

Studies on Terpenes. Part III.¹ Synthesis of (–)-Neoverbanol (Pinan-4-ol)

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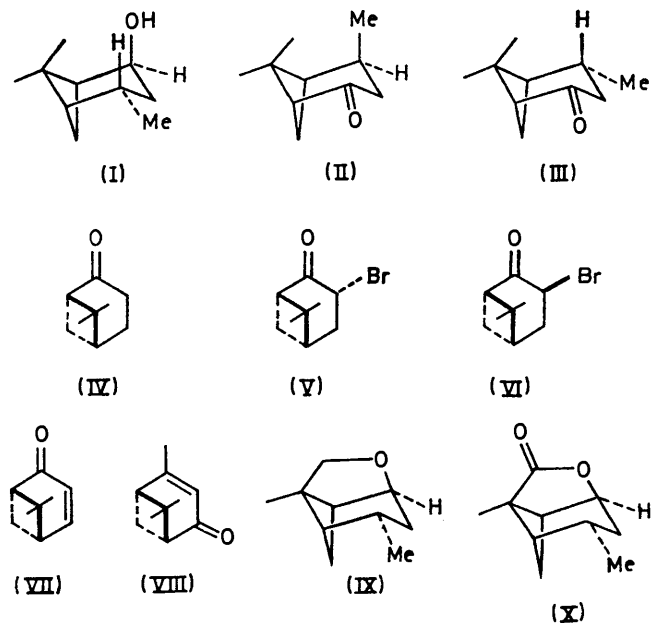
The structure of (–)-neoverbanol (I) has been established by unambiguous synthesis from optically pure starting materials.

WHILE engaged on work directed towards utilising optically pure terpenes as starting materials for the synthesis of natural products we required a source of so-called neoverbanol (I). The method described in the literature^{1,2} did not appear suitable for the preparation of large quantities of neoverbanol since separation of the *cis*- and *trans*-verbanones [(II) and (III), respectively] was required.† Consequently we have conducted a synthesis of *trans*-verbanone, subsequently converted into neoverbanol, that stereospecifically introduces the 2-methyl group *trans* to the *gem*-dimethyl bridge.

(+)-Nopinone (6,6-dimethylnorpinan-2-one) (IV) was treated with *N*-bromosuccinimide to give 3 α -bromopinone (V), which was chromatographed over neutral alumina to give 3 β -bromopinone (VI).³ Dehydrobromination of 3 β -bromopinone (VI) in dimethyl sulphoxide containing lithium carbonate and lithium bromide for 72 h at 140–145° gave pure apoverbenone (VII) (60%).³ This reaction was readily scaled up to 68 g.

Treatment of apoverbenone (VII) with lithium dimethylcuprate according to Marshall's procedure⁴ gave (+)-*trans*-verbanone [mirror image of (III)] in 90% yield. *cis*-Verbanone (II) was prepared by hydrogenation of (+)-verbenone (VIII);¹ its n.m.r. spectrum (see Table) was different from that of (+)-*trans*-verbanone (III). Reduction of (+)-*trans*-verbanone [mirror image of (III)] with lithium aluminium hydride gave (–)-neoverbanol (I) (90%), m.p. 77–77.5°, $[\alpha]_D^{21.5} -16.1^\circ$ (*c* 3% in benzene). The properties

recorded by Regan¹ do not agree with those of our sample of (–)-neoverbanol. As proof of the configuration of the newly introduced hydroxy-group,



All formulae are depicted in their correct absolute configuration

(–)-neoverbanol (I) was irradiated in the presence of mercuric oxide and bromine in pentane⁵ to give the ether (IX) (70%), which was oxidised to the lactone (X), ν_{\max} 1770 cm^{-1} .

† For a summary of the early literature see refs. 1 and 2.

¹ A. F. Regan, *Tetrahedron*, 1969, 3801.

² A. K. Bose, *J. Org. Chem.*, 1955, **20**, 1010; Y. Bessiere-Chretien and G. Grison, *Bull. Soc. chim. France*, 1970, 3103.

³ J. Grimshaw, J. T. Grimshaw, and H. R. Juneja, *J.C.S. Perkin I*, 1972, 50.

⁴ J. A. Marshall and R. A. Ruden, *J. Org. Chem.*, 1972, **37**, 659.

⁵ N. Bosworth and P. D. Magnus, *J.C.S. Perkin I*, 1972, 943, and references cited therein.

The structure of (–)-neoverbanol (I) is therefore established by unambiguous synthesis; the only remaining problem is the discrepancy between Regan's structure and ours (they are mirror images). This discrepancy is best explained in terms of optical purity. Regan's material was not optically pure since the α -pinene used to prepare the *trans*-verbenol [subsequently converted into (I)¹] was not optically pure; however the β -pinene used by us to prepare neoverbanol was optically pure.

EXPERIMENTAL

M.p.s were determined on a Kofler hot-stage apparatus. I.r. spectra were measured for Nujol mulls or thin films

N.m.r. data

Compound	τ Values (J in Hz) *
<i>cis</i> -Verbanone (III)	9.01 (3H, s), 8.82 (3H, d, J 7), 8.65 (3H, s) 8.97 (3H, s), 8.81 (3H, d, J 8.8), 8.64 (3H, s)
<i>trans</i> -Verbanone (III)	9.18 (3H, s), 8.94 (3H, d, J 7), 8.66 (3H, s) 9.14 (3H, s), 8.80 (3H, d, J 9), 8.65 (3H, s)
Neoverbanol (I)	9.12 (3H, d, J 7), 8.95 (3H, s), 8.80 (3H, s), 5.85 (1H, m) 9.10 (3H, d, J 6.5), 8.93 (3H, s), 8.77 (3H, s), 5.80 (1H, m)

* The methylene signals occurred at τ 7.9–9.0. Only diagnostic signals are mentioned. The upper set of figures are Regan's data,¹ the lower set are ours.

unless otherwise stated. N.m.r. spectra were recorded with a Varian A60 instrument for solutions in [²H]chloroform with tetramethylsilane as internal standard.

All solvents were purified prior to use by standard techniques. Light petroleum refers to the fraction b.p. 40–60°.

3 β -Bromo-6,6-dimethylnorpinan-2-one (VI) (3 β -Bromonopinone).—Prepared according to the method of Grimshaw,³ in 67% yield on a 75 g scale, this had m.p. 112–113° (from light petroleum) (lit.,³ 112–113°).

6,6-Dimethylnorpin-3-en-2-one (Apoverbenone) (VII).—Dehydrohalogenation of 3 β -bromonopinone (68 g) in dry dimethyl sulphoxide (500 ml) containing lithium carbonate (110 g) and lithium bromide (110 g) at 140–145° for 72 h gave apoverbenone (VII) (60%), whose physical properties were in accord with reported data.³

(+)-*trans*-Verbanone [Mirror Image of (III)].—To a stirred suspension of copper(I) iodide (5.53 g) in dry ether (190 ml) at 0° was added methyl-lithium (1.40M in ether; 48 ml). After 1 h a solution of apoverbenone (VII) (1.45 g) in ether (75 ml) was added during 20 min and the mixture was kept at 0° for 1 h. Work-up gave (+)-*trans*-verbanone (1.1 g, 90%), b.p. 70–74° at 6 mmHg, $n_D^{22.5}$ 1.4665, ν_{\max} 1713 cm⁻¹; for n.m.r. data see Table; $[\alpha]_D^{21} + 22.4^\circ$ (*c* 10% in benzene). The *oxime*, prepared in the usual way (NH₂OH, HCl-pyridine) had m.p. ca. 18°, $[\alpha]_D^{21} + 32.0^\circ$ (*c* 4% in CHCl₃) [lit.,² for (–)-*trans*-verbanone oxime, –30.5°] (Found: C, 71.7; H, 10.0;

N, 8.2. C₁₀H₁₇NO requires C, 71.8; H, 10.2; N, 8.4%). *cis*-Verbanone oxime had m.p. 60–62.5°.

(–)-Neoverbanol (Pinan-4-ol) (I).—(+)-*trans*-verbanone (5.00 g) in ether (100 ml) was treated with an excess of lithium aluminium hydride for 1 h at room temperature. Work-up in the usual way gave (–)-neoverbanol (I) (90%), m.p. 77–77.5° (from light petroleum), ν_{\max} 3250, 2900, 1475, 1380, 1355, 1340, 1320, 1275, 1130, 1105, 1075, 1040, and 870 cm⁻¹; for n.m.r. data see Table; $[\alpha]_D^{21.5} - 8.24$ (*c* 6% in CHCl₃) (Found: C, 78.1; H, 11.8. C₁₀H₁₈O requires C, 77.9; H, 11.8%).

4,9-Dimethyl-7-oxatricyclo[4.3.0.0^{3,9}]nonane (IX).—Neoverbanol (I) (1.65 g) and mercuric oxide (3.8 g) were stirred in pentane (50 ml) at reflux under argon. A solution of bromine (2.6 g) in pentane (15 ml) was added during 2 h

while the reaction mixture was irradiated with a 750 W tungsten lamp (the bromine-pentane solution was protected from light). The mixture was refluxed for a further 1 h then filtered. The pentane solution was washed with saturated aqueous sodium hydrogen carbonate, saturated aqueous sodium chloride, and aqueous pyridine (to remove any alkyl bromides), dried (Na₂SO₄), and evaporated, and the residue was chromatographed on alumina (G3) (elution with light petroleum). The ether (IX) (70%) had b.p. 62° at 5 mmHg, ν_{\max} 2950, 1460, 1475, 1375, 1150, 1050, 1030, 935, and 840 cm⁻¹, τ 8.72 (3H, s), 9.13 (3H, d, J 6 Hz), 6.40 (2H, ABq, J 9 Hz), and 5.47 (1H, m), $[\alpha]_D^{21.5} + 62.7^\circ$ (*c* 4% in CHCl₃) (Found: C, 78.6; H, 10.4. C₁₀H₁₆O requires C, 78.9; H, 10.6%).

4,9-Dimethyl-7-oxatricyclo[4.3.0.0^{3,9}]nonan-8-one (X).—The ether (IX) (1.3 g) in acetic anhydride (12 ml) was treated with a solution of chromium trioxide (1.60 g) in acetic acid (37 ml) and water (4 ml) at 100–110° for 4 h. To the cooled solution, ethanol (4 ml) was added; the mixture was poured on ice and extracted with ether. The extract was washed with saturated aqueous sodium hydrogen carbonate solution, dried (Na₂SO₄), and evaporated. Chromatography of the residue over alumina (G3) gave the lactone (X) (46%), m.p. 48–48.5° (from light petroleum), ν_{\max} 1770 cm⁻¹, τ 9.10 (3H, d, J 6 Hz), 8.67 (3H, s), and 4.08 (1H, m), $[\alpha]_D^{21} + 119.3^\circ$ (*c* 4% in CHCl₃) (Found: C, 72.1; H, 8.4. C₁₀H₁₄O₂ requires C, 72.3; H, 8.5%).

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