bromine (0.08 c.c.) in dry chloroform (2 c.c.) was added to a solution of the acid (XLVII) (0.5 g.) in the same solvent (12 c.c.) and after three hours at room temperature the crude product was recovered from the (water washed) solution. It was purified by conversion to the sparingly soluble sodium salt with concentrated aqueous sodium hydrogen carbonate. The bromo-acid was regenerated with dilute sulphuric acid and extracted with ether. The ether extract on concentration yielded a gum which crystallised from acetic

acid-water (1:1) in colourless plates, m.p. 163-164° (Found: C, 53.8; H, 4.8. $C_{19}H_{21}O_6$ Br requires C, 53.65; H, 5.0%).

Cyclisation of the above bromo-acid (XLIX).

The acid was treated with hydrogen fluoride as in previous experiments to yield 5:6:7-trimethoxy-4-(?-bromo-m-methoxyphenyl) indan-1-one which crystallised from methanol in colourless plates m.p. 115-116° (Found: C,56.1; H, 4.7. $C_{19}H_{19}O_5$ Br requires C, 56.0; H, 4.7%). The gum, recovered from the methanol mother liquors did not afford evidence of formation of a phenanthraquinone derivative when oxidised with sodium dichromate in acetic acid.

Debromination of the above bromo-indanone.

The bromo-indanone (0.047 g.) in methanol (20 c.c.) was shaken for one hour with 2% palladised strontium carbonate in an atmosphere of hydrogen. The filtered solution on concentration yielded 5:6:7-trimethoxy-4-m-methoxyphenylindan-1-one, m.p. and mixed m.p. 139-141°.

Methyl β-(2:3:4-trimethoxy-6-diphenylyl) propionate.

The acid (XLVI) (0.2 g.) was treated with an ethereal solution of diazomethane. On concentration and washing with sodium hydroxide the methyl ester crystallised from light petroleum (b.p. 40-60°) in colourless cubes m.p. 56° (Found: C, 69.3; H, 6.8. $C_{19}H_{21}O_5$ requires

C, 69.1; H, 6.7%).

5:6:7-Trimethoxy-4-phenylindan-1-one.

The acid (XLVI) (0.5 g.) was treated with hydrogen fluoride to give a neutral gum which crystallised from petroleum (b.p. 60-80°) in colourless needles m.p. 74° (Found: C, 72.9; H, 6.0. $C_{18}H_{18}O_4$ requires C, 72.5; H. 6.0%). Its oxime crystallised from ethanol in small colourless needles m.p. 200° (Found: C, 68.9; H, 6.0. $C_{18}H_{19}O_4N$ requires C, 69.0; H, 6.1%). Oxidation of the crude ketone gave no evidence of the formation of a coloured phenanthraquinone derivative.

β-(5-Bromo-2:3:4-trimethoxy-6-diphenylyl) propionic acid (XLVIII).

The acid (XXVII) (0.63 g.) was brominated and purified in a similar manner to that described for the preparation of the bromo-acid (XLIX). The product formed colourless plates from acetic acid-water (1:1), m.p. 164-165° (Found: C, 54.7; H, 4.8. $C_{18}H_{19}O_5$ Br requires C, 54.7; H, 4.8%). The methyl ester was obtained by treating the acid with an ethereal solution of diazomethane. The product was crystallised from methanol in colourless plates m.p. 95-96° (Found: C, 55.7; H, 5.0. $C_{19}H_{21}O_5$ Br requires C, 55.6; H, 5.1%).

Attempts to cyclise the above acid (XLVIII).

(a) With hydrofluoric acid. The neutral gum obtained by treating the acid (0.6 g.) with anhydrous hydrogen fluoride remained gummy after treatment with Girard's reagent T and hydrolysis of the resulting substituted hydrazone with sulphuric acid. The gum afforded a bright red 2:4-dinitrophenylhydrazone, but was not converted into a solid on debromination with hydrogen in the presence of palladised strontium carbonate.

(b) With aluminium chloride. The acid (0.7 g.) in dry benzene (10 c.c.) was shaken with phosphorus pentachloride (0.4 g.). Volatile materials were removed under reduced pressure and the residue on dissolution in carbon disulphide (3 c.c.) was treated with aluminium chloride (0.6 g.). After standing for two days at 0° the reaction mixture was diluted with hydrochloric acid and the carbon disulphide distilled off in steam. A chloroform extract of the residue was washed with dilute sodium carbonate, from which (0.5 g.) of the starting acid was recovered. On concentration the neutral extract afforded a gum which could not be obtained solid.

Neither of the (debrominated) gums showed any trace of a phenanthraquinone derivative on oxidation with sodium dichromate in acetic acid.

Experimental to Part II.

3:4:5-Trimethoxybenzoic acid was prepared as described in Organic Synthesis Coll. Vol. I. p. 537.

Methyl 3:4:5-trimethoxybenzoate (LXIV) was prepared by the method of Bargellini and Molina[98].

Methyl 2-Nitro-3:4:5-trimethoxybenzoate (LXV).

The method finally adopted for the preparation of this compound is described below. For variations see table on p. 35.

To a well stirred, cooled, suspension of 3:4:5-trimethoxy methyl benzoate (56 g.) in "Analar" acetic anhydride, was added ice cold "Analar" fuming nitric acid (d. 1.5, 28 c.c.). The rate of addition was adjusted so that the temperature did not exceed 5°. The resultant solution was left overnight and most of the acetic anhydride removed in vacuo. The remaining solution was poured into water and extracted with ether. The ether extract, after washing with 10% sodium hydroxide solution and water, was dried and concentrated to a red oil which solidified on cooling and rubbing. This solid was washed with methanol to give the required methyl 2-nitro-3:4:5-trimethoxy-benzoate as a yellow solid m.p. 64-66°. This material was used as such for the next stage in the synthesis.

2-Nitro-3:4:5-trimethoxybenzoic acid was prepared by the method of Overmeyer[99].

2-Nitro-3:4:5-trimethoxybenzoyl chloride was prepared from the above acid by the method of Overmeyer[99].

1-(2-nitro-3:4:5-trimethoxybenzoyl)-1:2-dihydroquinaldinonitrile (LXVI) was prepared by the method of Buchanan, Cook and Loudon[18]. The anhydrous hydrogen cyanide required forthis preparation was prepared by the method of Slotta[100].

2-Nitro-3:4:5-trimethoxybenzaldehyde (LXVII) was prepared by the hydrolysis of the above "Reissert" compound (LXVI). The following method is an improvement on that of Buchanan, Cook and Loudon . The "Reissert" compound (LXVI; 10 g.) was finely powdered and wet with an aqueous solution of "Aerosol O T" wetting agent. To this was added, with stirring, a 15 N solution of sulphuric acid (1250 c.c.) and the whole was heated, on an air funnel, at 80-85° for 2.5 hours. The resulting solution was filtered hot (30-40°) and the unchanged residue washed with ether. The filtrate was thoroughly extracted with chloroform-ether, washed with water, sodium bicarbonate and again with water and finally dried and concentrated to yield

2-nitro-3:4:5-trimethoxybenzaldehyde m.p. 77-78°, after crystallisation from ethanol.

m-Methoxyphenylacetic acid (LXIX) was prepared by the Erlenmeyer's azlactone synthesis from m-methoxybenzaldehyde following the method of Pschorr[101].

cis- and trans-2-Nitro-3:4:5-trimethoxy-m-methoxyphenyl-cinnamic acids (LXX).

m-Methoxyphenylacetic acid (6.7 g.) was heated at 85-90° for eighteen hours with acetic anhydride (80 c.c.) and powdered 2-nitro-3:4:5-trimethoxybenzaldehyde, in the presence of triethylamine (4.1 g.) as condensing agent. On pouring into water (300 c.c.) a red oil was obtained which solidified on standing. The solid was collected and the filtrate extracted with ether. The ethereal extract was washed with a limited quantity of aqueous sodium carbonate to remove acetic acid. The solid was then added to this ether solution which was thoroughly extracted with alkali. Acidification and crystallisation of the resulting product from acetic acid gave the mixed acids (LXX) m.p. 135-170°.

The method described ~~below~~ above is modified from the preparation of Buchanan, Cook and Loudon[18].

The next stages in the synthesis of the two methoxylated 9-methylphenanthrenes were carried out following the method of Buchanan, Cook and Loudon[18]. These steps will not be described but several amendments are to be noted.

Methyl 2:3:4:5-tetramethoxy-9-phenanthroate.

This substance was previously described as a gummy oil but has now been obtained as colourless plates (from methanol) m.p. 100°. (Found: C, 67.15; H, 5.6. $C_{20}H_{20}O_6$ requires C, 67.4; H, 5.6%).

The hydrazide from the above methyl ester had a m.p. of 193° in comparison with the sample m.p. 182° previously obtained. Mixed m.p. of the two samples 185-189°.

2:3:4:5-Tetramethoxy-9-phenanthraldehyde as now obtained had m.p. 101° (from ethanol). (Found: C, 69.8; H, 5.5. $C_{19}H_{18}O_5$ requires C, 69.9; H, 5.5%).

2:3:4:5-Tetramethoxy-9-methylphenanthrene (LXXII).

This substance was prepared by the reported method but it was very conveniently purified by passing the crude product in benzene solution through a column of alumina. The required product was not readily absorbed and was easily eluted with benzene. It crystallised from ethanol in colourless needles m.p. 116-117°. The original sample

of m.p. 102° had changed on storage to m.p. 116-117°. Mixed m.p. of the two samples 116-117°.

cis-9:10-Dihydro-9:10-dihydroxy-2:3:4:5-tetramethoxy-9-methylphenanthrene (LXXIV).

To a solution of osmium tetroxide (0.49 g.) in sodium dried, thiophene free benzene (3.5 c.c.) was added 2:3:4:5-tetramethoxy-9-methylphenanthrene (0.54 g.) followed by dry pyridine (0.28 c.c.). The reddish-brown coloured solution on standing overnight at room temperature deposited a light brown complex which was hydrolysed by shaking for two hours with a 1% aqueous potassium hydroxide solution containing 10% mannitol, in the presence of methylene dichloride. The organic layer was washed, dried and concentrated. The resulting crude diol crystallised from ethanol in colourless needles (0.53 g. 90% yield) m.p. 215-216°. (Found: C, 66.1; H, 6.25. $C_{19}H_{22}O_6$ requires C, 65.9; H, 6.4%).

6'-Acetyl-6-formyl-2:2':3:4-tetramethoxydiphenyl (LXXV).

The diol (LXXIV. 0.2 g.) dissolved in sulphur free benzene (ca. 80 c.c.) was shaken with a benzene solution of lead tetra-acetate (0.3 g.) for three hours and the resulting precipitate removed by filtration through charcoal. The excess lead tetra-acetate was destroyed by

shaking the benzene solution with ethylene glycol. The water washed benzene solution was then concentrated to a colourless gum which on scratching gave (LXXV). Crystallisation from methanol afforded bi-prisms m.p. 113-114° (74% yield). (Found: C, 66.1; H, 5.9; $-OCH_3$, 35.3. $C_{19}H_{20}O_6$ requires C, 66.25; H, 5.8; $-OCH_3$, 36.0%). It yielded a dioxime which formed colourless prisms from aqueous methanol m.p. 179-180°. (Found: C, 61.2; H, 5.95; N, 7.7. $C_{19}H_{22}O_6N_2$ requires C, 61.0; H, 5.9; N, 7.5%).

Oxidation of (LXXV).

(a) With sodium dichromate in acetic acid. To the above keto-aldehyde (LXXV. 0.08 g.) in glacial acetic acid (1 c.c.) was added sodium dichromate (0.16 g.) in a solution of water (0.3 c.c.) and glacial acetic acid (1 c.c.). The resulting solution was refluxed for one hour (in a second experiment refluxing was continued for two and a half hours). The colourless chloroform extract was washed with sodium carbonate solution, water and then dried. Concentration of the chloroform yielded unchanged (LXXV. 0.061 g.) m.p. and mixed m.p. 108-111°. The sodium carbonate extract was acidified and extracted with chloroform. The dried chloroform solution on evaporation yielded a gum (0.014 g.) which crystallised by leaving its ethanol solution to

evaporate spontaneously. It formed a few colourless crystals of m.p. 180°. Admixed with a specimen of the permanganate oxidation product (LXXVI) (see below) gave no depression in m.p.

(b) With potassium permanganate in acetone. To the keto-aldehyde (LXXV. 0.1 g.) dissolved in "Annalar" acetone (4 c.c.) (previously freed from readily oxidisable matter) was added a solution of potassium permanganate (0.07 g.) in the same solvent (10 c.c.). The resulting solution was left at room temperature for forty eight hours, diluted with an equal volume of water and sulphur dioxide passed into the solution until all the inorganic material was dissolved. The clear solution was then extracted with ether and the latter extract washed with sodium hydroxide solution. The alkaline extract on acidification and extraction with ether afforded a gum (0.06 g.) which was crystallised from benzene-petroleum (b.p. 60-80°) in almost colourless needles m.p. 181-183°. Recrystallisation from the same mixture (charcoal) afforded colourless needles m.p. 183-184° (with slight decomposition). The analytical values obtained for this product were not consistent, the figures being either too high or too low in carbon content after heating in vacuo. However by its

further oxidation to 4:5:6:6'-tetramethoxydiphenic acid (LXXVII) this substance is regarded as possessing the structure (LXXVI).

Sodium hypobromite oxidation of the above keto-acid (LXXVI).

The keto-acid (LXXVI. 0.02 g.) was added to a solution (3 c.c.) of sodium hypobromite, prepared by slowly adding bromine (1 c.c.) to an ice cold solution of sodium hydroxide (3.4 g.) in water (100 c.c.). The resulting solution was heated at 100° for one and a half hours, a sickly smell being noted. The cooled solution was saturated with sulphur dioxide and extracted with ether. The ether extract on concentration gave a gum which crystallised from a drop of methanol in small rosettes of crystals (micro-) m.p. 240-250°. A (micro-) mixed m.p. with the presumed diphenic acid (LXXVII) (m.p. 214-216°) depressed the melting point of the latter. The m.p. was not reduced, 238-248°, when the product was mixed with a specimen of the true 4:5:6:6'-tetramethoxy-diphenic acid (LXXVII).

2:3:4:5-Tetramethoxyphenanthraquinone (LXXVIII).

After Barton, Cook and Loudon[19]. The phenanthra-quinone thus obtained crystallised from benzene-petroleum (b.p. 60-80°) in red needles m.p. 125-126° (literature m.p. 120-122°). The acidic by-product of m.p. 214-216°

presumed to be 4:5:6:6'-tetramethoxydiphenic acid, was also obtained m.p. 210-212° (decomp.).

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

To the above phenanthraquinone (LXXVIII; 0.061 g.) suspended in methanol (1 c.c.) containing hydrogen peroxide (30%. 0.15 c.c.) was added 2 N. sodium hydroxide solution (0.2 c.c.) with shaking. A further 0.2 c.c. of hydrogen peroxide was added and the resulting solution heated on the steam bath for half an hour and left overnight. A small amount of suspended material (ca. 5 mgms.) was filtered off and discarded. The alkaline filtrate was acidified and extracted with ether. On concentration the ether extract afforded a slightly yellow coloured solid which crystallised from ethanol in colourless diamond shaped prisms of m.p. 247-249°. (Found: C, 59.4; H, 5.0. $C_{18}H_{18}O_8$ requires C, 59.7; H, 5.0%).

Attempted cyclisation of (LXXV).

(a) With hydrochloric acid gas in ether. To the keto-aldehyde (LXXV. 0.08 g.) ~~was~~ dissolved in dry ether (10 c.c.) was added an equal volume of the dry ether which had been saturated with dry hydrochloric acid gas. The resulting solution was left at room temperature for forty hours, washed and concentrated to a gum which crystallised from

methanol m.p. and mixed m.p. with starting material 109-112°.

(b) With acetic anhydride. The keto-aldehyde (LXXV. 0.1 g.) was refluxed with acetic anhydride (6 c.c.) for one hour, with and without the addition of anhydrous sodium acetate (0.08 g.). The resulting solution was poured on to ice and extracted with ether. Concentration of the ether extract afforded the starting material m.p. and mixed m.p. 108-111°.

7-Hydroxy-11:12:13:14-tetramethoxy-3:4-5:6-dibenzocyclohepta-3:5-dien-2-one (LXXIX).

(1) A solution of the keto-aldehyde (LXXV) (0.6 g.) in methanol (50 c.c.), treated with a few drops of dilute aqueous sodium hydroxide solution, gradually deposited a high-melting (ca. 253°) solid which was not further investigated. An ethereal extract of the diluted reaction mother liquor gave a gum which afforded the hydroxy-ketone (LXXIX) as colourless needles m.p. 179-180°, from methanol, either directly or after its solution in benzene had been passed through a column of alumina whereby a first small, yellowish eluate was separated. (Found: C, 66.3; H, 6.0. $C_{19}H_{20}O_6$ requires C, 66.3; H, 5.8%).

(2) The keto-aldehyde (LXXV. 0.1 g.) in dry pyridine (4 c.c.) containing piperidine (0.3 c.c.) was left at room temperature

for two days. The solution was then refluxed for one hour and poured into dilute sulphuric acid and extracted with ether. Concentration of the dried ether extract afforded the hydroxy-ketone (LXXIX) as a gum which crystallised from methanol m.p. and mixed m.p. 176-178°.

(3) The keto-aldehyde (LXXV. 0.1 g.) was dissolved in acetic anhydride (1 c.c.) and a small drop of concentrated sulphuric acid added. There was an immediate change to a dark red colour. This coloured solution was allowed to stand at room temperature for twenty four hours and was then poured on to ice. The collected solid after repeated crystallisation from benzene-petroleum (b.p. 60-80°) and washing with ether afforded some crystals (micro-) m.p. 123-125° and mixed m.p. with the starting material 94°. This substance was probably the diacetate of (LXXV). It was hydrolysed by heating at 100° in a solution of glacial acetic acid containing dilute hydrochloric acid (0.2 c.c.). Dilution and ether extraction yielded the hydroxy-ketone (LXXIX) of (micro-) m.p. 175° and mixed m.p. 173°.

Oxidation of the above hydroxy-ketone (LXXIX).

To a solution of (LXXIX) (25 mgms.) in glacial

acetic acid (1 c.c.) was added a solution of sodium dichromate (0.1 g.) in water (0.2 c.c.) and acetic acid (1.5 c.c.) and the resulting solution refluxed for one hour. The diluted reaction mixture was extracted with chloroform from which 2:3:4:5-tetramethoxyphenanthraquinone (LXXVIII) was obtained of (micro-) m.p. and mixed m.p. 123-125°.

11:12:13:14-Tetramethoxy-3:4-5:6-dibenzocyclohepta-3:5:7-trien-2-one (LXXX).

The above named product was prepared by the following two methods.

(a) By the action of acetic anhydride on the hydroxy-ketone (LXXIX). A pyridine (0.6 c.c.) solution of (LXXIX. 0.1 g.) was refluxed with acetic anhydride (0.04 c.c.) for one hour and the resulting solution poured into iced dilute sulphuric acid. An ether extract, after washing with dilute sulphuric acid and water, was concentrated to give a slightly yellow coloured gum which could not be obtained crystalline. Distillation of this gum at ca. 200° (bath) / 1.5 m.m. gave a yellow distillate which on rubbing with methanol afforded the trienone (LXXX), m.p. 174-175°.

(b) By the action of dry hydrogen chloride on the keto-aldehyde (LXXV). The keto-aldehyde (0.1 g.) was dissolved in redistilled glacial acetic acid (ca. 5 c.c.) and saturated with dry hydrochloric acid gas at room temperature. The resulting red-coloured solution was allowed to stand at room temperature overnight. The reaction mixture was then diluted with water to give a yellow coloured solution which was extracted with ether. The yellow ether extract was washed repeatedly with sodium bicarbonate solution and then water. On concentration it afforded a yellow gum which was chromatographed in benzene solution on a column of alumina and eluted with the same solvent. The first fraction contained the required dibenzocyclo-heptatrienone (LXXX) which crystallised from methanol in pale yellow-green coloured needles m.p. 174-175°. (Found: C, 69.7; H, 5.7. $C_{19}H_{18}O_5$ requires C, 69.9; H, 5.6%). A second band which was more strongly absorbed was eluted and crystallised from methanol in colourless prisms m.p. and mixed m.p. with the hydroxy-ketone (LXXIX) 179-180°.

11:12:13:14-Tetramethoxy-3:4-5:6-dibenzocyclohepta-3:5-dien-2-one.

The trienone (LXXX) was hydrogenated in acetic

acid solution in the presence of palladium black. The calculated volume of hydrogen (1 mol.) was absorbed in half an hour and resulting colourless solution filtered to remove the catalyst. Concentration of the filtrate afforded a gum which crystallised from methanol in colourless prisms m.p. 162-163°. (Found: C, 69.2; H, 6.1. $C_{19}H_{20}O_5$ requires C, 69.5; H, 6.1%).

2:3:4:7-Tetramethoxy-9-methylphenanthrene (LXXIII).

This compound, like the 2:3:4:5-isomer, was prepared by the method of Buchanan, Cook and Loudon[18]. It was purified by chromatography on alumina, the required product being easily eluted with benzene. It formed colourless prisms (from methanol) of m.p. 116-117° (literature 116-117°). A small amount of a second substance was obtained from the chromatogram by continued elution. It was considered to be an azine derivative formed by condensation of two molecules of 2:3:4:7-tetramethoxy-9-phenanthraldehyde and a molecule of hydrazine. The new substance formed yellow prisms from acetic acid m.p. 246-247°.

9:12:13:14-Tetramethoxy-3:4-5:6-dibenzocyclohepta-1:3:5-trien-7-one (LXIII).

The required gummy keto-aldehyde (LXII) was prepared from the diol (LXI) as described by MacMillan[21,22]. It was cyclised to (LXIII) by the two following methods.

(a) With sodium methoxide. A solution of the gummy keto-aldehyde (LXII; 0.09 g.) in dry methanol (5 c.c.) was treated with a 5% solution of sodium methoxide in methanol (0.2 c.c.). After twenty four hours at 0°, the solution was neutralised with acetic acid, concentrated, and extracted with benzene. Chromatography on a column of alumina gave a yellow band which fluoresced in ultra-violet light and, after elution and recovery, afforded the trienone (LXIII; 0.03 g.), m.p. and mixed m.p. 107-109°.

(b) With hydrochloric acid. The gummy keto-aldehyde (LXII; 0.09 g.) dissolved in glacial acetic acid (5 c.c.) wassaturated with dry hydrogen chloride. After twelve hours at room temperature the deep red solution was diluted with water and extracted with ether. The ethereal extract was washed with sodium hydrogen carbonate solution, then with water, and was dried and concentrated, affording a yellow gum. This solidified when rubbed with methanol, giving the trienone (LXIII; 0.07 g.) of m.p. and mixed m.p. 109-110° (from methanol).

cis-9:10-Dihydro-9:10-dihydroxy-2:3:4:7-tetramethoxy-9-methylphenanthrene (LXXXI).

To a solution of osmium tetroxide (1.3 g.) in sodium dried, thiophene free benzene (5 c.c.) was added 2:3:4:7-tetramethoxy-9-methylphenanthrene (1.3 g.), followed by dry pyridine (0.7 c.c.). The reddish-brown coloured solution did not deposit any solid complex even after standing for several months at room temperature. Addition of more pyridine failed to produce a solid. The light brown complex was precipitated by the addition of n-hexane. The complex could be crystallised from methylene dichloride - n-hexane m.p. ca. 200° (with decomposition). The complex was hydrolysed in a similar manner as described for the 2:3:4:5 isomer. The washed and dried methylene dichloride solution on concentration deposited small prisms which on recrystallisation from ethanol yielded the required product as colourless prisms m.p. 172-174°. (Found: C, 65.9; H, 6.5. $C_{19}H_{22}O_6$ requires C, 65.9; H, 6.4%).

6'-Acetyl-6-formyl-2:3:4:4'-tetramethoxydiphenyl (LXXXII).

The above diol (LXXXI. 0.1 g.) was treated with lead tetra-acetate (0.2 g.) as described for the other isomer (LXXIV). Concentration of the benzene solution

yielded a colourless gum which could not be obtained solid. The gummy keto-aldehyde (LXXXII) was distilled unchanged at ca. 170° (bath) / 0.5 m.m. but the resulting gum still resisted all attempts to obtain it solid. On treatment with hydroxylamine it afforded a dioxime which crystallised from ethanol in small colourless hexagonal plates m.p. 186-187°. (Found: N, 7.7. $C_{19}H_{22}O_6N$ requires N, 7.5%).

Attempted cyclisation of the above keto-aldehyde (LXXXII).

When the gummy keto-aldehyde was treated in methanol solution with a few drops of dilute sodium hydroxide solution only a high melting (262-264°) material was obtained. This was not further investigated.

9:12:13:14-Tetramethoxy-3:4-5:6-dibenzocyclohepta-3:5:7-trien-2-one (LXXXIII).

The gummy keto-aldehyde (LXXXII. 0.39 g.) was dissolved in redistilled glacial acetic acid (ca. 15 c.c.) and saturated with dry hydrochloric acid gas. The resulting red coloured solution was allowed to stand at room temperature for twenty four hours and worked up as described for the other isomer. The resulting yellow gum was taken up in benzene and passed through a column of alumina. A yellow band of general absorption resulted which was eluted with benzene. Removal of the solvent

afforded a yellow gum which could not be immediately obtained solid, even after distillation at 165-180° (bath) / 3 m.m. On standing for several weeks a quantity of this gum slowly solidified and the resulting solid trienone (LXXXIII) was crystallised from methanol in yellow prisms m.p. 97-99°. (Found: C, 69.9; H, 5.65. $C_{19}H_{18}O_5$ requires C, 69.9; H, 5.6%).

9:12:13:14-Tetramethoxy-3:4-5:6-dibenzocyclohepta-3:5-dien-2-one (LXXXIV).

The trienone (LXXXIII) in the gummy form (0.35 g.) was hydrogenated in acetic acid (10 c.c.) over palladium black (0.1 g.). The theoretical amount of hydrogen (1 mol.) was absorbed in half an hour. The catalyst was removed by filtration and the solvent removed to give a practically colourless gum which crystallised from methanol in colourless prisms (0.24 g.) m.p. 142-143°. (Found: C, 69.5; H, 5.9. $C_{19}H_{20}O_5$ requires C, 69.5; H, 6.1%). The oxime crystallised from methanol and had at first a m.p. of 193-194° but after four crystallisations from the same solvent it formed colourless prisms m.p. 203-204°. (Found: C, 66.6; H, 6.4; N, 4.1. $C_{19}H_{21}O_5N$ requires C, 66.4; H, 6.2; N, 4.1%). Rapoport, Williams and Cisney[49,50] quote a m.p. of 194-196° for the oxime.

(+)-Colchinol methyl ether (LXXXV).

The oxime of (LXXXIV. 0.2 g.) dissolved in dry methanol (ca. 80 c.c.) was hydrogenated (4 hours) at 80-90° / 65-75 atmospheres in the presence of Raney Nickel (ca. 0.5 g.). After filtration and concentration the diluted reaction mixture was extracted with ether. The ether extract was washed with dilute sulphuric acid and the amine recovered from the acid extract by basification and ether extraction. The crude amine had m.p. 142-146°. The analytical specimen crystallisated from ether in small colourless rods m.p. 144-146°. (Found: C, 69.1; H, 7.1; N, 4.3. $C_{19}H_{23}O_4N$ requires C, 69.3; H, 7.4; N, 4.25%). (+)-N-acetylcolchinol methyl ether was obtained by shaking (one hour) the amine with redistilled acetic anhydride in the presence of a micro-drop of concentrated sulphuric acid. It crystallised from aqueous methanol in colourless plates m.p. 179-180°. (Found: C, 67.9; H, 6.9; N, 4.3. $C_{21}H_{25}O_4N$ requires C, 67.9; H, 6.8; N, 3.9%). The hydrochloride had a m.p. 254° (decomp.). Rapoport, Williams and Cisney[49,50] do not report the m.p. of the above amine but record m.p. 178-179° for the acetyl compound and 258-259° for the hydrochloride.

Attempted resolution of (±)-colchinol methyl ether.

(a) With (-)-malic acid. By mixing dry ether solutions of (±)-colchinol methyl ether (0.1 g.) and (-)-malic acid (0.05 g.) a solid hydrogen malate was obtained. Crystallisation of this salt from methanol afforded colourless prisms m.p. 213-217° and mushroom like clumps of small needles m.p. 206-210°. These two different forms could be interconverted by further crystallisation. When separately decomposed neither crystalline form afforded the optically active amine.

(b) With (+)-tartaric acid. The tartaric acid salt was prepared as described for the above malate. After crystallisation from ethanol afforded small rods which were triangular in section. When this salt was decomposed the resulting amine was optically inactive.

(c) With camphor-10-sulphonic acid and with α-bromocamphor π-sulphonic acid.

No crystalline salt could be obtained with either of the above named acids. Only a gum was obtained on mixing an aqueous solution of either acid with an alcoholic solution of the amine.

(±)-α-Phenylethylamine. This amine required for the resolution of 6,6'-dinitrodiphenic acid, was prepared as described in Organic Synthesis[58].

Resolution of α-phenylethylamine.

The (+)- and (-)- forms were obtained by fractional crystallisation of the malate and tartarate respectively, following the method described in Organic Synthises[58].

Resolution of (±)-6,6'-dinitrodiphenic acid.

The (+)- and (-)- forms of the above named acid required for the resolution of (±)-colchinol methyl ether, were obtained after the method of Ingersoll and Little[54].

Resolution of (±)-colchinol methyl ether.

The amine (LXXXV. 0.4 g.) was dissolved in methanol (5 c.c.) and mixed with a solution of (+)-6,6'-dinitrodiphenic acid (0.4 g.) in the same solvent (5 c.c.). The resulting crystalline salt (0.364 g.) was recrystallised three times from methanol. [(-)-Colchinol methyl ether] [hydrogen (+)-6,6'-dinitrodiphenate] crystallised, with a molecule of methanol, in pale yellow rods, m.p. 257-258° (decomp.), $[\alpha]^{16}_{5900}$ +51°, $[\alpha]^{16}_{5461}$ +67° (c,0.33 in methanol). (Found: C, 55.8; H, 5.05. $C_{19}H_{23}O_4N$, $C_{14}H_8O_8N_2,CH_4O$ requires C, 58.9; H, 5.1%). The same acid salt, m.p. and mixed m.p. 258° (decomp.), $[\alpha]^{18}_{5900}$ +54, $[\alpha]^{18}_{5461}$ +69° (c,0.33 in methanol), was prepared from colchinol methyl

ether obtained by degradation of colchicine.

(-)-Colchinol methyl ether.

A solution of the synthesised acid salt (0.2 g.) in methanol was basified with N. sodium hydroxide solution. The resulting solution was diluted with water and extracted with ether. On concentration the water washed ether extract afforded (-)-colchinol methyl ether (78 mgms.) which crystallised from ether-petroleum (b.p. 40-60°) in micro-crystals m.p. 90-92° and had $[\alpha]^{16}_{5900}$ -85° and $[\alpha]^{16}_{5461}$ -111° (c,0.74 in methanol). An authentic specimen of colchinol methyl ether had m.p. and mixed m.p. 90-92°, $[\alpha]^{17}_{5900}$ -84°, and $[\alpha]^{17}_{5461}$ -111° (c,0.74 in methanol). The picrate formed bright yellow prisms from methanol m.p. and mixed m.p. with an authentic specimen (prepared by Dr. Barton[45]) 223-225°.

(-)-N-Acetylcolchinol methyl ether. The synthetic (-)-colchinol methyl ether, recovered from the optical measurements, was acetylated as described (±)-compound. The product crystallised from methanol in colourless prisms m.p. 202-204°, $[\alpha]^{16}_{5900}$ -92°, $[\alpha]^{16}_{5461}$ -118° (c,0.67 in methanol). An authentic specimen prepared from colchicine had m.p. and mixed m.p. 202-204°, $[\alpha]^{17}_{5900}$ -94°, $[\alpha]^{17}_{5461}$ -118° (c,0.67 in methanol). Rapoport, Williams

and Cisney[49,50] record m.p. 201-202° and $[\alpha]_D^{20}$ -88.6 (c,0.67 in methanol) for the degradation product.

[(+)-Colchinol methyl ether][hydrogen (-)-6,6'-dinitrodiphenate] was obtained by treating the amine, recovered from the mother liquors of the above salt, with (-)-6,6'-dinitrodiphenic acid. It crystallised from methanol in yellow rods m.p. 257° (decomp.). (Found: N, 6.5. $C_{19}H_{23}O_4N$, $C_{14}H_8O_8N_2$ requires N, 6.35%).

Experimental to Part III.

(±)-2-Hydroxy-9:12:13:14-tetramethoxy-3:4-5:6-dibenzocyclohepta-3:5-diene (LXXXVIII).

To the ketone (LXXXIV; 0.05 g.) in dry ether (10 c.c.) was added a suspension of lithium aluminium hydride (0.1 g.) in the same solvent. The reaction mixture was refluxed for fifteen minutes and the product worked up as described for (XCI). The required compound crystallised from benzene-petroleum in colourless rod-like prisms of m.p. 148-150°. (Found: C, 69.1; H, 6.8. $C_{19}H_{22}O_5$ requires C, 69.05; H, 6.7%). This alcohol gave a red coloured solution in concentrated sulphuric acid. The above named product did not afford a p-phenylbenzoate under the conditions described for the corresponding derivative of (XCI), the starting material being recovered unchanged.

2:3:4:7-Tetramethoxy-9:10-dihydrophenanthrene-9-carboxylic acid.

The cyanide (XC; 1.1 g.) was refluxed for seventy hours in methanol (35 c.c.) containing potassium hydroxide (4 g.). Most of the methanol was then removed by distillation and the resulting solution diluted with water.

The ether extract of the latter was washed with dilute sodium hydroxide solution to remove the required acid. The acid was recovered in ether after acidification. Evaporation of the ether followed by crystallisation from methanol afforded the acid (0.83 g.) as colourless prisms m.p. 191°. The methyl ester, prepared with diazomethane in ether, crystallised from methanol in colourless prisms, m.p. 123-124°. (Found: C, 66.9; H, 6.4. $C_{20}H_{22}O_6$ requires C, 67.0; H, 6.2%). The ether solution remaining after extraction of the acid was concentrated and afforded the acid amide which crystallised from methanol in colourless prisms of m.p. 168° (Found: C, 66.25; H, 5.9; N, 4.3. $C_{19}H_{21}O_5N$ requires C, 66.4; H, 6.2; N, 4.1%).

(±)-9:10-Dihydro-9-hydroxymethyl-2:3:4:7-tetramethoxyphenanthrene (XCI).

To the above methyl ester (0.75 g.) dissolved in dry ether (30 c.c.) was added a suspension of lithium aluminium hydride (ca. 2 g.) in the same solvent. The reaction mixture was refluxed for twenty minutes and then cautiously decomposed by the addition of dilute sulphuric acid. The resulting ether layer was separated and the aqueous layer extracted twice with fresh ether. The

combined ether extracts were concentrated to give the required carbinol (0.6 g.) which crystallised from benzene-petroleum in colourless rods m.p. 165-166°. (Found: C, 68.8; H, 6.6. $C_{19}H_{22}O_5$ requires C, 69.05; H, 6.7%). The p-phenylbenzoyl derivative was obtained by refluxing the carbinol (0.1 g.) in dry pyridine (3 c.c.) with p-phenylbenzoylchloride (0.08 g.) for one hour. Dilute sulphuric acid was added to the reaction mixture and the alkali washed ether extract was concentrated to give the required derivative which crystallised from methanol in colourless plates or needles m.p. 125-126°. (Found: C, 75.0; H, 5.7. $C_{32}H_{30}O_6$ requires C, 75.3; H, 5.9%).

Carbinol B, obtained from colchinol methyl ether, had a m.p. and mixed m.p. (with the above synthetic carbinol) of 164-166°. A very small specimen of the degradation carbinol (B) was examined for optical activity in chloroform solution but appeared to be inactive.

Dehydration of above carbinol (XCI).

The carbinol (XCI; 0.5 g.) was refluxed in pure dry xylene (30 c.c.) over phosphorus pentoxide (1.5 g.) for fifteen minutes. The xylene solution was decanted off and the residue washed with fresh xylene. The combined

xylene washings were washed with sodium carbonate solution. Concentration of the dried xylene extract under vacumn afforded a gummy residue which was distilled under high vacumn. The fraction distilling up to 160° (air-bath) was collected, leaving a considerable quantity of undistilled material. The distillate was very viscous but could not be induced to crystallise.

The gum was hydrogenated in acetic acid (10 c.c.) using palladised charcoal (0.05 g.). After the uptake of hydrogen had ceased the catalyst was removed by filtration. The solvent was removed under vacumn to give dihydro-deaminocolchinol methyl ether as a gum which crystallised from methanol in small colourless prisms m.p. and mixed m.p. 94-96°.

9-Aminomethyl-9:10-dihydro-2:3:4:7-tetramethoxyphenanthrene (XCVII).

The cyanide (XC, 1 g.) in a solution of acetic acid (40 c.c.) containing concentrated sulphuric acid (1.5 c.c.) was hydrogenated at atmospheric pressure over active Adam's catalyst (0.15 g.). Absorption was complete in three hours. The filtered solution was diluted with ether and extracted with water. Ether extraction of the basified aqueous extract followed by concentration gave the required amine (0.9 g.) which crystallised from ether in small colourless prisms m.p. 138-140°. (Found: C, 69.8; H, 7.2; N, 4.5. $C_{19}H_{23}O_4N$ requires C, 69.3; H, 7.1; N, 4.25%).

Ring-enlargement of (XCVII).

The amine (XCVII. 0.55 g.) dissolved in acetic acid (5 c.c.) was treated with a solution of sodium nitrite (1 g.) in water (10 c.c.). The resulting solution was heated on a steam bath for half an hour, after which time a dark oil had separated. The oil was extracted with ether and the ether extract washed with acid and alkali. Evaporation of the ether afforded a dark coloured gum. This gum was distilled at 200-240° (bath) / 0.2 m.m. to

give a resinous brown distillate (0.47 g.) which could not be induced to crystallise. The gum, dissolved in benzene was passed through a column of alumina and the following fractions eluted with benzene.

The first washings were yellow in colour and afforded a solid which crystallised from methanol in yellow needles m.p. 115-116°. (Found: C, 64.0; H, 5.15; N, 3.8. $C_{19}H_{19}O_6N$ requires C, 63.9; H, 5.4; N, 3.9%). The third eluate on evaporation afforded 2:3:4:7-tetramethoxy-9-methylphenanthrene which crystallised from methanol in colourless prisms m.p. and mixed m.p. with an authentic sample 114-116°. It formed a picrate m.p. and mixed m.p. with the picrate of 2:3:4:7-tetramethoxy-9-methylphenanthrene 145-147°. The next eluate afforded a gum which on repeated crystallisation from methanol afforded deaminocolchinol methyl ether m.p. and mixed m.p. 105-110°. The second fraction afforded a yellow gum which could not be induced to solidify.

In one experiment the crude reaction gum was refluxed in pyridine (10 c.c.) with p-phenylbenzoylchloride (0.4 g.) for one hour. The cooled reaction mixture was diluted with ether and washed with dilute hydrochloric acid, sodium hydroxide solution and water in that order. Evaporation of the dried ether solution afforded a gummy solid which

crystallised from ethanol in beautiful long colourless needles m.p. 143-144°. This substance proved to be the unknown p-phenylbenzoic acid anhydride (Found: C, 82.2; H, 4.6 $C_{26}H_{18}O_3$ requires C, 82.5; H, 4.8%) as on hydrolysis with alkali it yielded p-phenylbenzoic acid m.p. and mixed m.p. 224-226°.

Experimental to Part IV.

Hydrolysis of colchicine to colchiceine.

Colchicine (1 g.) in water (60 c.c.) containing concentrated hydrochloric acid (0.6 c.c.) was refluxed for two hours. On cooling colchiceine (0.6 g.) crystallised out. It was used as such for the next stage.

N-Acetyliodocolchinol was best prepared by the method described by Lettre and Fernholz[103].

N-Acetylcolchinol was prepared by deiodination of the above iodo compound with zinc dust as described by Windaus[8].

Attempted reduction of N-acetylcolchinol.

(a) With Adam's catalyst at atmospheric pressure

Micro-hydrogenation of the above named compound in acetic acid solution using very active Adam's catalyst showed no absorption of hydrogen.

(b) With Adam's catalyst under pressure.

A solution of N-acetylcolchinol (0.2 g.) in ethanol (50 c.c.) containing two drops of 10% aqueous potassium hydroxide solution was agitated in a hydrogenation bomb with active Adam's catalyst (0.1 g.)

at 23° and under six atmospheres pressure of hydrogen. After six hours the catalyst was removed and the resulting solution concentrated under vacuo. The resulting gum dissolved completely in potassium hydroxide solution from which N-acetylcolchinol (0.15 g.) was recovered by acidification and ether extraction.

(c) With palladium on strontium carbonate.

A solution of N-acetylcolchinol (0.1 g.) in pure dioxan (50 c.c.) was hydrogenated at 150 to 180° and 111 to 130 atmospheres in the presence of 10% palladised strontium carbonate (0.1 g.). After four hours at the above temperature the catalyst was removed and the solvent removed under vacuo. The resulting gum was again soluble in potassium hydroxide solution from which N-acetylcolchinol (0.06 g.) was recovered.

(d) With sodium in liquid ammonia.

To liquid ammonia (15 c.c.) was added a solution of N-acetylcolchinol (0.36 g.) in ethanol (10 c.c.) followed by sodium (0.075 g.) i.e. two and a half atoms. After most of the ammonia had evaporated off water was added and the resulting solution extracted with ether. The ether extract did not afford any residue on evaporation. Acidification of the alkaline layer followed by ether

extraction afforded N-acetylcolchinol (0.3 g.).

Attempted reduction of N-acetylcolchinol methyl ether.

(1) With theorectical amount of sodium

A solution of the above named compound (0.18 g.) in ethanol (2 c.c.) was added to liquid ammonia (20 c.c.), followed by sodium (0.05 g.). The reaction mixture was worked up as described above but again only afforded the starting material (0.15 g.).

(2) With excess sodium.

N-acetylcolchinol methyl ether (0.1 g.) in ethanol (10 c.c.) was added to liquid ammonia (30 c.c.) followed by sodium (c.a. 1 g.). The ether extract of the diluted reaction mixture afforded a gum which gave an orange-red coloured 2:4-dinitrophenylhydrazone. Attempted hydrolysis of this gum with 10 N hydrochloric acid gave a gum which still gave an intractible orange-red coloured 2:4-dinitrophenylhydrazone. The gum could not be induced to solidify even after chromatography on magnesium carbonate.

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