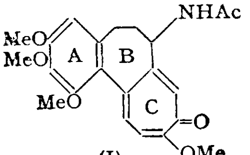
110. *Colchicine and Related Compounds. Part XII.* Some Molecular Rearrangements.*

By J. W. Cook, J. Jack, and J. D. Loudon.

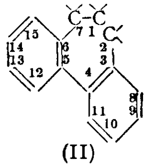
(±)-9 : 12 : 13 : 14-Tetramethoxy-3 : 4-5 : 6-dibenzo*cyclo*hepta-3 : 5-dien-2-ol (V) has now been synthesised and is shown to be structurally distinct from the (—)-carbinol formed by the action of nitrous acid on colchinol methyl ether (III). The latter reaction involves Demjanow rearrangement, accompanied by some racemisation, affording (—)- and (±)-9 : 10-dihydro-9-hydroxymethyl-2 : 3 : 4 : 7-tetramethoxyphenanthrene (VI). The (±)-form of this carbinol has also been synthesised and is shown to revert, on dehydration, to the dibenzo*cyclo*heptatriene type of structure.

The interaction of nitrous acid and (±)-9-aminomethyl-9 : 10-dihydro-2 : 3 : 4 : 7-tetramethoxyphenanthrene (VIII) affords, among other products, deaminocolchinol methyl ether (IV) and 2 : 3 : 4 : 7-tetramethoxy-9-methylphenanthrene.

The structural chemistry of colchicine (I) is complicated by the frequent incidence of molecular rearrangement. This is incurred in the reactions by which ring C becomes benzenoid and is also found at a subsequent stage of degradation wherein contraction of ring B gives rise to derivatives of phenanthrene. Rearrangements of the first type are now recognised as consequences of the tropolone structure present in ring C (for discussion, cf. Cook and Loudon, *Quart. Reviews*, 1951, **5**, 99) : those of the second type appear to reflect a fairly general tendency among derivatives of dibenzo*cyclo*hepta-diene or -triene.



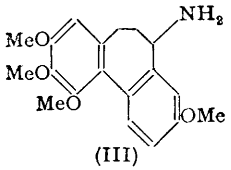
(I)



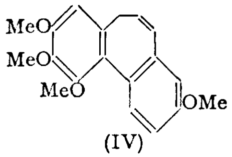
(II)

7 1 2

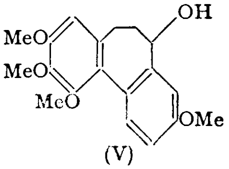
$\cdot CH_2\cdot CH{:}CH\cdot$	(II*a*)
$\cdot CO\cdot CH_2\cdot CH_2\cdot$	(II*b*)
$\cdot CH_2\cdot CO\cdot CH_2\cdot$	(II*c*)
$\cdot CO\cdot CH_2\cdot CH(OH)\cdot$	(II*d*)
$\cdot CO\cdot CH{:}CH\cdot$	(II*e*)



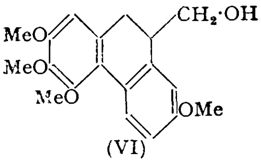
(III)



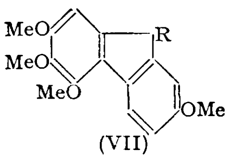
(IV)



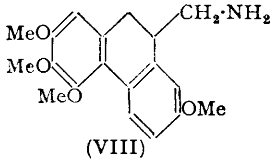
(V)



(VI)



(VII)



(VIII)

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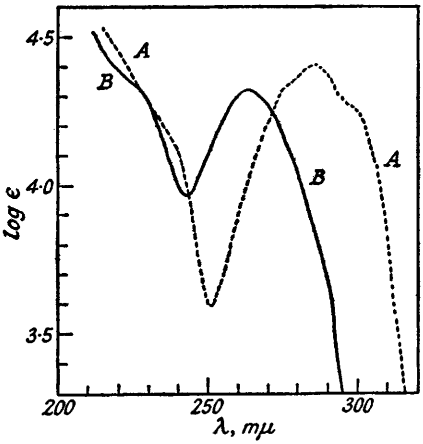
* Part XI, *J.*, 1951, 1397.

The latter tendency is particularly prominent in oxidation reactions and in previous Parts of this series the formation is recorded of appropriate phenanthraquinones from compounds of type (II) comprising the variants (II*a*—*e*) in the three-carbon bridge, with or without methoxyl substituents in the lateral rings [(II*a*), Part V, Barton, Cook, and Loudon, *J.*, 1945, 176, and Part VI, Cook, Dickson, and Loudon, *J.*, 1947, 746; (II*b* and *c*), Part VI, *loc. cit.* : (II*d* and *e*), Part XI, Cook, Jack, and Loudon, *J.*, 1951, 1397]. The course of these oxidation reactions is uncertain but phenanthrene-9-carboxylic acids are occasionally found in the products (cf. Part VI, *loc. cit.*) and are probable intermediates. It is noteworthy that 2 : 3 : 4 : 7-tetramethoxyphenanthraquinone could not be detected in comparable oxidations of *N*-acetylcolchinol methyl ether (III; NHAc for NH_2) or similar compounds (cf. Experimental). On the other hand the hydrochloride of an analogous amine (III; H for each OMe) on thermal decomposition affords 9-methylphenanthrene which is also produced by isomerisation from the hydrocarbon (IV; H for each OMe) (Part VI, *loc. cit.*). This last rearrangement explains the conversion of deaminocolchinol methyl ether (IV) into 9-methylphenanthrene by successive treatment with hydriodic acid and distillation from zinc (cf. Parts V and VI, *locc. cit.*).

It was shown in Part I (Cohen, Cook, and Roe, *J.*, 1940, 194) that the action of nitrous acid on colchinol methyl ether yields a mixture of products from which a carbinol, $C_{19}H_{22}O_5$, of m. p. 115·5—116·5° (now designated carbinol-A) was isolated and purified through its *p*-phenylbenzoate. Carbinol-A was lævorotatory (cf. Part V, *loc. cit.*) and was sometimes accompanied by a difficultly separable isomer, carbinol-B (of highest recorded m. p. 157—160°), which we now find to be optically inactive. At that time the structure of colchinol methyl ether was uncertain and formula (VI) was considered for carbinol-A, but was not proved. Dehydration of carbinol-A was later found to yield a mixture of deaminocolchinol methyl ether (IV) and its bond-isomer, *iso*deaminocolchinol methyl ether, of which the structures were unambiguously proved. This dehydration result, when considered together with the now established structure (III) of colchinol methyl ether (Part XI, *loc. cit.*), would suggest formula (V) as the simplest representation of carbinol-A. Such a conclusion, however, would ignore the shift in ultra-violet absorption spectrum in passing from *N*-acetylcolchinol methyl ether to carbinol-A (Part I, *loc. cit.*). Horowitz, Ullyot, Horning, Horning, Koo, Fish, Parker, and Walker (*J. Amer. Chem. Soc.*, 1950, **72**, 4331) pointed out that the absorption spectra of colchinol methyl ether (III) and its *N*-acetyl derivative are not significantly different from that of the parent deaminodihydrocolchinol methyl ether (III; H for NH_2) and it may be inferred that a similarly close relationship would be maintained in the hydroxy-derivative (V). Accordingly, these authors conclude that a central 7-membered ring cannot be present in carbinol-A and, although they do not propose a formula for this compound, they note that its absorption spectrum resembles that of the fluorene derivatives (VII; R = H and $CH_2{\cdot}CH_2{\cdot}OH$).



A, Carbinol (VI) *in ethanol.*
B, Carbinol (V) *in ethanol.*

In a re-examination of this question the (±)-carbinol (V) was prepared by reduction of the corresponding ketone (Part XI, *loc. cit.*). Its absorption spectrum (see figure) was found to have the expected close relationship to that of *N*-acetylcolchinol methyl ether (III; NHAc for NH_2) (cf. Part I, *loc. cit.*) and to differ from that of (—)-carbinol-A. The latter carbinol, moreover, gave an apple-green solution in concentrated sulphuric acid, whereas (V) dissolved to a red solution. The two carbinols are therefore structurally different.

Since dehydration of (VII; R = $CH_2{\cdot}CH_2{\cdot}OH$) would be expected to produce the corresponding ethylidenefluorene rather than (IV), attention was next directed to the carbinol (VI). This (±)-carbinol was prepared by reduction of methyl 9 : 10-dihydro-2 : 3 : 4 : 7-tetramethoxy-9-phenanthroate (cf. Part VII, Cook, Dickson, Ellis, and Loudon, *J.*, 1949, 1074) with lithium aluminium hydride. Its absorption spectrum (see figure) and colour test with concentrated sulphuric acid were indistinguishable from those of (−)-carbinol-A although the melting points of the two carbinols were distinct. However, in respect of all three criteria carbinol (VI) proved to be identical with (±)-carbinol-B. The conclusion may therefore be drawn that (−)-carbinol-A and (±)-carbinol-B are stereoisomers of structure (VI) and are formed respectively with retention and loss of optical activity through rearrangement from (III) in reaction with nitrous acid. On this basis a further rearrangement, essentially the reverse of the first, must be involved in the dehydration of carbinol-A to a mixture of (IV) and its isomer. Confirmation of this point was accordingly sought by dehydrating carbinol (VI) with phosphoric oxide in boiling xylene. The immediate product was a gum which, in view of the small quantity available, was hydrogenated directly and afforded deaminodihydrocolchinol methyl ether (III; H for NH_2) identical with an authentic sample. These results therefore show that in successive reactions the carbon structure of (III) is rearranged to, and is regenerated from, that of (VI).

The formation of (VI) from (III) is a particular instance of the Demjanow rearrangement, a process which may also be associated with ring-expansion as in the reactions of nitrous acid with certain aminomethyl*cyclo*alkanes (Demjanow, *Chem. Zentr.*, 1903, I, 828; *Ber.*, 1907, **40**, 4961; cf. Nightingale and Maienthal, *J. Amer. Chem. Soc.*, 1950, **72**, 4823). It was therefore of interest to examine the action of nitrous acid on the (±)-amine (VIII) (cf. Part VII, *loc. cit.*). Analogous reactions are known to give rise to complex mixtures of carbinols and olefins (cf. Babier, *Helv. Chim. Acta*, 1940, **23**, 519, 524). In the present case all attempts to isolate a carbinol failed, but the gummy product was separated by chromatography into three crystalline components. Two of these were respectively identified as deaminocolchinol methyl ether (IV) and 2 : 3 : 4 : 7-tetramethoxy-9-methylphenanthrene, of which the former is obviously a product of rearrangement. Analysis of the third compound showed it to be a product of nitration but it was not further investigated.

Finally it may be remarked that the production of deaminocolchinol methyl ether (IV) from (VI), and of its dihydride (III; H for NH_2) from (VIII), constitutes a new synthesis of each of these two degradation products of colchicine. In the light of present experience, however, neither route appears to afford a generally practicable method for the synthesis of dibenzo*cyclo*heptatriene derivatives.

EXPERIMENTAL

Attempted Oxidation of Compounds of Type (III) [With J. MACMILLAN].—(*a*) A solution of *N*-acetylcolchinol methyl ether (0·2 g.) and sodium dichromate (0·45 g.) in acetic acid (0·6 c.c.) and water (1 c.c.) was heated under reflux for 30 minutes. Neutral material was recovered in chloroform and afforded unchanged *N*-acetylcolchinol methyl ether (0·14 g.) of m. p. and mixed m. p. 202—203° from methanol. There was no evidence of the formation of 2 : 3 : 4 : 7-tetramethoxyphenanthraquinone and the concentrated methanol mother-liquor gave no ketonic product when treated with Girard's reagent T.

(*b*) Under similar conditions 1-acetamido-3 : 4-5 : 6-dibenzo*cyclo*hepta-3 : 5-diene (0·2 g.) was recovered (0·14 g.) without detectable formation of phenanthraquinone.

(*c*) 1-Amino-3 : 4-5 : 6-dibenzo*cyclo*hepta-3 : 5-diene—used as the gummy base from the hydrochloride and alkali—when exposed to similar oxidising conditions was partly recovered as the hydrochloride (0·16 g.) but phenanthraquinone formation was not observed.

(±)-9 : 12 : 13 : 14-*Tetramethoxy*-3 : 4-5 : 6-*dibenzo*cyclo*hepta*-3 : 5-*dien*-2-*ol* (V).—A suspension of lithium aluminium hydride (0·1 g.) in ether was added to a solution of 9 : 12 : 13 : 14-tetramethoxy-3 : 4-5 : 6-dibenzo*cyclo*hepta-3 : 5-dien-2-one (0·05 g.) (Part XI, *loc. cit.*) in the same solvent (10 c.c.). The mixture was heated under reflux for 15 minutes and then cautiously treated with dilute sulphuric acid, and the *alcohol* (V) was recovered from the washed and dried ethereal layer. It formed colourless prisms, m. p. 148—150°, from benzene–light petroleum (b. p. 60—80°) (Found: C, 69·1; H, 6·8. $C_{19}H_{22}O_5$ requires C, 69·05; H, 6·7%) and dissolved in cold concentrated sulphuric acid forming a red solution.

Methyl 9 : 10-*Dihydro*-2 : 3 : 4 : 7-*tetramethoxy*-9-*phenanthroate* was prepared by the action of diazomethane on the corresponding acid (Part VII, *loc. cit.*) and had m. p. 123—124° (from methanol) (Found : C, 66·9; H, 6·4. $C_{20}H_{22}O_6$ requires C, 67·0; H, 6·2%). The *amide* was encountered in course of alkaline hydrolysis of the corresponding nitrile (Part VII, *loc. cit.*) and had m. p. 168° (from methanol) (Found : C, 66·25; H, 5·9; N, 4·3. $C_{19}H_{21}O_5N$ requires C, 66·4; H, 6·2; N, 4·1%).

(±)-9 : 10-*Dihydro*-9-*hydroxymethyl*-2 : 3 : 4 : 7-*tetramethoxyphenanthrene* (VI).—A suspension of lithium aluminium hydride (*ca.* 2 g.) in ether was added to a solution of the above ester (0·75 g.) in ether (30 c.c.). The mixture was heated under reflux for 20 minutes, then cautiously treated with dilute sulphuric acid, and the *carbinol* (VI) was recovered from the washed and dried ethereal layer. It formed colourless rods, m. p. 165—166°, from benzene–light petroleum (b. p. 60—80°) (Found : C, 68·8; H, 6·6. $C_{19}H_{22}O_5$ requires C, 69·05; H, 6·7%) and dissolved in cold concentrated sulphuric acid forming an apple-green solution. The p-*phenylbenzoate* was obtained by heating the carbinol (0·1 g.) with *p*-phenylbenzoyl chloride (0·08 g.) in dry pyridine for 1 hour, and formed colourless plates or needles, m. p. 125—126°, from methanol (Found : C, 75·0; H, 5·7. $C_{32}H_{30}O_6$ requires C, 75·3; H, 5·9%).

The main characteristics of the four carbinols are assembled in the following table :

	Carbinol A	Carbinol B *	Carbinol (VI)	Carbinol (V)
M. p.†	115—116°	157—160°	165—166°	148—150°
M. p. of *p*-phenylbenzoate ...	146—147°	108—109 (cloudy melt)	125	—
Colour with conc. H_2SO_4	Apple-green	Apple-green	Apple-green	Red

* Determined on the very small quantity of B available; $[\alpha]_D^{18}$ in chloroform was zero within experimental limits.

† Mixed m. p. of B and (VI), 164—166°. Mixed m. p. of B and (V), *ca.* 140°.

Dehydration of Carbinol (VI).—Phosphoric oxide (1·5 g.) was added to a solution of the carbinol (0·5 g.) in pure xylene, and the whole was heated under reflux for 15 minutes. The hot xylene solution was decanted and the residue was washed with fresh boiling xylene. The combined xylene solutions were concentrated *in vacuo* affording a gum which was distilled up to 160° (air-bath)/2 × 10^{-4} mm. The gummy distillate was hydrogenated in solution in acetic acid (10 c.c.) over palladised charcoal (0·05 g.). From the filtered solution deaminodihydrocolchinol methyl ether was recovered as a gum which crystallised from methanol as small colourless prisms, m. p. and mixed m. p. 94—96°.

9-*Aminomethyl*-9 : 10-*dihydro*-2 : 3 : 4 : 7-*tetramethoxyphenanthrene* (VIII).—The corresponding 9-cyano-compound was hydrogenated as described in Part VII (*loc. cit.*), and the *amine* (VIII) was recovered in ether from the filtered and basified reaction solution. It formed small colourless prisms, m. p. 138—140° (Found : C, 69·8; H, 7·2; N, 4·5. $C_{19}H_{23}O_4N$ requires C, 69·3; H, 7·1; N, 4·25%).

Action of Nitrous Acid on Amine (VIII).—A solution of the amine (0·55 g.) in acetic acid (5 c.c.) was treated with a solution of sodium nitrite (1 g.) in water (10 c.c.). The resulting solution was heated at 100° for ½ hour and the dark oil which separated was recovered and washed in ether. Evaporation of the ethereal solution afforded a gum which was distilled at 200—240° (bath-temp.)/0·2 mm. and yielded a brown resinous distillate (0·47 g.). Attempts to form a solid *p*-phenylbenzoate from this distillate were unsuccessful. A solution of the distillate in benzene was passed through a column of alumina. Elution with benzene—controlled by the colour of the bands and their appearance in ultra-violet light—gave four successive fractions yielding respectively (i) an apparently nitrated *substance* obtained as yellow needles, m. p. 115—116°, from methanol (Found : C, 64·0; H, 5·15; N, 3·8. $C_{19}H_{19}O_6N$ requires C, 63·9; H, 5·4; N, 3·9%), (ii) a yellow uncrystallisable gum, (iii) 2 : 3 : 4 : 7-tetramethoxy-9-methylphenanthrene as colourless prisms, m. p. and mixed m. p. 114—116°, affording the picrate of m. p. and mixed m. p. 145—147°, and (iv) deaminocolchinol methyl ether, m. p. and mixed m. p. 105—110° after repeated crystallisation from methanol.

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