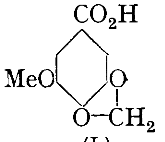
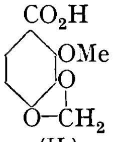
142. *The Constitution of Croweacin.*

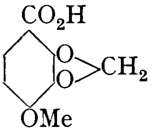
By A. R. PENFOLD, G. R. RAMAGE, and J. L. SIMONSEN.

The phenolic ether, croweacin, $C_{11}H_{12}O_3$, occurring in the essential oil from the leaves and terminal branchlets of *Eriostemon crowei* (*Crowei saligna*) has been shown to be represented by (VII), since it yields on oxidation croweacic acid, $C_9H_8O_6$, shown by synthesis to be 2-*methoxy*-3 : 4-*methylenedioxybenzoic acid* (II), and a glycol oxidisable by lead tetra-acetate to 2-*methoxy*-3 : 4-*methylenedioxybenzaldehyde* (VI), which also has been synthesised.

SOME years ago Penfold and Morrison (*J. Proc. Roy. Soc., N.S.W.*, 1923, **56**, 227) separated from the leaves and terminal branchlets of *Eriostemon crowei* (*Crowei saligna*) an essential oil the main constituent of which was a phenolic ether, croweacin, $C_{10}H_9O_2(OMe)$. This ether gave on oxidation with potassium permanganate a neutral product, now known to be a glycol, $C_{11}H_{14}O_5$, m. p. 97°, and an acid, croweacic acid, $C_9H_8O_6$, m. p. 153°. A consideration of these results suggested that the acid was a methoxymethylenedioxybenzoic acid isomeric with myristicic acid (5-methoxy-3 : 4-methylenedioxybenzoic acid) (I). This view was confirmed by the bromination of the acid : like myristicic acid, it gave 1 : 5 : 6-tribromo-2-methoxy-3 : 4-methylenedioxybenzene. It followed, therefore, that croweacic acid must be either 2-methoxy-3 : 4-methylenedioxybenzoic acid (II) or 4-methoxy-2 : 3-methylenedioxybenzoic acid (III). Synthesis has shown the former of these alternatives to be correct.

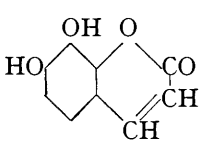

(I.)

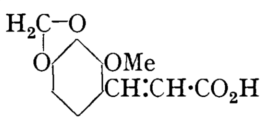

(II.)

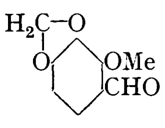

(III.)

By the methylenation of methyl 2 : 3-dihydroxy-4-methoxybenzoate (Herzig and Pollak, *Monatsh.*, 1902, **23**, 707; 1904, **25**, 506) an *ester* was obtained which on hydrolysis gave 4-*methoxy*-2 : 3-*methylenedioxybenzoic acid* (III), m. p. 256°, different from croweacic acid.

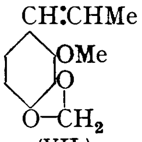
Considerable difficulty was encountered in synthesising (II). Attempts to methylenate pyrogallol, its monoacetyl derivative, and methyl 2 : 3 : 4-trihydroxybenzoate with methylene sulphate or methylene iodide failed, a somewhat unexpected result in view of the ease with which the ester yields a dimethyl ether. Success was finally achieved by using daphnetin (IV) as the starting material. The phenol, obtained in poor yield by the facile method of v. Pechmann (*Ber.*, 1884, **17**, 929), gave on treatment with methylene sulphate *daphnetin methylene ether*, m. p. 188°, from which by methylation with methyl sulphate in alkaline solution α-2-*methoxy*-3 : 4-*methylenedioxycinnamic acid* (V), m. p. 131°, was prepared. This acid on ozonolysis in sodium carbonate solution gave 2-*methoxy*-3 : 4-*methylenedioxybenzaldehyde* (VI), m. p. 104°, which was unaffected by an excess of ozone. Oxidation of the aldehyde with potassium permanganate in water–acetone solution gave 2-*methoxy*-3 : 4-*methylenedioxybenzoic acid* (II), identical in all respects with croweacic acid. The low melting point (131°) of the substituted cinnamic acid was somewhat unexpected and this acid probably represents the *cis*-modification, since an isomeric β-*form*, m. p. 212—213°, was prepared by the condensation of the aldehyde (VI) with malonic acid.


(IV.)

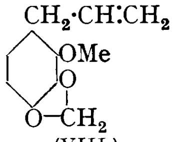

(V.)


(VI.)

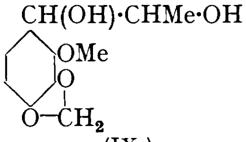
The structure of croweacic acid being established, it followed that croweacin must be either the propenyl ether (VII) or the allyl isomer (VIII). Unlike the closely related ethers myristicin and eugenol, croweacin must be represented by (VII) ; the glycol obtained from it on oxidation with potassium permanganate is (IX), since it yields on further degradation with lead tetra-acetate an aldehyde, m. p. 104°, identical with 2-methoxy-3 : 4-methylenedioxybenzaldehyde (VI).



(VII.)



(VIII.)



(IX.)

EXPERIMENTAL.

Oxidation of Croweacin.—Croweacin (1·8 g.; b. p. 129—131°/10 mm., $d_{15^\circ}^{15^\circ}$ 1·1324, $n_D^{20^\circ}$ 1·5339) in pure acetone (20 c.c.) was treated with finely powdered potassium permanganate (5 g.) in portions with shaking and cooling in water. The manganese dioxide sludge was collected, washed with acetone, suspended in water, and dissolved by passage of sulphur dioxide. The solution was extracted with ether, the extract washed with water and dried, and the solvent removed. The residue, which solidified, was crystallised from dilute alcohol (1 : 1), croweacic acid (0·5 g.) separating in fine needles, m. p. 153° [Found : C, 55·0; H, 4·1; OMe, 16·1. Calc. for $C_8H_5O_4(OMe)$: C, 55·1; H, 4·1; OMe, 15·8%]. The acetone filtrate was evaporated; the residue (0·2 g.) solidified on keeping. The glycol crystallised from ligroin (b. p. 100—120°) in needles, m. p. 97°.

2-*Methoxy*-3 : 4-*methylenedioxybenzaldehyde*.—The glycol (0·2 g.) and lead tetra-acetate in acetic acid (2·81N/50, 10 c.c.) were kept for 10 days, water then added, and the solution extracted with ether. After being washed with sodium carbonate solution, the extract was dried, and the solvent removed; the residue solidified. The *aldehyde* crystallised from hot water in fine long needles, m. p. 104°, both alone and in admixture with a synthetic specimen (Found : C, 60·3; H, 4·6. $C_9H_8O_4$ requires C, 60·0; H, 4·4%). The semicarbazone was identical with the synthetic specimen described on p. 758.

Dibromocroweacin Dibromide.—Bromine (1 c.c.) was added to croweacin (0·3 g.) in acetic acid (5 c.c.), and the solution kept for 12 hours prior to dilution with water. The precipitated solid was filtered off from much oily impurity, which did not solidify. The *dibromocroweacin dibromide* crystallised from dilute alcohol in fine needles, m. p. 108° (Found : C, 26·1; H, 2·2; Br, 62·4. $C_{11}H_{10}O_3Br_4$ requires C, 25·9; H, 2·0; Br, 62·7%).

1 : 5 : 6-*Tribromo*-2-*methoxy*-3 : 4-*methylenedioxybenzene*.—(i) Croweacic acid (and the synthetic acid) or 4-methoxy-2 : 3-methylenedioxybenzoic acid (0·2 g.), prepared as described below, and bromine (1 g.) were heated for 1 hour on the water-bath, early elimination of carbon dioxide occurring smoothly. Water was added and the precipitated solid was collected, washed with warm sodium carbonate solution, and crystallised from alcohol, the bromo-derivative separating in long needles, m. p. 157° (Found : C, 24·6; H, 1·4. Calc. for $C_8H_5O_3Br_3$: C, 24·6; H, 1·3%). (ii) When myristicic acid (5-methoxy-3 : 4-methylenedioxybenzoic acid) was used, the above treatment failed to remove the carboxyl group, but the same neutral product, m. p. 157°, resulted when the heating was continued for 4 hours.

Methyl 2 : 3 : 4-*Trihydroxybenzoate*.—Pyrogallol (50 g.) by Kostanecki's method (*Ber.*, 1885, **18**, 3205) gave 2 : 3 : 4-trihydroxybenzoic acid (30 g.), which was refluxed with methyl-alcoholic hydrogen chloride (250 c.c.) for 8 hours. Most of the alcohol was distilled and the ester was then taken up in ether and distilled, giving an oil (25 g.), b. p. 182—184°/14 mm., which quickly solidified. Methyl 2 : 3 : 4-trihydroxybenzoate crystallised from water or dilute methyl alcohol in long needles, m. p. 148°, with considerable softening after air-drying (Found : C, 43·5; H, 5·5. Calc. for $C_8H_8O_5,2H_2O$: C, 43·6; H, 5·4%). Will (*Ber.*, 1888, **21**, 2023) records results agreeing for $C_8H_8O_5,2{\cdot}5\ H_2O$. The anhydrous ester, m. p. 153°, was obtained by heating the hydrate at 100° under reduced pressure, the ester showing a slight tendency to sublime (Found : C, 52·2; H, 4·4. Calc. : C, 52·2; H, 4·3%).

2 : 3-*Dihydroxy*-4-*methoxybenzoic Acid*.—Anhydrous methyl 2 : 3 : 4-trihydroxybenzoate (25 g.) in ether was cooled in ice-water, and an ethereal solution of diazomethane (from nitrosomethylurea, 16 g.) slowly added. After removal of the ether, the ester, which failed to crystallise, was hydrolysed by alcoholic potassium hydroxide solution, giving a mixture of acids, separable by fractional crystallisation from water. 2-Hydroxy-3 : 4-dimethoxybenzoic acid (2·0 g.) separated first in long prisms, m. p. 170°, followed by fractions (5 g.), m. p. about 200°, which, when repeatedly crystallised, gave needles, m. p. 222° (Will, *loc. cit.*, gives m. p.

204—206°) (Found : C, 52·5; H, 4·5. Calc. for $C_8H_8O_5$: C, 52·3; H, 4·3%). On esterification with methyl-alcoholic hydrogen chloride the highly crystalline methyl ester, m. p. 101°, was obtained, which on hydrolysis regenerated the acid, m. p. 222°.

4-Methoxy-2 : 3-methylenedioxybenzoic Acid.—Methylene sulphate (1·5 g.) was added in portions to the above ester (1·2 g.), potassium hydroxide (1 g.), water (10 c.c.), and acetone (10 c.c.), and the solution warmed until it became acid to litmus. The acetone was distilled off; on addition of water *methyl 4-methoxy-2 : 3-methylenedioxybenzoate* (0·8 g.) separated, which crystallised from dilute alcohol or water in needles, m. p. 122—123° (Found : C, 57·2; H, 4·9. $C_{10}H_{10}O_5$ requires C, 57·1; H, 4·8%). The ester gave no colour with ferric chloride and was hydrolysed by aqueous sodium hydroxide solution (8%), the solution on acidification giving *4-methoxy-2 : 3-methylenedioxybenzoic acid*, which crystallised from dilute alcohol in needles, m. p. 256° (Found : C, 55·4; H, 4·4. $C_9H_8O_5$ requires C, 55·1; H, 4·1%).

Daphnetin Methylene Ether.—To a solution of daphnetin (2 g.) in potassium hydroxide (2 g.), water (20 c.c.), and acetone (20 c.c.), warmed on the water-bath, methylene sulphate (3 g.) was added in portions, the red colour of the solution gradually changing to brown. From the product of three similar experiments the acetone was removed, and water added; on cooling, a crystalline solid quickly separated. This was immediately filtered off and treated with sodium carbonate solution to remove unchanged daphnetin. The resulting *daphnetin methylene ether* (1·6 g.) crystallised from alcohol in plates, m. p. 188° (Found : C, 63·0; H, 3·3. $C_{10}H_6O_4$ requires C, 63·2; H, 3·1%). From the acidified mother-liquors, unchanged daphnetin (3·5 g.) was obtained.

α-2-Methoxy-3 : 4-methylenedioxycinnamic Acid.—Daphnetin methylene ether (1 g.) was heated on the water-bath with sodium hydroxide solution (10 c.c., 20%) and to the clear solution methyl sulphate (8 g.) was added with shaking until clouding occurred owing to the separation of the methyl ester. A similar further quantity of sodium hydroxide solution was added, and the mixture heated on the water-bath until a clear solution was obtained. This was cooled and acidified, the precipitated solid collected and treated with sodium carbonate solution, a little unchanged daphnetin methylene ether filtered off, and the filtrate acidified. The *cinnamic acid* (0·8 g.) crystallised from dilute alcohol (1 : 1) in long needles, m. p. 131° (Found : C, 59·3; H, 4·5. $C_{11}H_{10}O_5$ requires C, 59·5; H, 4·5%).

2-Methoxy-3 : 4-methylenedioxybenzaldehyde.—The cinnamic acid (1 g.) was dissolved in aqueous sodium carbonate (10 c.c., 8%), and ozone passed through the solution for 4 hours, as it was not completely absorbed. A white precipitate, which gradually separated, was collected on completion of the oxidation. The *aldehyde* (0·6 g.) crystallised from water in long fine needles, m. p. 104° (Found : C, 60·1; H, 4·4. $C_9H_8O_4$ requires C, 60·0; H, 4·4%). The *semicarbazone*, prepared in aqueous solution, crystallised from alcohol, in which it was somewhat sparingly soluble, in hair-like needles, m. p. 238° (Found : N, 17·1. $C_{10}H_{11}O_4N_3$ requires N, 17·7%). The *2 : 4-dinitrophenylhydrazone* crystallised from ethyl acetate in red needles, m. p. 254° (Found : N, 15·5. $C_{15}H_{12}O_7N_4$ requires N, 15·6%).

2-Methoxy-3 : 4-methylenedioxybenzoic Acid.—The aldehyde (0·25 g.) in acetone (10 c.c.) was maintained at 40° while aqueous potassium permanganate (6 c.c., 3%) was added slowly. When the purple colour was discharged, the acetone was removed in a current of air, water (5 c.c.) added, and sulphur dioxide passed through the mixture to remove the manganese dioxide. The precipitated solid was collected and digested with sodium carbonate solution, and the unchanged aldehyde (0·1 g.) removed. *2-Methoxy-3 : 4-methylenedioxybenzoic acid* (0·15 g.) was precipitated on acidification of the sodium carbonate filtrate; it crystallised from water in needles, m. p. 153°, both alone and in admixture with croweacic acid (Found : C, 55·1; H, 4·2. $C_9H_8O_5$ requires C, 55·1; H, 4·1%).

β-2-Methoxy-3 : 4-methylenedioxycinnamic Acid.—2-Methoxy-3 : 4-methylenedioxybenzaldehyde (0·2 g.), malonic acid (0·3 g.), pyridine (2 c.c.), and piperidine (1 drop) were heated for 2 hours on the water-bath. An excess of dilute hydrochloric acid precipitated the *β-cinnamic acid*, which crystallised from alcohol in needles, m. p. 212—213° (Found : C, 59·2; H, 4·6. $C_{11}H_{10}O_5$ requires C, 59·5; H, 4·5%).

We are indebted to the Government Grants Committee of the Royal Society and to Imperial Chemical Industries, Limited, for grants, and to Dr. T. A. Henry for the gift of a specimen of myristicic acid.

TECHNOLOGICAL MUSEUM, SYDNEY, NEW SOUTH WALES.
UNIVERSITY COLLEGE OF NORTH WALES, BANGOR.

[*Received, April 4th,* 1938.]