Terpenoids. Part V.[1] Rearrangement of *ent*-Kaurane 15β,16β-Epoxide to *ent*-(16*R*)-Atisan-15-one

By J. MacMillan • and E. R. H. Walker, School of Chemistry, The University, Bristol BS8 1TS

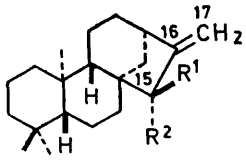
Treatment of *ent*-kaurane 15β,16β-epoxide (5) with boron trifluoride–ether complex in benzene yields *ent*-(16*R*)-atisan-15-one (11) and small amounts of the 16*S*-epimer (4) of *ent*-kauran-15-one. In the conversion of *ent*-(16*R*)-atisan-15-one (11) into *ent*-atis-15-ene (16), the 15-tosylates (13) and (15) of the epimeric *ent*-atisan-15-ols (12) and (14) were found to rearrange to the olefin (18) in high yield.

ALTHOUGH 15α,16α-hydride shift occurs [2] readily in the acid-induced rearrangement of *ent*-kaur-16-en-15α-ol (1) to give the 16*R*-ketone (3) 15β,16β-hydride shift is not observed [2] in the 15-epimeric alcohol (2) which is stable under the same conditions. Similarly, 15β,16β-hydride shift is not observed in the reaction of the 15α,16α-epoxide (5) with magnesium bromide–ether complex; instead the allylic alcohol (2) is formed,[3] presumably because loss of a proton from carbon-17 in the intermediate (6) is much faster than 15β,16β-hydride transfer. In contrast, the 15α,16α-epoxide (8) of 13β-kaur-15-ene is smoothly converted [3] into the 16*S*-ketone (9) under similar conditions. The more recent observation [4] that the 13β-kaurane 15α,16α-epoxide (8) is rearranged both to the 16*S*-ketone (9) and to (16*S*)-12β-atisan-15-one (10) [5] by boron trifluoride–ether complex prompted us to reinvestigate the reaction of the *ent*-kaurane epoxide (5) with this Lewis acid in the expectation that the *ent*-atisan-15-one (11) would be formed in high yield in the absence of 15β,16β-hydride shift.

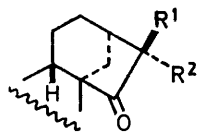
In contrast to the previous report [2] that the epoxide (5) was stable to boron trifluoride–ether at 0°, reaction in benzene at room temperature yielded ketonic products (30%) and a hydrocarbon fraction (70%). The latter was shown to be a complex mixture of isomeric dienes by g.l.c. and by g.l.c.–mass spectroscopy, and was not investigated further. The ketonic fraction contained less than 1% of a minor product shown to be the 16*S*-ketone (4) [6] by g.l.c. and by g.l.c.–mass spectroscopy. Thus, even under these conditions, 15β,16β-hydride shift does not occur to a significant extent. The major ketonic product (95% of the total fraction) was assigned the expected structure (11) on the following evidence.

The ketone, $C_{20}H_{32}O$, differed from the 16*R*-ketone (3).[6] The i.r. absorption at 1716 cm^{-1} could be assigned to a six-membered ring carbonyl group in the absence of vinylic or aldehydic proton signals in the n.m.r.

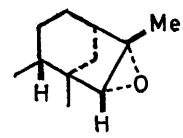
[1] Part IV, J. MacMillan and E. R. H. Walker, preceding paper.
[2] M. F. Barnes and J. MacMillan, *J. Chem. Soc.* (*C*), 1967, 361.
[3] L. H. Briggs, R. C. Cambie, and P. S. Rutledge, *J. Chem. Soc.*, 1963, 5374.
[4] J. G. St. C. Buchanan and B. R. Davis, *Chem. Comm.*, 1967, 1142.
[5] P. A. Gunn, R. McCrindle, and R. G. Roy, *J. Chem. Soc.* (*C*), 1971, 1018.
[6] J. MacMillan and E. R. H. Walker, *J.C.S. Perkin I*, 1972, 986.



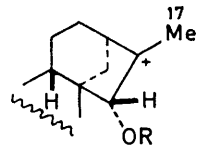
(1) R^1 = OH, R^2 = H
(2) R^1 = H, R^2 = OH



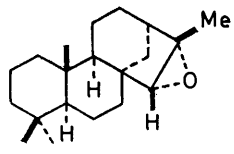
(3) R^1 = Me, R^2 = H
(4) R^1 = H, R^2 = Me



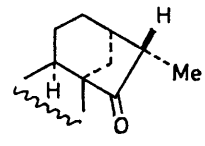
(5)



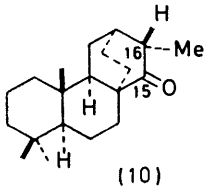
(6) R = H
(7) R = BF_3



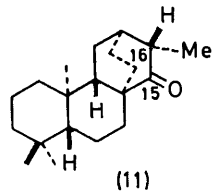
(8)



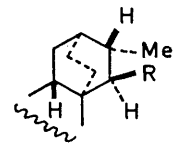
(9)



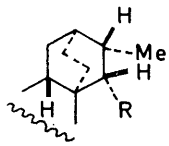
(10)



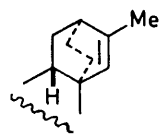
(11)



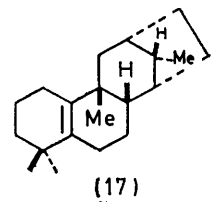
(12) R = OH
(13) R = OTs



(14) R = OH
(15) R = OTs



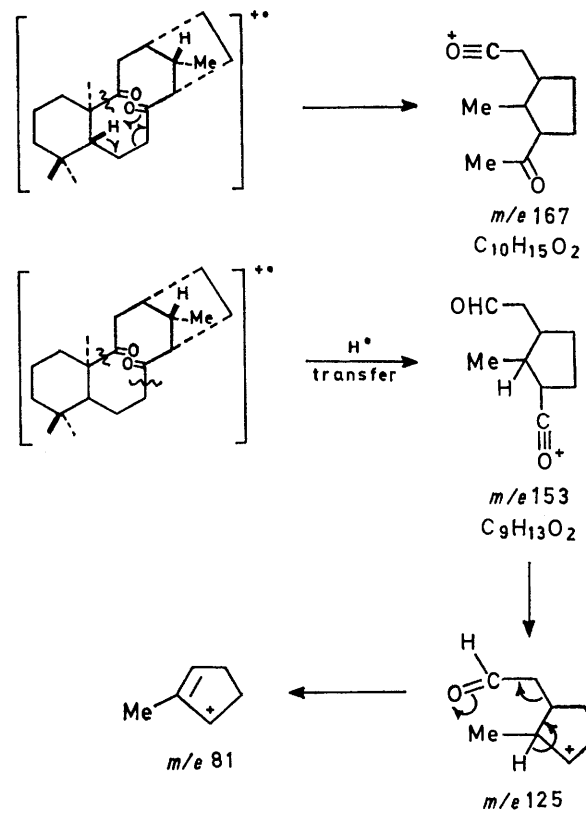
(16)



(17)

spectrum. The latter contained three methyl singlets due to the 10-methyl and the *gem*-4-methyl groups, and a methyl doublet at τ 8·89 (J 7 Hz) which collapsed to a singlet on irradiation at τ 7·9 (the expected value for a proton α to a carbonyl group). The presence of the grouping, –CHMe·CO– was further supported by epimerisation with base to give a 1 : 1 mixture of epimers, and by the mass spectrum of the ketone, which showed fragmentation of the molecular ion to the base peak, *m/e* 230, by loss of this grouping and two hydrogens.[6]

Lithium aluminium hydride reduction of the major ketonic product (11) gave an inseparable 1 : 1 mixture of the 15-epimeric alcohols (12) and (14). The n.m.r. spectrum of the mixture showed the 15-proton doublets corresponding to the two epimers at τ 7·31 (J 4 Hz) and 6·75 (J 9·5 Hz). The higher field doublet was assigned to the epimer (12) in view of the expected anisotropic shielding by the eclipsing methyl group;[1,7,8] the values of J were consistent with this assignment. The mixture of epimeric alcohols (12) and (14) was directly treated with toluene-*p*-sulphonyl chloride in pyridine at room temperature. Column chromatography of the mixture afforded three isomeric hydrocarbons, $C_{20}H_{32}$. Of the two minor products, one was identical with authentic *ent*-atis-15-ene (16); the other was not identified. The n.m.r. spectrum of the major product showed three tertiary methyl signals and a methyl doublet at τ 9·24 (J 6 Hz) which collapsed to a singlet on irradiation at τ 8·0; vinylic proton signals were absent. The presence of a tetrasubstituted double bond was indicated by the intense end-absorption in the u.v. region and confirmed by oxidation to a diketone (see later). Of the two mechanistically probable olefins (17) and (18) the former would be expected to show an $M^+ - 28$ fragment ion in the mass spectrum, formed by a retro-Diels–Alder process. Since this fragmentation was not observed the olefin was assigned structure (18), which was supported by osmium tetroxide–sodium periodate oxidation to a diketone (19). The mass spectrum of the latter was consistent with structure (19) and two characterising fragmentation pathways are shown in the Scheme.



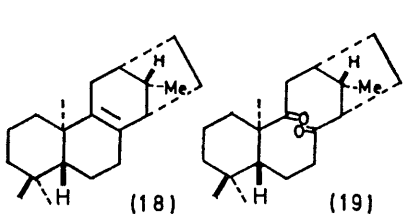
SCHEME Two fragmentation pathways in the mass spectrum of the diketone (19)

In one tosylation experiment, the n.m.r. spectrum of the crude product showed the presence of only one (15) of the epimeric tosylates, characterised by the 15-proton n.m.r. absorption as a doublet (J 9·5 Hz) at τ 5·62. This observation suggests that the 15β-tosylate (13) rearranges more rapidly to the olefin (18), perhaps by the cyclic mechanism (20). This rearrangement

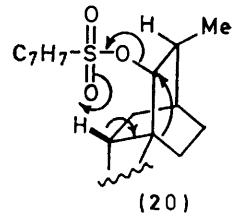
[7] J. W. ApSimon, W. G. Craig, P. V. Demarco, D. W. Mathieson, L. Saunders, and W. B. Whalley, *Tetrahedron*, 1967, **23**, 2339.

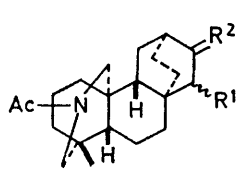
[8] J. W. ApSimon, W. G. Craig, P. V. Demarco, D. W. Mathieson, L. Saunders, and W. B. Whalley, *Tetrahedron*, 1967, **23**, 2375.

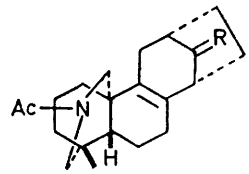
is analogous to previously reported rearrangements of derivatives of atisine. Thus both 15-epimers (21) of noratisine give [9] the olefin (24) on treatment with phosphorus tribromide, the 15β-alcohol reacting faster

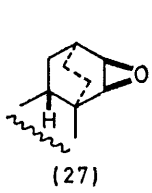

(18)

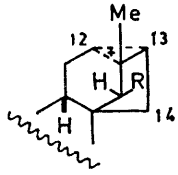
(19)

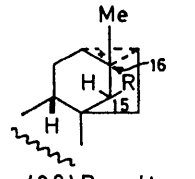

(20)

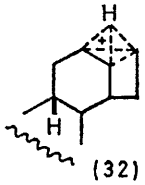

(21) R^1 = OH, R^2 = H_2
(22) R^1 = α-OTs, R^2 = H_2
(23) R^1 = OTs, R^2 = O

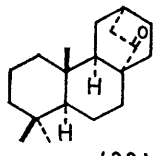

(24) R = H_2
(25) R = α-H, β-OH
(26) R = O

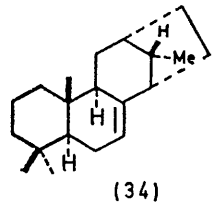

(27)


(28) R = H
(29) R = OBF_3


(30) R = H
(31) R = OBF_3


(32)


(33)


(34)

than the 15α-epimer. Similarly the β-epoxide (27) reacts [9] preferentially with the acid to give the olefin (25) and solvolyses of the 15α-tosylate (22) [9] and of the epimeric tosylates (23) [10] afford the olefins (24) and (26), respectively.

Formation of the ketone (11) from the epoxide (5) provides another example of the rearrangement of an *ent*-kaurane to an *ent*-atisane. These interconversions are currently regarded [11] as occurring *via* the interconverting bridged ions (28) and (30) rather than the face-protonated ion (32) of the Wenkert type. The sequence (5) ⟶ (7) ⟶ (29) ⟶ (31) followed by a 15β,16β-hydride shift in the ion (31) leads to the 16*S*-stereochemistry in the ketone (11). Subsequent epimerisation of the initially formed ketone was ruled out by showing that both the ketone (11) and its 16-epimer were stable under the rearrangement conditions. The Cotton effect of the ketone (11) was of equal magnitude but opposite sign to that of the unsubstituted enantiomer (33) but provides no additional information on the stereochemistry at carbon-16 since the major contribution to the sign is the second sphere effect of the boat conformation of the cyclohexanone.

There is a marked difference in the reactivity of the atisane and the 12β-atisane series at carbons-15 and -16. Gunn *et al.*[5] found that the 15-ketone (10) was epimerised by base to an epimeric mixture containing the 16*S*-epimer predominantly and that this ketone (10) was reduced solely to the 15β-ol. This contrasts with our findings in the *ent*-atisanes that base-catalysed epimerisation of the ketone (11) gives a 1 : 1 mixture of the 16*R*- and 16*S*-ketones and that reduction gives a 1 : 1 mixture of the epimeric 15-alcohols. Further, Gunn *et al.*[5] have shown that treatment of the 15β-ol from (10) with phosphoryl chloride in pyridine brings about rearrangement to the 7,8-ene (34) with no dehydration to the 15-ene. This contrasts with our finding that treatment of the toluene-*p*-sulphonyl derivative of the 15β-ol (12) gives the rearranged 8,9-ene (18) together with small amounts of *ent*-atis-15-ene (16). Zalkow and Girotra [12] also found that α- and β-attack occur to a similar extent in the hydroboration of *ent*-17-noratis-15-ene. These differences can be ascribed to the shielding of the β-face of the 15,16-bridge in the 12β-atisane derivatives by the 10β-methyl group. Also the dichlorophosphate ester of the 15β-ol from (10) is unable to dehydrate by a cyclic mechanism [*cf.* (20)] to an 8,9-ene.

EXPERIMENTAL

General experimental procedures are given in Part II.[13]

ent-Kaurane 15β,16β-*Epoxide* (5).—In a typical experiment, *m*-chloroperbenzoic acid (85%; 503 mg) in chloroform (5 ml) was added to a stirred solution of *ent*-kaur-15-ene (370 mg) in chloroform (10 ml) at 0°. After 50 min, excess of sodium iodide was added. The mixture was then washed with solutions of sodium thiosulphate (2 × 5 ml) and sodium hydrogen carbonate (2 × 5 ml) and water (2 × 5 ml.), dried, and evaporated to give *ent*-kaurane 15β,16β-epoxide (5) as a white crystalline solid (355 mg), a portion of which crystallised from methanol as plates, m.p. 125—127°, $\nu_{max.}$ 840 cm^{-1}, τ 9·23, 9·18, 9·04, and 8·63 (each 3H, s), and 7·42 (1H, s).

Rearrangement of ent-*Kaurane* 15β,16β-*Epoxide* (5) *by Boron Trifluoride*.—In a typical experiment, boron trifluoride–ether complex (2 ml) was slowly added to a stirred solution of the epoxide (400 mg) in sodium-dried benzene (48 ml). The solution went pink. After 15 min, water (10 ml) was added. The solution was shaken with water until it was clear, dried, and evaporated to dryness to give a yellow oil (398 mg), which was chromatographed on silica gel (75 g). Elution with light petroleum gave a clear oil (234 mg) which was shown by g.l.c. and g.l.c.–

[9] S. W. Pelletier and A. Ichihara, *Chem. and Ind.*, 1967, 2149.
[10] J. P. Johnson and K. H. Overton, *Chem. Comm.*, 1969, 329.
[11] R. M. Coates and E. F. Bertram, *Chem. Comm.*, 1969, 797.
[12] L. H. Zalkow and N. N. Girotra, *J. Org. Chem.*, 1964, **29**, 1299.
[13] J. MacMillan and E. R. H. Walker, *J.C.S. Perkin I*, 1972, 981.

mass spectroscopy to be a complex mixture of isomeric hydrocarbons, *M*, 270, which was not further characterised. Elution with 75% benzene in light petroleum gave *ent*-(16*R*)-atisan-15-one (11) (116 mg), which crystallised from acetone as needles, m.p. 112·5—3·5° (Found: M^+, 288·244. $C_{20}H_{32}O$ requires *M*, 288·245), $\nu_{max.}$ ($CHCl_3$) 1710, 1460, 1390, and 1370 cm^{-1}, τ 9·19, 9·16, and 8·97 (each 3H, s), and 8·89 (3H, d, $J_{16.17}$ 7 Hz). G.l.c. and g.l.c.–mass spectroscopy of the mother liquors from the crystallisation of *ent*-(16*S*)-atisan-15-one revealed the presence of *ent*-(16*S*)-kauran-15-one (9) (4 mg), identical with that described in Part III.[6]

Epimerisation of ent-(16R)-*Atisan*-15-*one* (11).—The ketone (1 mg) was refluxed for 9 h in 2% sodium hydroxide in methanol. After recovery of the organic matter in ether, g.l.c. revealed the presence of a mixture of *ent*-(16*R*)-atisan-15-one and (presumably) *ent*-(16*S*)-atisan-15-one in the ratio of 1 : 1.

Reduction of ent-(16R)-*Atisan*-15-*one* (11).—The ketone (11) (55 mg) in sodium-dried ether (3 ml) was added to a stirred suspension of lithium aluminium hydride (40 mg) in sodium-dried ether (4 ml) at room temperature. After 4 h the excess of hydride was discharged with water. The organic material was recovered in ether to yield a 3 : 2 mixture (60 mg), m.p. 87—100°, of *ent*-(16*R*)-atisan-15α-ol (14) and *ent*-(16*R*)-atisan-15β-ol (12), $\nu_{max.}$ ($CHCl_3$) 3660, 3600, 3450, 1390, and 1370 cm^{-1}, τ 9·22, 9·18, and 9·04 (each 3H, s), 9·0 (3H, two d, $J_{16.17}$ 7 Hz), 7·31 (1H, d, $J_{15.16}$ 4 Hz), and 6·75 (1H, d, $J_{15.16}$ 9·5 Hz). The two epimers were chromatographically inseparable on silica gel.

Tosylation of the Epimeric ent-(16R)-*Atisan*-15-*ols* (12) *and* (14).—The foregoing mixture (3 : 2; 60 mg) of alcohols and toluene-*p*-sulphonyl chloride (3 g) were dissolved in pyridine (1·5 ml) and left at room temperature in the dark for 11 days. The brown product was poured into ether (15 ml) and the solution was extracted with 3N-hydrochloric acid (3 × 3 ml), sodium hydrogen carbonate solution (2 × 3 ml), and water (2 × 3 ml), dried, and evaporated to yield a white solid (2 g). Chromatography on silica gel (200 g) and elution with light petroleum gave the *olefin* (18) (25 mg), which crystallised from ethanol as needles, m.p. 84·5—85·5°, $[\alpha]_D^{22}$ −53° ($CHCl_3$), $\lambda_{max.}$ 215 (ε 4080) and 225 nm (3264), $\nu_{max.}$ 2900, 1315, 1205, and 940 cm^{-1}, τ 9·20, 9·16, and 9·13 (each 3H, s), and 9·24 (3H, d, $J_{16.17}$ 6 Hz). Elution with 10% acetone in light petroleum gave *ent*-atis-15-ene (16) (2 mg), which crystallised from ethanol as plates, m.p. 79—82°, τ 9·22, 9·18, 8·90, and 8·34 (each 3H, s), and 4·5 (1H, s), together with unidentified material (1 mg), M^+ 272, major fragmentation *M* − 15 (*m/e* 257), which was not further investigated. In one experiment further elution gave a fraction shown (n.m.r. spectrum) to contain only one tosylate [τ 5·62 (1H, d, $J_{15.16}$ 9·5 Hz)].

Oxidative Fragmentation of the Olefin (18).—Osmium tetroxide (100 mg) was added to a stirred solution of olefin (18) (6 mg) in dry pyridine (10 ml). After 3·5 h excess of sodium disulphite (500 mg) and water (10 ml) was added and the black solution was stirred for a further 30 min. The organic solvent was then removed and the solution was extracted with ether (5 × 5 ml). The combined ethereal solutions were evaporated to dryness and the resulting brown solid treated with sodium periodate (1 g) in methanol (30 ml) and water (10 ml) for 2 h. After evaporation of the methanol, the product was recovered in ether. Evaporation gave a dark brown oil (8·4 mg), which was shown by g.l.c. to be approximately 85% pure (19), $\nu_{max.}$ 1700 cm^{-1}; *m/e* 304 ($C_{20}H_{32}O_2$, 5%), 276 (20), 207 (10), 205 (16), 194 (15), 191 (20), 179 ($C_{11}H_{15}O_2$, 20), 167 ($C_{10}H_{15}O_2$, 25), 161 (20), 153 [$C_{12}H_9$:$C_9H_{13}O_2$ (4 : 1), 21], 136 ($C_{10}H_{13}$, 52), 123 (C_9H_{15}, 39), 121 (26), 109 (C_9H_{13}, 52), 107 (26), 97 (41), 95 (51), 93 (25), 81 (82), 69 (85), 67 (49), 57 (31), 55 (100), 44 (74), 43 (62), 41 (89), and 40 (71).

Treatment of ent-*Atisan*-15-*ones with Boron Trifluoride*.—A mixture of (16*R*)- and (16*S*)-epimers of *ent*-atisan-15-one (1 : 1; 1 mg) was recovered quantitatively, with no change in the ratio of epimers, after treatment with boron trifluoride–ether under conditions which rearranged *ent*-kaurane 15β,16β-epoxide.

We thank the Worshipful Company of Salters for a Research Scholarship (to E. R. H. W.).

[1/2301 *Received*, 3*rd December*, 1971]