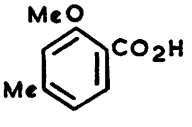
425. *Studies in Mycological Chemistry. Part V.* Synthesis of 2 : 5-Dihydroxy-7-methyl-1 : 4-naphthaquinone.*

By J. E. Davies and John C. Roberts.

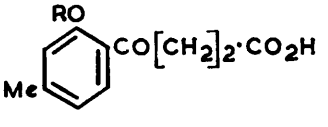
One of the products resulting from the reaction of *m*-cresol with succinic anhydride, in presence of aluminium chloride, has been proved to be β-(2-hydroxy-4-methylbenzoyl)propionic acid (II; R = H). From this readily available acid, 2 : 5-dihydroxy-7-methyl-1 : 4-naphthaquinone (VI; R = H) has been synthesised.

The quinone named above was required as a reference compound in an attempt to identify a pigment which had been obtained by degradation of purpurogenone,[1] a metabolic product of *Penicillium purpurogenum* Stoll. Furthermore, it was thought that a readily practicable synthesis, once established for a quinone of this structure, might serve as a prototype which could be developed into a synthesis of purpurogenone.

The unambiguous synthesis of 2-hydroxy-1 : 4-naphthaquinones, unsymmetrically substituted in the *ar*-ring, is best accomplished by a method [2] which proceeds by way of the tetralone. In our initial experiments the substituted butyric acid (III; R = Me) (required for ring-closure to the tetralone) was prepared by conversion (using the Bowman [3]



(I)



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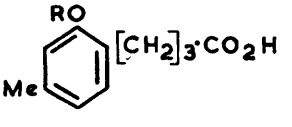

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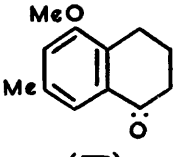

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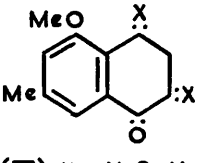
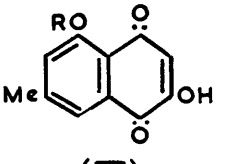


(V) X = N·C6H4·NMe2



(VI)

method) of *O*-methyl-*m*-cresotinic acid (I) into β-(2-methoxy-4-methylbenzoyl)propionic acid (II; R = Me), followed by reduction of the keto-acid by the modified Wolff–Kishner procedure. In a search for a more convenient synthesis of the substituted butyric acid

* Part IV, *J.*, 1955, 2992.

[1] Roberts and Warren, *J.*, 1955, 2992.

[2] (*a*) Pfeiffer and Hesse, *J. prakt. Chem.*, 1941, **158**, 315; Buu-Hoï and Cagniant, *Compt. rend.*, 1942, **214**, 87; (*b*) Davies, King, and Roberts, *J.*, 1955, 2782.

[3] (*a*) Bowman, *J.*, 1950, 325; (*b*) Davies *et al.*, ref. 2(*b*).

(III; R = Me) our attention was drawn to the work of Nargund and his co-workers [4] who had separated two β-(hydroxy-methylbenzoyl)propionic acids from the mixture formed by reaction of *m*-cresol with succinic anhydride in presence of anhydrous aluminium chloride. These workers considered one of their acids (m. p. 154—156°), on the basis of its analysis and its positive ferric reaction, to be β-(2-hydroxy-4-methylbenzoyl)propionic acid (II; R = H) but this did not finally prove its orientation. We have, however, proved its correctness by establishing the identity of the *O*-methyl derivative with the keto-acid (II; R = Me) which we had already synthesised by the Bowman method. Reduction of the acid (m. p. 154—156°) by the Clemmensen method yielded the acid (III; R = H), methylation of which yielded the required acid (III; R = Me). This route to the butyric acid proved the more expeditious.

Ring-closure of the butyric acid (by means of " polyphosphoric acid ") yielded the tetralone (IV) which was converted *via* the dianil (V) into the naphthaquinone (VI; R = Me). Demethylation then gave the required 2 : 5-dihydroxy-7-methyl-1 : 4-naphthaquinone (VI; R = H).

This substance differed from the purpurogenone degradation product both in its light-absorption and in certain of its colour reactions. Subsequent work has revealed that the degradation product (which is obtainable only in minute quantities [1]) is probably a naphthapurpurin derivative.

Experimental

O-*Methyl*-m-*cresotinic Acid*.—This was prepared by methylation of *m*-cresotinic acid (2-hydroxy-4-methylbenzoic acid) with methyl sulphate and alkali [5] or, better, by the following method. A solution of *m*-cresotinic acid (18 g.) and of methyl sulphate (39 c.c.) in acetone (300 c.c.), with anhydrous potassium carbonate (51 g.), was heated under reflux for 12 hr. The oily residue admixed with potassium salts, which remained after evaporation of the acetone, was heated under reflux with 5N-aqueous sodium hydroxide (300 c.c.) for 2½ hr. The resulting solution, when cooled, washed with ether, and acidified, gave the required acid, m. p. 99—104°, in yields of *ca.* 80%. Perkin *et al.*[5] give m. p. 103°.

O-*Methyl*-m-*cresotinoyl Chloride*.—The foregoing acid (13·9 g.) was heated under reflux with redistilled thionyl chloride (9·8 c.c.) for 1 hr. Removal of excess of reagent and distillation gave the acid chloride (14 g., 91%), b. p. 148—149°/12·5 mm., which solidified in an ice-bath. (Use of pyridine in this preparation [6] led to yields of 40%.)

β-(2-*Methoxy*-4-*methylbenzoyl*)*propionic Acid*.—(i) A solution of the foregoing acid chloride (16·2 g.) in sodium-dried benzene (50 c.c.; " AnalaR ") was added dropwise, with stirring, to a benzene solution of benzyl sodioethane-1 : 1 : 2-tricarboxylate which had been prepared by Bowman's method [3a] from sodium (1·8 g.), ethanol (55 c.c.), benzyl alcohol (28·5 g.), and ethyl ethane-1 : 1 : 2-tricarboxylate (22 g.). The ester produced was isolated and hydrogenated [first with 10% palladised charcoal (0·8 g.) and then palladised strontium carbonate (1·0 g.) during a total absorption of 4·75 l. of hydrogen], and the acid was decarboxylated in the usual way.[3] A solution of the oily product, of semicarbazide hydrochloride, and of sodium acetate in aqueous ethanol was kept at −2° for 48 hr. and the resulting solid was collected, washed with water, and crystallised from ethanol, to give β-(2-*methoxy*-4-*methylbenzoyl*)*propionic acid semicarbazone* as prisms, m. p. 186° (decomp.) (Found: C, 56·2; H, 5·8. $C_{13}H_{17}O_4N_3$ requires C, 55·9; H, 6·1%). This material was heated under reflux for 10 min. with an excess of 2N-hydrochloric acid. The mixture was cooled and the solid product was recrystallised from aqueous acetic acid, to give the desired keto-acid, m. p. 126—128° (9·3 g., 44% from the *O*-methyl-*m*-cresotinoyl chloride).

(ii) β-(2-Hydroxy-4-methylbenzoyl)propionic acid, m. p. 154—156° (Found: C, 63·3; H, 5·8. Calc. for $C_{11}H_{12}O_4$: C, 63·4; H, 5·8%), was prepared (in 37% yield) by the method of Raval *et al.*,[4a] who give the same m. p. Methylation of this acid (17 g.) [methyl sulphate (20·5 c.c.), acetone (225 c.c.), and anhydrous potassium carbonate (42·5 g.)] by the method described for the methylation of *m*-cresotinic acid gave β-(2-methoxy-4-methylbenzoyl)propionic acid (16 g., 66%) which crystallised from aqueous acetic acid in prisms (Found: C, 64·7; H,

[4] (*a*) Raval, Bokil, and Nargund, *J. Univ. Bombay*, 1938, **7**, Pt. 3, 184; (*b*) Trivedi and Nargund, *ibid.*, 1941, **10**, Pt. 3, 99.
[5] Perkin and Weizmann, *J.*, 1906, **89**, 1658.
[6] Cf. Carré and Libermann, *Compt. rend.*, 1934, **199**, 1422.

6·25. Calc. for $C_{12}H_{14}O_4$: C, 64·9; H, 6·35%), m. p. 126—128° (Trivedi *et al.*[4b] give the same m. p.) unaltered by admixture with the acid prepared by route (i).

γ-(2-Hydroxy-4-methylphenyl)butyric Acid.—β-(2-Hydroxy-4-methylbenzoyl)propionic acid, m. p. 154—156°, was reduced by the modified Clemmensen method [7] to give the crude acid (m. p. 70—72°; 96%). Recrystallisation from *n*-hexane yielded pure *γ-(2-hydroxy-4-methylphenyl)butyric acid* in small plates, m. p. 76—78° (Found: C, 68·4; H, 7·3. $C_{11}H_{14}O_3$ requires C, 68·0; H, 7·25%).

γ-(2-Methoxy-4-methylphenyl)butyric Acid.—(i) The foregoing hydroxy-acid (17 g.) was methylated in the way described for β-(2-hydroxy-4-methylbenzoyl)propionic acid. The product (14·3 g., 78%) was collected in the usual manner and recrystallised from *n*-hexane to give *γ-(2-methoxy-4-methylphenyl)butyric acid* in plates, m. p. 47·5—49·5° (Found: C, 69·5; H, 7·8. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·7%).

(ii) β-(2-Methoxy-4-methylbenzoyl)propionic acid (20·5 g.) was reduced [8] with potassium hydroxide (12·8 g.), diethylene glycol (93 c.c.), and 90% hydrazine hydrate (8·8 c.c.), and the product was isolated in the usual way. A solution of the crude acid in 3% aqueous sodium hydroxide (200 c.c.), containing a little sodium dithionite to prevent discoloration, was treated, portion-wise, at 80° with methyl sulphate (50 c.c.) and potassium hydroxide (61 g.). The solution was cooled and acidified and the crude γ-(2-methoxy-4-methylphenyl)butyric acid (12·5 g., 65%) was isolated by ether-extraction. Two recrystallisations from *n*-hexane yielded the pure acid, m. p. 47·5—49·5°.

5-Methoxy-7-methyltetral-1-one.—(i) The foregoing acid (3·0 g.) was added, with vigorous stirring, to "polyphosphoric acid" [phosphoric oxide (12 g.) and syrupy phosphoric acid (10 c.c.)] at 165°. The mixture was kept for 3 min. at this temperature, cooled to 90°, and then triturated with water. The product, isolated in the usual way, was distilled *in vacuo*, to give *5-methoxy-7-methyltetral-1-one* (1·75 g., 64%) as an almost colourless oil, b. p. 114—118°/0·05 mm. (Found: C, 75·9; H, 7·1. $C_{12}H_{14}O_2$ requires C, 75·8; H, 7·4%). Use of a lower temperature (90—100°) and of longer heating (25 min.) [9] gave a 30% yield. The 2 : 4-*dinitrophenylhydrazone* crystallised from chloroform–methanol in needles, m. p. 232—233° (decomp.) (Found: C, 58·4; H, 5·1. $C_{18}H_{18}O_5N_4$ requires C, 58·4; H, 4·9%).

(ii) Phosphoryl chloride (3 c.c.) was added dropwise to the butyric acid (6 g.) in tetrachloroethane (120 c.c.).[10] The solution was heated under reflux for 2½ hr. and poured on ice. The solvent was removed by steam-distillation and the residue collected in ether and purified in the usual way to give the tetralone (2·7 g., 50%) which was, however, less pure than that produced by the first method.

2 : 4-*Bis*-p-*dimethylaminophenylimino*-1 : 2 : 3 : 4-*tetrahydro*-5-*methoxy*-7-*methyl*-1-*oxonaphthalene.*—A solution made by the addition of 2N-sodium hydroxide (4 c.c.) to a solution of the foregoing tetralone (2·8 g.) and of *p*-nitrosodimethylaniline (5·6 g.) in ethanol (43 c.c.) was kept at room temperature for 2 days. The precipitated *dianil* (5·3 g., 78%) was collected and was crystallised from benzene–light petroleum (b. p. 40—60°) to give permanganate-coloured needles, m. p. 165—166° (decomp.) (Found: C, 74·1; H, 6·9. $C_{28}H_{30}O_2N_4$ requires C, 74·0; H, 6·65%).

2-*Hydroxy*-5-*methoxy*-7-*methyl*-1 : 4-*naphthaquinone.*—The dianil (2·15 g.) and 25% v/v sulphuric acid (60 c.c.) were heated under reflux for 1 hr. The mixture was cooled, diluted with water, and extracted with chloroform. The chloroform extract was then shaken with successive portions of saturated aqueous sodium hydrogen carbonate until the latter was no longer coloured. The combined aqueous extracts were acidified and extracted with chloroform. The chloroform solution was dried (Na_2SO_4) and the solvent was evaporated. Chromatography of a benzene solution of the residue on a column of anhydrous magnesium sulphate (11 × 4 cm.), development with benzene, elution of the yellow band with benzene containing 10% v/v of ether, and evaporation of the solvents from the eluate yielded *ca.* 0·5 g. of khaki-coloured material which was recrystallised from benzene–light petroleum (b. p. 100—120°) to give *2-hydroxy-5-methoxy-7-methyl-1 : 4-naphthaquinone* as yellow-ochre plates, m. p. 180—182° (decomp.) (Found: C, 66·0; H, 4·8. $C_{12}H_{10}O_4$ requires C, 66·0; H, 4·6%).

2 : 5-*Dihydroxy*-7-*methyl*-1 : 4-*naphthaquinone.*—Powdered aluminium chloride (75 g.) and sodium chloride (15 g.) were mixed in a warm mortar and then transferred to a small flask. The mixture was heated, with stirring, at 160° until dissolution was complete. The solution was

[7] Martin, *J. Amer. Chem. Soc.*, 1936, **58**, 1438.
[8] Huang-Minlon, *ibid.*, 1946, **68**, 2487.
[9] Cf. Koo, *ibid.*, 1953, **75**, 1891.
[10] Cf. Lockett and Short, *J.*, 1939, 789.

cooled to 90° and then poured, with stirring, on 2-hydroxy-5-methoxy-7-methyl-1 : 4-naphthaquinone (250 mg.). This mixture was kept, with stirring, at 180° for 4 min. and was then allowed to cool.[11] The mass was set aside overnight with a mixture of ice and concentrated hydrochloric acid. The resulting solution was diluted with water and extracted with ether. The ethereal solution was dried (Na_2SO_4), and the solvent was evaporated. The residue was dissolved in benzene and chromatographed on anhydrous magnesium sulphate (10 × 5 cm.), and the yellow band was eluted with benzene containing 10—15% by volume of ether. The solvent was removed from the eluate by distillation *in vacuo* and the residue was crystallised from light petroleum (b. p. 100—120°) to give 2 : 5-*dihydroxy*-7-*methyl*-1 : 4-*naphthaquinone* (150 mg., 64%) as orange plates, m. p. 200° (decomp.) (Found : C, 64·8; H, 4·1. $C_{11}H_8O_4$ requires C, 64·7; H, 3·95%). Light absorption in EtOH : $\lambda_{max.}$ 247, 290, 411 mμ (log ε 4·11, 4·06, and 3·59 respectively).

One of us (J. E. D.) thanks the Essex Education Committee for a grant.

THE UNIVERSITY, NOTTINGHAM. [*Received, January* 11*th*, 1956.]

[11] Cf. Brunner and Singule, *Monatsh.*, 1948, **79**, 81.