# The Synthesis of Compounds Related to Colchicine

A thesis submitted for the degree of
Doctor of Philosophy
at the University of Glasgow

by

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July 1954.

## Preface.

The author wishes to express his gratitude to Professor J. W. Cook, F.R.S., and Dr. J. D. Loudon, for their guidance and advice in the work described. He is also indebted to the Carnegie Trust for the Universities of Scotland, for the award of a Research Scholarship. Because of war-time demands, this scholarship was held for only one year, and covers Part I of this thesis. There is an interval of about four years between the work described in Parts I and II, and this has necessitated a somewhat lengthy Historical Introduction to Part II.

The micro-analyses, unless otherwise acknowledged, were carried out by Mr. J. M. L. Cameron and his staff, to whom the author is also grateful.

# INDEX

# PART I

## Attempts to synthesise Deaminocolchinol Methyl Ether.

## Historical Introduction

The seeds and corms of the Autumn Crocus or Meadow Saffron (Colchicum Autumnale, Linn.) yield an alkaloid Colchicine, together with a number of related substances (1). Although known from earliest times as a specific for gout, later interest in colchicine centred on its property of arresting cell-division, and recent chemical interest in the alkaloid has been stimulated by the claim (2) that it caused regression of tumours in mice.

Colchicine, originally isolated in 1820, (3) was only obtained in a pure state in 1915, by Clewer, Green and Tutin (4). More recently, chromatography has been used (5) to obtain the pure alkaloid of m.p. 155°, $[\alpha]_D^{17}$, - 120.7°.

The chemical investigation of colchicine was begun by Zeisel (6), who showed that it had the molecular formula $C_{22}H_{25}O_6N$, and that on mild hydrolysis, it lost methanol, yielding an acidic product - Colchiceine - of formula $C_{21}H_{23}O_6N$.

$$C_{21}H_{22}O_5N(OCH_3) \longrightarrow C_{21}H_{22}O_5N(OH)$$

In contrast to colchicine, this hydrolysis product gives a green colouration with aqueous ferric chloride, and forms a copper salt (7). Hydrolysis of colchiceine under less mild conditions gives acetic acid, and an amphoteric substance - trimethyl colchicinic acid - $C_{19}H_{21}O_5N$. Zeisel was able to show by exhaustive methylation of this latter product, that the nitrogen was present as a primary amino group, and formulated the second hydrolysis step as follows,

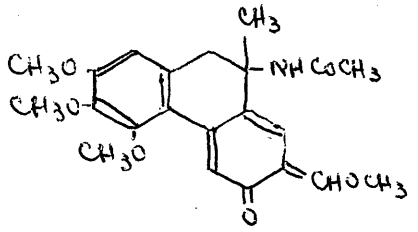
$$C_{19}H_{18}O_4.(OH)(NHCOCH_3) \longrightarrow C_{19}H_{18}O_4(OH)(NH_2)$$

Analysis showed also the presence of three methoxyl groups, and these observations led Zeisel to assume that colchicine was the methyl ester of an acetamido acid. This allocation of the oxygen atoms was apparently supported by the fact that neither colchicine nor its hydrolysis products gave carbonyl derivatives. A ketonic derivative, oxy-colchicine ($C_{22}H_{23}O_7N$) was obtained (14) by oxidation of the alkaloid and revealed the presence of a methylene group in the molecule, whose partial structure was apparently I

$$(CH_3O)_3.C_{14}H_7.(CH_2)(NH.COCH_3)(COOCH_3)$$

I

This formulation was re-examined and modified by Windaus (8), in a series of investigations (9) which eventually led him to propose the following structure for the alkaloid.

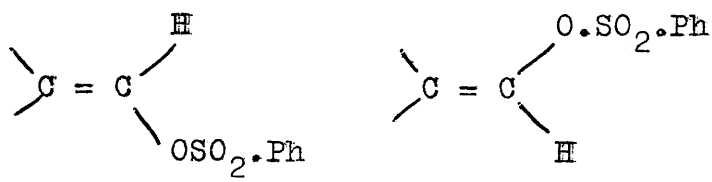



He showed that trimethyl colchicinic acid could readily be acylated, yielding O,N-diacyl derivatives. This, he pointed out, was indicative of an enol rather than a carboxyl structure, and this concept is supported by the green colouration shown by colchiceine and trimethyl colchicinic acid with aqueous ferric chloride. Windaus therefore postulated a tautomeric aldehyde hydroxy-methylene structure to account for the acid oxygen function of colchiceine, and supported it with three pieces of evidence:-

a) On treatment with bromine water (10) colchiceine is converted into an acid with the same number of carbon atoms

$$C_{20}H_{22}O_5N.(CHO) \longrightarrow C_{20}H_{19}Br_3.O_5N.(CO_2H)$$

b) The O,N-dibenzene sulphonyl derivative of trimethyl colchicinic acid exists in two distinct forms. This cannot be explained on a carboxylic acid formula, but may be readily accommodated in a hydroxy-methylene formula, where two stereo-isomers II may be expected.

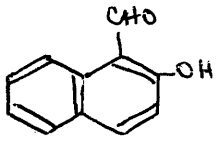


II

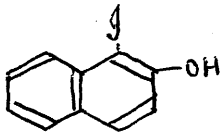
c) Colchiciene reacts with iodine and caustic potash, to give a phenolic product, N-acetyl iodocolchinol, in which the -CHO group is replaced by iodine

$$C_{20}H_{22}O_5N.(CHO) \longrightarrow C_{20}H_{22}O_5NI$$

This reaction may be compared with that of hydroxymethylene camphor with bromine and KOH (11) or iodine and KOH (12). In these latter cases, the hydroxymethylene group is removed, and a halogenated camphor is obtained. Windaus showed moreover (13) that under identical conditions, 2-hydroxy-1-naphthaldehyde III, (but not m-hydroxy aldehydes) gave the iodophenol IV

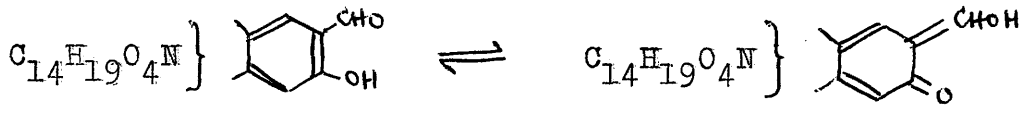



III



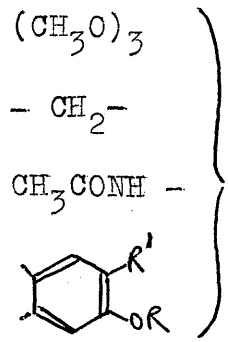

IV

These analogies led Windaus to postulate for colchiceine the phenol-aldehyde, hydroxymethylene-ketone formula V, although he appreciated its shortcomings.




V

In particular, it does not account for the absence of carbonyl properties in colchicine or its hydrolysis products. The Windaus partial V may be re-written as Va, in the light of Zeisel's work, and it therefore



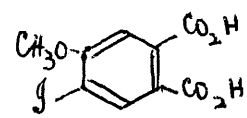

$C_8H_4$

Va R = H; R′= CHO

Vb R = H; R′= I

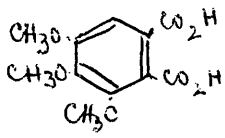
Vc R = $CH_3$; R′= I

Vd R = $CH_3$; R′= H

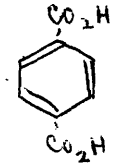



VI

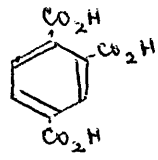
follows that N-acetyl iodocolchinol is represented by Vb, and its methyl ether by Vc. This latter substance may be reduced to N-acetyl colchinol methyl ether Vd. The structure of N-acetyl iodocolchinol methyl ether was supported by its oxidation to an iodomethoxy phthalic acid (16), which Grewe (15) subsequently identified as VI. The oxidation of colchicine to VII (16) served to locate the remaining three methoxy groups, and revealed the presence of another ring.



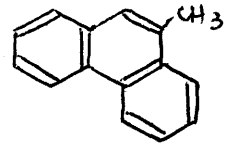

VII




VIII



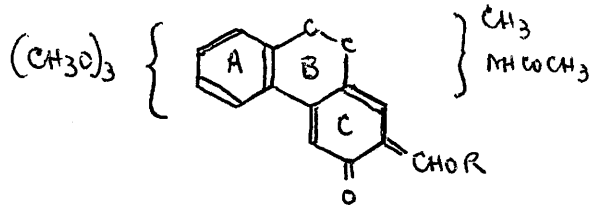

IX



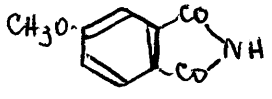

X

When the oxidation of colchicine is preceded by alkali-fusion, two non-methoxylated acids VIII and IX are obtained, and although open to re-interpretation in the light of the modern tropolone formula, this was taken by Windaus as evidence of a third, central, ring in the colchicine molecule. He was also able to show (9) that the tricyclic ring system was of the phenanthrene type. Hoffmann deamination of colchinol methyl ether gave a tetramethoxylated hydrocarbon, deamino colchinol methyl ether, which on demethylation and zinc dust distillation yielded 9-methyl phenanthrene X (17).

From its degradation to X, Windaus, assumed a partial formula XI for colchiceine and XII for colchicine with the proviso that the substituents of ring C may require to be interchanged. Orientation of the




XI : R=H XII : R=CH3



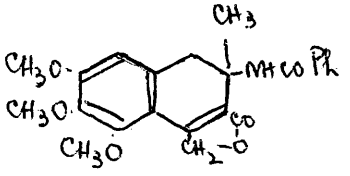

XIII

remaining substituents was accompanied (9) in the following manner:-

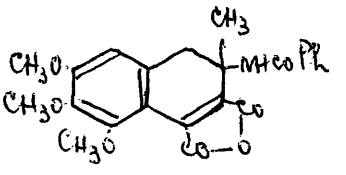
a) From the oxidation of N-acetyl colchinol methyl ether, 4-methoxy phthalimide XIII was isolated. This demonstrated that the nitrogen atom was situated adjacent to ring C.

b) Since Zeisel (14) had previously demonstrated the presence of a methylene group in the molecule, the methyl group was assumed to be located on the same carbon atom as the nitrogen.

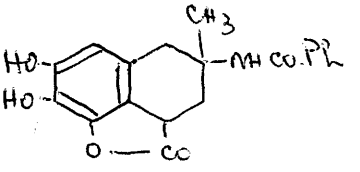
c) Careful oxidation of N-benzoyl trimethyl colchicinic acid gave two degradation products whose compositions indicated that only 3 carbon atoms had been lost, and whose properties suggested a lactone and an anhydride respectively. They were formulated as XIV (N-benzoyl colchide) and XV



XIV



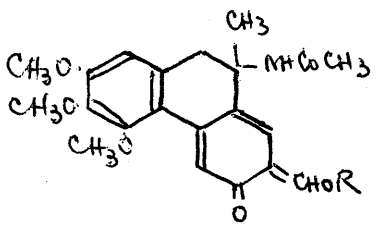
XV



XVI

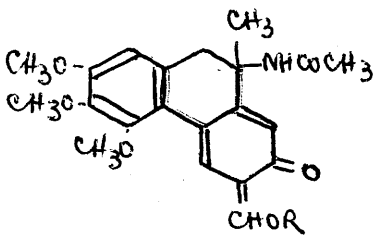
(N–benzoyl colchinic anhydride) in the light of structure XII. This orientation of the methoxy groups follows from a further degradation of the anhydride XV. Reduction of the olefinic double bond, and simultaneous hydrolysis of the anhydride, gave a dicarboxylic acid ($C_{23}H_{25}O_8N$) which on demethylation with HI lost one molecule of $CO_2$, and yielded a lactone. The formation of a lactone in such a molecule is only possible when both groups are in the peri–positions (18), and Windaus accordingly formulated the lactone as XVI.

With the orientation of the substituents now complete, Windaus was able to formulate colchicine as XVII or XVIII, and colchiceine as XIX or XX. It followed therefore




XVII : R = $CH_3$

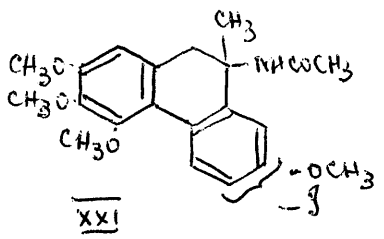
XIX : R = H



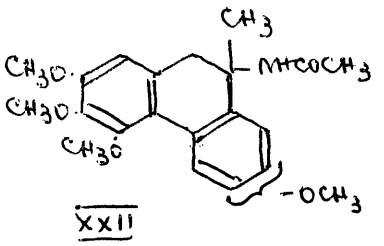

XVIII : R = $CH_3$

XX : R = H

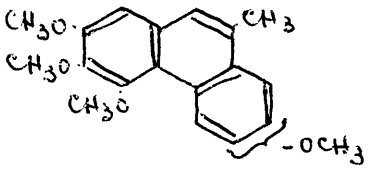
that N-acetyl iodocolchinol methyl ether, must be represented by XXI, colchinol methyl ether by XXII, and deaminocolchinol methyl ether by XXIII.



XXI



XXII



XXIII

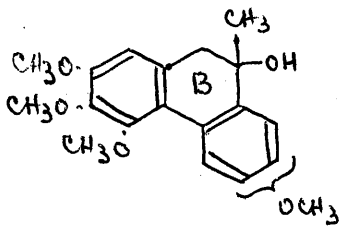
Concluding his notable examination of the alkaloid, Windaus investigated its reduction. The product, erroneously described by him as an octahydro-derivative, was later shown by Bursian (19) to be a hexahydrocolchicine, retaining a resistant double bond. In contrast to colchicine, this substance contained no readily hydrolysable methoxy group, and although this provided no direct support for the Windaus formula, it was compatible with it.

Windaus was nevertheless dissatisfied with this colchicine formula for a number of reasons (9). These may be summarised as follows:-

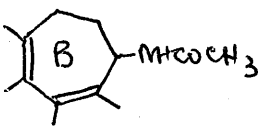
a) It does not readily account for the formation of oxalic and succinic acids in certain oxidations (9).

b) Neither colchicine nor colchiceine gives carbonyl derivatives and colchiceine (XIX or XX) which should readily isomerise to a phenolic aldehyde, can be reconverted (6) by methylation, to the readily hydrolysed methyl ether (colchicine).

Further criticism came from Cohen, Cook and Roe (20), who questioned the dihydrophenanthrene formula of colchinol methyl ether XXI. Its resistance to deamination (21), and the stability of the corresponding carbinol (XXIV) obtained by nitrous acid treatment (20), cannot be reconciled with such a formulation, and




XXIV




XXV

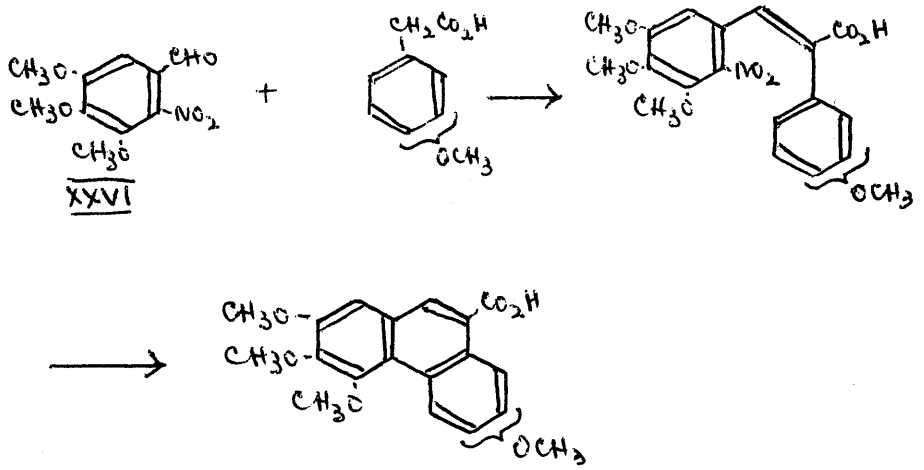
they suggested a 7-membered ring structure XXV, for ring B. Windaus' isolation of 9-methyl phenanthrene

from the degradation of colchinol methyl ether may be accounted for by isomerisation during the drastic zinc dust distillation.

There was thus considerable doubt at this stage, about rings B and C in colchicine, and about ring B in colchinol methyl ether. In order to resolve these difficulties, and to orient the methoxy group in ring C of deaminocolchinol methyl ether, steps were taken to synthesise the methyl tetramethoxy phenanthrene structures XXIII, proposed for this degradation product.

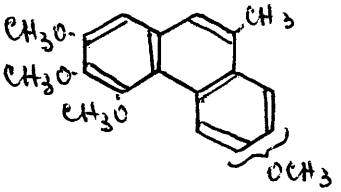
## Theoretical Discussion

The synthesis of phenanthrenes of type XXII is most readily envisaged by the classical Pschorr route (22) viz:

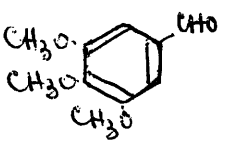


XXVI

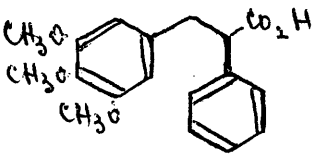
However, this approach is hampered by the relative inaccessibility of the requisite nitro-aldehyde XXVI. Although Sharp (23) obtained it by direct nitration of 3:4:5-trimethoxybenzaldehyde XXVII, his yields were low and unpredictable. Attempts to prepare this key intermediate by nitration of the anil (25) or the diacetate (24) of the aldehyde XXVII, were equally unsuccessful, and to circumvent these difficulties,



XXIII



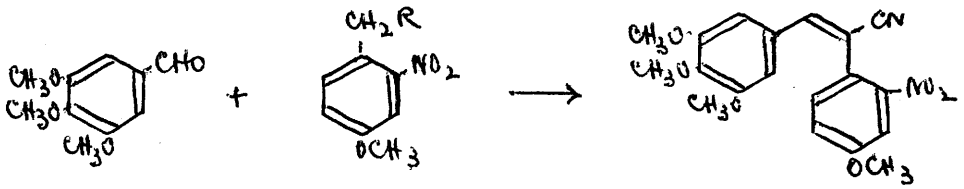
XXVII



XXVIII

Cook and Engel (25) attempted to postpone the nitration till a later stage. As a model substance, they prepared the trimethoxy acid XXVIII, by the Perkin reaction, and attempted unsuccessfully to introduce a nitro group into the methoxylated ring.

A possible route to XXIII, which avoids the nitro aldehyde, involves the condensation of trimethoxy benzaldehyde XXVII with 2-nitro-4-methoxyphenyl acetic acid XXIX, or the nitrile XXX. These reactions were considered and the latter was preferred in view of

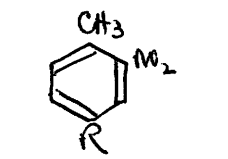


XXVII XXIX R = $CO_2H$ XXXI

XXX R = CN

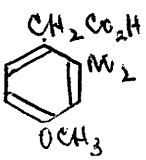
the work of Higginbottom, Hill and Short (26), who showed that under Perkin-reaction conditions, o-nitrophenyl acetic acid was substantially decarboxylated.

The nitrile XXX, was obtained by the following route. Nitration in strong acid as described by Nölting and Collin (27) gave 2-nitro-4-toluidine XXXII, which was converted (28) via the diazo-compound to the ether XXXIII, and thence by condensation with ethyl oxalate (29) to the

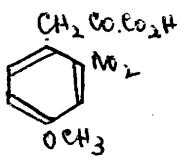


XXXII R = $NH_2$

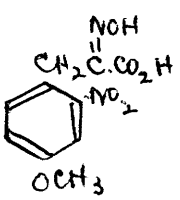
XXXIII R = $OCH_3$



XXXV



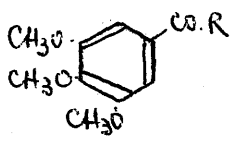
XXXIV



XXXVI

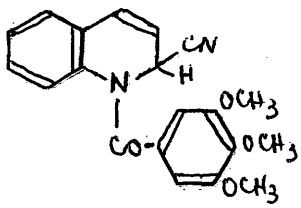
pyruvic acid XXXIV. This was characterised by oxidation to the acid XXXV, as described by Kermack, Perkin and Robinson (29). The required nitrile XXX was prepared by dehydrating the oxime XXXVI with acetic anhydride.

The aldehyde component XXVII had previously been prepared from 3:4:5-trimethoxy benzoic acid XXXVII, by the Sonn-Müller reaction, and by the Rosenmund reduction of the acid chloride XXXVIIa. In the former case (30) the yield was low, and in the latter, the reported yields (31)

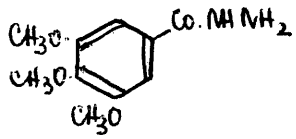



XXXVII : R=OH

XXXVII : R=OH=Cl




XXXVIII



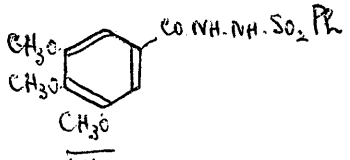

XXXIX

vary between 27 and 80%. In our hands, the Rosenmund method was unpredictable, and never gave high yields, so a search was made for a reliable route to XXVII. The

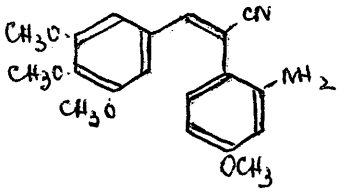
following two methods were investigated.

a) The Reissert reaction. (33). 3:4:5-Trimethoxybenzoic acid XXXVII was converted to the corresponding acid chloride XXXVIIa and coupled with quinoline in presence of HCN. The complex (XXXVIII) was decomposed with acid, yielding the required aldehyde XXVII, and quinaldonitrile.

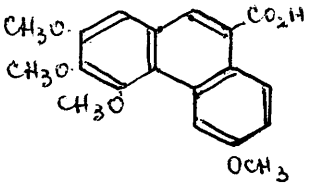
b) The McFadyen-Stevens reaction. (33). The acid XXXVII was esterified and converted via the hydrazide XXXIX, to be sulphonyl hydrazide XL.




XL




XLI




XLII

Alkaline decomposition of this product gave the aldehyde XXVII in good yield.

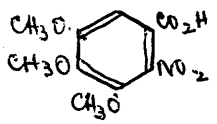
Condensation of the two components afforded the cyanostilbene XXXI, which was reduced to the amine XLI.

However, attempts to repeat the condensation reaction, yielded a new, isomeric, product, of higher m.p., and marked insolubility in common solvents. On standing for several days, the first (lower-melting) form changed into the second (higher-melting) form. They are probably stereo-isomers, but the relative insolubility of the second form, made it impossible to repeat the catalytic reduction under the same conditions. Reduction under pressure produced an intractable gum, and chemical methods were also unsuccessful, yielding in one instance a gum, and in another, an acidic product of formula $C_{19}H_{18}O_5N_2$. This is probably a partial reduction product, but no structural formula has been found to account for its chemical properties, and the work was discontinued.

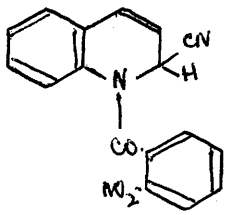
This line of approach being blocked, it was decided to revert to the Pschorr route described above. Although this involved the highly inaccessible (23, 24, 25) nitro-aldehyde XXVI, its successful application by Sharp (23) to the synthesis of XLII, and the obvious proximity of such structures to those under consideration (XXIII), prompted us to reinvestigate the preparation of XXVI.

One attempt was made to nitrate 3:4:5-trimethoxybenzaldehyde XXVII by means of copper nitrate (34), but the only product isolated contained no nitrogen. Analytical results suggest the formula $C_{10}H_{12}O_5$, but the substance is neutral, and hence cannot be trimethoxybenzoic acid. Its constitution is unknown.

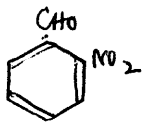
Although the nitroaldehyde XXVI is not readily accessible the corresponding acid XLIII is well known, and offered a route to XXV, if a method could be found,




XLIII



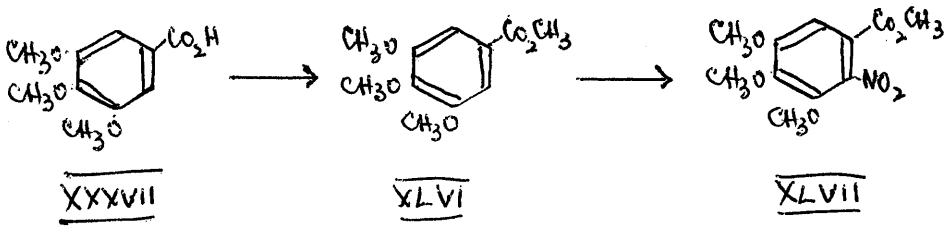

XLIV



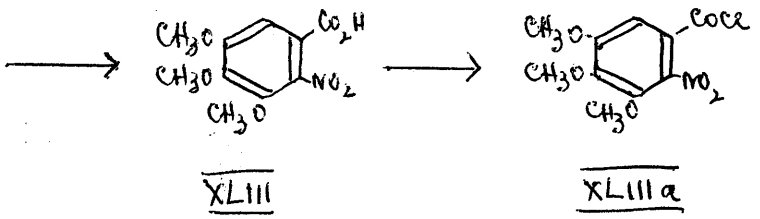

XLV

for converting nitro acids to nitro aldehydes. Almost all methods available for converting acids to aldehydes, involve a reduction step, and so cannot be applied to a nitro acid. However, two exceptions are the McFadyen-Stevens (33) and Reissert (32) reactions described above.

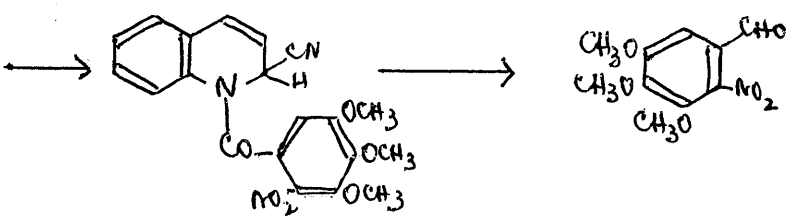
Of these, the former has been successfully applied to the preparation of m-nitrobenzaldehyde from the corresponding acid (33), but fails with the o- and p- isomers (41). The Reissert reaction has not been applied to nitro acids, and was therefore investigated, using o-nitrobenzoic acid as a model compound. With quinoline and HCN, o-nitrobenzoyl chloride gave the usual Reissert complex XLIV, which was decomposed with acid, yielding o-nitrobenzaldehyde XLV, in good yield. With this route now available, the trimethoxy-o-nitro series was then investigated. The required acid XLIII cannot be prepared in good yield by direct nitration of trimethoxybenzoic acid (35, 36), but nitration of the corresponding ester XLVI (37) gives XLVII, which is readily hydrolysed (36) to the nitro acid XLIII. The corresponding acid chloride XLIIIa (38) was found to undergo the Reissert reaction, but hydrolysis of the quinaldonitrile intermediate XLVIII proved troublesome. Weak acid did not bring about the hydrolysis, whilst strong acid caused decomposition of the product. Suitable conditions were eventually found, giving the much sought 2-nitro-3:4:5-trimethoxybenzaldehyde XXVI. The total preparation scheme is as follows:-



XXXVII XLVI XLVII



XLIII XLIIIa



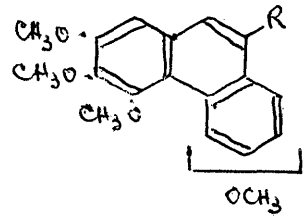
XLVIII XXVI

Yields were fairly good, except at the nitration step, where they averaged 30%, in the initial experiments. In an extensive series of experiments, covering a wide variety of conditions, the 80-90% yields claimed by Bogert and Hamburg (37) could not be duplicated. Under

optimum conditions, the nitration was effected in ca. 50% yield.

The above preparation scheme now gives a reliable, if somewhat tedious route to 2-nitro-3:4:5-trimethoxy-benzaldehyde, XXVI, and a considerable quantity of this intermediate was prepared. This work was later published (45).

The nitro-aldehyde (XXVI), was later used by another worker in a synthesis of the three tetramethoxyphenanthrenes (XLIX: R = $CH_3$). The corresponding phenanthrene carboxylic acids XLIX: R = $CO_2H$) were prepared by the




XLIX

Pschorr-route already explored by Sharp (23), and converted into the aldehydes (XLIX: R = CHO) by the McFadyen-Stevens reaction (33). Reduction of these aldehydes by Kishner's method (46) gave the three tetramethoxy-methyl-phenanthrenes (XLIX: R = $CH_3$). It was found (45) that none of them was identical with deaminocolchinol methyl ether, and so the Windaus formulae (XXIII) for this degradation product must be rejected.

## Experimental.

Only original work is reported in detail. Melting points are uncorrected.

o-Nitro-p-toluidine (XXXII) was prepared by the method of Nolting and Collin (27). It was not isolated as such. The bisulphate which is formed in the reaction was used directly in the preparation of the ether XXXIII.

2-Nitro-4-methoxy toluene (XXXIII) was obtained from the above product, by the method of Harvey and Robson (28). Yield from p-toluidine 30% b.p. 152°/28mm.

2-Nitro-4-methoxy-phenylpyruvic acid (XXXIV). The method of Kermack, Perkin and Robinson (29) gave the acid in ca. 30% yield. m.p. 134°.

2-Nitro-4-methoxyphenyl acetic acid (XXXV). Oxidation of the pyruvic acid (29) gave the product m.p. 158°.

2-Nitro-4-methoxybenzyl cyanide (XXX). The pyruvic acid (5 g.) was treated with 1.25g. NaOH and hydroxylamine hydrochloride (2.2 g.), and refluxed for 45 mins., in aqueous alcohol. The resulting oxime, was crystallised from methanol in cream needles, m.p. 170° (decomp.). Yield 84%.

Found: C, 47.5; H, 4.1; N, 10.9.

$C_{10}H_{10}O_6N_2$ requires C, 47.25; H, 3.95; N, 11.0 %.

This oxime (0.55 g.) was refluxed with acetic anhydride (40 c.c.) for 2½ hrs., and concentrated in vacuo. On adding water, the product crystallised and was recrystallised from alcohol m.p. 73-4°, yield 74%.

Found: C, 56.4; H, 4.5; N, 15.0.

$C_9H_8O_3N_2$ requires C, 56.3; H, 4.2; N, 14.6 %.

3:4:5-Trimethoxybenzoic acid (XXXVII) was prepared by the method of Slotta and Szyszka (31) which was found to be superior to that described in Org. Synth., VI, 96. Using purified dimethyl sulphate the yield was 72%. m.p. 165-6°.

3:4:5-Trimethoxybenzoyl chloride (XXXVIIa). This was prepared as described by Slotta and Szyszka (31), in 83% yield and b.p. 185°/18mm. m.p. 77°.

3:4:5-trimethoxy benzaldehyde (XXVII). (a) Rosenmund reaction. The acid chloride (22 g.) in dry xylene (110c.c.) was treated with palladised-barium sulphate (9.9 g., 3%) - prepared as described by Houben-Weyl Vol. II, 323. The mixture was refluxed whilst a vigorous stream of dry hydrogen was passed through for 55 hours. The catalyst was filtered off and the solution cooled. This gave a small amount of anhydride m.p. 156°. By extracting with saturated sodium bisulphite, 1.9 gms. of aldehyde was obtained, and recrystallised from ligroin.

m.p. 73-4°. Yield 11.5%. A repeat experiment using sulphur-free xylene, and running for 30 hours gave 20% of aldehyde.

(b) Reissert reaction. The acid chloride (3.5 g.) in dry benzene (5 c.c.) was added to a mixture of pure quinoline (5 c.c.) and anhydrous HCN. (1 c.c.) at -10°. (The anhydrous HCN was prepared according to the method of Slotta (39)). After standing for 16 hours ether was added, and the solution washed in turn with water, $5NH_2SO_4$, dilute sodium bicarbonate and water. A solid separated and was combined with that obtained, by evaporation of the ethereal solution. The crude product was crystallised from alcohol and gave a small quantity of trimethoxy-benzoic anhydride m.p. 159°, together with the required 1-(3′:4′:5′-trimethoxy benzoyl)-1:2-dihydroquinaldinonitrile (XXXVIII), m.p. 176-7°.

Found: C, 68.8; H, 4.9 ; N, 8.2.

$C_{20}H_{18}O_4N_2$ required C, 68.6; H, 5.1; N, 8.0 %.

Hydrolysis of the above nitrile, by shaking for several hours with $10NH_2SO_4$, followed by Ether extraction, gave 3:4:5-trimethoxybenzaldehyde. m.p. 73-4°C.

(c) McFadyen-Stevens reaction.

Methyl 3:4:5trimethoxy benzoate (XLVI) was most easily prepared by the method of Bargellini and Molina (40). b.p. 167°/10mm. m.p. 84°. Yield 82%.

3:4:5-trimethoxy benz-hydrazide XXXIV. The above ester (17g) was refluxed for 2 hours with hydrazine hydrate (18 c.c. 50%) and methanol (30 c.c.). Cooling gave crude hydrazide in 70% yield. Cryst from methanol m.p. 129°.

Found: C, 51.3; H, 6.65.

$C_{10}H_{14}O_4N_2.CH_3CH$ requires C, 51.2; H, 6.9 %.

After heating at 100° in vacuo the m.p. rose to 158°.

Found: C, 53.2; H, 6.2; N, 12.5.

$C_{10}H_{14}O_4N_2$ requires C, 53.1; H, 6.2; N, 12.4 %.

Benzene Sulphonyl - 3:4:5-trimethoxy benzhydrazide (XL). Benzene sulphonyl chloride (7.3 g.) was added slowly to a stirred, cooled, solution of the benzhydrazide (9.1 g.) in pyridine. After 2 hours, it was poured on to ice-HCl. The precipitated product was washed with dilute HCl, and water, and crystallised from acetic acid. Yield 67%. m.p. 250° (decomp.).

Found: C, 52.2; H, 4.7; N, 7.6.

$C_{11}H_{16}O_6N_2S$ requires C, 52.5; H, 4.9; N, 7.65 %.

3:4:5-trimethoxy-benzaldehyde (XXVII). The sulphonyl benzhydrazide (9.3 g) was dissolved in ethylene glycol (94 g) and heated to 160° in an oil-bath. Solid sodium carbonate (6.76 g.) was then added, and after 75 seconds hot water in excess was added, to stop the reaction. Ether extraction gave the aldehyde in 72% yield. m.p. 74°.

α-(2-nitro-4methoxyphenyl)-3:4:5trimethoxycinnamonitrile XXXI.

a) The aldehyde (XXVII) (0.28 g.) and the nitrile(XXX) (0.25 g.) dissolved in the minimum quantity of alcohol was treated with a few drops of piperidine and allowed to stand overnight. The product was filtered off and crystallised from alcohol in needles, m.p. 153-4°. Yield 84%.

Found: C, 61.9; H, 4.6; N, 7.6.

$C_{19}H_{18}O_6N_2$ requires C, 61.6; H, 4.9; N, 7.6 %.

b) A repeat experiment gave a product of m.p. 184-5°, which was almost insoluble in most organic solvents. It was recrystallised from chloroform.

Found: C, 61.8; H, 4.7; N, 7.4.

Calc. for $C_{19}H_{18}O_6N_2$ C, 61.6; H, 4.9; N, 7.6 %.

On standing, the lower melting form changed to m.p. 184°, and showed no depression in mixed m.p. with the other isomer.

Reduction of the nitrile (XXXI). The palladium catalyst was prepared by the method of Heilbron, Sexton and Spring (42).

a) The lower melting isomer of the nitrile (1.3 g.) in 70 c.c. acetone, was reduced by hydrogen and palladium (60 mgm.). Uptake 120c.c. Evaporation of the solvent gave a green oil, which solidified on standing, and was recrystallised from methanol, m.p. 177-8°.

Found: C, 67.1; H, 6.2; N, 8.5.

$C_{19}H_{20}O_4N_2$ requires C, 67.05; H, 5.9; N, 8.2 %.

b) The higher melting isomer (1.9 g.) suspended in acetone (310 c.c.) was hydrogenated at 80°/ 30 atmos., in presence of 0.1 g. palladium - black. Evaporation yielded a gum, from which no pure material could be isolated. Chromatography on alumina was unsuccessful.

A second attempt was made to effect reduction, by adding 0.1 g. of the high-melting isomer to a boiling solution of stannous chloride (0.2 g.) in methanol (30 c.c.) containing a little conc. HCl, and refluxing for 15 mins. After cooling, the resulting solution was neutralised with sodium carbonate solution. A crystalline product separated, and was recrystallised from methanol in needles, m.p. 199-200°. This product gave a

negative test for tin, with Cacotheline (43), and was insoluble in mineral acid. It dissolved in alkali, and was reprecipitated by acid. It was light sensitive

Found: C, 64.4; H, 4.9; N, 7.2.

$C_{19}H_{18}O_5N_2$ requires C, 64.4; H, 5.1; N, 7.9%.

Nitration of 3:4:5-trimethoxybenzaldehyde. (XXVII). The aldehyde (1 g.) was added gradually to copper nitrate (0.615 g.) and acetic anhydride (10 c.c.) at 30°C. After standing overnight, the solution was poured into water, and the yellow oil dissolved in ether. This solution was washed with water and aqueous sodium bicarbonate and extracted with sodium bisulphite solution.
Decomposition of the bisulphite solution yielded nothing, but concentration of the ether solution gave a neutral, nitrogen - free product, which crystallised from water in colourless needles. m.p. 113°.

Found C, 56.8; H, 5.8.

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

1-(2-Nitrobenzoyl)-1:2-dihydroquinaldonitrile. (XLIV).
A mixture of quinoline (14 g.) and dry HCN (3 c.c.) was maintained at -10°, whilst a solution of o-nitrobenzoyl chloride (10 g.) in dry benzene (10 c.c.) was added dropwise over a period of 10 minutes. After standing overnight, benzene (130 c.c.) was added, and the solution washed successively with water, 5N sulphuric acid, aqueous

sodium bicarbonate, and again with water. The benzene solution was then dried and concentrated. The resulting solid was washed with ether, and crystallised from alcohol. Yield ca. 80%. m.p. 173°.

Found: C, 67.4; H, 3.8; N, 13.5.

$C_{17}H_{11}O_3N_3$ requires, C, 66.9; H, 3.6; N, 13.8 %.

o-Nitrobenzaldehyde XLV. (a) The nitrile (XLIV) (2 g.) and 5N sulphuric acid (500 c.c.) containing a small amount of acetic acid was refluxed for 3 hours, cooled, and extracted with ether. The extract was washed, dried and concentrated. The product crystallised from ligroin m.p. 39°. Yield 18%. It gave a 2:4-dinitrophenyl hydrazone m.p. 250°, identical with authentic material. Many reference books quote a m.p. of 192° for this derivative, but the true m.p. is given by Blanksma and Wackers (44).

(b) Repetition of the hydrolysis with 15N acid, gave the aldehyde in 73% yield.

Methyl 2-nitro-3:4:5-trimethoxybenzoate XLVII. The following twelve experiments were carried out in an attempt to duplicate the very high yields claimed (37) for this reaction.

(1) A solution of methyl 3:4:5-trimethoxy benzoate (12 g.) in acetic anhydride (48 c.c.) was cooled to 0°C, and 8.5 c.c. nitric acid (1 c.c. of d. 1.5 + 7.5 c.c. of d. 1.42) added dropwise with shaking. The solution was left overnight and the acetic anhydride was then removed in vacuo leaving a tarry residue. Trituration with water gave a pasty solid which was crystallised from ether in yellow prisms of m.p. 67°. The yield by this method was initially ca. 40%, but in later experiments on a larger scale, the yield rose to ca. 50%. Bogert and Plaut (37) claimed a yield of 80% by this method.

(2) The above experiment was repeated with two modifications. During the addition of the nitric acid, the solution was kept at −5 to −10°C, and the final solution was kept overnight in ice water. Yield 29%.

(3) The ester (5 g.) in 20 c.c. acetic anhydride was cooled to −10°C and treated dropwise with 2 c.c. of nitric acid of d. 1.5. After standing overnight the solution was poured into water (150 c.c.) and extracted with ether. This gives a yield of 34%.

(4) A sample of the ester was nitrated as in experiment (3) above but left for 2 hours instead of overnight. It was worked up as before, giving a yield of 24%.

(5) A solution of concentrated nitric acid (2 c.c.) (d. 1.42) in acetic anhydride (20 c.c.) was added slowly and with shaking, to the ester (2.5 g.) in acetic anhydride (10 c.c.) at -10°C. After standing overnight, the excess acetic anhydride was removed in vacuo, and the residue triturated with water. Yield 15%.

(6) The ester (2.5 g) in acetic anhydride (10 c.c.) was cooled to -5°C and treated dropwise and with shaking, with 2 c.c. of conc. nitric acid which had been previously saturated with nitrous fumes. The solution was left overnight, poured into water and yielded a paste. After trituration with dilute sodium carbonate solution, the product was crystallised from ether. Yield 27%. Using these conditions, Hamburg (37) claims a yield of 90% and Overmeyer (37) claims that his yield was "satisfactory".

(7) The above experiment was repeated using a modified nitrating agent. The conc. nitric acid was saturated with nitrous fumes, as before, and its density was adjusted to 1.43 by addition of fuming nitric acid (d. 1.5). Yield 38%.

(8) The ester (2.5 g.) was added portionwise to copper nitrate (1.34 g.) in acetic anhydride (10 c.c.) at 20°. The solution was left overnight, and then poured

into water (150 c.c.). This gave an oil, which was taken up in ether, and washed with dilute sodium carbonate solution. The ethereal solution yielded the nitro-ester, on concentration. Yield 43%.

(9) The ester (2.5 g.) was dissolved in 20 c.c. chloroform and $NO_2$ bubbled through the solution for 3 hrs. After standing overnight the solution was evaporated, redissolved in ether, and the ether solution washed with dilute NaOH, and then with water. Evaporation gave the nitro-ester in 22% yield.

(10) Experiment (3) was repeated with two modifications. Instead of fuming nitric acid (d 1.5), nitric acid of d. 1.52 was used, and the temperature during the addition of the acid was kept at 0°C, instead of -10°. Yield 22%.

(11) Nitration by copper nitrate was carried out as in experiment (8), but during the addition of the ester, the temperature was kept at 30-35°, instead of 20°. Yield 44%.

(12) The ester (30 g.) in acetic anhydride (120 c.c.) was kept at -10°, and stirred, during the addition of a mixture of fuming nitric acid (d 1.5) (25 c.c.) and conc. nitric acid (1 c.c.) saturated with nitrous fumes. After standing overnight, the solution was poured on to ice,

and extracted with ether. The ether solution was washed with water, and concentrated, giving a 30% yield of the nitro-ester.

2-Nitro-3:4:5-trimethoxybenzoic acid (XLIII). Hydrolysis of the nitro-ester (XLVII) by the method of Thoms and Siebeling (36) gave the nitro acid in 95% yield. It was crystallised from benzene, m.p. 165°.

1-(2-Nitro-3:4:5-trimethoxybenzoyl)-1:2-dihydroquinaldonitrile (XLVIII). The nitro acid was converted to the corresponding acid chloride by the method of Auwers and Düesberg (38) in almost quantitative yield, and crystallised from benzene - ligroin m.p. 93°.

The acid chloride (4.3 g.) in dry benzene (10 c.c.) was added slowly and with swirling to quinoline (5 g.) and dry HCN (1 c.c.) at 0°C. Addition was complete in 15 minutes, and the mixture was left overnight in ice. Addition of ether (65 c.c.) precipitated a solid which was filtered off. The ether solution was washed with water, dilute sulphuric acid, sodium becarbonate solution, and finally with water. Concentration yielded an oil which solidified. The combined solid fractions was recrystallised from alcohol m.p. 167°. Yields varied

between 65 and 80%.

Found: C, 60.9; H, 4.4; N, 10.7.

$C_{20}H_{17}O_6N_3$ requires C, 60.75; H, 4.3; N, 10.6%.

It was later found preferable to use benzene or chloroform instead of ether.

2-Nitro-3:4:5-trimethoxybenzaldehyde (XXVI). The following experiments were carried out, to find the best conditions for hydrolysis of the nitrile (XLVIII).

(1) The nitrile (0.33 g.) was refluxed for ¾hr., with 5N sulphuric acid (20 c.c.). It was recovered unchanged.

(2) The nitrile (0.2 g.) in acetic acid (20 c.c.) was treated with conc. sulphuric acid (3 c.c.) and left overnight at room temperature. On pouring into water, the nitrile was recovered.

(3) Refluxing the nitrile (0.5 g.) in 5N sulphuric acid (100 c.c.) for 5½ hrs., led to partial decomposition to the aldehyde. This was detected by means of 2:4-dinitrophenyl hydrazine. Yield of recovered nitrile 0.37 g.

(4) Using 0.5 g., of the nitrile, 100 c.c. of 10N sulphuric acid, and 15 c.c. of acetic acid, the

hydrolysis was effected by refluxing for 2 hrs., and then distilling into a solution of 2:4-dinitrophenyl hydrazine in 2NHCl. The precipitated product was crystallised from acetic acid m.p. 225°.

Found: N, 16.15.

$C_{16}H_{15}O_9N_5$ requires N, 16.6% .

(5) The nitrile (1 g.) was refluxed for 30 mins., with 15N sulphuric acid (125 c.c.) and a little acetic acid. A small quantity (0.22 g.) of insoluble material was filtered off, and the solution extracted with ether. Concentration yielded the aldehyde m.p. 76°, in 53% yield.

(6) Sulphuric acid (60 c.c.; 20N) and 100 c.c. ether were added to 1 g. of the nitrile, and the mixture warmed at 40-45° for 4 hours. The ether layer was then washed with water, and dried. On evaporation, the aldehyde was obtained in ca. 40% yield.

(7) Large scale preparations were carried out as follows:-

The nitrile (10 g.) was powdered, and shaken at ca. 80°, with 15-N sulphuric acid (1250 c.c.) for 2½ hrs., filtered and extracted with chloroform. This extract was washed with sodium bicarbonate solution, and then with water, dried, and concentrated. This gave the required aldehyde in ca. 60% yield. It was recrystallised from aqueous alcohol, in pale yellow needles m.p. 76°.

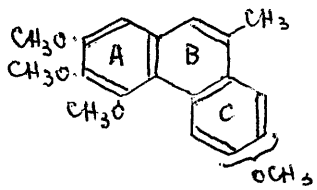
# PART II

## An investigation of rings B and C in Colchicine.

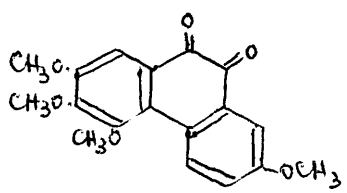
## Historical Introduction

This section describes developments which took place during the period 1943-1947, and restates the problem as it appeared at the end of that period.

The discovery (45) that deaminocolchinol methyl ether had not the methyl phenanthrene structure XXIII ascribed to it by Windaus (9), cast doubt on his formulation of ring B in other degradation products and hence in the alkaloid itself. It thus became




XXIII

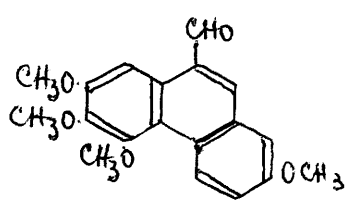



L

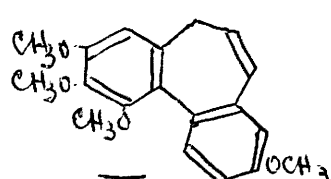
vital to establish the true structure of this degradation product.

Consideration of an alternative structure for deaminocolchinol methyl ether, had to take into account the discovery of an isomeric substance (iso-deamino-

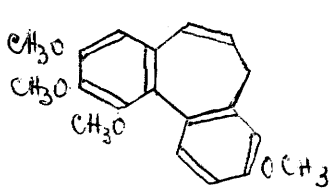
colchinol methyl ether) by Barton, Cook and Loudon (47). These authors found that dehydration of Cook's carbinol (20) -originally formulated as XXIV - or deamination of Colchinol methyl ether by the method of Cook and Graham (21), gave a mixture of the two isomers. They showed also, that both yielded the same dihydride, and yielded on oxidation, the quinone L which was obtained synthetically, from the appropriate methyl phenanthrene (XXIII). This established the orientation of the methoxyl groups, and they went on to investigate the nature of ring B. Deaminocolchinol methyl ether reacted with $OsO_4$, to give a glycol, which on cleavage by lead tetra-acetate and treatment with alkali, gave the phenanthrene-10-aldehyde LI. Similar treatment of iso-deaminocolchinol methyl ether gave the isomeric 9-aldehyde, and it was thus established that




LI



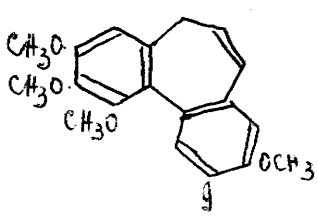

LII



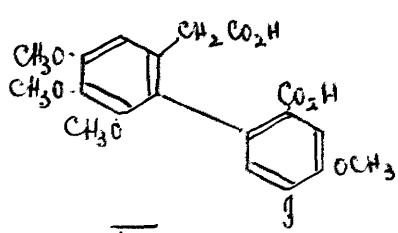

LIII

deaminocolchinolmethyl ether and iso-deaminocolchinol methyl ether are respectively LII and LIII. Confirmation of the 3-carbon bridge between rings A and C, was provided by Tarbell, Frank and Fanta (48). By careful oxidation of deaminoiodocolchinol methyl ether LIV, they obtained a dicarboxylic acid (LV), and demonstrated the presence of an α-methylene grouping by Dieckmann cyclisation of its diester, to a phenanthrol. This 7-membered ring structure has also been reconciled with the Windaus degradation (9) to 9-methyl phenanthrene. Cook, Dickson and Loudon (49), have synthesises the parent hydrocarbon LVII, and demonstrated that under the HI-zinc dust distillation conditions employed by Windaus, the model substance LVII also yielded 9-methyl phenanthrene.

Although the structure of deaminocolchinol methyl ether was thus firmly established, and the 7-membered central ring was presumed to be present also in N-acetyl-colchinol methyl ether and in colchicine, there was no

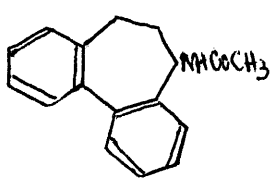



LIV

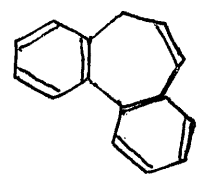



LV

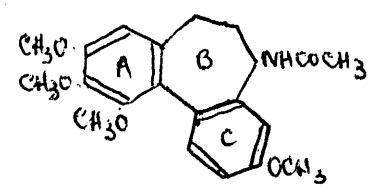
concrete evidence for this assumption. It was still possible that the deamination process involved an alteration of the central ring. This doubt was largely removed by Cook, Dickson and Loudon (49) who found that deamination of the model substance LVI led analogously to LVII.




LVI



LVII




LVIII

With the evidence available at this stage, and Windaus' evidence (Part I. p. 9. ) for the location of the acetamido-group, it seemed highly probable that N-acetylcolchinol methyl ether had the structure LVIII, and consequently that ring B might be regarded as 7-membered in the alkaloid itself. This formula resolves the difficulties originally voiced by Cohen, Cook and Roe (20), and by Windaus (9) with respect to ring B

(Part I, p. 12.), and it was therefore highly desirable to obtain confirmation, by a synthesis of N-acetylcolchinol methyl ether.

Some unsuccessful attempts had already been made (50, 51) and so, part of the work described in this section, is the investigation of a possible route to N-acetylcolchinol methyl ether. The remainder of the work relates to ring C which must now be discussed.

The Windaus formula for colchicine gave a less satisfactory representation of ring C than of ring B, but no noteworthy alternatives were advanced, and the difficulty of providing an alternative structure was enhanced by the absence of any degradative evidence. Apart from the rearrangement to the phenol, N-acetyl-iodocolchinol, the only known degradation product of ring C was a non-ketonic acid, $C_{21}H_{23}O_8N$, of unknown constitution, obtained by periodate oxidation of colchiceine (52).

A satisfactory formulation of ring C had to account for the following facts:-

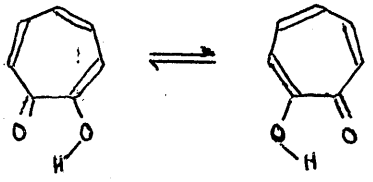
1. Colchicine shows feebly basic properties (8) and is readily hydrolysed to methanol and an acidic product, colchiceine. The latter may be re-methylated,

yielding a mixture of colchicine and an isomer iso-colchicine, which on hydrolysis regenerates colchiceine. (53).

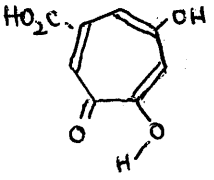
2. No carbonyl derivatives can be prepared, although colchiceine can be reduced to a diol (19).
3. Colchiceine is converted into an iodo-phenol, by iodine in presence of alkali (9).

Dewar (56) noted that these properties are similar to those of Stipitatic Acid, a mould product which was isolated and investigated by Birkinshaw, Chambers and Raistrick (54) in 1942. Stipitatic Acid is amphoteric, and possesses two acid functions in addition to the readily detectable carboxyl group; like colchiceine it gives two isomeric methyl derivatives, and it shows no ketonic properties, although the presence of a carbonyl group has been detected in partially reduced material. On complete reduction, it gives a trihydric alcohol, and on alkali fusion, it rearranged to a phenolic acid. Although stipitatic acid ($C_8H_6O_5$) is a simple molecule no satisfactory formula could be found for it, till Dewar (55) postulated that it was an example of a new aromatic type, based on cycloheptatrienolone LIX which

he named "Tropolone". Dewar accordingly formulated

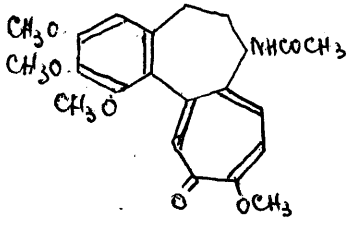


LIX

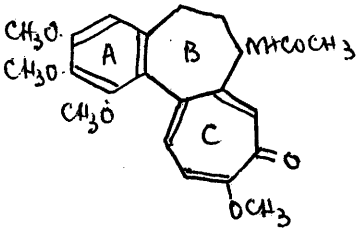


LX

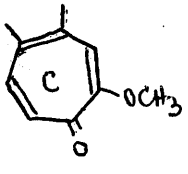
stipitatic acid as LX, and predicted that such a structure would account for its known chemistry. In view of the similarities already mentioned, he later formulated Colchicine (56), as a tropolone methyl ether LXI (later corrected by Loudon (57) to LXIIa or b). It follows therefore that colchiceine will be represented by LXIII.



LXI



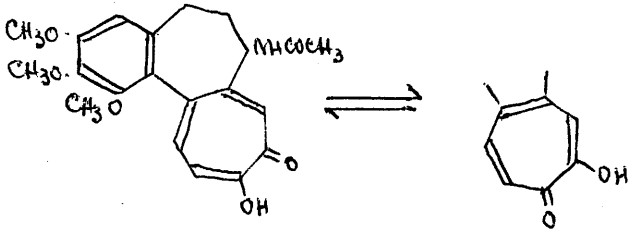
LXIIa



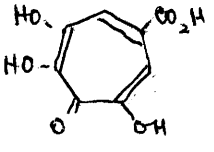
LXIIb.

The properties predicted for tropolone LIX by Dewar, were later confirmed when the substance was synthesised (58) and his formula for stipitatic acid LX, has also been proved by synthesis (59). Several other natural tropolones have been described (60), and of these may be mentioned Puberulic Acid (LXIV), which is a mould product, and Purpurogallin (LXV) which occurs in certain galls.

With the natural occurrence of tropolone derivatives thus established, the marked similarity in the properties



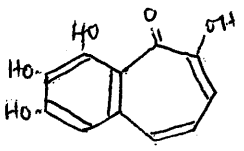

LXIII



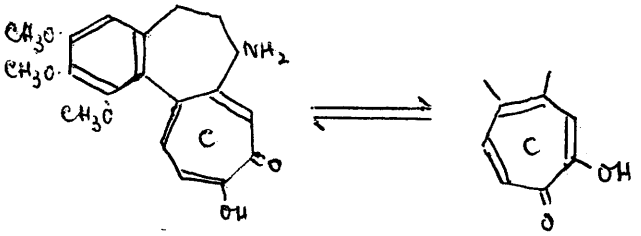

LXIV

of colchiceine LXIII, and the known tropolones, pointed strongly to the Dewar formulation of colchicine (LXIIa or b). It accounted for its ready hydrolysis to colchiceine, the acidity of the latter, the formation of the isomers

colchicine and iso-colchicine (LXIIa and b) when it was remethylated (53), and the production of ketonic material when it was only partially hydrogenated (67). Dewar's formula also accommodates Windaus' discovery that trimethylcolchicinic acid (LXVI) yields two isomeric

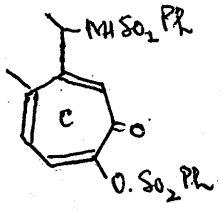


LXV

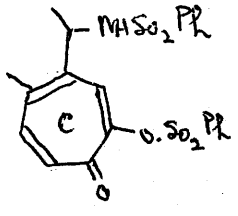


LXVI

di-(benzene sulphonyl) derivatives (LXVII) and (LXVIII), (8).

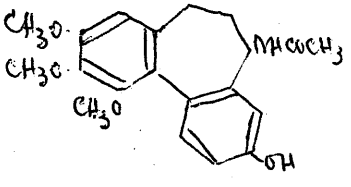


LXVII

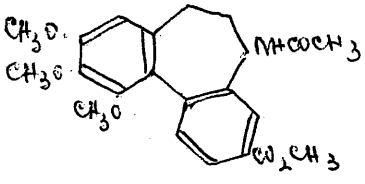


LXVIII

A number of characteristic properties and reactions have been shown to be common to both tropolones and colchiceine. Thus both give copper complexes and a green coloration with ferric chloride (6, 58), and the methyl ethers react with amines to give amides (76, 58b). Basic properties have also been demonstrated in both series (8, 58b). It has furthermore been shown (58b), that the rearrangement with alkaline sodium hypoiodite, which converts colchiceine into an iodo-phenol (LIV), can be duplicated in the tropolone series. Recent work on colchicine has revealed further rearrangements in which ring C becomes benzenoid. Thus Cech and Santavy (62) obtained N-acetylcolchinol (LXIX) direct from colchiceine by treatment with alkaline $H_2O_2$, and Santavy (63), found



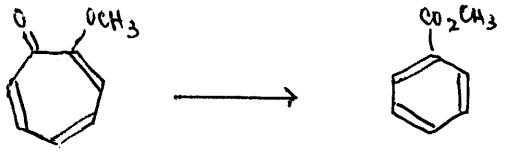

LXIX




LXX

that colchicine was isomerised by sodium methoxide to a carboxylic ester. This product was named allo-colchicine

by Fernholz (64), and identified as LXX by degradation of the $-CO_2CH_3$ group to $-NH_2$ and thence to the known phenol (LXIX). This latter rearrangement has also been carried out on tropolone methyl ether by Doering and Knox (58b), and the product was shown to be methyl benzoate (LXXII).

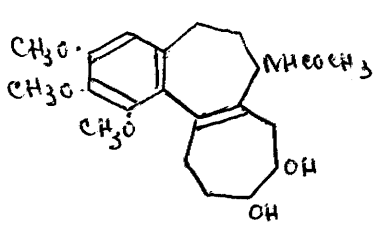



LXXI LXXII

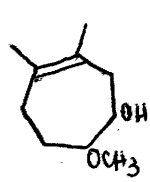
The analogy with tropolone is thus almost complete. There remains only one serious divergence. The alkaline $H_2O_2$ rearrangement described above has not yet been demonstrated in authenticated tropolones. Under these conditions, tropolone (LIX), stipitatic acid (LX), and puberulic acid (LXIV) undergo ring fission (58a, 72, 73) to unsaturated acids. Colchicine also fails to undergo the Diels-Alder reaction with maleic anhydride (19), although tropolone gives a bis-adduct (65), but this may be a function of the peculiar environment of the tropolone ring in colchicine.

Polarographic (74) and Infra-Red (75) measurements support the tropolone structure for colchicine, and from X-ray studies (90) it appears, moreover, that colchicine has structure LXIIa rather than LXIIb. Nevertheless it is desirable to obtain direct chemical proof of the size of ring C, and this was the second object of the work in this section.

Several workers have already attempted to prove that ring C of colchicine is 7-membered. Thus hexahydrocolchiceine, which has been ascribed the structure LXXIII (61), has been shown to behave as a 1:2-diol towards potassium methyl osmiate (69), lead tetra-acetate (66, 69), and periodic acid (61, 67), although no definite product has been isolated from any of these experiments. Attempts to oxidise hexahydrocolchicine LXXIV and hexahydrocolchiceine LXXIII with




LXXIII

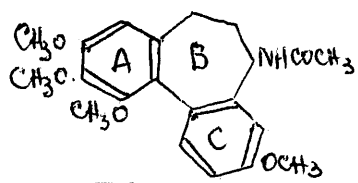



LXXIV

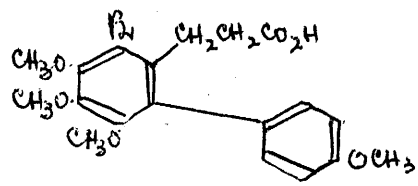
potassium permanganate or chromium trioxide (68, 70) failed to yield recognisable products, and an attempt to oxidise colchicine with lead tetra-acetate (71) was equally unsuccessful.

## Theoretical Discussion.

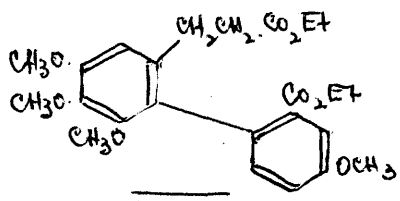
The first problem in this section, the investigation of a synthetic route to N-acetylcolchinol methyl ether (LVIII) had already been attempted by a number of workers (50, 51, 77, 78). In these investigations unsuccessful attempts were made to build ring B on to a suitable




LVIII



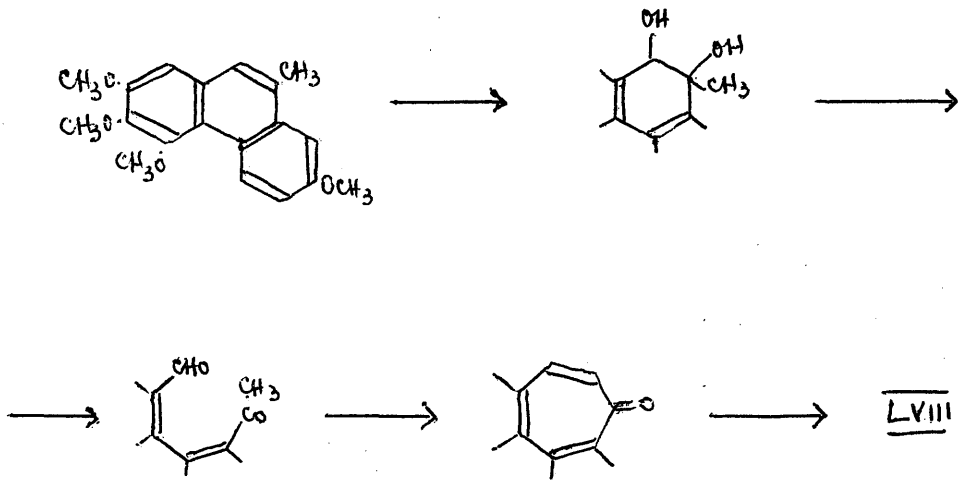

LXXV




LXXVI

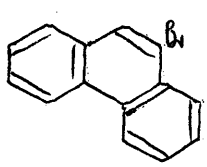
diphenyl (rings A --- C) structure. Thus the ring closure of LXXV led to bromine migration, and the production of an indanone, whilst attempts to prepare the di-ester LXXVI for Dieckmann cyclisation were unsuccessful. The fundamental ring system has been obtained by a variety of routes (84, 49, 85, 86) but many of these model syntheses require starting materials not readily available in the tetra-methoxy series. With these considerations in mind, attention was directed to

the ring expansion of a suitably methoxylated phenanthrene by the following method:-

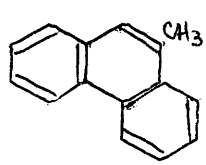



Model experiments were therefore conducted on a simple phenanthrene derivative.

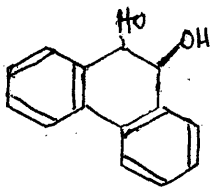
Crude phenanthrene was purified as its 9:10-dibromide (79) and the latter converted into 9-bromphenanthrene LXXVII from which the 9-methyl compound LXXVIII was prepared by the Grignard reaction (80). Phenanthrene had previously been converted via the complex LXXIXa,



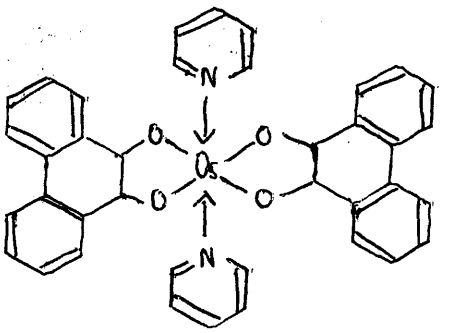

LXXVII




LXXVIII

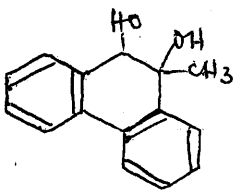



LXXIX

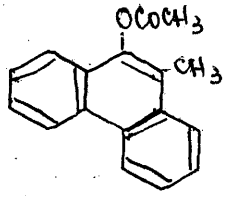



LXXIXa

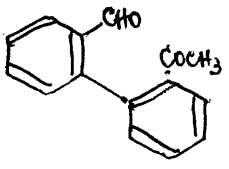
into the glycol LXXIX, by Criegee, Marchand and Wannowius (81), using Osmium tetroxide in presence of pyridine, and by the same method 9-methylphenanthrene gave the glycol LXXX. Its structure was proved by its ready



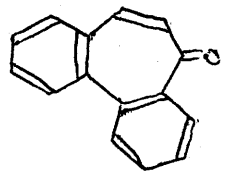

LXXX




LXXXI



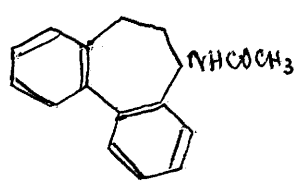

LXXXII



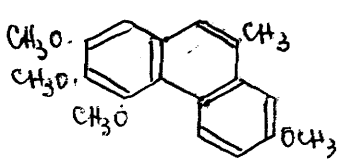

LXXXIII

dehydration by acetic anhydride to the acetate (LXXXI). In an effort to prepare diols of this type by less expensive means, phenanthrene was treated with, (a) The Milas reagent (82)-$H_2O_2$,t-butanol and a trace of $OsO_4$. (b) Ethereal $H_2O_2$ and a trace of $OsO_4$ (83). Neither reagent brought about hydroxylation, and the phenanthrene was recovered.

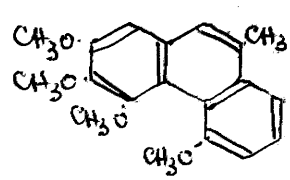
The diol (LXXX) was readily cleaved by lead tetra-acetate in benzene, yielding presumably the keto aldehyde (LXXXII) which was not isolated. The crude scission product was cyclised with dilute alkali to the ketone (LXXXIII). This was identified by comparison with an authentic specimen (49). The oxime was reduced catalytically in acetic anhydride solution to the




LXXXIV




LXXXV

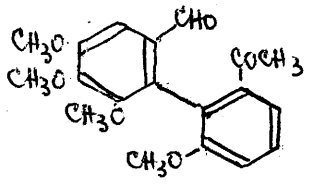



LXXXVI

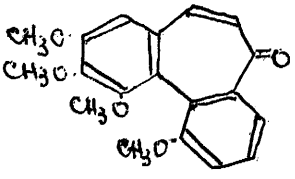
acetamido-dibenzocycloheptadiene (LXXXIV). Reduction of the oxime in acetic acid, led to an oily mixture, which was neutral in character. Chromatography separated a very small amount of solid material, but this was not identified. It is probable that these neutral products arise from hydrogenolysis of an intermediate allylic-amine (87). The work described above was later published (89).

The synthesis of this model substance points the way to a synthesis of N-acetylcolchinol methyl ether (LVIII) and a few experiments were carried out on the small amounts of the tetramethoxy-phenanthrenes (LXXXV) and (LXXXVI) available (45). None of these was conclusive. In a micro-experiment with the 2:3:4:7-isomer (LXXXV), the hydroxylation, scission, and cyclisation procedure described above (LXXX → LXXXII → LXXXIII) was repeated without isolation of intermediates, and yielded a few milligrams of ketonic material. This was not identified. Two similar experiments on the 2:3:4:5-isomer (LXXXVI) led to two products of m.p. 113-114° and 170-172°. Neither analysed satisfactorily, but in the light of

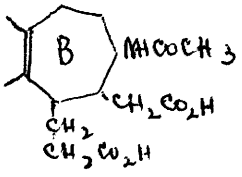
later work by Cook, Jack and Loudon (88), these products are almost certainly the keto-aldehyde (LXXXVII) and the unsaturated ketone (LXXXVIII) respectively. These experiments formed a model for the later, successful synthesis of colchinol methyl ether, by Cook, Jack and Loudon (88).




LXXXVII




LXXXVIII



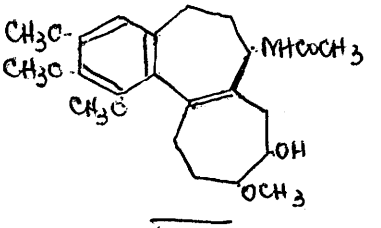

LXXXIX

In the following experiments on ring C, it was hoped to confirm the 7-membered structure, by ring opening to a di-carboxylic acid such as (LXXXIX) followed by cyclisation to a 6-membered ketone.

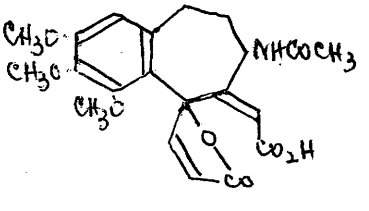
Although previous workers had failed in their attempts (68, 70) to open ring C by oxidation of hexahydrocolchicine or of hexahydrocolchiceine, this approach was reinvestigated. The former (LXXIV)

was treated with potassium permanganate under varied conditions, but only intractable gums were obtained. Oxidation with chromic acid was equally unsuccessful. Under mild conditions the starting material was returned, but more vigorous oxidation led to gums. Oxidation was also attempted using hydrogen peroxide, and lead tetra-acetate. In both cases substantial amounts of starting material were recovered, and no other product was isolated. An attempt was made to reduce the remaining double bond in (LXXIV) using purified hydrogen, purified solvent, and an excess of Adams' ($PtO_2$) catalyst, but no reduction was achieved.

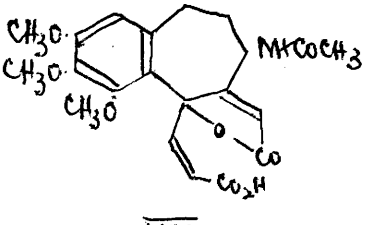
Since this approach was unpromising, attention was turned to the periodic acid oxidation of colchiceine originally carried out by Meyer and Reichstein (52).




LXXIV




XC




XCI

The product of this reaction was shown by these authors to be a mono-carboxylic acid and was given the formula $C_{21}H_{23}O_8N$.

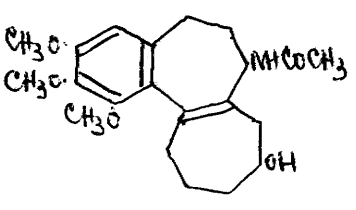
In an examination of this substance, the presence of one carboxyl group was verified by titration, and it was also found that heating with dilute alkali, revealed a second acid group, which is presumably present as a lactone. Acidification of the acid solution regenerated the mono-carboxylic acid, thereby proving that the acetamido group had remained intact throughout the operation. The acid was shown to contain two double bonds by micro-hydrogenation and by perbenzoic acid titration. Meyer and Reichstein noted (52), that colchicine is not attacked by periodic acid and it therefore appears reasonable to assume that the attack is on the adjacent, free, oxygens of colchiceine. This leads to only two possible formulae (XC) and (XCI), for the lactonic acid, and in spite of the poor yields attending this oxidation it appeared to offer a route to the desired di-carboxylic acid (LXXXIX). However all attempts at reduction of the lactonic acid or of its ester, failed, and $LiAlH_4$ gave a gum.

In view of the divergence in properties, between

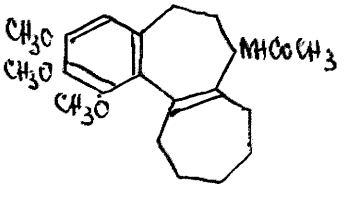
colchiceine and tropolone already noted it was of interest to carry out the periodic acid oxidation on tropolone. Profound decomposition took place, and the only identified product was iodoform, whose formation requires not only cleavage, but disruption of the tropolone ring. In contrast, the acid isolated by Meyer and Reichstein still contained the original 21 carbon atoms. Unfortunately the yields of identified products in both cases are too low to permit a valid comparison.

With the failure of this second oxidative approach to the ring C problem, an attempt was made to open the ring by nonoxidative means.

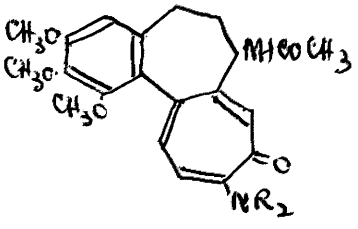
Several workers have shown that hydrogenation of colchicine or colchiceine yields, in addition to the hexahydro-derivative, a number of by-products, in which one or more of the original oxygen atoms has been lost (19, 68). A similar effect has been noted in an authentic tropolone (91). In terms of the modern formula, these have probably the structures (XCII)




XCII

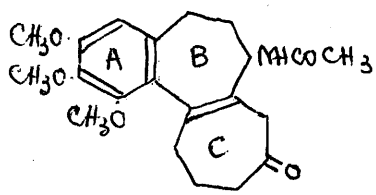



XCIII

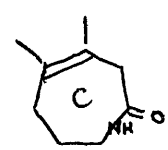



XCIV

and (XCIII). A similar reaction has been reported by Rapoport and Williams (76) who claimed that reduction of the dimethylamide (XCIV: R = $CH_3$) gave a ketone (XCV), which on further reduction was converted to the alcohol (XCII). This third degradation scheme depended on the isolation of this ketone. It was hoped that its oxime could be converted by a Beckmann rearrangement to




XCV




XCVI

a cyclic amide such as (XCVI), which could be ring-opened by hydrolysis. All attempts to prepare a crystalline sample of the dimethylamide (XCIV: R = $CH_3$), yielded a gum, which however gave a picrate of the correct m.p. Hydrogenation of the gum gave a small amount of non-ketonic material, of m.p. 143° (raised on drying to 163°), which on treatment with acetic anhydride yielded a new substance of m.p. 196-8°. These melting points are very close to those reported (76; 68) for (XCII) and its acetate, but the yields were very poor.

Attempts to oxidise the non-ketonic material (i.e. presumably XCII) to the required ketone (XCV) by the Oppenauer method or by chromic acid, failed to yield any solid product. A similar hydrogenation experiment was carried out on the amide (XCIV): R = H), which was prepared by the literature methods (92; 93). This gave a trace of ketonic material of micro-m.p. 143°, which was shown to be different from the non-ketonic product of similar m.p., derived from the dimethylamide (XCIV; R = $CH_3$). However the yield was so low, that further work along this line was not feasible.

## Experimental.

Analyses were by Drs. Weiler and Strauss, Oxford, and Dr. J. W. Minnis, University of Edinburgh.

Only original work is reported in detail.

9-Bromo-phenanthrene (LXXVII): Crude phenanthrene was converted into the pure 9-10-dibromide as described by Price Arntzen and Weaver (79), and thence to 9-bromo-phenanthrene of m.p. 63° as described by Austin (94). The yield was 16% based on phenanthrene.

9-Methyl phenanthrene (LXXVIII): Bachmann's method (80) gave a 70% yield of the hydrocarbon m.p. 92°.

9-Methyl-9:10-dihydroxy-9:10-dihydrophenanthrene (LXXX): Osmium tetroxide (2 g.) in dry benzene (10 cc.) was treated with 9-methyl phenanthrene (1.5g.) in dry benzene (5cc.). To this was added anhydrous pyridine (1.25cc.) and the deep red solution left at room temperature for 7-14 days. The crystalline product was obtained in 78-98% yield according to the time of standing. This product (4.5g.) in methylene dichloride (75cc.) was shaken mechanically with mannitol (20g.) and KOH (2g.) in water (120cc.) for 2 hrs. The organic layer was separated washed with water, and concentrated in vacuo to an oil. This oil was treated with water and

reconcentrated in vacuo. The solid product was crystallised from water in needles m.p. 132°. Yield 85%. No satisfactory analysis of this substance could be obtained, but a sample prepared later, by a colleague in Glasgow (89), and analysed by Mr. J. M. L. Cameron, gave satisfactory results.

Found: C, 79.9 ; H, 6.1.

$C_{15}H_{14}O_2$ requires, C, 79.7 ; H, 6.2%.

9-Methyl-10-phenanthryl acetate (LXXXI): The diol (LXXX) (0.25g.) in acetic anhydride (10cc.) was refluxed for ½ hr., concentrated under reduced pressure, and crystallised from dilute methanol. m.p. 149-150°.

Found: C, 81.6 ; H, 5.5.

$C_{17}H_{14}O_2$ requires, C, 81.6 ; H, 5.6 %.

Purification of phenanthrene: Commercial phenanthrene was twice recrystallised from alcohol, and then converted to its picrate. This product was recrystallised and had m.p. 144°. It was decomposed with alkali, and the phenanthrene extracted with ether and re-cycled. The final product was colourless, m. p. 103-4°.

Attempted hydroxylation of phenanthrene: (a) Phenanthrene (1.4g.) in ether (40cc.) was treated with 12cc. 5.52N

ethereal $H_2O_2$ solution, and 10mgm. $OsO_4$ dissolved in 5cc. ether. After 50 hours the solution was extracted, sodium bicarbonate solution, and dilute sodium hydroxide solution. It was finally washed with water and concentrated, yielding phenanthrene (1.35g.) m.p. and mixed m.p. 103°.

(b) Phenanthrene (1.4g.) in t-butanol (50cc.) was treated with 4cc of 0.25% $OsO_4$ in t-butanol, and 8.2cc. of a t-butanol solution of $H_2O_2$, containing 0.07g.$H_2O_2$/cc. To prevent crystallisation, this was kept in a warm room, for 7 days, and then concentrated in vacuo. The residue was crystallised, and yielded 1.2g. phenanthrene m.p. and mixed m.p. 103°. The residues could not be obtained crystalline.

Lead tetra-acetate was prepared by the method of Oesper and Deasy (95).

3:4:5:6-dibenzocycloheptatrien-7-one (LXXXIII): The following represents optimum conditions discovered from over a dozen experiments. The essential feature is the exclusion of oxygen.

The diol (LXXX) (58mgm.) in dry benzene (10cc.) was treated with lead tetra-acetate (0.12g.), and shaken periodically for 4 hrs. It was then treated with

ethylene glycol till the KI - starch test was negative, and filtered. The filtrate was concentrated in vacuo to an oil. This was redissolved in methanol saturated with nitrogen, and a drop of dilute sodium hydroxide solution added, followed by enough water to produce turbidity. Finally, the flask was stoppered and left at room temperature for 36 hrs. The product was crystallised from dilute methanol in needles, m.p. 84°. Yield 46 mgm. (87%). It gave a 2:4-dinitrophenyl hydrazone of m.p. 240° from dilute acetic acid. Both the ketone and its derivative showed no depression in mixed m.p. with authentic samples (49).

The oxime was prepared as follows. The ketone (50 mgm.) in ethanol (3cc.) was treated with hydroxylamine hydrochloride (35 mgm.) in water (1.2cc.) and 0.6cc. of 0.1N NaOH added. After refluxing for 2 hrs., the solution was diluted, and the product crystallised from ethanol m.p. 190-2°. Yield 87%.

Found: C, 81.8 ; H, 5.3 ; N, 6.0.

$C_{15}H_{11}ON$ requires C, 81.4; H, 5.0 ; N, 6.3%.

5-Acetamido-1:2:3:4-dibenzocyclohepta-1:3-diene (LXXXIV): The oxime (0.12g) in acetic anhydride (8cc.) was hydrogenated in presence of Adam's (P t $O_2$) catalyst

(0.05g.). Uptake ceased after 3 mols had been absorbed. Concentration gave the product which was recrystallised from ethanol m.p. 233°.

Found: C, 81.35 ; H, 6.9 ; N, 5.5.

$C_{17}H_{17}ON$ requires C, 81.3 ; H, 6.8; N, 5.6%.

When the reduction was carried out in acetic acid solution, 3 mols were absorbed. The solution was neutralised with ammonia, and extracted with ether. Concentration yielded an oil, which was insoluble in mineral acid, and did not give a picrate. It was chromatographed in benzene on alumina, and yielded one solid fraction of micro - m.p. 190°, which was depressed on admixture with the above oxime. The other fractions darkened on standing.

Ring expansion of 2:3:4:5-tetramethoxy-9-methyl phenanthrene (LXXXVI): (a) The methoxyphenanthrene (60 mgm.) and $OsO_4$ (50 mgm.) in dry benzene (0.5cc.) was treated with dry pyridine (0.04cc.) and left for 4 days, when the osmium complex crystallised out. Petroleum ether was added to precipitate the remainder. The crude Os-complex (0.131g.) in methylene dichloride (12cc.) was shaken for 3 hrs., with KOH (0.6g.) and mannitol (6.0g.) in 12cc. water. The organic layer was separated off, washed with

water, and concentrated. The product was crystallised from benzene in colourless needles m.p. 210° (Cook et. al. (88) report 215°). This material (63 mgm.) in dry benzene (15cc.) was treated with lead tetra-acetate (0.125g.) and left at room temperature, with intermittent shaking for 48 hrs., and the excess lead tetra-acetate destroyed by ethylene glycol. The mixture was filtered, and the filtrate concentrated in vacuo to an oil, which was redissolved in aqueous methanol, and a drop of dilute sodium carbonate solution added. After standing overnight, the product crystallised. Yield 49 mgm. (78%). It was crystallised from dilute methanol m.p. 112-3 (Cook et. al. (88) report 113-4°).

Found: C, 67.1 ; H, 5.9.

$C_{19}H_{20}O_6$ requires C, 66.25; H 5.8%. (i.e. the keto-aldehyde LXXXVII)

This substance gave a test for unsaturation and carbonyl function.

(b) The above experiment was repeated on 100 mgm. of (LXXXVI), but on this occasion, the final product did not crystallise. It was left for a further 10 days, and distilled into two fractions.

(1) b.p. 120° (bath)/0.03mm. (15 mgm.)

(2) b.p. 200° (bath)/0.03mm. (95 mgm.)

The first fraction remained oily, but the second slowly crystallised from methanol, with considerable loss, yielding 20 mgm. of a product of m.p. 170°-2° (Cook et, al. (88) report 172-4° for the ketone LXXXVIII). It gave an unsaturation test.

Attempted ring expansion of 2:3:4:7-tetramethoxy-9-methyl phenanthrene (LXXXV). The methoxyphenanthrene (60 mgm.) and $OsO_4$ (50 mgm.) in dry benzene (0.5cc.) was treated with dry pyridine (0.04 cc.). After standing for 7 days, no osmium adduct had separated so petroleum ether was added till no more precipitate was formed. This material (0.136g.) in 12cc. methylene dichloride was shaken for 3 hrs., with KOH (0.6 g.) and mannitol (5.0g.) in 25cc. water. The organic layer was washed with water, and concentrated to dryness, yielding a crude solid (60 mgm.) which was shaken in benzene (10cc.) with lead tetra-acetate (80 mgm.) for 4 hrs. A few drops of ethylene glycol were then added, and the mixture filtered, and concentrated under reduced pressure. The resulting oil was dissolved in aqueous methanol, and a few drops of dilute sodium carbonate solution added. After standing for 2 days, a gummy solid separated out. It was distilled at 200°(bath)/0.05mm., yielding a viscous

oil (21 mgm.) which slowly crystallised from methanol with considerable loss. The product (4 mgm.) had micro-m.p. ca. 116°, and gave a test for unsaturation, and carbonyl function.

Purification of colchicine. The procedure of Ashley and Harris (5) gave an almost colourless product, which was recrystallised from pure ethyl acetate, m.p. 153°.

Hexahydrocolchicine (LXXIV): The purified alkaloid was reduced by the method of Bursian (19), and the product was crystallised from water in colourless needles m.p. 123°.

Oxidation of hexahydrocolchicine. (a) Hexahydrocolchicine (50 mgm.) in water (10cc.) was heated at 100° with sufficient 0.1% aqueous potassium permanganate to retain a slight pink colour, after 1 hr. It was acidified with dilute acetic acid, filtered and concentrated in vacuo. The residue was dissolved in chloroform, washed, and concentrated. This gave a dark red viscous oil which could not be crystallised. An unsuccessful attempt was made to form a picrate.

(b) Hexahydrocolchicine (0.1g.) in water, (35cc.) was cooled to 0°C, and treated with potassium permanganate (0.15g.) and KOH (0.15g.) in water (35cc.). The

solution was maintained at 0°C for 20 hrs., acidified and treated with $SO_2$ till a clear solution was obtained. This solution was concentrated, and extracted with chloroform yielding a yellow gum, which could not be obtained solid, and failed to give a precipitate with 2:4-dinitrophenyl hydrazine. Treatment with diazomethane gave a water-insoluble gum, which could not be crystallised.

(c) Hexahydrocolchicine (0.1g.) in water (10cc.) was treated with potassium permanganate (0.08g.) and sodium carbonate (0.1g.) in 5cc. water, and left at room temperature for 3 days. The solution was cleared with $SO_2$, filtered from unreacted starting material, and extracted with chloroform. This solution was re-extracted with sodium carbonate solution and acidified. Extraction yielded nothing.

(d) Hexahydrocolchicine (0.1g.) in 20cc. water was treated with chromium trioxide (0.05g.) and a little dilute sulphuric acid. After standing for 1 hr., the solution was heated at 100° for ½ hr., and concentrated till crystalline material separated out. m.p. and mixed m.p. with starting material 120°. (Yield 65 mgm.). Further concentration of the mother liquors yielded a dark red oil.

(e) Hexahydrocolchicine (0.1g.) in acetic acid (3cc.) was treated with chromium trioxide (0.1g.) in 1:1 aqueous acetic acid, and left overnight. The solution was neutralised, and filtered, the filtrate evaporated in vacuo, and the product triturated with dilute acid. The dark red oil did not solidify, and trituration with solvents failed to effect any purification.

(f) Hexahydrocolchicine (50 mgm.) in 10cc. water was treated with 1cc. of $H_2O_2$ (30%), and left for 2 days at room temperature. Concentration gave crystalline material (35 mgm.) which was shown to be starting material by mixed m.p.

(g) Hexahydrocolchicine (50 mgm.) in dry benzene (10cc.) was treated with lead tetra-acetate (60 mgm.) and shaken periodically, over 2 hrs. After standing overnight the solution was treated with ethylene glycol until the KI - starch test was negative, filtered and concentrated. The crude product was crystallised from water m.p. 121°, and gave no depression in mixed m.p. with hexahydrocolchicine. Yield 20 mgm. The mother liquor gave a precipitate with 2:4-dinitrophenyl hydrazine in 6N HCl, but it was amorphous, and could not be crystallised.

Attempted reduction of hexahydrocolchicine. Pure hexahydrocolchicine (0.123g.) in acetic acid (15cc.) which had been distilled from chromium trioxide, was shaken with Adams' (P t $O_2$) catalyst (0.1g.) in presence of hydrogen which had been washed successively with alkaline pyrogallol, aqueous potassium permanganate and silver sulphate in sulphuric acid. After 9 hours, there was no uptake, and the starting material was recovered.

Colchiceine (LXIII): Colchicine was hydrolysed by the method of Zeisel (6) as modified by Dickson (70). Yield 71% m.p. 146-8°.

Periodate oxidation product (XC or XCI): The method of Meyer and Reichstein (52) gave a colourless product which crystallised from alcohol in needles m.p. 234°. The best yield obtained in six experiments was 18%.

Analytical Investigations. (a) The above acid (3.89 mgm.) was reported to absorb 0.460 cc. hydrogen at 19°C/753mm; in 15 mins. This corresponds to 2.0 mols., and hence to 2 double bonds.

(b) An ethereal solution of perbenzoic acid was titrated against 0.01N sodium thiosulphate solution, as follows:-

1cc. perbenzoic acid solution = 1.30cc. 0.01N $Na_2S_2O_3$ = 0.000104 gm. available oxygen.

A sample of the periodate oxidation product (18.5 mgm.) was treated with 25cc. of this ethereal perbenzoic acid solution, kept at 0°C for 70 hrs., and back titrated with KI - $Na_2S_2O_3$, as follows:-

Volume required = 15.5cc. 0.01N $Na_2S_2O_3$. = 11.9cc perbenzoi acid solution.

Hence volume of perbenzoic acid solution consumed = 13.1cc. = 0.00136g. oxygen.

If 1 mole (417g.) of the periodate oxidation product requires 1 gm. atom of oxygen per double bond, 18.5 mgm. requires 0.0007g. oxygen.

Since oxygen consumed = 0.00136g., 2 double bonds are present.

(c) The above acid (6.4 mgm.) in alcohol (1cc.) was treated with 1cc. 0.1N NaOH, and back titrated with 0.1N $H_2SO_4$. Volume required = 0.82cc. Hence volume consumed = 0.17cc. 0.1N NaOH.

If 1 carboxyl group is present, 417 gm. (1 mole) of the oxidation product requires 10 litres 0.1N NaOH. Hence 0.0064gm. requires 0.154cc. Therefore 1 carboxyl group is present.

(d) The above acid (6.0 mgm.) in 1.5cc. alcohol, was treated with 0.5cc 0.1N NaOH, and heated at 100° for 45 mins.

On cooling, it was back-titrated with 0.1N $H_2SO_4$. Volume required = 0.2cc. Hence alkali consumed = 0.30cc. Since 0.006gm. of acid requires 0.144cc. for 1 carboxyl group it follows that there are 2 carboxyl groups present. A repeat gave the same result, and a blank alcohol solution of 0.52cc. 0.1N NaOH, required 0.51cc. 0.1N $H_2SO_4$.

Acidification of these solutions, and removal of the alcohol yielded a solid product, which was soluble in alkali, and reprecipitated by acid. It was crystallised from alcohol, and gave colourless crystals of micro m.p. 220°. A micro-mixed m.p. with the original acid was undepressed.

Attempted reduction of the acid (XC or XCI): (a) The acid (35 mgm.) and Pd-black (50 mgm.) in acetic acid, was shaken with hydrogen for 3½ hrs. There was no uptake, and the starting material was recovered from the filtered solution m.p. 220°.

(b) An identical experiment, on 50 mgm. of acid, using Adams' (P t $O_2$) catalyst, led to the recovery of 46 mgm. of the starting material, and a repeat experiment in all-glass apparatus, gave the same result.

(c) The acid (42 mgm.) in dry dioxane (10cc.) was added to lithium aluminium hydride (2g.) in ether. A vigorous

reaction ensued, and after an hour, excess reagent was decomposed with ice-water, and alkali. Ether extraction yielded a trace of neutral material as an intractable gum.

(d) The mono-methyl ester of the above acid, was prepared by the literature method (52), and crystallised from methanol in needles. m.p. 93-4°.

A sample of the ester (40 mgm.) in alcohol (6cc.) was shaken with Pd-black (50 mgm.) in a hydrogen atmosphere, for 3 hrs. There was no uptake, and evaporation of the filtered solution gave the original ester m.p. and mixed m.p. 94°.

(e) Repetition of the above experiment using Adams' (P t $O_2$) catalyst, gave an identical result.

Tropolone LIX: Tropolone was prepared by the method of Cook, Gibb, Raphael and Somerville (58a), and crystallised from petroleum ether in needles m.p. 49-51°.

Periodate oxidation of tropolone: Tropolone (0.33g.) in dioxan (10cc.) was treated with periodic acid (1.3g.) in water (4cc.) and left for 4 days at room temperature. The dioxan was removed under reduced pressure, and water added. This precipitated a red solid which was triturated with dilute NaOH, leaving iodoform m.p. and mixed m.p. 123°. Investigation of the alkaline liquors yielded no pure material.

In a subsequent experiment, the iodoform was isolated by vacuum sublimation of the precipitated solid. This means that the iodoform was present before the addition of alkali, and hence that it was not formed from NaOI, by an "iodoform reaction".

The use of sodium metaperiodate was also investigated, in the hope of isolating other fragments of the molecule, but without success.

Colchicine dimethylamide (XCIV; R = $CH_3$): (a) The procedure described by Rapoport and Williams (76) gave only a gum, and all attempts to crystallise it from the recommended solvents or others, failed. Vacuum sublimation at 190°/$10^{-4}$mm., gave an orange product of m.p. 120-140°, but this material also resisted all attempts to crystallise it. (b) Colchicine (0.1g.) in 5cc. of 25% aqueous dimethylamine was left for a week at room temperature. It was then concentrated in vacuo, and the resulting oil taken up in chloroform, washed with dilute NaOH and then with water, and concentrated to a glass. It resisted all attempts to bring about crystallisation, and was chromatographed in benzene on alumina. Elution with benzene and benzene-chloroform, gave four fractions, all of which set to glasses, and resisted repeated attempts at crystallisation.

(c) Colchicine (0.15g.) was dissolved in an excess of methanolic dimethylamine (33%), and kept at room temperature for 16 hrs. It was then heated on the steam bath for 1 hr., and concentrated in vacuo. The product was dissolved in chloroform, washed with dilute NaOH, and water, dried and concentrated. The hard resinous product could not be crystallised, but gave an easily crystallisable picrate of m.p. 184-5° (Rapoport and Williams report 186° (76)).

Hydrogenation. The crude dimethylamide above (0.5g.) was hydrogenated in acetic acid (25cc.) in presence of Adams' (P t $O_2$) catalyst (0.15g.), as described by Rapoport and Williams (76). The oily product was recrystallised from ethyl acetate in fine needles, m.p. 142-3°, rising to 164°, on drying under vacuum. Yield 0.115g. These figures are close to those quoted for the alcohol XCII by several workers. Rapoport and Williams (76) give 168-170°. Kemp and Tarbell give 130-140° (68), rising to 168-170° on drying, and Bursian (19) gave 171° for what appears to be the same compound.

The alcohol was refluxed with excess acetic anhydride for 1 hr., and concentrated, yielding a substance of m.p. 196-8°, crystallising from dilute methanol or ethyl

acetate - petroleum ether. This must be the acetate of XCII, for which Rapoport and Williams give m.p. 206°, (76) and Bursian (19) gives 210°.

Oxidation of the alcohol XCII: (a) Freshly distilled aluminium isopropoxide (1.3g.) was dissolved in dry toluene (10cc.) and treated with redistilled cyclohexanone (5cc.). To this solution, was added the alcohol (XCII) (52 mgm.) in 8cc. hot toluene, the mixture refluxed for 10 hrs., and finally concentrated to small bulk. This was steam distilled to remove residual cyclohexanone, acidified and extracted with ether. Concentration gave a brown gum which could not be crystallised.

A repeat experiment using benzene and acetone, in place of toluene and cyclohexanone, was equally unsuccessful. The product in each case gave a faint reaction with 2:4-dinitrophenyl hydrazine.

Colchicine amide (XCIV ; R = H): This was obtained by Graham's method (92) m.p. 257°.

Hydrogenation: Colchicine amide (0.12g.) in acetic acid (5cc.) was hydrogenated in presence of Adams' (P + $O_2$) catalyst (50 mgm.). The uptake was 38cc. The filtered solution was concentrated in vacuo to a gum, which proved

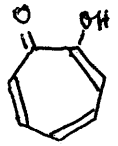
to be water-soluble, and was acetylated by refluxing for 1 hr., with acetic anhydride. The solution was again concentrated under reduced pressure. Yielding a gum, which on trituration with ether afforded a few milligrams of a crystalline product micro-m.p. 143-6°. This substance gave a precipitate with 2:4-dinitrophenyl hydrazine, and was depressed in a mixed m.p. with the product (m.p. 142-3°) obtained by reduction of the dimethylamide of colchicine (XCIV: R = $CH_3$.).

# PART III

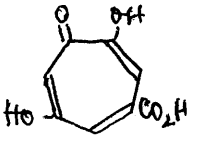
## Isotropolones.

## Historical Introduction.

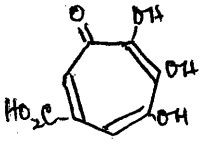
The concept of cycloheptatrien-1:2-olone (tropolone) (I), as a new aromatic ring system was originated by Dewar (55) in 1945, to account for the unusual properties of the mould product, stipitatic acid. These properties have already been discussed in Part II of this thesis,



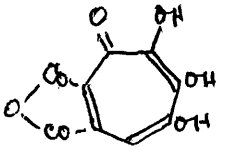
I



II



III

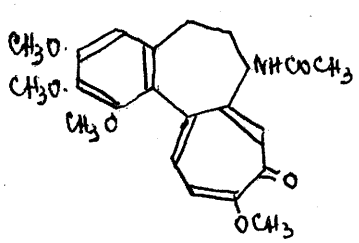


IV

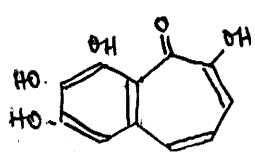
and it will be sufficient to say that no structural formula accommodated the chemistry of this substance, until Dewar formulated it as a tropolone derivative (II). In doing so, he had to ascribe certain properties to the then hypothetical ring system (I); these predictions were confirmed when tropolone was synthesised (58).

Since 1945, several other natural tropolones have been recognised. Puberulic (III) and Puberulonic (IV) acids, are mould products whose similarity to stipitatic

acid (II) was noted by Birkinshaw, Chambers and Raistrick (54), and by Dewar (66), but their formulation as III and IV is due to Johnson, Todd, and co-workers (72, 73, 96) and to Madame Aulin-Erdtmann (97). Only stipitatic acid has been synthesised (59). Dewar also suggested (56) that the alkaloid colchicine, was a tropolone derivative, and the implications of this have been discussed in detail in Part II of this thesis. The formula V is now generally accepted. Other natural

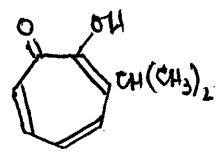



V

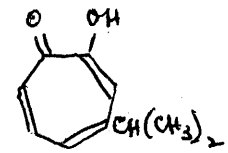



VI

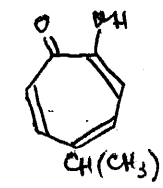
tropolones are purpurogallin VI and the three thujaplicins VII, VIII and IX. The former is a gall product originally investigated 50 years ago by Perkin (99). The structure VI, suggested by Barltrop and Nicholson (100), has been confirmed by synthesis (98). The thujaplicins (named



VII



VIII

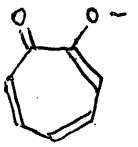


IX

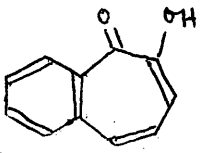
respectively α, β and ) are wood products whose isolation and characterisation are due to American (101) and Swedish (102) workers. All three have been synthesised (103).

The investigation of these natural products and related substances, has provided a body of information from which it is now possible to give a generalised account of their properties and reactions.

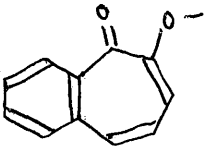
Tropolones are weak acids, but they also display feeble basic properties. Thus the parent compound (I) (pk7), reacts with sodium bicarbonate forming a yellow sodium salt, but it also gives a hydrochloride and a picrate (58). The high acidity of tropolone is explained by the equivalence of the two principal resonance forms (X) of the anion (55). In the



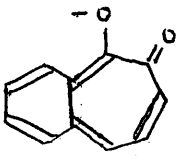
X



XI

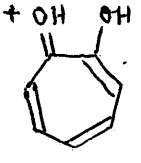


XII

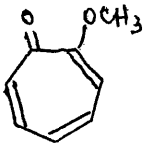


XIII

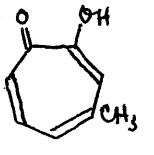
benzotropolones (e.g. XI), where the anion resonance involves two non-equivalent structures (XII) and (XIII) the acidity is lower (pk9). Dewar accounted for the basic properties of tropolone (55) by postulating symmetrical structures (XIV) for the salt-cation.



XIV



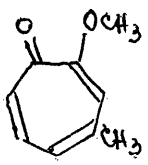
XV



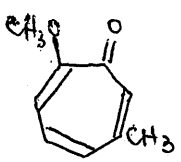
XVI

Tropolone may be regarded as a vinylogue of a carboxyl group (58), and like acids, tropolones are esterified by diazomethane, by methyl sulphate or methyl iodide and alkali, and by the normal Fischer-

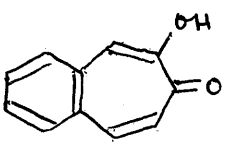
Speier method. Tropolone itself, gives only one methyl ether (XV) but unsymmetrical tropolones (e.g. XVI) give rise to two methyl ethers (104), (XVII) and (XVIII). The only known exceptions to this rule are the benzotropolones XI and XIX



XVII

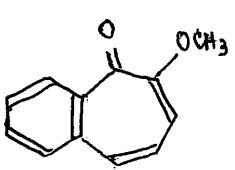


XVIII

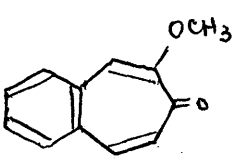


XIX

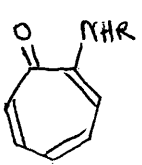
which each give only one ether (XX) and (XXI). (105;106). The resemblance between tropolones and carboxylic acids



XX



XXI

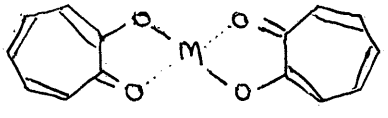


XXII : R=H

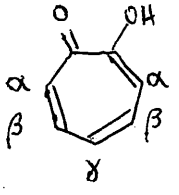
XXIII : R=NH$_2$

is further exemplified by their failure to give ketonic derivatives, and by their reaction with thionyl chloride to give reactive chloro-derivatives (113) such as XXVI. The ethers of tropolones show many of the characteristics of esters. With ammonia they form amino-derivatives (XXII) (58b) and with hydrazine they yield hydrazides (XXIII) (108). They are readily hydrolysed to the original tropolone (58), and with the exception of the benzo-series (XX) and (XXI), they fail to react with the usual carbonyl reagents (58; 105; 106). Tropolones are not readily O-acylated (54) and when forcing conditions are employed (55) nuclear substitution may occur in preference to O-acylation.

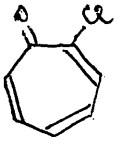
One novel characteristic of tropolones, is their ability to form deeply coloured co-ordination complexes of type XXIV with ferric and copper salts (58a). It has been remarked (60) that although this property is well known in 1:3-diketones, it is unique in the 1:2-diketone series, of which tropolone is formally a member. These colour reactions are used as diagnostic




XXIV




XXV

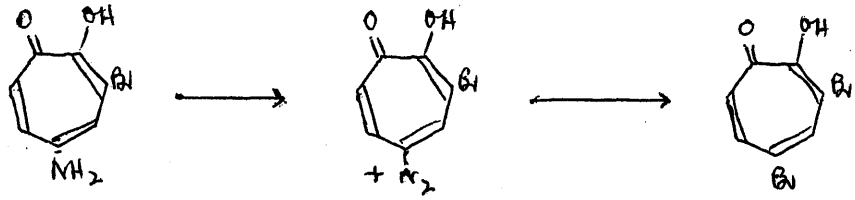



XXVI

tests for tropolones, monocyclic tropolones giving a green colour with ferric chloride, and the benzotropolones giving brown-red colourations with the same reagent.

The aromatic character of the tropolone ring is revealed in a number of electrophilic substitution reactions. Tropolone and its simple derivatives have been brominated (110), nitrosated (58b; 107), nitrated (58b)(107), and sulphonated (111), and undergo coupling with diazotates (58). Dewar's prediction (112) that electrophilic substitution in tropolones would take place almost exclusively in the $\gamma$-position (XXV) is largely borne out. Exceptions are, the bromination of tropolone (but not of its copper salt) (110), and the nitration (107) and sulphonation (114) of the $\beta$-substituted tropolones VIII and XVI, which yield a proportion of the $\alpha$-isomer. However, in these latter cases, the $\beta$-substituent probably interferes with the normal orienting factors. Although these reactions may be taken as evidence of aromatic character, it has also been found (155) that the Friedel-Crafts, Gattermann, Kolbe-Schmidt and chloro-methylation reactions fail to give substitution products with tropolone.

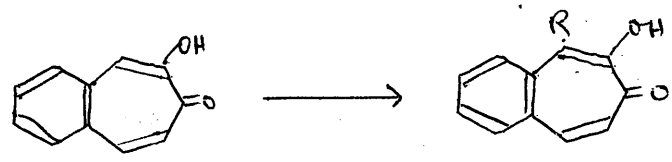
A further indication of the aromatic nature of the ring, is the diazotisation of amino-tropolones. This reaction allowed Nozoe (116) to convert the amino-bromo-tropolone (XXVII) to $\alpha\gamma$-dibromotropolone (XXIX), by the Sandmeyer reaction.



XXVII XXVIII XXIX

The tropolone ring is more easily substituted than benzene, and in the benzotropolones XI or XIX, nitration (105), sulphonation (115), bromination (105) and diazo-coupling (105), occur exclusively in the tropolone ring:-

XI

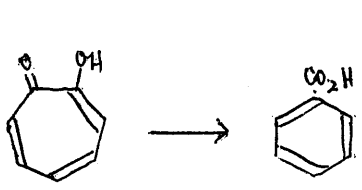


XIX

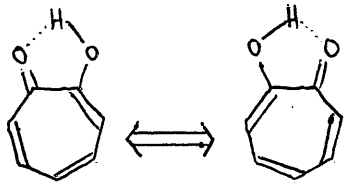
The products are α-substituted, but in these cases, the fused benzene ring presumably influences the orientation.

Tropolones show some resistance to oxidation, and reduction, as might be expected of an aromatic type. Thus, potassium permanganate (58b), selenium dioxide and silver oxide (58c.) have been used with impunity in tropolone syntheses, although more vigorous oxidation destroys the ring (106). Resistance to reduction varies considerably, but the ring has been shown to withstand hydrogenation in presence of Pd(58a) and in some cases even Pt (116, 117) catalysts.

The most striking feature of tropolone chemistry is the ease with which rearrangement takes place. A detailed account of these rearrangements, is not necessary to this discussion, and it is sufficient to note that in each case, the end product is a benzenoid compound. The rearrangement can be brought about by alkali-fusion, when tropolone (I) yields benzoic acid (58b)

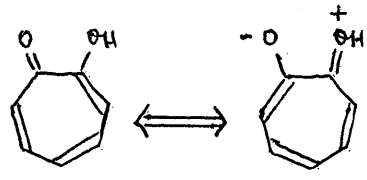



I

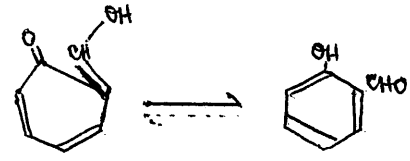



XXX

It is clear, from the above account, that the tropolone molecule is aromatic in character, but less so than benzene. It has a resonance energy of 28.6 k. cals. per mole (58a) which is about two-thirds that of benzene, and almost exactly the value quoted (154) for a carboxyl group. To account for this aromaticity Dewar (55) originally postulated resonance between the H-bonded structures XXX, but later revised it in favour of the ionic resonance structures XXXI, when calculation



XXXI



XXXII

showed that the oxygen atoms were too far apart to permit normal hydrogen bonding (66). Infra-red studies (118; 58b.) have supported the view that intra-molecular H-bonding is, at most, very weak. Although ionic resonance (XXXI) appears to give a satisfactory representation of the aromatic character of tropolone, it has been criticised in one respect (60).

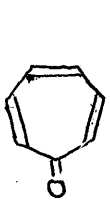
In both XXX and XXXI, the bond between the oxygen-bearing carbon atoms, is always represented as a single bond, and is therefore not involved in, and unnecessary to, the conjugated double-bond system. From this observation, two conclusions may be drawn.

(a) The bond in question should be longer than the other C - C bonds in the ring.

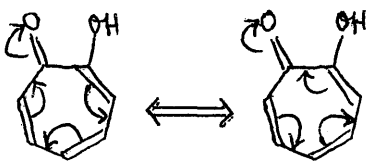
(b) It should be possible to remove or move, the bond without altering the (tropolone) character of the molecule. Thus, XXXII should show properties similar to those of tropolones.

In fact, neither of these conclusions can be supported. Salicylaldehyde (XXXII), although aromatic, behaves normally towards carbonyl reagents; and it has been shown by X-ray measurements (119) that the 7-membered ring is regular, with an average C - C bond length of 1.4Å. This value lies between those of a single bond (1.54Å) and a double bond (1.32Å), and is very close to the aromatic C - C bond length (1.39Å) in benzene (120).

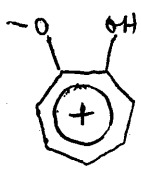
These difficulties are overcome in a suggestion made by the author (122) and by Doering and Knox (123), that tropolone is merely a hydroxy-derivative of cyclo-heptatrienone XXXIII (tropone). The latter would therefore be the fundamental aromatic structure, and



XXXIII

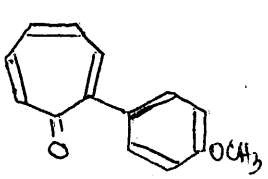


XXXIV

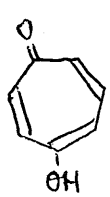


XXXV

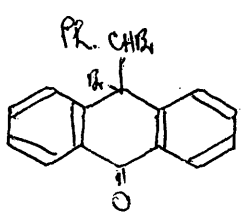
tropolone would be related to it, as phenol is to benzene. The resonance in tropolone would then involve major contributions from structures XXXIV (which may be written comprehensively as XXXV) and would lead to a symmetrical ring and to bond orders compatible with the X-ray data. Tropone (XXXIII) has been synthesised (121) and although accounts of its properties are not consistent, there is a superficial resemblance to tropolone. Thus, it is said to give salts with HCl, and picric acid, couple with diazotates and it gives carbonyl derivatives with difficulty (and with concommittant substitution) (121). A substituted tropone (XXXVI) has also been reported (125) to



XXXVI



XXXVII

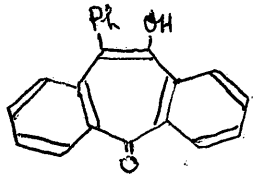


XXXVIII

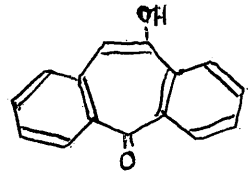
undergo ring-contraction to a substituted benzoic acid, on alkali fusion.

If the ground-state resonance in tropolone is largely identified with structures XXXV, it follows that the second oxygen atom is not vitally implicated, and hence that its position in the ring could be varied without affecting the fundamental character of the ring. It is therefore important to examine isomeric structure such as XXXVII, in which the oxygen atoms are not vicinal - i.e. iso-tropolones.

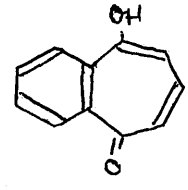
The only known iso-tropolone is the dibenzo-compound XXXIX obtained by Cook (124)




XXXIX




XL

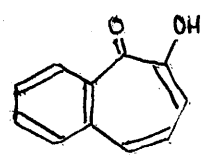



XLI

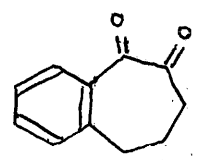
from benzal-anthrone dibromide XXXVIII, by the action of moist silver oxide. However, in this case, the presence of so many benzene nuclei will certainly modify the character of the iso-tropolone ring, and the object of the work described in this section was the synthesis of simpler molecules, such as XL and XLI.

## Theoretical Discussion.

The successful dehydrogenation of benzo-cyclo-hepten-3:4-dione (XLII) to αβ-benzotropolone XI by Pd, or bromine (106), suggested the application of the same technique to the synthesis of the benzo-isotropolone XLI. The appropriate dione XLIII,

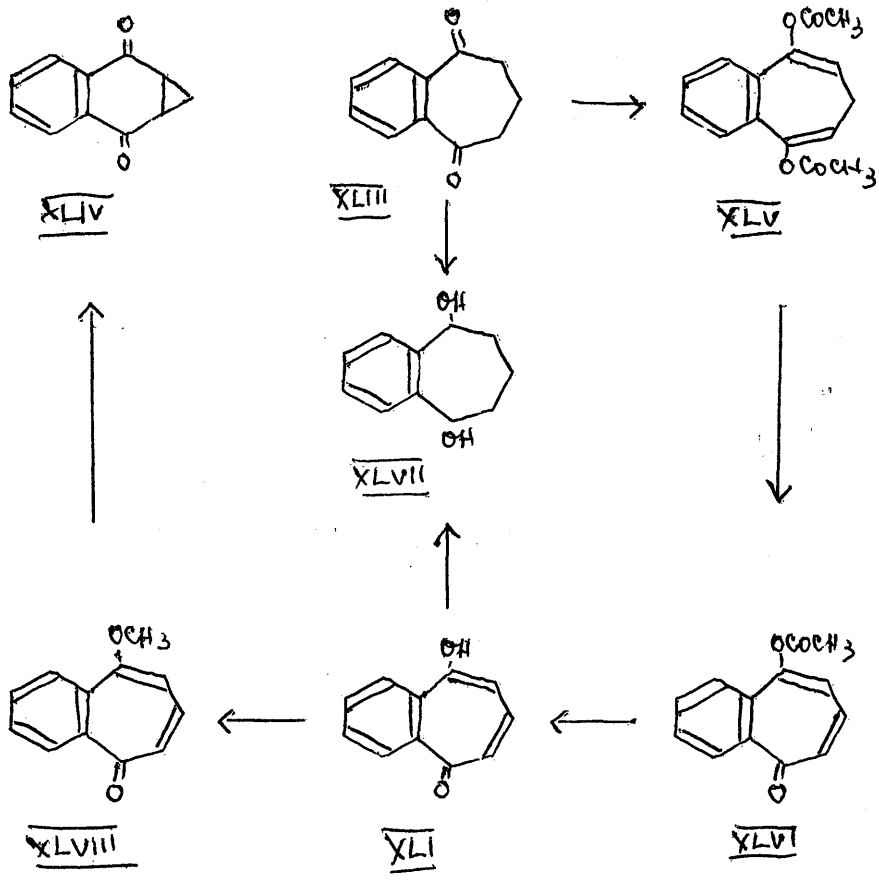



XI




XLII

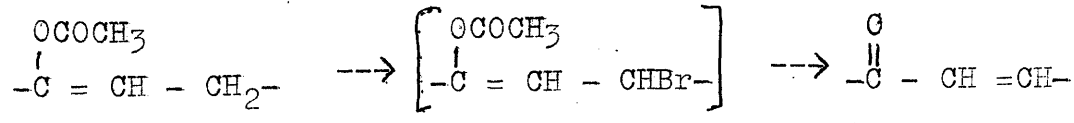
was obtained from diethyl phthalate, and diethyl glutarate, as described by Barltrop Johnson and Meakins (126) and an attempt was made to dehydrogenate it to XLI by means of Pd-C in boiling trichlorobenzene. No acidic material was obtained, and the bromination method was equally unsuccessful. Addition of bromine in acetic acid, followed by alkaline dehydrobromination gave only dark tars. Bromination of the diketone XLIII by N-bromosuccinimide was much cleaner, and dehydrobromination of the product gave crystalline substance $C_{11}H_8O_2$, in




fairly good yield. This compound was neutral in character, and stable towards cold aqueous potassium permanganate. It gave a bis-2:4-dinitrophenyl hydrazone, but failed to give a picrate, or a coloration with ferric chloride. Such properties are clearly incompatible with an unsaturated enol structure such as XLI and this substance has been ascribed the structure XLIV. No

proof of this is at present available, but the dehydrogenation of γ-bromo-ketones is a well-known route to cyclopropyl ketones (127). Catalytic hydrogenation of this substance gave a mixture from which no pure product was obtained. In contrast, the dione XLIII gave the diol XLVII in excellent yield. An attempt was made to rearrange the diketone (XLIV) to benzo-isotropolone (XLI) by heating with Pd-Charcoal in vacuo. Under these conditions cyclopropane derivatives have been isomerised to propenes (130), but in this instance, the diketone sublimed unchanged. Similarly, heating with sodium ethoxide in alcohol, has been used to isomerise cyclopropane derivatives, and in this case, an alkali-soluble product was obtained, but attempted vacuum sublimation of the product led to decomposition.

To avoid the formation of a cyclopropane ring, the diketone was converted into its enol acetate XLV by means of iso-propenyl acetate (128) and the latter treated with N-bromosuccinimide. This type of reaction has been shown (129) to produce αβ-unsaturated ketones, as follows:-



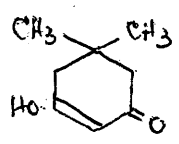
and the neutral oily product from XLV is presumably XLVI. Alkaline hydrolysis gave the isotropolone XLI as a yellow powder subliming in vacuo. Its structure was confirmed by reduction to the diol XLVII.

The iso-tropolone (XLI), like its isomer XI gives a 3:5-dinitrobenzoate, an oily acetate, a yellow picrate, a red-brown colour with ferric chloride, and couples with diazotised aniline to give a crimson dye. It also gives a hydrochloride and a perchlorate, and differs from XI in giving a 2:4-dinitrophenyl hydrazone. It is a stronger acid (pK 6.4) than αβ-benzotropolone (pK ca. 9) and does not form a copper complex, or suffer rearrangement on KOH - fusion at 220°. In contrast to the cyclopropane compound(LXIV) it rapidly decolorises aqueous potassium permanganate.

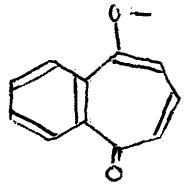
With ethereal diazomethane, the isotropolone XLI gives a methyl ether which is readily hydrolysed by dilute alkali. Distillation of the crude ether gave a mixture of pure ether and the cyclopropyl ketone (XLIV). The mechanism of this transformation has not been investigated.

These results show a general similarity between αβ-benzotropolone (XI), and 7-hydroxybenzocycloheptatrien-

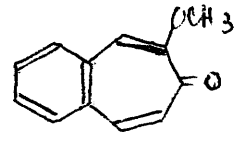
3-one (XLI) - the benzo-iso-tropolone which is further illustrated by the ultra-violet absorption spectra shown below: but they do not constitute unequivocal evidence of aromaticity. The acidity, and ferric chloride coloration may equally be the properties of a conjugated enolic ketone. Thus dimethyl dihydroresorcinol (XLIX) has a pK of 5.25 (132) and gives a red colour with



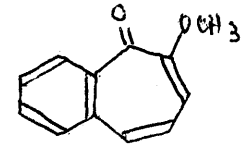
XLIX



L



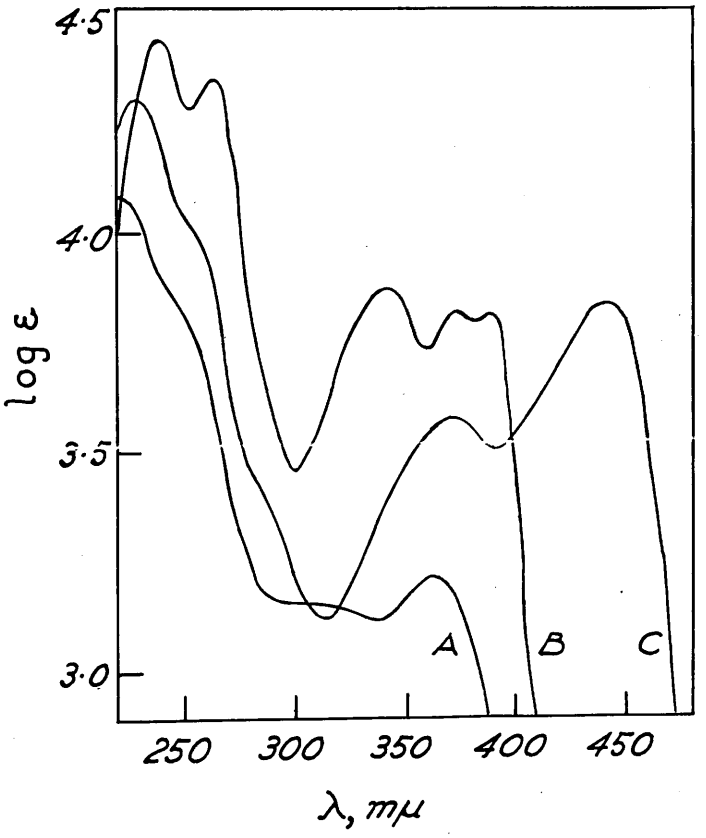
XXI



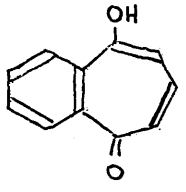
XX

ferric chloride (133). Salt formation is also shown by unsaturated ketones (134) and coupling is a wellknown reaction of enols (135). That the benzo-iso-tropolone (XLI) is a stronger acid than its isomer (XI) is to be expected from the symmetry of the anion (L). Resonance in this anion involves two identical canonical forms, and so produces maximum stabilisation.

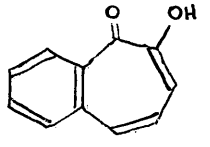
The appearance of ketonic properties in XLI but not in XI (106) or in XIX (105) suggests that hydrogen




C =




B =

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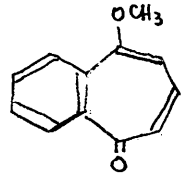
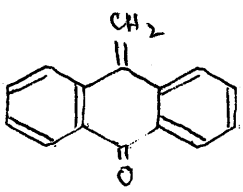


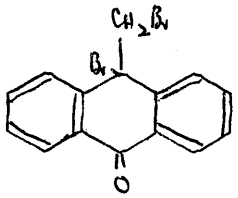
interaction between the two oxygen atoms, plays some part in depressing the activity of the carbonyl group. In this connection, it is significant that the ethers XX and XXI (105; 106), in which no hydrogen interaction is possible give carbonyl derivatives.

This work has been published (J., 1954, 1060).

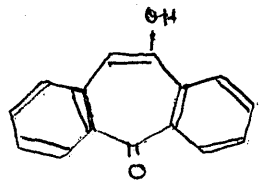
Attempts to prepare dibenzo-iso-tropolone (XL) were made initially by the method used by Cook (124),



LI

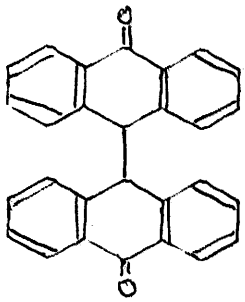


LII

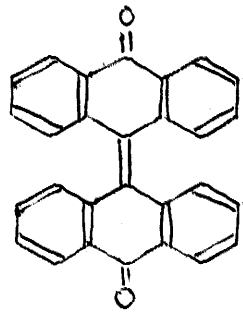


XL

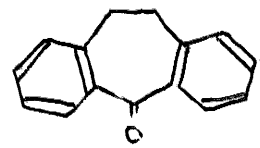
in preparing the phenyl derivative XXXIX. Methylene anthrone LI, was converted into its dibromide LII, as described by Meyer (137). When this compound was warmed in aqueous acetone with or without silver oxide, there resulted a mixture from which bianthronyl LIII was isolated. The constitution of this product was



LIII



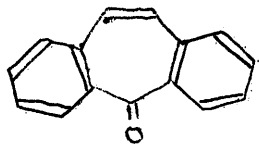
LIV



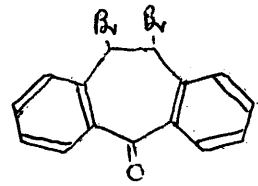
LV

corroborated by oxidation to dianthronylidene LIV, and by comparison with an authentic sample of LIII (138). The use of silver acetate in benzene, gave the same product.

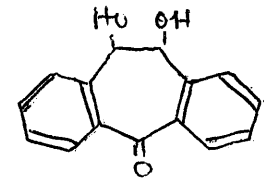
As the desired result was not obtained by this route, attention was turned to compounds such as LV, containing the required carbon skeleton. This ketone had been prepared by Treibs (140) and by Cope and Fenton (141) and efforts were made to convert it to the required ketol (XL). Treibs (140) also attempted to prepare XL in this way. He dehydrogenated the ketone LV to LVI, prepared the dibromide LVII, and hydrolysed it to the glycol (LVIII). He then tried to dehydrate the glycol



LVI

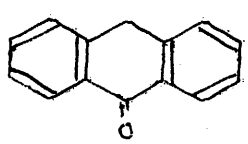


LVII

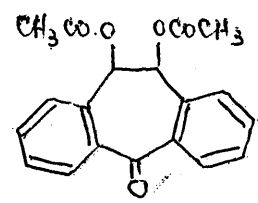


LVIII

to XL using formic or sulphuric acids, but isolated only anthrone LIX. The dehydration of Treibs' glycol LVIII was re-examined, in the hope of finding more suitable conditions. Drastic dehydrating agents such as potassium bisulphate or iodine were found to give anthrone LIX, heating <u>in vacuo</u> at 280° produced no



LIX

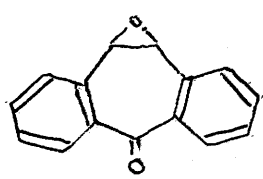


LX

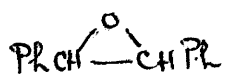
change, and heating with acetic anhydride gave only the diacetate (LX), which was readily re-hydrolysed to the glycol LVIII. Treibs prepared the glycol LVIII from the dibromide LVII, and the hydroxyl groups are

therefore presumably in the trans-configuration (142). It was therefore decided to investigate the dehydration of the corresponding cis-glycol since dehydration takes place preferentially by trans-elimination (151). To this end, the unsaturated ketone (LVI) was hydroxylated by means of $OsO_4$. This reagent is known to produce cis-glycols (142), and it was therefore surprising to find that the product was identical with that prepared via the dibromide. Although unusual, this result is not unique. Bergmann, Pappo and Ginsburg (152), have reported an almost identical case, involving a substituted cyclohexene. An attempt was made to oxidise the ketone (LV) with selenium dioxide, but the only products isolated were the unsaturated ketone (LVI) and anthraquinone.

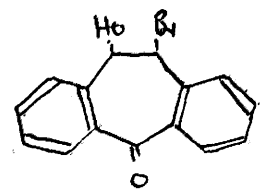
Ketones can often be prepared from olefins via a suitable addition product such as an epoxide (143), and efforts were therefore made to prepare the epoxide LXI. Neither perbenzoic nor perphthalic acids reacted with LVI,



LXI

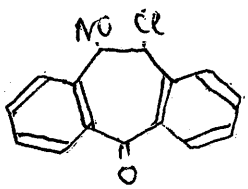


LXII

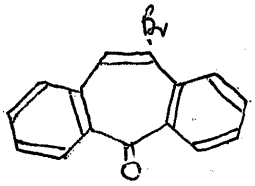


LXIII

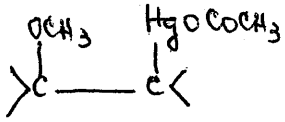
although it is known that under such conditions stilbene gives LXII in good yield (144). Alkaline hydrogen peroxide (145) was also tried, but here again the starting material was returned. Since direct methods had failed, the preparation of the bromhydrin (LXIII) was investigated, by the aqueous N-bromo-succinimide method (146). No reaction occurred. The inertness of this double bond was also illustrated by its failure to react with nitrosyl chloride or mercuric acetate. The former reagent was expected to yield the nitrosochloride LXIV, which might be hydrolysed to a chloroketone, and the latter reagent normally (147) gives adducts (LXVa) which can be




LXIV




LXV

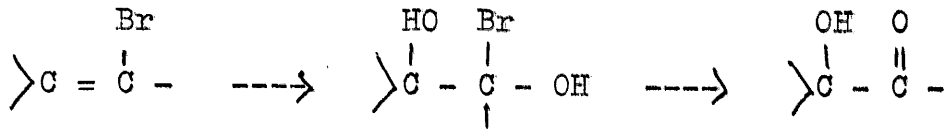



LXVa

converted to bromhydrins (147).

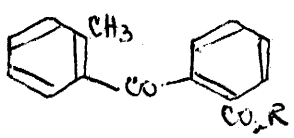
From these experiments, it was clear, that the only reagents capable of attacking this double bond, were

$OsO_4$ and bromine. On this basis, an attempt was made to convert the unsaturated ketone LXV (140) to a ketone by means of $OsO_4$. Such a reaction normally yields acyloins, as follows:-

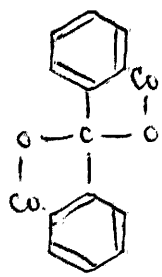


However, when the reaction was applied to LXV, only anthraquinone, and starting material were isolated.

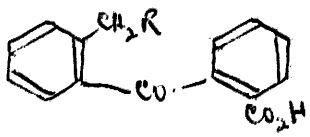
All attempts to prepare the required hydroxy-ketone (XL) from tricyclic intermediates had thus been unsuccessful, and a more orthodox approach was investigated. Phthalic anhydride was reacted with o-bromotoluene through its Grignard complex, and the product (LXVI ; R = H) obtained (153). It was intended to convert it to (LXVII ; R = Br)



LXVI



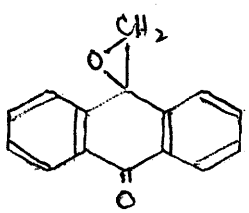
LXVIII



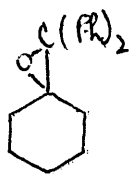
LXVII

and thence to the dicarboxylic acid (LXVII; R = $CO_2H$) which could readily be cyclised to XL. However, all attempts to brominate the keto-ester (LXVI : R = $CH_3$) were unsuccessful. N-bromosuccinimide did not react, and the use of bromine led to partial oxidation to the dilactone (LXVIII). This substance was identified by synthesis (140).

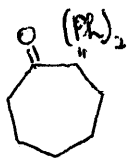
In a final effort to prepare the diketone (XL), methylene anthrone (LI) was epoxidised by means of alkaline $H_2O_2$, and the product (LXIX) treated with conc. sulphuric acid. By such a method, the exocyclic oxide LXX gives the seven membered ketone LXX, by ring



LXIX

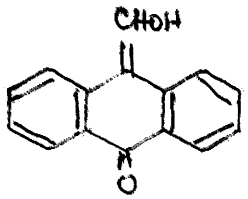


LXX

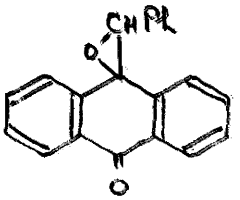


LXXI

expansion. However, the rearrangement product from LXIX appears to be hydroxymethylene anthrone LXXII. On gentle oxidation, it gives anthraquinone, and from



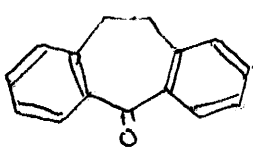

LXXII



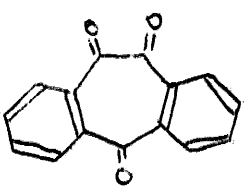

LXXV

the chemistry of LVI (140) and XXXIX (124), it seems certain that a 7-membered ring would yield a dicarboxylic acid, or the derived lactone (LXVIII). Application of this reaction to benzal-anthrone epoxide (LXXV) (145) was expected to give Cook's compound (XXXIX), but only anthraquinone could be isolated from the complex reaction mixture.

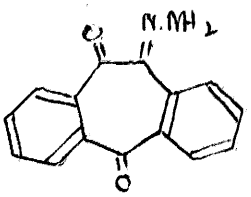
Whilst this work was in progress, Rigandy and Nedelec (150) reported a synthesis of the ketol (XL). By careful $SeO_2$ oxidation of Treibs' ketone LV, they




LV




LXXIII




LXXIV

isolated the triketone (LXXIII). This substance gave a monohydrazone LXXIV which decomposed at room temperature to yield the desired dibenzo-iso-tropolone(XL). Its properties were not examined, but from the m.p. of the substance and its benzoate, it is clearly different from the rearrangement product derived from LXIX.

## Experimental

Only original work is reported in full, melting points are uncorrected.

Benzocyclohepten-3:7dione (XLIII) was prepared by the method of Barltrop, Johnson, and Meakins (126) b.p. 175°/10mm., m.p. 46°.

Dehydrogenation of Benzocyclohepten-3:7-dione.

(a) A solution of the dione (XLIII) (2 g.) in 1:2:4-trichlorobenzene (50 c.c.), was refluxed with palladium-charcoal (5%; 4 g.) for 12 hrs. under nitrogen, and the filtered solution extracted with dilute sodium hydroxide solution. Acidification and ether extraction, yielded nothing.

(b) The dione (1 g.) in glacial acetic acid (5 c.c.) was treated with bromine (0.95 g., 1.1 mol.) in glacial acetic acid (10 c.c.). When warmed on the steam-bath, the solution became almost colourless, hydrogen bromide was evolved, and the colour reappeared. The solution was concentrated in vacuo, made alkaline with sodium hydroxide solution, washed with chloroform, and acidified. This gave a dark intractable gum.

(c) A solution of the dione (2.6 g.) in chloroform (10 c.c.) and carbon tetrachloride (10 c.c.) was

refluxed with N-bromosuccinimide (2.6 g.), for 15 min., under a 200-watt lamp. The solution was then washed with water and concentrated in vacuo to a pale yellow oil. An excess of aqueous trimethylamine was added, and the mixture warmed on the steam-bath for 5 min., and left overnight. The resulting solid product crystallised from dilute methanol, and was further purified by chromatography in benzene on alumina. Recrystallisation from ethanol gave plates, m.p. 130-131° (Found: C, 76.8; H, 4.8. $C_{11}H_8O_2$ requires C, 76.7; H, 4.65%). This substance, for which structure (XLIV) is advanced, gave no picrate, decolorised aqueous potassium permanganate solution very slowly, and was insoluble in sodium hydroxide solution. It failed to give a colour with aqueous or alcoholic ferric chloride, but yielded a bis-2:4-dinitro-phenylhydrazone which crystallised from nitrobenzene in scarlet micro-needles, m.p. 318° (decomp.) (Found: N, 20.75. $C_{23}H_{16}O_8N_8$ requires N, 21.05%).

The cyclopropane derivative XLIV (0.1 g.) in ethanol (15 c.c.) was hydrogenated in presence of Adams' catalyst (0.05 g.). Uptake was 38 c.c. at N. T. P. (3 mols.). Concentration yielded an oily solid, which

after repeated crystallisation had m.p. 150-165°.

The cyclopropane derivative (50 mgm.) and palladium charcoal (0.5 g., 5%) was heated to 200°/$10^{-4}$mm., for ½ hr. The white sublimate was crystallised from dilute methanol, m.p. 131° and gave no depression with starting material.

The cyclopropane derivative (0.1 g.) was added to sodium (0.25 g.) in ethanol (5 c.c.) and refluxed for 2 hrs. After removal of the ethanol, water was added, and the filtered solution acidified. The crude product decomposed at 170°/$10^{-4}$ mm.

3:7-Diacetoxybenzocyclohepta-1:3:6-triene (XLV). A solution of the dione (15 g.) and toluene-p-sulphonic acid (0.75 g.) in isopropenyl acetate (120 c.c.), was refluxed for 16 hr., and then distilled until 80-100 c.c. had been collected. The residue was dissolved in benzene and the solution washed with dilute sodium carbonate solution and then with water, and finally concentrated in vacuo to an oil. This oil was triturated with ether, the solid diacetate filtered off, and the filtrate re-concentrated and re-cycled. From four operations the yield was 15.5 g. The diacetate crystallised from methanol in cream rhombs,

m.p. 125-126° (Found: C, 69.6; H, 5.6. $C_{15}H_{14}O_4$ requires C, 69.8; H, 5.4%).

7-Hydroxybenzocycloheptatrien-3-one (XLI). The diacetate (XLV) (3 g.), in carbon tetrachloride (65 c.c.), was heated under reflux with N-bromosuccinimide (2.1 g.) and a trace of dibenzoyl peroxide, for 5 hrs., under a 200-watt lamp. The solution was then washed with water and concentrated in vacuo. The resulting pale yellow oil was heated on the steam-bath for 30 min. with an excess of dilute caustic soda solution, and a few drops of ethanol. This gave a dark red solution, which was filtered and acidified. The yellow precipitate was washed, dried on a tile, and sublimed at 150-180°/$10^{-4}$ mm., yielding 0.65 g. of the hydroxy-ketone, m.p. 188° (Found: C, 76.6; H, 4.8. $C_{11}H_8O_2$ requires C, 76.7; H, 4.65%). This compound was soluble in sodium hydrogen carbonate solution, and rapidly decolorised aqueous potassium permanganate. It gave a reddish-brown colour with ferric chloride in ethanol, but did not react with copper salts. Its picrate crystallised from dilute methanol in yellow needles, m.p. 155-158° (Found: C, 50.65; H, 3.2; N, 10.3. $C_{11}H_8O_2,C_6H_3O_7N_3$ requires C, 50.9; H, 2.7; N, 10.5%); an unstable hydrochloride was prepared by passing dry hydrogen chloride through a

solution of the hydroxy-ketone in dry acetone, it crystallised from acetone-ether in buff needles, m.p. 150° (decomp.) (Found: C, 58.45; H, 5.1. $C_{11}H_8O_2$,HCl,$H_2O$ requires C, 58.2; H, 4.9%), and slowly lost hydrochloric acid. On the addition of water, it rapidly reverted to the yellow hydroxy-ketone, m.p. and mixed m.p. 186-188°. Treatment with aqueous perchloric acid gave a brown solution, from which brown needles were obtained by concentration. These decomposed violently when heated. When the hydroxy-ketone was heated with acetic anhydride, it gave an oily product, but on treatment with 3:5-dinitrobenzoyl chloride in dry benzene-pyridine, yielded a solid 3:5-dinitrobenzoate, m.p. 186° (Found: C, 59.3; H, 2.95; N, 7.4. $C_{18}H_{10}O_7N_2$ requires C, 59.0; H, 2.7; N, 7.65%). It also gave a mono-2:4-dinitro-phenyl-hydrazone, m.p. 198° (Found: N, 15.9. $C_{17}H_{12}O_5N_4$ requires N, 15.8%), and reacted readily with ethereal diazomethane, to give an oil methyl ether hydrate, b.p. 170-172° (bath)/1.5 mm. (Found: C, 73.85; H, 5.9. $C_{12}H_{10}O_2$,$\frac{1}{2}H_2O$ requires C, 73.8; H, 5.6%). This ether was readily hydrolysed by aqueous alkali at 100°, to the parent hydroxy-ketone, and an attempt to form the picrate

of the ether, gave instead, the picrate, m.p. and mixed m.p. 155°, of the hydroxy-ketone. A solid by-product isolated during the purification of the ether, crystallised from carbon tetrachloride in needles, m.p. 129-130° (Found: C, 76.6; H, 4.85. Calc. for $C_{11}H_8O_2$: C, 76.7; H, 4.65%). It gave no depression in mixed m.p. with the tricyclic ketone (XLIV).

The hydroxy-ketone in alkaline solution, coupled with diazotised aniline, yielding a crimson dye. An electrometric titration carried out on a 30% alcoholic solution, by Dr. J. C. Speakman, indicated a pK value of 6.40. From this, the estimated value for water is ca. 6.1.

Hydrogenation.- (a) The dione (XLIII) (1 g.), in ethanol (10 c.c.) was reduced in presence of Adams's ($PtO_2$) catalyst (0.1g.). Uptake was rapid until 2 mols. of hydrogen had been absorbed and slow thereafter. Concentration gave the diol, which crystallised from aqueous alcohol in needles, m.p. 179-180°. (Found: C, 74.4; H, 8.1. $C_{11}H_{14}O_2$ requires C, 74.2; H, 7.9%). The slow uptake probably represents hydrogenolysis of the diol (XLVII).

(b) The hydroxy-ketone (XLI) (0.1 g.) in ethanol (5 c.c.), was hydrogenated in presence of palladium-

calcium carbonate (2%; 0.75 g.). Uptake almost ceased after 3.6 mols. of hydrogen had been absorbed, and the product crystallised in needles, m.p. and mixed m.p. with (XLVII) 178-179°.

Alkali Fusion. The hydroxy-ketone (XLI) (40 mg.) was added to a melt of potassium hydroxide (1 g.) and water (0.3 c.c.), and heated at ca. 220° with intermittent stirring for 30 min. After the melt had cooled water was added and the solution was filtered. Acidification yielded starting material, which was identified by mixed m.p.

Absorption Spectra. These were determined by using a "Unicam" Spectrophotometer.

Methylene Anthrone was prepared by Clar's method (136) m.p. 144°. The dibromide (LII) was prepared according to the instructions of Meyer (137) and had m.p. 148-150° (decomp.).

Rearrangement. The dibromide LII (5 g.) was dissolved in acetone (50 c.c.) and refluxed for 1½ hrs. On cooling, the crystalline precipitate was purified by recrystallising from dioxan, m.p. 274°. (Found: C, 86.8; H, 4.65. $C_{28}H_{18}O_2$ requires, C, 87.0; H, 4.7). This gave no depression in m.p. with bianthronyl (LIII)

prepared from anthrone by Dimroth's method (138). When the above rearrangement was carried out in presence of silver oxide (5 g.), the same product was isolated.

Dianthronylidene (LIV). The above product LIII was oxidised to LIV by the procedure of Barnett and Matthews (139). m.p. 300°.

Rearrangement. The dibromide (LII) (3.6 g.) and silver acetate (3.6 g.) were refluxed in benzene (75 c.c.) for 3½ hrs., filtered and concentrated to an oil. On trituration with ethanol this yielded a solid which was recrystallised from dioxan in cream needles m.p. 270°. No depression in mixed m.p. with bianthronyl (LIII).

1:3:4:5-Dibenzo-cyclohepta-1:4-dien-3-one-6:7;diol (LVIII). This was obtained by Treibs' method (140) m.p. 130° (anhydrous) or 110° (hydrate).

Attempted dehydrations - (a) The diol (0.3 g.) was mixed with $KHSO_4$ (0.3 g.) and heated to 150-160°/10 mm. for 15 mins. Water was added and chloroform extraction gave anthrone m.p. and mixed m.p. 148-150°.

(b) The diol (1.5g) was melted, treated with a crystal of iodine, and kept at 230° for ½ hr., (odour of formic acid) and finally vacuum distilled at 250°/10 mm. The product was recrystallised from methanol in needles m.p.

with anthrone 148-150°.

(c) A sample of the diol (0.5gm.) was heated at 280°/10 mm., for a few minutes. A product distilled over and was recrystallised from water m.p. and mixed m.p. with diol 110°.

(d) A sample of the diol (0.5 g.) was refluxed for 3 hrs., with 10 c.c. of acetic anhydride. On removal of the excess acetic anhydride, an oil remained and was crystallised from methanol. m.p. 156-7°.

(Found: C, 70.4; H, 5.5. $C_{19}H_{16}O_5$ requires, C, 70.4; H, 4.9%. On hydrolysis with alcoholic potash, a gummy solid was obtained and recrystallised from water, m.p. and mixed m.p. with diol 110°.

1:2:4:5-Dibenzo-cycloheptatriene-3-one (LVI) was obtained by bromination and dehydrobromination of the saturated ketone LV (140) m.p. 89-90°.

Osmium tetroxide oxidation. A solution of the unsaturated ketone LVI (0.85 gm) in dry benzene (5 c.c.) was treated with $OsO_4$ (1 g.) in 4.5 c.c. dry benzene and dry pyridine (0.62c.c.) added. After six days, the solid complex was filtered off. Yield 2.5 gm.

The complex (2.5 g.) suspended in alcohol (80 c.c.) was treated with 20 gm. sodium sulphite, in 40 c.c. water, and heated on the steam-bath for ½ hr. The mixture was filtered, the solid re-extracted with alcohol 3 times,

and the combined filtrates concentrated. The oily product solidified and was crystallised from methanol-water, m.p. 108-110°. No depression in mixed m.p. with the diol LVIII.

Selenium dioxide oxidation. The saturated ketone (LV) (4.5 gm.) and $SeO_2$ (2.4 g.) (1 mol.) were heated to 200° for 2 hrs. A crystalline sublimate formed on the upper parts of the flask, m.p. 270-5°. This gave no depression in mixed m.p. with anthraquinone. The residue in the flask was extracted with methanol, and yielded a substance of m.p. 88-9°. The m.p. was not depressed on admixture with LVI.

Perbenzoic Acid was prepared by the method of Organic Syntheses, Coll. Vol. I, p. 431.

Perphthalic Acid was prepared by the method of Organic Syntheses, 20, 70.

Attempts to epoxidise LVI. (a) The unsaturated ketone (LVI) (0.25 g.) in 75 c.c. ether was treated with ethereal perbenzoic acid (10 fold excess) and allowed to stand at room temperature for 6 days. The solution was then washed with sodium carbonate solution and concentrated. The resulting oil recrystallised from methanol m.p. and mixed m.p. with starting material 89-90°. Yield almost quantitative.

(b) The unsaturated ketone (LVI) (0.52 gm.) in 25 c.c. anhydrous ether was treated with ethereal perphthalic acid (2 mols.) and left for 4 days. The ethereal solution was worked up as in (a) and gave starting material m.p. and mixed m.p. 90°, in almost quantitative yield.

(c) The ketone (LVI)(0.4 g.) in methanol (25 c.c.) was treated with 2 c.c. of 30% $H_2O_2$ and 2.5 c.c. of dilute sodium hydroxide solution, and left overnight. A product crystallised out, and on dilution, the solution deposited a further quantity of the same product, m.p. 88-90°. The m.p. was not depressed by admixture with the starting material.

Attempts to form addition products of LVI. (a) The unsaturated ketone (LVI) (1.2 gm.) and N-bromosuccinimide (1.1 gm.) suspended in 50 c.c. water and 5 c.c. ether, were shaken for 23 hrs. On removal of the ether, the odour of HOBr was observed. The crude product was recrystallised from methanol m.p. 87-9°. This was shown by mixed m.p. to be identical with the starting material.

(b) The unsaturated ketone (1 g.) was treated with mercuric acetate (1.6 g.) and 50 c.c. methanol, and warmed till everything dissolved. After standing for 4 days, 1.75 gm. potassium bromide was added, in 10 c.c.

water, the mixture warmed for 5 mins., and then treated with an excess of water. The product which crystallised out was shown to be starting material m.p. and mixed m.p. 89°. The yield was 90%.

(c) The unsaturated ketone (0.2 g.) and amyl nitrite (0.12 g.) in acetic acid (2 c.c.) was treated with conc. HCl (0.15 c.c.) and left for 24 hrs. Dilution gave the starting material, m.p. and mixed m.p. 89-90°.

1-Bromo-2:3:5:6 dibenzo-cycloheptatriene-4-one (LXV). This was obtained by bromination and dehydrobromination of the ketone (LVI) as described by Treibs (140). m.p. 115-6°.

Reaction of Osmium tetroxide with LXV. The bromo ketone (LXV) (1.12 g.) in dry benzene (5 c.c.) was treated with $OsO_4$ (1 g.) in dry benzene (5 c.c.) and 6.2 c.c. dry pyridine added. After standing for 24 hrs., the solid product was filtered off. Concentration of the filtrate gave a small quantity of starting material m.p. and mixed m.p. 116°. The solid material was suspended in ethanol (60 c.c.) and treated with $Na_2SO_3$ (17 g.) in 35 c.c. water. After standing overnight it was heated on the steam-bath for ½ hr., filtered and the solid residue re-extracted with boiling ethanol.

When these extracts were concentrated, anthraquinone was obtained m.p. and mixed m.p. 273°.

2-(2'-Toluoyl)-benzoic acid (LXVI) and its methyl ester were prepared by the literature methods (153). The acid had m.p. 129° and the methyl ester b.p. 210°/12 mm. m.p. 40°C.

Attempted bromination of LXVI. (a) The keto ester (LXVI : R = Me) (2.5 g.) in chloroform (25 c.c.) and carbon tetrachloride (25 c.c.) was treated with N-bromosuccinimide (2 g.) and a trace of benzoyl peroxide, and refluxed for 5 hrs., under a 200 watt lamp. The solution was then washed with water, dried and evaporated to an oil, which distilled at 220°(bath)/10 mm. $n_D^{20}$ 1.5854. (Found: C, 75.5; H, 6.0. $C_{16}H_{14}O_3$ requires C, 75.6; H, 5.5%). These figures correspond to the starting product, and on seeding with starting material the oil crystallised m.p. and mixed m.p. 38-40°.

(b) The keto ester (2.5 g.) in carbon tetrachloride (20 c.c.) was covered with 5 c.c. water and a trace of iodine added. The mixture was refluxed whilst bromine (1.6 g. i.e. 1 mol.) in carbon tetrachloride (10 c.c.) was added in portions, and during this reaction, the mixture was illuminated by a 150 watt

lamp. On standing, a crystalline material separated out and was purified by recrystallisation from ethanol m.p. 207-8°. (Found: C, 71.7; H, 3.5. $C_{15}H_8O_4$ requires, C, 71.45; H, 3.2%). These figures correspond to the di-lactone LXVIII, and a mixed m.p. with a synthetic sample (140) was undepressed.

The mother liquors on concentration yielded a quantity of starting material b.p. 165°(bath)/1mm. $n_D^{20}$ 1.5863 which crystallised on seeding m.p. and mixed m.p. 40°.

Methylene Anthrone epoxide (LXIX). Methylene anthrone (0.5 g.) suspended in ethanol (10 c.c.) was treated with dilute NaOH solution (1 c.c.) and 1 c.c. $H_2O_2$ (15%). The mixture turned reddish brown and on gentle warming everything passed into solution. On standing, the product crystallised out and was purified by recrystallising from ethanol m.p. 128-9° (Found: C, 81.1; H, 4.7. $C_{15}H_{10}O_2$ requires, C, 81.1; H, 4.5%).

Rearrangement. The above epoxide (3 g.) was treated with ice cold conc. sulphuric acid (30 c.c.), and kept at 0°C for 1 hr. The resulting deep red solution was poured on to ice, and the yellow precipitate washed, dissolved in aqueous NaOH and filtered.

Acidification of the filtrate gave the product which was purified by sublimation at 180°/$10^{-4}$mm. m.p. 185-7° (Found: C, 81.4; H, 4.6. $C_{15}H_{10}O_2$ requires C, 81.1; H, 4.5%). The substance gave a benzoate by the usual Schotten-Baumann technique, m.p. 150°, and the derivative was purified by recrystallisation from ethanol m.p. 160-2°. (Found: c, 80.7; H, 4.3. $C_{22}H_{14}O_3$ requires, C, 81.0; H, 4.3%).

Oxidation. The rearrangement product (0.1 g.) in acetone (10 c.c.) was shaken up with a solution of potassium permanganate in acetone, until a slight pink colour remained. The solution was then concentrated to dryness, dilute sulphuric acid added, and $SO_2$ passed through the mixture until all the inorganic material had dissolved. The insoluble product was recrystallised from dioxan, m.p. 273°, and gave no depression in mixed m.p. with anthraquinone.

Benzal-anthrone epoxide was prepared by the literature method (145) m.p. 132°.

Rearrangement. The epoxide (1.5 g.) in 15 c.c. ice cold conc. $H_2SO_4$, was maintained at 0°C for 1 hr. and then poured into ice-water. The yellow product had a distinct

odour of benzaldehyde. Extraction with alcohol gave an insoluble material of m.p. 275°, which was shown to be anthraquinone by mixed m.p. The soluble fraction was fractionally crystallised, but the only pure material isolated crystallised from ethanol in yellow needles m.p. 112° (Found: C, 92.0; H, 5.0%). The remainder was amorphous.

# Publications.

Reprinted from the Journal of the Chemical Society, 1944

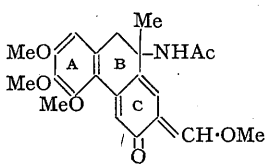
# 87. *Colchicine and Related Compounds. Part IV. Synthesis of 2 : 3 : 4 : 5-, 2 : 3 : 4 : 6-, and 2 : 3 : 4 : 7-Tetramethoxy-9-methylphenanthrenes.*

By G. L. Buchanan, J. W. Cook, and J. D. Loudon.

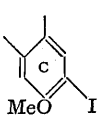
The three compounds named in the title have been synthesised, by the Pschorr method, from 2-nitro-3 : 4 : 5-trimethoxybenzaldehyde and *m*- and *p*-methoxyphenylacetic acids. The tetramethoxyphenanthrene-9-carboxylic acids, which were the primary products, were reduced to the 9-*aldehydes* and thence to the 9-*methyl* compounds. All three of these were different from the colchicine degradation product, hitherto believed to be 2 : 3 : 4 : (6 or 7)-tetramethoxy-9-methylphenanthrene, which Windaus prepared and converted into 9-methylphenanthrene.

2-Nitro-3 : 4 : 5-trimethoxybenzaldehyde, which is obtained only in small yield by nitration of trimethoxybenzaldehyde, was prepared in sufficient quantity for our synthetical reactions from 2-nitro-3 : 4 : 5-trimethoxybenzoic acid, through the intermediary of a "Reissert compound." *o*- and *m*-Nitrobenzaldehydes were similarly prepared, but the method failed to give *p*-nitro-, 2 : 4-dinitro-, or 3 : 5-dinitro-benzaldehyde.

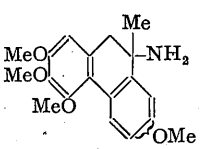
The structure (I) proposed by Windaus (*Annalen*, 1924, **439**, 59) for colchicine is supported by a considerable body of evidence. It accords with the oxidation of colchicine to 2 : 3 : 4-trimethoxyphthalic acid (Windaus, *Sitzungsber. Heidelberg. Akad. Wiss.*, Math.-Nat. Kl. *A*, 1914, 18 Abh.), and the ready lactonisation of another degradation product (*idem, ibid.*, 1911, 2 Abh.) appears to establish the positions of the methoxyl groups in ring A of colchicine. Moreover, hydrolysis of the methoxymethylene group in ring C, followed by treatment with iodine and potassium hydroxide, leads to an iodo-phenol, methylated to *N*-acetyliodocolchinol methyl ether (II) (*idem, ibid.*, 1914, 18 Abh.; 1919, 16 Abh.). This was oxidised to a compound identified by Grewe (*Ber.*, 1938, **71**, 907) as 4-iodo-5-methoxyphthalic acid. Hence the nature and positions of substitution of ring C in *N*-acetyliodocolchinol methyl ether are established, with the proviso that the two substituents may be interchanged. This leads to two alternative structures (III) for colchinol methyl ether, obtained from (II) by reduction followed by acid hydrolysis. Windaus (*Annalen*, 1924, **439**, 59) submitted colchinol methyl ether to Hofmann degradation and obtained a product, hereafter termed deaminocolchinol methyl ether, which he regarded as 2 : 3 : 4 : 6- or 2 : 3 : 4 : 7-tetramethoxy-9-methylphenanthrene, (IV) or (V). In support of this formulation Windaus found that deaminocolchinol methyl ether was converted into 9-methylphenanthrene, by demethylation followed by zinc dust distillation.



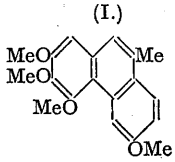

(I.)



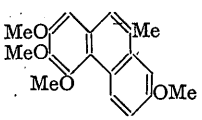

(II.)



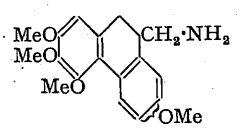

(III.)




(IV.)




(V.)




(VI.)

Cohen, Cook, and Roe (J., 1940, 194) suggested that the structure of ring B in Windaus's formula for colchicine (I) was not in complete accord with the experimental evidence, and they advanced alternative structures (including VI) for colchinol methyl ether. These workers also pointed out that the drastic conditions of zinc dust distillation might induce alteration of the ring system during formation of 9-methylphenanthrene. Exception has been taken to these views by Lettré (*Naturwiss.*, 1942, **30**, 34) and Lettré and Fernholz (*Z. physiol. Chem.*, 1943, **278**, 175), who suggest that structures of type (VI) are incompatible with the oxidation of partially hydrolysed *N*-acetylcolchinol methyl ether to 4-methoxyphthalimide (Windaus, *Sitzungsber. Heidelberg. Akad. Wiss.*, Math.-Nat. Kl. *A*, 1919, 16 Abh.). This is a valid argument, but we do not regard it as conclusive. Much less convincing is the additional argument advanced by Lettré that activity as mitotic poisons shown by simple synthetic analogues of (I) contrasts with the biological inactivity of analogues of (VI), and hence indicates a colchicine formulation of type (I) rather than type (VI).

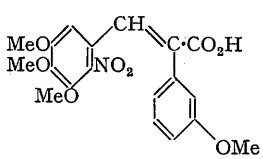
Clearly, the synthesis of 2 : 3 : 4 : 6- and 2 : 3 : 4 : 7-tetramethoxy-9-methylphenanthrene is important since, by identification of one of these synthetic compounds with deaminocolchinol methyl ether, not only would the methoxylation pattern be established, but extensive confirmation would be afforded of the general structural features of colchicine itself. Such evidence, however, would not determine whether the acetamido-group is attached to the nucleus (type I) or in the side chain (type VI). We have now synthesised these two tetramethoxymethylphenanthrenes and have found both of them to be different from deaminocolchinol methyl ether, for which, accordingly formulæ (IV) and (V) must be abandoned. Indeed, we have obtained evidence, which will be detailed in a further communication, that deaminocolchinol methyl ether is not a tetramethoxymethylphenanthrene at all.

2 : 3 : 4 : 6-Tetramethoxyphenanthrene-9-carboxylic acid was prepared by the Pschorr reaction following (and confirming) Sharp's description (J., 1936, 1234). The acid was converted into the corresponding *aldehyde* by the method of McFadyen and Stevens (J., 1936, 584), *viz.*,

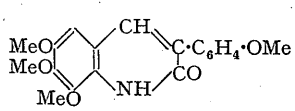
$$R{\cdot}CO_2H \longrightarrow R{\cdot}CO_2Me \longrightarrow R{\cdot}CO{\cdot}NH{\cdot}NH_2 \longrightarrow R{\cdot}CO{\cdot}NH{\cdot}NH{\cdot}SO_2Ph \longrightarrow R{\cdot}CHO$$

Wolff reduction of this aldehyde gave mainly phenolic products, but Kishner's procedure (compare Asahina and Yasue, *Ber.*, 1936, **69**, 2327) gave the required 2 : 3 : 4 : 6-*tetramethoxy*-9-*methylphenanthrene* (IV) in good yield.

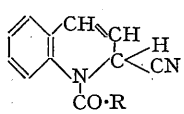
Condensation of 2-nitro-3 : 4 : 5-trimethoxybenzaldehyde with sodium *m*-methoxyphenylacetate gave a mixture of stereoisomerides consisting chiefly of the required cis-*compound* (VII) together with a small percentage of the trans-*isomeride*. On reduction, the latter readily underwent ring-closure to the corresponding *carbostyril* (VIII), and was conveniently removed in this form after reduction of the original mixture. Acid solutions of diazotised 2-*amino*-3 : 4 : 5-*trimethoxy*-α-m-*methoxyphenylcinnamic acid* proved to be stable to heat, but in neutral or slightly alkaline solution evolution of nitrogen proceeded smoothly. This led to approximately equal amounts of 2 : 3 : 4 : 5- and 2 : 3 : 4 : 7-*tetramethoxyphenanthrene*-9-*carboxylic acids*, which were separated by means of their different solubilities in acetic acid. Similar pairs of isomerides have been obtained by Pschorr (*Annalen*, 1912, **391**, 40) and by Rapson and Robinson (J., 1935, 1533) in analogous phenanthrene syntheses involving a *m*-methoxyphenyl nucleus. Even so, it is surprising, in view of the great difficulty of formation of 4 : 5-dimethylphenanthrene (see *Ann. Reports*, 1942, **39**, 172), that the 2 : 3 : 4 : 5-tetramethoxy-compound should have been formed so readily and to such an extent, when an alternative mode of ring-closure (to the 2 : 3 : 4 : 7-structure) is possible (see also Pschorr, *loc. cit.*). This suggests that some influence other than steric factors operates in preventing the formation of 4 : 5-dimethylphenanthrene. The two new acids were not individually oriented, although this is in progress. They were converted into the *tetramethoxy*-9-*methylphenanthrenes* by the reactions outlined above for the 2 : 3 : 4 : 6-isomeride. Obviously, one of these two products has the structure (V).



(VII.)



(VIII.)



(IX.)

The principal reason why these Pschorr syntheses had not been undertaken at an earlier stage of our investigations was the difficulty of obtaining an adequate quantity of 2-nitro-3 : 4 : 5-trimethoxybenzaldehyde (Sharp, *loc. cit.*; compare Part III). The yield in the nitration of trimethoxybenzaldehyde and its derivatives is low and variable (compare Parts II and III). We therefore sought an alternative route to this nitro-aldehyde. The reported preparation of methyl 2-nitro-3 : 4 : 5-trimethoxybenzoate in high yield by nitration of methyl trimethylgallate (Hamburg, *Monatsh.*, 1898, **19**, 599; Bogert and Plaut, *J. Amer. Chem. Soc.*, 1915, **37**, 2727; Overmyer, *ibid.*, 1927, **49**, 503) suggested a method based on indirect reduction of the nitro-acid. The method of McFadyen and Stevens (*loc. cit.*) is known to be unsuitable for the preparation of nitrobenzaldehydes (compare Niemann and Hays, *J. Amer. Chem. Soc.*, 1943, **65**, 482). However, Reissert (*Ber.*, 1905, **38**, 1610), by shaking together benzoyl chloride, aqueous potassium cyanide, and quinoline, prepared 1-benzoyl-1 : 2-dihydroquinaldinonitrile (Reissert's compound) (IX; R = Ph) which on hydrolysis yielded benzaldehyde and quinaldinic

acid. Moreover, successful extensions of this method by Woodward (*J. Amer. Chem. Soc.*, 1940, **62**, 1626) and by Grosheintz and Fischer (*ibid.*, 1941, **63**, 2021), although not covering the case of nitrobenzaldehydes, emphasised its possibilities, and the 2-nitro-3 : 4 : 5-trimethoxybenzaldehyde used in our synthetical experiments was prepared by a procedure which was essentially that of Grosheintz and Fischer. The method proved laborious, largely on account of the quantity of mineral acid required for the final hydrolysis, and the high yields claimed in the nitration of methyl trimethylgallate could not be substantiated. Even so, we obtained overall yields of the nitro-aldehyde in excess of 20%.

It was found also that trimethylgallic acid could be converted into trimethoxybenzaldehyde by this method, as also by the method of McFadyen and Stevens. *o*-Nitrobenzoyl chloride likewise gave a "Reissert compound," from which *o*-nitrobenzaldehyde was obtained in good yield. Further experiments by Mr. J. M. Bremner showed that *m*-nitrobenzoyl chloride could be similarly converted into *m*-nitrobenzaldehyde, but neither *p*-nitrobenzoyl chloride nor 3 : 5-dinitrobenzoyl chloride yielded a "Reissert compound"; the crystalline products were not derivatives of quinoline. 3 : 4-Dinitrobenzoyl chloride gave an uncrystallisable gum.

## Experimental.

1-(3′: 4′ : 5′-*Trimethoxybenzoyl*)-1 : 2-*dihydroquinaldinonitrile* [IX; R = $C_6H_2(OMe)_3$].—3 : 4 : 5-Trimethoxybenzoyl chloride (3·5 g.) in benzene (5 c.c.) was added to anhydrous hydrogen cyanide (1 c.c.) in quinoline (5 c.c.) at −10°. After 16 hours, ether was added and the mixture was washed in turn with water, 5N-sulphuric acid, sodium hydrogen carbonate solution, and again with water. Crystals which separated were added to the residue obtained by evaporating the ethereal solution and the solid was extracted in two stages with hot ethanol (50 c.c. each). The first extract gave on cooling a crop of plates which were filtered off and combined with the solid from the second extraction. The plates, after recrystallisation, had m. p. 176—177° (Found: C, 68·8; H, 4·9; N, 8·2. $C_{20}H_{18}O_4N_2$ requires C, 68·6; H, 5·1; N, 8·0%). The mother-liquor from the first extract deposited a second crop of needles which were identified as 3 : 4 : 5-trimethoxybenzoic anhydride, probably formed through access of moisture in the early stages of the experiment.

3 : 4 : 5-Trimethoxybenzaldehyde was prepared in each of the two following ways and was identified by mixed m. p. with a specimen obtained by Rosenmund reduction of the acid chloride (cf. Sharp, *loc. cit.*) which appears to be the most convenient source of the compound. (*a*) The powdered nitrile (above) was hydrolysed by prolonged shaking with 10N-sulphuric acid, followed by gentle warming, extraction of the cooled, filtered solution with ether, and evaporation of the solvent. (*b*) Methyl 3 : 4 : 5-trimethoxybenzoate (17 g.) was refluxed for 2 hours with hydrazine hydrate (18 c.c.; 50%) in methanol (30 c.c.). The *hydrazide* obtained on cooling had m. p. 128—129° and crystallised with a molecule of solvent (Found: C, 51·3; H, 6·65. $C_{10}H_{14}O_4N_2,CH_4O$ requires C, 51·2; H, 7·0%) which was removed by heating at 100° in a vacuum, the m. p. rising to 168° (Found: C, 53·2; H, 6·2; N, 12·5. $C_{10}H_{14}O_4N_2$ requires C, 53·1; H, 6·2; N, 12·4%). The *benzenesulphonyl* derivative, m. p. 250° (decomp.), was prepared from the hydrazide and benzenesulphonyl chloride in pyridine (Found: C, 52·2; H, 4·7; N, 7·6. $C_{16}H_{18}O_6N_2S$ requires C, 52·5; H, 4·9; N, 7·65%). It (9·3 g.) was dissolved in ethylene glycol (94 g.) and sodium carbonate (6·8 g.) was added to the solution heated to 160°. After 75 seconds, hot water was added, and the mixture was cooled and extracted with ether, from which the aldehyde was obtained on evaporation.

1-(*o*-*Nitrobenzoyl*)-1 : 2-*dihydroquinaldinonitrile* (IX; R = $C_6H_4{\cdot}NO_2$).—To a solution of anhydrous hydrogen cyanide (3 c.c.) in quinoline (14 g.), protected from moisture at −10°, *o*-nitrobenzoyl chloride (10 g.) in benzene (10 c.c.) was added during 10 minutes. After 12 hours at room temperature, during which some crystals formed, benzene (130 c.c.) was added, the resulting mixture was washed successively with water, 5N-sulphuric acid, sodium hydrogen carbonate and water, and was then dried and concentrated. The crystalline product had m. p. 173° (from ethanol), yield 80%. (Found: C, 67·4; H, 3·8; N, 13·5. $C_{17}H_{11}O_3N_3$ requires C, 66·9; H, 3·6; N, 13·8%). It (1 g.) was hydrolysed by boiling for 3 hours in 15N-sulphuric acid (250 c.c.); *o*-nitrobenzaldehyde, identified by mixed m. p. and formation of its 2 : 4-dinitrophenylhydrazone, was isolated from an ethereal extract of the product after washing with sodium hydrogen carbonate solution (yield, 73%).

1-(m-*Nitrobenzoyl*)-1 : 2-*dihydroquinaldinonitrile* (IX; R = $C_6H_4NO_2$) was prepared by adding a solution of *m*-nitrobenzoyl chloride (6·2 g.) in benzene (15 c.c.) to quinoline (8·5 c.c.) and hydrogen cyanide (5 c.c.) at −8°. The solid which separated after 12 hours was augmented by extracting the mother-liquor with ether. It had m. p. 171° (from ethanol) (Found: C, 66·8; H, 3·5. $C_{17}H_{11}O_3N_3$ requires C, 66·9; H, 3·6%) and was hydrolysed by adding 30N-sulphuric acid (125 c.c.) to its suspension (1 g.) in water (125 c.c.) containing a little "Aerosol" (a commercial wetting agent consisting of dioctyl sodium sulphosuccinate), and heating the mixture for 2 hours. After filtration through glass wool the solution was extracted with chloroform, the extract washed with bicarbonate solution, and *m*-nitrobenzaldehyde obtained on evaporation.

When *p*-nitrobenzoyl chloride was treated in the above fashion the product was a colourless crystalline solid of m. p. 185° (from chloroform–ethanol) (Found: C, 55·2; H, 2·4; N, 15·6; *M*, cryoscopic, in dioxan, 282. $C_8H_4O_3N_2$ requires C, 54·5; H, 2·3; N, 15·9%; *M*, 176), but after it had been ascertained that *p*-nitrobenzoic acid was produced on hydrolysis with acid, further examination was discontinued.

3 : 5-Dinitrobenzoyl chloride, treated in the same way, gave a product which, when crystallised from ethanol, yielded a sparingly soluble fraction consisting of colourless plates, m. p. 276°, probably analogous to the last compound (Found: C, 44·2; H, 2·0%), and a more soluble fraction identified by m. p. (92°) and mixed m. p. as ethyl 3 : 5-dinitrobenzoate, probably derived from unreacted acid chloride.

Methyl 3 : 4 : 5-trimethoxybenzoate, nitrated by Bogert's method (*loc. cit.*), or by variants of this method, gave the 2-nitro-derivative in yields of 50—60%. The nitro-ester was hydrolysed with aqueous-alcoholic potassium hydroxide and the resulting acid, after drying, yielded the corresponding acid chloride (90% over-all yield) when treated with thionyl chloride (compare Overmyer, *loc. cit.*).

1-(2′-*Nitro*-3′ : 4′ : 5′-*trimethoxybenzoyl*)-1 : 2-*dihydroquinaldinonitrile* [IX; R = $C_6H(NO_2)(OMe)_3$].—The above acid chloride (75 g.) in dry benzene (200 c.c.) was added in the course of an hour, with shaking and exclusion of moisture, to a solution of anhydrous hydrogen cyanide (22 c.c.) in redistilled quinoline (75 c.c.) at −5°. After 16 hours at room temperature, water was added to the partly crystalline mixture, which was then shaken out, with the aid of 200 c.c. of chloroform, into *ca.* 60 c.c. of 5N-sulphuric acid. The product partly separated and was filtered off. The chloroform solution was washed with sulphuric acid, several times with a saturated solution of sodium hydrogen carbonate, again with water, dried, and concentrated. The combined solid fractions yielded colourless plates of m. p. 168° (from chloroform–ethanol) in more than 80% yield (Found: C, 60·9; H, 4·4; N, 10·7. $C_{20}H_{17}O_6N_3$ requires C, 60·75; H, 4·3; N, 10·6%). It was hydrolysed by shaking (10 g., finely powdered) for 2½ hours with 15N-sulphuric acid (1250 c.c.) at 80—85°. Unchanged material (1—2 g.) was filtered off, and the filtrate, which often deposited the product as long colourless needles,

was extracted with chloroform from which, after thorough washing with water, sodium hydrogen carbonate solution, and again with water, the aldehyde was isolated. 2-Nitro-3 : 4 : 5-trimethoxybenzaldehyde forms colourless silky needles of m. p. 78°, which rapidly turn yellow on exposure. The yield, allowing for recovered material, was 60—70%.

2 : 3 : 4 : 6-*Tetramethoxyphenanthrene*-9-*aldehyde*.—*Methyl* 2 : 3 : 4 : 6-*tetramethoxyphenanthrene*-9-*carboxylate* was prepared from the corresponding acid (Sharp, *loc. cit.*) (3·5 g.) and diazomethane in ether. A specimen, after distillation in a high vacuum, was obtained as colourless needles, m. p. 96—97° (Found: C, 67·3; H, 5·4; OMe, 43·9. $C_{20}H_{20}O_6$ requires C, 67·4; H, 5·6; OMe, 43·5%). The crude ester, 50% hydrazine hydrate (12 c.c.), and sufficient ethanol to give a hot homogeneous solution, were heated under reflux for 4 hours. The hydrazide, which separated on cooling (m. p. 190°; Sharp, *loc. cit.*, gives m. p. 191—196°), was dried at 110° and was then dissolved (2·4 g.) in pyridine (25 c.c.), and benzenesulphonyl chloride (1·2 g.) was added at 0°. After 12 hours the solution was poured into iced dilute hydrochloric acid, and the precipitated solid was collected, washed, and dried at 110°. This *benzenesulphonyl* derivative, m. p. 237° (decomp.) (from alcohol–dioxan) (Found: C, 60·7; H, 4·9. $C_{25}H_{24}O_7N_2S$ requires C, 60·5; H, 4·8%), was dissolved (3 g.) in ethylene glycol (40 c.c.) at 160°, anhydrous sodium carbonate was added (1·8 g.) and, after 80 seconds, the reaction was stopped by addition of warm water (50 c.c.). The cooled solution was extracted with ether, the extract dried, concentrated to 50 c.c., filtered, and allowed to evaporate. After two crystallisations from ethanol the residue yielded almost pure *aldehyde*; a sample, distilled in a high vacuum, formed pale cream crystals (from ethanol), and had m. p. 119° (Found: C, 69·8; H, 5·5. $C_{19}H_{18}O_5$ requires C, 69·9; H, 5·5%).

2 : 3 : 4 : 6-*Tetramethoxy*-9-*methylphenanthrene* (IV).—The aldehyde (0·2 g.) in ethanol (6 c.c.) and hydrazine hydrate (99%; 0·5 c.c.) were heated under reflux for 2 hours; the solvent was removed (finally in a vacuum) and powdered potassium hydroxide (0·3 g.) was added to the gummy residue maintained at 120—125° in an oil bath. After 20 minutes, the mixture was cooled, water added, and the suspension extracted with ether. The extract was dried, concentrated, and the residue distilled in a high vacuum. The solid distillate crystallised in long, colourless needles from hot concentrated solution in methanol, and in shorter, hexagonal crystals, by slow evaporation of a dilute solution; m. p. 108—109° (Found: C, 72·8; H, 6·55; OMe, 39·0. $C_{19}H_{20}O_4$ requires C, 73·1; H, 6·4; OMe, 39·7%). It formed a *picrate*, slender crimson needles, m. p. 115° (from methanol), when concentrated solutions of the components in methanol were mixed (Found: C, 55·7; H, 4·45. $C_{19}H_{20}O_4,C_6H_3O_7N_3$ requires C, 55·5; H, 4·25%).

cis- *and* trans-2-*Nitro*-3 : 4 : 5-*trimethoxy*-α-m-*methoxyphenylcinnamic Acids* (VII).—Sodium *m*-methoxyphenylacetate (8·2 g.) (dried at 130°) was heated with acetic anhydride (80 c.c.) and 2-nitro-3 : 4 : 5-trimethoxybenzaldehyde (10·5 g.) for 8 hours at 120—130°. After addition of water and cautious warming to decompose acetic anhydride, the resulting mixture was cooled and thoroughly extracted with ether. The ethereal solution was first washed with limited quantities of aqueous sodium carbonate, which removed much of the acetic acid, and was then extracted with alkali. Acidification of the alkaline extract yielded a gum which solidified when warmed and rubbed with methanol. Fractionation from methanol–water, assisted by mechanical separation, gave the cis-*acid* (VII) as main product—compact, diamond-shaped, pale yellow crystals, m. p. 139—140°, readily soluble in methanol (Found: C, 58·85; H, 5·0. $C_{19}H_{19}O_8N$ requires C, 58·6; H, 4·9%)—and a small quantity of the less soluble trans-*acid*, long, pale yellow needles, m. p. 181° (Found: C, 59·0; H, 4·9%).

6 : 7 : 8-*Trimethoxy*-3-(m-*methoxyphenyl*)*carbostyril* (VIII).—The *trans*-acid (0·3 g.) in concentrated ammonia (6 c.c.) was added to a mixture of ferrous sulphate (2 g.), water (6·5 c.c.), and concentrated ammonia (6 c.c.), maintained at 70°. After one hour, the filtrate and washings from the iron hydroxide were acidified and the precipitate was crystallised from ethanol, forming nearly colourless plates, m. p. 185—186° (Found: C, 67·0; H, 5·65. $C_{19}H_{19}O_5N$ requires C, 66·85; H, 5·6%).

2-*Amino*-3 : 4 : 5-*trimethoxy*-α-m-*methoxyphenylcinnamic Acid*.—The crude mixture of nitro-acids (above) was similarly reduced; the ammoniacal filtrate was acidified (Congo-red) and the *amino-acid* was extracted from the precipitate by means of aqueous sodium carbonate (the residue consisted of the above carbostyril) and was reprecipitated by acid. It formed bright yellow needles of m. p. 162° (from ethanol), identical with a specimen prepared by reducing the pure *cis*-nitro-acid (Found: C, 63·3; H, 5·9. $C_{19}H_{21}O_6N$ requires C, 63·5; H, 5·85%).

*Isomeric* 2 : 3 : 4 : (5 and 7)-*Tetramethoxyphenanthrene*-9-*carboxylic Acids*.—A solution of the amino-acid (14 g.) in methanol (70 c.c.) and 5N-sulphuric acid (40 c.c.) was treated at 0° with N-sodium nitrite solution (40 c.c.). The resulting diazo-solution, after dilution with water (500 c.c.), was neutralised with a concentrated solution of sodium carbonate and then warmed at 50° until a coupling test was negative. The cooled solution was acidified, the solid was dried and crystallised from hot acetic acid (*ca.* 110 c.c.), yielding *acid-A*. This acid, which formed soft, pale yellow needles of m. p. 236° after several crystallisations from acetic acid, was used for the later work but had a rather low carbon content (Found: C, 66·0; H, 5·3%); a specimen obtained from hydrolysis of the distilled methyl ester (below) had the same appearance and m. p. (Found: C, 66·3; H, 5·2. $C_{19}H_{18}O_6$ requires C, 66·7; H, 5·3%). Dilution of the acetic mother-liquor from acid-A gave the crude *acid-B*, which was at first obtained as colourless, highly refractive needles of m. p. 162—163° from methanol–water, but in later experiments these were superseded by massed prisms of m. p. 185° and the original samples then acquired the higher value (Found: C, 66·6; H, 5·55. $C_{19}H_{18}O_6$ requires C, 66·7; H, 5·3%).*

2 : 3 : 4 : (5 or 7)-*Tetramethoxyphenanthrene*-9-*aldehyde* (*Aldehyde-A*).—By methods similar to those described for the isomeric 2 : 3 : 4 : 6-compound, the *methyl* ester of the acid-A, obtained from the acid and diazomethane in ether as cream-coloured needles of m. p. 103° (from methanol) (Found: C, 67·2; H, 5·7; OMe, 43·1. $C_{20}H_{20}O_6$ requires C, 67·4; H, 5·6; OMe, 43·5%), was converted into the *hydrazide*, lustrous plates of m. p. 199° (from ethanol) (Found: N, 7·9. $C_{19}H_{20}O_5N_2$ requires N, 7·9%), and thence into the *benzenesulphonhydrazide*, m. p. 250° (from dioxan–ethanol) (Found: C, 60·9; H, 4·9. $C_{25}H_{24}O_7N_2S$ requires C, 60·5; H, 4·8%). This last compound (3 g., dried at 110°) in ethylene glycol (50 c.c.) at 160° was treated with anhydrous sodium carbonate (1·8 g.) in the usual way and the *aldehyde*, extracted with ether, was distilled in a high vacuum (slight decomp.). It formed bright yellow needles, m. p. 134—135° (from methanol) (Found: C, 67·0; H, 5·6. $C_{19}H_{18}O_5$ requires C, 69·9; H, 5·5%).

2 : 3 : 4 : (5 or 7)-*Tetramethoxy*-9-*methylphenanthrene* (*A*).—Aldehyde-A (0·2 g.) was heated with hydrazine hydrate (99%, 0·5 c.c.) and ethanol (6 c.c.) for 2½ hours. The crystalline residue obtained on removal of the solvent was dried, heated to 120°, and mixed with powdered potassium hydroxide (0·3 g.). Gas evolution, initially rapid, abated after 10 minutes, and the mixture was then cooled, shaken with water, and the whole extracted with ether, an insoluble yellow solid being discarded. The dried, concentrated extract was distilled in a high vacuum, and the solid distillate crystallised from methanol, yielding colourless plates of m. p. 116—117° (Found: C, 72·9; H, 6·5; OMe, 40·5. $C_{19}H_{20}O_4$ requires C, 73·1; H, 6·4; OMe, 39·7%). A *picrate*, crimson needles, m. p. 150°, was obtained from the components in methanol (Found: C, 55·6; H, 4·4. $C_{19}H_{20}O_4,C_6H_3O_7N_3$ requires C, 55·5; H, 4·25%).

2 : 3 : 4 : (7 or 5)-*Tetramethoxyphenanthrene*-9-*aldehyde* (*Aldehyde-B*).—Acid-B with diazomethane in ether yielded a

* (*Added in proof, July 24th.* Experiments carried out by Mr. N. Barton have shown that the "A series" has the 2 : 3 : 4 : 7-tetramethoxy-structure, so the "B series" has the 2 : 3 : 4 : 5-structure. Details of this work will be reported later.

gummy methyl ester which was converted directly into the *hydrazide*, m. p. 182° (Found : C, 64·3; H, 5·5. $C_{19}H_{20}O_5N_2$ requires C, 64·0; H, 5·6%), and *benzenesulphonhydrazide*, m. p. 232° (with gas evolution) (from dioxan–ethanol) (Found : N, 5·65. $C_{25}H_{24}O_7N_2S$ requires N, 5·6%), by the methods already described. The *aldehyde*, obtained in the usual way, formed a gum which solidified when rubbed with benzene and was crystallised from a small quantity of methanol in which there was a tendency to supersaturate. A sample, after vacuum distillation, formed yellow needles, m. p. 92° (from methanol) (Found : C, 70·1; H, 5·55. $C_{19}H_{18}O_5$ requires C, 69·9; H, 5·5%).

2 : 3 : 4 : (7 or 5)-*Tetramethoxy-9-methylphenanthrene* (*B*) was obtained from the aldehyde-B in the usual way. After distillation it was obtained as a gum which readily crystallised from a small quantity of methanol when seeded, but showed a very strong tendency to supersaturate. It formed colourless, pointed slabs of m. p. 102° (Found : C, 73·1; H, 6·4; OMe, 40·5. $C_{19}H_{20}O_4$ requires C, 73·1; H, 6·4; OMe, 39·7%) and gave a *picrate*, crimson needles of m. p. 135° (from methanol) (Found : C, 55·7; H, 4·45. $C_{19}H_{20}O_4,C_6H_3O_7N_3$ requires C, 55·5; H, 4·25%).

Deaminocolchinol methyl ether was prepared from colchinol methyl ether by Hofmann degradation (Windaus and Schiele, *Annalen*, 1924, **439**, 71). On slow heating it melted at 100—102°, resolidified in crystalline form at 103—105°, and finally melted at 111—112°. Mixed m. p. determinations with all three synthetic tetramethoxy-9-methylphenanthrenes showed marked depressions.

We are indebted to the Carnegie Trust for the Universities of Scotland for the award of a scholarship to (G. L. B.), and to the Chemical Society for a grant from the Research Fund. The microanalyses recorded in this and the preceding paper were carried out by Mr. J. M. L. Cameron.

UNIVERSITY OF GLASGOW. [*Received, April 24th,* 1944.]

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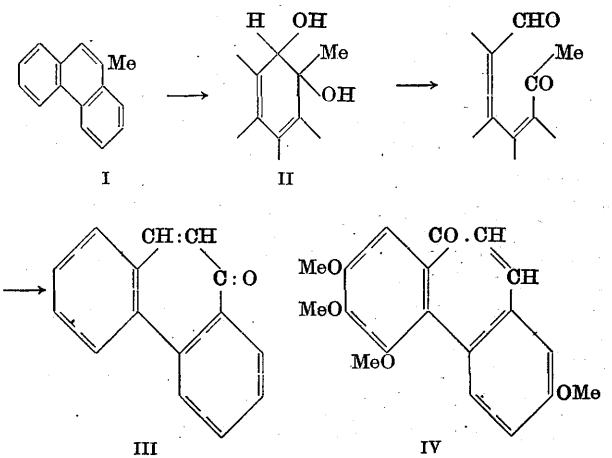
(*Reprinted from Nature, vol.* 162, *p.* 692, *October* 30, 1948)

## Synthesis of Colchicine Derivatives

WHILE the methoxylated carbon-system of (IV) is conclusively established for certain degradation products of colchicine[1,2], the synthesis of such unsymmetrically substituted dibenz*cyclo*heptatrienes, necessary for further work, has hitherto miscarried, because of difficulties which are partly concealed and partly apparent[2–4]. A synthesis which promises to afford the requisite degree of adaptability has now been found and is based on the oxidation of appropriate 9- or 10-methylphenanthrenes with osmium tetroxide in benzene-pyridine[5,6]. In a model experiment, 9-methylphenanthrene (I) was thereby oxidized to 9 : 10-dihydroxy-9 : 10-dihydro-9-methylphenanthrene (II), m.p. 130–131° (found : C, 79·9 ; H, 6·1 ; $C_{15}H_{14}O_2$ requires C, 79·7 ; H, 6·2 per cent), from which, by cleavage with lead tetra-acetate and renewed cyclization, there was obtained the known 3 : 4 : 5 : 6-dibenz*cyclo*hepta-1 : 3 : 5-trien-7-one (III)[2]. Similarly, 2 : 3 : 4 : 7-tetramethoxy-10-methylphenanthrene, m.p. 134–135° (found : C, 73·2 ; H, 6·4 ; $C_{19}H_{20}O_4$ requires C, 73·1 ; H, 6·4 per cent), was converted *via* the corresponding 9 : 10-dihydro-9 : 10-diol, m.p. 156° (found : C, 66·0 ; H, 6·4 ; $C_{19}H_{22}O_6$ requires C, 65·9 ; H, 6·4 per cent) into the unsaturated ketone (IV), which was identical with the part-product previously obtained[1] by oxidizing deaminocolchinol methyl ether with sodium dichromate in acetic acid.



2 : 3 : 4 : 5- and 2 : 3 : 4 : 7-Tetramethoxy-9-methylphenanthrenes[7] have given apparently analogous results, and full experimental details will be published when the developments now in hand, which include the attempted synthesis of colchinol methyl ether, have been completed. One of us (J. M.) thanks the Department of Scientific and Industrial Research for a maintenance allowance.

G. L. Buchanan
J. W. Cook
J. D. Loudon
J. MacMillan

Universities of Glasgow and
Aberdeen.

[1] Barton, Cook and Loudon, *J. Chem. Soc.*, 176 (1945).
[2] Cook, Dickson and Loudon, *J. Chem. Soc.*, 746 (1947).
[3] Frank, Fanta and Tarbell, *J. Amer. Chem. Soc.*, **70**, 2314 (1948).
[4] Barton, Cook and Loudon, *J. Chem. Soc.* (in the press).
[5] Criegee, Marchand and Wannowius, *Annalen*, **550**, 99 (1942).
[6] Cook and Schoental, *J. Chem. Soc.*, 170 (1948).
[7] Buchanan, Cook and Loudon, *J. Chem. Soc.*, 325 (1944).

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# COLCHICINE AND RELATED COMPOUNDS. PART XI. SYNTHESIS OF *N*-ACETYL-COLCHINOL METHYL ETHER

BY

J. W. COOK,

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J. D. LOUDON,

AND (IN PART)

G. L. BUCHANAN

AND

J. MACMILLAN

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This Communication is preprinted from the
Journal of the Chemical Society, June, 1951, pages 1397—1403.

**Preprinted from the Journal of the Chemical Society, 1951.**

# 321. *Colchicine and Related Compounds. Part XI. Synthesis of N-Acetylcolchinol Methyl Ether.*

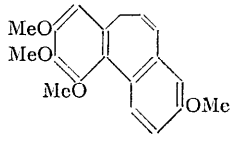
By J. W. Cook, J. Jack, J. D. Loudon, and (in part) G. L. Buchanan and J. MacMillan.

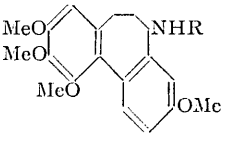
Model experiments with 9-methylphenanthrene and with its 2 : 3 : 4 : 5-tetramethoxy-derivative showed that such compounds may be hydroxylated to *cis*-9 : 10-dihydro-9 : 10-dihydroxy-9-methylphenanthrenes. Cleavage of these diols by lead tetra-acetate and cyclisation of the resulting keto-aldehydes afforded the parent dibenzo*cyclo*heptatrienone (XII) and its tetramethoxy-derivative (XIX). The process therefore provides a means of synthesising this type of colchicine degradation product.

The trienone (XV), synthesised in this way from 2 : 3 : 4 : 7-tetramethoxy-10-methylphenanthrene, was identical with the ketonic by-product earlier obtained by oxidising deaminocolchinol methyl ether (Part V; Barton, Cook, and Loudon, *J.*, 1945, 176). The isomeric trienone (XXI), synthesised in similar fashion from 2 : 3 : 4 : 7-tetramethoxy-9-methylphenanthrene, was converted, *via* the dienone (XXII) and its oxime, into the primary (±)-amine of the structure proposed for colchinol methyl ether (Part V, *loc. cit.*). Resolution of this amine by means of (+)-6 : 6′-dinitrodiphenic acid afforded the (−)-base and hence its (−)-*N*-acetyl derivatives, which were respectively identical with colchinol methyl ether and its *N*-acetyl derivative as obtained by degradation of colchicine.

In Part V of this series (Barton, Cook, and Loudon, *J.*, 1945, 176) the structure (I) for deaminocolchinol methyl ether was established on the evidence of degradation and, as one immediate consequence, the conclusion was there reached that formula (II; R = H) represents the most probable structure for colchinol methyl ether. This conclusion has now been confirmed by the synthesis and resolution of the (±)-amine of which the (−)-form and its (−)-*N*-acetyl derivative have proved to be identical with the compounds as obtained by the degradation of colchicine. In the interval between the commencement and completion of our synthetical experiments, other groups of investigators have been attracted to this field and we have been obliged to reaffirm our own active interest by publishing two brief announcements of progress (Buchanan, Cook, Loudon, and MacMillan, *Nature*, 1948, **162**, 692; Cook, Jack, and Loudon, *Chem. and Ind.*, 1950, 650) during the course of the work which is here described in full.

(I.)

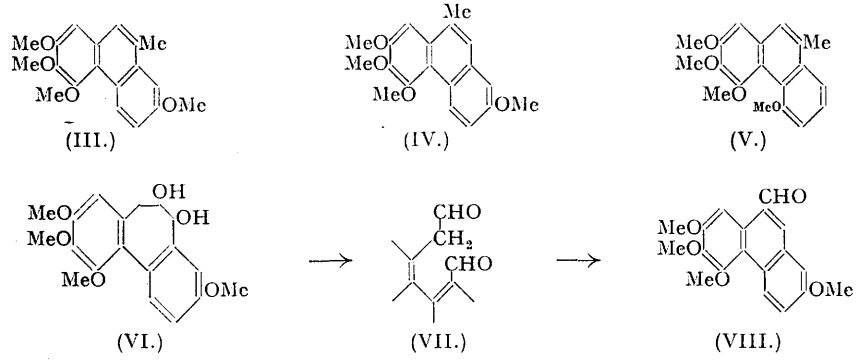


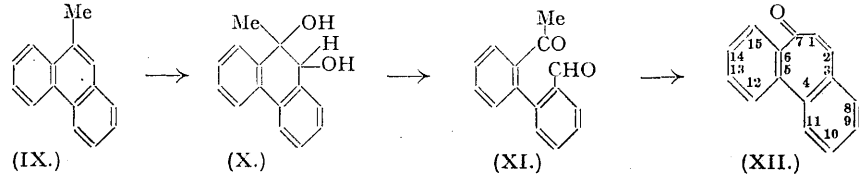

(II.)

Early attempts to synthesise dibenzo*cyclo*heptadienones, *e.g.*, (XXII), from methoxylated β-2-diphenylylpropionic acids having failed for the reasons discussed in Parts VIII and IX (*J.*, 1949, 1079 and *J.*, 1950, 139), attention was turned to methods of expanding the central ring of suitably substituted phenanthrenes. Criegee, Marchand, and Wannowius (*Annalen*, **1942, 550,** 99) showed that their improved procedure for hydroxylating ethylenic bonds is applicable to the 9 : 10-double bond of phenanthrene. The hydrocarbon is thereby converted into *cis*-9 : 10-dihydro-9 : 10-dihydroxyphenanthrene and the process was extended by Cook and Schoental (*J.*, 1948, 170) to the preparation of similar diols from a number of polycyclic aromatic hydrocarbons. Preliminary experiments now showed that a diol is also obtainable by the same means from 9-methylphenanthrene and this opened up the prospect of a flexible synthesis of dibenzo*cyclo*heptatrienones, *e.g.*, (XII), from derivatives of 9- (or 10-)methylphenanthrene by the successive steps of hydroxylation, cleavage, and recyclisation illustrated in the reaction sequence (IX) to (XII).

On these lines the synthesis of degradation products of colchicine requires as starting materials the two isomeric 2 : 3 : 4 : 7-tetramethoxy-9- and -10-methylphenanthrenes, (III) and (IV) respectively. The first of these is already known and like a third isomer, namely (V) which served here for model experiments, was prepared as described in Part IV (Buchanan, Cook, and Loudon, *J.*, 1944, 325) through the corresponding 9-phenanthroic acid. The second isomer, hitherto unknown, was likewise prepared from 2 : 3 : 4 : 7-tetramethoxy-10-phenanthroic acid which was synthesised as described in Part V (*loc. cit.*) and was now converted *via* the hydrazide and phenylsulphonhydrazide into the corresponding 10-phenanthraldehyde and thence into (IV). This 10-phenanthraldehyde (VIII) had already been encountered as a degradation product of colchicine, having been produced (Part V, *loc. cit.*) from deaminocolchinol methyl ether (I), through the intermediates (VI) and (VII), by hydroxylation, cleavage, and recyclisation : samples of the compound from both sources were shown to be identical.

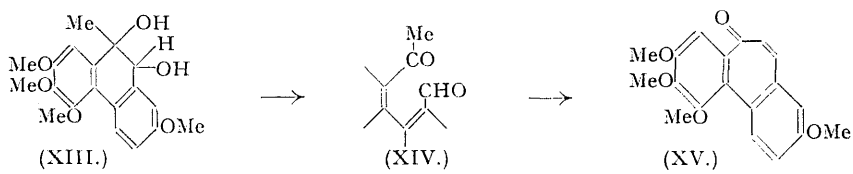



The procedure of Criegee, Marchand, and Wannowius (*loc. cit.*) consists in allowing the compound to be hydroxylated to react with osmium tetroxide in presence of pyridine and generally with benzene as solvent. Thereby the diol is gradually precipitated as a crystalline complex of the osmic ester with pyridine and is liberated by shaking the complex with mannitol in presence of alkali. When applied to 9-methylphenanthrene (IX) this procedure readily afforded the crystalline diol (X) in good yield. Cleavage of the diol was effected by means of lead tetra-acetate and the gummy product, presumably containing the keto-aldehyde (XI), on treatment with sodium hydroxide in methanol afforded 3 : 4-5 : 6-dibenzo*cyclo*hepta-1 : 3 : 5-trien-7-one (XII) which was identical with the compound earlier prepared by the action of selenium dioxide on the parent dibenzo*cyclo*heptatriene (I; H for each OMe) (Part VI, Cook, Dickson and Loudon, *J.*, 1947, 746). The oxime derived from the trienone (XII), when hydrogenated in acetic anhydride and in presence of Adams's catalyst, was reduced to 2-acetamido-3 : 4-5 : 6-dibenzo*cyclo*hepta-3 : 5-diene (II; R = Ac and H for each OMe).



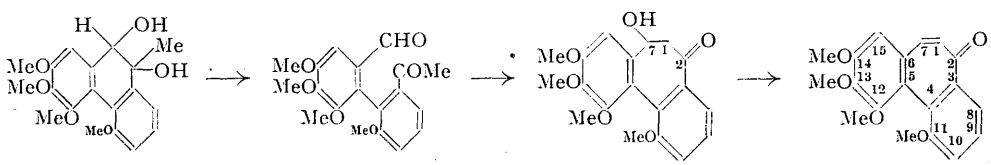

The yield of (XII) from (X), although somewhat variable, was occasionally very good and appeared to warrant the application of the same procedure to the less accessible tetramethoxy 10-methylphenanthrene (IV). This compound was chosen for investigation at this stage because the product of ring expansion was expected to be identifiable as the unsaturated ketonic by-product obtained from the oxidation of deaminocolchinol methyl ether (I) with chromic acid (Part V, *loc. cit.*). Experiment indeed verified this expectation and the trienone (XV) accordingly becomes the first degradation product of colchicine, for which the central 7-membered ring is established by synthesis. Nevertheless the poor yield obtained made it clear that the discovery of more favourable reaction conditions was a pre-requisite of further progress. The preparation of the diol (XIII) was satisfactory and the process of cleavage appeared to be normal, although again the product was a gum, but cyclisation yielded a mixture of compounds which

contained, in addition to (XV), a large proportion of a high-melting solid. While the precise nature of this solid was not ascertained, its properties sufficiently indicated that it was a condensate formed ultimately from two moles of the intermediate (XIV) and therefore at the expense of (XV). It may be interpolated here that this condensate and the unsaturated ketone (XII) are oxidised by sodium dichromate in acetic acid to the corresponding phenanthraquinones and are therefore to be added to the list of compounds which respond to this test of the bridged diphenyl system (cf. Part VI, *loc. cit.*).




(XIII.) (XIV.) (XV.)

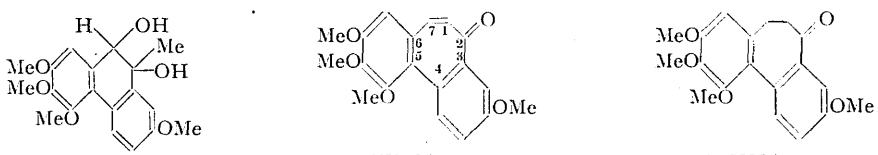
The diol (XVI) obtained by hydroxylating 2 : 3 : 4 : 5-tetramethoxy-9-methylphenanthrene (V) was found to undergo cleavage with the formation of a crystalline keto-aldehyde (XVII) and this facilitated a closer examination of the critical cyclisation stage. When treated with sodium hydroxide in methanol the keto-aldehyde afforded some high-melting solid together with a second product which, from its analysis and its oxidation to 2 : 3 : 4 : 5-tetramethoxyphenanthraquinone, is regarded as the hydroxy-ketone (XVIII). This hydroxy-ketone was the sole product obtained by heating (XVII) with pyridine containing a few drops of piperidine. On attempted acetylation with acetic anhydride in pyridine, the hydroxy-ketone yielded an




(XVI.) (XVII.) (XVIII.) (XIX.)

uncrystallisable gum from which, by distillation, there was obtained the unsaturated ketone (XIX). The latter, however, although still accompanied by some of the hydroxy-ketone, was best prepared by dissolving the keto-aldehyde in acetic acid saturated with hydrogen chloride, and this procedure proved to be most effective for converting (XIV) into (XV), in which case the corresponding hydroxy-ketone was not encountered.

In striking contrast to the other methylphenanthrenes examined here, 2 : 3 : 4 : 7-tetramethoxy-9-methylphenanthrene (III) did not 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 *n*-hexane afforded an osmic



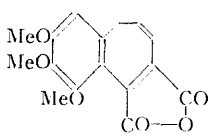

(XX.) (XXI.) (XXII.)

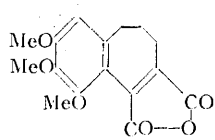
ester from which the diol (XX) was obtained without difficulty. Cleavage by lead tetra-acetate and treatment of the gummy product with acetic–hydrochloric acid yielded the unsaturated ketone (XXI). This was hydrogenated with palladium as catalyst to the saturated ketone (XXII) the oxime of which, when hydrogenated under pressure with Raney nickel as catalyst, afforded (±)-colchinol methyl ether (II; R = H). The melting points found for the optically inactive base and its immediate derivatives (cf. Cook, Jack, and Loudon, *loc. cit.*) differed markedly from those of the optically active forms which are obtained by degradation of colchicine. They were in fair agreement, however, with the values for corresponding compounds recorded by Rapoport, Williams, and Cisney (*J. Amer. Chem. Soc.*, 1950, **72**, 3324) who in a recent preliminary notice reported a synthesis of (±)-colchinol methyl ether and proved the authentic nature of their product by comparing it with the racemised degradation product.

For the resolution of (±)-colchinol methyl ether, (−)-malic, (+)-tartaric, (+)-camphor-10-sulphonic and (+)-α-bromocamphor-π-sulphonic acids were unsuccessfully tried, although the first two readily afforded crystalline salts. (+)-6 : 6′-Dinitrodiphenic acid, however, proved to be effective, the acid salt of the (−)-base being easily separated from its diastereoisomeride by crystallisation from methanol. By direct comparison of melting points and optical rotations it was shown that the recovered (−)-amine, its salts, and its *N*-acetyl derivative were respectively identical with colchinol methyl ether, its salts, and *N*-acetylcolchinol methyl ether as prepared from colchicine.

It will be observed that this synthesis of *N*-acetylcolchinol methyl ether completes an interesting set of reactions by which the compound is converted into, and is regenerated from, derivatives of phenanthrene. After deamination (II; R = H or Ac) ⟶ (I) (cf. Part V, *loc. cit.*), the process of ring-contraction, (I) ⟶ (VI) ⟶ (VIII), leads to a 9-substituted and ultimately, (VIII) ⟶ (IV), to a 9-methyl derivative of phenanthrene. The contrary, but similarly effected process of ring-expansion, (III) ⟶ (XX) ⟶ (XXI), starts from the isomeric 10-methylphenanthrene and is followed by amination, (XXI or XXII) ⟶ (II). Regarded from a slightly different standpoint these combined processes constitute the interconversion of isomeric 9- and 10-methylphenanthrenes and accordingly would be linked in a continuous reaction-cycle if the lateral nuclei were symmetrically substituted.

(XXIII.)



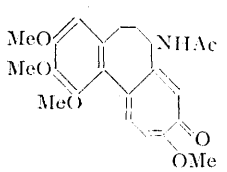



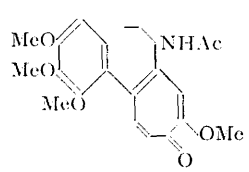

(XXIV.)

In Part X (Cook, Johnstone, and Loudon, *J.*, 1950, 537) it was shown conclusively that the compounds obtained by Windaus by oxidising colchiceine with potassium permanganate were not hydronaphthalene derivatives as he supposed (cf. *Annalen*, 1924, **439**, 59). In particular it was shown that Windaus's *N*-benzoylcolchinic anhydride could be converted into deaminocolchinic anhydride which is quite distinct from the synthesised 6 : 7 : 8-trimethoxy-3-methylnaphthalene-1 : 2-dicarboxylic anhydride and, therefore, like the colchinol derivatives, probably contains the 7-membered ring B, as in (XXIII). This conclusion has recently been substantiated in the synthesis of the dihydride of (XXIII), *viz.*, (XXIV), by Horning and Ullyot and their colleagues (*J. Amer. Chem. Soc.*, 1950, **72**, 4840) of whose work in project we were courteously informed by Dr. G. E. Ullyot. There is consequently good reason to believe that the 7-membered ring B, now established for both the colchinol and colchinic series of degradation products, also occurs in colchicine itself.

*Added in Proof.*—The recent work of Doering and Knox (*J. Amer. Chem. Soc.*, 1951, **73**, 828) on the transformation of tropolone into tri-iodophenol has now provided a simple counterpart for the change by which ring C of colchiceine becomes phenolic, as in the formation of *N*-acetyliodocolchinol. This provides strong corroboration for the tropolone methyl ether structure of ring C of colchicine. In view of the evidence of structure now provided for compounds of the colchinol type we may conclude that colchicine and *iso*colchicine are correctly formulated as (XXV) and (XXVI), not necessarily respectively.

(XXV.)




(XXVI.)

## Experimental.

2 : 3 : 4 : 7-*Tetramethoxy*-10-*phenanthraldehyde* (VIII).—A suspension of 2 : 3 : 4 : 7-tetramethoxy-10-phenanthroic acid (4·5 g.; Part V, *loc. cit.*) in methanol (65 c.c.) and concentrated sulphuric acid (5 c.c.) was heated under reflux for 1 hour and the methyl ester, m. p. (crude) 102°, was recovered from the resulting solution after concentration. The crude ester (5 g.) was heated for 2 hours with 90% hydrazine hydrate (10 c.c.) in ethanol (30 c.c.), thereby yielding the corresponding *hydrazide* as platelets of m. p. 216° (from ethanol) (Found : N, 8·0. $C_{19}H_{20}O_5N_2$ requires N, 7·8%). A solution of the hydrazide (4·1 g.) in pyridine (50 c.c.) was treated with benzenesulphonyl chloride (2·1 g.) and, after 12 hours at room tem-

perature, on being poured into dilute hydrochloric acid at 0°, afforded the *phenylsulphonhydrazide*, m. p. 230—231° (from acetic acid) (Found : N, 5·6. $C_{25}H_{24}O_7N_2S$ requires N, 5·6%). A solution of this compound (5·7 g.; previously dried at 120°) in ethylene glycol (80 c.c.) at 160° was treated with anhydrous sodium carbonate (3·6 g.) and, after 80 seconds, boiling water (100 c.c.) was added. 2 : 3 : 4 : 7-Tetramethoxy-10-phenanthraldehyde was recovered in ether and had m. p. 130° (from methanol), undepressed by admixture with the sample described in Part V (*loc. cit.*) and yielding the same oxime of micro-m. p. and mixed micro-m. p. 164—166°.

2 : 3 : 4 : 7-*Tetramethoxy*-10-*methylphenanthrene* (IV).—The above aldehyde (1·1 g.) was heated for 2 hours with 99% hydrazine hydrate (4 c.c.) in ethanol (40 c.c.). Removal of the solvent afforded a yellow solid of m. p. 145—150°, but this when intimately mixed with powdered potassium hydroxide (2 g.) at 120—125° (oil-bath) readily gave an effervescent melt. Heating was maintained at this temperature for 5—10 minutes, whereafter water was added and the product was recovered in chloroform. 2 : 3 : 4 : 7-*Tetramethoxy*-10-*methylphenanthrene* was conveniently purified by passing its solution in benzene through a column of alumina. It formed colourless prisms, m. p. 134—135°, from benzene (Found : C, 73·2; H, 6·4. $C_{19}H_{20}O_4$ requires C, 73·1; H, 6·4%).

cis-9 : 10-*Dihydro*-9 : 10-*dihydroxy*-9-*methylphenanthrene* (X).—Pyridine (2·4 c.c.) was added to a solution of 9-methylphenanthrene (2 g.) and osmium tetroxide (3 g.) in sodium-dried, thiophen-free benzene (15 c.c.). After 7 days the dark-brown precipitate was collected, dissolved in chloroform and shaken for 2 hours with a solution of mannitol (50 g.) and potassium hydroxide (2 g.) in water (200 c.c.). The yellow chloroform layer was washed and dried and, on evaporation *in vacuo*, afforded the *diol* (X) as a gum which crystallised in colourless prisms (1·75 g.) of m. p. 130—131° from methanol–water (Found, after drying for 1 hour at 100°/18 mm. : C, 79·9; H, 6·1. $C_{15}H_{14}O_2$ requires C, 79·7, H, 6·2%).

9-*Methyl*-10-*phenanthrol* was produced when a solution of the diol (X) (0·1 g.) in glacial acetic acid (2 c.c.) and concentrated hydrochloric acid (0·2 c.c.) was briefly heated under reflux (1 minute). It was isolated from the cooled solution by dilution with water and formed almost colourless needles of m. p. 125° from methanol–water (Found : C, 86·2; H, 5·7. $C_{15}H_{12}O$ requires C, 86·5; H, 5·7%). 9-*Methyl*-10-*phenanthryl acetate*, m. p. 150—151° (from methanol–water), was produced when the diol (X) was heated for a short time with acetic anhydride (Found : C, 81·6; H, 5·5. $C_{17}H_{14}O_2$ requires C, 81·6; H, 5·6%).

3 : 4-5 : 6-*Dibenzo*cyclo*hepta*-1 : 3 : 5-*trien*-7-*one* (XII).—A solution of the diol (X) (0·1 g.) in dry benzene (20 c.c.) was treated with lead tetra-acetate (0·21 g.) and the whole was shaken for 2 hours and heated under reflux for ½ hour. The cooled suspension was filtered through charcoal, and the filtrate was washed with water, dried, and concentrated at 40°, affording a colourless gum. This was dissolved in methanol, a drop of dilute sodium hydroxide solution was added and then sufficient water to cause a slight turbidity. The mixture was gently warmed and was set aside for 48 hours under nitrogen in a stoppered tube at room temperature. Usually the trienone (XII) separated in crystalline form and where a gum was obtained this was induced to solidify after chromatography on alumina with benzene as solvent. The trienone formed almost colourless prisms, m. p. 83—85°, from benzene–light petroleum, undepressed on admixture with an authentic sample (Part VI, *loc. cit.*). When heated (½ hour) with sodium dichromate in acetic acid it afforded phenanthraquinone which was isolated as a neutral extract in chloroform from the diluted reaction-liquor and was identified by mixed m. p. and diazine formation.

2-*Acetamido*-3 : 4-5 : 6-*dibenzo*cyclo*hepta*-3 : 5-*diene*.—The *oxime* (0·12 g.) of the above trienone (XII), colourless needles, m. p. 190° (from ethanol) (Found : C, 81·8; H, 5·3; N, 6·0. $C_{15}H_{11}ON$ requires C, 81·5; H, 5·0; N, 6·3%), dissolved in acetic anhydride (8 c.c.), was hydrogenated in presence of Adam's catalyst. Absorption was complete in 1¼ hours and the *acetamido*-compound, obtained by concentration, formed colourless needles, m. p. 233°, from ethanol (Found : C, 81·3; H, 6·9; N, 5·5. $C_{17}H_{17}ON$ requires C, 81·3; H, 6·8; N, 5·6%).

The experiments described above were carried out in conjunction with G. L. Buchanan and J. MacMillan.

On repetition of the preparation of 2 : 3 : 4 : 5-tetramethoxy-9-methylphenanthrene several additions and amendments were noted in respect of the description of the " B-series " of compounds as given in Part IV (*loc. cit.*). In the interval, methyl 2 : 3 : 4 : 5-tetramethoxy-9-phenanthroate—there described as a gum—solidified and, as in the repeated preparation, was readily obtained as colourless plates, m. p. 100°, from methanol (Found : C, 67·15; H, 5·6. $C_{20}H_{20}O_6$ requires C, 67·4; H, 5·6%). From this purer sample of the ester the corresponding hydrazide was obtained with m. p. 193° instead of 182°, the mixed m. p. of the two samples being intermediate.

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%) but a mixture with the beautifully crystalline sample of recorded m. p. 92° again gave this lower value. This is probably another of the numerous cases of polymorphism which have been encountered in these investigations. Still another is found in the case of 2 : 3 : 4 : 5-tetramethoxy-9-methylphenanthrene of which both the original sample —of recorded m. p. 102°—and the new sample were now found to melt at 116—117° (depressed to *ca.* 90° on admixture with 2 : 3 : 4 : 7-tetramethoxy-9-methylphenanthrene, also of m. p. 116—117°), although the lower value had been checked for the original sample on several earlier occasions.

cis-9 : 10-*Dihydro*-9 : 10-*dihydroxy*-2 : 3 : 4 : 7-*tetramethoxy*-10-*methylphenanthrene* (XIII) [with J. MacMillan].—After 14 days at room temperature the pyridine–osmic ester complex from (IV) (0·75 g.) and osmium tetroxide (0·68 g.) in benzene (25 c.c.) and pyridine (1 c.c.) was collected and dissolved in methylene chloride. The filtered solution was shaken with a solution of mannitol (10 g.) and potassium hydroxide (1 g.) in water (100 c.c.) until the organic layer became colourless (1 hour). The gum recovered from this layer afforded the *diol* (XIII) as colourless prisms (0·62 g.), m. p. 155—156°, from methanol–water (Found : C, 66·0; H, 6·4. $C_{19}H_{22}O_6$ requires C, 65·9; H, 6·4%).

9 : 12 : 13 : 14-*Tetramethoxy*-3 : 4-5 : 6-*dibenzo*cyclo*hepta*-1 : 3 : 5-*trien*-7-*one* (XV) [with J. MACMILLAN].—Lead tetra-acetate (0·08 g.) was added to a solution of the diol (XIII) (0·1 g.) in dry benzene (8 c.c.), and the whole was shaken for 2 hours. The oil (0·085—0·09 g.) recovered from the filtered and washed benzene solution was treated in different experiments in several ways: (*a*) Its solution in methanol was treated with aqueous sodium hydroxide and set aside at room temperature under nitrogen for 3 days. The gummy deposit partly solidified when rubbed with methanol affording a yellow solid (A) and methanol washings. The latter on concentration yielded a gum which was combined with neutral material recovered from the reaction mother-liquor by extraction with chloroform. A solution of these combined gums in benzene was passed through a short column of alumina. Elution of the diffuse yellow band afforded, after recovery, a pale yellow gum which crystallised as yellow sheaves of micro-m. p. 109—111° from ethanol, unchanged on admixture with the ketonic oxidation product of deaminocolchinol methyl ether (Part V, *loc. cit.*). The solid (A) formed cream-coloured needles, micro-m. p. 208—209°, from acetic acid [Found: C, 69·65; H, 6·0%; *M* (micro-Rast), 663; micro-hydrogenation with a palladium catalyst showed absorption of 2 moles of hydrogen]. On oxidation with sodium dichromate in acetic acid this compound gave 2 : 3 : 4 : 7-tetramethoxyphenanthraquinone of micro-m. p. and mixed micro-m. p. 192—194°.

(*b*) Its solution in dry methanol (5 c.c.) was treated with a 5% solution of sodium methoxide in methanol (0·2 c.c.). After 24 hours at 0°, the solution was neutralised with acetic acid, concentrated, and extracted with benzene. Chromatography on alumina gave a yellow band which fluoresced in ultraviolet light and, after elution and recovery, afforded the trienone (0·03 g.), m. p. and mixed m. p. 107—109°.

(*c*) Its solution in glacial acetic acid (5 c.c.) was saturated with dry hydrogen chloride. After 12 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 (0·07 g.) of m. p. and mixed m. p. 109—110° (from methanol).

cis-9 : 10-*Dihydro*-9 : 10-*dihydroxy*-2 : 3 : 4 : 5-*tetramethoxy*-9-*methylphenanthrene* (XVI).—After 3 days at room temperature the pyridine–osmic ester complex formed from (V) (0·54 g.) and osmium tetroxide (0·49 g.) in benzene (3·5 c.c.) and pyridine (0·28 c.c.) was collected. Its solution in methylene chloride was shaken as in previous cases with an aqueous solution of mannitol and sodium hydroxide. The recovered *diol* formed colourless needles (0·53 g.), m. p. 215—216°, from methanol (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* (XVII).—The diol (XVI) (0·2 g.) was cleaved with lead tetra-acetate in benzene as described for (XV). Recovery from benzene gave the *keto-aldehyde* (XVII) as a colourless gum which formed colourless prisms, m. p. 113—114°, from methanol (Found: C, 66·1; H, 5·9; OMe, 35·3. $C_{19}H_{20}O_6$ requires C, 66·25; H, 5·8; OMe, 36%). It yielded a *dioxime*, prisms, m. p. 179—180°, from methanol–water (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%) and gave no trace of the corresponding phenanthraquinone, being recovered largely unchanged, but with some unidentified acidic product, from oxidation with sodium dichromate in acetic acid.

7-*Hydroxy*-11 : 12 : 13 : 14-*tetramethoxy*-3 : 4-5 : 6-*dibenzo*cyclo*hepta*-3 : 5-*dien*-2-*one* (XVIII).—(*a*) A solution of the keto-aldehyde (XVII) (0·6 g.) in methanol (50 c.c.), treated with a few drops of dilute aqueous sodium hydroxide, gradually deposited (4 days) a high-melting (*ca.* 253°) solid which was discarded. An ethereal extract of the diluted reaction-liquor gave a gum which afforded the *hydroxy-ketone* (XVIII) 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%). (*b*) The same hydroxy-ketone, m. p. 177—179°, was recovered in ether from a reaction mixture of the keto-aldehyde (0·1 g.) in pyridine (2 c.c.) and piperidine (0·3 c.c.) which had been heated under reflux for 2 hours and then left at room temperature for 2 days before being poured into dilute sulphuric acid at 0°. When oxidised with sodium dichromate in acetic acid the hydroxy-ketone (XVIII) afforded 2 : 3 : 4 : 5-tetramethoxyphenanthraquinone, m. p. and mixed m. p. 123—125° (cf. Part V, *loc. cit.*).

11 : 12 : 13 : 14-*Tetramethoxy*-3 : 4-5 : 6-*dibenzo*cyclo*hepta*-3 : 5 : 7-*trien*-2-*one* (XIX).—(*a*) A solution of the hydroxy-ketone (XVIII) (0·1 g.) in pyridine (0·6 c.c.) was treated with acetic anhydride (0·4 c.c.), and the whole was heated for 1 hour at 100° before being cooled and added to dilute sulphuric acid at 0°. Concentration of a dried ethereal extract yielded an uncrystallisable gum which was distilled at 200° (bath-temp.)/1·5 mm. The distillate when rubbed with methanol afforded the *trienone* (XIX), m. p. 174—175°, from methanol. (*b*) A solution of the keto-aldehyde (XVII) (0·1 g.) in glacial acetic acid (5 c.c.) was saturated with dry hydrogen chloride and, after 12 hours, the resulting red solution was diluted with water. The yellow gum, recovered from an acid-free ethereal extract, was dissolved in benzene, adsorbed on an alumina column and eluted with benzene in two fractions. The first, yellow fraction afforded, after recovery, the trienone (XIX) of m. p. and mixed m. p. with the product from (*a*) 174—175° (from methanol) (Found: C, 69·7; H, 5·7. $C_{19}H_{18}O_5$ requires C, 69·9; H, 5·6%). The second, colourless fraction gave the hydroxy-ketone (XVIII), m. p. and mixed m. p. 179°.

cis-9 : 10-*Dihydro*-9 : 10-*dihydroxy*-2 : 3 : 4 : 7-*tetramethoxy*-9-*methylphenanthrene* (XX).—A solution of (III) (1·3) g. and osmium tetroxide (1·3 g.) in benzene (5 c.c.) and pyridine (0·7 c.c.) after 7 days was red-brown but remained homogeneous. The complex, however, was readily precipitated by the addition of *n*-hexane. It was hydrolysed as described for (XIII), affording the *diol* (XX) as colourless prisms (0·9 g.), m. p. 172—174°, from ethanol (Found: C, 65·9; H, 6·5. $C_{19}H_{22}O_6$ requires C, 65·9; H, 6·4%).

9 : 12 : 13 : 14-*Tetramethoxy*-3 : 4-5 : 6-*dibenzo*cyclo*hepta*-3 : 5 : 7-*trien*-2-*one* (XXI).—The diol (XX) was cleaved with lead tetra-acetate as described in the preparation of the trienone (XV). The cleavage

product was a gum which could not be induced to crystallise but reacted with hydroxylamine to form the *dioxime* of 6′-acetyl-6-formyl-2 : 3 : 4 : 4′-tetramethoxydiphenyl, colourless hexagonal plates, m. p. 186—187° (from ethanol) (Found : N, 7·7. $C_{19}H_{22}O_6N_2$ requires N, 7·5%). An attempt to cyclise the gummy cleavage product by means of sodium hydroxide in ethanol yielded only a high-melting solid which was not investigated. Cyclisation was effected in acetic acid saturated with hydrogen chloride as described under section (*c*) for the isomer (XV), affording a gum which was dissolved in benzene and adsorbed on alumina. The resulting yellow band, which fluoresced in ultra-violet light, was preferentially eluted with benzene again affording a gum which, however, slowly solidified yielding the *trienone* (XXI) as yellow prisms, m. p. 98—99° (from methanol) (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-*dibenzo*cyclo*hepta*-3 : 5-*dien*-2-*one* (XXII).—The gummy trienone (XXI) was hydrogenated in acetic acid solution in presence of palladium black. The calculated volume of hydrogen (1 mol.) was absorbed in ½ hour and the colourless gum recovered from the filtered solution afforded the dienone (XXII) as colourless prisms, m. p. 142—143°, from methanol (Found : C, 69·5; H, 5·9. Calc. for $C_{19}H_{20}O_5$: C, 69·5; H, 6·1%). It formed an oxime of m. p. 203—204° (from methanol) (Found : C, 66·6; H, 6·4; N, 4·1. Calc. for $C_{19}H_{21}O_5N$ : C, 66·4; H, 6·2; N, 4·1%). Rapoport, Williams, and Cisney (*loc. cit.*) who also prepared these compounds report m. p.s 140·5—141° and 194—196° for the dienone and its oxime respectively.

(±)-*Colchinol Methyl Ether* (II; R = H).—This was obtained when the oxime (0·2 g.) mentioned in the last section was hydrogenated at 80—90°/65—75 atm. (4 hours) in methanol (80 c.c.) with Raney nickel. After filtration from the catalyst, the solution was concentrated, water was added, and the base was recovered in dilute sulphuric acid from an ethereal extract. The acid solution was made alkaline and the crude *amine* was obtained by renewed extraction with ether. It formed small colourless rods, m. p. 144—146°, from ether (Found : C, 69·1; H, 7·1. $C_{19}H_{23}O_4N$ requires C, 69·3; H, 7·1%) and when shaken with acetic anhydride in presence of a trace of concentrated sulphuric acid it yielded (±)-N-*acetylcolchinol methyl ether*, m. p. 179—180° (from methanol–water) (Found : C, 67·9; H, 6·9. $C_{21}H_{25}O_5N$ requires C, 67·9; H, 6·8%). The hydrochloride of the (±)-amine had m. p. 254° (decomp.). Rapoport, Williams, and Cisney (*loc. cit.*) do not report the m. p. of the amine but record m. p. 178—179° for the acetyl compound and 258—259° for the hydrochloride.

*Resolution of* (±)-*colchinol methyl ether.* Solutions of the (±)-amine (0·4 g.) and (+)-6 : 6′-dinitrodiphenic acid (0·4 g.) in methanol (5 c.c. each) were mixed and the resulting crystalline salt (0·364 g.) was crystallised thrice from methanol. [(−)-*Colchinol methyl ether*] [*hydrogen* (+)-6 : 6′-*dinitrodiphenate*] crystallised, with a molecule of methanol, as pale yellow rods, m. p. 257—258° (decomp.), $[\alpha]_{5900}^{16}$ +51°, $[\alpha]_{5461}^{16}$ +67° (*c*, 0·33 in methanol) (Found : C, 58·8; 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.), $[\alpha]_{5900}^{16}$ +54°, $[\alpha]_{5461}^{16}$ +69° (*c*, 0·33 in methanol), was prepared from colchinol methyl ether obtained by degradation of colchicine. A solution of the synthesised acid salt (0·2 g.) in methanol was basified by N-sodium hydroxide, and the free base, after recovery in ether, formed very small crystals, m.p. 90—92°, from ether–light petroleum (b. p. 40—60°) and had $[\alpha]_{5900}^{16}$ −85° and $[\alpha]_{5461}^{16}$ −111° (*c*, 0·74 in methanol). An authentic specimen of colchinol methyl ether had m. p. and mixed m. p. 90—92°, $[\alpha]_{5900}^{17}$ −84°, and $[\alpha]_{5461}^{17}$ −111° (*c*, 0·74 in methanol). Samples of the *picrate* of the natural base (prepared by Dr. N. Barton) and of the resolved base had m. p. and mixed m. p. 223—225° (from methanol) (Found : C, 54·1; H, 4·6. $C_{19}H_{23}O_4N,C_6H_3O_7N_3$ requires C, 53·8; H, 4·7%).

*N*-Acetylcolchinol methyl ether was prepared from resolved synthetic colchinol methyl ether as described for the racemic compound. It crystallised from methanol as colourless prisms, m. p. 202—204°, $[\alpha]_{5900}^{16}$ −92°, $[\alpha]_{5461}^{16}$ −118° (*c*, 0·67 in methanol). An authentic specimen prepared from colchicine had m. p. and mixed m. p. 202—204°, $[\alpha]_{5900}^{17}$ −94°, $[\alpha]_{5461}^{17}$ −118° (*c*, 0·67 in methanol). Rapoport, Williams and Cisney (*loc. cit.*) record m. p. 201—202° and $[\alpha]_D^{20}$ −88·6° (*c*, 0·67 in methanol) for the degradation product.

We are indebted to the Department of Scientific and Industrial Research for Maintenance Allowances (to J. MacM. and J. J.) and to Mr. G. G. Doig for assistance in the preparation of the methylphenanthrenes. Microanalyses were carried out by Miss R. H. Kennaway.

UNIVERSITY OF GLASGOW. [*Received, February 12th,* 1951.]

PRINTED IN GREAT BRITAIN BY RICHARD CLAY AND COMPANY, LTD.,
BUNGAY, SUFFOLK.

*Reprinted from Chemistry and Industry*, 1952, *p.* 855

# DIBENZ-TROPONE AND A HYDROXYLATED DERIVATIVE

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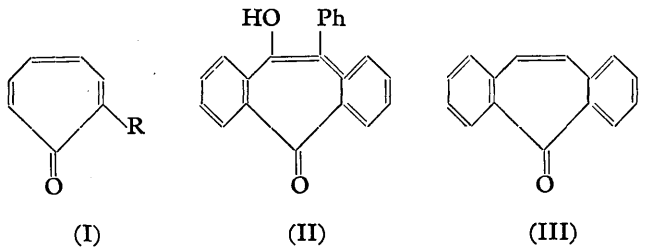
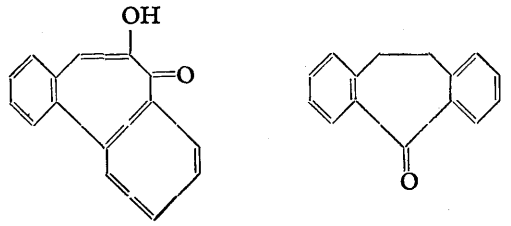
The chemistry of tropolone (I; R=OH) has derived added interest from the recent discovery (Doering & Detert, 1951; Dauben & Ringold, 1951) that tropone (I; R=H) possesses many of the characteristics of the former compound. Indeed, it seems probable that tropone is the parent substance of this new aromatic system, and tropolone merely a hydroxylated derivative. In order to test this thesis, it is of interest to examine hydroxylated tropones in which the oxygen atoms are not vicinal, as in the polycyclic substance II, and to compare their properties with those of related tropones (e.g. III) and tropolones (e.g. IV). In view of interest recently shown in these polycyclic




(I) (II) (III)




(IV) (V)

substances (Birch, 1951; Bergmann, *et al.*, 1951) it seems worth while recording some results obtained in these laboratories.

The tetracyclic ketone II was obtained by Cook (1928), who showed that it gave a mono-acetate and a mono-oxime, and a red solution in alkali. It has now been shown that this substance does not react with copper acetate, gives no picrate, and fails to give a colour with $FeCl_3$ solution. It is thus devoid of many of the characteristics of a tropolone, but it dissolves in $Na_2CO_3$ solution. The red colour of the solution is intensified by addition of an organic solvent.

The dibenz-tropone III was prepared by Treibs & Klinkhammer (1951) and has been further investigated by Bergmann, *et al.* (*loc. cit.*). Treibs showed that although bromine could be added to the C=C double bond, hypochlorous acid failed to react. This lack of reactivity has been corroborated here, using aqueous *N*-bromosuccinimide as a source of HOBr (Raphael, 1949) and the double bond has also been found resistant to epoxidation by perbenzoic or perphthalic acids, and is unaffected by the Milas reagent. On the other hand, III does not form a picrate or hydrochloride, and undergoes no rearrangement with alkali. Bergmann, *et al.* (*loc. cit.*) have also been unable to prepare salts. However, they describe a 2 : 4-dinitrophenyl hydrazone of m.p. 253—4°, although they give no analytical data. In contrast it has been found impossible here to obtain either a 2 : 4-dinitrophenylhydrazone or an oxime, and the saturated ketone (V) is equally inert. These latter findings have been corroborated by Prof. Treibs (private communication).

These results suggest that, as in (IV) (Sakan & Nakazaki, 1950), the presence of two flanking benzene rings suppresses the aromatic character of the central ring. A similar phenomenon is, of course, evident in anthracene and phenanthrene. A fuller account of this, and related, work will be published shortly.

*Received August* 6, 1952

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# TROPOLONES. PART VIII. SYNTHESIS AND PROPERTIES OF 7-HYDROXYBENZO*cyclo*HEPTATRIEN-3-ONE

BY
G. L. BUCHANAN

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Preprinted from the
Journal of the Chemical Society, March, 1954, pages 1060—1063.

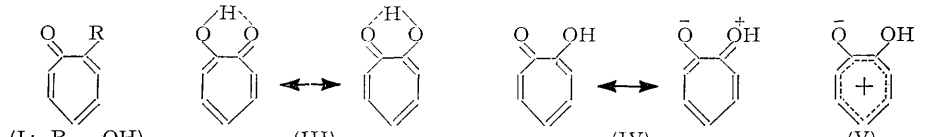
# *Tropolones. Part VIII.* Synthesis and Properties of 7-Hydroxybenzocycloheptatrien-3-one.*

By G. L. Buchanan.

[Reprint Order No. 4793.]

The bicyclic compound (X), named in the title, has been synthesised from benzo*cyclo*heptene-3 : 7-dione (VI), and its properties compared with those of αβ-benzotropolone.

Considerations of fine structure have led to two conflicting views on the aromaticity of tropolone (I). The first was advanced by Dewar (*Nature*, 1945, **155**, 50), who originally postulated hydrogen-bonded structures (III) as the principal resonance forms, but later (*idem, ibid.*, p. 479) modified this in favour of the ionic resonance structures (IV). Koch (*J.*, 1951, 512) subscribed to this latter view on the basis of infra-red studies, and postulated simple prototropy to account for the symmetry of the molecule. These views agree in implicating both oxygen atoms in the fundamental resonance of the molecule. They are, however, open to the criticism (Cook and Loudon, *Quart. Reviews*, 1951, **5**, 99) that the bond between the oxygen-bearing carbon atoms is always represented as a single bond, whereas, lack of double-bond character is not substantiated by bond-length measurements (Robertson, *J.*, 1951, 1222). A second view, relating tropolone to *cyclo*heptatrienone (II), suggests that the latter is the parent substance of this new aromatic system (Buchanan, *Chem. and Ind.*, 1952, 855; Doering and Knox, *J. Amer. Chem. Soc.*, 1952, **74**, 5683). This implies major contributions from structures (V) in agreement with Nozoe's opinion (*Proc. Japan Acad.*, 1950, **26**, 30), and seems more satisfactory since it demands a regular heptagon



(I; R = OH)
(II; R = H)

(III) (IV) (V)

structure, in agreement with *X*-ray data (Robertson, *loc. cit.*). It implies, however, that the second oxygen atom is not involved in the fundamental resonance of the molecule, and hence, that its position in the ring may be varied without affecting the fundamental character of the ring. It is therefore of interest to examine the properties of isomeric structures (*i.e. iso*tropolones) in which the oxygen atoms are not vicinal. The present communication describes the preparation and properties of 7-hydroxybenzo*cyclo*heptatrien-3-one (X), an isomer of αβ-benzotropolone (XII).

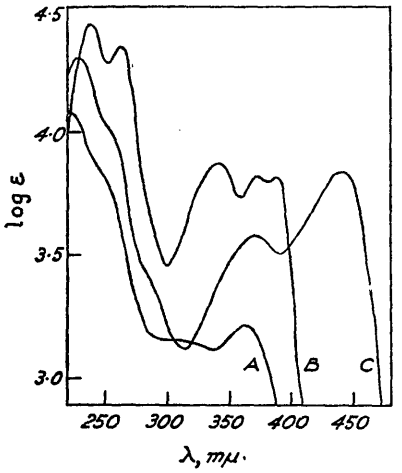
Preparation of the hydroxy-ketone (X) was attempted initially by the methods used in the preparation of the tropolone (XII) (Cook and Somerville, *Nature*, 1949, **163**, 410; Cook, Gibb, Raphael, and Somerville, *J.*, 1952, 603). Dehydrogenation of the dione (VI) by means of palladium–charcoal, however, failed to give an acidic product, and bromination by bromine in glacial acetic acid followed by alkali treatment yielded only dark oils. A much cleaner reaction took place with *N*-bromosuccinimide, and the bromo-derivative was readily dehydrobrominated by aqueous trimethylamine, affording a product, $C_{11}H_8O_2$, which gave a bis-2 : 4-dinitrophenylhydrazone but no picrate. It was insoluble in aqueous alkali, stable towards cold aqueous potassium permanganate, and failed to give a colour with ferric chloride. Such properties are incompatible with structure (X) (see below), and the compound is provisionally assigned the formula (VII).

To avoid ring formation during the dehydrogenation of the diketone (VI) the latter was converted by means of *iso*propenyl acetate (Hagemeyer and Hull, *Ind. Eng. Chem.*, 1949, **41**, 2920) into the bis-enol acetate (VIII), which was brominated by means of *N*-bromosuccinimide. This type of reaction produces αβ-unsaturated ketones (Gallacher, *J. Org. Chem.*, 1949, **14**, 660), and the neutral oily product obtained here is presumably the acetate

* Part VII, *J.*, 1953, 530.

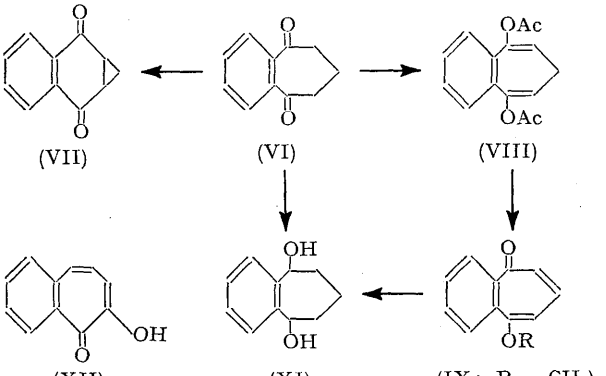
of (X). Alkaline hydrolysis followed by acidification gave 7-hydroxybenzo*cyclo*heptatrien-3-one (X) as a yellow solid, readily subliming *in vacuo*. It behaves as an acid (p$K$ 6·40), dissolves with effervescence in sodium hydrogen carbonate solution, and rapidly decolorizes aqueous potassium permanganate. Its structure was confirmed by its reduction to the diol (XI), which can also be prepared from the diketone (VI).

The *iso*tropolone (X) resembles αβ-benzotropolone (XII) in some respects. It gives a 3 : 5-dinitrobenzoate, an oily acetate, a yellow picrate, a red-brown colour with ferric chloride, and it couples with diazotised aniline, giving a crimson dye. It also forms unstable salts with hydrochloric and perchloric acids, but in contrast to (XII) it forms a 2 : 4-dinitrophenylhydrazone, is almost insoluble in non-polar solvents, fails to form a copper




*A*, 7-*Methoxybenzo*cyclo*heptatrien*-3-*one* (IX).
*B*, αβ-*Benzotropolone* (XII).
*C*, 7-*Hydroxybenzo*cyclo*heptatrien*-3-*one* (X).
*Solvent : ethanol.*

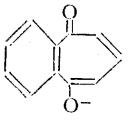
complex, and is not affected by fusion with potassium hydroxide at 220°. Being more acidic than the tropolone (XII) it reacts readily with ethereal diazomethane, and the resulting methyl ether (IX) resembles tropolone methyl ether (Cook, Gibb, Raphael, and Somerville, *J.*, 1951, 503) in forming a stable hemihydrate and in being readily hydrolysed by dilute alkali. During the purification of the methyl ether (IX), a quantity of substance (VII) was isolated, and a fuller examination of this material will be reported later.

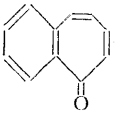


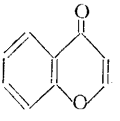

Further evidence of similarity between the *iso*tropolone (X) and αβ-benzotropolone (XII) is to be seen in their ultra-violet absorption spectra. The absorption spectrum of the methyl ether (IX) is also given in the Figure.

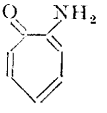
These results indicate a general similarity between the *iso*tropolone (X) and αβ-benzotropolone (XII), but they do not provide unequivocal evidence of aromatic character. The acidity, salt formation, coupling, and coloration with ferric chloride displayed by (X) may equally be the properties of a conjugated enol-ketone. The fact that (X) is a stronger acid

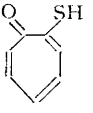
than the tropolone (XII) is to be expected, since resonance in the anion (XIII) involves two identical canonical structures, but the appearance of ketonic properties in (X) requires further comment. It is evident that oxygenated derivatives of benzo*cyclo*heptatrien-3-one (XIV) only show ketonic properties when there is no possibility of hydrogen interaction between the two oxygen atoms. Thus both $\alpha\beta$- and $\beta\gamma$-benzotropolones are devoid of ketonic activity though their methyl ethers, and their isomer (X) gives normal ketone derivatives (Cook, Gibb, Raphael, and Somerville, *ibid.*, 1952, 603; Tarbell and Bill, *J. Amer. Chem. Soc.*, 1952, **74**, 1234). The electronic ($+E$) effect exerted by the hydroxy- or methoxy-groups has no apparent effect on the character of the carbonyl function. In the monocyclic series (II) the evidence is not complete; however, it seems to indicate that in this case the electronic ($+E$) effect of substituents is the important factor. Thus *cyclo*heptatrienone (II) gives ketonic derivatives (Doering, *Chem. Eng. News*, 1953, 2677; Nozoe, *Proc. Japan Acad.*, 1952, **28**, 477), although tropolone (I) and its methyl ether, 2-amino*cyclo*heptatrienone (XVI) (Nozoe, *Sci. Rep. Tohoku*, 1952, **36**, 126) and thiotropolone (XVII) (*idem*, *Proc. Japan Acad.*, 1953, **29**, 22) are all devoid of ketonic properties. Hydrogen bonding has no apparent effect on the character of the carbonyl function. This difference between the monocyclic and the benzo-series, finds a parallel in the chemistry of


(XIII)


(XIV)


(XV)


(XVI)


(XVII)

$\gamma$-pyrone and its benzo-derivative, chromone (XV). In the former, the electronic ($+E$) effect of the heterocyclic oxygen atom suppresses the ketonic properties of the carbonyl group, but in the latter (XV) its effect is so diminished that normal ketone derivatives are formed (Elderfield, " Heterocyclic Compounds," Wiley and Co., New York, 1951, Vol. 2, p. 254).

## Experimental

Benzo*cyclo*heptene-3 : 7-dione (VI) was prepared by the method of Barltrop, Johnson, and Meakins (*J.*, 1951, 181).

*Dehydrogenation of Benzo*cyclo*heptene*-3 : 7-*dione*.—(*a*) A solution of the dione (VI) (2 g.) in 1 : 2 : 4-trichlorobenzene (50 c.c.) was refluxed with palladium–charcoal (5%; 4 g.) for 12 hr. under nitrogen, and the filtered solution extracted with dilute sodium hydroxide solution. Acidification and ether extraction yielded nothing.

(*b*) The dione (VI) (1 g.) in glacial acetic acid (5 c.c.) was treated with bromine (0·95 g., 1·1 mol.) in glacial acetic acid (10 c.c.); when warmed on the steam-bath, the solution became almost colourless, hydrogen bromide was evolved, and the colour reappeared. The solution was concentrated *in vacuo*, made alkaline with sodium hydroxide solution, washed with chloroform, and acidified. This gave a dark intractable gum.

(*c*) A solution of the dione (VI) (2·6 g.) in chloroform (10 c.c.) and carbon tetrachloride (10 c.c.) was refluxed with *N*-bromosuccinimide (2·6 g.) for 15 min. under a 200-watt lamp. The solution was then washed with water and concentrated *in vacuo* to a pale yellow oil. An excess of aqueous trimethylamine was added, and the mixture warmed on the steam-bath for 5 min., and left overnight. The resulting solid *product* crystallised from dilute methanol, and was further purified by chromatography in benzene on alumina. Recrystallisation from ethanol gave plates, m. p. 130—131° (Found: C, 76·8; H, 4·8. $C_{11}H_8O_2$ requires C, 76·7; H, 4·65%). This substance, for which structure (VII) is advanced, gave no picrate, decolorised aqueous potassium permanganate solution very slowly, and was insoluble in sodium hydroxide solution. It failed to give a colour with aqueous or alcoholic ferric chloride, but yielded a *bis*-2 : 4-*dinitrophenylhydrazone* which crystallised from nitrobenzene in scarlet micro-needles, m. p. 318° (decomp.) (Found: N, 20·75. $C_{23}H_{16}O_8N_8$ requires N, 21·05%).

3 : 7-*Diacetoxybenzo*cyclo*hepta*-1 : 3 : 6-*triene* (VIII).—A solution of the dione (VI) (15 g.) and toluene-*p*-sulphonic acid (0·75 g.) in *iso*propenyl acetate (120 c.c.) was refluxed for 16 hr., and then distilled until 80—100 c.c. had been collected. The residue was dissolved in benzene, and the solution washed with dilute sodium carbonate solution and then with water, and finally concentrated *in vacuo* to an oil. This oil was triturated with ether, the solid *diacetate* filtered off,

and the filtrate re-concentrated and re-cycled. From four operations the yield was 15·5 g. The diacetate crystallised from methanol in cream rhombs, m. p. 125—126° (Found : C, 69·6; H, 5·6. $C_{15}H_{14}O_4$ requires C, 69·8; H, 5·4%).

7-*Hydroxybenzo*cyclo*heptatrien*-3-*one* (X).—The diacetate (VIII) (3 g.), in carbon tetrachloride (65 c.c.), was heated under reflux with *N*-bromosuccinimide (2·1 g.) and a trace of dibenzoyl peroxide, for 5 hr., under a 200-watt lamp. The solution was then washed with water and concentrated *in vacuo*. The resulting pale yellow oil was heated on the steam-bath for 30 min. with an excess of dilute sodium hydroxide solution and a few drops of ethanol. This gave a dark red solution, which was filtered and acidified. The yellow precipitate was washed, dried on a tile, and sublimed at 150—180°/$10^{-4}$ mm., yielding 0·65 g. of the *hydroxy-ketone*, m. p. 188° (Found : C, 76·6; H, 4·8. $C_{11}H_8O_2$ requires C, 76·7; H, 4·65%). This compound was soluble in sodium hydrogen carbonate solution, and rapidly decolorised aqueous potassium permanganate. It gave a reddish-brown colour with ferric chloride in ethanol, but did not react with copper salts. Its *picrate* crystallised from dilute methanol in yellow needles, m. p. 155—158° (Found : C, 50·65; H, 3·2; N, 10·3. $C_{11}H_8O_2,C_6H_3O_7N_3$ requires C, 50·9; H, 2·7; N, 10·5%); an unstable *hydrochloride* was prepared by passing dry hydrogen chloride through a solution of the hydroxy-ketone in dry acetone; it crystallised from acetone–ether in buff needles, m. p. 150° (decomp.) (Found : C, 58·45; H, 5·1. $C_{11}H_8O_2,HCl,H_2O$ requires C, 58·2; H, 4·9%), and slowly lost hydrochloric acid. On the addition of water, it rapidly reverted to the yellow hydroxy-ketone, m. p. and mixed m. p. 186—188°. Treatment with aqueous perchloric acid gave a brown solution, from which brown needles were obtained by concentration. These decomposed violently when heated. When the hydroxy-ketone was heated with acetic anhydride, it gave an oily product, but on treatment with 3 : 5-dinitrobenzoyl chloride in dry benzene–pyridine, yielded a solid 3 : 5-*dinitrobenzoate*, m. p. 186° (Found : C, 59·3; H, 2·95; N, 7·4. $C_{18}H_{10}O_7N_2$ requires C, 59·0; H, 2·7; N, 7·65%). It also gave a *mono*-2 : 4-*dinitrophenylhydrazone*, m. p. 198° (Found : N, 15·9. $C_{17}H_{12}O_5N_4$ requires N, 15·8%), and reacted readily with ethereal diazomethane, to give an oil *methyl ether hydrate*, b. p. 170—172° (bath)/1·5 mm. (Found : C, 73·85; H, 5·9. $C_{12}H_{10}O_2,\frac{1}{2}H_2O$ requires C, 73·8; H, 5·6%). This ether was readily hydrolysed by aqueous alkali at 100° to the parent hydroxy-ketone (X), and an attempt to form the picrate of the ether gave instead the picrate, m. p. and mixed m. p. 155°, of the hydroxy-ketone. A solid by-product isolated during the purification of the ether crystallised from carbon tetrachloride in needles, m. p. 129—130° (Found : C, 76·6; H, 4·85. Calc. for $C_{11}H_8O_2$ : C, 76·7; H, 4·65%). It gave no depression in mixed m. p. with the tricyclic ketone (VII). The hydroxy-ketone (X) in alkaline solution coupled with diazotised aniline, yielding a crimson dye. An electrometric titration carried out on a 30% alcoholic solution, by Dr. J. C. Speakman, indicated a p$K$ value of 6·40. From this, the estimated value in water is *ca.* 6·1.

*Hydrogenation.*—(*a*) The dione (VI) (1 g.) in ethanol (10 c.c.) was reduced in presence of Adams's ($PtO_2$) catalyst (0·1 g.). Uptake was rapid until 2 mols. of hydrogen had been absorbed and slow thereafter. Concentration gave the *diol* (XI), which crystallised from aqueous alcohol in needles, m. p. 179—180° (Found : C, 74·4; H, 8·1. $C_{11}H_{14}O_2$ requires C, 74·2; H, 7·9%). The slow uptake probably represents hydrogenolysis of the diol.

(*b*) The hydroxy-ketone (X) (0·1 g.), in ethanol (5 c.c.), was hydrogenated in presence of palladium–calcium carbonate (2%; 0·75 g.). Uptake almost ceased after 3·6 mols. of hydrogen had been absorbed, and the product crystallised in needles, m. p. and mixed m. p. with (XI) 178—179°.

*Alkali Fusion.*—The hydroxy-ketone (X) (40 mg.) was added to a melt of potassium hydroxide (1 g.) and water (0·3 c.c.), and heated at *ca.* 220° with intermittent stirring for 30 min. After the melt had cooled water was added and the solution was filtered. Acidification yielded starting material, which was identified by mixed m. p.

*Absorption Spectra.*—These were determined by using a " Unicam " Spectrophotometer.

The author thanks Professor J. W. Cook, F.R.S., for his interest and advice. He is also indebted to Dr. J. C. Speakman for the dissociation-constant determination, and to Drs. J. D. Loudon and R. A. Raphael for helpful discussion. Microanalyses were by Mr. J. M. L. Cameron and Miss M. W. Christie.

UNIVERSITY OF GLASGOW. [*Received, November 13th,* 1953.]

PRINTED IN GREAT BRITAIN BY RICHARD CLAY AND COMPANY, LTD., BUNGAY, SUFFOLK.

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