641. *Colchicine and Related Compounds. Part XVI.* Periodate Oxidation of Colchiceine.*

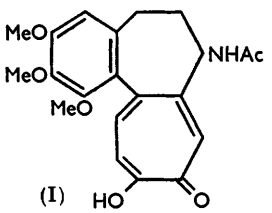
By K. Ahmad, G. L. Buchanan, and J. W. Cook.

The periodate oxidation of colchiceine yields a product which is shown to contain αβ-unsaturated acid and γ-lactone groupings. Two, alternative structures are proposed (II and III).

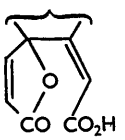
The chemistry of colchicine provides two instances in which the tropolone ring undergoes controlled oxidation, without loss of carbon.[1,2] These reactions are unique in tropolone chemistry, and since both yield products of unknown structure, they merit further attention. The first affords a ketonic product, which is now being studied; the second yields an acid which is the subject of the present communication.

Meyer and Reichstein observed [2] that colchiceine (I) is oxidised by periodic acid to a product $C_{21}H_{23}O_8N$ which titrated as a monocarboxylic acid, and afforded a monomethyl ester, but failed to show carbonyl reactivity.

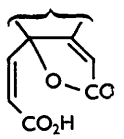
As no carbon has been lost in the oxidation, the three methoxyl groups and the acetyl group are intact, and so the functions of all but two of the oxygen atoms are defined. We have re-examined Meyer and Reichstein's acid, and find that although it reacts with only one equivalent of cold alkali, it consumes two equivalents of hot alkali, and the original monocarboxylic acid is regenerated when the hot alkaline solution is acidified. This eliminates the possibility that the second equivalent of alkali was employed in amide



(I)



(II)



(III)

hydrolysis, and suggests the presence of a γ-lactone ring. Microhydrogenation and titration with perbenzoic acid indicate two double bonds. These facts can best be reconciled with the two structures (II) or (III); no choice can be made here between them, and they are equally supported also by the following evidence.

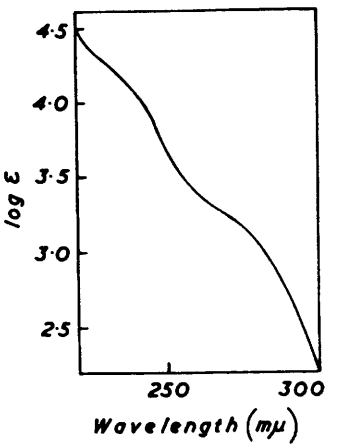
Meyer and Reichstein's acid fails to give a Legal reaction,[3] which is consistent with its

* Part XV, *J.*, 1957, 2334.

[1] Zeisel and Friedrich, *Monatsh.*, 1913, **34**, 1181.
[2] Meyer and Reichstein, *Pharm. Acta Helv.*, 1944, **19**, 127.
[3] Jacobs, Hoffmann, and Gustus, *J. Biol. Chem.*, 1926, **70**, 1.

formulation as an αβ-unsaturated γ-lactone. Although its infrared spectrum shows only a thick, inflected band (1776—1697 cm.$^{-1}$) in the carbonyl region, its methyl ester has sharp bands at 1747 and 1710 cm.$^{-1}$ assignable to αβ-unsaturated γ-lactone and αβ-unsaturated ester functions respectively. Reduction of the acid or ester was unusually difficult, and was possible on a preparative scale only by the use of Raney nickel alloy in alkali.[4] The reduced acid, which showed no unsaturation, had infrared absorption bands at 1780 (γ-lactone) and 1710 cm.$^{-1}$ (saturated acid) and afforded a methyl ester with infrared absorption at 1778 (γ-lactone) and 1743 cm.$^{-1}$ (saturated ester). The ultraviolet absorption spectrum (see Figure) indicates the absence of the tropolone chromophore [5] and when compared with a collection of relevant spectra [6] is compatible with the structure of an unconjugated trimethoxybenzene derivative as in (II) or (III).

Oxidation of tropolone under identical conditions yielded a gum, separable by sodium hydrogen carbonate solution into iodoform and an acidic fraction, which could not be further purified. The iodoform may well arise from the action of the iodine and alkali on tropolone, this reaction being already established.[7]



Ultraviolet absorption spectrum of Meyer and Reichstein's acid in ethanol.

Experimental

Meyer and Reichstein's acid,[2] m. p. 230° (decomp.) (from ethanol), had infrared max. at 3250, 1727, 1655, 1598 cm.$^{-1}$, and its methyl ester, m. p. 93—94° (from methanol), at 1743, 1709, 1643, 1595 cm.$^{-1}$.

The acid (6·4 mg.) (*M*, 417) in a little ethanol and 0·1N-sodium hydroxide (1 ml.) was neutralised to phenolphthalein by 0·1N-sulphuric acid (0·82 ml.), *i.e.*, 0·18 ml. was consumed (Calc. for $1CO_2H$, 0·154 ml.). The acid (6 mg.) in a little ethanol and 0·1N-sodium hydroxide (0·5 ml.) was heated at 100° for 45 min. and was neutralised by 0·1N-sulphuric acid (0·2 ml.), *i.e.*, 0·3 ml. was consumed (Calc. for $2CO_2H$, 0·29 ml.). In the latter experiment, excess of mineral acid was added, and the ethanol was removed *in vacuo*, leaving a product, m. p. 220° (decomp.) (from ethanol), which did not depress the m. p. of Meyer and Reichstein's acid. A blank titration showed that the ethanol consumed no alkali.

On hydrogenation with platinum in acetic acid, the acid (3·89 mg.) absorbed 0·43 ml. (N.T.P.) of hydrogen in 15 min. and without a break (Calc. for 2╞: 0·418 ml.). In 70 hr. at 0° the acid (18·5 mg.) consumed 13·1 ml. of 0·0065M-perbenzoic acid (Calc. for 2╞: 13·6 ml.).

Meyer and Reichstein's acid (34 mg.) in 10% aqueous sodium hydroxide (2 ml.) was kept at 100° whilst Raney nickel (0·2 g.) was added in portions, and agitated by a gentle stream of nitrogen. After 1 hr. at 100°, the mixture was filtered into cooled concentrated hydrochloric acid (1 ml.). The *product* was thrice extracted with ether and, crystallised from methanol, had m. p. 256° (Found : C, 59·9; H, 5·7; N, 3·5. $C_{21}H_{27}O_8N$ requires C, 59·9; H, 6·4; N, 3·3%), $\nu_{max.}$ 1780, 1707, 1597 cm.$^{-1}$. Microhydrogenation as above did not then occur.

The nickel-reduced acid (60 mg.) in dry methanol (10 ml.) was treated at 0° with anhydrous hydrogen chloride for 3 hr., then left overnight at room temperature. After the methanol had been removed *in vacuo*, the *methyl ester* was extracted with chloroform. It had m. p. 174° (from methanol) (Found : C, 60·8; H, 6·2. $C_{22}H_{29}O_8N$ requires C, 60·7; H, 6·7%), $\nu_{max.}$ 1776, 1740, 1643, 1592 cm.$^{-1}$.

Oxidation of Tropolone.—Tropolone (0·33 g.) in dioxan (10 ml.) was treated with periodic acid (1·3 g.) in water (4 ml.) and left at room temperature for 4 days. The solvents were removed *in vacuo* and the residual gum was separated by sodium hydrogen carbonate solution into acidic and neutral fractions. The neutral product crystallised from dilute

[4] Schwenk, Papa, Whitman, and Ginsberg, *J. Org. Chem.*, 1944, **9**, 175.
[5] Cf. Cook and Loudon, *Quart. Rev.*, 1951, **5**, 99.
[6] Buchanan and Sutherland, unpublished results.
[7] Cook, Gibb, and Raphael, *J.*, 1951, 2244.

methanol in yellow needles, m. p. 123°, undepressed on admixture with iodoform. The acidic fraction could not be purified.

One of us (K. A.) is grateful to the University of Dacca for leave of absence. Microanalyses were by Mr. J. M. L. Cameron and his staff. The ultraviolet spectrum was measured on a Unicam S.P. 500 Spectrophotometer, and the infrared spectra on a Perkin-Elmer Model 13 double-beam instrument.

THE UNIVERSITY, GLASGOW, W.2.
[Present address (K. A.): BIOCHEMISTRY DEPARTMENT,
UNIVERSITY OF DACCA, EAST PAKISTAN.] [*Received, March 18th,* 1957.]