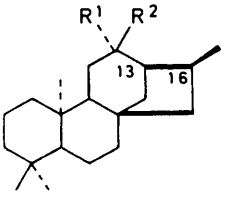
Ring c Functionalised Diterpenoids. Part V.[1] Preparation and Formolysis of (16*S*)-*ent*-12β-*p*-Tolylsulphonyloxykaurane and the (16*S*)-*ent*-13-*p*-Tolylsulphonyloxyatisanes

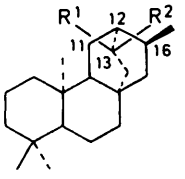
By **Alan J. McAlees** * and **Robert McCrindle,*** Department of Chemistry, University of Guelph, Guelph N1G 2W1, Ontario, Canada

The preparation and characterisation of the ring c functionalised (16*S*)-*ent*-kauranols (1a and b) and (4a and b) and (16*S*)-*ent*-atisanols (2a and b), and the corresponding ketones (1c), (4c), and (2c) are described. The room temperature formolysis of the toluene-*p*-sulphonate esters of (1a), (2a), and (2b) [(1d), (2d), and (2e), respectively] followed by basic hydrolysis, gives mixtures which contain products [(7a), (7b), and (9)] of 1,3-hydride shift. It is suggested that a classical bicyclo[2.2.2]octyl-type cation (F) is a significant intermediate in these solvolyses, and that differences in the amounts of hydride shift products obtained from (1d) on the one hand, and (2d) and (2e) on the other, result from differing degrees of solvation of (F).

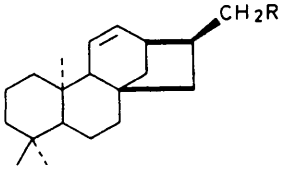
In Part I [2] we indicated that we were exploring routes to 13-substituted atisanes and 12-substituted kauranes, which were required for a study of carbocation rearrangements of the bicyclo-octane unit of the tetracyclic diterpenoids. We now describe the preparation of (16*S*)-*ent*-kauran-12β-ol (1a) and the (16*S*)-*ent*-atisan-13-ols (2a and b), and the formolysis of the corresponding tosylates.



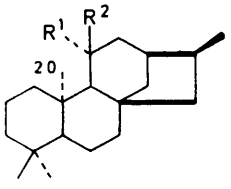
(1) a; R^1 = OH, R^2 = H
b; R^1 = H, R^2 = OH
c; R^1R^2 = O
d; R^1 = *p*-$MeC_6H_4\cdot SO_3$, R^2 = H
e; R^1 = R^2 = H



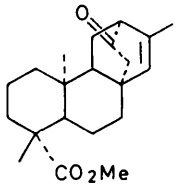
(2) a; R^1 = OH, R^2 = H
b; R^1 = H, R^2 = OH
c; R^1R^2 = O
d; R^1 = *p*-$MeC_6H_4\cdot SO_3$, R^2 = H
e; R^1 = H, R^2 = *p*-$MeC_6H_4\cdot SO_3$



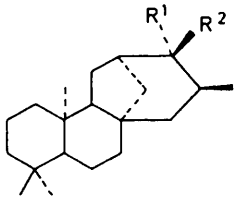
(3) a; R = H
b; R = *p*-$MeC_6H_4\cdot SO_3$
c; R = OH



(4) a; R^1 = OH, R^2 = H
b; R^1 = H, R^2 = OH
c; R^1R^2 = O



(5)



(6) a; R^1 = OH, R^2 = H
b; R^1R^2 = O

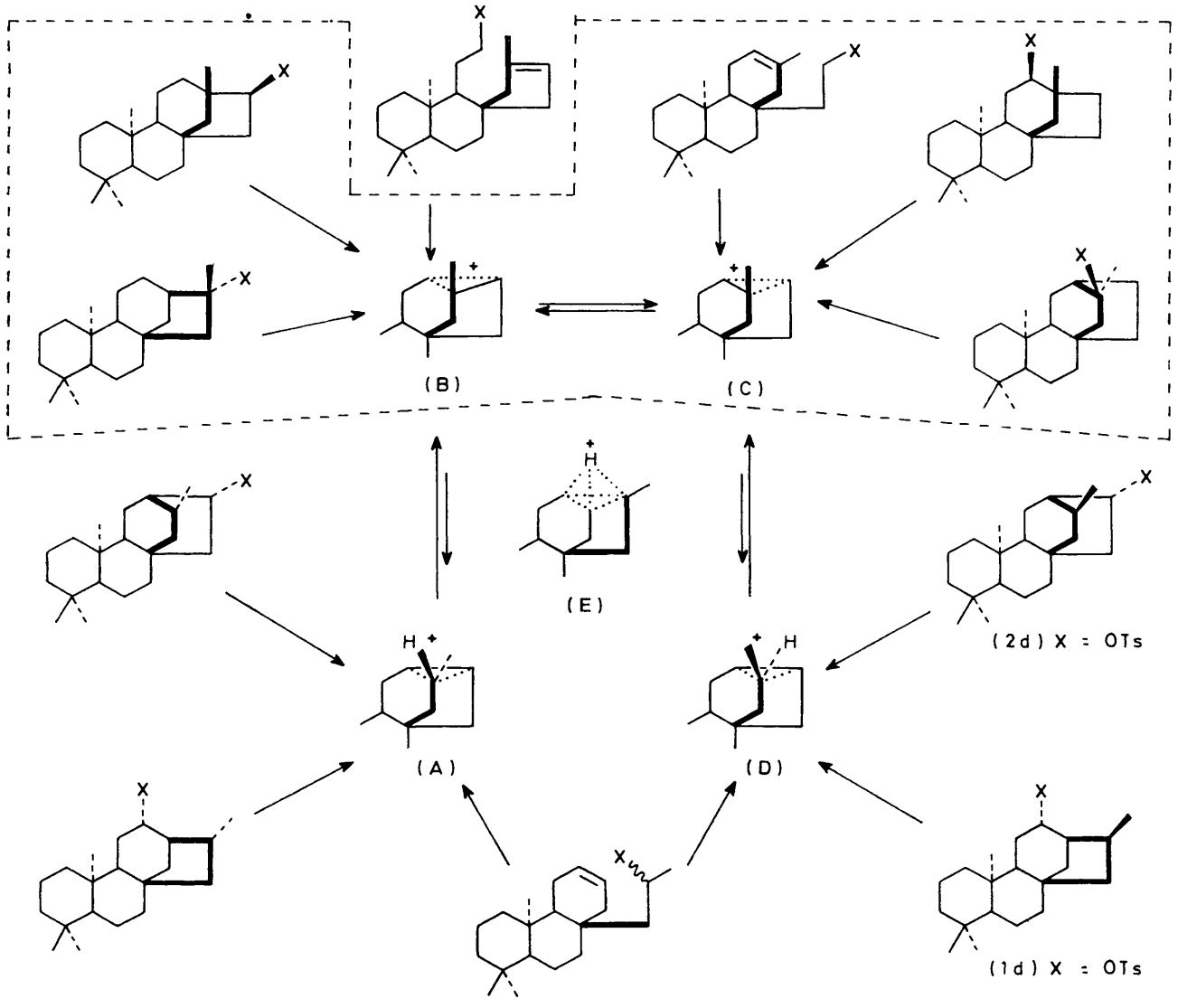
The considerable amount of work devoted to the study of carbocation rearrangements of the tetracyclic diterpenoids has been summarised by Coates and Bertram.[3] The kinds of rearrangement described to date are outlined in the section of Scheme 1 enclosed by the dotted line, and can be considered to involve the carbocations (B) and (C) (or equivalents; see caption to Scheme 1), which can be interconverted by a hydride shift. However, solvolysis of 12α-substituted (*i.e.* *ent*-12β-) kauranes or of 13-*pro*-*R*-substituted atisanes would be expected to involve the new carbocations (A) or (D) (Scheme 1), depending on the initial stereochemistry at C-16. (A) and (D) are related to (B) and (C) by formal hydride shifts. If hydride shift involves initial formation of delocalised carbocations (as drawn in Scheme 1), and then migration of hydrogen along an edge of the plane defined by the three electron-deficient carbon atoms, the successive interconversions (A) ⇌ (B) ⇌ (C) ⇌ (D) could result. On the other hand, migration of hydrogen across the face of the carbocation [intermediate (E), Scheme 1] would permit more direct conversion of any one of (A)—(D) into all the others. In addition, whereas the bulk of the positive charge on ions (B) and (C) is shared between a secondary and a tertiary carbon atom, the positive charge on ions (A) and (D) is carried mainly by secondary carbon atoms. Thus (B) and (C) should be more stable than

[1] Part IV, H. M. Campbell, P. A. Gunn, A. J. McAlees, and R. McCrindle, *Canad. J. Chem.*, in the press.

[2] A. J. McAlees and R. McCrindle, *Canad. J. Chem.*, 1973, **51**, 4103.

[3] R. M. Coates and E. F. Bertram, *J. Org. Chem.*, 1971, **36**, 3722.

(A) and (D). Indeed the fact that in all the earlier work on rearrangememts of the tetracyclic diterpenoids related to (−)-kaurene, and involving the intermediacy of ions (B) and (C), no products derivable from (A) and (D) have been reported suggests that the conversion of



SCHEME 1 Although only non-classical species are written here, this is done for convenience, and is not meant to rule out the possibility of the involvement of classical ions

(B) and (C) into (A) and (D) is relatively difficult. However, it would be expected that if ions (A) and (D) could be generated, the reverse rearrangement to give (B) and (C) should take place, and probably proceed more readily than the known [3] interconversion of (B) and (C). (Methyl substitution at C-6 in the norbornyl system has been found to increase the rate of hydride shift from C-6.[4]) To test this expectation we carried out the solvolyses of the tosylates (1d) and (2d) which could act as precursors of the ion (D). Formolysis at room temperature (20—25°) was chosen since such conditions should maximise the lifetime of the intermediate carbocations and provide a better chance of observing the hydride shift which converts (D) into (C) [or (E)]. However, they should not be sufficient to allow a significant amount of the hydride shift which interconverts (C) and (B).[3]

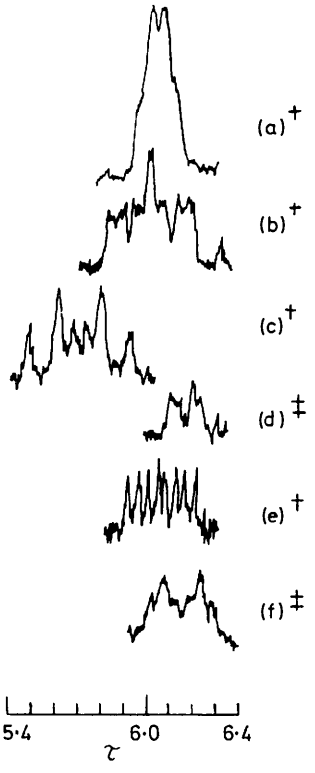
[4] R. G. Bergman, J. A. Berson, J. H. Hammons, and A. W. McRowe, *J. Amer. Chem. Soc.*, 1967, **89**, 2573, 2581.

RESULTS

Preparation and Hydroboration–Oxidation of (16S)-ent-*Kaur*-11-*ene* (3a).—The kaurene (3a) was obtained in high yield by reduction with lithium aluminium hydride of the tosylate (3b) derived from (16*S*)-*ent*-kaur-11-en-17-ol (3c).[2] Hydroboration–oxidation of (3a) gave a mixture from which (16*S*)-*ent*-kauran-12β-ol (1a) was isolated as the principal product. The mixture also contained, in order of decreasing polarity on t.l.c.,

small amounts of (16*S*)-*ent*-kauran-12α- (1b), 11β- (4a), and 11α-ols (4b), (16*S*)-*ent*-kauran-12-one (1c) and (16*S*)-*ent*-kaurane (1e).

Formation of (1a) as the major product was anticipated from molecular models, which show that attack on the double bond of (3a) should occur preferentially α (*i.e.* *ent*-β) and that attack at C-11 is hindered by the C-10 methyl group. The assignment of an axial configuration to the hydroxy-function is supported by the n.m.r. spectrum, in which the low-field proton signal appears as a relatively narrow multiplet [Figure (a)]: the α- (*ent*-β) orientation is suggested by the observation that the C-10 methyl resonance in (1a) is deshielded by 0·17 p.p.m. in comparison with the C-10 methyl in (1e) ($CDCl_3$ solution; *cf.* ref. 5). Oxidation of (1a) gave the ketone (1c), which proved identical with a very minor product of hydroboration–oxidation of (3a). Reduction of (1d) with lithium



N.m.r. spectra (60 MHz) of the carbinyl proton region for the diterpenoid ring c alcohols: † $CDCl_3$; ‡ CCl_4

aluminium hydride gave (16*S*)-*ent*-kauran-12α-ol (1b) as the principal product, along with some of the epimer (1a). In the n.m.r. spectrum of the former alcohol, which was identical with the most polar alcohol obtained from (3a), the C*H*OH signal appeared as a broad multiplet [Figure (b)]. The C-10 methyl resonance for (1b) appears at slightly higher field (+0·06 p.p.m.) than that for (1e) and in the ketone (1c) the same methyl group is still more highly shielded [+0·16 p.p.m. *vs.* (1e)].[5] The deshielding influence of the hydroxy-group is again evident in a comparison of the chemical shift of the secondary methyl group (C-17) in (1b) with that in (1e), (1a), or (1c).

In the n.m.r. spectrum of the more polar C-11 alcohol, (16*S*)-*ent*-kauran-11β-ol (4a), the low-field proton resonance appears as a pair of overlapping triplets [Figure (c)], and the C-10 methyl group is deshielded (τ 8·79), indicating that the hydroxy-group is equatorial and has the α- (*ent*-β) configuration. The presence of an *ent*-11β-hydroxy-function is confirmed by the appearance, at τ 7·37, of a broad doublet assignable to *ent*-H-1β, which would be strongly deshielded by the hydroxy-function.[6] Oxidation of (4a) gave (16*S*)-*ent*-kauran-11-one (4c), the i.r. spectrum of which shows a sharp peak at 3021 cm^{-1}, clearly resolved from the broad envelope due to C–H stretching modes below 3000 cm^{-1}. This peak may reflect steric interaction of the C-11 oxo-group with *ent*-H-1β, which would require that ring c adopt a flattened chair conformation. Models indicate that such flattening relieves a non-bonded interaction between the C-10 methyl group and the 14-*pro*-*S*-proton. Reduction of (4c) with lithium aluminium hydride gave a mixture of (4a) and (16*S*)-*ent*-kauran-11α-ol (4b) in which (4a) predominated. The new alcohol was identical with the least polar alcohol obtained from hydroboration–oxidation of (3a). Models of (4b) indicate that if ring c were to adopt the chair conformation, a very severe non-bonded interaction would exist between the axial hydroxy-function and the secondary methyl group (C-17). Conversion of ring c into the boat form would introduce an interaction between the hydroxy-function and *ent*-H-1β, which should result in the appearance of a low-field resonance for the latter. However, the n.m.r. spectrum of (4b) shows no resonances in the range τ 7·0—7·9. Further, the C*H*OH resonance [Figure (d)] appears as a fairly narrow doublet, while the resonance expected for (4b) with ring c in the boat conformation, in which *ent*-H-11β is *trans*-antiparallel to *ent*-H-9α and *ent*-H-12α, should be broad, as it would involve two large couplings. The observed resonance is consistent with ring c being in a flattened chair conformation in which the torsion angles between *ent*-H-11β and both *ent*-H-9α and *ent*-H-12α are *ca.* 90°.

Preparation and Formolysis of (16S)-ent-12β-p-*Tolylsulphonyloxykaurane* (1d).—Reaction of the alcohol (1a) with toluene-*p*-sulphonyl chloride in pyridine gave the tosylate (1d), which tends to decompose to the kaurene (3a). Solvolysis of (1d) in buffered formic acid followed by hydrolysis gave a mixture of hydrocarbons and three alcohols [(2a), (2b), and (6a)] which were separated by preparative t.l.c.

The n.m.r. spectrum of the most polar, major alcohol (2b) showed a C*H*OH signal as a clearly resolved eight-line multiplet [Figure (e)]. It seemed probable that

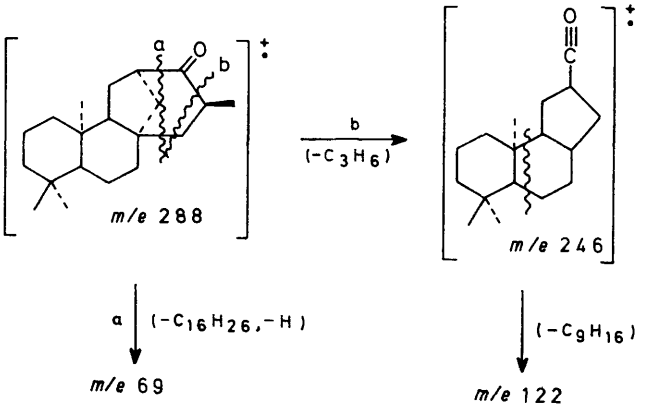
[5] P. R. Jefferies and R. W. Retallack, *Austral. J. Chem.*, 1968, **21**, 2085.

[6] D. H. Williams, N. S. Bhacca, and C. Djerassi, *J. Amer. Chem. Soc.*, 1963, **85**, 2810.

this product had resulted simply from Wagner–Meerwein rearrangement of the starting kaurane (1d), and was therefore an atisane derivative. This conclusion was supported by examination of the ketone (2c) obtained on oxidation of (2b). The i.r. spectrum of (2c) shows a strong band at 1725 cm^{-1} which suggests that the carbonyl function is in a bicyclo[2.2.2]octane system.[7] A double doublet at τ 7·52 in the n.m.r. spectrum of (2c) can be ascribed to H-14-*pro-R*, the smaller splitting arising from W-coupling with H-15-*pro-R* [*cf.* the 14-*pro-R*-proton in methyl *ent*-13-oxo-atis-15-en-19-oate (5) [8]]. Reduction of the ketone (2c) with lithium aluminium hydride gave a mixture of epimeric atisan-13-ols (2a and b). Compound (2a) was identical with the second principal alcohol obtained from the solvolysis of (1d). The assignment of stereochemistry to the hydroxy-functions in (2a and b) was made by comparison of their n.m.r. spectra. Thus, in the spectrum of (2a), the resonance due to one tertiary methyl group lies at noticeably lower field (τ 8·95) than those for the other two (τ 9·18 and 9·15), whereas in the spectrum of (2b) all three tertiary methyl groups resonate in the latter region. The low-field position of one tertiary methyl resonance in (2a) is probably due to deshielding of C-20 by the hydroxy-group, which then can be assigned the α- (*i.e. ent*-β-) configuration. This assignment is supported by comparison of the low-field C*H*OH resonances of (2a and b) [Figure, (f) and (e) respectively]. The resolved multiplet for (2b) arises from coupling of H-13 with three other protons (at positions 12 and 14), and the more broadened multiplet for (2a) is caused by coupling to four protons, the additional splitting being due to W-coupling with *ent*-H-11α.

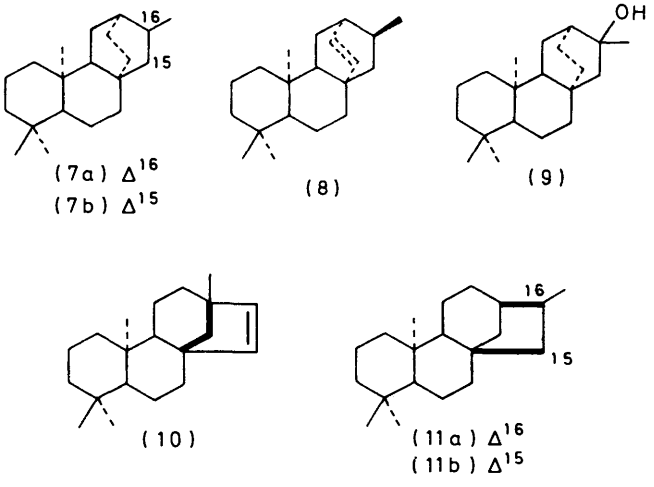
The minor alcohol obtained from (1d) was characterised by i.r. and n.m.r. spectroscopy only. The n.m.r. spectrum showed the presence of three tertiary methyl groups, one secondary methyl group, and a C*H*OH system. Oxidation of this alcohol gave a ketone, ν_{CO} 1711 cm^{-1}, suggesting a cyclohexanone. On the basis of this evidence and mechanistic considerations (see later), structures (6a and b) are suggested tentatively for the alcohol and the ketone, respectively. The structure (6b) for the ketone is consistent with the presence of peaks in its mass spectrum at *m/e* 246, 122 (base peak), and 69 which can be ascribed to the modes of fragmentation outlined in Scheme 2.

Analytical t.l.c. (silver nitrate-impregnated silica gel) of the hydrocarbon fraction from formolysis of (1d) showed the presence of about nine components, one of the least polar of which (16*S*)-*ent*-kaur-11-ene (3a), was by far the major constituent. The instability of the starting tosylate (1d) makes it likely that the major portion of this olefin was formed by direct elimination rather than *via* solvolysis. Pure samples of the three most polar olefins were obtained in amounts which were not sufficient to give meaningful n.m.r. spectra. However, comparison by analytical t.l.c. (silver nitrate-impregnated silica gel) and mass spectrometry showed the most polar and least polar of the three to be atisene



SCHEME 2

(7a) and isoatisene (7b), respectively. A strong peak at *m/e* 230 (*M* − 42, *ca.* 100%) in the mass spectrum of the hydrocarbon of intermediate polarity, and the observation that the spectrum at lower values of *m/e* is virtually identical with that of isoatisene (7b), led



to the conclusion that this product is (16*S*)-*ent*-atis-13-ene (8). Samples of the remaining hydrocarbons were not obtained in sufficient amounts or state of purity to permit their characterisation.

In an attempt to obtain additional quantities of (16*S*)-*ent*-atis-13-ene (8), dehydration of the (16*S*)-*ent*-atisan-13-ols (2a and b) with phosphoryl chloride in pyridine was investigated. The *ent*-β-alcohol (2a) gave a mixture containing mainly atisene (7a) and isoatisene (7b) and only a very small amount of material with an R_F value corresponding to that of (8). The hydrocarbon mixture from the *ent*-α-alcohol (2b) contained comparable amounts of compounds (7a and b) and (8).

[7] G. Hugel, L. Lods, J. M. Mellor, and G. Ourisson, *Bull. Soc. chim. France*, 1965, 2894.

[8] H. M. Campbell, P. A. Gunn, A. J. McAlees, and R. McCrindle, *Canad. J. Chem.*, 1973, **51**, 4167.

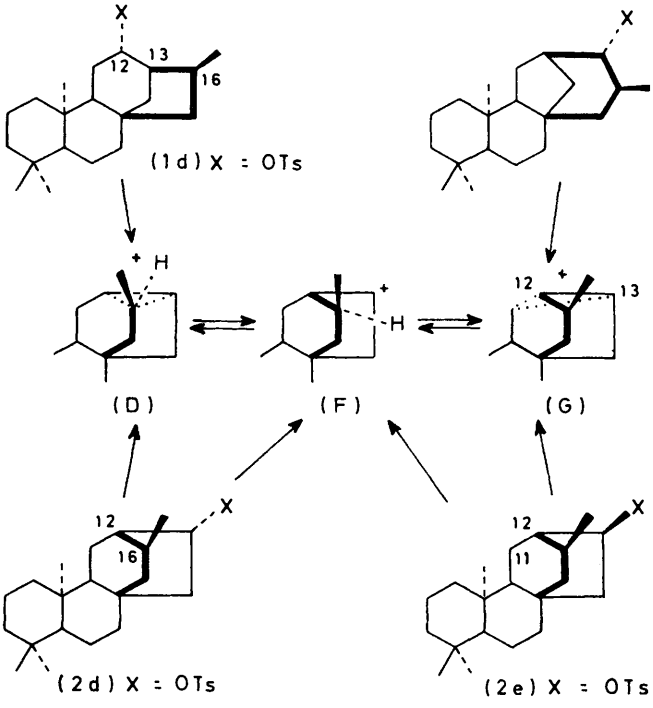
Preparation and Solvolysis of the (16S)-ent-13-p-*Tolylsulphonyloxyatisanes* (2d and e).—Since the results of the formolysis of (1d) and of phosphoryl chloride–pyridine treatment of the alcohols (2d and e) suggested significant involvement of a classical C-13 carbocation [(F), Scheme 3] derived from *ent*-atisane (see later), it was decided to examine the formolysis of both the tosylates (2d and e). Reaction of the alcohols (2a or b) with tosyl chloride in pyridine did not go to completion even on prolonged exposure to a large excess of reagent. Formolysis was therefore carried out using the crude tosylates, which in both cases contained a small amount of unchanged alcohol (t.l.c.), and an excess of tosyl chloride. T.l.c. of the resulting mixtures after basic hydrolysis to convert formates into the corresponding alcohols indicated that they were almost identical. The alcohol fractions obtained from both (2d and e) contained (13*S*,16*S*)-*ent*-atisan-13-ol (2b) as the major constituent, relatively minor amounts [compared with that obtained from (1d)] of the epimer (2a),* a very minor constituent with an R_F value identical with that of (6a), and a new product (9). The n.m.r. spectrum of the product (9) showed four singlets ascribable to tertiary methyl groups. The low-field position of one of these suggested that it is attached to a carbon atom which carries a hydroxy-function, whose presence was confirmed by its i.r. absorption. The n.m.r. data agree closely with those reported [7] for *ent*-atisan-16ξ-ol (9). However, attempts to recrystallise the alcohol obtained here only gave an oil which could not be persuaded to solidify until the solvent was removed and it was therefore treated with thionyl chloride in pyridine to effect dehydration. Examination of the hydrocarbon fraction thus obtained showed the presence of only two products, the major of which was isoatisene (7b) and the minor atisene (7a). The fact that no trace of any other hydrocarbon was found strongly suggests that the tertiary alcohol is indeed one of the epimeric atisanols (9) or possibly a mixture of the two.

Silver nitrate-impregnated silica gel t.l.c. plates run on the hydrocarbon fractions obtained on formolysis of (2d and e) differed only in that a spot due to a minor component with an R_F value appropriate to (16*S*)-*ent*-kaur-11-ene (3a) was present for the mixture from (2d) but not for that from (2e). The remaining components [*ca.* eight, including (7a and b) and (8)] appeared identical with those obtained previously from (1d).

DISCUSSION

It is notable that none of the other known tetracyclic diterpenoid hydrocarbons, beyerene (10), kaurene (11a), and isokaurene (11b), or the alcohols from which they could be derived by dehydration, were detected in the products from the formolyses of (1d), (2d), or (2e). The absence of such products indicates again [3] that the ion (E) (Scheme 1) does not participate to any significant extent in the solvolyses.

On the basis of the results of other workers on solvolyses involving the parent bicyclo[2.2.2]octyl and bicyclo[3.2.1]octyl systems [9] it might have been expected that analogous derivatives in the tetracyclic diterpenoid series (1d) and (2d) should give identical product mixtures. This has been found not to be the case, since the mixture obtained from (2d) contained significantly more material resulting from hydride shift [(7a and b) and (9)] than that obtained from (1d).† In addition, the ratio (5—10 : 1) of (2b) to (2a) obtained from the atisanol tosylate (2d) and its epimer (2e) is significantly higher than that (1·6 : 1) obtained from the kauranol tosylate (1d). These observations, and the finding that kaurane derivatives (1a) and (3a) are only very minor products of the formolyses, appear to indicate that the non-classical structure (D) (Schemes 1 and 3) is relatively unfavourable, and is readily rearranged *via* (F) and (G) (Scheme 3). Thus, the major portion



SCHEME 3

of the (13*R*,16*S*)-*ent*-atisan-13-ol (2a) obtained from (1d) may have resulted from capture while the C(13)–C(16) bond of (1d) was in the process of migration [nucleophilic attack on (D) would be expected to take place preferentially at C-13 owing to steric hindrance at C-12]. The relatively minor amount of (2a) obtained

* The ratio of (2b) to (2a) was estimated to be 5—10 : 1.

† While *ca.* 20% of the product from (2d) must have been formed *via* hydride shift, less than 2% of that from (1d) was formed similarly. Although the tertiary alcohol (9) was not detected on t.l.c. of the reaction mixture obtained from (1d), very minor amounts could have been present.

[9] See *e.g.* H. L. Goering and G. N. Fickes, *J. Amer. Chem. Soc.*, 1968, **90**, 2849, 2856, 2862; H. Kwart and J. L. Irvine, *ibid.*, 1969, **91**, 5541; L. A. Spurlock and R. J. Schultz, *ibid.*, 1970, **92**, 6302.

from (2d) reflects the reluctance of the C(12)–C(16) bond to participate in the solvolysis of (2d), which may therefore proceed largely through the classical ion (F). The apparently significant involvement of (F) in the solvolyses of (1d) and (2) led us to examine the solvolysis of (2e). The C(11)–C(12) bond of (2e) is suitably disposed to participate in the ionisation step with formation of the non-classical ion (G) (Scheme 3) which could be in equilibrium with (F). The reaction of (2e) to give a mixture of products virtually identical with that obtained from (2d) points to the involvement of the same intermediates in both cases. If the principal intermediate were the non-classical ion (G), one would expect to find significant amounts of both alcohols (6a) and (2b) in the product obtained after hydrolysis, examination of models suggesting that nucleophilic attack at C-12 of (G) is not obviously less favourable sterically than attack at C-13. However the low yield of the product to which we tentatively assign the structure (6a) suggests that the ion (G), like (D), is a relatively unfavourable intermediate in the solvolyses of (1d), (2d), and (2e). This appears to lead to the conclusion that the classical ion (F) is the most favourable intermediate in these solvolyses, although if such were the case, one might have expected to obtain rather lower ratios of (2b) to (2d) from (2e) than those actually found (5—10 : 1). Attack on the α-face of (F) is hindered to some extent by the C-10 methyl group, but this hindrance does not seem to be severe, as judged by the observation that lithium aluminium hydride reduction of the ketone (2c) gave (2a) and (2b) in the ratio 1·2 : 1. A possible explanation may be that a partially delocalised ion somewhat similar to (G), but with a major share of the positive charge still located at C-13, is formed. Such an ion would be subject to preferential attack on the β-face at C-13.

The finding that the kauranol tosylate (1d) gives rise to much less hydride-shift product than the atisanol tosylates (2d and e), even allowing for the fact that up to about 25% of (1d) probably underwent direct elimination to (16*S*)-*ent*-kaur-11-ene (3a), can be explained if solvolysis of (2d and e) results in the formation of a more reactive classical ion (F) than solvolysis of (1d). That this is feasible can be shown by a closer consideration of the individual steps involved. Thus, the reaction of (1d) proceeds by ionisation with migration of the C(13)–C(16) bond. As positive charge accumulates on C-13, a solvation shell will tend to be built up around it. During this stage, some capture of solvent will occur on the α-face of C-13. When the classical ion (F) is eventually formed, it will be fairly well solvated. However, if (2d and e) ionise with little or no participation by the C(12)–C(16) and C(11)–C(12) bonds respectively, ion (F) so formed will be initially less strongly solvated, and hence more reactive. Thus, most of the hydride-shift product obtained from (2d and e) must be formed in the initial stage of ionisation (rearrangement of carbocation in intimate ion pair?). It may also be noted that strong solvation of the β-face of ion (F) would block migration of hydride from C-16.

[10] E. Wenkert, *Chem. and Ind.*, 1955, 281.

CONCLUSIONS

The results of the formolyses of the tetracyclic diterpenoid ring c tosylates (1d) and (2d and e) are not consistent with the significant intermediacy of the ' nortricyclonium ' ion [10] (E).

The differences in solvolytic behaviour between the parent bicyclo-octyl esters and the diterpenoid derivatives seem to result from the differing relative stabilities of the non-classical and classical intermediates in the two series. For the parent system, the non-classical intermediate is preferred,[9] whereas in the diterpenoids the classical ion (or partially delocalised ion) is preferred. The kinds of differences seen here for the products from (1d) and (2d), which we suggest reflect differing degrees of solvation of an intermediate carbonium ion (F), would not be likely to be apparent for the parent methyl-substituted bicyclo-octane derivatives where the classical carbocation is less favourable than the non-classical intermediate.

The greater ease of hydride shift in (F) compared to that which interconverts (B) and (C) reflects not only the fact that the former shift results in the transfer of positive charge from a secondary to a tertiary centre, but also the higher concentration of positive charge on the migratory terminus in the former.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. N.m.r. spectra were run on a Varian A-60A spectrometer and i.r. spectra on a Beckman IR12 spectrophotometer for solutions in carbon tetrachloride. Mass spectra were recorded on a Varian CH7 instrument. Microanalyses were performed by Mr. H. S. McKinnon, Guelph. The alumina (Fisher) used in column chromatography was 80—200 mesh. Ordinary analytical and preparative t.l.c. chromatoplates were spread with Kieselgel G (Merck); the coating for silver nitrate-impregnated silica gel chromatoplates contained 12·5% of silver nitrate. Light petroleum refers to the fraction of b.p. 40—60°.

Preparation of (16S)-ent-*Kaur*-11-*ene* (3a).—A solution of (16*S*)-*ent*-kaur-11-en-17-ol [2] (3c) (1·017 g) and toluene-*p*-sulphonyl chloride (1·0 g) in pyridine (5 ml) was left for 24 h at room temperature. The resulting mixture was poured into ice–water and extracted with ether. The extract was washed with ice-cold hydrochloric acid (conc. HCl–water, 1 : 1) then with ice–water, dried (Na_2SO_4 and K_2CO_3), filtered, and evaporated to leave a white crystalline solid (3b) which was used directly in the next step. The tosylate (3b) was heated in refluxing ether (150 ml) overnight with lithium aluminium hydride (150 mg) and heating was continued for a further 24 h after the addition of fresh hydride (300 mg). The mixture was then cooled and ethyl acetate (2 ml), water (0·45 ml), 15% sodium hydroxide solution (0·45 ml), and water (1·35 ml) were added in succession, dropwise, with stirring. Filtration of the ethereal solution from the precipitated salts and evaporation gave an oil which solidified. This was chromatographed on alumina (25 g), elution with light petroleum

followed by evaporation *in vacuo* giving an oil [0·892 g, 93% from (3c)], which slowly afforded a white, crystalline solid (16S)-ent-*kaur*-11-*ene* (3a), m.p. 62·5—63·5° (from ether–methanol); τ(CCl_4) 9·21, 9·14, and 9·09 (all 3H, s), 9·05 (lower field component of d due to secondary Me), 4·49 (1H, dd, J_{obs} 9·5 and 3·5 Hz), and 4·14 (1H, broadened dd, J_{obs} *ca.* 9·5 and *ca.* 5·5 Hz) (Found: C, 88·25; H, 11·85. $C_{20}H_{32}$ requires C, 88·15; H, 11·85%).

Hydroboration–Oxidation of (16S)-ent-*Kaur*-11-*ene*.—Lithium aluminium hydride (350 mg) in ether (100 ml) was added dropwise with stirring under nitrogen to a solution of (3a) (1·140 g) and boron trifluoride–ether complex (1·15 g) in ether (100 ml), cooled in a water-bath, over 30 min. The resulting mixture was stirred at room temperature for 3 h then acetone (5 ml) was added gradually, followed by saturated sodium sulphate solution (150 ml). The mixture was shaken in a separating funnel and the ether layer was separated and evaporated. The residue was dissolved in tetrahydrofuran (25 ml), sodium hydroxide (2 g) in methanol (20 ml) was added, and the mixture was stirred during dropwise addition of hydrogen peroxide solution (10 ml; 50%). After stirring overnight at room temperature, the solvents were evaporated off *in vacuo* and the residue was partitioned between ether and water. The ether layer was separated, dried (Na_2SO_4), filtered, and evaporated to give an oil which solidified. Analytical t.l.c. (ethyl acetate–light petroleum, 1 : 9) showed the presence of six components which were subjected to preparative t.l.c. (ethyl acetate–light petroleum, 7 : 93; run twice) to give pure samples of the major products (1a and e). Fractions containing the minor products were combined with the corresponding fractions from hydroboration–oxidation of a further sample (1·012 g) of (16*S*)-*ent*-kaur-11-ene (3a) and rechromatographed to give (1b) (ethyl acetate–light petroleum, 7 : 93; run twice), (1c), (4a), and (4b) (ethyl acetate–light petroleum, 3 : 97; run five times). Yields and physical data for these products, in order of decreasing polarity, were as follows.

(16S)-ent-*Kauran*-12α-*ol* (1b) [66·7 mg, 2·9% from 2·152 g of (3a)] had m.p. 165—165·5° (from hexane); ν_{OH} 3629 cm^{-1}; τ($CDCl_3$) 9·20, 9·15, and 9·04 (all 3H, s), 8·78 (3H, d, *J* 6·6 Hz), and 5·83—6·27 (1H, m, $W_{\frac{1}{2}}$ 23 Hz) (Found: C, 82·35; H, 11·8. $C_{20}H_{34}O$ requires C, 82·7; H, 11·8%). (16S)-ent-*Kauran*-12β-ol (1a), the major product (0·839 g, 69·5%), had m.p. 111—113° (from hexane); ν_{OH} 3626 cm^{-1}; τ($CDCl_3$) 9·18, 9·14, and 8·80 (all 3H, s), 9·01 (3H, d, *J* 6·3 Hz), and 6·05 (1H, m, $W_{\frac{1}{2}}$ 9 Hz) (Found: C, 82·45; H, 11·85%). (16S)-ent-*Kauran*-11β-*ol* (4a) (35·6 mg, 1·6%) had m.p. 159—159·5° (from hexane); ν_{OH} 3628 cm^{-1}; τ(CCl_4) 9·19, 9·16, and 8·79 (all 3H, s), 9·00 (3H, d, *J* 6 Hz), 7·37 (1H, broadened d, *J* 12 Hz), and 5·72 (1H, apparent d, J_{obs} 11·5 and 7·5 Hz) (Found: C, 82·85; H, 11·7%). (16S)-ent-*Kauran*-11α-*ol* (4b) (21·0 mg, 0·9%) had m.p. 131—135° (from aqueous methanol); ν_{OH} 3622 cm^{-1}; τ(CCl_4) 9·20, 9·14, and 9·12 (all 3H, s), 8·91 (3H, d, *J* 5·6 Hz), and 6·17 (1H, m, $W_{\frac{1}{2}}$ 9 Hz) (Found: C, 82·5; H, 11·65%).

(16S)-ent-*Kauran*-12-*one* (1c). Since the fraction containing this ketone (33·5 mg) also contained some (4b), it was combined with a further residual fraction (23·5 mg) containing (4a and b) and oxidised with Collins reagent [CrO_3 (100 mg) and pyridine (160 mg) in dichloromethane (20 ml)] to a mixture of 11- and 12-ketones which were readily separated by preparative t.l.c. (ethyl acetate–light petroleum, 3 : 97). This gave (4c) (24·0 mg, 1·1%) and (1c) (18·7 mg, 0·8%), which proved to be identical with the products of oxidation of (4a) and (1a), respectively (see later).

(16S)-ent-*Kaurane* (1e). This hydrocarbon (0·158 g, 13·8%) had m.p. 82—86° (from ether–methanol) (lit.,[11] 84—85°); τ(CCl_4) 9·19, 9·15, and 8·97 (all 3H, s) and 8·99 (3H, d, *J* 5·7 Hz) (Found: C, 87·65; H, 12·65. Calc. for $C_{20}H_{34}$: C, 87·5; H, 12·5%).

Oxidation of (16S)-ent-*Kauran*-12β-*ol* (1a).—The alcohol (100 mg) in dichloromethane (5 ml) was added to a solution prepared by stirring chromium trioxide (250 mg) and pyridine (400 mg) in dichloromethane (40 ml), and the mixture was stirred at room temperature for 15 min. The resulting yellow solution was filtered and washed with dilute sodium hydroxide solution to give a colourless organic layer, which was dried (Na_2SO_4), filtered, and evaporated to give a clear oil (96·2 mg) which rapidly crystallised. T.l.c. (ethyl acetate–light petroleum, 1 : 19) showed the presence of a single product, (16S)-ent-*kauren*-12-*one* (1c) which, on crystallisation from aqueous methanol, had m.p. 101·5—103·5°; ν_{CO} 1706 cm^{-1}; τ(CCl_4) 9·20 and 2 × 9·14 (all 3H, s), and 9·03 (3H, d, *J* *ca.* 7 Hz) (Found: C, 82·95; H, 11·2. $C_{20}H_{32}O$ requires C, 83·25; H, 11·2%).

Reduction of (16S)-ent-*Kauran*-12-*one* (1c) *with Lithium Aluminium Hydride*.—The ketone (136 mg) was stirred at room temperature with lithium aluminium hydride (200 mg) in ether (50 ml) for 30 min. Fresh hydride (100 mg) was then added, and stirring was continued for a further 2 h at room temperature, then for 1 h under reflux. The mixture was cooled and worked up as described for the reduction of (1d) to give a solid product (129·6 mg), t.l.c. of which (ethyl acetate–light petroleum, 1 : 9) showed the presence of two components. Preparative t.l.c. (ethyl acetate–light petroleum, 1 : 19; run three times) gave (16*S*)-*ent*-kauran-12β-ol (1a) (12·7 mg) and the *ent*-12α-epimer (1b) (96·6 mg).

Oxidation of (16S)-ent-*Kauran*-11β-*ol* (4a).—The alcohol (30·4 mg) was oxidised in dichloromethane (25 ml) with chromium trioxide (80 mg)–pyridine (130 mg). Work-up as described earlier gave a single, crystalline product, the ketone (4c) (29·4 mg), m.p. 106—112·5° (from methanol); ν_{CO} 1699, ν_{CH} 3021 cm^{-1}; τ(CCl_4) 9·18, 9·13, and 8·97 (all 3H, s), and 9·02 (lower field component of d due to secondary Me).

Reduction of (16S)-ent-*Kauran*-11-*one* (4c) *with Lithium Aluminium Hydride*.—Reduction of this ketone (38·7 mg) with lithium aluminium hydride (150 mg) in ether (30 ml) was carried out as outlined for (1c) to give a mixture of two alcohols. Preparative t.l.c. (ethyl acetate–light petroleum, 3 : 97; run five times) gave (4a) (18·2 mg), (4b) (11·0 mg), and a fraction (6·3 mg) containing a mixture of (4a and b).

Preparation of (16S)-ent-12β-p-*Tolylsulphonyloxykaurane* (1d).—A solution of (16*S*)-*ent*-kauran-12β-ol (1a) (250 mg) and toluene-*p*-sulphonyl chloride (300 mg) in pyridine (3 ml) was left for 2 days at room temperature; analytical t.l.c. then indicated that all the alcohol had reacted. The mixture was taken up in ether and the solution was shaken with ice-cold hydrochloric acid (1 : 1 conc. HCl–water; 30 ml). The ether layer was separated, dried (Na_2SO_4 and K_2CO_3), filtered, and evaporated to give an oil which solidified. Crystallisation from pentane gave the *tosylate* (1d) (166 mg), m.p. 63—65° with formation of new needle-like crystals which in turn melted completely below 90°

[11] L. H. Briggs, B. F. Cain, R. C. Cambie, B. R. Davis, P. S. Rutledge, and J. K. Wilmhurst, *J. Chem. Soc.*, *1963*, 1345.

(Found: C, 72·85; H, 9·05. $C_{27}H_{40}O_3S$ requires C, 72·95; H, 9·05%).

Formolysis of the Tosylate (1d).—The crude tosylate (1d) (0·945 g) prepared from (1a) (0·540 g) and toluene-*p*-sulphonyl chloride (0·70 g) in pyridine (5 ml) as outlined above was used without prior crystallisation. It was dissolved in chloroform (30 ml) and added to a solution prepared by dissolving anhydrous potassium carbonate (0·42 g) in formic acid (50 ml). The resulting solution was left for 7 h at room temperature, then, t.l.c. having confirmed that all the tosylate had reacted, the solvents were evaporated off *in vacuo* (below 40°). The residue was partitioned between water and pentane, and the pentane extract was evaporated to give an oil which was heated at reflux with a solution of sodium hydroxide (1·0 g) in aqueous ethanol (20 ml; 1 : 1) for 3 h. Evaporation *in vacuo* and partition of the residue between ether and water, followed by separation, drying (Na_2SO_4), filtration, and evaporation of the ethereal layer, gave an oil (0·495 g) which solidified partly. Analytical t.l.c. (ethyl acetate–light petroleum, 1 : 9) initially showed the presence of two alcohols and non-polar material, but on closer examination traces of product(s) of intermediate polarity could be distinguished. Preparative t.l.c. (ethyl acetate–light petroleum, 1 : 9; run four times) resulted in separation of the two alcohols (2a and b) and the hydrocarbon fraction, which are discussed below, and material of intermediate polarity (14·8 mg, 3% of recovered product). The last proved to consist of two components, the minor and more polar of which had the same R_F value as (16*S*)-*ent*-kauran-12β-ol (1a). Combination of this fraction with similar fractions obtained from subsequent solvolyses of (2d and e), and rechromatography (ethyl acetate–light petroleum, 3 : 97; run four times) gave a pure sample (11·0 mg) of the less polar minor alcohol, ν_{OH} 3628 cm^{-1}; τ(CCl_4) 9·18, 9·14, and 9·09 (all 3H, s), 8·85 (3H, d, *J* 6·3 Hz), and 6·25 (1H, m, $W_{\frac{1}{2}}$ *ca.* 9 Hz); and some (2·6 mg) of the more polar alcohol. The former alcohol (6a) was oxidised with chromium trioxide (50 mg)–pyridine (100 mg) in dichloromethane (25 ml) to give a single product (6b) (10·8 mg) which, on crystallisation from methanol, had m.p. 101—105° with prior softening and formation of long, crystalline spars; ν_{CO} 1711 cm^{-1}; τ(CCl_4) 9·17, 9·13, and 9·02 (all 3H, s), absorption due to secondary Me obscured by CH_2 absorption at 8·55—8·75?; mass spectrum shows heaviest fragments at *m/e* 288 (65%), 273 (31·5), 270 (21), 246 (18), 214 (17), 165 (55), 152 (90), 122 (100), and 69 (42·5) (intensities relevant to that of *m/e* 122).

(13R,16S)-ent-*Atisan*-13-*ol* (2a) (122·9 mg, 24·9% of recovered product), the less polar of the major alcohols from (1d), had m.p. 114·5—116·5° (from aqueous methanol); ν_{OH} 3624 cm^{-1}; τ($CDCl_3$) 9·18, 9·15, and 8·95 (all 3H, s), 8·99 (3H, d, *J* 7·2 Hz), and 6·12 (1H, apparent d, J_{obs} 9·5 and 3 Hz) (Found: C, 82·4; H, 11·6. $C_{20}H_{34}O$ requires C, 82·7; H, 11·8%). (13S,16S)-ent-*Atisan*-13-*ol* (2b) (199·1 mg, 40·4%), the major product from (1d), had m.p. 164—165° (hexane); ν_{OH} 3624 cm^{-1}; τ($CDCl_3$) 9·18 and 2 × 9·16 (all 3H, s), 9·03 (3H, d, *J* 6·8 Hz), and 6·07 (well-resolved eight-line m, J_{obs} 9·4, 5·3, and 3 Hz) (Found: C, 82·7; H, 11·7%).

Hydrocarbon Fraction from the Formolysis of (1d). Analytical t.l.c. of this fraction (156·5 mg, 31·7%) ($AgNO_3$–SiO_2; light petroleum) showed the presence of about nine components. Preparative t.l.c. (conditions as for analytical t.l.c.) gave the major component (106·8 mg, 72·7% of recovered hydrocarbon), (16*S*)-*ent*-kaur-11-ene (3a). The less polar fractions (11·0 mg, 7·5%) contained at least two components with very similar polarities, and were not examined further. The more polar fractions (29·0 mg, 19·8%), which contained six components (t.l.c.), were combined with similar fractions obtained on formolysis of (2d and e). Rechromatography on silver nitrate-impregnated silica gel gave fractions (i)—(v) in order of decreasing polarity. (i) Atisene (7a) (1·3 mg) was identified by t.l.c. and mass spectral comparison with authentic material. (ii) (16*S*)-*ent*-atis-13-ene (8) (2·5 mg), was identified on the basis of mass spectral evidence and the observation that it is obtained on dehydration of (2a or b). The mass spectrum shows strong peaks at *m/e* 272 (M^+), 257, and 230. The intensity of the last is virtually equal to that of the base peak (*m/e* 106) and is ascribable to a retro-Diels–Alder fragmentation ($M - C_3H_6$). The remainder of the spectrum is identical with that of isoatisene (7b). (iii) Isoatisene (7b) (3·6 mg) was identified by t.l.c. and mass spectral comparison with authentic material. (iv) This crystalline fraction (14·0 mg) contained two components, the less polar of which was a fairly minor constituent. The close similarity in R_F values of these compounds precluded further purification of the major component, which was not examined further. (v) The least polar of the six hydrocarbons was obtained as an oil (7·9 mg) which was not examined further.

Oxidation of (13S,16S)-ent-*Atisan*-13-*ol* (2b).—Oxidation of (2b) (100 mg) with chromium trioxide (250 mg)–pyridine (400 mg) in dichloromethane (40 ml), and work-up as described earlier, gave a crystalline product (2c) (98·1 mg), which ran as a single spot on t.l.c. (ethyl acetate–light petroleum, 1 : 19). Crystallisation from aqueous methanol gave (16S)-ent-*atisan*-13-*one*, m.p. 139—143°; ν_{CO} 1725 cm^{-1}; τ(CCl_4) 2 × 9·19 and 9·13 (all 3H, s), 8·92 (3H, d, 6·1 Hz), and 7·52 (1H, dd, *J* 19 and 3·3 Hz) (Found: C, 83·25; H, 11·2. $C_{20}H_{32}O$ requires C, 83·25; H, 11·2%).

Reduction of (16S)-ent-*Atisan*-13-*one* (2c) *with Lithium Aluminium Hydride*.—Reduction of the ketone (83·6 mg) with lithium aluminum hydride (150 mg) in ether (25 ml), and work-up as described previously, gave an oil which contained two products (t.l.c.). Preparative t.l.c. (ethyl acetate–light petroleum, 1 : 19; run four times) gave (13*R*,16*S*)-*ent*-atisan-13-ol (2a) (39·0 mg, 54·8% of recovered material) and the 13-epimer (2b) (32·2 mg, 45·2%).

Dehydration of the (16S)-ent-*Atisan*-13-*ols*.—Phosphoryl chloride (6 drops) was added to an ice-cold solution of the atisanol (2a) (33·8 mg) in pyridine (0·5 ml). The solution was kept at 0° for 24 h then partitioned between dilute hydrochloric acid and pentane. The pentane extract was dried (Na_2SO_4), filtered, and evaporated to give an oil which was dissolved in fresh pentane, and filtered through a short column of alumina (3 g). The pentane eluate was evaporated to give an oil (8·5 mg). Analytical t.l.c. ($AgNO_3$–SiO_2; ethyl acetate–light petroleum, 1 : 199) of this material indicated that it contained two major products, a small amount of material of intermediate polarity, and a trace of non-polar material. Preparative t.l.c. (light petroleum; run twice) gave atisene (7a) (1·4 mg), (16*S*)-*ent*-atis-13-ene (8) (0·6 mg), and isoatisene (7b) (4·6 mg). These were identified by t.l.c. and mass spectral comparison with authentic material (7a and b) and with the products from (1d).

Dehydration of (2b) (61·7 mg) was carried out similarly.

Preparative t.l.c. of the hydrocarbon fraction thus obtained (24·0 mg) gave atisene (7a) (6·2 mg), (16*S*)-*ent*-atis-13-ene (8) (4·8 mg), and isoatisene (7b) (7·8 mg).

Preparation and Formolysis of (13R,16S)-ent-13-p-*Tolylsulphonyloxyatisane* (2d).—A solution of the atisanol (2a) (120 mg) and toluene-*p*-sulphonyl chloride (150 mg) in pyridine (5 ml) was left for 24 h at room temperature. Since t.l.c. after this time indicated that only about half of the alcohol had reacted, fresh tosyl chloride (150 mg) was added. This procedure was repeated at intervals during 7 days until a molar ratio of alcohol to chloride of *ca.* 1 : 8 was reached. At this point, only a very small spot corresponding to (2a) was evident on t.l.c. The mixture was therefore worked up as described for the preparation of (1d) and the crude tosylate (2d), which contained an excess of tosyl chloride, was used in the formolysis. A solution of (2d) in chloroform (20 ml) was added to formic acid (30 ml) in which potassium carbonate (0·5 g) had been dissolved. The solution was left at room temperature for 18 h and then worked up, the residue being subjected to basic hydrolysis as described before. T.l.c. (ethyl acetate–light petroleum, 1 : 9) of the mixture thus obtained indicated that it contained the same products as the mixture obtained from (1d) plus a new alcohol of polarity intermediate between (2a) and (2b). Preparative t.l.c. (ethyl acetate–light petroleum, 1 : 19; run four times) gave, in order of decreasing polarity; (13*S*,16*S*)-*ent*-atisan-13-ol (2b) (54·5 mg, 52·0% by weight of recovered material); a tertiary alcohol (9) (22·1 mg, 21·1%) which could not be persuaded to crystallise from aqueous methanol or aqueous ethanol, but, after sublimation at 80—100° and 0·02—0·05 mmHg had m.p. 106—109° with softening beginning at *ca.* 80°; ν_{OH} 3604 and 3617 cm^{-1}; $\tau(CDCl_3)$ 9·18, 9·15, 9·05, and 8·73 (all 3H, s); (13*R*,16*S*)-*ent*-atisan-13-ol (2a) (12·3 mg, 11·7%); a fraction (3·5 mg, 3·3%) containing material with the same R_F values as the minor alcohols (6a) and (1a) obtained from (1d), the less polar component (6a) being the major one; and a hydrocarbon fraction (12·5 mg, 11·9%) which contained the same components as that obtained from (1d). However in the former case, in contrast to the latter, the product with R_F value appropriate to (16*S*)-*ent*-kaur-11-ene (3a) was very minor.

Preparation and Formolysis of (13S,16S)-ent-13-p-*Tolylsulphonyloxyatisane* (2e).—Reaction of the alcohol (2b) (108·7 mg) with an excess of toluene-*p*-sulphonyl chloride (1 : 8 molar ratio) in pyridine (5 ml) under the same conditions as used for (2a), and work up as before, gave the crude tosylate (2e) which contained a little unchanged alcohol (t.l.c.) and an excess of tosyl chloride. Formolysis [18 h; chloroform (20 ml), formic acid (40 ml), potassium carbonate (0·5 g)] at room temperature followed by basic hydrolysis and preparative t.l.c. (ethyl acetate–light petroleum, 1 : 19; run four times) gave (13*S*,16*S*)-*ent*-atisan-13-ol (2b) (50·0 mg, 47·9% by weight of recovered material); the tertiary alcohol (9) (20·4 mg, 19·6%); (13*R*,16*S*)-*ent*-atisan-13-ol (2a) (5·7 mg, 5·5%); the minor alcohol (6a) (3·0 mg, 2·9%), which in this instance was not accompanied by material with R_F value appropriate to (1a); and a hydrocarbon fraction which differed from that obtained from (2d) only in the absence of a spot with R_F value appropriate to (16*S*)-*ent*-kaur-11-ene (3a).

Dehydration of the Tertiary Alcohol (9).—Thionyl chloride (3 drops) was added to an ice-cold solution of (9) (13·8 mg) in pyridine (0·2 ml), and the solution was left for 3 h at 0°. The mixture was partitioned between water and pentane, and the pentane layer was separated, dried (Na_2SO_4), filtered, and evaporated *in vacuo*. The oil (8·9 mg) thus obtained was dissolved in fresh pentane, and filtered through a short column of alumina (3 g). The pentane eluate was evaporated to give a clear oil (5·1 mg) which solidified readily, and showed only two spots on t.l.c. ($AgNO_3$–SiO_2; ethyl acetate–light petroleum, 1 : 199). Comparison with authentic samples by t.l.c. and mass spectrometry showed the major, less polar of these two components to be isoatisene (7b), and the minor one to be atisene (7a).

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