Attempts to prepare 2-(2-hydroxyethyl)-6,6-dimethylbicyclo[3.1.1]hept-2-ene (nopol; 1) labelled with deuterium at C-10 by a process of oxidation of the primary alcohol group of nopol to the aldehyde, followed by H/D exchange and reduction back to alcohol, were unsuccessful because various oxidation procedures, including reaction with A-chlorosuccinimide at –78 °C, gave instead a carboxylic acid having an oxygen at C-3. Nopol, labelled at C-11 with deuterium, was obtained through Prins reaction of β-pinene with deuteriated paraformaldehyde. This labelled nopol was converted into its toluene-p-sulfonate ester, and was solvolyzed in acetic acid containing acetate ion to give 8,8-dimethyltricyclo[4.2.1.03,7]nonan-6-yl acetate, which is an earlier reported novel fused ring system (fortesyl acetate; 2 acetate). The position of the label in the product showed that the mechanism of this deep-seated carbon skeletal rearrangement proceeds through the intermediate formation of a cyclobutane ring, followed by shift of a methylene bridge to expand the original cyclobutane ring and then subsequent expansion of the new cyclobutane ring. Calculations of heats of formation of possible ions involved in these shifts confirm the proposed mechanism as the most likely pathway.

Introduction

Acetolysis of the toluene-p-sulfonate ester1,2 of nopol (2-(2-hydroxyethyl)-6,6-dimethylbicyclo[3.1.1]hept-2-ene: 1) yields the acetate of fortesol, (8,8-dimethyltricyclo[4.2.1.03,7]nonan-6-ol; 2). The structure of the 2-phenylpropionate ester of the novel fused ring compound 2 has been determined by X-ray spectroscopy. Two plausible mechanisms for the rearrangement of structure 1 to 2 have been proposed2 and are summarised in Scheme 1.

Formation of the parent alkane of 2 has been reported to occur by reaction of the toluene-p-sulfonate 1 with organoaluminium compounds, from which the alkanes 13,14 (Scheme 2) were isolated. The ethyl derivatives of the alkanes were obtained when the toluene-p-sulfonate was reacted with triethylaluminium. The proposed mechanism, shown in Scheme 2, differs from those (A, B) shown in Scheme 1. A serious objection can be raised to the formation of ion 17 from 16, which requires a hydride shift that is unprecedented in carboamination chemistry. Any hydride shift would be expected to give ion 18 (Scheme 3), leading to the formation of structure 19.

In the acetolysis of nopol toluene-p-sulfonate reported earlier,1,2 derivatives of the structures 13, 14 are not found. An acetate at C-3 of structure 13 has been observed as a product of the deamination of nopylamine in acetic acid.1,3 The first step in all three mechanisms (A, B, C; Schemes 1, 2) is formation of a second cyclobutyl ring by cyclisation of the nopol side-chain during synchronous loss of the toluene-p-

sulfonate group. The process is consistent with the familiar, well-known cyclisations of toluene-p-sulfonate esters of β,γ-alkenyl alcohols. This cyclisation would be expected to give an ion 4 with the fused ring oriented away from the gem-dimethyl bridge. Fused cyclobutane ring derivatives of the pinane system have not been recorded but cyclohexane rings fused to pinane in a similar position are orientated away from the gem-dimethyl bridge.

The next step in the reaction would be the expansion of the original cyclobutane ring to form bornyl (5 or 7) or fenchyl (6 or 8) systems. This is the point at which the present proposed mechanisms diverge. Mechanisms A, C require expansion of the gem-dimethyl bridge to yield a bornyl system, while mechanism B requires expansion of the methylene bridge to give the fenchyl system. At first sight, this appears to favour the former mechanisms (A, C) because the pinane ring usually expands by shift of the gem-dimethyl rather than methylene bridge. However, in this case, the reaction is controlled by strain in the product. If the fused cyclobutane ring in structure 20 involves the exo-2 position, molecular models suggest it to be very strained; at the same time, endo-2 fusion in structure 21 cannot be reconstructed with models because carbon atoms C-1 and C-6 are too far apart to be joined by a normal C–C bond. Thus, structure 3 forms and not 6 (Scheme 1) and 4 forms 8 and not 7. Mechanism B then requires only a simple bond shift in ion 8 to give the ion 12 and hence the observed product. Mechanism A, proceeding from ion 4 involves formation of a bridgehead carbocation 10, which would be expected to be relatively
unstable, rearranging to ion 12 and its mirror image. Mechanism C avoids the problem of the bridgehead ion by delocalisation but presents the problem that rearrangement to ion 17 would have to proceed through the bridgehead ion 10, so there is a barrier to reaction.

To distinguish between the mechanisms, use is made of the symmetry in the system. Mechanism B does not involve a symmetrical intermediate and should give an optically active product starting from optically active nopol; any isotopic label put at C-10 in the optically active starting material should be found at C-5 in the product. Mechanisms A and C both involve the symmetrical ion 10 and should form a racemic product; an isotopic label placed at C-10 in the starting material should appear distributed between C-4 and C-5 in the product. Since the reaction is carried out in acetic acid, in which ion pairing is often important, it may be considered that the observed retention of optical activity is insufficient basis alone for selecting mechanism B as being the correct one.

Results and discussion

A commercial sample of nopol 1 ([α]D⁰ -37⁰; neat) was converted into its toluene-p-sulfonate and then solvolysed in acetic acid to give the acetate of fortesol 2, which was reduced to fortesol ([α]D⁰ -54⁰; c = 5, EtOH).

In a first attempt to label the side-chain of nopol, the alcohol was reacted with pyridine dichromate¹¹ so as to form the corresponding aldehyde. The resulting colourless crystals were examined by X-ray diffraction,¹² which showed that a keto alkenoic acid had been formed (structure 22). Accordingly, the oxidation was attempted with the milder oxidant, N-chlorosuccinimide, at -78 °C.¹³ Again a white crystalline material was isolated, which was shown by X-ray diffraction to have structure 23. This was still an alkenoic acid but, compared with compound 22, it had been oxidised only to the hydroxy stage rather than to the ketone. It appears never to have been reported that oxidation with N-chlorosuccinimide gives a
carboxylic acid. It is not clear whether the oxidation follows an unusual pathway or whether the initial aldehyde product is unusually susceptible to further oxidation.

The next attempts involved Oppenauer oxidation,14 which gave a mixture of products and finally manganese dioxide,15 which did not oxidise nopol.

The direct oxidation approach to give an aldehyde, which could have been exchanged to incorporate deuterium on C-10 was abandoned and, instead, nopol labelled on C-11 was synthesised directly from β-pinene by utilising a Prins reaction16 with perdeuterioparaformaldehyde. To minimise any potential loss of the deuterium label by exchange with a Brønsted acid, Lewis acid catalysis was used. Experiments with the two most popular catalysts, zinc(ii) chloride17 and tin(iv) chloride18 showed that the first gave a higher yield of nopol. Reaction of perdeuterioparafomaldehyde with β-pinene catalysed by zinc chloride gave nopol labelled with two deuterium atoms at C-11 (structure 24). Both 1H and 13C NMR spectroscopy showed that the hydrogen at C-11 had been replaced completely by deuterium. The C-11-labelled nopol was converted into its toluene-p-sulfonate ester with no loss of label as shown by 1H and 13C NMR spectroscopy. Mass spectrometry also showed an increase in molecular mass to 322, compared with 320 in the unlabelled noply toluene-p-sulfonate. Finally, the toluene-p-sulfonate was solvollised in acetic acid in the normal way to give the fortesyl acetate product (Scheme 4).

Examination of the resulting labelled acetate by MS showed that the molecular mass of the labelled acetate at 210 was two mass units greater than that of the corresponding unlabelled fortesyl acetate. 13C NMR spectroscopy revealed that the C-4 signal at δ 28.5, which is present in unlabelled fortesyl acetate, had disappeared because of the deuterium attached to this carbon. Substitution of hydrogen by deuterium causes a large increase in the relaxation time of the carbon spin states compared with their short relaxation times when hydrogen is attached. In keeping with the expected absence of deuterium at C-5, its signal at δ 37.9 remained unaffected in the labelled molecule. As a further check, the acetate was reduced to fortesol with lithium tetrahydroaluminate. MS on this alcohol gave a molecular ion peak at m/z 207.1, a primary carbocation formed by removal of the toluene-p-sulfonate anion as the electron capture product (Scheme 4).

The signal from the equatorial proton at δ 1.35 closely overlapped the axial proton signal on C-9 at δ 1.40, so that the product spectrum only indicates that the pattern of peaks is different from that in unlabelled fortesol in this small region.

It is clear from these results that the overall rearrangement proceeds as shown in Scheme 4. The deuterium label remains intact during the solvolysis, yielding structure 25, and it is not spread over two carbons as required by mechanisms A, C. From these data, together with the optical activity results, it is concluded that the mechanism outlined in mechanism B is correct.

The stereoselectivity of this rearrangement of nopol to fortesol is unexpected in a scheme as complex as that outlined in Scheme 1. To help resolve the complexity, the MOPAC PM3 method19 was used to calculate enthalpies of formation for the various ions depicted in Scheme 1 and to calculate various transitions state energies (saddle points) along the different reaction pathways. The calculations began with ion 1* (Scheme 1), a primary carbocation formed by removal of the toluene-p-sulfonate group from the ester 1 (Scheme 1), although acetylation of the toluene-p-sulfonate I probably proceeds through concerted departure of the toluene-p-sulfonate anion as the electrons of the double bond approach C-11 on the opposite side to the departing sulfonate. However, calculation of the enthalpies of formation of the ions 3, 4 (Table 1) shows that they are very similar, but the transition state energy in proceeding from ion 1* to 3 is much greater than that in going from 1* to 4. Thus, kinetically, mechanism B is preferred from the outset of reaction. Proceeding along the path of mechanism B, the next
possible divergence of ion 4 to either 7 or 8 is again controlled mostly by transition state energies in favour of the rearrangement of 4 to 8 (the rearrangement of 4 to 7 is also disfavoured in being endothermic). Completion of mechanism B requires only a small transition state energy in rearranging ion 8 into ion 12 (the product ion isolated in the solvolysis as its acetate). The outline of the salient energy changes is given in Fig. 1. Although the calculations are certainly subject to some error, the differences in both the transition state energies and the enthalpies of formation revealed for the two mechanisms A, B are so large as to give confidence in their significance.

The other product observed during acetylation of nopyl toluene-sulfonate is 1-ethyl-1-(2-propyl)benzene (26), probably arising as a result of breaking the gem-dimethyl bridge.\(^1\) This contrasts with the observation\(^2\) that the parent hydrocarbon of 2 (brendane, 27) can be converted easily into noradamanate 28. Calculation of the enthalpies of formation of these molecules confirms that such rearrangement is energetically favourable.\(^2\) Therefore, an attempt was made to convert fortesyl acetate into dimethylnoradamanate or possibly methyldamantenate by refluxing it in acetic acid containing 1 M H\(_2\)SO\(_4\) at 118 °C for 24 hours. The small amount of decomposition of fortesyl acetate that occurred gave only black tar. The gem-dimethyl bridge is probably a weak link in the structure of both nopol and fortesol. It has been observed already that nopol toluene-sulfonate can cleave at this centre, offering a ring-opening reaction as an alternative to formation of fortesol. Should any of the methylene bridges of brendane 27 open, the reaction would have to give a primary carbocation, whereas opening of the gem-dimethyl bridge of fortesol gives a much more stable tertiary carbocation. Accordingly, brendane reacts by rearrangement to the thermodynamically more favourable structure 28.

### Experimental

\(^1\)H NMR spectra were recorded in CDCl\(_3\) on a Varian Gemini spectrometer at 300 MHz and \(^13\)C spectra on the same spectrometer at 75 MHz with Me\(_4\)Si as internal standard. Infrared spectra were recorded on a Perkin-Elmer 1320 instrument, solid samples in Nujol and liquid samples as neat films. Reaction mixtures were monitored by GC with OV351 or FFAP capillary columns on a DANI 3800 chromatograph with flame ionisation detection. Mass spectra were measured on a Fisons Trio 1000 spectrometer, using electron ionisation at 70 volts.

### Preparation of materials

Unlabelled nopol, [\(\alpha\)]\(^D\)~37°, was obtained commercially (Aldrich) and was used without further purification. It was converted into its toluene-sulfonate ester by conventional methods\(^1\) and was subjected to acetylation in acetic acid as described earlier.\(^1\) The product was distilled to yield fortesyl acetate, bp 70–74 °C/0.5 Torr \(\uparrow\) (lit.\(^1\) bp 116 °C/12 Torr), which was pure by GC on an OV351 column. Reduction with lithium tetrahydridaluminate gave fortesol 2, mp 72–75 °C (from diethyl ether; lit.\(^1\) 75–77 °C), [\(\alpha\)]\(^D\)~35–48 °C (c = 5; EtOH).

### Acetylation of labelled nopol toluene-sulfonate

Acetylation of [\(\alpha\)]\(^11\)-\(\text{H}\)\(_2\)-2-(6,6-dimethylbicyclo[3.1.1]-hept-2-en-2-yl)toluene-sulfonate 24 was carried out by refluxing the ester (4 g) at 118 °C for 100 h in acetic acid (50 mL), containing sodium acetate (1.3 g).\(^\ast\) The cooled solution was poured into water (50 mL) and extracted with diethyl ether (3 × 20 mL). The combined extracts were washed with water, aqueous sodium hydrogen carbonate and water again before being dried (MgSO\(_4\)). The product was distilled to yield fortesyl acetate \(792\) J. Chem. Soc., Perkin Trans. 2, 1999, 789–793.

\(\uparrow\) 1 Torr = 133.22 Pa.
unlabelled fortesol was absent in this labelled material. The $^1$H NMR spectrum showed that a multiplet at $\delta$ 1.88 corresponding to the equatorial hydrogen on C-4 was absent. The signal for the corresponding axial hydrogen at $\delta$ 1.35 was too close to the signal at $\delta$ 1.4 to be certain that it had disappeared, though the coupling pattern in this region had changed.

**Calculation of enthalpies of formation and transition state energies**

The enthalpies of formation for the various ions listed in Table 1 were calculated using the MOPAC semi-empirical quantum chemical approach at the PM3 level, which was developed for the purpose of accurately estimating molecular properties. Similarly, the same programme was used to estimate transition state energies through calculation of ‘saddle points’, the stationary geometries for which total energy increases when atoms are displaced in any direction except one; at this point, only one of the force constants at the transition state energy is negative. Rather than quote the absolute calculated enthalpies, which are essentially gas phase values, enthalpies relative to that of the ion $^1$I$^*$ are given in Table 1. The enthalpy of formation for the positive ion $^1$I$^*$ was calculated to be 236 kcal mol$^{-1}$, very similar to typical measured values for such hydrocarbon gas phase ions, for which considerable amount of data is available.

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**References**