SOME DERIVATIVES OF NOPINONE

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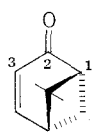
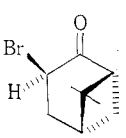
During other studies we required the conjugated ketone (1), which has been reported[1] to be formed by collidine dehydrobromination of the 3β-bromo ketone (2). Direct bromination of nopinone (3) gave (cf.[2]) a mixture of the 3β- and 3α-bromo ketones (2) and (4), which could not be smoothly dehydrobrominated with collidine. The formation and attempted dehydrobromination of each bromo ketone was therefore examined.



(1)



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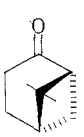

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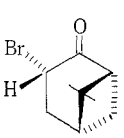

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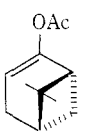

(5)

Reaction of nopinone (3) with isopropenyl acetate–toluene-*p*-sulphonic acid gave the enol acetate (5), the structure of which was confirmed by infrared and n.m.r. spectra. Bromination of the enol acetate (5) using bromine in carbon tetrachloride afforded the known[2] 3β-bromo ketone (2). The H 3α n.m.r. resonance of this bromo ketone (2) appeared as a quartet ($J_{3\alpha,4\beta}$ (app.) 11 Hz; $J_{3\alpha,4\alpha}$ (app.) 8 Hz); this result confirms that the bromo ketone (2) is in the down-conformation, with an equatorial bromine atom, in solution as in the solid phase.[3] Addition of anhydrous sodium carbonate to the bromination system resulted in the conversion of the enol acetate (5) exclusively into the 3α-bromo ketone (4). For this bromo ketone (4) the H 3β n.m.r. resonance was a quartet ($J_{3\beta,4\beta}$ (app.) 7·5 Hz; $J_{3\beta,4\alpha}$ (app.) 3·5 Hz). These values for the 3β,4α and 3β,4β coupling constants suggest[4] a conformation in which ring carbon atoms 1–5 are essentially coplanar. The hydrogen bromide catalysed isomerization of the 3α-bromo ketone (4) to the 3β-bromo ketone (2) was inefficient (c. 33%) and also gave *p*-isopropylphenol (30%) and 11 minor components. Lower hydrogen bromide concentrations resulted in lower conversion of the 3α-bromo ketone (4) into the same products.

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[1] Retamar, J. A., *Bull. Soc. chim. Fr.*, 1966, 1227.

[2] Feugas, J., and Colette, C., *C. r. Séanc. hebd. Acad. Sci., Paris*, 1960, **251**, 2972.

[3] Barrons, Y., *C. r. Séanc. hebd. Acad. Sci., Paris*, 1964, **259**, 796.

[4] Conroy, H., *Adv. org. Chem.*, 1960, **2**, 311.

Reaction of the 3α-bromo ketone (4) with collidine gave the conjugated ketone (1) only in low yield (*c.* 7%); apart from the 3α-bromo ketone (4) the major products were the epimeric 3β-bromo ketone (2; 50%) and nopinone (3; 13%). Attempted dehydrobromination using lithium carbonate–dimethylformamide resulted only in partial epimerization at C3. Reaction of the 3α-bromo ketone (4) with either sodium methoxide–methanol or potassium t-butoxide–t-butanol resulted mainly in debromination to nopinone (3).

O.R.D. and C.D. Data

It has been recognized[5] for some time that the o.r.d. data for bromopinan-3-ones could not be rationalized in terms of the application of the octant rule[6] to the more probable conformations of these ketone derivatives. Subsequently attempted interpretation[7] of physicochemical data, including o.r.d. and c.d. measurements, has led to incorrect stereochemical assignments for the products of α-pinene oxidation (cf.[8]).

We now report that c.d. measurements obtained for nopinone and the 3α- and 3β-bromo ketones [(4) and (2)] also are not in accord with the predictions based on the application of the octant rule. It is therefore clear that the deviations of the c.d. and o.r.d. data for substituted pinan-3-ones from the octant rule cyclohexanone pattern are not simply a function of the particular relative positions of the carbonyl group and the four-membered ring in those compounds but are a more general feature of pinanones.

Experimental

Infrared spectra were recorded on a Shimadzu IR27G spectrophotometer; ultraviolet spectra on a Shimadzu MPS-50L; n.m.r. spectra on a Varian A60 spectrometer for $CDCl_3$ solutions with $CHCl_3$ and TMS as internal standards. Analytical g.l.c. was performed on a MicroTek 2500 IIR; preparative g.l.c. was performed on a Varian Autoprep 705.

Nopinone

Prepared from β-pinene ($[\alpha]_D$ −17°) by ozonolysis,[9] it had b.p. 71°/7 mm, $[\alpha]_D$ +32·4° (*c*, 1·01; $CHCl_3$); ν_{max} (liquid film) 1715 cm^{-1}; λ_{max} 285 nm (ε 15); c.d. $\Delta\epsilon$ +1·77 (282 nm), $\Delta\epsilon$ 0·16 (208 nm); n.m.r. δ 1·33 (C 8–H_3), 0·85 (C 9–H_3) (lit.[10] $[\alpha]_D^{20}$ +34° ($CHCl_3$), n_D^{20} 1·4787).

Enol Acetylation of Nopinone (3)

Nopinone (10 g) and toluene-*p*-sulphonic acid (1 g) in isopropenyl acetate (200 ml) were heated to reflux and the acetone formed in the reaction fractionally distilled from the system through a 12-in. column packed with glass helices. After 5 hr, during which time 30 ml distillate had been collected, the remaining isopropenyl acetate was removed under reduced pressure. The residue was diluted with ether (400 ml), washed with water, and dried. Fractional distillation

[5] Hartshorn, M. P., and Wallis, A. F. A., *Tetrahedron*, 1965, **21**, 273.

[6] Moffit, W., Woodward, R. B., Moscowitz, A., Klyne, W., and Djerassi, C., *J. Am. chem. Soc.*, 1961, **83**, 4013.

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[8] Coxon, J. M., Dansted, E., Hartshorn, M. P., and Richards, K. E., *Tetrahedron*, 1968, **24**, 1193; Coxon, J. M., Dansted, E., Hartshorn, M. P., and Richards, K. E., *Tetrahedron Lett.*, 1969, 1149.

[9] Brus, G., and Peyresblanques, G., *C. r. Séanc. hebd. Acad. Sci., Paris*, 1928, **187**, 984.

[10] "Dictionary of Organic Compounds." Vol. 4, p. 2529. (Eyre & Spottiswoode: London 1965.)

allowed the isolation of the *enol acetate* (5) (9·4 g), b.p. 72°/4·6 mm; n_D^{20} 1·4689; $[\alpha]_D^{26}$ −18·6° (*c*, 1·05; $CHCl_3$); ν_{max} (liquid film) 1760 cm^{-1}; n.m.r. δ 5·18 ($W_{\frac{1}{2}}$ 6 Hz, C3–H), 2·08 (OAc), 1·31 (C8–H_3), 0·96 (C9–H_3) (Found: C, 73·3; H, 9·0. $C_{11}H_{16}O_2$ requires C, 73·3; H, 8·95%).

3β-Bromo Ketone (2)

Bromine (0·15 ml; 1·07 mole) in carbon tetrachloride (2 ml) was added over 5 min to a stirred solution of 500 mg of the enol acetate (5) in carbon tetrachloride (2·5 ml) at 0°, and the resulting solution was kept at 0° for a further 5 min. Isolation of the terpenoid material by means of ether and crystallization from methanol gave the 3β-bromo ketone (2) (448 mg), m.p. 109·5–110·5°, $[\alpha]_D$ +19° (*c*, 1·06; $CHCl_3$); ν_{max} (CCl_4) 1734 cm^{-1}; λ_{max} 291 nm (ε 55); c.d. Δε +3·14 (287 nm), Δε −1·5 (216 nm); n.m.r. δ 4·83 (C3–H), 1·38 (C8–H_3), 0·88 (C9–H_3) (lit.[2] m.p. 110°, ν_{max} (CCl_4) 1731 cm^{-1}).

3α-Bromo Ketone (4)

Bromine (0·3 ml; 1·07 mole) in carbon tetrachloride (4 ml) was added over 5 min to a stirred suspension of sodium carbonate (1 g; anhydrous) in a solution of the enol acetate (5) (1·05 g) in carbon tetrachloride (4 ml) at 0°, and the resulting suspension kept for a further 5 min. Isolation, as above, and crystallization from methanol gave the *3α-bromo ketone* (4) (990 mg), m.p. 69·5–70·0°, $[\alpha]_D^{23}$ +146° (*c*, 1·05; $CHCl_3$); ν_{max} (CCl_4) 1730 cm^{-1}; λ_{max} 313 nm (ε 81); c.d. Δε +1·30 (312 nm), Δε −0·97 (230 nm); n.m.r. δ 4·48 (C3–H), 1·38 (C8–H_3), 0·84 (C9–H_3) (Found: C, 49·7; H, 6·05; Br, 37·4. $C_9H_{13}BrO$ requires C, 49·8; H, 6·0; Br, 36·8%).

Hydrogen Bromide Catalysed Reaction of 3α-Bromo Ketone (4)

3α-Bromo ketone (4) (2 g) in carbon tetrachloride (10 ml) was shaken with hydrogen bromide–acetic acid (2 ml; 50 w/v) for 10 min. The crude product, isolated by means of ether, was shown by g.l.c. (5% SE30 on Chromosorb G) to consist of two major components, 3β-bromo ketone (2) (33%) and *p*-isopropylphenol (31%), and 11 minor components (total 36%). The *p*-isopropylphenol was isolated by preparative g.l.c. (7% FFAP on Chromosorb W, acid-washed, HMDS-treated). ν_{max} (liquid film) 3310 cm^{-1} (OH), 830 cm^{-1} (1,4-disubstituted benzene); n.m.r. δ 7·08 (2H, doublet, *J* 8·5 Hz), 6·75 (2H, doublet, *J* 8·5 Hz), 5·13 ($W_{\frac{1}{2}}$ 4 Hz, OH), 2·83 (1H, septet), 1·20 (6H, doublet) (lit.[11]); ν_{max} (Nujol) 3310, 830 cm^{-1}.

Attempted Dehydrobromination of the 3α-Bromo Ketone (4)

(i) The 3α-bromo ketone (4) (400 mg) was added to a suspension of lithium carbonate (500 mg) in dry dimethylformamide (5 ml) at 153°, and the mixture heated under reflux for 2 hr. The crude product, isolated by means of ether, was shown (g.l.c. on 5% SE 30 on Chromosorb G) to be a mixture (1 : 1) of the 3α- and 3β-bromo ketones (4) and (2).

(ii) A solution of the 3α-bromo ketone (4) (200 mg) in collidine (2·5 ml) was heated under reflux for 8 hr. The crude product, isolated by means of ether, was shown (g.l.c., as above) to consist of the 3β-bromo ketone (2) (50%), 3α-bromo ketone (4) (30%), nopinone (13%), and the conjugated ketone (1) (7%).

(iii) The 3α-bromo ketone (4) (480 mg) was added to methanol (10 ml) containing sodium methoxide (1·5 g) and the mixture heated under reflux for 3 hr. The crude product, isolated by means of ether, was shown (g.l.c., as above) to consist of nopinone (78%), 3α-bromo ketone (4) (19%), and 3β-bromo ketone (2) (3%).

(iv) Reaction at reflux of the 3α-bromo ketone (4) (400 mg) with potassium t-butoxide in t-butanol for 15 min gave a crude product (g.l.c.) shown to be essentially pure nopinone.

Acknowledgments

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[11] Brown, I., Eglinton, G., and Martin-Smith, M., *Spectrochim. Acta*, 1962, **18**, 1593.