THE ACTION OF HEXAMETHYLENE TETRAMINE ON PHENOLS AND THE METHYL ESTERS OF PHENOL CARBOXYLIC ACIDS

Part II. The Synthesis and Study of Methyl-2 : 3 : 4 Trihydroxy-5-formyl-benzoate

BY R. D. DESAI, (MISS) K. S. RADHA AND R. C. SHAH

(From the Department of Chemical Technology, University of Bombay and the Department of Chemistry, Royal Institute of Science, Bombay)

Received December 26, 1945

2 : 4-Dihydroxy-5-formyl benzoic acid was synthesised by Desai and Radha,[1] by the action of hexamethylene tetramine on methyl-β-resorcylate in glacial acetic acid. The same reaction has now been extended to some phenols and to methyl-2 : 3 : 4-trihydroxy-benzoate.

Methyl-2 : 3 : 4- trihydroxy-benzoate on formylation with hexamethylene tetramine in glacial acetic acid, yielded methyl-2 : 3 : 4- trihydroxy-5-formyl-benzoate, which was characterized by the preparation of its 2 : 4-dinitro-phenyl hydrazone, 4-nitrophenyl-hydrazone and semicarbazone derivatives.

The ortho-hydroxy-aldehydic structure of the formyl ester was proved by the preparation of the coumarin derivatives of the formyl ester with ethyl acetoacetate and ethyl malonate by the Knoevenagel condensation. Thus, with ethyl acetoacetate, the ester gave methyl-7 : 8-dihydroxy-3-acetyl-coumarin-6-carboxylate and with ethyl malonate, it afforded ethyl-7 : 8-dihydroxy-6-carbomethoxy coumarin-3-carboxylate.

Clemmensen reduction of the formyl ester afforded methyl-2 : 3 : 4-trihydroxy-5-methyl benzoate.

Hydrolysis of the ester gave the corresponding aldehydo-acid, 2 : 3 : 4-trihydroxy-5-formyl benzoic acid, which when subjected to decarboxylation underwent decomposition.

On Perkin's acetylation and condensation with bromacetic ester, the formyl ester was recovered unchanged.

Attempts were made to formylate orcinol, methyl-*p*-orsellinate, phloroglucinol, resacetophenone, methyl-resaceto-phenone carboxylate, hydroquinone, 1 : 3 : 5-triacetoxy benzene, methyl-α-resorcylate, γ-resorcylic acid, and methyl-γ-resorcylate. Of these, orcinol, methyl-*p*-orsellinate, phloroglucinol, γ-resorcylic acid and methyl-γ-resorcylate gave amorphous, yellowish-brown, high-melting compounds which contained appreciable amount

Ethyl-7: 8-dihydroxy-6-carbomethoxy-coumarin-3-carboxylate.—Piperidine (3 drops), was added to a mixture of the formyl ester (1 g.) and ethyl malonate (1 g.) dissolved in pyridine (10 c.c.) and the mixture was heated on boiling water-bath for two hours. The solid obtained on acidifying with dilute hydrochloric acid, crystallized from hot alcohol in colourless needles (0·25 g.), m.p. 245–47°. (Found: C, 54·2; H, 3·5; $C_{14}H_{12}O_8$ requires C, 54·5; H, 3·8 per cent.).

Methyl-2: 3: 4-trihydroxy-5-methyl benzoate.—The formyl ester (1·5 g.), dissoved in hot alcohol (20 c.c.), was gradually added to a mixture of zinc amalgam (prepared from 20 g. of zinc dust according to Robinson and Shah[2]) and dilute hydrochloric acid (50 c.c., 1: 1) at 100°, more alcohol being added to keep the ester in solution whenever it was necessary. After one hour, concentrated hydrochloric acid (10 c.c.) was added and the heating continued for a further half hour. The hot liquid, after filtration deposited shining, greyish micro-crystals, m.p. 178–79°, on cooling. The ethereal extract of the zinc amalgam gave a further yield of the same compound. Total yield (0·8 g.). (Found: C, 54·3; H, 5·0; $C_9H_{10}O_5$ requires C, 54·5; H, 5·0 per cent.) It did not react with 2: 4-dinitrophenyl hydrozine and the mixed melting point with the formyl ester was 130–40°.

2: 3: 4-*trihydroxy-5-formyl-benzoic acid.*—The aldehydo-ester (0·7 g.) was dissolved in sodium hydroxide solution (20 c.c., 10%) and heated on a water-bath for 2–3 hours. The hot solution was filtered and acidified with hydrochloric acid. The solid was purified through sodium-bi-carbonate solution and crystallized from very dilute alcohol in colourless micro-crystals, m.p. 221–22°, (Found: C, 48·7; H, 3·0; $C_8H_6O_6$ requires C, 48·5; H 3·0 per cent.)

The foregoing formyl acid (0·2 g.) was heated in a hard glass sealed tube with water (10 c.c.) and hydrochloric acid (1 c.c.) for 5–6 hours at 160–70°. The dark brown solid purified through sodium bicarbonate solution did not give tests for the aldehydo group with 2: 4-dinitro-phenyl-hydrazine.

Summary

1. Methyl-2: 3: 4-trihydroxy benzoate was formylated by the action of hexamethylene-tetramine in glacial acetic acid and methyl-2: 3: 4-trihydroxy-5-formyl benzoate was obtained. Several derivatives of the formyl ester were prepared and the structure established.

2. Formylation of several hydroxy compounds was also attempted.

References

1. Desai and Radha .. *Proc. Ind. Acad. Sci.*, A, 1940, **11**, 422.
2. Robinson and Shah .. *J.*, 1934, 1497.

of nitrogen. Resacetophenone and hydroquinone gave oily products which did not solidify, whereas in the case of methyl resacetophenone carboxylate and 1 : 3 : 5-triacetoxy benzene, no reaction took place and the starting compounds were recovered. Methyl-α-resorcylate afforded a yellowish, nitrogenous amorphous, and high-melting compound which reacted with dinitrophenyl-hydrazine, indicating the presence of traces of the aldehyde compound.

Experimental

Formylation of methyl-2 : 3 : 4-trihydroxy benzoate: Methyl-2 : 3 : 4-trihydroxy-5-formyl benzoate. A mixture of methyl-2 : 3 : 4-trihydroxy benzoate (12 g.), hexamethylene tetramine (36 g.), glacial acetic acid (60 c.c.) and sodium bi-sulphite (6 g.) was heated on a water-bath for 8–10 hours and for further 3–4 hours after the addition of dilute hydrochloric acid (130 c.c., 1 : 1). An orange-red compound, which separated, was filtered off. The filtrate was salted and both the filtrate and the orange-red solid, were extracted with ether, when a pale-yellow mass was obtained on the evaporation of the ether. On crystallizing from dilute hot alcohol, whitish, shiny, microcrystals were obtained (6·7 g.), m.p. 169–70°. (Found: C, 51·4; H, 4·3; $C_9H_8O_6$ requires C, 50·9; H, 3·8 per cent.) It gave a dark green colouration with alcoholic ferric chloride.

The 2 : 4-dinitrophenyl hydrazone of the formyl ester prepared in the usual manner and crystallized from glacial acetic acid in tiny orange-red crystals, melted at 295°. (Found: N, 14·2; $C_{15}H_{12}O_9N_4$ requires N 14·3 per cent.)

The 4-nitrophenyl hydrazone of the ester, prepared by the usual method and crystallized from acetic acid in orange red micro-crystals, melted at 285° with decomposition. (Found: N, 12·1, $C_{10}H_{12}O_4N_2$ requires N, 12·5 per cent.)

The semicarbazone of the ester, prepared in the usual manner, gave colourless micro-crystals, m.p. 238°. (Found: N, 15·6; $C_{10}H_{11}O_6N_3$ requires N, 15·7 per cent.)

Methyl-7 : 8 dihydroxy-3-acetyl-coumarin-6-carboxylate.—Piperidine (3 drops) was added to a mixture of the formyl ester (1 g.) and ethyl acetoacetate (1 g.) dissolved in pyridine (10 c.c.), and the mixture was heated at 100° for one hour. The solid obtained on the addition of dilute hydrochloric acid was triturated with 2 N-potassium hydroxide solution to remove the unreacted formyl ester. The insoluble solid obtained crystallized in greyish-white needles from dilute hot alcohol, m.p. 263–64°. (Found: C, 56·3; H, 4·0; $C_{13}H_{10}O_7$ requires C, 56·1; H, 3·6 per cent.)