Apoverbenone (6,6-Dimethylnorpin-3-en-2-one). An Investigation into its Preparation by Dehydrobromination of a Sterically Hindered Bromo-ketone

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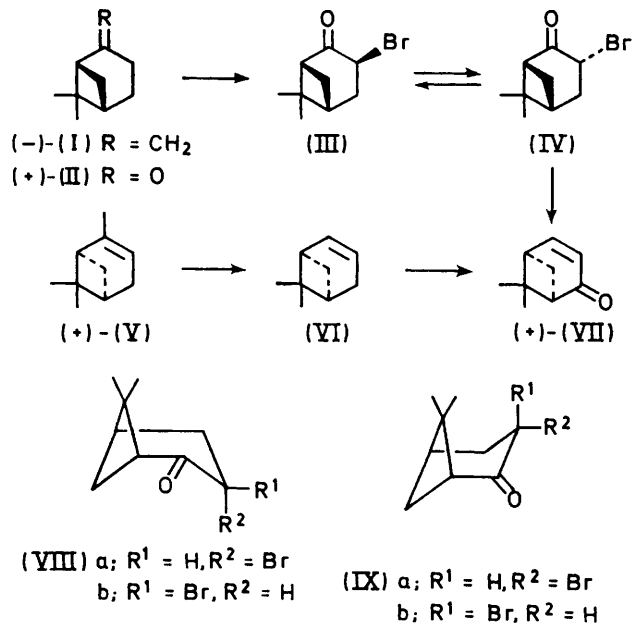
The dehydrobromination of 3-bromo-6,6-dimethylbicyclo[3,1,1]heptan-2-one has been studied. Treatment with lithium bromide and lithium carbonate in dimethyl sulphoxide gave 6,6-dimethylnorpin-3-en-2-one (apoverbenone) in good yield. From (−)-pin-2(10)-ene, optical purity 91%, we obtained (+)-apoverbenone, $[\alpha]_D$ + 319° (*c* 2·4% in $CHCl_3$).

APOVERBENONE (VII) has been prepared in very low yield [1] by dehydrobromination of bromonopinone (III) and in acceptable yield [2] by the oxidation of apopinene (VI) with either lead tetra-acetate or chromium trioxide in benzene. In the latter work, (+)-pin-2-ene (V), optical purity [3] 43%, gave (+)-apoverbenone with $[\alpha]_D$ +16·3°. This oxidation is probably a radical process and we suspected that the apoverbenone so obtained would be substantially racemised. Racemisation results from the radical or ion intermediates, which are stabilised by the double bond, being subject to further attack either on the original site or on the allylic site. Because of the molecular symmetry, these two modes of attack lead to products of opposite absolute configuration. Since we required optically pure apoverbenone, we undertook a study of the dehydrobromination of bromonopinone.

Ozonolysis of (−)-pin-2(10)-ene (I) in methanol and decomposition of the initial products with dimethyl sulphide [4] gave (+)-nopinone (6,6-dimethylnorpinan-2-one) (II) in better yield than that obtained by other published procedures.[5] Treatment of the ketone with *N*-bromosuccinimide in carbon tetrachloride gave predominantly α-bromonopinone (3α-bromo-6,6-dimethylnorpinan-2-one) (III) [1] as an oil. Isomerisation on alumina gave a mixture of the two isomeric bromoketones and crystallisation gave pure β-bromonopinone (IV).[1,6] The terms α- and β- are used in the sense of Coxon *et al.*,[1] *viz.* the β-face is adjacent to the *gem*-dimethyl system. Baretta *et al.*[7] use the opposite convention.

Conformations of α- and β-Bromonopinones.—The three-carbon bridge of nopinone is conformationally mobile.[7-9] The structure of β-bromonopinone has been determined by *X*-ray crystallography [6] and the compound has been shown to possess conformation (VIIIb) in the solid phase. Both bromo-ketones have been characterised by their n.m.r. spectra; in both the sum of the coupling constants for the proton in the group CHBr with adjacent protons is large (see Table 1). This



suggests that in solution both isomers exist to a considerable extent in the conformation $CH_{ax}Br_{eq}$.[10] If the corresponding sum of coupling constants for the *cis*- and *trans*-2-bromo-4-t-butylcyclohexanones is taken as standard, an approximate position for the conformational equilibrium in the two bromonopinones can be calculated.[10] Further calculation based on the CHBr line positions is meaningless since the values observed are outside the range for the corresponding protons in the two reference ketones. The n.m.r. spectrum of nopinone has been interpreted in detail.[11] The weighted mean of conformations for this molecule has the three-carbon

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bridge *exo* with respect to the *gem*-dimethyl system and slightly flattened from the fully chair-like conformation.

TABLE 1

^{1}H N.m.r. data for the H_X portion of the ABX system $CH_2{\cdot}CH_XBr$ (7 mole % in CCl_4)

Ketone	τ (Me)	$J_{AX} + J_{BX}$/ Hz	τ (H_X)	% conformer according to ref. 10	
α-Bromonopinone (III)	8·60, 9·16	10·8	5·73	(IXa)	42
β-Bromonopinone (IV)	8·62, 9·16	18·0	5·28	(VIIIb)	100

Either bromonopinone was rapidly brought to the same equilibrium mixture by the action of a base in methanol and at equilibrium there is present 81 ± 3% of the β-ketone (IV). Here the α-isomer (III) must be disfavoured because of interactions between the bromine atom and the 7-proton in conformer (VIIIa) and the methyl group and the 3-proton in conformer (IXa). These effects outweigh the dipole–dipole interactions between the equatorial bromine atom and the carbonyl group in conformer (VIIIb), particularly in a solvent of high dielectric constant such as methanol.

Kinetic control in the bromination of nopinone gave the α-bromo-ketone as a major product under a variety of conditions described here and elsewhere.[1] The three-carbon bridge of nopinone enol is rigid. Bromination therefore could be expected to yield the observed isomer (III) by attack on the less hindered side away from the *gem*-dimethyl system.

Dehydrobromination Reaction.—Attempted dehydrobromination with semicarbazide [12] was unsuccessful. Attention was then turned to the use of various basic solvents and basic reagents. Under such conditions the pure β-bromonopinone was rapidly converted first into a mixture of the α- and β-compounds. Presumably the transition state for the required elimination to give (VII) involves a *trans*-diaxial arrangement of departing groups. The reaction was expected to be difficult for two reasons. Firstly the solvents used generally have a large dielectric constant so that the proportion of conformers in solution having axial bromine groups would be less than found by n.m.r. techniques in carbon tetrachloride. Secondly the *gem*-dimethyl system would seriously hinder approach of the base which is needed for dehydrobromination of (VIIIa).

In order to achieve any reaction a high temperature was required. Refluxing pyridine and collidine and quinoline at 150° proved almost ineffective. What little reaction occurred in pyridine gave the desired apoverbenone, but the other solvents gave mostly nopinone in poor yield. Substantial conversion of the bromo-ketone into nopinone, but none at all into apoverbenone, occurred in dimethylaniline at 150°. In dimethylformamide and dimethylacetamide containing lithium carbonate and lithium bromide substantial conversion into a mixture of nopinone and apoverbenone occurred. In dimethyl sulphoxide containing the lithium salts the conversion into apoverbenone was almost complete. In these four cases the product was isolated by preparative g.l.c. and shown by n.m.r. spectroscopy to have the composition given in Table 2. At first nopinone and apoverbenone could not be separated by analytical g.l.c., though subsequently separation was achieved.[13]

Dimethyl sulphoxide is a very good solvent for this difficult dehydrobromination reaction, presumably because preferential solvation of cations allows the bromide ion to act as a more powerful Lewis base. In other solvents nopinone is probably formed in a radical process which can compete successfully with the dehydrobromination reaction because the latter is so slow.

From (−)-pin-2(10)-ene, 91% optical purity,[3] we obtained (+)-apoverbenone, $[\alpha]_D$ +319°. The absolute configurations of the various intermediates are known; [14] in particular isomerisation of (−)-pin-2(10)-ene gives (−)-pin-2-ene.[15] Retamer's sample of (+)-apoverbenone has the same sign of rotation as ours for a given absolute configuration but his product has undergone extensive racemisation during the reaction sequence. The optical purity of our product is probably greater than 91%, since the intermediate β-bromonopinone was purified by several recrystallisations. A sample was hydrogenated to nopinone, $[\alpha]_D$ +39·0° (MeOH). The most extensive data on the specific rotation of nopinone refer to material prepared from nopinic acid.[16] The combination of these data with our data and those of other workers [11] for the rotation of nopinone from pin-2(10)-ene gives the most probable specific rotation ($[\alpha]_D$) for optically pure nopinone as +39·9°. Thus the optical purity of our apoverbenone is probably 98%.

Dehydrobromination in dimethylacetamide or dimethylformamide gave a second product (from preparative g.l.c.) with a longer retention time than apoverbenone. This material contained 2-isopropylphenol along with a new and unidentified unsaturated ketone.

EXPERIMENTAL

^{1}H N.m.r. spectra were determined for solutions in carbon tetrachloride with a Varian A60 instrument and tetramethylsilane as internal reference. Mass spectra were obtained with an A.E.I. MS9 instrument, ionizing beam 70 eV. A Perkin-Elmer F11 analytical g.l.c. instrument was used with nitrogen pressure 20 lb in^{-2} and a stainless steel column (2 m × ⅛ in diam.). Packing A consisted of 1·5% silicone gum rubber on Chromosorb W, and packing B 2·5% 2-cyanoethylmethylsilicone on Chromosorb G. Preparative g.l.c. was carried out on an Autoprep Aerograph model A700 fitted with an aluminium column (20 ft × ⅜ in diam.) of 30% silicone gum rubber on Chromosorb W (helium pressure 40 lb in^{-2}).

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[15] R. E. Fuguitt and J. E. Hawkins, *J. Amer. Chem. Soc.*, 1947, **69**, 319.
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Pin-2(10)-*ene*.—Commercial pin-2(10)-ene (containing pin-2-ene, *p*-mentha-1,8-diene, and a trace of 2,2-dimethyl-3-methylenebicyclo[2,2,1]heptane was fractionated with a Fenske column (150 cm). Two distillations afforded pin-2(10)-ene, b.p. 168° at 770 mmHg, α_D^{22} −18·0° (neat liquid) (lit.,[3] $[\alpha]_D^{25}$ −19·7°; $[\alpha]_D^{25}$ −22·7°), t_R (column A; 70°) 3·7 min.

6,6-*Dimethylnorpinan*-2-*one* (*Nopinone*) (II).—Pin-2(10)-ene (25 g) in anhydrous methanol (100 ml) was treated at −60 to −70° with a stream of ozonised oxygen (1·2% ozone; 2 l min^{-1}) for 5 h. Dimethyl sulphide (20 ml) was then added and the mixture was allowed to warm from −10° to room temperature during 3 h. It was then diluted with water and the product was extracted with light petroleum (b.p. 30—40°). The extract was washed with water, dried ($MgSO_4$), and evaporated. The residue was distilled through a 50 cm spinning-band column to give two fractions: (*a*), b.p. up to 50° at 2·0 mmHg, pin-2(10)-ene plus some nopinone (2 g), and (*b*), b.p. 50—51° at 2·0 mmHg, nopinone (17·5 g, 70%), $[\alpha]_D^{22}$ +17·4° (neat liquid), $[\alpha]_D^{22}$ +36·5° (*c* 4 in MeOH) {lit.,[16] $[\alpha]_D$ +18·5° (neat), $[\alpha]_D$ +38·3° (*c* 8 in MeOH)}, τ 8·66 (3H, s, Me) and 9·15 (3H, s, Me), t_R (column A; 70°) 8·5 min. If no change in optical purity during the ozonolysis is assumed then pure nopinone probably has $[\alpha]_D^{22}$ +39·9° ±0·3° (*c* 4 in MeOH) in view of our data and refs. 11 and 16.

3β-*Bromo*-6,6-*dimethylnorpinan*-2-*one* (β-*Bromonopinone*) (IV).—Nopinone (5 g) in anhydrous carbon tetrachloride (50 ml) was refluxed for 3 h with recrystallised *N*-bromosuccinimide (8·0 g) and benzoyl peroxide (0·25 g). The mixture was then filtered and evaporated *in vacuo*. The residue showed two peaks on g.l.c. (column A; 100°), larger peak t_R 12·5, smaller peak 19·0 min. It was chromatographed in ether over neutral alumina (100 g) and the eluate was reduced in volume to 25 ml; β-bromonopinone (4·5 g) then crystallised, m.p. 112—113° [from light petroleum (b.p. 40—60°)] (lit.,[1] 109—110°), t_R 19 min (conditions as above) (Found: C, 50·4; H, 6·0; Br, 37·2. Calc. for $C_9H_{13}BrO$: C, 50·1; H, 6·4; Br, 36·8%).

β-Bromonopinone (0·05 g) was dissolved in a solution of sodium (0·01 g) in methanol (1 ml) and set aside for 10 min. Water was then added and the bromo-ketone was recovered in ether. The product now showed two peaks on g.l.c. as above and the n.m.r. spectrum indicated the presence of a mixture of the two epimeric bromonopinones with 81 ± 3% β-isomer. Since the β-isomer had been obtained pure the spectrum of the α-isomer could be deduced.

Trial Dehydrobromination.—β-Bromonopinone (1·0 g) in solvent [(*a*), 12·5 ml alone or (*b*), 50 ml, containing lithium carbonate (3·5 g) and lithium bromide (4·0 g)] was heated for 48 h. The product was isolated in ether and examined by g.l.c. (column A). Where possible the material of retention time corresponding to nopinone plus apoverbenone was collected and examined by n.m.r. spectroscopy (Table 2). There was no significant reaction in pyridine under reflux or in 2,4,6-trimethylpyridine or quinoline at 150°, all under conditions (*a*).

6,6-*Dimethylnorpin*-3-*en*-2-*one* (*Apoverbenone*) (VII).—β-Bromonopinone (10 g) and anhydrous dimethyl sulphoxide (100 ml) were heated at 140—150° and stirred under nitrogen with anhydrous lithium bromide (20 g) and lithium carbonate (17·5 g). After 60 h the mixture was cooled and the filtrate was diluted with water. The residue was washed with ether and this solvent was used to extract the filtrate. The combined extracts were washed with water, dried ($MgSO_4$), and evaporated and the residue was distilled (50 cm spinning-band column) to give apoverbenone (4·6 g, 77%), b.p. 48·5—49° at 1·9 mmHg, m.p. 17—19°, ν_{CO} (CCl_4 or neat) 1695 cm^{-1}, $\lambda_{max.}$ 244 nm (ε 5740), n_D^{22} 1·4958,

TABLE 2

Proportions (n.m.r.) of nopinone and apoverbenone formed by reaction of β-bromonopinone

Solvent	Conditions	Temp.	G.l.c. fraction of (II) + (VII) % (VII)
Dimethylaniline	(*a*)	Reflux	0
Dimethylformamide	(*b*)	140—150°	30
Dimethylacetamide	(*b*)	140—150°	35
Dimethyl sulphoxide	(*b*)	140—150°	>98

$[\alpha]_D^{25}$ +319° (*c* 2·4% in $CHCl_3$) (Found: C, 79·3; H, 8·8. Calc. for $C_9H_{12}O$: C, 79·4; H, 8·8%), τ 2·62 (1H, q, *J* 9 and 6 Hz), 4·17 (1H, d, *J* 9 Hz), 7·0—7·6 (3H, m), 7·95 (1H, d, *J* 10 Hz), 8·50 (3H, s), and 9·00 (3H, s) (peaks due to nopinone <2%), *m/e* 136 (25%; M^+), 121 (29, M^+ −Me), 108 (17, M^+ −CO), 93 (19, M^+, $-C_3H_7$), 92 (38), 74 (36), 73 (100), 72 (67), 70 (38), 52 (54), 51 (47), 50 (32), and 39 (50), t_R (column A; 70°) 8·5 min. A column (2 m) of 5% FFAP (free fatty acid phase) on Chromosorb G,[13] at 80°, was found to separate nopinone (t_R 73 min) and apoverbenone (84 min). The foregoing product contained *ca.* 1% of nopinone.

Alternatively, apoverbenone could be purified by preparative g.l.c. at 118° (t_R 28 min).

Apoverbenone (1·0 g) in methanol (20 ml) was hydrogenated (uptake as calculated) over 5% palladium–charcoal (0·2 g) for 2 h at room temperature and pressure. The resulting nopinone, b.p. 51—52° at 2 mmHg was free from apoverbenone (F11, 2 m 5% FFAP column, 80°) and showed $[\alpha]_D^{22}$ +39·0° and +39·5° (*c* 4 in MeOH; two separate samples).

Dehydrobromination in Dimethylacetamide.—β-Bromonopinone (15 g) in dimethylacetamide (225 ml) was heated at 200—205° with lithium carbonate (52·5 g) and lithium bromide (60·0 g) for 22 h. The mixture was then worked up to yield a crude brown oil which showed two peaks on g.l.c. (column A, 70°) in addition to traces of bromonopinones. Preparative g.l.c. (118°) gave a peak (t_R 28 min) of nopinone and apoverbenone and a peak (t_R 47 min) showing ν_{CO} (neat) 1660 cm^{-1}, $\lambda_{max.}$ 230 (ε 4850) and 277 nm (2720), $[\alpha]_D^{25}$ +7·4° (*c* 1·75% in $CHCl_3$), t_R, (column A; 70°) 13·5 min, *m/e* 136 (M^+). On column A (70°) the sample had the same retention time as 2-isopropylphenol (13·5 min) but contained no 4-isopropylphenol (17·5 min). Column B (125°; composition by peak areas) showed the sample to contain apoverbenone (t_R 3·7 min, 6%), a new conjugated ketone (5·5 min, 78%), and 2-isopropylphenol (8·5 min, 16%). The n.m.r. spectrum indicated the presence of 2-isopropylphenol (28%): τ 3·0—3·3 (m), 6·71 (7 lines, *J* 7 Hz), 8·75 (d, *J* 7 Hz), and the new ketone (72%): τ *ca.* 3·2 (m), 4·03 (d, *J* 10 Hz), 7·2—7·8 (m), 7·90 (s, Me), and 8·12 (s, Me).

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