The Chemistry of Fungi. Part LXXI.[1] Synthesis of 3,5-Dihydroxy-4-methylbenzoic Acid

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A five-step synthesis of 3,5-dihydroxy-4-methylbenzoic acid from tri-*O*-methylgallic acid is described.

OUR syntheses[2] of the sclerotiorin group of fungal metabolites and of their numerous degradation products use 3,5-dihydroxy-4-methylbenzoic acid as the starting material. The supply of this deceptively simple substance has caused substantial problems since it is only rarely available commercially and is extremely inaccessible by the three previously reported syntheses.

In the first method[3] 4-methylbenzoic acid is converted into the 3,5-bispotassiosulphonate, which is fused with potassium hydroxide. The fusion is most difficult to reproduce[4] and usually furnishes largely (and frequently entirely) 3,5-dihydroxybenzoic acid, by oxidative removal of the methyl residue. The second[5] method, which involves selective oxidation of β-orcinol dimethyl ether, is lengthy and gives the product in low yield, and the starting material is expensive and not readily available. The third preparation[6] involves conversion of 3-methoxy-2-methylphenol by lead tetra-acetate into 2-acetoxy-3-methoxy-2-methylcyclohexa-3,5-dienone. Hydrogen cyanide is then added to the αβ-unsaturated ketonic system to yield the nitrile (1), which is methylated. Sublimation of the methylation product furnishes 3,5-dimethoxy-4-methylbenzonitrile (2), from which the requisite acid is obtained by hydrolysis and demethylation—a low yielding multi-step process.

None of these methods is suitable for large-scale preparative operation, and after many unsuccessful investigations we have devised a more practical synthesis from gallic acid, an inexpensive, easily available material.

Thus, Birch reduction[7] of 3,4,5-trimethoxybenzoic acid, combined with an improved isolation procedure, gives 1,4-dihydro-3,5-dimethoxybenzoic acid in 94% yield. The n.m.r. spectrum of this acid exhibits long-range coupling, $J_{1,4}$ 6.5 Hz, a feature observed in other 1,4-dihydrobenzenes.[8] 1,4-Dihydrobenzenes are considered to exist in the boat form and the magnitude of this 1,4-coupling is regarded as indicative of stereo-

[1] Part LXX, M. Ahbab, A. D. Borthwick, J. W. Hooper, W. B. Whalley, G. Ferguson, and F. C. Marsh, preceding paper.

[2] See, for example, R. W. Gray and W. B. Whalley, *J. Chem. Soc.* (*C*), 1971, 3575 and references cited therein.

[3] (*a*) Y. Asahina and J. Asano, *Ber.*, 1933, **66B**, 687; (*b*) E. H. Charlesworth and R. Robinson, *J. Chem. Soc.*, 1934, 1531.

[4] W. B. Whalley (unpublished work) and personal communications from (the late) Alexander Robertson and (the late) Sir Robert Robinson and Dr. F. E. King.

[5] F. Fujikawa and T. Kobayashi, *J. Pharm. Soc. Japan*, 1944, **64**, 7.

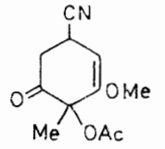
[6] F. Wessely, J. Swoboda, and V. Guth, *Monatsh.*, 1964, **95**, 649.

[7] (*a*) A. J. Birch, P. Hextall, and S. Sternhell, *Austral. J. Chem.*, 1954, **7**, 256; (*b*) M. E. Kuehne and B. F. Lambert, *J. Amer. Chem. Soc.*, 1959, **81**, 4278.

[8] E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, 'Conformational Analysis,' Interscience, New York, 1965, p. 125.

chemistry. Thus with 1,4-dihydro-4-phenyl-1-tritylbenzene [9] the coupling constant ($J_{1,4}$) of 11 Hz has been assigned to the '*cis*' structure (3), whereas the lower value (7.5 Hz) has been associated with the '*trans*' structure (4). By analogy 1,4-dihydro-3,5-dimethoxybenzoic may be assigned a similar '*trans*' structure.

Demethylation of this acid yields (quantitatively) 3,5-dioxocyclohexanecarboxylic acid (5; R = H). By



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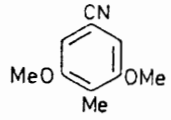

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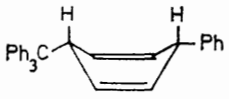

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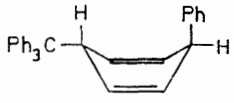

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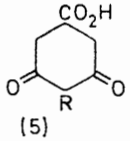

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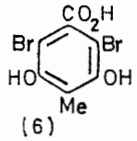

(6)

using aqueous dioxan in a two-phase system we have substantially improved the process of Stetter and Meisel [10] to yield the acid (5; R = Me), in 54% yield, identical with the product from the Birch reduction of 3,5-dihydroxy-4-methylbenzoic acid.

Bromination of the acid (5; R = Me) furnished a product which, in accord with the n.m.r. spectral data, is formulated as 2,6-dibromo-3,5-dihydroxy-4-methylbenzoic acid, from which the halogen was removed almost quantitatively by alkaline Raney nickel.

A similar sequence of reactions with methyl 3,5-dioxocyclohexanecarboxylate gave methyl 3,5-dihydroxy-4-methylbenzoate.

EXPERIMENTAL

1,4-Dihydro-3,5-dimethoxybenzoic Acid.—Reduction of 3,4,5-trimethoxybenzoic acid (24.5 g), dissolved in ethanol (300 ml) and liquid ammonia (1 l), by addition of sodium (15 g) was complete in 0.5 h, and ammonium chloride (60 g) was then added. Next day the remaining solvent was removed under vacuum and the residue dissolved in ice–water (1 l); the solution was subjected to alternate addition of 10% hydrochloric acid (at −5 °C) and immediate extraction with dichloromethane. The yield of product is substantially reduced if extraction is carried out at a temperature exceeding *ca.* −5 °C. The total yield of 1,4-dihydro-3,5-dimethoxybenzoic acid, m.p. 106—107° (decomp.) [lit.,[7] 105° (decomp.)] was 19.6 g (94%); the product possessed the requisite spectral properties.

Methyl 3,5-Dioxocyclohexanecarboxylate.—(i) An excess of ethereal diazomethane was added, at 0 °C, to a solution of 1,4-dihydro-3,5-dimethoxybenzoic acid (1 g) in methanol (25 ml), and 1 h later the excess of diazomethane and most of the solvent were removed *in vacuo*. Hydrochloric acid (4%; 10 ml) was added to the residue and 2.5 h later the solid was collected and purified from aqueous methanol to yield *methyl 3,5-dioxocyclohexanecarboxylate* in prisms, m.p. 122° (Found: C, 56.5; H, 6.0. $C_8H_{10}O_4$ requires C, 56.5; H, 5.9%), readily soluble in 2N-sodium hydrogen carbonate.

(ii) An excess of diazomethane (in ether) was added to a solution of 1,4-dihydro-3,5-dimethoxybenzoic acid (1 g) in methanol at 0 °C. Isolation of the product 15 min later gave methyl 1,4-dihydro-3,5-dimethoxybenzoate, which formed unstable needles (0.8 g), m.p. 35° (from aqueous methanol), τ 6.38 (6 H, s, C:C·OMe) and 6.28 (3 H, s, CO_2Me). When this ester was stirred vigorously during 30 min with hydrochloric acid (4%; 10 ml), methyl 3,5-dioxocyclohexanecarboxylate (0.6 g) was formed, identical with that obtained from method (i).

Treatment of this ester (0.5 g) in solution in methanol (80 ml) at 0 °C with an excess of diazomethane gave *methyl 3-methoxy-5-oxocyclohex-3-enecarboxylate* (0.5 g) in plates, m.p. 72° (from ether) (Found: C, 58.5; H, 6.5. $C_9H_{12}O_4$ requires C, 58.7; H, 6.5%), insoluble in 2N-sodium hydrogen carbonate.

4-Methyl-3,5-dioxocyclohexanecarboxylate.—(i) A solution of sodium hydroxide (15%; 40 ml) was added to a solution of 3,5-dioxocyclohexanecarboxylic acid (11.7 g) in water (20 ml) and dioxan (40 ml). Methyl iodide (10.7 g) was added to the cold, stirred solution, which was refluxed for 16 h; a further addition of methyl iodide (1.1 g) was followed by refluxing for 4 h. The cold mixture was acidified with 10% hydrochloric acid and maintained at 0 °C; several crops of yellow crystals were obtained; after separation of each batch, the solution was concentrated *in vacuo*. Purification from water gave 4-methyl-3,5-dioxocyclohexanecarboxylic acid (6.7 g) in pale yellow prisms, m.p. 244° (decomp.) (Found: C, 55.9; H, 5.9. Calc. for $C_8H_{10}O_4$: C, 56.5; H, 5.9%) (lit.,[10] m.p. 227°).

(ii) Reduction of 3,5-dimethoxy-4-methylbenzoic acid (1.0 g) in liquid ammonia (50 ml) and ethanol (10 ml) by addition of sodium (0.35 g) gave *1,4-dihydro-3,5-dimethoxy-4-methylbenzoic acid* (0.4 g) in needles, m.p. 130° (from ether) (Found: C, 60.5; H, 7.1. $C_{10}H_{14}O_4$ requires C, 60.6; H, 7.1%). Treatment of this acid (0.2 g) with hydrochloric acid (2%; 5 ml) at 100 °C during 15 min gave a quantitative yield of 4-methyl-3,5-dioxocyclohexanecarboxylic acid, identical (t.l.c., i.r., and m.p. and mixed m.p.) with that prepared by method (i).

3,5-Dihydroxy-4-methylbenzoic Acid.—(i) A suspension of 4-methyl-3,5-dioxocyclohexanecarboxylic acid (1.4 g) in acetic acid (40 ml) was treated (with stirring) with a solution of bromine (3.1 g) in acetic acid (20 ml) during 10 min. The resultant solution was stirred at 65 °C during 1.5 h, and the solvent was removed *in vacuo* to yield 2,6-dibromo-3,5-dihydroxy-4-methylbenzoic acid as a yellow solid (2.8 g). This was dissolved, without purification, in sodium hydroxide (2M; 70 ml) at 0 °C, and Raney nickel alloy (2.7 g) was added in small portions. The mixture was stirred overnight. Next day 3,5-dihydroxy-4-methylbenzoic acid (1.1 g) was isolated, m.p. 264—265°, identical with an authentic sample.

(ii) Methylation of 4-methyl-3,5-dioxocyclohexanecarboxylic acid (1.1 g) in methanol at 0 °C with an excess of ethereal diazomethane gave *methyl 3-methoxy-4-methyl-5-oxocyclohex-3-enecarboxylate* (0.9 g) in needles, m.p. 95° (from ether) (Found: C, 60.5; H, 7.2. $C_{10}H_{14}O_4$ requires C, 60.6; H, 7.1%). When this ester (0.6 g) was stirred with hydrochloric acid (4%; 12 ml) during 15 min the product (0.5 g) separated from dichloromethane to yield *methyl 4-methyl-3,5-dioxocyclohexanecarboxylate* in squat prisms, m.p. 161—162.5° (Found: C, 58.5; H, 6.6. $C_9H_{12}O_4$

[9] L. J. Durham, J. Studebaker, and M. J. Perkins, *Chem. Comm.*, 1965, 456.

[10] H. Stetter and H. Meisel, *Chem. Ber.*, 1957, **90**, 2928.

requires C, 58.7; H, 6.5%). A solution of this acid (0.28 g) in acetic acid (5 ml) was treated dropwise with bromine (0.65 g) dissolved in acetic acid (5 ml). After 2 h at 55 °C the product was isolated and purified from carbon tetrachloride to yield *methyl 2,6-dibromo-3,5-dihydroxy-4-methylbenzoate* in prisms (0.15 g), m.p. 161° (Found: C, 31.4; H, 2.6; Br, 46.1. $C_9H_8Br_2O_4$ requires C, 11.8; H, 2.4; Dr, 47.1%). Treatment of this ester in 2N-sodium hydroxide with an excess of Raney nickel during 1.5 h gave an almost quantitative conversion into 3,5-dihydroxy-4-methylbenzoic acid, identical (m.p., mixed m.p., t.l.c., and i.r., n.m.r., and mass spectra) with an authentic sample.

3-Ethoxy-5-oxocyclohex-3-enecarboxylic Acid.—A suspension of 3,5-dioxocyclohexanecarboxylic acid (0.35 g) in ether (50 ml) was added to a suspension of sodamide [from sodium (1 g)] in liquid ammonia (100 ml). After removal of the ammonia the resultant sodio-derivative was refluxed with ether (50 ml) containing ethyl iodide (20 ml) during 24 h, to yield *3-ethoxy-5-oxocyclohexanecarboxylic acid* (0.2 g) in prisms, m.p. 119° (from dioxan) (Found: C, 58.6; H, 6.4. $C_9H_{12}O_4$ requires C, 58.7; H, 6.5%). Formed similarly, the 3-methoxy-derivative was identical with that prepared previously by an alternative process.

Methyl 4,4-Dimethyl-3,5-dioxocyclohexanecarboxylate.—Methylation of methyl 3,5-dioxocyclohexanecarboxylate (0.2 g) by the methyl iodide (1 g)–potassium carbonate (2 g)–acetone (5 ml) method during 5 h gave *methyl 4,4-dimethyl-3,5-dioxocyclohexanecarboxylate* (0.7 g) in needles, m.p. 65° (from ether) (Found: C, 60.9; H, 7.0. $C_{10}H_{14}O_4$ requires C, 60.6; H, 7.1%).

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