Inhibition of Ring Expansion Reactions in the Norbornane System by Neighbouring Methyl Groups

By **P. Ian Meikle** and **David Whittaker,*** The Robert Robinson Laboratories, University of Liverpool, P.O. Box 147, Liverpool L69 3BX

Solvolysis of *endo*-3,3-dimethylnorborn-2-ylmethyl toluene-*p*-sulphonate proceeds *via* a hydride shift without any expansion of the cyclohexane ring, in contrast to the *endo*-norborn-2-ylmethyl ester, which readily undergoes ring expansion on solvolysis. The amines of both systems, however, give ring expanded products on deamination. The change in mechanism is discussed in terms of the electronic effects of the 3,3-dimethyl substituent. Failure of pinan-10-yl toluene-*p*-sulphonate to undergo ring expansion is believed to be due to the relative instability of the bicyclo[4.1.1]octane system.

DURING work [1] on the reaction of 2α*H*-10-aminopinane with nitrous acid, it became necessary to synthesise a number of compounds in which the cyclohexane ring, common to many monoterpenoids, was expanded to cycloheptane. Expansion of a cyclohexylmethyl system to cycloheptyl *via* solvolysis of a toluene-*p*-sulphonate or similar ester is a well known reaction,[2] and is known to proceed with bridged cyclohexyl systems.[3-6] We attempted this type of ring expansion on our systems, but found that they proceeded much less readily than for unsubstituted norbornanes. We have therefore investigated the reason for inhibition of expansion of bicyclic rings by methyl substituents.

EXPERIMENTAL

endo-3,3-*Dimethylnorborn*-2-*ylmethyl Toluene*-p-*sulphonate*.—Hydroboration of camphene yielded the parent alcohol,[7] m.p. 79—80° (lit.,[7b] m.p. 80—81°), which was converted into its *toluene*-p-*sulphonate via* a standard route.[8] Purification of the oily product by chromatography on a Florisil column with 5% ether–n-hexane as eluant gave a crystalline solid, m.p. 48—48·5° (Found: C, 66·1; H, 7·9; S, 10·8. $C_{17}H_{24}O_3S$ requires C, 66·2; H, 7·8; S, 10·4%).

endo-3,3-*Dimethylnorborn*-2-*ylmethylamine Hydrochloride*.—The amine was prepared from camphene *via* hydroboration.[9] The hydrochloride was precipitated from hexane as a crystalline solid, which decomposed on heating to 180—200°.

2α-*Hydroxypinan*-10-*yl Toluene*-p-*sulphonate*.—The published synthesis [10] of this compound was followed, yielding a gummy liquid.

endo-3,3-*Dimethylnorborn*-2-*ylmethyl Acetate*.—This was prepared from the alcohol by a standard route.[11]

endo-4,4-*Dimethylbicyclo*[3.2.1]*oct*-2-*yl Acetate*.—Oxidation of camphene with lead tetra-acetate [12] yielded 4,4-dimethylbicyclo[3.2.1]octan-2-one. Reduction with sodium borohydride for 1 h at room temperature yielded a mixture of 66% *endo*-alcohol and 34% *exo*-alcohol, which were separated by preparative g.l.c. Acetylation [11] of the alcohol gave the acetate as a yellow oil, $\nu_{max.}$ 977, 1023, 1120, 1145, 1153, 1180, 1243, 1355, 1466, 1734, 2872, and 2950 cm^{-1}.

2α,10-*Epoxypinane*.—This was prepared as described by Huckel,[13] and its identity confirmed by reduction with lithium aluminium hydride to give pinan-2α-ol.

2β-Methoxy-2α,3,3-trimethylnorbornane was available from earlier work,[14] and isobornyl acetate was a commercial sample.

Deamination.—The procedure of Jones [15] was followed, except that sodium acetate was not used.

Product Studies.—Reaction mixtures were extracted by standard procedures,[14] and the products analysed by g.l.c., using a Perkin-Elmer F11 chromatograph, with a 22 ft packed glass capillary column, 10% Carbowax 20M on Chromosorb W at 170°. For confirmation of identities of materials, samples were separated on a Pye 105 chromatograph, with a 30 ft × 3/8 in column, 25% Carbowax 20M on Chromosorb W at 210°; i.r. spectra were then recorded on a Perkin-Elmer 125 spectrometer.

The main unidentified product was an acetate found in 26% yield in the products of deamination of *endo*-3,3-dimethylnorborn-2-ylmethylamine. This acetate had $\nu_{max.}$ at 895 (s), 940 (s), 960 (s), 969 (m), 1031 (l), 1096 (m), 1238 (l), 1250 (l), 1367 (l), 1736 (l), 2870 (l), and 2950 (l) cm^{-1}. It was clearly not the acetate of any of the hydride transfer products (bornan-2α-ol, bornan-2β-ol, and 2α,3,3-trimethylnorbornan-2β-ol), a rearranged ring expansion product (5,5-dimethylbicyclo[2.2.2]octan-2-ol), or unrearranged alcohol.

The n.m.r. spectrum, however, showed only two methyl proton peaks, at τ 8·94 and 8·98, consistent with ring expansion having taken place.

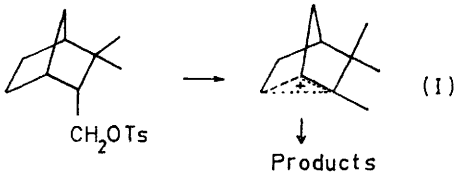
RESULTS AND DISCUSSION

Solvolysis of *endo*-3,3-dimethylnorborn-2-ylmethyl toluene-*p*-sulphonate (0·033M) in methanol containing sodium methoxide (0·035M) at 85° for 120 h gave a mixture of 51% camphene and 49% 2β-methoxy-2α,3,3-

[1] P. I. Meikle and D. Whittaker, preceding paper.
[2] C. D. Gutsche and D. Redmore, 'Carbocyclic Ring Expansion Reactions,' Academic Press, New York, 1968, p. 41.
[3] W. Kraus, *Chem. Rev.*, 1964, **97**, 2726; K. Alder and R. Reubke, *ibid.*, 1958, **91**, 1525; R. R. Sauers and R. J. Tucker, *J. Org. Chem.*, 1963, **28**, 876.
[4] J. A. Berson and P. Reynolds-Warnhoff, *J. Amer. Chem. Soc.*, 1964, **86**, 595.
[5] J. A. Berson and D. Willner, *J. Amer. Chem. Soc.*, 1964, **86**, 609.
[6] J. A. Berson and A. Remanick, *J. Amer. Chem. Soc.*, 1964, **86**, 1749.
[7] (*a*) G. Zweifel and H. C. Brown, *J. Amer. Chem. Soc.*, 1964, **86**, 393; (*b*) R. Dulou and Y. Chretien-Bessiere, *Bull. Soc. chim. France*, 1959, 1362.
[8] R. S. Tipson, *J. Org. Chem.*, 1944, **9**, 235.
[9] H. C. Brown, W. R. Heydkamp, E. Brewer, and W. S. Murphy, *J. Amer. Chem. Soc.*, 1964, **86**, 3565.
[10] J. M. Coxon, E. Dansted, M. P. Hartshorn, and E. K. Richards, *Tetrahedron*, 1968, **24**, 1193.
[11] H. L. Goering and G. N. Fickes, *J. Amer. Chem. Soc.*, 1968, **90**, 2862.
[12] J. Wolinsky, *J. Org. Chem.*, 1961, **23**, 704.
[13] W. Huckel and E. Gelchsheimer, *Annalen*, 1959, **625**, 12.
[14] P. Beltrame, C. A. Bunton, A. Dunlop, and D. Whittaker, *J. Chem. Soc.*, 1964, 658.
[15] D. G. Cooper and R. A. Jones, *J. Chem. Soc.* (*C*), 1971, 3920.

trimethylnorbornane. These results are fairly similar to those obtained for the solvolysis of 2α-chlorobornane,[14] in methanol containing 0·2M-sodium methoxide at 100°, when the yield of camphene was 61%. There is no trace of any ring expanded products; the reaction has proceeded entirely by hydride shift to the ion (I), either *via* a classical ion or directly.

In the hope of observing some ring expansion in a solvent less able to stabilise the carbonium ion, we repeated the solvolysis in acetic acid containing an excess of sodium acetate for 144 h at 85°. The products differed from those noted above: 61% of camphene, with 22% of born-2β-yl acetate, and five trace products, two of which had g.l.c. retention times similar to those



(I)

of the acetates of the *exo*- and *endo*-3,3-dimethylnorborn-2-ylmethyl alcohols. The only unidentified trace acetate constituted *ca.* 1% of the mixture.

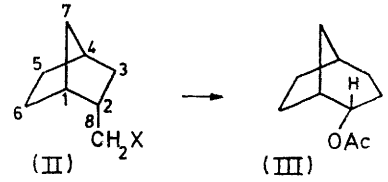
In contrast to the methanolysis reaction, the main ester product was derived from norbornan-2β-ol; it has been shown,[16] however, that 2α,3,3-trimethylnorborn-2β-yl acetate is unstable under the reaction conditions, and would undergo spontaneous heterolysis to yield ion (I). The acetolysis of the original ester has thus followed closely the path of the methanolysis, the hydride shift having excluded a carbon shift. A possible explanation of the results is that the reaction involving shift of the C(2)–C(3) bond is impossible in the substituted system. To demonstrate that it can take place, we turned to conditions known to favour ring expansion, namely, deamination. Reaction of *endo*-3,3-dimethylnorborn-2-ylmethylamine hydrochloride with nitrous acid in acetic acid at 30° yielded a complex mixture of products, the main products being *endo*-4,4-dimethylbicyclo[3.2.1]-oct-2-yl acetate (43%), an unidentified acetate (26%), and an unknown chloride (9%) together with materials of similar retention time to camphene (6%), tricyclene (5%), and five unknowns comprising, in total, 10% of the products. The unknown acetate differed from all the bicyclo[2.2.1]heptyl acetates which we had available.

Identification of *endo*-4,4-dimethylbicyclo[3.2.1]oct-2-yl acetate clearly shows that ring expansion has taken place under the conditions of deamination, though not under those of solvolysis. This contrasts with the observation of Berson [4] that acetolysis of the *p*-bromobenzenesulphonate of *endo*-norborn-2-ylmethyl alcohol (IIa) yields 77% *endo*-bicyclo[3.2.1]oct-2-yl acetate (III) while the reaction of *endo*-norborn-2-ylmethylamine(IIb) with nitrous acid in acetic acid yields (III) in 83% yield.

[16] C. A. Bunton, C. O'Connor, and D. Whittaker, *J. Org. Chem.*, 1967, **32**, 2812.

[17] P. von R. Schleyer, M. M. Donaldson, and W. E. Watts, *J. Amer. Chem. Soc.*, 1965, **87**, 375.

Examination of models of the reactant and products indicate that steric effects of the 3,3-dimethyl group are

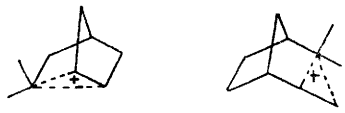


(II) (III)

a; X = OBs
b; X = NH_2

unimportant. Since the release of ring strain in the substituted system should be at least as great as in the unsubstituted system, we then considered the electronic effects of the dimethyl group.

Formation of (III) from (II) must involve a shift of the C(2)–C(3) bond electrons to form a bond between C(3) and C(8), leaving a positive centre at C(2). This may accompany or follow removal of the group X. It is known, however, that *exo*-norborn-2-yl bromobenzenesulphonate undergoes acetolysis more rapidly than *exo*-6,6-dimethylnorborn-2-yl bromobenzenesulphonate [17] by a factor of *ca.* 20, the dimethyl substituent retarding the reaction, presumably by retarding the bond shift. The ion formed in this latter reaction [(IV)] is similar to the transition state (V) postulated [6] for the bond shift required to form (III) from (II).



(IV) (V)

We suggest that a similar effect is observed here; the dimethyl group on C(3) retards shift of the C(2)–C(3) bond in the product-determining step (which may or may not be identical with the rate-determining step) so that a hydride shift to give products with the camphene structure becomes the dominant reaction. In the higher energy ion generated by deamination, the product distribution is less sensitive to small differences in the heights of energy barriers, so that an appreciable fraction of reaction proceeds *via* ring expansion.

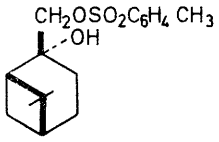
The origin of this rate decrease is not certain; increase of steric hindrance in the ion relative to the ground state has been suggested,[17] but observation of this effect in our more flexible system suggests that this may not be correct.

This simple rationalisation cannot be extended to reactions of the pinan-10-yl system. We have already shown that unimolecular methanolysis of the pinan-10-yl toluene-*p*-sulphonates involves exclusive hydride shift in the rate-determining step,[18] whereas ring expansion is observed in deamination.[1] The *gem*-dimethyl group on

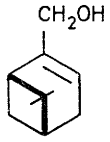
[18] P. I. Meikle, J. R. Salmon, and D. Whittaker, *J.C.S. Perkin II*, 1972, 23.

the cyclobutane ring would not be expected to exert a strong influence on the pinan-10-yl ester reactions.

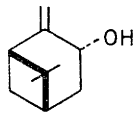
We therefore attempted to expand the cyclohexane ring of the pinane system by treating nopinone with diazomethane and to expand the cyclobutane ring by treating 6,6-dimethylnorpinan-7-one with diazomethane.[19] Both reactions failed completely, yielding only unchanged ketone. We next attempted to expand the cyclohexane ring by use of a pinacol shift. It has been shown [20] that treatment of the monotoluene-*p*-sulphonate of the glycol from pin-2-ene with methanolic potassium hydroxide gave a ring contracted product, so ring expansion by treatment of (VI) with methanolic potassium hydroxide seemed probable.



(VI)



(VII)



(VIII)

The reaction failed completely, yielding 2β,10-epoxypinane, pin-2(10)-en-3α-ol (VIII), and pin-2-en-10-ol (VII). Refluxing (VI) with pyridine and triethylamine [21] yielded pin-2-en-10-ol as the main product; passing (IV) down an alumina column [22] gave a complex mixture of products which we were unable to resolve.

We suggest that expansion of the cyclohexane ring of pinane is a particularly difficult reaction. Failure of a technique similar to that which successfully contracts the ring suggests that the bicyclo[4.1.1] system is strained and therefore difficult to prepare. Although it occurs naturally in the sesquiterpene alcohol khusimol, extracted from South Indian vetiver oil,[23] it is difficult to prepare, having been obtained only by cyclisation of a bromoketone [24] and photochemical rearrangement of an unsaturated ketone.[25] Ring expansion of pin-2-ene by addition of dibromocarbene has been reported [26] but the product is difficult to characterise,[27] and of 2α*H*-10-aminopinane gives only 8% bicyclo[4.1.1]octane, the reaction favouring a [1,3] carbon shift.

We conclude that pinane ring expansion is a special case, and does not invalidate our conclusions on the inhibition of expansion of the norbornane system by a neighbouring *gem*-dimethyl group.

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[26] M. K. Saxena and M. M. Bokadia, *J. Indian Chem. Soc.*, 1968, **45**, 769.
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