

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

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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 dibenzocycloheptatrienone (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 deaminocolchinel 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 ( $\pm$ )-amine of the structure proposed for colchinel 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 colchinel methyl ether and its *N*-acetyl derivative as obtained by degradation of colchicine.

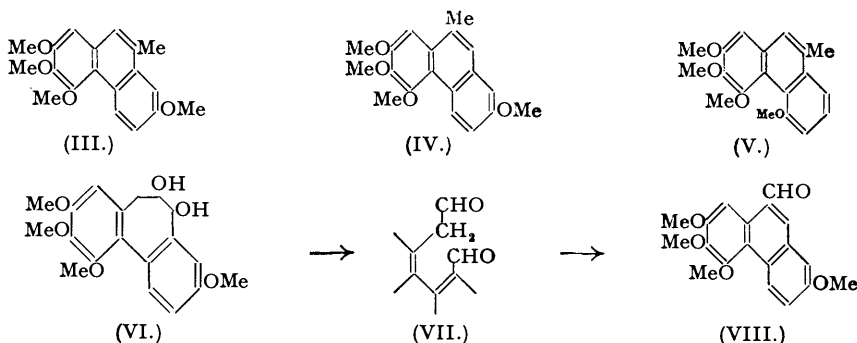
In Part V of this series (Barton, Cook, and Loudon, *J.*, 1945, 176) the structure (I) for deaminocolchinel methyl ether was established on the evidence of degradation and, as one immediate consequence, the conclusion was there reached that formula (II; R = H) represents the most probable structure for colchinel methyl ether. This conclusion has now been confirmed by the synthesis and resolution of the ( $\pm$ )-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



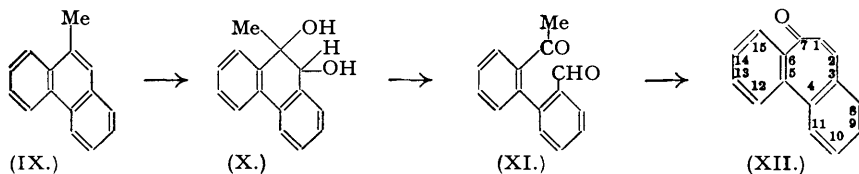
reaffirm our own active interest by publishing two brief announcements of progress (Buchanan, Cook, Loudon, and MacMillan, *Nature*, 1948, **162**, 692; Cook, Jack, and Loudon, *Chem. and Ind.*, 1950, 650) during the course of the work which is here described in full.

Early attempts to synthesise dibenzocycloheptadienones, *e.g.*, (XXII), from methoxylated  $\beta$ -2-diphenylpropionic 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 dibenzocycloheptatrienones, *e.g.*, (XII), from derivatives of 9- (or 10-)methylphenanthrene by the successive steps of hydroxylation, cleavage, and recyclicalisation 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 deaminocolchicol methyl ether (I), through the intermediates (VI) and (VII), by hydroxylation, cleavage, and recyclicalisation: samples of the compound from both sources were shown to be identical.

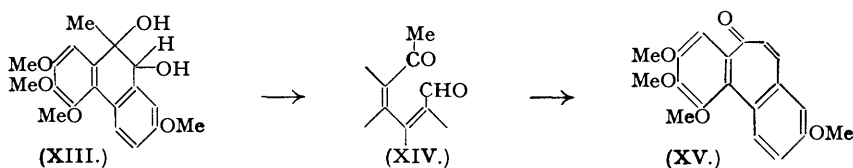


The procedure of Criegee, Marchand, and Wannowius (*loc. cit.*) consists in allowing the compound to be hydroxylated to react with osmium tetroxide in presence of pyridine and generally with benzene as solvent. Thereby the diol is gradually precipitated as a crystalline complex of the osmic ester with 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 tetracetate and the gummy product, presumably containing the keto-aldehyde (XI), on treatment with sodium hydroxide in methanol afforded 3:4:5:6-dibenzocyclohepta-1:3:5-trien-7-one (XII) which was identical with the compound earlier prepared by the action of selenium dioxide on the parent dibenzocycloheptatriene (I; H for each OMe) (Part VI, Cook, Dickson, and Loudon,

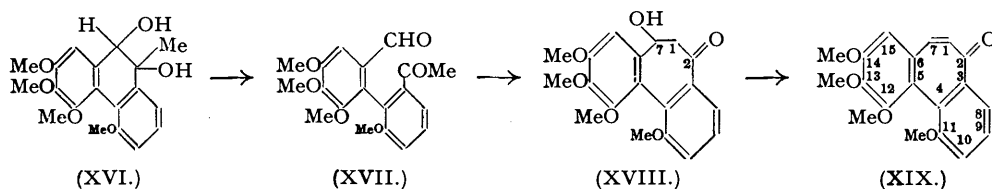


*J.*, 1947, 746). The oxime derived from the trienone (XII), when hydrogenated in acetic anhydride and in presence of Adams's catalyst, was reduced to 2-acetamido-3:4:5:6-dibenzocyclohepta-3:5-diene (II; R = Ac and H for each OMe).

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 deaminocolchicol 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.*).

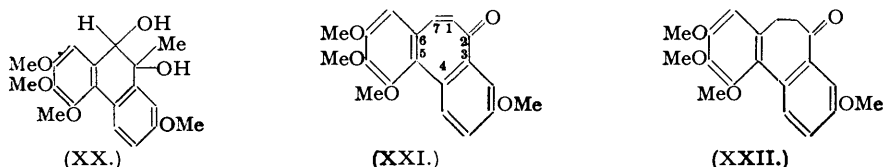


The diol (XVI) obtained by hydroxylating 2 : 3 : 4 : 5-tetramethoxy-9-methylphenanthrene (V) was found to undergo cleavage with the formation of a crystalline keto-aldehyde (XVII) and this facilitated a closer examination of the critical cyclisation stage. When treated with sodium hydroxide in methanol 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



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

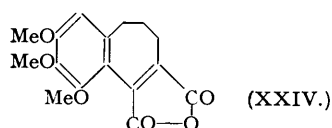
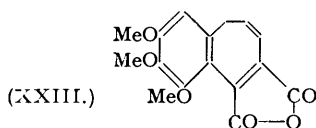


osmium tetroxide in benzene-pyridine. In other respects, however, the reaction appeared to proceed normally and, after a suitable interval, the addition of *n*-hexane afforded an osmic ester from which the diol (XX) was obtained without difficulty. Cleavage by lead tetra-acetate and treatment of the 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 ( $\pm$ )-colchinal 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 ( $\pm$ )-colchinal methyl ether and proved the authentic nature of their product by comparing it with the racemised degradation product.

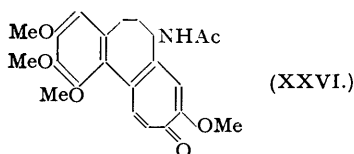
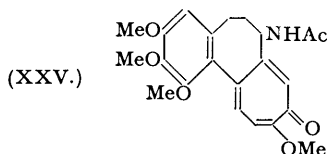
For the resolution of ( $\pm$ )-colchinal methyl ether, (-)-malic, (+)-tartaric, (+)-camphor-10-sulphonic and (+)- $\alpha$ -bromocamphor- $\pi$ -sulphonic acids were unsuccessfully tried, although the first two readily afforded crystalline salts. (+)-6:6'-Dinitrodiphenic acid, however, proved to be 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 colchinal methyl ether, its salts, and *N*-acetylcolchinal methyl ether as prepared from colchicine.

It will be observed that this synthesis of *N*-acetylcolchinal 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)  $\rightarrow$  (I) (cf. Part V, *loc. cit.*), the process of ring-contraction, (I)  $\rightarrow$  (VI)  $\rightarrow$  (VIII), leads to a 9-substituted and ultimately, (VIII)  $\rightarrow$  (IV), to a 9-methyl derivative of phenanthrene. The contrary, but similarly effected process of ring-expansion, (III)  $\rightarrow$  (XX)  $\rightarrow$  (XXI), starts from the isomeric 10-methylphenanthrene and is followed by amination, (XXI or XXII)  $\rightarrow$  (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.



In Part X (Cook, Johnstone, and Loudon, *J.*, 1950, 537) it was shown conclusively that the compounds obtained by Windaus by oxidising colchicine with potassium permanganate were not hydronaphthalene derivatives as he supposed (cf. *Annalen*, 1924, **439**, 59). In particular it was shown that Windaus's *N*-benzoylcolchicinic anhydride could be converted into deaminocolchicinic anhydride which is quite distinct from the synthesised 6:7:8-trimethoxy-3-methylnaphthalene-1:2-dicarboxylic anhydride and, therefore, like the colchinal 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 Ulyot and their colleagues (*J. Amer. Chem. Soc.*, 1950, **72**, 4840) of whose work in project we were courteously informed by Dr. G. E. Ulyot. There is consequently good reason to believe that the 7-membered ring B, now established for both the colchinal and colchicinic 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 colchicine becomes phenolic, as in the formation of



*N*-acetyliodocolchinal. 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 colchinal type we may conclude that colchicine and *isocolchicine* are correctly formulated as (XXV) and (XXVI), not necessarily respectively.

## 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 temperature, 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-Dibenzocyclohepta-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  $\frac{1}{2}$  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 ( $\frac{1}{2}$  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-dibenzocyclohepta-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  $1\frac{1}{4}$  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.  $C_{20}H_{20}O_8$  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.  $C_{19}H_{18}O_6$  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.  $C_{18}H_{22}O_6$  requires C, 65.9; H, 6.4%).

9 : 12 : 13 : 14-Tetramethoxy-3 : 4 : 5 : 6-*dibenzocyclohepta*-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 deaminocolchinal 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 ultra-violet 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.  $C_{18}H_{22}O_6$  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.  $C_{18}H_{22}O_6$  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-*dibenzocyclohepta*-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-*dibenzocyclohepta*-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.  $C_{19}H_{18}O_6$  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-dibenzocyclohepta-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-dibenzocyclohepta-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  $\frac{1}{2}$  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.

(±)-Colchicol 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*-acetylcolchicol 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 (±)-colchicol methyl ether. Solutions of the (±)-amine (0.4 g.) and (+)-6 : 6'-dinitrophenic 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. [(−)-Colchicol methyl ether] [hydrogen (+)-6 : 6'-dinitrodiphenate] crystallised, with a molecule of methanol, as pale yellow rods, m. p. 257—258° (decomp.),  $[\alpha]_{590}^{18} + 51^\circ$ ,  $[\alpha]_{5461}^{18} + 67^\circ$  (*c*, 0.33 in methanol) (Found : C, 58.8; H, 5.05.  $C_{19}H_{23}O_4N, C_{14}H_8O_6N_2, CH_4O$  requires C, 58.9; H, 5.1%). The same acid salt, m. p. and mixed m.p. 258° (decomp.),  $[\alpha]_{590}^{18} + 54^\circ$ ,  $[\alpha]_{5461}^{18} + 69^\circ$  (*c*, 0.33 in methanol), was prepared from colchicol 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  $[\alpha]_{590}^{18} - 85^\circ$  and  $[\alpha]_{5461}^{18} - 111^\circ$  (*c*, 0.74 in methanol). An authentic specimen of colchicol methyl ether had m. p. and mixed m. p. 90—92°,  $[\alpha]_{590}^{17} - 84^\circ$ , and  $[\alpha]_{5461}^{17} - 111^\circ$  (*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*-Acetylcolchicol methyl ether was prepared from resolved synthetic colchicol methyl ether as described for the racemic compound. It crystallised from methanol as colourless prisms, m. p. 202—204°,  $[\alpha]_{590}^{18} - 92^\circ$ ,  $[\alpha]_{5461}^{18} - 118^\circ$  (*c*, 0.67 in methanol). An authentic specimen prepared from colchicine had m. p. and mixed m. p. 202—204°,  $[\alpha]_{590}^{17} - 94^\circ$ ,  $[\alpha]_{5461}^{17} - 118^\circ$  (*c*, 0.67 in methanol). Rapoport, Williams and Cisney (*loc. cit.*) record m. p. 201—202° and  $[\alpha]_{590}^{20} - 88.6^\circ$  (*c*, 0.67 in methanol) for the degradation product.

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