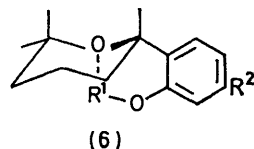
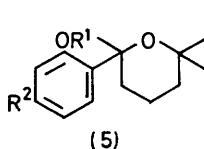
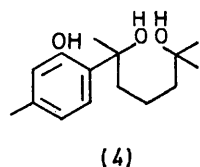
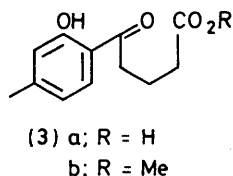
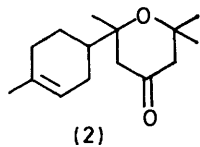
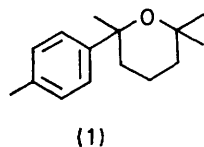


## Studies in Terpenoids. Part 40.<sup>1</sup> Synthesis of (±)-Sydowic Acid

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5-Methyl-2-(2,6,6-trimethyltetrahydropyran-2-yl)phenol (5a), a phenolic analogue of the naturally occurring curcumen ether (1), has been synthesised *via* 5-(2-hydroxy-4-methylphenyl)-5-oxopentanoic acid (3a). Oxidation with alkaline permanganate or treatment with *N*-bromosuccinimide of the acetate (5b) followed by hydrolysis gave (±)-sydowic acid [3-hydroxy-4-(2,6,6-trimethyltetrahydropyran-2-yl)benzoic acid] (5c), a fungal metabolite isolated from *Aspergillus sydowi*.

A PHENOLIC tetrahydropyran sesquiterpenoid named sydowic acid (5c) has been isolated recently from



- a; R<sup>1</sup> = H, R<sup>2</sup> = Me  
b; R<sup>1</sup> = Ac, R<sup>2</sup> = Me  
c; R<sup>1</sup> = H, R<sup>2</sup> = CO<sub>2</sub>H  
d; R<sup>1</sup> = Ac, R<sup>2</sup> = CHBr<sub>2</sub>

*Aspergillus sydowi*.<sup>2</sup> The closely related non-phenolic tetrahydropyran, curcumen ether<sup>3</sup> (1) and the pyranone

<sup>1</sup> Part 39, T. K. John and G. S. Krishna Rao, *Indian J. Chem.*, in the press.

<sup>2</sup> (a) T. Hamasaki, Y. Sato, Y. Hatsuda, M. Tanabe, and L. W. Cary, *Tetrahedron Letters*, 1975, 659; (b) T. Hamasaki, Y. Sato, and Y. Hatsuda, *Agric. and Biol. Chem. (Japan)*, 1975, **39**, 2337; (c) K. Fukuyama, T. Tsukihara, Y. Katsube, T. Hamasaki, and Y. Hatsuda, *Agric. and Biol. Chem. (Japan)*, 1976, **40**, 1053.

deodarone<sup>4</sup> (2) of plant origin have been synthesised.<sup>4-6</sup> As part of a programme of synthesis of phenolic sesquiterpenoids<sup>1,7</sup> and sesquiterpene acids,<sup>8</sup> we undertook the synthesis of sydowic acid.

Acylation of *m*-cresol with glutaric anhydride furnished the phenolic oxo-acid (3a), the methyl ester of which on treatment with an excess of methylmagnesium iodide afforded the phenolic diol (4) as a crystalline solid. Ring closure to the tetrahydropyran (5a) proceeded smoothly on treatment with aqueous sulphuric acid at 0 °C. The ether (5a) is of interest because of (i) its relationship with the naturally occurring curcumen ether<sup>3</sup> (1) and (ii) its conformation.

Conformationally, (6a) appears a satisfactory representation of the ether (5a), with the aryl ring equatorial to the tetrahydropyran ring, the ring oxygen and the aromatic hydroxy-group being involved in intramolecular hydrogen bonding<sup>2c</sup> [ $\nu_{\max}$  (CCl<sub>4</sub>) 3300 cm<sup>-1</sup> (OH), no change in maximum in solutions of different dilutions]. Each of the three methyl groups on the tetrahydropyran ring in compounds (5a—d) invariably gives rise to a well separated <sup>1</sup>H n.m.r. singlet, as expected for the conformational model (6).

The ether (5a) was acetylated; oxidation of the acetate

<sup>3</sup> B. Tomita, Y. Hirose, and T. Nakatsuka, *Mokuzai Gakkaishi*, 1969, **15**, 47 (*Chem. Abs.*, 1969, **71**, 50250t).

<sup>4</sup> R. Shankaranarayanan, S. Krishnappa, S. C. Bisarya, and Sukh Dev, *Tetrahedron Letters*, 1973, 427.

<sup>5</sup> O. P. Vig, H. Kumar, J. P. Salota, and S. D. Sharma, *Indian J. Chem.*, 1973, **11**, 86.

<sup>6</sup> Y. Gopichand and K. K. Chakravarthi, *Tetrahedron Letters*, 1974, 3851.

<sup>7</sup> (a) J. Alexander and G. S. Krishna Rao, *Tetrahedron*, 1971, **27**, 645; (b) V. Viswanatha and G. S. Krishna Rao, *Tetrahedron Letters*, 1974, 243; (c) R. B. Mane and G. S. Krishna Rao, *Indian J. Chem.*, 1974, **12**, 938; (d) G. Usha Devi and G. S. Krishna Rao, *ibid.*, 1976, **14B**, 162.

<sup>8</sup> K. Subrahmanya Ayyar and G. S. Krishna Rao, *Perfumery Essent. Oil Record*, 1968, **58**, 114.

(5b) with alkaline permanganate<sup>9</sup> followed by hydrolysis of the crude acetoxy-acid furnished ( $\pm$ )-sydowic acid (5c), m.p. 144° (lit.,<sup>2</sup> 151° for the optically active natural product), identical in i.r. and n.m.r. spectra with the natural product. Though several other attempts to oxidise the aromatic methyl group of the acetoxy-compound (5b) [by cerium(IV) ammonium nitrate,<sup>10</sup> chromic acid,<sup>11,12</sup> or neutral permanganate<sup>13</sup>] proved unrewarding, side-chain halogenation with a large excess of *N*-bromosuccinimide<sup>11</sup> followed by refluxing with ethanolic potassium hydroxide afforded, in comparable yield and purity, crystalline ( $\pm$ )-sydowic acid (5c), formed presumably by aerial oxidation of the aldehyde resulting from the dibromomethyl compound (5d).

#### EXPERIMENTAL

I.r. spectra were recorded on a Perkin-Elmer Infracord 127 or Zeiss UR-10 instrument, u.v. spectra with a Unicam SP 700 spectrometer and n.m.r. spectra with a Varian HA-100D or T-60 instrument. Light petroleum refers to the fraction with b.p. 40–60 °C. Solvent extracts were appropriately washed and dried (Na<sub>2</sub>SO<sub>4</sub>) before evaporation.

**5-(2-Hydroxy-4-methylphenyl)-5-oxopentanoic Acid (3a).**—To a mixture of *m*-cresol (43.2 g), glutaric anhydride (45.6 g), and tetrachloroethane (188 ml), aluminium chloride (112 g) was added in portions with stirring during 1 h. The mixture was then gradually heated on an oil-bath to 130 °C, maintained at this temperature for 2 h, cooled, and poured into ice (500 g) and concentrated hydrochloric acid (200 ml). The organic layer was separated and the aqueous phase was extracted with chloroform (200 ml). The combined organic phase was washed with water (200 ml) and extracted with saturated sodium carbonate solution (5 × 100 ml). After being washed with ether (200 ml), the sodium carbonate solution was acidified with concentrated hydrochloric acid. The precipitated yellow solid was crystallised from benzene to give the pure *oxo-acid* (3a) (25 g), m.p. 135° (Found: C, 64.8; H, 6.6. C<sub>12</sub>H<sub>14</sub>O<sub>4</sub> requires C, 64.85; H, 6.35%).

Refluxing the *oxo-acid* (3a) (18.5 g) with methanol (150 ml) and concentrated sulphuric acid (3.5 ml) on a water-bath for 10 h and work-up in the usual manner gave the *methyl ester* (3b) (12 g), m.p. 50° (from hexane),  $\nu_{\max}$  (Nujol) 1 739 (ester C=O) and 1 639 cm<sup>-1</sup> (hydrogen-bonded ketonic C=O),  $\delta$  (CCl<sub>4</sub>) 2.05 (m, 3-H<sub>2</sub>), 2.33 (5 H, merged s and m, ArMe and 2-H<sub>2</sub>), 3.02 (2 H, t, 4-H<sub>2</sub>), 3.65 (3 H, s, CO<sub>2</sub>Me), 6.67 (2 H, d, aryl H-3 and -5), 7.63 (1 H, d, *J* 8 Hz, aryl H-6), and 12.1 (1 H, s, OH) (Found: C, 66.05; H, 7.0. C<sub>13</sub>H<sub>16</sub>O<sub>4</sub> requires C, 66.1; H, 6.85%).

**2-(2-Hydroxy-4-methylphenyl)-6-methylheptane-2,6-diol (4).**—To a suspension of Grignard reagent prepared from methyl iodide (23 ml) and magnesium (8.5 g) in dry ether (250 ml) was added with stirring a solution of the phenolic *oxo-ester* (3b) (11.7 g) in dry ether (100 ml) during 3 h. The mixture was then refluxed for 2 h, left overnight, and decomposed with cold saturated ammonium chloride solution (300 ml). The ether layer was separated and the aqueous layer was extracted with ether (150 ml). Removal of the solvent from the combined organic phase gave the phenolic *diol* (4) (12 g) as a white solid, m.p. 140° (from ethanol),  $\nu_{\max}$  (Nujol) 3 636

(free OH) and 3 390 cm<sup>-1</sup> (hydrogen-bonded OH),  $\delta$  [(CD<sub>3</sub>)<sub>2</sub>CO] 1.10 (6 H, s, CMe<sub>2</sub>OH), 1.60 (3 H, s, 2-Me), 2.22 (3 H, s, ArMe), 3.08br (1 H, s, OH, exchanges with D<sub>2</sub>O), 6.58 (2 H, m, aryl H-3 and -5), 6.98 (1 H, d, *J* 8 Hz, aryl H-6), and 9.70 (1 H, s, phenolic OH, exchanges with D<sub>2</sub>O) (Found: C, 71.4; H, 9.5. C<sub>15</sub>H<sub>24</sub>O<sub>3</sub> requires C, 71.4; H, 9.6%).

**5-Methyl-2-(2,6,6-trimethyltetrahydropyran-2-yl)phenol (5a).**—Sulphuric acid (70%; 50 ml) was added dropwise to the phenolic diol (4) (10 g) dissolved in distilled ether (300 ml) at 0 °C. The mixture was stirred at room temperature for 7 h. The ether layer was separated and the aqueous phase was extracted with ether (100 ml). The combined ethereal extract was washed until neutral and dried. Removal of the solvent gave a viscous liquid (8 g) which was purified by passing twice through a silica gel column. Elution with benzene gave the *phenolic tetrahydropyran* (5a) (5.0 g), b.p. 120° at 3 mmHg,  $\nu_{\max}$  (CCl<sub>4</sub>) 3 300 cm<sup>-1</sup>,  $\delta$  (CCl<sub>4</sub>) 0.93 (3 H, s, Me), 1.32 (3 H, s, Me), 1.43 (3 H, s, Me), 1.20–1.87 (6 H, m, CH<sub>2</sub>), 2.25 (3 H, s, 5-Me), 6.40–6.87 (3 H, m, ArH), and 8.63 (1 H, s, phenolic OH, exchanges with D<sub>2</sub>O) (Found: C, 77.05; H, 9.65. C<sub>15</sub>H<sub>22</sub>O<sub>2</sub> requires C, 76.9; H, 9.45%). The phenol (5a) (5.0 g) was heated with acetic anhydride (50 ml) and pyridine (50 ml) on a boiling water-bath for 10 h. The mixture was poured into hydrochloric acid (5%; 250 ml). The product was extracted with ether (5 × 100 ml). The usual work-up followed by column chromatography (silica gel; benzene) gave the *acetate* (5b) (4.9 g), b.p. 138° at 3 mmHg,  $\nu_{\max}$  (neat) 1 776 cm<sup>-1</sup> (phenolic acetate),  $\delta$  (CCl<sub>4</sub>) 0.75 (3 H, s, Me), 1.13 (3 H, s, Me), 1.48 (3 H, s, Me), 1.33–1.83 (6 H, m, CH<sub>2</sub>), 2.20 (3 H, s, 5-Me or OAc), 2.27 (3 H, s, 5-Me or OAc), 6.73 (2 H, m, aryl H-3 and -5), and 7.20 (1 H, d, *J* 8 Hz, aryl H-6) (Found: C, 73.95; H, 8.75. C<sub>17</sub>H<sub>24</sub>O<sub>3</sub> requires C, 73.9; H, 8.7%).

**( $\pm$ )-Sydowic Acid [3-Hydroxy-4-(2,6,6-trimethyltetrahydropyran-2-yl)benzoic Acid] (5c).**—(a) A mixture of the foregoing acetate (5b) (250 mg), potassium permanganate (1 g), sodium carbonate (125 mg), and water (20 ml) was refluxed for 3 h, cooled, acidified with dilute sulphuric acid, and heated on a water-bath for 10 min. The manganese salts were decolourised with sodium hydrogen sulphite. The product was extracted with ether (150 ml). Removal of the solvent gave the crude acetoxy-acid (120 mg), which was hydrolysed with ethanolic potassium hydroxide (20%; 10 ml) by heating on a water-bath for 6 h. The usual work-up after acidification gave ( $\pm$ )-sydowic acid (5c) (50 mg), m.p. 144° (from ethyl acetate–hexane).

(b) A mixture of the acetate (5b) (276 mg), carbon tetrachloride (60 ml), *N*-bromosuccinimide (1.05 g), and a catalytic amount of benzoyl peroxide was heated on a water-bath for 2 h, then cooled and the separated succinimide was filtered off. Removal of the solvent left the *dibromomethyl compound* (5d) (400 mg),  $\delta$  (CCl<sub>4</sub>-CDCl<sub>3</sub>) 0.59 (3 H, s, Me), 0.98 (3 H, s, Me), 1.30 (3 H, s, Me), 1.3–1.85 (6 H, m, CH<sub>2</sub>), 2.08 (3 H, s, OAc), 6.5 (1 H, s, Br<sub>2</sub>CH), and 7.1–7.54 (3 H, m, aryl H-3, -5, and -6) (Found: C, 47.4; H, 4.75. C<sub>17</sub>H<sub>22</sub>Br<sub>2</sub>O<sub>3</sub> requires C, 47.0; H, 5.05%). The dibromomethyl compound (5d) was refluxed (6 h) with ethanolic potassium hydroxide (10%; 25 ml). The usual work-up after acidification gave ( $\pm$ )-sydowic acid (5c) (80 mg) identical with the above, m.p. 144° (from ethyl acetate–hexane),

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<sup>12</sup> C. Enzell and H. Erdtman, *Tetrahedron*, 1958, **4**, 361.

<sup>13</sup> A. W. Singer and S. M. McElvain, *Org. Synth.*, Coll. Vol. III, 1955, p. 740.

<sup>9</sup> A. I. Vogel, 'A Text Book of Practical Organic Chemistry,' Longmans, London, 1971, 3rd edn., p. 520.

<sup>10</sup> T. L. Ho, *Synthesis*, 1973, 347.

$\nu_{\max.}$  (CHCl<sub>3</sub>) 4 000—3 200br (OH and CO<sub>2</sub>H) and 1 685 cm<sup>-1</sup> (C=O of CO<sub>2</sub>H) (the spectrum of a KBr pellet agreed with the spectrum of the natural product),  $\lambda_{\max.}$  (EtOH) 238 (4 800) and 290 nm ( $\epsilon$  1 800),  $\delta$  (CDCl<sub>3</sub>) 0.97 (3 H, s, Me), 1.30 (3 H, s, Me), 1.50 (3 H, s, Me), 1.5—1.93 and 2.27—2.56 (6 H, m, CH<sub>2</sub>), 7.12 (1 H, d,  $J$  9 Hz, aryl H-6), 7.56 (2 H, m, aryl H-3 and -5), 9.33 (1 H, s, OH or CO<sub>2</sub>H), and 10.38br (1 H, s, OH or CO<sub>2</sub>H) (identical with an authentic spectrum of the

natural product) (Found: C, 67.8; H, 7.4. C<sub>15</sub>H<sub>20</sub>O<sub>4</sub> requires C, 68.15; H, 7.65%).

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