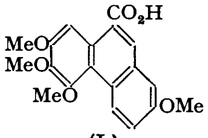
44. *Colchicine and Related Compounds. Part V. The Structure of Windaus's Deaminocolchinol Methyl Ether.*

By Norman Barton, J. W. Cook, and J. D. Loudon.

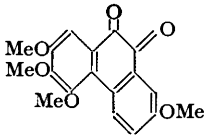
Deaminocolchinol methyl ether, obtained by Windaus by exhaustive methylation of colchinol methyl ether, is not a tetramethoxy-9-methylphenanthrene as he believed. It is an unsaturated compound containing one ethylenic linkage, and gives on oxidation with chromic acid an unsaturated *ketone* and 2 : 3 : 4 : 7-*tetramethoxyphenanthraquinone*. The formation of this quinone establishes the methoxylation pattern of colchinol methyl ether, and hence the positions of five of the substituents in the ring system of colchicine.

Colchinol methyl ether has been converted by a variety of routes into deaminocolchinol methyl ether, which is usually (perhaps invariably) accompanied by an isomeric iso*deaminocolchinol methyl ether*; both isomerides are hydrogenated to the same *dihydride*. By stepwise oxidation, deaminocolchinol methyl ether and its isomeride have been converted into 2 : 3 : 4 : 7-tetramethoxy-10-phenanthraldehyde and -9-phenanthraldehyde, respectively. These transformations show that deaminocolchinol methyl ether and its isomeride have the structures (XII) and (XIII).

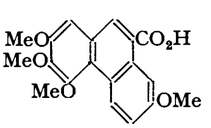
In Part IV (Buchanan, Cook, and Loudon, J., 1944, 325) the syntheses of 2 : 3 : 4 : 6- and 2 : 3 : 4 : 7-tetramethoxy-9-methylphenanthrene were described and it was shown that, contrary to the views of Windaus (*Annalen*, 1924, **439**, 59), neither of these compounds was identical with deaminocolchinol methyl ether, an important degradation product of colchicine. The synthetic work did not, however, distinguish the 2 : 3 : 4 : 7-isomer from 2 : 3 : 4 : 5-tetramethoxy-9-methylphenanthrene, since these two compounds were obtained from the corresponding 9-carboxylic acids (acid-A, m. p. 236°, and acid-B, m. p. 185°), which were simultaneous products of a Pschorr reaction and were not individually oriented. This distinction has now been made. 2-Nitro-5-methoxybenzaldehyde was condensed with sodium 3 : 4 : 5-trimethoxyphenylacetate, the *product* reduced, and the resulting *amino-acid* converted into 2 : 3 : 4 : 7-*tetramethoxyphenanthrene*-10-*carboxylic acid* (I). Oxidation of this acid furnished 2 : 3 : 4 : 7-*tetramethoxyphenanthraquinone* (II), which was characterised by the *diazine* derived from *o*-phenylenediamine. The same quinone and diazine were also obtained in similar fashion from acid-A (corresponding to the tetramethoxy-9-methylphenanthrene, m. p. 116—117°; Part IV), whereas acid-B yielded quite distinct *products*. Accordingly acid-A is (III) and in Part IV the A-series of compounds has the 2 : 3 : 4 : 7-, and the B-series has the 2 : 3 : 4 : 5-tetramethoxyphenanthrene structure. Incidentally it may be noted that the alternative method of orientation based on decarboxylation of the 9- and the 10-acid to the parent phenanthrene is probably here subject to complications, for Pschorr found (*Annalen*, 1912, **391**, 40) that dry distillation of 3 : 4 : 5-trimethoxyphenanthrene-9-carboxylic acid produced the corresponding methyl ester and we have encountered a similar case in 2 : 3 : 4 : 6-tetramethoxyphenanthrene-9-carboxylic acid, which was converted into its methyl ester when slowly distilled in presence of copper in a high vacuum.



(I.)

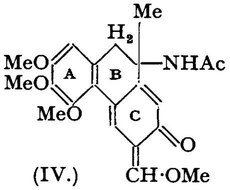


(II.)

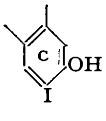


(III.)

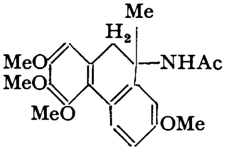
When oxidised with sodium dichromate in acetic acid, deaminocolchinol methyl ether yielded a quinone identical with (II) and distinct from 2 : 3 : 4 : 6-*tetramethoxyphenanthraquinone* prepared for comparison from 2 : 3 : 4 : 6-tetramethoxyphenanthrene-9-carboxylic acid. This result is of considerable importance—by establishing the methoxylation pattern of *N*-acetylcolchinol methyl ether and thereby defining the position of the phenolic group in ring C of *N*-acetylcolchinol, it removes the existing ambiguity regarding the positions of substituents in ring C of colchicine itself and, at the same time, confirms the arrangement of methoxyl groups in ring A. In terms of the Windaus formulation colchicine accordingly becomes (IV), *N*-acetyliodocolchinol (V) and *N*-acetylcolchinol methyl ether (VI).



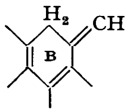
(IV.)



(V.)



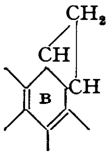
(VI.)



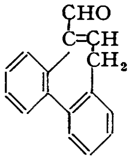
(VII.)

Deaminocolchinol methyl ether is produced by Hofmann degradation of colchinol methyl ether (Windaus, *loc. cit.*) or by elimination of acetamide from the *N*-acetyl derivative (Part III; Cook and Graham, J., 1944, 322). It is not only distinct from 2 : 3 : 4 : 7-tetramethoxy-9-methylphenanthrene, but differs from this and from the other synthetic isomerides in two significant respects. It gives no sign of picrate formation when treated with picric acid in methanol, whereas under similar conditions the synthetic compounds immediately give red solutions from which the picrates separate. Secondly, it is readily hydrogenated to a *dihydride* in presence of a palladium catalyst, under conditions which leave the synthetic compounds and also *N*-acetylcolchinol methyl ether unchanged. These facts indicate that deaminocolchinol methyl ether does not contain a phenanthrene arrangement of double bonds and, together with the oxidation to 2 : 3 : 4 : 7-tetramethoxyphenanthraquinone, suggest the alternative structures 2 : 3 : 4 : 7-tetramethoxy-9- or -10-methylene-9 : 10-dihydrophenanthrene (*e.g.*, VII). The further implications of these formulæ are not, however, borne out by the chemical behaviour of the compound. It is not, as would be expected, readily isomerised to an aromatic structure. For instance, in course of its preparation it survives moderately intense conditions of heat and alkalinity (see Experimental) and it was recovered unchanged after 3 hours' boiling with sodium methoxide in methanol. It was also recovered, although in diminished quantity, after heating with a mixture of hydrochloric and acetic acids. Further, the dihydride has not the properties expected of a 9- or 10-methyl-9 : 10-dihydrophenanthrene, for it resists dehydrogenation with palladium and with selenium under conditions considerably more severe than suffice to effect a rapid conversion of 9 : 10-dihydrophenanthrene into phenanthrene. These objections to structure (VII) for deaminocolchinol methyl ether and to the reduced form for its dihydride are essentially the same as the objections previously raised against the Windaus formula for *N*-acetylcolchinol methyl ether (Part I; Cohen, Cook, and Roe, J., 1940, 194). In general, the formulation of ring B as six-membered in these and similar degradation products of colchicine implies a facile aromatisation which is not found in practice.

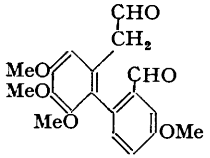
In Part I it was shown that colchinol methyl ether in reaction with nitrous acid yielded a carbinol which from its stability must be either primary or secondary. Although the point was not finally settled, failure to obtain an aldehyde or corresponding acid on oxidation, together with the behaviour of the carbinol with phthalic anhydride, indicated that it is probably a secondary alcohol. We have now found that the carbinol is strongly lævorotatory and that on dehydration it yields a mixture of products from which deaminocolchinol methyl ether and an isomeric substance, iso*deaminocolchinol methyl ether*, have been isolated. Re-investigation showed that a small quantity of the *iso*-compound is also produced together with deaminocolchinol methyl ether during the elimination of acetamide from *N*-acetylcolchinol methyl ether and it is possible that the same compound was formed but escaped detection in the earlier Hofmann degradations of colchinol methyl ether. The new product resembles its isomeride in its failure to form a picrate and in its ability to undergo hydrogenation with a palladium catalyst, whereby from both isomerides the same dihydride is produced. Since their properties preclude an aromatic structure for the isomerides, these hydrogenation results cannot be interpreted in terms of a 6-membered ring B, except by assigning to one of the isomerides a fused *cyclo*propane structure (VIII) and improbabilities are incurred in regard to both its formation and its subsequent unilateral reduction to the dihydride of (VII). On the other hand, the more accommodating possibilities of a 5- and 7-membered ring B are not at first sight in accord with a simple oxidation of deaminocolchinol methyl ether to 2 : 3 : 4 : 7-tetramethoxyphenanthraquinone. The quinone, however, is not the only product of this oxidation, for a second *product*, $C_{19}H_{18}O_5$, having properties suggestive of an αβ-unsaturated ketone was also isolated. Such a product could be accommodated almost equally well in a 6- or 7-membered ring B and even in a 5-membered ring B, although here perhaps with less acceptance because of the separation of the oxidised methylene group from the aromatic nucleus. At the same time, in view of the ease with which diphenyl triketone is oxidised to benzil in an acid medium (Schönberg and Azzam, J., 1939, 1428), it suggests one possible route by which an appropriate dibenz*cyclo*heptatriene might be converted into the phenanthraquinone (II). An actual instance of the latter type of reaction, although the mechanism remains obscure, is recorded by Weitzenböck (*Monatsh.*, 1913, **34**, 199), who obtained phenanthraquinone from the compound (IX) by oxidation with chromic acid in acetic acid.



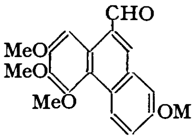
(VIII.)



(IX.)



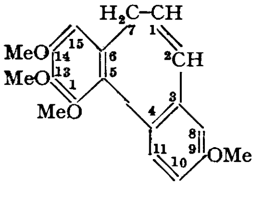
(X.)



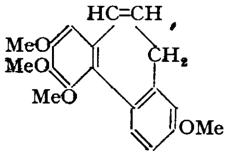
(XI.)

In order to secure more precise information attention was next turned to the controlled stepwise oxidation of the olefinic centre in deaminocolchinol methyl ether. The compound was largely unaffected by hydrogen peroxide in *tert.*-butyl alcohol with osmium tetroxide as catalyst (cf. Milas and Sussman, *J. Amer. Chem. Soc.*, 1936, **58**, 1302), but it readily afforded a *glycol*, $C_{19}H_{22}O_6$, by Criegee's method using osmium tetroxide in ether (*Annalen*, 1936, **522**, 77). Fission of the glycol by means of lead tetra-acetate in benzene (Criegee, *Ber.*, 1931, **64**, 260; Criegee, Kraft, and Rank, *Annalen*, 1933, **507**, 159) yielded a gum which slowly crystallised to a monoaldehyde, $C_{19}H_{18}O_5$. The latter must be 2 : 3 : 4 : 7-*tetramethoxy*-10-*phenanthraldehyde* (XI), since on oxidation with permanganate it gave the corresponding acid indistinguishable from the synthetic acid (I) and affording the same *methyl* ester. The production of the 10-aldehyde in this way strongly indicates the intermediate formation of the dialdehyde (X) and it may be added in confirmation of this view that the reluctance to solidify shown by the crude gum is immediately overcome by warming with a trace of sodium carbonate in methanol. Finally, a similar series of oxidations was carried out with *iso*deaminocolchinol methyl ether.

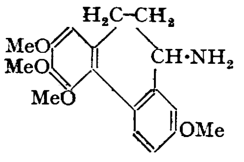
In this case, because of the small amount of material available, the crystalline product corresponding to (but distinct from) the above glycol was not fully characterised, but was oxidised directly with lead tetra-acetate and gave 2 : 3 : 4 : 7-tetramethoxy-9-phenanthraldehyde identical with a synthetic specimen (Part IV) and yielding the same *oxime*.



(XII.)



(XIII.)



(XIV.)

These results appear to us to show conclusively that deaminocolchinol methyl ether is 9 : 12 : 13 : 14-tetramethoxy-3 : 4 : 5 : 6-dibenz-$\Delta^{1:3:5}$-*cyclo*heptatriene (XII) * and that *iso*deaminocolchinol methyl ether is 9 : 12 : 13 : 14-tetramethoxy-3 : 4 : 5 : 6-dibenz-$\Delta^{3:5:7}$-*cyclo*heptatriene (XIII). This conclusion is not necessarily in conflict with the isolation by Windaus (*loc. cit.*) of a small amount of 9-methylphenanthrene from deaminocolchinol methyl ether, by demethylation, followed by zinc dust distillation. Contraction of the 7-membered ring to a 6-membered ring might well have taken place under the drastic conditions of zinc dust distillation, as has been pointed out previously (Part I). It might even have occurred during the prior demethylation with boiling hydriodic acid (compare Cook, J., 1928, 62). The ketone which we obtained by chromic acid oxidation of deaminocolchinol methyl ether (XII) is evidently formed by oxidation of the methylene group at position 7. As mentioned above, this ketone may be an intermediate in the formation of the quinone (II). It is possible, nevertheless, that the ketone and the quinone represent different paths of oxidation, and that in the formation of the quinone the initial attack is on the ethylenic linkage, as in the stepwise conversion of (XII) into tetramethoxyphenanthrenecarboxylic acid (I).

If it is assumed that the Hofmann deamination of colchinol methyl ether to (XII) is unaccompanied by rearrangement of the carbon skeleton, an assumption that seems well founded (compare Stevens and Richmond, *J. Amer. Chem. Soc.*, 1941, **63**, 3132), the further conclusion may be drawn that colchinol methyl ether also contains a 7-membered ring, carrying an amino-substituent (*e.g.*, XIV); the precise location of the amino-group requires further investigation. While it would be premature to assume the presence of a *cyclo*heptane system in colchicine itself, yet the extensive degradations of the alkaloid carried out by Windaus are not inconsistent with such a structure. In particular, it may be remarked that the oxidation of colchicine to succinic acid (Windaus, *loc. cit.*, and *Sitzungsber. Heidelberg. Akad. Wiss., Math.-Nat. Kl. A*, 1914, 18 Abh.), which is difficult to reconcile with formula (IV), is readily explicable on the basis of a structure corresponding with (XIV). We are continuing the investigation, with special reference to the implications of our present results.

EXPERIMENTAL.

2-*Nitro*-5-*methoxy*-α-(3′ : 4′ : 5′-*trimethoxyphenyl*)*cinnamic Acid*.—Sodium 3 : 4 : 5-trimethoxyphenylacetate (Part III, *loc. cit.*) (19·1 g.; dried at 130°), 2-nitro-5-methoxybenzaldehyde (Mason, J., 1925, **127**, 1195) (13·9 g.), and acetic anhydride (190 c.c.) were heated at 125—130° for 8 hours. After addition of water and cautious warming to decompose acetic anhydride the mixture was thoroughly extracted with ether. The product partly separated in the process and was combined with the remainder, which was recovered from the ethereal extract by shaking with aqueous sodium carbonate, followed by acidification. 2-*Nitro*-5-*methoxy*-α-(3′ : 4′ : 5′-*trimethoxyphenyl*)*cinnamic acid* (55% yield) formed yellow needles (from methanol); the m. p. was at first 137°, and later changed spontaneously to 158—159° (Found : C, 58·8; H, 4·7. $C_{19}H_{19}O_8N$ requires C, 58·6; H, 4·9%).

2-*Amino*-5-*methoxy*-α-(3′ : 4′ : 5′-*trimethoxyphenyl*)*cinnamic Acid*.—A solution of the nitro-acid (15·9 g.) in concentrated aqueous ammonia (64 c.c.) and water (250 c.c.) was added to a mixture of ferrous sulphate (110 g.), water (340 c.c.), and concentrated aqueous ammonia (285 c.c.) maintained, with stirring, at 70°. After 2 hours the filtrate and washings from the iron hydroxide were acidified, and the precipitated *amino-acid* was crystallised from ethanol, forming masses of colourless needles, m. p. 189—190°, which became yellow when pressed on porous plate, and gave yellow solutions in ethanol (yield, 75%) (Found : C, 63·6; H, 6·0. $C_{19}H_{21}O_6N$ requires C, 63·5; H, 5·85%).

2 : 3 : 4 : 7-*Tetramethoxyphenanthrene*-10-*carboxylic Acid* (I).—N-Sodium nitrite (34 c.c.) was added at 5° to a solution of the amino-acid (11·3 g.) in 2·5N-sulphuric acid (113 c.c.) and sufficient acetic acid to give a clear solution when warmed. After dilution with water (400 c.c.), the resulting diazo-solution was neutralised with sodium carbonate and heated at 50° until a coupling test was negative. Tarry matter which separated was redissolved by addition of dilute sodium hydroxide solution and, after cooling, the solution was acidified. The precipitated *acid* (I) crystallised from dilute ethanol in small, pale yellow needles, m. p. 200° (Found: C, 66·6; H, 5·3. $C_{19}H_{18}O_6$ requires C, 66·7; H, 5·3%), and with ethereal diazomethane gave a *methyl* ester, which, after distillation in a high vacuum (bath temperature, 245°), crystallised from methanol in colourless prisms, m. p. 103—104° (Found : C, 67·5; H, 5·55. $C_{20}H_{20}O_6$ requires C, 67·4; H, 5·6%). After the ester had distilled, a higher fraction was obtained (bath at 250—290°) which, after repeated crystallisation from methanol, formed brown plates, m. p. 210·5—211° (Found : C, 63·7; H, 5·45; N, 8·3%). This *compound*, which was insoluble in sodium bicarbonate solution but soluble in sodium hydroxide solution, had already been obtained

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* We adopt the system of numbering used by Kenner and Turner (J., 1911, **99**, 2104; compare Kenner, J., 1913, **103**, 613, and Tauriņš, *J. pr. Chem.*, 1939, **153**, 192) for dibenz*cyclo*heptatriene. Patterson and Capell ("The Ring Index," New York, 1940, p. 280) suggest a different system, which seems less suitable, as it involves different schemes of numbering for the two isomeric dibenz*cyclo*heptadienes. Moreover, as Kenner and Turner point out, it is logical to number first all the carbon atoms of the 7-membered ring, if the compounds are named as derivatives of *cyclo*heptane.

by extraction of a chloroform solution of the crude acid (I) with sodium hydroxide after the acid itself had been extracted with sodium carbonate. It possibly corresponded with a similar *compound*, m. p. 159—160°, which had been isolated in the preparation of 2 : 3 : 4 : 6-tetramethoxyphenanthrene-9-carboxylic acid (Part IV, *loc. cit.*; compare Sharp, J., 1936, 1235) (Found : C, 63·7; H, 5·7; N, 8·7%). These by-products, neither of which gave a colour with ferric chloride in alcoholic solution, have not been investigated further.

2 : 3 : 4 : 7-*Tetramethoxyphenanthraquinone* (II).—(*a*) A solution of 2 : 3 : 4 : 7-tetramethoxyphenanthrene-10-carboxylic acid (0·3 g.) in boiling acetic acid (3 c.c.) was treated with a solution of sodium dichromate (0·6 g.) in water (0·3 c.c.) and acetic acid (0·6 c.c.). After being heated under reflux for ½ hour and then diluted with water (25 c.c.), the mixture was extracted with chloroform. The extract was washed with dilute sulphuric acid and then dilute sodium carbonate solution (which removed a small amount of organic acid), dried, and evaporated. A solution of the residue in benzene–ligroin (3 : 2) was passed through a column of alumina, from which a dark red band was eluted with benzene. The eluate gave the *quinone* (II) as red-violet needles or deep violet prisms (from benzene–ligroin), m. p. 193—194° (Found : C, 66·2; H, 5·0. $C_{18}H_{16}O_6$ requires C, 65·9; H, 4·9%). A solution of this quinone in hot acetic acid, treated with a warm solution of *o*-phenylenediamine in methanol, gave a *diazine* which crystallised from methanol in lemon-yellow needles, m. p. 176—177° (Found : C, 72·0; H, 4·8; N, 6·8. $C_{24}H_{20}O_4N_2$ requires C, 72·0; H, 5·0; N, 7·0%).

(*b*) The same quinone and diazine, identified by mixed m. p.'s, were obtained from acid-A (III) (m. p. 236°; Part IV, *loc. cit.*). In this case the diazine was obtained in two interconvertible forms, *viz.*, the lemon-yellow needles, m. p. 176—177°, and orange needles, m. p. 185—186°. The m. p. of the lemon-yellow form changed to the higher value on cooling and remelting.

2 : 3 : 4 : 5-*Tetramethoxyphenanthraquinone*, fan-shaped clusters of red needles, m. p. 120—122°, was obtained similarly from acid-B (m. p. 185°; Part IV) (Found : C, 66·05; H, 5·0. $C_{18}H_{16}O_6$ requires C, 65·9; H, 4·9%). The corresponding *diazine* formed orange prisms, micro-m. p. 143° * (Found : N, 7·0. $C_{24}H_{20}O_4N_2$ requires N, 7·0%). An acidic by-product of the oxidation, probably 4 : 5 : 6 : 6′-*tetramethoxydiphenic acid*, m. p. 214—216° (decomp.), was recovered from the sodium carbonate washings (Found : C, 59·8; H, 4·85. $C_{18}H_{18}O_8$ requires C, 59·7; H, 5·0%).

2 : 3 : 4 : 6-*Tetramethoxyphenanthraquinone*, prepared by similar oxidation of 2 : 3 : 4 : 6-tetramethoxyphenanthrene-9-carboxylic acid (Sharp, *loc. cit.*), crystallised from benzene–ligroin in two interconvertible forms, (i) long orange needles, m. p. 184°, and (ii) red rods, micro-m. p. 193°; admixture with 2 : 3 : 4 : 7-tetramethoxyphenanthraquinone (II) gave an indefinite m. p. *ca.* 180°, after sintering (Found : C, 65·9; H, 4·9. $C_{18}H_{16}O_6$ requires C, 65·9; H, 4·9%). The corresponding *diazine* formed pale lemon-yellow crystals, m. p. 180—181°, depressed to *ca.* 150° by admixture with the diazine from (II) (Found: N, 7·7. $C_{24}H_{20}O_4N_2$ requires N, 7·0%).

Attempted Decarboxylation of 2 : 3 : 4 : 6-*Tetramethoxyphenanthrene*-9-*carboxylic Acid.*—A mixture of the acid (0·2 g.) and freshly precipitated copper was slowly distilled in a high vacuum from an air bath at *ca.* 200°. The pinkish distillate was dissolved in ether, and the solution washed with dilute aqueous sodium hydroxide; the gum which remained after evaporation of the ether, when rubbed with methanol, gave crystals of methyl 2 : 3 : 4 : 6-tetramethoxyphenanthrene-9-carboxylate, m. p. and mixed m. p. 96—97°.

Deaminocolchinol Methyl Ether (XII).—This was prepared (*a*) as described by Windaus and Schiele (*Annalen*, 1924, **439**, 71) from the quaternary ammonium hydroxide obtained by exhaustive methylation of colchinol methyl ether; (*b*) by heating the corresponding carbonate alone at 250° or mixed with solid potassium hydroxide at 120°, followed by distillation in a high vacuum (air-bath at 140—150°); (*c*) as described in Part III, by the action of phosphoric oxide on *N*-acetylcolchinol methyl ether. In all of these cases the product, crystallised from methanol, melted finally within the range 111—113°, but in most cases there was a noticeable shrinking, and sometimes melting, followed by re-solidification, within the range 98—105°. A more intensive search in the crystallisation mother-liquors from (*c*), not attempted in the earlier experiments (*a*) and (*b*), yielded a few crystals, m. p. 99—100°, depressed to *ca.* 84° by the above compound, but not depressed by the *iso*deaminocolchinol methyl ether described below.

Deaminocolchinol methyl ether gave no intensification of colour or other evidence of picrate formation when added to a methanolic solution of picric acid. It was recovered unchanged (50 mg. from 60 mg.) after boiling for 3 hours with sodium methoxide (100 mg. of sodium in 2 c.c. of methanol). When it (50 mg.) was boiled for 2½ hours in acetic acid (1 c.c.) and hydrochloric acid (0·5 c.c.), a red-brown solution was obtained, from which, after dilution, washing its ethereal extract with dilute sodium hydroxide, and then distilling it in a high vacuum, a small amount of the original material was recovered, m. p. and mixed m. p. 109—110°, after softening at 101°.

Dehydration of the Carbinol formed by the Action of Nitrous Acid on Colchinol Methyl Ether.—This carbinol, prepared as described in Part I and purified through its *p*-phenylbenzoate, had m. p. 116° and $[\alpha]_{5461}^{17^\circ}$ −138° ($c = 2$, in chloroform).

(*a*) A solution of the carbinol (600 mg.) in xylene (30 c.c.) was refluxed with phosphoric oxide (1·5 g.) for 10—15 minutes. The xylene solution was decanted, the residue extracted with hot xylene, and the solvent removed under reduced pressure from the combined solutions. The residual gum was distilled in a high vacuum from an air-bath at 145°, and gave a viscous distillate (230 mg.) and a non-volatile residue, which was not examined. The distillate, when rubbed with methanol, gave a solid, which was separated, by repeated crystallisation from methanol, into two main fractions : (i) a small quantity of deaminocolchinol methyl ether (XII), m. p. and mixed m. p. 109—111° (micro-hydrogenation with palladium-black gave 1·01 double bonds), and (ii) *isodeaminocolchinol methyl ether* (XIII), isolated in larger amount, m. p. 100—101°, depressed to 80—85° by admixture with (XII) (Found : C, 73·2; H, 6·3; double bond, by micro-hydrogenation with palladium-black, 0·93. $C_{19}H_{20}O_4$ requires C, 73·1; H, 6·4%). The presence of a third compound was established in the course of this fractional crystallisation. It was responsible for the cloudiness of the melts (*ca.* 100°) observed with several intermediate fractions, and eventually a few crystals, micro-m. p. 167—169°, were obtained, but the amount was insufficient for further examination.

(*b*) A mixture of the carbinol (200 mg.), m. p. 116°, and powdered potassium hydrogen sulphate (500 mg.) was heated for 1¾ hours in an oil-bath at 170—180°, in a slow stream of dry carbon dioxide. The cooled mass was extracted with water and ether, leaving a small amount of white residue. This was soluble in benzene, but very sparingly soluble in methanol or *cyclo*hexane. Its mode of formation is uncertain, as the ether used for extraction was subsequently found to contain an appreciable amount of peroxide. This product, m. p. 205—207°, was not examined further. The resin obtained from the above ethereal extract was distilled in a vacuum. The distillate yielded a solid when rubbed and warmed with methanol, and fractional crystallisation gave deaminocolchinol methyl ether, m. p. and mixed m. p. 109—110°, as the chief constituent. The methanol mother-liquors deposited a second fraction from which, by recrystallisation, there was obtained a mixture in which individual crystals appeared to be the *iso*-compound (XIII) (micro-m. p. and mixed m. p. 91—95°), while other crystals (micro-m. p. 131—143°) appeared to contain the high-melting solid mentioned in the preceding paragraph.

9 : 12 : 13 : 14-*Tetramethoxy*-3 : 4 : 5 : 6-*dibenz*-$\Delta^{3:5}$-cyclo*heptadiene*.—(*a*) Deaminocolchinol methyl ether (XII) (150 mg.) was hydrogenated by means of palladium-black in acetic acid at room temperature and pressure, hydrogen

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* Micro-melting points were determined by observing a crystal on an electrically heated microscope stage (H. Meyer, "Analyse und Konstitutionsermittlung organischer Verbindungen," Vienna, 1938, p. 86).

absorption (1·1 mols.) ceasing after an hour. The solvent was distilled under reduced pressure from the filtered solution; the residual *dihydride* crystallised in clusters of prisms (from methanol), m. p. 97° (Found: C, 72·7; H, 7·0. $C_{19}H_{22}O_4$ requires C, 72·6; H, 7·0%). (*b*) Micro-hydrogenation of *iso*deaminocolchinol methyl ether (XIII) under similar conditions gave the same dihydride, m. p. and mixed m. p. 96—97°.

The dihydride was recovered unchanged after being heated at 250—290° for 3 hours with palladium-black in a slow stream of carbon dioxide (under which conditions 9 : 10-dihydrophenanthrene gave phenanthrene in high yield) and also after being heated with selenium for 18 hours in open or evacuated sealed tubes at temperatures between 260° and 305°.

Oxidation of Deaminocolchinol Methyl Ether.—(a) *With sodium dichromate.* In view of the possibility that the compound was a fluorene derivative a quantity of oxidising agent insufficient for complete quinone formation was at first used. A solution of the compound (300 mg.) in acetic acid (0·6 c.c.) was treated with a solution of sodium dichromate (400 mg.) in water (0·15 c.c.) and acetic acid (0·5 c.c.), and the whole was heated at 100° for ½ hour. After dilution with water a chloroform extract of the mixture was washed with aqueous sodium carbonate and evaporated. The residual gum was warmed and rubbed with methanol, and the quinone, which crystallised in part, was collected. The mother-liquor was evaporated, and the residue dissolved in benzene–ligroin (1 : 3) and passed through a column of alumina, where separation occurred into a red upper band and a lower region of general adsorption. These were separately eluted, benzene alone ultimately being used as the solvent. The red eluate furnished some quinone, a further quantity being obtained from the yellow eluate after renewed oxidation and separation on alumina. The pale yellow gum which was the other product of this second chromatographic separation was worked up as described below. The combined quinone fraction crystallised from acetic acid in the two forms, m. p. 193°, and did not depress the m. p. of synthetic 2 : 3 : 4 : 7-tetramethoxyphenanthraquinone (II). The corresponding diazines also were identical, m. p. and mixed m. p. 175—176°, rising to 185° on remelting.

The aforesaid pale yellow gum set to a glass on standing. When warmed and rubbed with methanol, this yielded a small amount of a solid, which, after several recrystallisations from methanol, formed cream-coloured needles, m. p. 109—111° (Found: C, 69·45; H, 5·5. $C_{19}H_{18}O_5$ requires C, 69·9; H, 5·5%). This compound was probably 9 : 12 : 13 : 14-*tetramethoxy*-3 : 4 : 5 : 6-*dibenz*-$\Delta^{1:3:5}$-cyclo*heptatrien*-7-*one*, but because of the small quantity available no derivative was prepared. It was insoluble in alkali, gave an immediate red precipitate with 2 : 4-dinitrophenylhydrazine in ethanol–sulphuric acid, and dissolved in concentrated hydrochloric acid to an orange-red solution.

(b) *With osmium tetroxide.* A solution of deaminocolchinol methyl ether (100 mg.) in dry ether (5 c.c.) was treated with osmium tetroxide (90 mg.) in ether (5 c.c.). After 4 days, the ether was evaporated, and the residual black powder heated under reflux for 2½ hours with a solution of hydrated sodium sulphite (0·9 g.) in water (10 c.c.) and methanol (20 c.c.). Undissolved solid was collected, extracted twice with boiling methanol, and the combined filtrate and extract boiled with charcoal and evaporated under reduced pressure. The residue was treated with water, and the suspension extracted with ether. Evaporation of the ether gave cis-1 : 2-*dihydroxy*-9 : 12 : 13 : 14-*tetramethoxy*-3 : 4 : 5 : 6-*dibenz*-$\Delta^{3:5}$-cyclo*heptadiene* as colourless slender rods (from aqueous methanol), m. p. 165—166° (Found: C, 66·0; H, 5·9. $C_{19}H_{22}O_6$ requires C, 65·9; H, 6·4%).

2 : 3 : 4 : 7-*Tetramethoxy*-10-*phenanthraldehyde* (XI).—Lead tetra-acetate (80 mg.) was added portionwise, with shaking and exclusion of moisture, to a solution of the aforesaid *cis*-glycol (60 mg.) in dry benzene (12 c.c.), maintained at 40°. The mixture was heated to boiling and then set aside for an hour at room temperature. After filtration, the benzene solution was washed with water, dried, and evaporated. A solution of the resulting gum in methanol very slowly deposited (2 days) a few crystals of the *aldehyde* (XI), but subsequent experience showed that addition of a trace of sodium carbonate to the warm solution caused immediate crystallisation of the aldehyde (73% yield). It formed a mass of bright yellow needles, m. p. 130—131°, depressed to 100—110° by admixture with 2 : 3 : 4 : 7-tetramethoxy-9-phenanthraldehyde (Found: C, 69·7; H, 5·9. $C_{19}H_{18}O_5$ requires C, 69·9; H, 5·5%), and gave an *oxime*, m. p. 169—170°, depressed to *ca.* 140° by admixture with the oxime of the 9-aldehyde (below) (Found: C, 66·8; H, 5·3; N, 4·6. $C_{19}H_{19}O_5N$ requires C, 66·85; H, 5·6; N, 4·1%).

A solution of the aldehyde (XI) (18 mg.) in purified acetone (1 c.c.) was oxidised at 50—60° by addition of a 6% solution of potassium permanganate in acetone (0·1 c.c.). After the mixture had been kept overnight at room temperature, sulphurous acid was added, and the whole extracted with chloroform. The acidic product was separated from unchanged aldehyde (12 mg. recovered) by extraction with sodium carbonate solution; the precipitated acid formed pale yellow needles (from dilute ethanol), micro-m. p. 198—201°, not depressed by admixture with a synthetic specimen of 2 : 3 : 4 : 7-tetramethoxyphenanthrene-10-carboxylic acid (I). Ethereal diazomethane gave the corresponding methyl ester, micro-m. p. and mixed m. p. 101—103°.

Action of Nitrosyl Chloride on Deaminocolchinol Methyl Ether.—Attempts were made to effect addition of nitrosyl chloride to the double bond, with a view to subsequent elimination of hydrogen chloride and production of the oxime of the corresponding unsaturated ketone. When deaminocolchinol methyl ether was treated with amyl nitrite and hydrogen chloride in acetic acid at −15°, it did not react and was recovered. Reaction took place by addition of excess of a solution of nitrosyl chloride in ether to an ethereal solution of the unsaturated compound at −15° to −20°. The crystalline *product* separated from methanol as a yellow powder, micro-m. p. 136—143° (Found: C, 52·9; H, 4·4%). This substance was heated with pyridine on the water-bath, and the product distilled from a bath at 180—210°/0·2 mm. The resulting yellow prisms had m. p. 174—175° (from methanol). It was evident from the analytical figures that nitrosyl chloride had effected chlorination in addition to possible addition to the double bond, and the *compound* obtained with pyridine was not further investigated (Found: C, 58·9; H, 5·1; N, 3·9; Cl, 9·6%).

Oxidation of iso*Deaminocolchinol Methyl Ether.*—A slightly impure specimen of the *iso*-compound (XIII) (34 mg.), m. p. 93—99°, was oxidised as described above, with osmium tetroxide in ether. The crude product was crystallised from methanol and a crystal examined had micro-m. p. 162—168°, depressed to 140—160° by admixture with the diol formed from (XII). The crystallised product, together with that recovered from the mother-liquor, was oxidised with lead tetra-acetate in the manner described. The resulting gummy aldehyde crystallised from methanol in presence of a trace of sodium carbonate, and had micro-m. p. 129—133°, raised to 130—134° by admixture with 2 : 3 : 4 : 7-tetramethoxy-9-phenanthraldehyde (aldehyde-A of Part IV), and depressed to 112—116° by admixture with the 10-aldehyde (XI). It gave an *oxime*, micro-m. p. 166—169°, not depressed by a specimen, m. p. 169—170°, prepared from the synthetic 9-aldehyde (Found: C, 67·1; H, 5·3; N, 4·5. $C_{19}H_{19}O_5N$ requires C, 66·85; H, 5·6; N, 4·1%).

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