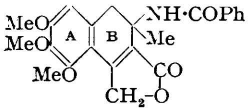
103. *Colchicine and Related Compounds. Part X.*

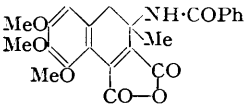
By J. W. Cook, T. Y. Johnston, and J. D. Loudon.

6 : 7 : 8-*Trimethoxy*-3-*methylnaphthalene*-1 : 2-*dicarboxylic acid anhydride* (VII) has been obtained by dehydrogenation of the 3 : 4-*dihydronaphthalene* derivative (VI) which, in turn, has been synthesised from *iso*elemicine and chloromaleic anhydride. *N*-Benzoylcolchinic anhydride, formulated by Windaus as (II), does not behave as a dihydronaphthalene derivative since it has now been deaminated to *deaminocolchinic anhydride* which (*a*) is isomeric, and not identical, with 6 : 7 : 8-trimethoxy-3-methylnaphthalene-1 : 2-dicarboxylic anhydride (VII), and (*b*) has olefinic properties as shown by its susceptibility to hydrogenation with a palladium catalyst. Deaminocolchide also has olefinic properties. Oxidation of colchiceine and of *N*-acetylcolchinol to the same product, namely, N-*acetylcolchinic anhydride*, indicates that the size of ring B is the same in the colchinic acid as in the colchinol series of colchicine degradation products.

According to Windaus (*Annalen*, 1924, **439**, 59) hydronaphthalene derivatives are produced when *N*-benzoyltrimethylcolchicinic acid is oxidised with cold alkaline potassium permanganate. The two main products, namely, *N*-benzoylcolchide and *N*-benzoylcolchinic anhydride, were formulated as (I) and (II), respectively, although minor modification, particularly in the structure (I), was not excluded. This interpretation accounted for the known facts and contributed to the conclusion that ring B of colchicine is six-membered. It has since been established, however, that in another series of degradation products ring B occurs as a seven-membered ring (Barton, Cook, and Loudon, Part V, *J.*, 1945, 176; Buchanan, Cook, Loudon, and MacMillan, *Nature*, 1948, **162**, 692), and in consequence re-examination of the supposed hydronaphthalene structures becomes desirable. It is consistent with the dihydronaphthalene structure (I) that *N*-benzoylcolchide eliminates benzamide during hydrolysis or sublimation (Windaus, *Sitzungsber. Heidelberg. Akad. Wiss.*, Math.-Nat. Kl., *A*, 1911, 2 Abh.). The deaminocolchide so produced was regarded as the " trimethoxyhomonaphthide " (III), and it might be expected on this basis that the corresponding acid anhydride (VII) would be formed either by oxidation of deaminocolchide or by deamination of *N*-benzoylcolchinic anhydride. Accordingly, the *compound* of structure (VII) has been synthesised for reference purposes.



(I.)



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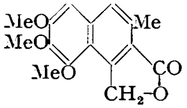
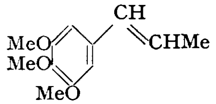


(III.)

Hudson and Robinson (*J.*, 1941, 715) recorded successful condensations of the Diels–Alder type between β-alkylated styrenes and either maleic anhydride or ethyl acetylenedicarboxylate. More recently Synerholm (*J. Amer. Chem. Soc.*, 1945, **67**, 345) reported good results by use of chloromaleic anhydride, which is satisfactorily prepared from chlorofumaric acid (Perkin, *J.*, 1888, **53**, 695) by Walden's method (*Ber.*, 1897, **30**, 2885; cf. von Auwers and Harres, *ibid.*, 1929, **62**, 1686). The diene component for our synthetic work, namely, 3 : 4 : 5-trimethoxypropenylbenzene (IV), is already known as *iso*elemicine and was prepared by Semmler (*Ber.*, 1908, **41**, 2186), who obtained it through isomerisation of elemicine, the naturally occurring 3 : 4 : 5-trimethoxyallylbenzene. Although elemicine may be prepared from the allyl ether of 2 : 6-dimethoxyphenol (Hahn and Wassmuth, *Ber.*, 1934, **67**, 696; Pearl, *J. Amer. Chem. Soc.*, 1948, **70**, 1746) and might therefore be used as a source of *iso*elemicine, we have prepared the latter by dehydrating the carbinol which is produced from 3 : 4 : 5-trimethoxybenzaldehyde and ethylmagnesium bromide.

A preliminary experiment showed that, under the conditions used by Hudson and Robinson, condensation between *iso*elemicine and maleic anhydride was accompanied by much polymerisation although the formation of (V) was indicated by isolation of the corresponding dibasic *acid* from which the *anhydride* itself was obtained on sublimation. The condensation of *iso*elemicine with chloromaleic anhydride was then examined in various solvents, and the *anhydride* (VI) was ultimately obtained in 45—50% yield by heating the reactants in xylene with the addition of quinol to inhibit polymerisation (cf. Norton, *Chem. Reviews*, 1942, **31**, 319). It might be expected from the work of Bergmann (*J. Amer. Chem. Soc.*, 1942, **64**, 176; *J. Org. Chem.*, 1943, **8**, 183) that condensation to the dihydronaphthalene derivative (VI) when conducted in nitrobenzene would be followed by dehydrogenation to the naphthalene derivative (VII), but in practice under these conditions dehydrogenation was not observed. On the other hand, when (VI) was submitted to slow sublimation there occurred disproportionation of hydrogen with formation of (VII) and (V), the latter again being isolated as the dibasic acid;



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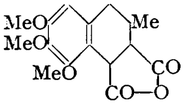
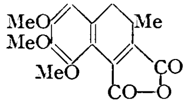
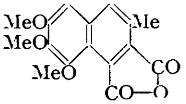


(V.)



(VI.)



(VII.)

moreover, dehydrogenation of (VI) to (VII) was readily effected by heating with palladium in a current of carbon dioxide. In contrast to the tetrahydronaphthalene (V), which is colourless, the anhydrides (VI) and (VII) are yellow and orange respectively. All three anhydrides dissolved in alkali to give colourless solutions from which on acidification the colourless dibasic *acids* corresponding to (V) and (VI) were respectively obtained, but the acid corresponding to

(VII) rapidly reverted to the anhydride and was not analysed. The facility with which anhydrides are obtained from naphthalene-1 : 2-dicarboxylic acids has already been noted by Hudson and Robinson (*loc. cit.*) and our observations are consistent with increasing ease of formation in the order (V) $<$ (VI) $<$ (VII).

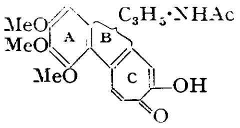
As expected, the naphthalene derivative (VII) was unaffected by exposure to hydrogenation conditions with a palladium catalyst, but under the same conditions an abnormal behaviour was shown by the dihydronaphthalene derivative (VI). This compound, dissolved in acetic acid, rapidly absorbed one mole of hydrogen and then, unexpectedly, slowly absorbed a second mole, the initial yellow colour of the solution being discharged only during the latter stage of absorption. Subsequent isolation of 6 : 7 : 8-trimethoxy-3-methyl-1 : 2 : 3 : 4-tetrahydronaphthalene-1 : 2-dicarboxylic acid in considerable quantity showed that (V) is a major product of the reaction but the nature of the side reaction remains undetermined. The same dicarboxylic acid was formed by reduction of (VI) with zinc and acetic acid.

Part of the colchicine required for degradative work was purchased from Messrs. Ransom (Hitchin, Herts.) as the concentrates of an alcohol extract of *Colchicum* seeds, and the alkaloid was isolated by the procedure of Chemnitius (*J. pr. Chem.*, 1928, **118**, 29) combined with chromatographic purification (cf. Ashley and Harris, *J.*, 1944, 677). The derived *N*-benzoyltrimethylcolchicinic acid was prepared as described by Windaus (*loc. cit.*, **1911**) but attempted repetition of his oxidation experiments on this compound gave much less satisfactory results. Although *N*-benzoylcolchide and *N*-benzoylcolchinic anhydride were both identified, the smallness of the yields severely restricted the scope of further degradative work. Moreover, even under the experimental conditions which are stated (Windaus, *loc. cit.*, **1911**) to afford *N*-benzoylcolchide, the anhydride appeared to be the predominant product. In addition to benzamide, benzoic acid, and probably *N*-benzoylcolchinic acid, which were incidentally isolated, two unidentified oxidation products were obtained in small quantities and have not yet been examined in detail.

Thermal decomposition of *N*-benzoylcolchinic anhydride takes a different course from that described by Windaus for *N*-benzoylcolchide. The latter compound yields benzamide and deaminocolchide whereas it is now found that the anhydride yields benzamide only in traces; the main product of the decomposition is a neutral nitrogenous *substance* to which the provisional formula, $C_{21}H_{19}O_5N$, is assigned pending fuller investigation when an adequate supply of material becomes available. However, when heated with phosphoric oxide in xylene (cf. Cook and Graham, Part III, *J.*, 1944, 322; Cook, Dickson, Ellis, and Loudon, Part VII, *J.*, 1949, 1074), *N*-benzoylcolchinic anhydride yielded *deaminocolchinic anhydride*, and this compound proved to be quite distinct from the synthetic 6 : 7 : 8-trimethoxy-3-methylnaphthalene-1 : 2-dicarboxylic anhydride (VII).

When subjected to quantitative micro-hydrogenation over a palladium catalyst neither *N*-benzoylcolchide nor *N*-benzoylcolchinic anhydride absorbed hydrogen, although the latter compound is already known (Windaus, *loc. cit.*, **1911**) to contain one ethylenic linkage which can be reduced by means of zinc and acetic acid. It may be recalled that in both colchicine and colchiceine, apart from the aromatic ring, there is one double bond which resists catalytic hydrogenation (Bursian, *Ber.*, 1938, **71**, 245) and a similar resistant double bond therefore appears to be maintained in the above degradation products. On the other hand, both deaminocolchide—prepared as described by Windaus (*loc. cit.*, **1911**) by hydrolysis of *N*-benzoylcolchide—and deaminocolchinic anhydride undergo hydrogenation with palladium as catalyst, absorbing one and two moles of hydrogen, respectively. The difference in the extent of hydrogenation is remarkable but, although it was ascertained that in each case a crystalline product results, shortage of material prevented further inquiry. None the less, the fact of hydrogenation under these conditions strongly indicates that the double bond which is produced in each case by deamination does not form part of an aromatic ring. In the same connection it may be noted that *N*-benzoylcolchide is not completely deaminated by six hours' heating with concentrated hydrochloric acid in ethanol. The amine, colchide, is a part-product of the reaction and consequently survives conditions which, if it were correctly formulated as (I; H for COPh), should readily transform it into the aromatic structure (III). These objections to a (hydro)naphthalene structure in the present compounds find their counterparts in objections which led to revision of the (hydro)phenanthrene structure in colchinol derivatives (Cohen, Cook, and Roe, Part I, *J.*, 1940, 194; Part V, *loc. cit.*). They suggest that the size of ring B may not in fact be different in the two sets of colchicine degradation products.

In the series of reactions by which colchiceine is converted into the dibenz*cyclo*heptatriene (XI) there appear to be only two opportunities for rearrangement in the carbon structure of ring B. These opportunities occur (i) dnring the change from colchiceine to *N*-acetylcolchinol (X; R = H), whereby ring C becomes aromatic, and (ii) in the deamination of *N*-acetylcolchinol



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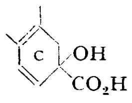

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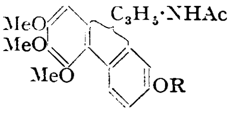
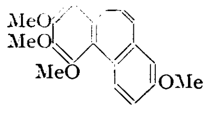


(X.)



(XI.)

methyl ether (X; R = Me) ⟶ (XI). The available evidence makes it rather unlikely that the size of ring B is affected at either stage. In particular, as discussed in Parts I, V, and VII, it is highly improbable that the deamination step involves expansion of a six- to a seven-membered ring. The process by which ring C becomes phenolic is more obscure, but in terms of Dewar's tropolone formula (VIII) for colchiceine (*Nature*, 1945, **155**, 141) the change may proceed through (IX) and ultimately to (X; R = H) without involving ring B. This change, however, is still without analogy among other tropolone compounds, where aromatisation generally leads to a derivative of benzoic acid rather than of phenol. It is of considerable interest, therefore, that by means of alkaline potassium permanganate we have now been able to oxidise both colchiceine and *N*-acetylcolchinol to the same product, namely, *N*-acetylcolchinic anhydride which Windaus (*loc. cit.*, 1911) had already obtained from the first-named source, although he does not record analytical figures. The possibility of molecular rearrangement during the course of these oxidations cannot be excluded. Indeed, the preparation of *N*-acetylcolchinol from colchiceine involves oxidation—by hypoiodite, followed by reduction of the intermediate *N*-acetyliodocolchinol (Windaus, *Sitzungsber. Heidelberg. Akad. Wiss.*, Math.-Nat.Kl., *A*, 1914, 18 Abh.), or by hydrogen, peroxide (Šantzavý, *Chem. Listy*, 1949, **43**, 156)—in an alkaline medium and the course of oxidation with permanganate may well be similar. Even so, unless invalidated by the *renewed* incidence of rearrangement, the conclusion follows that the carbon structure of ring B is the same in colchinol as in colchinic anhydride.

In general, therefore, the results described serve to unify the problems relating to the structure of ring B in the two main series of the alkaloid's degradation products. Questions of detailed structure in individual compounds remain unsettled and to these we hope to devote our attention.

EXPERIMENTAL.

3 : 4 : 5-*Trimethoxyphenylethylcarbinol.*—A solution of 3 : 4 : 5-trimethoxybenzaldehyde (20·3 g.) in anhydrous ether (400 c.c.) was added with cooling and stirring to the Grignard reagent prepared from ethyl bromide (20 g.), magnesium turnings (4·5 g.), and ether (40 c.c.). After 16 hours at 0°, the mixture was treated with a saturated aqueous solution of ammonium chloride. The ethereal layer, combined with ethereal washings of the aqueous layer, was washed with water, concentrated, and shaken with aqueous sodium hydrogen sulphite which removed a little unchanged aldehyde. The carbinol, obtained by evaporating the solvent from the washed and dried ethereal solution, was a viscous, pale yellow liquid (23·15 g.).

iso*Elemicine.*—The carbinol, to which a crystal of iodine had been added, was heated under distillation conditions at diminished pressure and with a tower of sodium hydroxide pellets in the circuit to trap uncondensed vapours. Vigorous effervescence occurred at relatively low temperatures and *iso*elemicine (85—87%) was collected up to 150°/0·4 mm., was redistilled, showing b. p. 110—115°/0·4 mm. (Found : C, 68·9; H, 7·7. Calc. for $C_{12}H_{16}O_3$: C, 69·2; H, 7·7%), and identified as the dibromide, m. p. 92—93° (Found : C, 39·5; H, 4·5. Calc. for $C_{12}H_{16}O_3Br_2$: C, 39·1; H, 4·35%) (Semmler, *loc. cit.*, gives m. p. 89—90°). Prepared in this way, the product was only slightly yellow and was accompanied by a small higher-boiling residue which afforded a second fraction, b. p. 204°/0·4 mm., as a yellow resin with violet fluorescence.

Less satisfactory yields of *iso*elemicine were obtained by heating the carbinol for 30 minutes at 160° with (*a*) dehydrated alum and some crystals of quinol (yield 46%) (cf. Barnett and Lawrence, *J.*, 1935, 1104) or (*b*) potassium hydrogen sulphate (yield 63%), whilst (*c*) with phosphoric oxide in boiling xylene or (*d*) with thionyl chloride in cold dry pyridine (cf. Ellis and Petrow, *J.*, 1939, 1081) the yields were very poor. In all of these cases the ether-soluble product, after distillation of *iso*elemicine, gave a high-boiling resin which in case (*b*) was heated for 1 hour at 140° with anhydrous oxalic acid and, after recovery in ether and washing with alkali, afforded a viscous fluorescent distillate, b. p. 200°/0·1 mm., which crystallised from light petroleum (b. p. 60—80°) as colourless needles, m. p. 187° (Found : C, 69·1; H, 7·6%), and was probably a dimer.

6 : 7 : 8-*Trimethoxy*-3-*methyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*-1 : 2-*dicarboxylic Acid and its Anhydride* (V).—A solution of *iso*elemicine (0·328 g.) and maleic anhydride (0·773 g.) in xylene (5 c.c.) was boiled under reflux for 8 hours and then left at room temperature for 2 days. Xylene and maleic anhydride were distilled off (up to 70°/0·6 mm.), and the residue, treated with ether, afforded an amorphous solid which was again heated (at 130°/0·1 mm.) to remove volatile material. Thereafter crystallisation from acetic acid gave the *acid* as colourless plates, initially melting at 197—198° but reverting on storage to m. p. 181—182° (Found : C, 59·2; H, 6·3. $C_{16}H_{20}O_7$ requires C, 59·3; H,

6·2%); when melted at atmospheric pressure and then sublimed at 200—210°/0·1 mm., the acid yielded the *anhydride*, micro-m. p. 93° [from ethyl acetate–light petroleum (b. p. 60—80°)] (Found: C, 63·0; H, 5·4. $C_{16}H_{18}O_6$ requires C, 62·75; H, 5·9%).

6 : 7 : 8-*Trimethoxy*-3-*methyl*-3 : 4-*dihydronaphthalene*-1 : 2-*dicarboxylic Acid and its Anhydride* (VI).—(*a*) A solution of *iso*elemicine (0·753 g.) and chloromaleic anhydride (2·4 g.) in dry nitrobenzene (8 c.c.) was heated under reflux for $1\frac{1}{4}$ hours. Nitrobenzene and chloromaleic anhydride were distilled off (up to 61°/1 mm.) and the residue was treated with ether, an insoluble, dark product being discarded. Concentration of the solution gave the anhydride (0·29 g., 26%), m. p. 132—135° [from ether–light petroleum (b. p. 40—60°)].

(*b*) A mixture of *iso*elemicine (6·02 g.), chloromaleic anhydride (6 g.), xylene (18 c.c.), and a few crystals of quinol was heated under reflux for 23 hours. From the clear solution, filtered if necessary, there were distilled off (i) xylene under water-pump pressure and (ii) a mixture of chloromaleic anhydride and *iso*elemicine (up to b. p. 140°/0·3 mm.) from which the latter (0·218 g.) was recovered by treatment with alkali and redistillation. The non-volatile residue when treated with ether afforded yellow needles of the *anhydride* (4·346 g.), m. p. 134—135° [from ether–light petroleum (b. p. 40—60°)] (Found: C, 63·1; H, 5·45. $C_{16}H_{16}O_6$ requires C, 63·2; H, 5·3%), and on concentration of the ethereal mother-liquor there first separated crystals of chlorofumaric acid (0·5 g.), m. p. and mixed m. p. 190—191°, and the remainder on extraction with alkali and acidification yielded an impure sample (0·126 g.) of the dibasic *acid* corresponding to (VI). The same acid was prepared by warming (VI) with 10% aqueous sodium hydroxide, followed by acidification of the cooled solution; it formed colourless crystals, m. p. 146—147° (effervescence) (from acetic acid), and appeared to retain solvent in the crystal (Found: C, 56·7; H, 5·6. $C_{16}H_{18}O_7,C_2H_4O_2$ requires C, 56·5; H, 5·8%), but gave the correct analytical figures—and same m. p. behaviour—after crystallisation from water (Found: C, 59·8; H, 5·5. $C_{16}H_{18}O_7$ requires C, 59·6; H, 5·6%).

When rapidly sublimed ($\frac{1}{4}$ hour) at 200°/0·1 mm., the acid yielded the anhydride (VI), m. p. and mixed m. p. 135°, but on slower sublimation at 190—200°/18 mm. the later fractions of the sublimate gave the dehydrogenated anhydride (VII), m. p. and mixed m. p. 190—192° (from acetic acid), whilst the mother-liquor on storage slowly deposited colourless plates of 6 : 7 : 8-trimethoxy-3-methyl-1 : 2 : 3 : 4-tetrahydronaphthalene-1 : 2-dicarboxylic acid, m. p. and mixed m. p. 208° and 208—210°, respectively (effervescence). The same acid was obtained when a solution of the anhydride (VI) in acetic acid was heated for 3 hours at 100° with an excess of zinc dust, the product being recovered from the filtered solution and purified by passage in benzene through a column of silica gel.

6 : 7 : 8-*Trimethoxy*-3-*methylnaphthalene*-1 : 2-*dicarboxylic Anhydride* (VII).—The anhydride (VI) (0·71 g.), mixed with palladium (0·19 g.), was heated in a slow stream of dry carbon dioxide at 230—240° for $1\frac{1}{2}$ hours. The product, which had partly sublimed, was recovered in ether and formed yellow needles, m. p. 194—194·5°, from ether (Found: C, 63·8; H, 4·65. $C_{16}H_{14}O_6$ requires C, 63·6; H, 4·6%). The anhydride was regenerated by dissolution in alkali and acidification.

Isolation of Colchicine.—A concentrated ethanolic extract of *Colchicum* seeds (333 g.; from Messrs. Ransom), diluted with water (450 c.c.), was heated with paraffin wax (75 g.), and the liquid mixture, after vigorous stirring, was cooled, the solidified wax layer was lifted off, and the aqueous layer was re-treated with fresh wax (75 g.). The wax layers were extracted with boiling water (3 × 100 c.c.), and the total aqueous solution was mixed with "Hyflo Supercel" (100 g.). After filtration, using a pre-coat of "Hyflo", the filter-bed was well washed. The combined filtrates were exhausted with acid-free chloroform (12 × 200 c.c.) which, after being dried (K_2CO_3) and concentrated, afforded a brownish-yellow syrup. A solution of the syrup in chloroform (150 c.c.) was passed through a column of alumina (25 × 3·5 cm.; from B.D.H.; saturated with benzene) which retained much adsorbed material in several distinct zones (still under examination), and the colchicine was eluted by continued passage of chloroform until the eluate, initially yellow, became colourless and left no residue on evaporation. The recovered syrup was dissolved in ethanol which was then distilled off, the process being repeated thrice to ensure removal of chloroform. The final residue crystallised from ethyl acetate in fine colourless needles of m. p. 148—150° raised by renewed chromatography to m. p. 155°; $[\alpha]_D^{13}$ −119·9°, $[\alpha]_{5461}^{13}$ −167·8° (c = 0·878 in chloroform).

N-*Benzoylcolchinic Anhydride.*—A solution of *N*-benzoyltrimethylcolchicinic acid (3·24 g.) in 3% aqueous potassium hydroxide (32 c.c.) was treated (20 minutes) under cooling with 4% potassium permanganate (208 c.c.). After 12 hours the mixture was acidified with sulphuric acid and clarified by a stream of sulphur dioxide. A chloroform extract yielded an orange syrup which was dissolved in ethyl acetate, the solution was shaken with 2% aqueous sodium carbonate (which extracted acidic material including some benzoic acid), washed, and concentrated. When rubbed with benzene the residue afforded a brown solid (*A*) (0·477 g.), m. p. 193° (from benzene), and the benzene mother-liquor when passed through a short column of silica gel and eluted with benzene yielded (*a*) in the first colourless eluate, a few crystals of benzamide, m. p. and mixed m. p. 127°, and (*b*), in the yellow eluate, the anhydride, m. p. 201—202° (Windaus records m. p. 207°). Solid (*A*) when similarly purified afforded the anhydride as rectangular yellow plates, m. p. 201—202° (Found: C, 65·3; H, 4·8; N, 3·5. Calc. for $C_{23}H_{21}O_7N$: C, 65·25; H, 5·0; N, 3·3%). Recrystallisation from chloroform–ethyl acetate (1 : 1) gave the compound as flat rectangular plates, m. p. 211—212°.

In course of exploratory experiments on the purification of solid (*A*), combined benzene mother-liquors were passed through a column of alumina (B.D.H.) on which, however, adsorption was rather strong. Elution with benzene gave (i) a faintly yellow eluate which on concentration afforded stout, almost colourless crystals of a neutral *substance* (*B*), m. p. 164° (from benzene), recrystallising as colourless hexagonal plates, micro-m. p. 157° (from the same solvent) (Found: C, 69·7; H, 5·0; N, 4·2. $C_{21}H_{17}O_5N$ requires C, 69·4; H, 4·7; N, 3·9%. $C_{21}H_{19}O_5N$ requires C, 69·05; H, 5·2; N, 3·8%), and (ii) a yellow eluate, from which on concentration some benzamide crystallised, m. p. and mixed m. p. 127·5°.

Sublimation of N-*Benzoylcolchinic Anhydride.*—When the anhydride (0·09 g.) was heated at 220—230°/18 mm. in a sublimation apparatus the melt bubbled vigorously for about 30 minutes, and the slight yellow sublimate at this stage crystallised from benzene as a mixture of radiating yellow needles of unchanged anhydride (probably present as the result of splashing) and a few colourless rectangular plates of benzamide, micro-m. p. 122° raised to 124—126° by admixture with an authentic specimen. The subsequent orange-red sublimate, collected during 90 minutes while the temperature was gradually raised to 250—260°/18 mm. (leaving a non-volatile, uncrystallisable residue), afforded small colourless prisms, which had micro-m. p. 159—160° after several crystallisations from benzene (Found: C, 69·3; H, 5·25; N, 4·0; OMe, 25·0. $C_{21}H_{19}O_5N$ requires C, 69·05; H, 5·2; N, 3·85; OMe, 25·5%).

Evaporation of the first benzene mother-liquor from this *substance* afforded a semi-crystalline gum from which there was obtained a mixture of colourless prisms, micro-m. p. 170—171°, and yellow needles, micro-m. p. 196—206° (effervescence) (from aqueous acetic acid). These are probably secondary products and await further investigation.

Deaminocolchinic Anhydride.—A hot solution of *N*-benzoylcolchinic anhydride (90 mg.) in purified xylene (8 c.c.) was treated with phosphoric oxide (250 mg.), and the whole was heated under reflux for 20 minutes. The hot solution was decanted from the red gelatinous phosphoric residues which were then washed (*a*) with fresh boiling xylene (2 × 6 c.c.) and (*b*) with boiling chloroform (3 × 8 c.c.). The combined and cooled xylene solution was again decanted from a slight deposit of gelatinous substance and was then concentrated at 18 mm. The cooled concentrates deposited masses of golden-yellow rectangular plates or prisms of micro-m. p. 170—171° from benzene–light petroleum (b. p. 60—80°) (Found: C, 63·8; H, 4·7. $C_{16}H_{14}O_6$ requires C, 63·6; H, 4·6%). A further small quantity of the same *substance* was recovered from the chloroform washings (*b*). It was only slowly affected by cold, but dissolved in hot, dilute alkali giving a colourless solution.

Hydrogenation.—The product (5·36 mg.) in acetic acid (4 c.c.) and in presence of palladium black absorbed 0·90 c.c. of hydrogen at 20°/760 mm., corresponding to 2·1 double bonds. There was recovered from the still faintly yellow solution a gum which crystallised from benzene–light petroleum (b. p. 60—80°) as needles of micro-m. p. 108—110°.

N-*Benzoylcolchide.*—A solution of *N*-benzoyltrimethylcolchicinic acid (7 g.) in 2% potassium hydroxide (70 c.c.) was treated at 0—3° with 4% potassium permangante (350 c.c.), and after 4 hours the manganese dioxide was filtered off and washed (i) with boiling water, the aqueous filtrates being combined, and (ii) with boiling ethanol, the (moist) solution on concentration affording a gummy solid in aqueous suspension. Separate extraction of the filtrate (i) and suspension (ii) with chloroform gave, after drying and recovery, brown amorphous solids (0·168 g. and 0·454 g., respectively), whilst, after concentration of the filtrate (i) to small bulk under reduced pressure and in a stream of carbon dioxide, renewed extraction afforded a further quantity (0·917 g.) of a similar solid. Attempts to purify the various fractions by selective extraction with ethyl acetate (cf. Windaus, *loc. cit.*) failed, and the combined material was dissolved in much benzene, transferred to a column of silica gel, and eluted with benzene. Concentration of the faintly yellow eluate afforded a mixture of colourless plates and needles, which was separated by fractional crystallisation from benzene–methanol into (i) benzamide, m. p. and mixed m. p. 127°, and (ii) *N*-benzoylcolchide (0·143 g.), micro-m. p. 236° (Windaus gives m. p. 239°). Final elution of the column with methanol gave a brown residue (1·237 g.) recoverable from the eluate, but attempts to purify this material or to obtain from it crystalline hydrolysis products were unsuccessful.

The manganese dioxide was added to the aqueous concentrates, and the acidified mixture was clarified by a stream of sulphur dioxide before being extracted with chloroform. The extract was washed with 2% sodium carbonate (which removed resinous acidic material; 1·805 g.), dried, and concentrated. A solution of the residue (2·3 g.) in benzene was separated on silica gel into an upper bright yellow section (brown in ultra-violet light) and a lower colourless section (yellow in ultra-violet light). Separate elution with benzene, followed by concentration, gave: (i) colourless rectangular plates (0·040 g.) probably of *N*-benzoylcolchinic acid (arising from incidental hydrolysis) since they melted and effervesced at 182° with formation of the anhydride and were also formed from the anhydride by dissolving the latter in alkali and acidifying the solution; (ii) yellow rectangular plates (1·432 g.) of *N*-benzoylcolchinic anhydride, m. p. 194—195°; and (iii) unidentified stout prisms of micro-m. p. 201°, which were soluble in hot alkali.

Deaminocolchide and Colchide Picrate.—A solution of *N*-benzoylcolchide (0·078 g.) in 95% ethanol (3·5 c.c.) and concentrated hydrochloric acid (3 c.c.) was heated under reflux for 6 hours. The ethanol was distilled off and water (3 c.c.) was added. After 24 hours the precipitate was collected and shaken with ether, unchanged *N*-benzoylcolchide (0·027 g.) remaining undissolved (and being re-treated). Deaminocolchide (0·014 g.), micro-m. p. 130° (from aqueous ethanol) (Windaus gives m. p. 138°), was recovered from the ethereal solution and was slightly augmented by material recovered from an alkali-washed ethereal extract of the aqueous mother-liquor. Concentration of the aqueous mother-liquor and addition of aqueous picric acid gave colchide picrate, micro-m. p. 160—161° (Windaus gives m. p. 165°). Anomalous hydrolysis results were obtained in one experiment where, instead of deaminocolchide, colourless crystals of micro-m. p. 153—155° (from aqueous ethanol) were isolated. This substance was distinct from the oxidation product, micro-m. p. 157°, of *N*-benzoyltrimethylcolchicinic acid and it was not again encountered.

Hydrogenation.—A solution of deaminocolchide (3·59 mg.) in acetic acid (4 c.c.) in presence of palladium black absorbed 0·310 c.c. of hydrogen at 18·8°/751 mm., corresponding to 1·03 double bonds. The product, recovered from the acetic acid solution, formed colourless prisms of micro-m. p. 79—81° from aqueous ethanol.

N-*Acetylcolchinic Anhydride.*—(*a*) A solution of colchiceine (2 g.) in 3% potassium hydroxide (25 c.c.) was treated during 9 hours at 0° with 4% aqueous potassium permanganate (150 c.c.). After a further 12 hours the mixture was acidified, sulphur dioxide was passed in to dissolve the manganese dioxide, and the whole was extracted with chloroform. The brown gum recovered from the chloroform was extracted with benzene, the solution was passed through a column of silica gel, and the yellow section of the resulting chromatogram was eluted with benzene. After renewed chromatography, concentration of the yellow eluate afforded a minute quantity of colourless nodules, micro-m. p. 200° (not further examined), mixed with a larger proportion of yellow needle clusters. The latter afforded *N*-acetylcolchinic anhydride, micro-m. p. 184—185° (from ether) (Found: C, 60·15; H, 4·9. Calc. for $C_{18}H_{19}O_7N$: C, 59·9; H, 5·3%) [Windaus, *loc. cit.*, 1911, records (macro-) m. p. 201°].

(*b*) A solution of *N*-acetylcolchinol (0·4 g.) in 3% potassium hydroxide (6 c c.) was titrated at 20° in the course of 48 hours with 4% potassium permanganate (23·8 c.c.). Discharge of the permanganate colour, at first rapid, was later very slow. The manganese dioxide was filtered off and washed with hot water and then with boiling ethanol, the washings being concentrated and added to the main filtrate, which was then acidified and extracted with chloroform. The recovered brown gum was dissolved in benzene–chloroform (1 : 1), and the solution was passed through a short column of silica gel, from which the yellow eluate on evaporation afforded clusters of yellow needles, micro-m. p. and mixed m. p. with the product from (*a*) 184—185°.

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