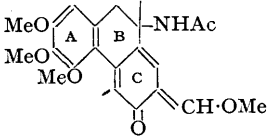
87. *Colchicine and Related Compounds. Part IV. Synthesis of* 2 : 3 : 4 : 5-, 2 : 3 : 4 : 6-, *and* 2 : 3 : 4 : 7-*Tetramethoxy*-9-*methylphenanthrenes.*

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

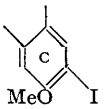
The three compounds named in the title have been synthesised, by the Pschorr method, from 2-nitro-3 : 4 : 5-trimethoxybenzaldehyde and *m*- and *p*-methoxyphenylacetic acids. The tetramethoxyphenanthrene-9-carboxylic acids, which were the primary products, were reduced to the 9-*aldehydes* and thence 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.)



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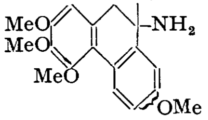

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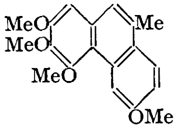

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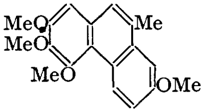
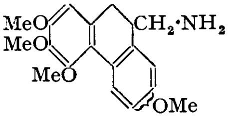


(V.)



(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).

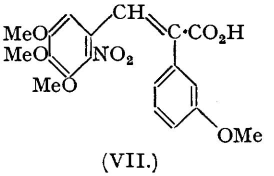
Clearly, the synthesis of 2 : 3 : 4 : 6- and 2 : 3 : 4 : 7-tetramethoxy-9-methylphenanthrene is important since, by identification of one of these synthetic compounds with deaminocolchinol methyl ether, not only would the methoxylation pattern be established, but extensive confirmation would be afforded 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.*,

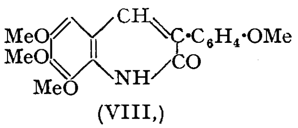
$$R{\cdot}CO_2H \longrightarrow R{\cdot}CO_2Me \longrightarrow R{\cdot}CO{\cdot}NH{\cdot}NH_2 \longrightarrow R{\cdot}CO{\cdot}NH{\cdot}NH{\cdot}SO_2Ph \longrightarrow R{\cdot}CHO$$

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.

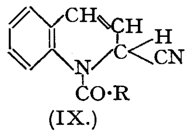
Condensation of 2-nitro-3 : 4 : 5-trimethoxybenzaldehyde with sodium *m*-methoxyphenylacetate gave a mixture of stereoisomerides consisting chiefly of the required cis-*compound* (VII) together with a small percentage of the trans-*isomeride*. On reduction, the latter readily underwent ring-closure to 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

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* (*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.

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