

Colchicine and Related Compounds. Part XIII.*

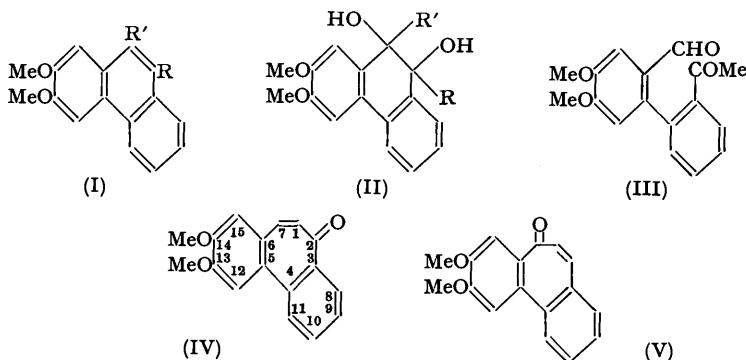
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By the methods developed in Part XI, 13 : 14-dimethoxy-3 : 4-5 : 6-dibenzocyclohepta-3 : 5 : 7-trien-2-one (IV) and -1 : 3 : 5-trien-7-one (V) were synthesised *via* 2 : 3-dimethoxy-9- and -10-methylphenanthrene respectively. The trienes were converted into 2- and 7-acetamido-13 : 14-dimethoxy-3 : 4-5 : 6-dibenzocyclohepta-3 : 5-dienes, (VI) and (VII), and the deamination of these compounds was examined.

In Part XI (Cook, Jack, Loudon, Buchanan, and MacMillan, *J.*, 1951, 1397) a method was described for the synthesis of dibenzocycloheptatrienones from 9- or 10-methylphenanthrenes and was there applied to the synthesis of colchicol methyl ether. The same method has now been used to expand the central rings of 2 : 3-dimethoxy-9- and -10-methylphenanthrene, and some transformations of the resultant dibenzocycloheptatrienones are also described.

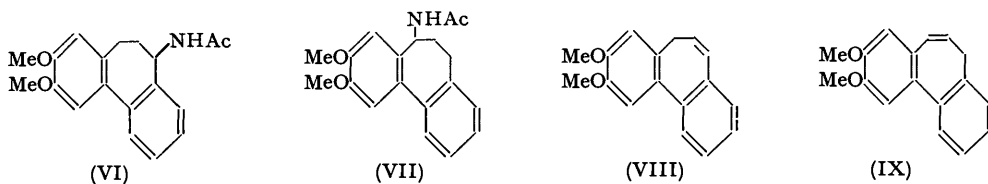
2 : 3-Dimethoxy- (Pschorr and Buckow, *Ber.*, 1900, 33, 1829) and 6 : 7-dimethoxy-9-phenanthroic acid (Pschorr and Treidel, *Annalen*, 1912, 391, 38) are known but the poor yield of the latter acid—due to incomplete elimination of nitrogen at the diazo-stage of the Pschorr synthesis—led to its preparation by Hewett's method (*J.*, 1940, 295), fusion of 2-chloro- α -(3 : 4-dimethoxyphenyl)cinnamic acid with alkali. The phenanthroic acids were reduced *via* their phenylsulphonylhydrazides to the corresponding phenanthraldehydes and hence to the methylphenanthrenes (I; R = Me, R' = H; and R = H, R' = Me). Hydroxylation of these methylphenanthrenes by osmium tetroxide in pyridine yielded the *cis*-diols (II; R = Me, R' = H; and R = H, R' = Me) which were oxidised by lead tetra-acetate. Of the two keto-aldehydes so produced, only one, (III), was obtained crystalline but, in each case, cyclisation by hydrogen chloride in acetic acid afforded the appropriate dibenzocycloheptatrienone (IV) or (V). Each of these trienones, when oxidised by sodium dichromate in acetic acid, yielded 2 : 3-dimethoxyphenanthraquinone which was also obtained by similar oxidation of 2 : 3-dimethoxy-9-phenanthroic acid.



By hydrogenating the oximes of (IV) and (V) over Adams's catalyst in presence of acetic anhydride the 2-acetamido-13 : 14- and -9 : 10-dimethoxydibenzocycloheptadienes (VI) and (VII) were respectively prepared. These two compounds are analogues of *N*-acetylcolchicol methyl ether which, when heated with phosphoric oxide in xylene, yields deamino- and *isodeamino*-colchicol methyl ethers, the elements of acetamide being eliminated (Part V, Barton, Cook, and Loudon, *J.*, 1945, 176). It was hoped to study this elimination reaction as applied to (VI) and (VII) and, more particularly, to investigate the possible interconversion of the expected products (VIII) and (IX). Unfortunately

* Part XII, *J.*, 1952, 607.

the nature of these products restricted the realisation of the project. Compound (VIII) was readily obtained from (VI) and its structure was established by hydroxylation of the ethylenic bond, followed by scission with lead tetra-acetate and incidental cyclisation to 6:7-dimethoxy-9-phenanthraldehyde. As derivatives of (VIII) the dihydro-derivative and dibromide were prepared. However, attempts to prepare (IX) from (VII), of which only a small quantity was available, gave less definite results although ultimately a



crystalline product was obtained. This had a constant m. p. which was lower than that of (VIII) but was not depressed on admixture of the two compounds. Similar low-melting material was encountered as by-product in the preparation of (VIII) from (VI) and was also produced when (VIII) was heated with potassium *tert.*-butoxide in the corresponding alcohol. Although it was shown—by conversion into 2:3-dimethoxy-9-phenanthraldehyde—that samples of this material certainly contained the triene (IX), yet the homogeneity of the material remained in doubt and, in view of the equivocal melting behaviour, the inquiry was discontinued.

EXPERIMENTAL

2:3-Dimethoxy-9-phenanthroic Acid.—4:5-Dimethoxy-2-nitro- α -phenylcinnamic acid, m. p. 219° from ethanol, was prepared as described by Pschorr and Buckow (*Ber.*, 1900, **33**, 1829) from sodium phenylacetate and 4:5-dimethoxy-2-nitrobenzaldehyde (Marr and Bogert, *J. Amer. Chem. Soc.*, 1935, **57**, 1329). On reduction by ferrous sulphate in ammonia it afforded the corresponding amino-compound which was isolated and diazotised as the sparingly soluble sulphate. The filtered diazonium solution was neutralised with sodium carbonate and heated at 50–60° until a coupling test was negative. A purified sample of the acid (which was recovered by cooling and acidification) had m. p. 267° (from ethanol), but the bulk was directly esterified with methanol-sulphuric acid, affording *methyl 2:3-dimethoxy-9-phenanthroate* as colourless cubes, (micro-)m. p. 137° after repeated crystallisation from methanol (charcoal) (Found: C, 72.9; H, 5.2. $C_{18}H_{16}O_4$ requires C, 73.0; H, 5.4%). Hydrolysis regenerated the acid, m. p. 267°; Pschorr and Buckow (*loc. cit.*) give m. p. 270°.

2:3-Dimethoxy-9-phenanthraldehyde.—The foregoing methyl ester (20 g.) when heated for 5 hr. with hydrazine hydrate (80 c.c., 90%) in ethanol (200 c.c.) afforded the *hydrazide* as needles, m. p. 249° (from ethanol) (Found: N, 9.2. $C_{17}H_{16}O_3N_2$ requires N, 9.4%), and this was converted by benzenesulphonyl chloride in pyridine into the *phenylsulphonhydrazide*, m. p. 243° (from acetic acid) (Found: N, 6.55. $C_{23}H_{20}O_5N_2S$ requires N, 6.4%). A solution of the sulphonhydrazide (10 g.) in ethylene glycol (145 c.c.) at 180° was treated with anhydrous sodium carbonate (6.5 g.) and, after 80 seconds, boiling water was carefully added. The resultant solid gave **2:3-dimethoxy-9-phenanthraldehyde** as pale yellow needles, m. p. 135–136°, from methanol (charcoal) (Found: C, 76.7; H, 5.7. $C_{17}H_{14}O_3$ requires C, 76.7; H, 5.6%).

2:3-Dimethoxy-9-methylphenanthrene.—The preceding aldehyde (1.1 g.) and hydrazine hydrate (4 c.c.; 99%) were heated together in ethanol (40 c.c.) for 2½ hr. The solid obtained by removal of the solvent gave an effervescent melt with powdered potassium hydroxide (2 g.) at 125–130° at which temperature the whole was kept for 10 min. before water was added. **2:3-Dimethoxy-9-methylphenanthrene** was collected and, after purification in benzene on alumina, had m. p. 130–131° (from benzene) (Found: C, 80.9; H, 6.7. $C_{17}H_{16}O_2$ requires C, 80.9; H, 6.4%).

2-Amino- α -(3:4-dimethoxyphenyl)cinnamic acid, m. p. 173°, was prepared as described by Pschorr and Treidel (*loc. cit.*) (Found: C, 68.35; H, 5.9; N, 5.1. Calc. for $C_{17}H_{17}O_4N$: C, 68.2; H, 5.7; N, 4.7%) but attempts, as there described or by modified procedures, to convert it into 6:7-dimethoxy-9-phenanthroic acid invariably produced an unidentified

substance, as colourless crystals, m. p. 180—181° (from methanol), soluble in hot alkali (Found : C, 67.8; H, 5.5; N, 8.9%).

2-Chloro- α -(3 : 4-dimethoxyphenyl)cinnamic Acid.—Sodium β -(3 : 4-dimethoxyphenyl)acetate (5 g.; dried at 130°), *o*-chlorobenzaldehyde (2.9 g.), and acetic anhydride (35 c.c.) were heated together at 100—110° for 24 hr. and the whole was then added to water. After 18 hr. the solid was collected, separated from tar by dissolution in aqueous sodium carbonate, and recovered by acidification. 2-Chloro- α -(3 : 4-dimethoxyphenyl)cinnamic acid had m. p. 127—128° (from aqueous acetic acid; charcoal) (Found : C, 63.8; H, 5.0. C₁₇H₁₅O₄Cl requires C, 64.0; H, 4.7%).

6 : 7-Dimethoxy-9-phenanthroic Acid.—The preceding acid (1 g.) was stirred into fused potassium hydroxide (5 g.) at 260—265°. A vigorous reaction ensued and stirring was continued for 10 min. Much of the lower hydroxide layer was then separated from the dark upper layer which was then cooled and dissolved in water. The alkaline solution was shaken with methyl sulphate at 60°, set aside at room temperature overnight, and finally heated at 100°. The cooled, clarified (charcoal) solution was acidified and the precipitate was dissolved in aqueous sodium carbonate (charcoal) and re-precipitated, affording 6 : 7-dimethoxy-9-phenanthroic acid as colourless needles, m. p. 252°, from aqueous ethanol (Found : C, 72.2; H, 5.3. Calc. for C₁₇H₁₄O₄ : C, 72.3; H, 5.0%) (Pschorr and Treidel, *loc. cit.*, give m. p. 254°). Esterification of the crude acid with methanol-sulphuric acid gave the methyl ester which, after recovery and distillation *in vacuo*, formed needles, m. p. 115—116°, from methanol (Found : C, 72.8; H, 5.3. C₁₈H₁₆O₄ requires C, 73.0; H, 5.4%).

6 : 7-Dimethoxy-9-phenanthraldehyde was prepared, essentially as described for its isomer, from the foregoing methyl ester through the *hydrazide*, m. p. 216—217° (from ethanol) (Found : N, 9.9%), and *phenylsulphonhydrazide*, m. p. 215—216° (from acetic acid) (Found : N, 6.5%). It formed pale-yellow needles, m. p. 172°, from methanol-chloroform (Found : C, 76.9; H, 5.7%).

2 : 3-Dimethoxy-10-methylphenanthrene, prepared and purified as in the isomeric series, had m. p. 137—138° (from benzene), depressed to m. p. 112—114° on admixture with the 9-methyl isomer (Found : C, 80.9; H, 6.1%).

2 : 3-Dimethoxyphenanthraquinone.—Solutions of purified 2 : 3-dimethoxy-9-phenanthroic acid in boiling acetic acid (30 c.c.) and sodium dichromate (1.8 g.) in water (1 c.c.)-acetic acid (5 c.c.) were mixed, heated under reflux for 1½ hr., and diluted with water (200 c.c.). The solution was extracted with chloroform, and the extract was washed with dilute sulphuric acid, then with aqueous sodium carbonate (which removed some organic acid), dried, and concentrated. The quinone crystallised from benzene as red-violet needles, m. p. 301—302° (Found : C, 71.4; H, 4.6. C₁₆H₁₂O₄ requires C, 71.6; H, 4.5%), and with *o*-phenylenediamine formed a *diazine*, lemon-yellow needles, m. p. 225—226° (from methanol) (Found : C, 77.65; H, 4.4; N, 8.4. C₂₂H₁₆O₂N₂ requires C, 77.6; H, 4.7; N, 8.2%).

cis-9 : 10-Dihydro-9 : 10-dihydroxy-2 : 3-dimethoxy-9-methylphenanthrene.—Anhydrous pyridine (12 c.c.) was added to a solution of 2 : 3-dimethoxy-9-methylphenanthrene (10 g.) and osmium tetroxide (15 g.) in dry, thiophen-free benzene (75 c.c.). After 9 days, the precipitate was collected, dissolved in chloroform (250 c.c.), and shaken (2½ hr.) with a solution of mannitol (300 g.) and potassium hydroxide (12 g.) in water (1500 c.c.). The *cis-diol*, recovered as a gum from the washed and dried chloroform layer, crystallised as needles (10.2 g.), m. p. 179—180°, from aqueous methanol (Found : C, 71.1; H, 6.4. C₁₇H₁₈O₄ requires C, 71.3; H, 6.3%).

13 : 14-Dimethoxy-3 : 4-5 : 6-dibenzocyclohepta-3 : 5 : 7-trien-2-one (IV).—Lead tetraacetate (0.42 g.) was added to a solution of the preceding diol (0.2 g.) in dry benzene (50 c.c.) and the mixture shaken for 2½ hr. and then heated under reflux for ½ hr. The filtered, water-washed, and concentrated (40—50°) benzene solution afforded 2'-acetyl-2-formyl-4 : 5-dimethoxy-diphenyl (III) as colourless needles, m. p. 88—89° (from aqueous methanol) (Found : C, 71.7; H, 5.6. C₁₇H₁₆O₄ requires C, 71.8; H, 5.6%) [*dioxime*, m. p. 182—183°, from aqueous methanol (Found : N, 8.7. C₁₇H₁₆O₄N₂ requires N, 8.9%)]. When a solution of the keto-aldehyde in acetic acid was saturated with hydrogen chloride it became red and, after 16 hr., dilution with water gave the *trienone* (IV) as colourless needles, m. p. 119° [from benzene-light petroleum (b. p. 40—60°)] (Found : C, 76.7; H, 5.5. C₁₇H₁₄O₃ requires C, 76.7; H, 5.3%). It formed an *oxime*, m. p. 192—193°, from methanol (Found : C, 72.6; H, 5.0; N, 5.2. C₁₇H₁₅O₃N requires C, 72.6; H, 5.3; N, 5.0%), and when oxidised with sodium dichromate in acetic acid gave 2 : 3-dimethoxyphenanthraquinone, m. p. and mixed m. p. 301—302°.

2-Acetamido-13 : 14-dimethoxy-3 : 4-5 : 6-dibenzocyclohepta-3 : 5-diene (VI).—When the oxime

of (IV) (0.7 g.) was hydrogenated in acetic anhydride (30 c.c.) in presence of Adams's catalyst absorption was complete in 3 hr. The *acetamido*-compound (VI) was recovered by concentration of the filtered solution *in vacuo* and formed colourless needles, m. p. 260—261°, from aqueous methanol (Found: C, 73.3; H, 6.2; N, 4.5. $C_{19}H_{21}O_3N$ requires C, 73.3; H, 6.7; N, 4.5%).

Deaminations.—In these experiments the need for xylene of good quality became apparent from the results attending the use of an inferior grade which presumably contained styrene-like impurities. When heated with phosphoric oxide alone this impure xylene gave a high-melting solid and its use in deamination reactions gave persistently gummy products. It (10 parts) was purified by being shaken (4 hr.) with concentrated sulphuric acid (1 pt. by wt.), washed, dried, distilled, and stored over phosphoric oxide.

13 : 14-*Dimethoxy*-3 : 4 : 5 : 6-*dibenzocyclohepta*-1 : 3 : 5-*triene* (VIII).—Phosphoric oxide (0.2 g.) was added to a solution of (VI) (0.1 g.) in purified xylene (12 c.c.), and the mixture heated under reflux for 25 min. The decanted solution, combined with xylene washings of the phosphoric residue, was washed with aqueous sodium carbonate, dried, and concentrated *in vacuo*. The resultant gum solidified when rubbed with methanol [for these methanol washings see under (IX)]. After chromatography (benzene—alumina) the solid gave the *triene* (VIII) as needles, m. p. 118—119°, from methanol (Found: C, 80.75; H, 6.6. $C_{17}H_{16}O_2$ requires C, 80.8; H, 6.4%. Microhydrogenation with palladium in acetic acid gave 0.97 double bond). With bromine in chloroform the triene formed a *dibromide* which crystallised from methanol as a mixture of platelets, (micro-)m. p. 138—142°, and needles, (micro-)m. p. 158—161° (Found for the mixture: C, 50.0; H, 3.9. $C_{17}H_{16}O_2Br_2$ requires C, 49.6; H, 3.9%).

13 : 14-*Dimethoxy*-3 : 4 : 5 : 6-*dibenzocyclohepta*-3 : 5-*diene* was obtained as plates, (micro-)m. p. 73—75°, from aqueous acetic acid, when the triene (VIII) was hydrogenated over palladium in acetic acid (Found: C, 80.1; H, 7.5. $C_{17}H_{18}O_2$ requires C, 80.3; H, 7.1%).

Structural Proof of (VIII).—Solutions of the triene (0.05 g.) and osmium tetroxide (0.06 g.) in ether (5 c.c. each) were mixed and, after 4 days, evaporated. The residual powder was heated under reflux for 2½ hr. with a solution of sodium sulphite (0.7 g. of hydrate) in water (10 c.c.) and methanol (15 c.c.), and the mixture was filtered. The combined filtrate and methanol washings were concentrated *in vacuo*, and the concentrates diluted with water and extracted in ether. 1 : 2-*Dihydroxy*-13 : 14-*dimethoxy*-3 : 4 : 5 : 6-*dibenzocyclohepta*-3 : 5-*diene* was recovered and formed colourless needles, (micro-)m. p. 166—167°, from aqueous methanol (Found: C, 71.4; H, 6.5. $C_{17}H_{18}O_4$ requires C, 71.3; H, 6.3%). To a solution of this diol (0.03 g.) in dry benzene (10 c.c.) maintained at 40° lead tetra-acetate (0.05 g.) was added portionwise with shaking and exclusion of moisture. The mixture was heated to boiling, then set aside for 1 hr. at room temperature, and the filtered benzene solution was washed with water, dried, and evaporated. A solution of the resultant gum in warm methanol was treated with a trace of sodium carbonate, whereupon 6 : 7-*dimethoxy*-9-*phenanthraldehyde*, m. p. and mixed m. p. 171—172°, crystallised.

The preparative details in the following cases closely resemble those given for isomeric compounds. *cis*-9 : 10-*Dihydro*-9 : 10-*dihydroxy*-2 : 3-*dimethoxy*-10-*methylphenanthrene*, m. p. 120—121° (from aqueous methanol), was prepared by hydroxylation of 2 : 3-*dimethoxy*-10-*methylphenanthrene* (Found: C, 71.3; H, 6.0%). In boiling organic solvents it showed a marked tendency to dehydration, forming 9-*hydroxy*-2 : 3-*dimethoxy*-10-*methylphenanthrene*, m. p. 184—185° (from methanol) (Found: C, 76.0; H, 5.8. $C_{17}H_{16}O_3$ requires C, 76.0; H, 6.0%), but was oxidised by lead tetra-acetate to a gummy keto-aldehyde which cyclised when treated with hydrogen chloride in acetic acid, affording 9 : 10-*dimethoxy*-3 : 4 : 5 : 6-*dibenzocyclohepta*-1 : 3 : 5-*trien-2-one* (V) as needles, m. p. 149—150°, from benzene-light petroleum (b. p. 40—60°) (Found: C, 76.8; H, 5.5%). This trienone was oxidised to 2 : 3-*dimethoxyphenanthraquinone*. The *oxime* of the trienone, m. p. 179—180° (from benzene) (Found: N, 4.9%), was hydrogenated in acetic anhydride, forming 2-*acetamido*-9 : 10-*dimethoxy*-3 : 4 : 5 : 6-*dibenzocyclohepta*-3 : 5-*diene* (VII) as needles, m. p. 162—163° (Found: C, 73.2; H, 6.5; N, 4.5%).

Experiments Relating to 13 : 14-Dimethoxy-3 : 4 : 5 : 6-dibenzocyclohepta-3 : 5 : 7-triene (IX).—

(a) Deamination of (VII) with phosphoric oxide in purified xylene, as described in the preparation of (VIII), gave a gum which solidified when rubbed with methanol. After chromatography in benzene on alumina, the solid formed platelets, (micro-)m. p. 90—92°, from methanol. This m. p. was unchanged by repeated crystallisation from methanol, or by admixture with (VIII), although crystals of the latter survived in the melt until *ca.* 102°. Insufficient of the substance was available for analysis but microhydrogenation afforded the dihydro-derivative, (micro-)m. p. 73—75°, unaffected by admixture with an authentic sample.

(b) The methanol washings from the preparation of (VIII) gave a solid which, after recrystallisation from methanol, had (micro-)m. p. 90—93° unchanged by admixture with the product from (a) and repeating its behaviour on admixture with (VIII).

(c) The gum obtained by deaminating (VII) in impure xylene was oxidised (i) with sodium dichromate in acetic acid whereupon 2 : 3-dimethoxyphenanthraquinone was produced and identified by mixed m. p., (ii) with osmium tetroxide in ether, the resultant gummy glycol being cleaved by lead tetra-acetate whereupon a crystalline mixture was obtained, (micro-)m. p. 92—104° raised by admixture with 2 : 3-dimethoxy-9-phenanthraldehyde to m. p. 120—125° : individual crystals mechanically separated from the mixture had (micro-)m. p. and mixed (micro-)m. p. with the aldehyde 134—135°.

(d) A solution of (VIII) and potassium *tert.*-butoxide in *tert.*-butyl alcohol was heated under reflux for 10 hr. The recovered solid product was fractionally crystallised from methanol, affording extreme fractions of (micro-)m. p. 96—102° and 93—96° only slightly altered (to intermediate values) by admixture with (VIII) or with the platelets (m. p. 90—92°) from (a).

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