429. *Studies in Mycological Chemistry. Part XVI.* Synthesis of the Di-O-methylcurvularin Rearrangement Product.*

By B. W. Bycroft, John C. Roberts, and (in part) P. M. Baker.

An unequivocal synthesis of 2-5′-hydroxyhexyl-6,8-dimethoxynaphthalene-1,3-diol is described. The identity of this naphthol with a rearrangement product of di-*O*-methylcurvularin is established.

An elegant investigation [1] has established the structure of the mould metabolite, curvularin, as (VII; R = H). In the course of this work there was observed [1a] an interesting, alkali-induced isomerisation of di-*O*-methylcurvularin (VII; R = Me) to a compound which was formulated, mainly on analytical and spectroscopic evidence, as the naphthalene derivative (V).

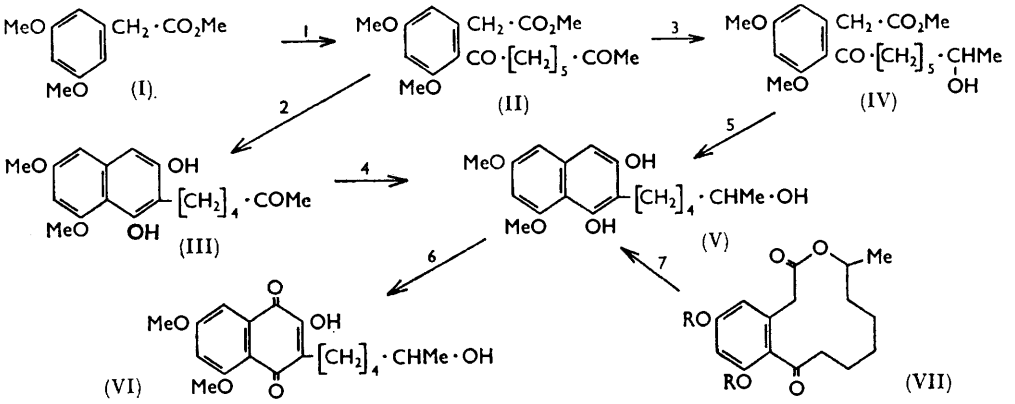
Our investigations into the synthesis of mould metabolites related to 1,3-dihydroxynaphthalenes [2] pointed the way to a synthesis of compound (V). This has been achieved by two routes, as shown. The synthetic naphthol (V) and the derived naphthaquinone

* Part XV, *J.*, 1963, 5148.

[1] (*a*) Birch, Musgrave, Rickards, and Smith, *J.*, 1959, 3146; (*b*) Musgrave, *J.*, 1957, 1104; 1956, 4301.

[2] Bycroft and Roberts, *J.*, (*a*) 1963, 4868; (*b*) 1962, 2063.

(VI) were identical with the corresponding compounds prepared from di-*O*-methylcurvularin (VII; R = Me). The structure deduced by earlier workers [1a] for the isomerisation product is thus confirmed.



Reagents: 1, $(CF_3CO)_2O$–MeCO·$[CH_2]_5$·CO_2H; 2, NaOMe–MeOH; 3, $NaBH_4$; 4, $NaBH_4$; 5, NaOMe–MeOH 6, NaOH–air; 7, NaOMe–MeOH.

Previous workers [1a] recorded a melting point of 103—105° for the naphthol (V) prepared from natural (optically active) curvularin by transannular cyclisation of its di-*O*-methyl derivative. From this preparation, using slightly different experimental conditions, we obtained a product having the same melting point (129—130°) as our synthetic naphthol. Furthermore, methylation (diazomethane) of our synthetic naphthol (V) gave the trimethoxynaphthol (V; OMe for OH at position 3) whose melting point (94·5—95·5°) was different from that (80—83°) previously recorded. However, the infrared spectrum of our synthetic trimethoxynaphthol was virtually identical with that of a specimen prepared from di-*O*-methylcurvularin. We cannot explain satisfactorily the discrepancies in melting points but suggest that they are mainly due to the occurrence of capricious racemisation during the isomerisation of di-*O*-methylcurvularin under the influence of alkali.

Experimental

Melting points were determined on a Kofler block apparatus. Ultraviolet spectra were measured for ethanolic solutions with a Perkin-Elmer spectrophotometer (model 137 UV). Infrared spectra were, unless otherwise stated, measured for compounds in potassium bromide discs with a Unicam S.P. 200 spectrophotometer.

7-Oxo-octanoic Acid.—Hydrolysis [3] of 2-acetylcyclohexanone [4] gave the acid (58%) as a colourless liquid, b. p. 151—152°/2 mm. (lit.,[3] 160—162°/4 mm.) [Found: Equiv. (by titration), 157. Calc. for $C_7H_{13}O(CO_2H)$, 158].

Methyl 3,5-Dimethoxy-2-7′-oxo-octanoylphenylacetate (II).—A solution of methyl 3,5-dimethoxyphenylacetate [2a] (I) (650 mg.) and 7-oxo-octanoic acid (500 mg.) in trifluoroacetic anhydride [5] (10 ml.) was kept, with stirring, at room temperature for 24 hr. and then poured into an excess of sodium hydrogen carbonate solution. The product was isolated with ether and the dry ethereal solution was chromatographed on a column (20 × 2 cm.) of acid-washed alumina (Spence, Type H). The column was developed with ether; elution with 5% ethanol–ether, and removal of the solvent, gave the *ester* (II) as a pale yellow oil (750 mg., 73%), $\lambda_{max.}$ 266 and 290 mμ (log ε 3·81 and 3·64), $\nu_{max.}$ (in CCl_4) 1740 (ester), 1717 (dialkyl ketone), and 1690 $cm.^{-1}$ (aryl alkyl ketone). The *monosemicarbazone* formed needles, m. p. 148—149° (from ethanol) (Found: C, 59·2; H, 7·2; N, 10·4. $C_{20}H_{29}N_3O_6$ requires C, 59·0; H, 7·2; N, 10·3%).

[3] Hauser, Swamer, and Ringler, *J. Amer. Chem. Soc.*, 1948, **70**, 4023.
[4] Manyik, Frostick, Sanderson, and Hauser, *J. Amer. Chem. Soc.*, 1953, **75**, 5030.
[5] Cf. Bourne, Stacey, Tatlow, and Tedder, *J.*, 1951, 718.

2-5′-*Hydroxyhexyl*-6,8-*dimethoxynaphthalene*-1,3-*diol* (V).—(*a*) A solution of the foregoing ester (II) (350 mg.) in methanol (2 ml.) was added dropwise during 3 min. to a refluxing solution of sodium methoxide (from 50 mg. of sodium) in methanol (3 ml.) under nitrogen. The solution was heated under reflux for a further 5 min., cooled, and acidified with 2N-sulphuric acid (5 ml.). Water (20 ml.) was added, and the solution was extracted several times with chloroform. The combined extracts were washed with water, dried ($MgSO_4$), and the solvent removed. To a solution of the residue (III) in ethanol (2 ml.) was added a solution of sodium borohydride (50 mg.) in 50% aqueous ethanol (5 ml.). The mixture was set aside for 15 min., acidified (2N-sulphuric acid), and diluted to 30 ml. with water. The product was extracted with chloroform, and the extract washed with sodium hydrogen carbonate solution and dried ($MgSO_4$). Removal of the solvent and repeated crystallisation of the residue from benzene gave the naphthol (V) as prisms (150 mg., 47%), m. p. 129—130° (Found: C, 67·2; H, 7·4; OMe, 19·2. Calc. for $C_{18}H_{24}O_5$: C, 67·5; H, 7·6; 2OMe, 19·4%), $\lambda_{max.}$ 245, 296, 302, 313, and 330 mμ (log ε 4·85, 3·59, 3·63, 3·56, and 3·37).

(*b*) To a solution of the ester (II) (300 mg.) in a minimum of ethanol was added a solution of sodium borohydride (50 mg.) in water (5 ml.). The mixture was kept at room temperature, with occasional shaking, for 15 min., acidified (2N-sulphuric acid), and diluted with water (15 ml.). Extraction with ether, reduction of the dried ($MgSO_4$) ethereal solution to small volume, passage through a small column of acid-washed alumina (Spence, Type H), and removal of the solvent gave the alcohol (IV) as a colourless oil (160 mg.), $\lambda_{max.}$ 266 and 291 mμ (log ε 3·79 and 3·63), $\nu_{max.}$ (in CCl_4) 1740 (ester) and 1690 $cm.^{-1}$ (aryl alkyl ketone), but no band near 1717 $cm.^{-1}$. Cyclisation of compound (IV) with sodium methoxide in methanol, under nitrogen, gave the naphthol (V), m. p. 129—130°. It gave a red ferric chloride reaction in ethanol.

2-*Hydroxy*-3-5′-*hydroxyhexyl*-5,7-*dimethoxy*-1,4-*naphthaquinone* (VI).—The foregoing naphthol (200 mg.) was dissolved in 2N-sodium hydroxide (10 ml.), and air was drawn through the solution for 5 hr. The resulting deep red solution was acidified (2N-sulphuric acid) and extracted several times with chloroform. The combined extracts were washed with water and dried ($MgSO_4$). Removal of the solvent and crystallisation of the amorphous residue from chloroform–benzene gave the *naphthaquinone* (VI) as yellow needles (180 mg.), m. p. 180—182° (Found: C, 64·4; H, 6·3; OMe, 18·8. $C_{18}H_{22}O_6$ requires C, 64·7; H, 6·6; 2OMe, 18·6%), $\lambda_{max.}$ 212, 261, 305, 370, and 423 mμ (log ε 4·49, 4·27, 4·03, 3·56, and 3·22). This spectrum is very similar to that of 2-hydroxy-5,7-dimethoxy-1,4-naphthaquinone.[2b]

Rearrangement of Di-O-methylcurvularin (VII; R = Me).—A solution of this ether (80 mg.) in methanol (2 ml.) was added dropwise during 5 min. to a refluxing solution of sodium methoxide (from 20 mg. of sodium) in methanol (3 ml.) under nitrogen. The solution was heated under reflux for a further 2 min., cooled, acidified (N-sulphuric acid), and diluted with water. The aqueous solution was extracted repeatedly with chloroform, and the combined extracts were washed with water and dried ($MgSO_4$). Removal of the solvent and repeated crystallisation of the residue from benzene gave the naphthol (V) as prisms (47 mg.) identical (m. p., mixed m. p., and ultraviolet and infrared spectra) with the synthetic material prepared as above.

Oxidation of the residues from the crystallisation of the naphthol prepared from the curvularin, by the method already described, and crystallisation of the product from chloroform–benzene, gave the quinone (VI) as yellow needles (7 mg.), identical (m. p., mixed m. p., and ultraviolet and infrared spectra) with the sample synthesised as above.

2-5′-*Hydroxyhexyl*-3,6,8-*trimethoxy*-1-*naphthol*.—(*a*) To a solution of the synthetic naphthol (V) (248 mg.) in a minimum of dry methanol, was added excess of an ethereal solution of diazomethane. The mixture was kept at 0° for 2 days. A solution of the crude product in dry benzene was chromatographed on a column (20 × 2 cm.) of silica. The column was developed with benzene and the desired product was eluted with benzene–ethyl acetate (7 : 3). Removal of the solvent and crystallisation of the residue from benzene–light petroleum (b. p. 40—60°) gave the trimethoxynaphthol (52 mg.) as prisms, m. p. 94·5—95·5° (Found: C, 68·3; H, 7·7; OMe, 28·0. Calc. for $C_{19}H_{26}O_5$: C, 68·2; H, 7·8; 3OMe, 27·8%), $\lambda_{max.}$ 246, 289, 299, 314, and 330 mμ (log ε 4·87, 3·63, 3·61, 3·46, and 3·34), $\nu_{max.}$ (in CS_2) 3414 and 1637 $cm.^{-1}$.

(*b*) A sample of the naphthol (V), m. p. 128—129°, prepared from di-*O*-methylcurvularin, was methylated, and the product was purified as in (*a*) above. The trimethoxynaphthol, m. p. 74—76° (lit.,[1a] 80—83°), had $\lambda_{max.}$ 246, 290, 303, 316, and 331 mμ (log ε 4·86, 3·60, 3·59, 3·44,

and 3·27). Its infrared spectrum (which included significant peaks at 3400, 2920, 1636, and 1150 cm.$^{-1}$) was virtually identical with that of the product prepared by method (*a*) above, and with that of a sample supplied by Professor Birch.

We thank Professor A. J. Birch, F.R.S., for a generous gift of curvularin and some of its derivatives, and the D.S.I.R. for the award of maintenance grants to B. W. B. and P. M. B.

THE UNIVERSITY, NOTTINGHAM. [*Received, July* 31*st*, 1963.]