Phthalaldehydes and Related Compounds. Part V. Phthalaldehydes derived from Hydrastal and Cotarnone.*

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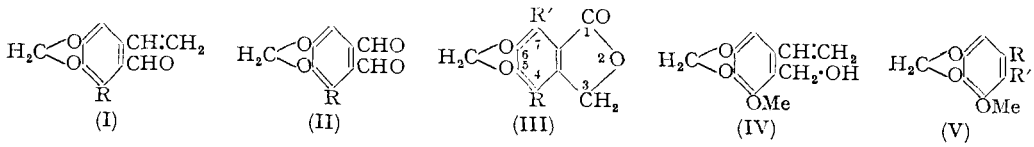
Hydrastal and cotarnone have been degraded to 4 : 5-methylenedioxyphthalaldehyde and its 3-methoxy-analogue respectively, and the action of alkali on the phthalaldehydes has been examined.

HYDRASTAL (I; R = H) was obtained as the end-product of a Hofmann elimination reaction applied to hydrastinine (Freund, *Ber.*, 1889, **22**, 2329) while cotarnone (I; R = OMe) resulted from the application of a similar process to cotarnine (Roser, *Annalen*, 1888, **249**, 156). We find that hydrastal is readily degraded to 4 : 5-methylenedioxyphthalaldehyde (II; R = H) by hydroxylation of the vinyl group by the osmium tetroxide method followed by periodate oxidation of the diol, which was not isolated. Treatment of (II; R = H) with concentrated aqueous potassium hydroxide gave 5 : 6-methylenedioxyphthalide (III; R = R′ = H) which has been prepared from homopiperonylic acid (Stevens, *J.*, 1927, 178; Stevens and Robertson, *ibid.*, p. 2790; Brown and Newbold, *J.*,

* Part IV, *J.*, 1954, 1076.

1952, 4397). Cotarnone is converted into 3-methoxy-4 : 5-methylenedioxyphthalaldehyde (II; R = OMe) either by the method used for hydrastal or more conveniently by ozonolysis at a low temperature. The phthalaldehyde (II; R = OMe) on being heated with concentrated aqueous alkali gave 4-methoxy-5 : 6-methylenedioxyphthalide (III; R = OMe, R′ = H) previously obtained by Späth, Schmid, and Sternberg (*Ber.*, 1934, **67**,



2095) by the action of formaldehyde and hydrochloric acid on myristicinic acid (V; R = CO_2H, R′ = H). We have prepared the phthalide (III; R = OMe, R′ = H) by another route; reduction of cotarnone (I; R = OMe) with sodium borohydride gave 2-hydroxymethyl-3-methoxy-4 : 5-methylenedioxystyrene (IV); this compound was benzoylated and submitted to low-temperature ozonolysis and the product, not isolated, was treated with concentrated alkali, whereupon 4-methoxy-5 : 6-methylenedioxyphthalide (III; R = OMe, R′ = H) was readily obtained.

An attempt was made to prepare the isomeric phthalide, 7-methoxy-5 : 6-methylenedioxyphthalide (III; R = H, R′ = OMe). Myristicinic acid (V; R = CO_2H, R′ = H) was converted into methyl myristicinate (V; R = CO_2Me, R′ = H), nitration of which proceeded smoothly to give methyl 3-methoxy-4 : 5-methylenedioxy-2-nitrobenzoate (V; R = CO_2Me, R′ = NO_2) the orientation of the entering nitro-group being inferred from the nitration of ethyl myristicinate to (V; R = CO_2Et, R′ = NO_2) (Salway, *J.*, 1911, **99**, 266). Catalytic hydrogenation of (V; R = CO_2Me, R′ = NO_2) afforded methyl 2-amino-3-methoxy-4 : 5-methylenedioxybenzoate (V; R = CO_2Me, R′ = NH_2) which was smoothly reduced to 2-amino-3-methoxy-4 : 5-methylenedioxybenzyl alcohol (V; R = CH_2·OH, R′ = NH_2) by the action of lithium aluminium hydride. Attempts to convert (V; R = CH_2OH, R′ = NH_2) by the Sandmeyer reaction into the nitrile and to hydrolyse this to the isomeric methoxymethylenedioxyphthalide [lactone of (V; R = CH_2·OH, R′ = CO_2H)] were unsuccessful.

Experimental

Ultra-violet absorption spectra were determined in ethanol solution.

4 : 5-*Methylenedioxyphthalaldehyde*.—A solution of hydrastal (176 mg.; Brown and Newbold, *J.*, 1952, 4397) in dry benzene (25 c.c.) containing pyridine (0·16 c.c.) was treated with osmic acid (260 mg.), and the solution which darkened and soon began to deposit brown crystals was kept overnight at *ca.* 15°. The osmic acid–pyridine complex (450 mg.) was separated and heated under reflux in ethanol (30 c.c.) with sodium sulphite (5 g.) in water (20 c.c.) for 1 hr. Ethanol (150 c.c.) was added, the mixture filtered, and the solid extracted with boiling ethanol (2 × 30 c.c.). The combined ethanolic extracts were evaporated under reduced pressure, the residue was extracted with boiling methanol (2 × 50 c.c.) and the combined extracts were evaporated to a yellow gum. This was dissolved in pure methanol (3 c.c.), water (30 c.c.) and potassium periodate (1·0 g.) were added, the mixture was kept overnight, with occasional shaking, and extracted with ether (2 × 25 c.c.). The combined ethereal extracts were washed with water (25 c.c.) and dried (Na_2SO_4). Evaporation of the ether and crystallisation of the solid from benzene (charcoal) and benzene–light petroleum (b. p. 60—80°) gave 4 : 5-*methylenedioxyphthalaldehyde* (70 mg.) as pale yellow needles, m. p. 149—150° (Found : C, 60·8; H, 3·6. $C_9H_6O_4$ requires C, 60·7; H, 3·4%). Light absorption : Max. at 2500 (ε 26,200) and 3220 Å (ε 5300). The compound, suspended in aqueous ammonia (10%) and acidified with acetic acid, gave a violet solution (Thiele test, *Annalen*, 1900, **311**, 360).

5 : 6-*Methylenedioxyphthalide*.—4 : 5-Methylenedioxyphthalaldehyde (50 mg.) was heated on the steam-bath with potassium hydroxide (2 c.c.; 50%) for 15 min. The filtered solution was acidified (Congo-red) with 3N-hydrochloric acid, and the precipitate was separated and crystallised from aqueous ethanol, to give 5 : 6-methylenedioxyphthalide (20 mg.) as needles, m. p. 187—188° alone or mixed with a specimen prepared by Brown and Newbold (*loc. cit.*)

(Found : C, 60·5; H, 3·6. Calc. for $C_9H_6O_4$: C, 60·7; H, 3·4%). Light absorption : Max. at 2210 (ε 23,000), 2560 (ε 5700), and 3000 Å (ε 7300).

Cotarninemethine Methiodide.—Cotarnine (4·0 g.) and methyl iodide (30 c.c.) were heated under reflux for 1 hr. and the excess of reagent was removed by distillation. Crystallisation of the residue from water gave cotarninemethine methiodide (70%) as needles, m. p. 217—218° (Found : C, 43·1; H, 5·3. Calc. for $C_{14}H_{20}O_4NI$: C, 42·8; H, 5·1%). Light absorption : Max. at 2180 (ε 26,600), 2420 (ε 22,100), and 2920 Å (ε 10,600). Roser (*loc. cit.*) prepared the compound but gave no constants though he gave an analysis, and Rodionow (*Bull. Soc. chim.*, 1926, **39**, 305) gave m. p. 219—220° but no analysis.

Cotarnone.—Roser (*loc. cit.*) gave insufficient details for the preparation of this compound. It is essential that our procedure be followed exactly. Pure cotarninemethine methiodide (15·0 g.) was rapidly heated with aqueous sodium hydroxide (250 c.c.; 10%) to the b. p., refluxed for 5 min., and then cooled. The oily phase rapidly solidified and was broken up, separated, washed with water, dried, and crystallised from light petroleum (b. p. 40—60°), to give cotarnone (6·2 g.) as plates, m. p. 78° (lit., 78°), giving a blue colour with acetic acid–sulphuric acid. Cotarnone had absorption max. at 2500 (ε 19,200) and 3020 Å (ε 6200).

3-*Methoxy*-4 : 5-*methylenedioxyphthalaldehyde.*—(*a*) A solution of cotarnone (810 mg.) in benzene (50 c.c.) containing pyridine (0·625 c.c.) was treated with osmic acid (1·0 g.) as given above for hydrastal, the complex was split, and the product oxidised with potassium periodate in aqueous methanol. 3-*Methoxy*-4 : 5-*methylenedioxyphthalaldehyde* (500 mg.), isolated by means of acid-free chloroform, separated from benzene as needles, m. p. 179° (Found : C, 57·5; H, 4·1. $C_{10}H_8O_5$ requires C, 57·7; H, 3·9%). Light absorption : Max. at 2560 (ε 26,900) and 3200 Å (ε 5900). The compound becomes brown on prolonged exposure to light.

(*b*) A solution of cotarnone (0·5 g.) in chloroform (200 c.c.) at −40° was treated with a stream of ozonised oxygen until 1 mol. of ozone had been absorbed. Water (10 c.c.) was added and the mixture heated to the b. p., with shaking, during 10 min. and refluxed for 15 min. The chloroform layer was separated, dried (Na_2SO_4), and evaporated under reduced pressure to a solid which after two crystallisations from benzene gave 3-methoxy-4 : 5-methylenedioxyphthalaldehyde (250 mg.) as needles, m. p. and mixed m. p. with preparation (*a*), 179° (Found : C, 58·1; H, 4·2%).

2-*Hydroxymethyl*-3-*methoxy*-4 : 5-*methylenedioxystyrene.*—A solution of cotarnone (200 mg.) in ethanol (10 c.c.) and water (25 c.c.) was treated with sodium borohydride (500 mg.) and kept at *ca.* 15° overnight. The solution was extracted with chloroform (3 × 25 c.c.), and the combined extracts were washed with water (20 c.c.) and dried (Na_2SO_4). Removal of the chloroform gave an oil which was distilled in a short-path still at 200° (bath-temp.)/0·5 mm. The distillate, which rapidly solidified, crystallised from light petroleum (b. p. 40—60°) to give 2-*hydroxymethyl*-3-*methoxy*-4 : 5-*methylenedioxystyrene* (150 mg.) as needles, m. p. 47° (Found : C, 63·7; H, 6·1. $C_{11}H_{12}O_4$ requires C, 63·45; H, 5·8%). Light absorption : Max. at 2220 (ε 27,000) and 2700 Å (ε 9700). A solution of the compound in glacial acetic acid gave a red-brown colour on addition of sulphuric acid (*d* 1·84).

4-*Methoxy*-5 : 6-*methylenedioxyphthalide.*—(*a*) 3-Methoxy-4 : 5-methylenedioxyphthalaldehyde (300 mg.) was heated on the steam-bath with aqueous potassium hydroxide (30 c.c.; 40%) for 1 hr. The cooled solution was extracted with ether (2 × 20 c.c.); evaporation of the combined, dried (Na_2SO_4) extracts gave a negligible residue. Acidification (Congo-red) of the aqueous phase with 3N-hydrochloric acid was followed by extraction with chloroform (3 × 35 c.c.). The combined chloroform extracts were washed with 10% aqueous sodium hydrogen carbonate and with water, dried (Na_2SO_4), and evaporated. The residue was twice crystallised from aqueous ethanol to give needles (171 mg.), m. p. 138—139° not rising on subsequent crystallisation. This material was heated at 100°/10^{-4} mm., partial sublimation taking place. Four crystallisations of the residue from aqueous ethanol gave 4-methoxy-5 : 6-methylenedioxyphthalide (50 mg.) as needles, m. p. 150—150·5° (Found : C, 58·05; H, 4·2. Calc. for $C_{10}H_8O_5$: C, 57·7; H, 3·9%). Light absorption : Max. at 2220 (ε 26,600) and 2730 (ε 7000) and inflexion at 2900—3000 Å (ε 4200). Späth, Schmid, and Sternberg (*loc. cit.*) give m. p. 150—151°.

(*b*) 2-Hydroxymethyl-3-methoxy-4 : 5-methylenedioxystyrene (600 mg.) was heated on the steam bath for ¾ hr. with benzoyl chloride (3 c.c.) and pyridine (5 c.c.), and the product was isolated by means of ether. Evaporation of the dried (Na_2SO_4) ethereal extract gave a viscous oil which was further purified by dissolving it in benzene (10 c.c.), adsorbing it on an alumina column (5 × 1·5 cm.), washing the column with benzene (200 c.c.), and evaporating the eluate to a colourless gum. The gum was dissolved in chloroform (150 c.c.) and treated

at −30° with ozonised oxygen (1·1 mols. of ozone) and worked up as for the previous ozonolysis, the aqueous phase giving the formaldehyde–dimedone compound, m. p. and mixed m. p. 190°. Removal of the chloroform gave a gum (which gave a precipitate, rapidly, with Brady's reagent) which was heated on the steam-bath with aqueous potassium hydroxide (30 c.c.; 40%) for ¾ hr., cooled, and extracted with ether. The aqueous phase was acidified (Congo-red) with 5N-hydrochloric acid, and the phthalide isolated by means of ether. Crystallisation from aqueous ethanol gave 4-methoxy-5 : 6-methylenedioxyphthalide (130 mg.) as needles, m. p. 151° alone or mixed with preparation (*a*) (Found: C, 57·6; H, 4·2%). Light absorption: Max. at 2230 (ε 26,500) and 2710 (ε 6600), inflexion at 2900—3000 Å (ε 4200).

Methyl Myristicinate.—Myristicinic acid (1·7 g.) in dry methanol (100 c.c.) containing sulphuric acid (4 c.c.; *d* 1·84) was heated under reflux for 2½ hr. The solution was concentrated to one-third of its volume under reduced pressure, then diluted with water, and the ester was isolated by means of chloroform. *Methyl myristicinate* (1·5 g.) separated from methanol as needles, m. p. 91° (Found: C, 57·1; H, 5·0. $C_{10}H_{10}O_5$ requires C, 57·1; H, 4·8%). Light absorption: Max. at 2230 (ε 19,900) and 2790 (ε 8100).

Methyl 3-Methoxy-4 : 5-methylenedioxy-2-nitrobenzoate.—Methyl myristicinate (1·13 g.) was added in portions to nitric acid (12 c.c.; *d* 1·42) cooled in ice at such a rate that the temperature did not rise above 10°. After 30 min. at 0° water (30 c.c.) was added, and the precipitate filtered off, washed with water, and crystallised from ethanol, to give *methyl 3-methoxy-4 : 5-methylenedioxy-2-nitrobenzoate* (1·0 g.) as needles, m. p. 127° (Found: C, 47·3; H, 3·85. $C_{10}H_9O_7N$ requires C, 47·1; H, 3·6%). Light absorption: Max. at 2230 (ε 28,000) and 2720 Å (ε 6300).

Methyl 2-Amino-3-methoxy-4 : 5-methylenedioxybenzoate.—The foregoing nitro-ester (960 mg.) in ethyl acetate (150 c.c.) was shaken with hydrogen in the presence of Raney nickel (0·4 g.; W6, prepared according to *Org. Synth.*, **29**, 25) until absorption ceased (2 hr.). The filtered solution was evaporated under reduced pressure and the residue crystallised from light petroleum (b. p. 60—80°) to give *methyl 2-amino-3-methoxy-4 : 5-methylenedioxybenzoate* (720 mg.) as needles, m. p. 89·5° (Found: C, 53·4; H, 4·7. $C_{10}H_{11}O_5N$ requires C, 53·3; H, 4·9%). Light absorption: Max. at 2260 (ε 23,000), 2690 (ε 5700), and 3660 Å (ε 6400).

2-Amino-3-methoxy-4 : 5-methylenedioxybenzyl Alcohol.—A solution of the amino-ester (610 mg.) in dry ether (10 c.c.) was added during 15 min. to a refluxing partial solution of lithium aluminium hydride (1·0 g.) in dry ether (40 c.c.). After 3 hours' refluxing the cooled mixture was treated with ice and made strongly alkaline with sodium hydroxide, and the ethereal phase was separated. After further extraction of the aqueous phase with ether (2 × 100 c.c.) the combined extracts were dried (Na_2SO_4) and evaporated to an oil which rapidly solidified. Crystallisation from benzene–light petroleum (b. p. 60—80°) gave *2-amino-3-methoxy-4 : 5-methylenedioxybenzyl alcohol* (470 mg.) as needles, m. p. 99° (Found: C, 55·0; H, 5·8. $C_9H_{11}O_4N$ requires C, 54·8; H, 5·6%). Light absorption: Max. at 2130 (ε 31,000 and 3000 (ε 3100); inflexion at 2420 Å (ε 5000). The compound sublimes rapidly at 80°/10^{-4} mm.

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