Syntheses of 1,3,3-Trimethyl-2-oxabicyclo[2.2.2]oct-5-ene (2,3-Didehydro-1,8-cineole), 6,6-Dimethyl-2-methylene-7-oxabicyclo[3.2.1]octane (Isopinol), 2,6,6-Trimethyl-7-oxabicyclo[3.2.1]oct-2-ene (Pinol), and 1-(3-Isopropylidenecyclopentyl)ethanone (Pinolone) from Hydroxy- and Bromo-derivatives of Cineole

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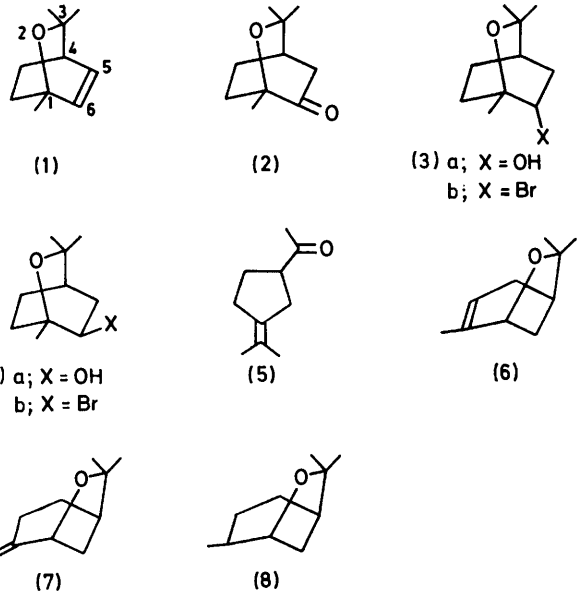
Treatment of (+)-1,3,3-trimethyl-2-oxabicyclo[2.2.2]octan-6-one *p*-tolylsulphonylhydrazone with n-butyl-lithium gave, in a low yield, 1,3,3-trimethyl-2-oxabicyclo[2.2.2]oct-5-ene (1), a terpene recently found in *Laurus nobilis* oil. Dehydration of the 1,3,3-trimethyl-2-oxabicyclo[2.2.2]octan-6-ols (an equilibrated *endo–exo*-mixture) with phosphoryl chloride–pyridine yielded mainly pinolone (5). The 1,3,3-trimethyl-2-oxabicyclo[2.2.2]octan-6-ols gave the 6-bromo-1,3,3-trimethyl-2-oxabicyclo[2.2.2]octanes (*endo–exo* mixtures) in 60 : 40 ratio with phosphorus tribromide–pyridine and in 80 : 20 ratio with triphenylphosphine dibromide. From treatment of the latter mixture with 1,5-diazabicyclo[5.4.0]undec-5-ene, (+)-pinol and a new terpenoid, (−)-isopinol, were obtained; with potassium t-butoxide in dimethyl sulphoxide, however, three products were obtained, namely the didehydrocineole (1), (+)-pinol, and (−)-isopinol. The structure of (−)-isopinol(6,6-dimethyl-2-methylene-7-oxabicyclo[3.2.1]-octane) and those of the other new compounds reported were determined from i.r., n.m.r., and mass spectral data.

1,3,3-TRIMETHYL-2-OXABICYCLO[2.2.2]OCT-5-ENE (2,3-didehydro-1,8-cineole) (1) is a terpene recently found in *Laurus nobilis* oil.[1] In the older literature [2] a product is described as having structure (1), but its preparation is



unreliable, because the starting material, 6-chloro-1,3,3-trimethyl-2-oxabicyclo[2.2.2]octane, was later found to be a complex mixture of chloro-derivatives.[3] As a consequence of our current interest in the cineole area,[4-7] we undertook a general investigation in order to achieve a convenient synthesis of compound (1).

Three routes were explored, namely treatment of (+)-1,3,3-trimethyl-2-oxabicyclo[2.2.2]octan-6-one (2) *p*-tolylsulphonylhydrazone with n-butyl-lithium; dehydration of the 1,3,3-trimethyl-2-oxabicyclo[2.2.2]octan-6-ols (*endo–exo*-mixture); and dehydrobromination of the 6-bromo-1,3,3-trimethyl-2-oxabicyclo[2.2.2]octanes (predominantly the *endo*-derivative). The reaction of the ketone of (2) *p*-tolylsulphonylhydrazone with n-butyl-lithium was undertaken first in the light of the high yields obtained in the similar preparation of bornene and other terpenoid olefins.[8] However the yield of the didehydrocineole (1) varied from only 10 to less than 30%, according to the concentration of n-butyl-lithium and the reaction temperature. The structure (1) was confirmed by spectral data (=CH and C=C i.r. stretching bands, ABX system of 6-, 5-, and 4-protons in the n.m.r. spectrum, and $M - CH_3$, $M - C_3H_7$, and retro-Diels–Alder fragmentation peaks in the mass spectrum). Dehydration of the 1,3,3-trimethyl-2-oxabicyclo[2.2.2]-octan-6-ols, as an equilibrated *endo–exo*-mixture [5] [(3a) and (4a)] was then tried, even though a mixture of terpenoid products was expected. Strong acids such as sulphuric were not employed owing to the sensitivity of the ether bridge towards such reagents. With phosphoryl chloride–pyridine, a complex mixture was obtained, not containing the didehydrocineole (1), and a carbonyl product was isolated as a semicarbazone and

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[6] F. Bondavalli, P. Schenone, and M. Longobardi, *Ann. Chim. (Italy)*, 1972, **62**, 207.
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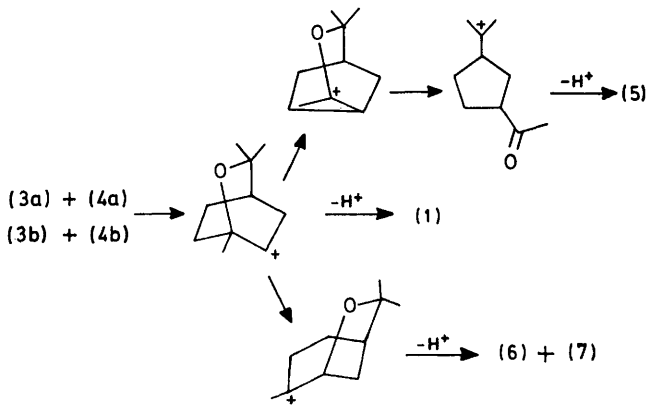
identified as 1-(3-isopropylidenecyclopentyl)ethanone (pinolone) (5) (yield 40%) from its i.r., n.m.r., and mass spectral data, as well as from the m.p. of the semicarbazone.[9] A possible route to (5) is outlined in the Scheme. This rearrangement seems to be similar to that leading to isocamphenone from the ketone (2) and concentrated sulphuric acid.[10]

We then resorted to the dehydrohalogenation procedure, and synthesized the starting compound, 6-bromo-1,3,3-trimethyl-2-oxabicyclo[2.2.2]octane, from an equilibrated mixture of (3a) and (4a).[5] With phosphorus tribromide–pyridine, a 60 : 40 mixture of (3b) and (4b) was obtained. Better results were achieved with triphenylphosphine dibromide,[11] which gave (3b) and (4b) in the ratio 80 : 20, respectively. This was ascertained from g.l.c.; the n.m.r. spectrum shows a near-quartet at δ 4.0, typical of the *exo*-proton geminal to a halogen atom in a terpenoid bicyclic system.[12]

Treatment of the 80 : 20 mixture with 1,5-diazabicyclo-[5.4.0]undec-5-ene (DBU) and with potassium t-butoxide as dehydrobrominating agents gave different results. With DBU, two products, in the ratio 90 : 10 (g.l.c.), were obtained, in an overall yield of 94%. The main



SCHEME

product was separated by chromatography on alumina and identified as (+)-2,6,6-trimethyl-7-oxabicyclo[3.2.1]-oct-2-ene[(+)-pinol] (6), from i.r., n.m.r.,[13] and mass spectral data. The minor constituent was a new terpenoid, later identified as (7) and better isolated by the following method. With potassium t-butoxide in dimethyl sulphoxide at room temperature, three products (overall yield 93%) were obtained in the ratios 62 : 13 : 25 (g.l.c.) and were separated by chromatography on alumina and on silica gel–silver nitrate. The first two components were identified, from g.l.c. retention time and comparison of i.r. and n.m.r. spectra, as (1) and (6), respectively. The third was identified as (−)-6,6-dimethyl-2-methylene-7-oxabicyclo[3.2.1]octane (isopinol) (7) on the following basis. Methylene i.r. absorption appeared at 3 060, 1 650, and 890 cm^{-1} and an n.m.r. multiplet was observed at δ 4.52 [*cf.* δ 4.58 in the case of pin-2(10)-ene[14]]. The n.m.r. singlets of the *gem*-dimethyl group were at δ 1.16 and 1.35, in good agreement with those of pinol.[13] A one-proton doublet at δ 4.35 (*J* 6.6 Hz) suggested a >CH·O− group forming a dihedral angle approaching 90° with one of the adjacent methylene protons and giving rise thus to a spin-coupling close to zero, whereas coupling with the other proton gave rise to the observed splitting. On the other hand, the downfield position of this doublet, as compared with those of pinol (δ 3.88) and dihydropinol (δ 3.91), strongly indicated that this proton was in the same plane as the double bond. The mass spectrum was very similar to that of pinol and showed the molecular ion at *m/e* 152. Major fragmentations involved loss of methyl, isopropyl, and acetone, to give peaks at *m/e* 137, 109, and 94, respectively. A metastable peak at *m/e* 66.3 correlated the *m/e* 94 ion with the base peak at *m/e* 79. The main difference from the pinol fragmentation concerned the intensity of the molecular ion, which was stronger in the pinol spectrum.

Catalytic hydrogenation of (7) gave (−)-*cis*-dihydropinol (8), already obtained from pinol (6).[15]

A possible pathway to compounds (1), (6), and (7) is outlined in the Scheme. Although some examples are known of the pinol ⟶ cineole rearrangement,[13,16] this seems to be one of the few cases of the reverse rearrangement (*cf.* ref. 16).

EXPERIMENTAL

I.r. spectra were measured with a Perkin-Elmer 257 spectrometer, and n.m.r. spectra with a Perkin-Elmer R12 instrument (60 MHz; tetramethylsilane as internal standard). Mass spectra were obtained with an A.E.I. MS902 spectrometer. G.l.c. was performed on a Fractovap GI instrument (C. Erba; 2000 × 3 dual column differential system, packed with 3% SE 30 on silanized Chromosorb W; linear temperature programming 80—150 °C during 15 min; helium flow rate 40 ml min^{-1}). M.p.s were determined with a Mettler FP1 apparatus.

1,3,3-Trimethyl-2-oxabicyclo[2.2.2]octan-6-one (2) *p-Tolylsulphonylhydrazone.*—*p*-Tolylsulphonylhydrazine (9.31 g, 50 mmol) and the ketone (2) [17] (8.41 g, 50 mmol) in anhydrous ethanol (100 ml) were heated to reflux for 1 h. Evaporation to half volume at reduced pressure and cooling gave a white crystalline precipitate, which was filtered off and washed with water to give the *hydrazone* (14.30 g, 85%), m.p. 145—146° (from 95% ethanol) (Found: C, 60.6; H, 7.1; N, 8.3. $C_{17}H_{24}N_2O_3S$ requires C, 60.7; H, 7.2; N, 8.3%); $\nu_{max.}$ (KBr) 3 210, 3 060, 3 040, 1 645, 1 600, 1 490, 1 330, and 1 170 cm^{-1}.

Reaction of the Ketone (2) *p-Tolylsulphonylhydrazone with*

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n-Butyl-lithium.—n-Butyl-lithium (2.3M-solution in n-hexane; 20 ml) was added dropwise with stirring to an ice-cooled slurry of the hydrazone (6.80 g, 20 mmol) in anhydrous ether (100 ml) under nitrogen. The brown-red solution was stirred at room temperature for 30 min and treated cautiously with water (50 ml). The ether layer was separated and the aqueous layer extracted thoroughly with ether. The combined extracts were dried ($MgSO_4$), filtered, and evaporated to leave an oil (3.50 g), which was chromatographed on neutral alumina (grade I). Elution with pentane gave 1,3,3-*trimethyl*-2-*oxabicyclo*[2.2.2]*oct*-5-*ene* (1) as a liquid (0.80 g, 26%), b.p. 78—80° at 40 mmHg, $[\alpha]_D^{20}$ −53° (*c* 3 in EtOH) (Found: C, 78.9; H, 10.3. $C_{10}H_{16}O$ requires C, 78.9; H, 10.6); $\nu_{max.}$ (neat) 3 040 and 1 618 cm^{-1}; * δ(CCl_4) 0.90 (3 H, s, CH_3), 1.20 (3 H, s, CH_3), 1.25 (3 H, s, CH_3), 6.05 (1 H, q, $J_{5.6}$ 8, $J_{4.6}$ 2 Hz, H-6), and 6.40 (1 H, q, $J_{5.6}$ 8, $J_{4.5}$ 6.6 Hz, H-5); *m/e* 152, 137, 124, 109 (base peak), 94, 91, 79, 77, and 43.

Pinolone (5) *by Dehydration of the Mixture of Alcohols* (3a) *and* (4a) *with Phosphoryl Chloride–Pyridine*.—Phosphoryl chloride (18.4 g, 120 mmol) was added dropwise at 0 °C to a solution of an equilibrated mixture of the alcohols (3a) and (4a) [5] (5.1 g, 30 mmol) in anhydrous pyridine (50 ml). After being stirred at room temperature for 48 h, the ice-cooled mixture was treated dropwise with water (20 ml) and extracted with ether. The combined extracts were washed with 5% hydrochloric acid and brine, dried ($MgSO_4$), filtered, and evaporated. The residue, g.l.c. of which showed several products, was treated with semicarbazide hydrochloride and sodium acetate in 50% ethanol to give a semicarbazone (2.51 g, 40%), m.p. 170—171° (from 80% ethanol) (lit.,[9] 171°). 1-(3-*Isopropylidenecyclopentyl*)*ethanone*(*pinolone*) (5) was obtained in near quantitative yield by steam-distillation of the semicarbazone in the presence of phthalic anhydride; b.p. 100—105° at 20 mmHg, $\nu_{max.}$ (neat) 3 070, 1 708, and 1 645 cm^{-1}; δ (CCl_4) 1.61 (6 H, m, 2 CH_3) and 2.10 (3 H, s, $COCH_3$); *m/e* 152, 137, 109, 107, 93, 91, 79, 77, 71, 67, 65, 55, and 43 (base peak).

6-endo-*and*-exo-*Bromo*-1,3,3-*trimethyl*-2-*oxabicyclo*[2.2.2]-*octanes* [(3b) a*nd* (4b)].—(i) *With phosphorus tribromide–pyridine*. An equilibrated mixture of alcohols (3a) and (4b) [5] (3.40 g, 20 mmol) in anhydrous benzene (5 ml) was added dropwise with stirring at −5 °C to the reagent prepared from freshly distilled phosphorus tribromide (1.15 ml) and pyridine (0.5 ml) in benzene (5 ml).[18] The mixture was set aside at room temperature for 60 h, treated cautiously with ice–water, and extracted with ether. The extracts were washed with brine, dried ($MgSO_4$), and evaporated. The oily residue was chromatographed on neutral alumina (grade I), giving with light petroleum (b.p. 40—70°) as eluant, a liquid (1.60 g, 34%), b.p. 68—70° at 0.1 mmHg. G.l.c. showed two components in the ratio *ca.* 60 : 40 [(3b) and (4b), respectively; see (ii)].

(ii) *With triphenylphosphine dibromide*. To the reagent prepared from bromine (5.30 ml) and triphenylphosphine (27.0 g, 103 mmol) in acetonitrile (80 ml),[11] a solution of an equilibrated mixture of alcohols (3a) and (4a) [5] (17.0 g, 100 mol) and triethylamine (15 ml) in anhydrous acetonitrile (20 ml) was added dropwise with stirring, with the temperature of the mixture kept at 10 °C. The mixture was stirred at 10 °C for 15 min and poured into ice–water (200 ml). Light petroleum (100 ml) was then added and stirring was continued until a precipitate of triphenylphosphine oxide was formed. The precipitate was filtered off, the organic layer was separated, and the aqueous layer was extracted with light petroleum. The combined extracts were dried ($MgSO_4$) and filtered; the solvent was removed and the residue distilled *in vacuo* (b.p. 68—70° at 0.1 mmHg) to give a liquid (12.70 g, 55%). G.l.c. showed two components, (3b) and (4b), in the ratio 80 : 20, respectively (Found: C, 51.6; H, 7.1. Calc. for $C_{10}H_{17}BrO$: C, 51.5; H, 7.3%); $\nu_{max.}$ (neat) 640 cm^{-1}; δ (CCl_4) 1.16 (6 H, s, 2 CH_3), 1.23 (3 H, s, CH_3), and 4.02 (1 H, m, CHBr) (this multiplet appeared as a near quartet further split, with a major splitting of 10 Hz and two minor spacings of 4.3 and 2 Hz; *cf.* ref. 12).

Dehydrobromination of the Mixture of Bromides (3b) *and* (4b) (80 : 20).—(i) *With DBU*. DBU (3.80 g, 25 mmol) was added to the mixture of (3b) and (4b) (4.66 g, 20 mmol) in dimethyl sulphoxide (10 ml) [19] and the solution was heated at 80—85 °C for 3 h, then cooled, poured into ice–water (100 ml), and extracted with pentane. The combined extracts were washed with 5% hydrochloric acid and brine, dried ($MgSO_4$), filtered, and evaporated. G.l.c. of the oily residue (2.85 g, 94%) showed two components in the ratio 90 : 10. The main product, isolated by chromatography on neutral alumina (grade I) with pentane as eluant, was 2,6,6-trimethyl-7-oxabicyclo[3.2.1]oct-2-ene [(+)-pinol] (6), $[\alpha]_D^{20}$ +92° (*c* 2.5 in EtOH), n_D^{20} 1.4680; $\nu_{max.}$ (neat) 3 070, 1 640, and 820 cm^{-1}; *m/e* 152, 137, 109, 94, 93, 79 (base peak), and 43; n.m.r. spectrum (CCl_4) identical with that already described.[13] The minor component was later identified as (−)-isopinol (7) by its g.l.c. retention time [see (ii)].

(ii) *With potassium t-butoxide*. The mixture of (3b) and (4b) (23.3 g, 100 mmol) in dimethyl sulphoxide (50 ml) was added dropwise to a solution of freshly prepared potassium t-butoxide [from potassium (5.9 g, 150 mmol)] in the same solvent (150 ml). After 48 h stirring at room temperature, the solution was poured into ice–water (400 ml) and extracted with pentane. The combined extracts were dried ($MgSO_4$), filtered, and evaporated to give a liquid (14.2 g, 93%), g.l.c. of which showed three components in the ratio 62 : 13 : 25. The mixture was chromatographed on neutral alumina (grade I) to give, with pentane as eluant, the main compound. This was recognized as the didehydrocineole (1) by its i.r., n.m.r., and mass spectra. Further elution, with ether, gave a mixture of the other two products, together with a little (1). Chromatography on a silica gel–silver nitrate column (10 g of silica gel and 2 g of silver nitrate for 1 g of mixture) with the series of eluants pentane, pentane–benzene (9 : 1 to 9 : 6), pentane–ether (4 : 1, 2 : 1, and 1 : 1), and ether, gave in the last fractions a g.l.c.-pure sample of 6,6-*dimethyl*-2-*methylene*-7-*oxabicyclo*[3.2.1]*octane* [(−)-*isopinol*] (7), identified as the third component, $[\alpha]_D^{20}$ −168° (*c* 4 in EtOH), n_D^{20} 1.4790, b.p. 70—72° at 15 mmHg (Found: C, 78.5; H, 10.4. $C_{10}H_{16}O$ requires C, 78.9; H, 10.6%); $\nu_{max.}$ (neat) 3 060, 1 650, and 890 cm^{-1}; δ (CCl_4) 1.16 (3 H, s, CH_3), 1.35 (3 H, s, CH_3), 4.35 (1 H, d, *J* 6.6 Hz, >CH·O−), and 4.52 (2 H, m, $=CH_2$); *m/e* 152, 137, 109, 94, 93, 79 (base peak), and 43. The second component was identified as (+)-pinol (6) by its g.l.c. retention time.

Reduction of (−)-*Isopinol* (7) *to* (−)-cis-*Dihydropinol* (8).—(−)-Isopinol (7) (1.52 g, 10 mmol) in glacial acetic acid (20 ml) was hydrogenated at atmospheric pressure and room

* The low C=C stretching frequency is common for a bicyclic olefin; *cf.* R. C. Lord and R. W. Walker, *J. Amer. Chem. Soc.*, 1954. **76**, 2518.

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temperature in the presence of pre-reduced platinum oxide (0.2 g). The solution was filtered, cooled, neutralized with 20% sodium hydroxide, and extracted with pentane. The solvent was removed and the residue (1.40 g) was treated with 5% potassium permanganate until a pink colour persisted, then taken up in pentane. The combined extracts were chromatographed on silica gel with pentane–ether (9 : 1) as eluant, giving the dihydropinol (8) as an oil (0.95 g, 62%), b.p. 98—100° at 40 mmHg, $[\alpha]_D^{20}$ −104° (*c* 2 in anhydrous EtOH), n_D^{20} 1.4580 {lit.,[15] $[\alpha]_D^{20}$ −103° (*c* 10 in EtOH), n_D^{20} 1.4597}; δ (CCl_4) 0.85br (3 H, d, *J* 2.6 Hz, CH_3), 1.13 (3 H, s, CH_3), 1.30 (3 H, s, CH_3), and 3.86 (1 H, d, *J* 6.6 Hz, >CH·O–).

We thank Dr. M. Canepa for the microanalyses, Mr. A. Panaro and Dr. S. Morasso for n.m.r. and i.r. spectra, and Mr. C. Sepe, University of Naples, for mass spectra.

[6/1227 *Received*, 24*th June*, 1976]