A Laboratory Model for the Atisane → Aconane Conversion †

By J. P. Johnston and K. H. Overton,* Department of Chemistry, University of Glasgow, Glasgow W.2

Atisine (1) has been converted into the epimeric toluene-*p*-sulphonates (28) and (29). On acetolysis either (28) or (29) affords the same 14(8 → 15)*abeo*-17-oxa-8-ene (19). In contrast, whereas gas phase pyrolysis of the ester (28) gives the olefin (19). the isomer (29) gives a 9(8 → 15)*abeo*-17-oxa-8(14)ene (20): each conversion takes place stereospecifically *via* a seven-membered transition state. The structure of the olefin (20) has been confirmed by an *X*-ray crystal structure analysis of the derived ethylene acetal hydriodide (48). An n.m.r. analysis of hindered rotation in two amides [(19) and (21)] is presented.

THE diterpene alkaloids comprise two well-defined groups, represented by the tetracarbocyclic C_{20} compounds [1] atisine (1) and veatchine (2), and the pentacarbocyclic C_{19} compounds lycoctonine (3) and aconitine (4).[2]

Synthetic work in the C_{20} series has been extensive and successful,[3] in contrast with efforts to solve the more difficult problem presented by the C_{19} group. Notable, however, are the resourceful experiments of Wiesner and his colleagues,[4] directed at total synthesis. Our synthetic approaches to the lycoctonine–aconitine group were influenced by a consideration of plausible biosynthetic pathways. In the work here described we aimed to effect *in vitro* the key step in the commonly accepted biosynthetic route.

The impressive body of degradative and correlative evidence,[2,5,6] accumulated in work on the C_{19} series of alkaloids during nearly a century, became rigorously interpretable following the *X*-ray crystal structure analysis [7] of de(oxymethylene)lycoctonine. There fol-

† Preliminary communication, J. P. Johnston and K. H. Overton, *Chem. Comm.*, 1969, 329.

[1] For reviews see (*a*) S. W. Pelletier, *Quart. Rev.*, 1967, **21**, 525; (*b*) J. R. Hanson, ' The Tetracyclic Diterpenes,' Pergamon, Oxford, 1968, p. 66; (*c*) S. W. Pelletier and L. H. Keith, ' Chemistry of the Alkaloids,' van Nostrand, New York, 1970, p. 503.

[2] (*a*) Ref. 1*b*, p. 82; (*b*) ref. 1*c*, p. 549.

[3] Ref. 1*b*, p. 106.

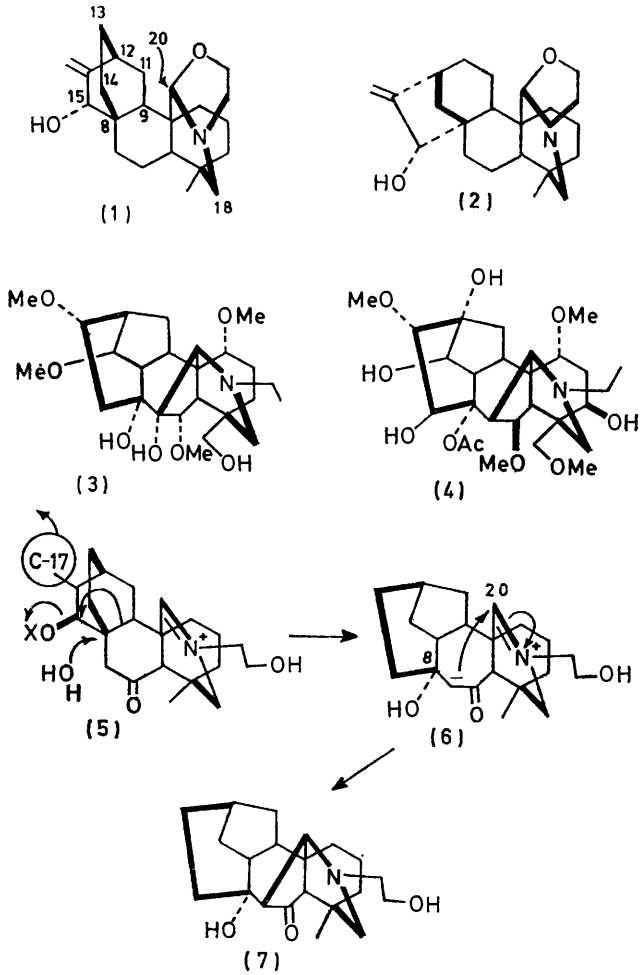
[4] K. Wiesner, A. Phillip, and Pak-tsun Ho, *Tetrahedron Letters*, 1968, 1209; K. Wiesner, E. W. K. Jay, C. Demerson, T. Kanno, J. Krepinsky, L. Poon, T. Y. R. Tsai, A. Vilim, and C. S. Wu, *Experientia*, 1970, **26**, 1030.

[5] Ref. 1*b*, p. 82.

[6] S. W. Pelletier and L. H. Keith in ' The Alkaloids,' ed. R. H. F. Manske, vol. 12, Academic Press, New York, 1970.

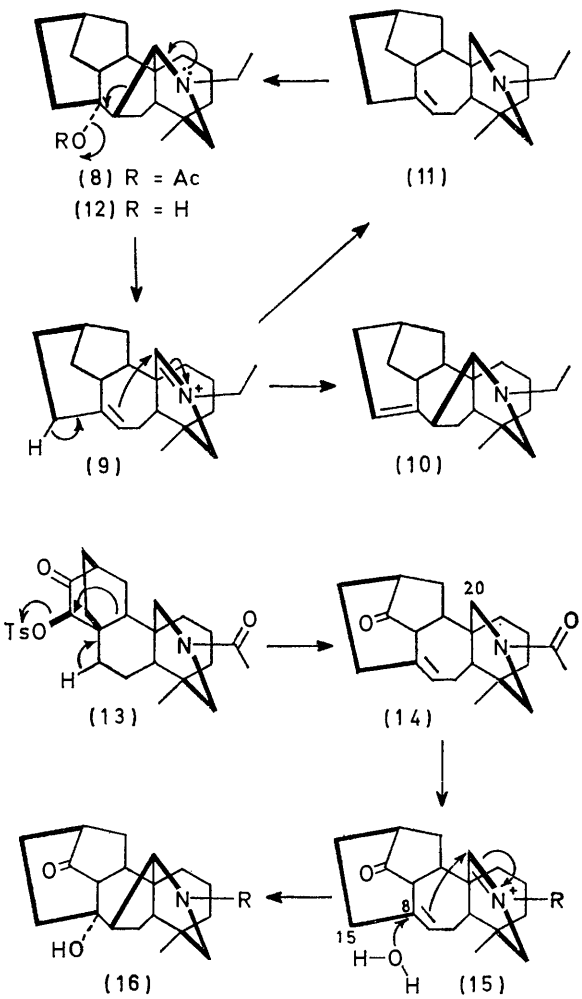
[7] M. Przybylska and L. Marion, *Canad. J. Chem.*, 1956, **34**, 542; 1959, **37**, 1843.

lowed almost immediately two suggestions [8,9] of a plausible biosynthetic pathway the essence of which is embodied in the sequence (5) ⟶ (6) ⟶ (7). The



point of departure is the iminium salt (5) derivable from atisine, the order of steps in this sequence not necessarily being that indicated. A modification of this hypothesis [10a] depended on a correct formulation of the mechanism which generates the well known 'pyro-compounds' [10b] in the aconitine series. Thus, aconitines with a β-acetoxy-group at C-8 typically lose the elements of acetic acid on mild pyrolysis to afford the $\Delta^{8(15)}$-compound. Edwards demonstrated [10a] the true nature [as (8) ⟶ (9) ⟶ (10); oxygen functions except at C-8 are omitted for the sake of clarity] of this apparent 1,2-elimination for the case of bikhaconitine by reductively trapping the intermediate (9) and reconverting the reduction product (11) into the parent alcohol (12) with mercury(II) acetate. He suggested that the last step may have a parallel in the biosynthesis of aconitine alkaloids.

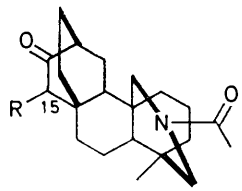
We chose for practical reasons to adopt this suggestion as the model for our synthetic route. This was to proceed from the atisine derivative (13) by Wagner–Meerwein rearrangement to (14) and ultimately *via* (15) by a Prins-type addition to the hexacyclic skeleton (16) of the aconitines. The last step [(15) ⟶ (16), or a modification thereof] seemed well founded in view of chemical [10a,11] and spectroscopic [12-14] evidence which indicated ready electronic interaction between the two π-electron systems of (15). Our major objective, and experimentally the least explored part of the route, was that embodied in the transformation (13) ⟶ (14).



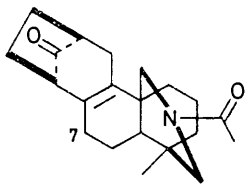
The present paper records the conversion of atisine (1) into the epimeric ketols (17) and (18) and conversion of their toluene-*p*-sulphonates on pyrolysis respectively into the olefins (19) and (20).

[8] Z. Valenta and K. Wiesner, *Chem. and Ind.*, 1956, 354.
[9] R. C. Cookson and M. E. Trevett, *J. Chem. Soc.*, 1956, 3121.
[10] (*a*) O. E. Edwards, *Chem. Comm.*, 1965, 318; (*b*) ref. 1*c*, p. 553.
[11] K. Wiesner, M. Gotz, D. L. Simmons, L. R. Fowler, F. W. Bachelor, R. F. C. Brown, and G. Buchi, *Tetrahedron Letters*, 1959, 15.
[12] K. Wiesner, H. W. Brewer, D. L. Simmons, D. R. Rabin, F. Bickelhaupt, J. Kallos, and T. Bogri, *Tetrahedron Letters*, 1960, 17.
[13] R. C. Cookson, J. Heustock, and J. Hudec, *J. Amer. Chem. Soc.*, 1966, **88**, 1060.
[14] K. Wiesner and T. Inaba, *J. Amer. Chem. Soc.*, 1969, **91**, 1036.

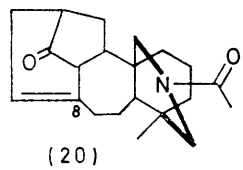
We chose (13) as the atisine derivative to be rearranged for two reasons. By selecting the 17-nor-ketone we hoped to remove the unwanted carbon atom at an early stage of the synthesis and to replace it by an oxygen



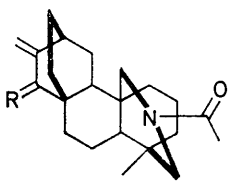
(17) R = α-OH
(18) R = β-OH
(25) R = α-OAc
(27) R = β-OAc
(28) R = α-OTs
(29) R = β-OTs



(19)
(45) Δ^7



(20)



(21) R = α-OH,H
(23) R = β-OH,H
(24) R = α-OAc,H
(26) R = β-OAc,H
(22) R = O

function such as is invariably found at this position in the aconitine alkaloids. Moreover, we hoped that presence of a ketone system α to the ester group being solvolysed would facilitate a concerted Wagner–Meerwein rearrangement and lead to a product of the desired constitution.

The acetylamino-group of (13), obtainable [15,16] from the oxazolidine ring of atisine, promised to serve as an effective protecting group, ultimately convertible into the ethylamine function of the aconitines. Atisine was accordingly converted [15,16] into the acetamido-alcohol (21) in 70% overall yield.

Our next task was to convert the allylic alcohol (21) into the α-ketols (17) and (18). To this end, alcohol (21) was oxidised with either the Sarett or the Snatzke (CrO_3–Me_2N·CHO) [17] reagent (MnO_2–$CHCl_3$ proved ineffective) to the known αβ-unsaturated ketone (22),[16] whose anomalously high wavenumber CO absorption ($\nu_{max.}$ 1712 cm^{-1}) is probably due to non-planarity of the chromophore. Reduction of the ketone (22) with sodium borohydride gave equal amounts of the original allylic alcohol (21) and its C-15 epimer (23), readily separable by preparative t.l.c., but these were accompanied by unacceptable amounts of saturated alcohols. The first specimens of the ketols (17) and (18) were nevertheless prepared from the allylic alcohols (21) and (23) obtained in this way. Thus the allylic acetate (24) on osmylation and periodate oxidation (or, more expeditiously, by the one-step procedure of Pappo [18]) afforded the keto-acetate (25) ($\nu_{max.}$ 1758 and 1743 cm^{-1}; abnormally high values owing to electrostatic interaction [19]). The epimeric allylic acetate (26) on ozonolysis gave the epimeric keto-acetate (27). Hydrolysis at 20° with methanolic sodium carbonate then afforded respectively the ketols (17) and (18). The derived toluene-*p*-sulphonate (28) was crystalline, but the epimer (29) resisted attempts at crystallisation in spite of analytical and spectroscopic properties which indicated its homogeneity.

A more effective route to the ketols (17) and (18) was eventually devised. The keto-acetate (25), obtained as already described, was transformed by acetalisation and hydrolysis into the hydroxy-acetal (30). Oxidation to the oxo-acetal (31) was followed by reduction with borohydride. Since chromatographic separation of the epimeric hydroxy-acetals proved difficult, the mixture was hydrolysed with hot aqueous acetic acid to the two hydroxy-ketones (17) and (18), which were obtained in approximately equal amounts; these could be readily separated.

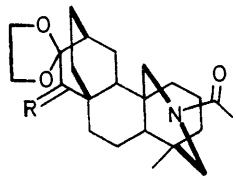
Some unsuccessful attempts to convert the hydroxy-ketone (17) or a derivative into the epimer (18) by equilibration are described in the Experimental section.

With the two oxo-toluene-*p*-sulphonates (28) and (29) in hand, we proceeded to study their solvolytic rearrangements. We hoped, for reasons previously outlined, that alkyl group migration might in each case be concerted with fission of the C–OTs bond. Under such circumstances the ester (28) should lead to the olefin (19) *via* the transition state (32), whereas ester (29) should lead to olefin (20) *via* (33). Contrary to our expectations, acetolysis of *either* (28) or (29) in buffered acetic acid at 150° led to the *same* oily olefin (19) as sole product. This showed an i.r. carbonyl band at 1760 cm^{-1}, typical [20] of a bicyclo[3,2,1]oct-2-en-8-one and its mass spectrum exhibited a prominent ion at *m/e* 299 (*M* − 28), reflecting the ready loss of carbon monoxide. The n.m.r. spectrum lacked olefinic signals. The oily olefin was characterised as the crystalline hydriodide (34), m.p. 228—232°, and hydrobromide (35), m.p. 245° (sublimes), of the derived acetal amine.

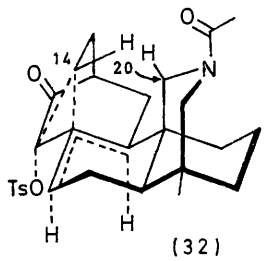
Chemical support for the proposed constitution (19) was obtained as follows. Reduction with sodium borohydride gave a single hydroxy-olefin (36) having $\nu_{max.}$ (0·03M in CCl_4) 3573 cm^{-1}, indicating exclusive formation of the intramolecularly hydrogen-bonded isomer, as in the parent system.[20] The olefin reacted slowly with osmium tetroxide to give a minor product whose t.l.c. behaviour was consistent with it being the expected diol and a major product ($\nu_{max.}$ 1722, 3600,

[15] D. Dvornik and O. E. Edwards, *Canad. J. Chem.*, 1957, **35**, 860.
[16] S. W. Pelletier and P. C. Parthasarathy, *J. Amer. Chem. Soc.*, 1965, **87**, 777.
[17] G. Snatzke, *Chem. Ber.*, 1961, **94**, 729.
[18] R. Pappo, D. S. Allen, R. U. Lemieux, and W. S. Johnson, *J. Org. Chem.*, 1956, **21**, 478.
[19] L. J. Bellamy, 'Advances in I.R. Group Frequencies,' Methuen, London, 1968, p. 141.
[20] N. A. Le Bel and L. A. Spurlock, *Tetrahedron*, 1964, **20**, 215.

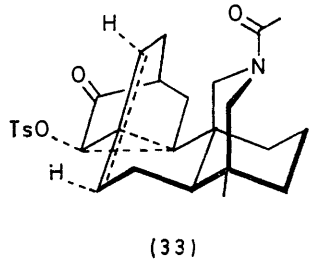
and 3340br cm^{-1}) presumably arising from fission of the β-hydroxy-ketone formed, which was not further investigated. An attempt to obtain support for the formation of the suspected bicyclo-octenone system by acid-catalysed cleavage failed. Thus, while the



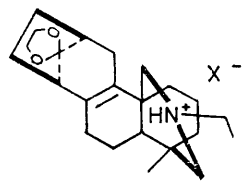
(30) R = α-OH,H
(30a) R = α-OAc,H
(31) R = O



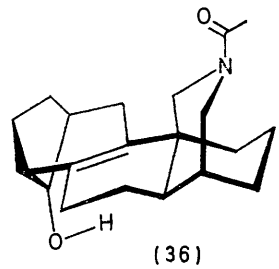
(32)



(33)



(34) X = I
(35) X = Br



(36)

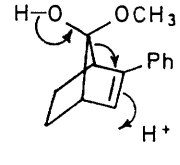
simple bicyclic model is readily cleaved (37; arrows)[21] by methanolic sulphuric acid, the unsaturated ketone (19) merely formed the dimethyl acetal.

Two questions arise at this stage: (*a*) by what mechanism does the toluene-*p*-sulphonate (29) rearrange to the unexpected olefin (19); (*b*) why does it so rearrange exclusively instead of forming the expected olefin (20)?

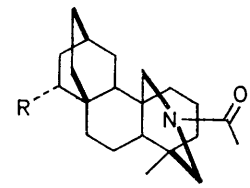
If one discounts the improbable α-keto-carbonium ion as a common intermediate in the two cases, then the rearrangement (29) ⟶ (19) is likely to be preceded by inversion of the configuration at C-15. Inversion of the tosylate system by acetate ion does not account for more than 10% of the observed olefinic product, as was shown by a control experiment in which the β-acetate (27) was subjected to the solvolysis conditions. The product after 48 h consisted predominantly of the two keto-acetates (25) and (27) in approximately equal amounts. On the other hand, rearrangement may well be preceded by epimerisation of the tosylate, either by enolisation or by ion pair return.[22] Thus when the β-tosylate was acetolysed under standard conditions, the ester fraction after 3·5 h contained 30% α-tosylate, and little rearrangement to olefin had occurred; upon further treatment gradual conversion into olefin (19) took place.

A sufficiently large rate difference between the two rearrangements (28) ⟶ (19) and (29) ⟶ (20) could account for the failure to observe the latter. The cause of such a difference may reside in the severe non-bonded interaction between the hydrogen atoms at C-14 and C-20, which is clearly indicated by models [see (32)] and amply supported[23-25] by the recorded reactions of atisine and its congeners. The transition state (32) [from (28)], unlike (33) [from (29)], probably relieves this unfavourable interaction substantially.

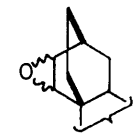
Soon after completion of the foregoing experiments analogous rearrangements with the C_{19} alcohols (40) and the epoxide (41) were reported[26] by Pelletier and Ichihara. They, like us, obtained as a result of



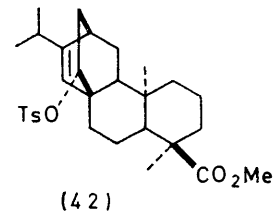
(37)



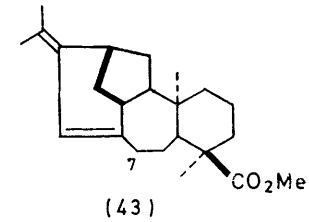
(39) R = β-OH
(40) R = α-OH



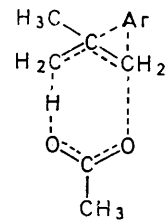
(41)



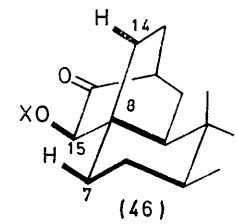
(42)



(43)



(44)



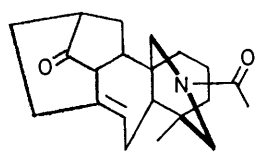
(46)

solvolyses only rearrangement products related to (19) and none related to (20). However, working with a simpler model system in which the special factors conducive to the formation of (19) do not operate, Ayer and Deshpande have converted[27] the toluenesulphonate

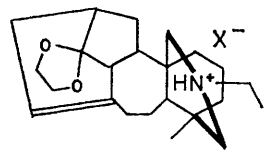
[21] G. L. Buchanan, A. C. W. Curran, J. M. McCrae, and G. W. McClay, *Tetrahedron*, 1967, **23**, 4729.
[22] S. Winstein, E. Clippinger, A. H. Fairberg, and G. C. Robinson, *J. Amer. Chem. Soc.*, 1954, **76**, 2597.
[23] O. E. Edwards and T. Singh, *Canad. J. Chem.*, 1955, **33**, 448.
[24] S. W. Pelletier, *Experientia*, 1964, **20**, 1; *Quart. Rev.*, 1967. **21**, 525.
[25] D. Dvornik and O. E. Edwards, *Tetrahedron*, 1961, **14**, 54.
[26] S. W. Pelletier and A. Ichihara, *Chem. and Ind.*, 1967, 2149.
[27] W. A. Ayer and P. D. Deshpande, unpublished results. We thank Professor Ayer for disclosure before publication.

(42) into the diene (43) either by acetolysis or even by simple passage through silica gel in benzene.

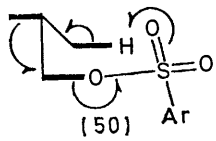
A possible escape from the impasse which we now faced was suggested by a communication [28] which reported that pyrolysis of 2-methyl-2-phenylpropyl acetate gave mainly the unconjugated olefin 2-methyl-3-phenylpropene. It was suggested [28] that this reaction might proceed through a seven-membered transition state (44) of a kind previously invoked [29] to account



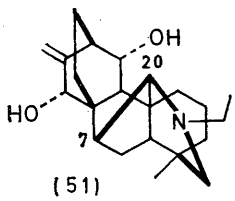
(47)



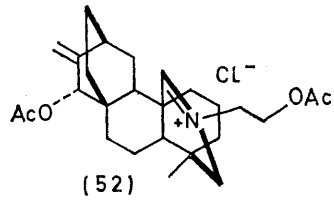
(48) X = I
(49) X = Br



(50)



(51)



(52)

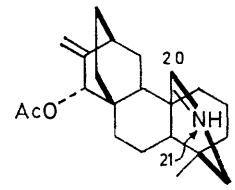
for the pyrolytic conversion of isobornyl xanthate into camphene of high optical purity. The pyrolytic conversion [30] of patchouli acetate into α- and γ-patchoulenes is apparently another example of this same type of rearrangement. In common with the examples quoted (isobornyl xanthate does afford bornylene in addition to camphene), the esters (25) and (27) lack α-hydrogen atoms but do possess the other features required for rearrangement, namely γ-hydrogen atoms and suitably oriented β-substituents. Models suggest that pyrolytic rearrangement should be stereospecific, *i.e.* that the α-oriented keto-ester (25) should lead to the rearranged olefin (19) or (45) and that the β-keto-ester [(27) ≡ (46)] should elicit rearrangement to the olefin (20) or (47) having the carbon skeleton that had eluded us in our solvolysis experiments.

Preliminary g.l.c. experiments which effected pyrolysis and product analysis in one operation were encouraging. Thus, whereas the acetates were inert, injection of the oxo-tosylate (28) into 5% SE30 at 225° afforded as major product (>90%) a single olefin [*M* 327 by g.l.c.–mass spectroscopy; R_t (relative to hexacosane) 1·86] which was identical (g.l.c.) with the oxo-olefin (19) obtained in the solvolysis experiments from both oxo-tosylates (28) and (29). The β-tosylate (29) under the same pyrolytic g.l.c. conditions afforded two new keto-olefins (*M* 327; R_t 2·06 and 2·18) in equal amounts and a minor amount (<20%) of the substance of R_t 1·86.

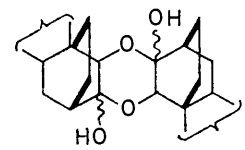
On a preparative scale, the pyrolysis was best effected in the gas phase at a nitrogen pressure of 0·5 mmHg at 500° (see Experimental section). Recycling (twice) of unchanged β-tosylate (29) gave the keto-olefin (20) in 77% yield (by g.l.c.). The olefinic fraction separated from the pyrolysate by preparative t.l.c. on silver nitrate–silica gel was shown by analytical g.l.c. (5% SE30 at 225°) to consist of the two keto-olefins (20) and (19) in the ratio of 19 (R_t 2·17) to 1 (R_t 1·85).

In subsequent experiments, acetalisation of the unstable keto-olefin prior to its isolation from the pyrolysis product by t.l.c. resulted in improved recovery. The regenerated keto-olefin was homogeneous (g.l.c. on 5% SE30 and 1% QF1 at 225°) and had *M* 327, $\nu_{max.}$ 1760 cm^{-1} (bridgehead CO in bicyclo[3,2,1]octane),[20] τ 4·80 (1H, m, vinyl H). For characterisation it was transformed into the crystalline hydriodide (48), m.p. 240—243°, and hydrobromide (49), m.p. 250° (sublimes), by acetalisation, reduction with lithium aluminium hydride, and careful neutralisation of a methanolic solution of the amino-acetal with hydriodic or hydrobromic acid. An *X*-ray crystal structure analysis [31] of the hydriodide (48) confirmed the constitution and stereochemistry of the pyrolysis product obtained from the oxo-toluenesulphonate (29) as that illustrated (20). All attempts to detect minor quantities of the alternative olefin (47) in the pyrolysis product or its derivatives (see Experimental section) were unsuccessful.

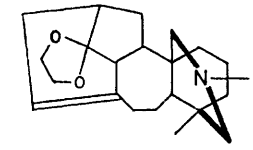
The reason for the observed regiospecificity in this rearrangement–elimination becomes clear if one assumes



(53)
(54) 20,21-Dihydro-(53)
(55) *N*-Acetyl-(54)



(56)



(57) R = Ac
(58) R = Et

that the optimum configuration for rearrangement is that shown in (50), *i.e.* that the C–H and C–O bonds broken in the reaction are 1,3-diaxial and both anti-

[28] H. Kwart and D. P. Hoster, *Chem. Comm.*, 1967, 1155.
[29] C. A. Bunton, K. Khaleeluddin, and D. Whittaker, *Nature*, 1961, **20**, 715.
[30] G. Buchi, R. E. Erickson, and N. Wakabyashi, *J. Amer. Chem. Soc.*, 1961, **83**, 927; M. Dobler, J. D. Dunitz, B. Gubler, H. P. Weber, G. Buchi, and J. Padilla O., *Proc. Chem. Soc.*, 1963, 383.
[31] G. Ferguson and J. P. Johnston, *Chem. Comm.*, 1969, 330.

periplanar to the bond migrating from the intermediate carbon atom. Models [see (46)] show that if the 7β-hydrogen atom is to participate in a concerted process resulting in migration of C-8 to C-15 then, unless ring B reacts in the improbable boat conformation, the product must be the exceedingly strained *trans*-cycloheptene (47). On the other hand, abstraction of the appropriately situated hydrogen atom at C-14 leads to the strain-free bicyclo[3,2,1]oct-2-en-8-one (20), which is the observed product.

Preparative gas-phase pyrolysis of the epimeric α-toluenesulphonate (28) afforded the oxo-alkene (19), identical by all physical criteria with the material obtained by acetolysis. The acetates (25) and (27) were recovered unchanged after attempted pyrolysis at 600°, possibly indicating that some charge separation occurs in the transition state.[32] The stereospecific course of the foregoing rearrangements establishes beyond doubt the configuration of the C-15 hydroxy-group in atisine as α, as strongly indicated by previous circumstantial evidence.[33-35]

The kinetic product of pyrolysis (20) is also the thermodynamically more stable isomer, as is indicated by its failure to isomerise to (14) under acidic conditions. However, it is probable that the major destabilising factor in structure (14) *vis-à-vis* its isomer (20) is the unfavourable interaction between the 7,8-double bond and the C-20 hydrogen atom directed towards it.

The final phase of this work, directed towards C-7,C-20 ring closure must therefore aim initially at creation of an iminium function [as (15)] to make C-20 trigonal and thereby substantially reduce the stability difference between the 7,8- and 8,15-double bonds.

After completion of the work here described, there appeared reports of two *X*-ray analyses [36,37] establishing the structure of denudatine (51). This is the first C_{20} diterpene alkaloid known to possess a 7,20-bond and for this reason its isolation may have some bearing on the sequence of steps in the Cookson–Wiesner hypothesis for the biosynthesis of C_{19} diterpene alkaloids. Future biosynthetically modelled synthetic efforts will take this into account.

Note on the Restricted Rotation of Amides derived from Atisine.—The *N*-acetyl compounds encountered in this study present an interesting case of hindered rotation in tertiary amides,[38] which is readily detected in their n.m.r. spectra, and is susceptible to detailed analysis. The acetamides (21) and (19) serve for illustration.

At room temperature, the CH_3·CO signal of the acetamide (21) appears as two singlets (65 : 35) at τ 7·88 and 7·92 (Figure 1a). This feature has received previous comment.[39] The four protons α to the nitrogen atom give a complex set of signals between τ 5 and τ 7. These represent the superposition of spectra for protons a, b, c, and d in each of the two amide conformations (A) and (B). By spin decoupling and integration it

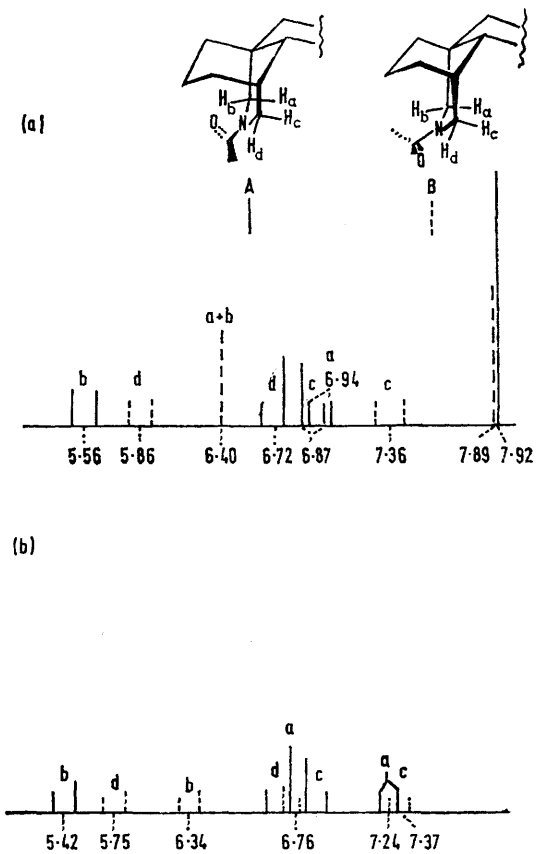


FIGURE 1 N.m.r. spectrum (100 MHz; line diagram) in the $-CH_2{\cdot}N{\cdot}CH_2-$ region of amides (21) (a) and (19) (b), showing restricted rotation of the acetyl group

was possible to separate the spectra corresponding to (A) (—— or ····) and (B) (···· or ——). In one conformation (——) protons H_a and H_b show a large chemical shift separation (1·38 Hz); in the other (···) it is H_c and H_d that show the large separation (1·50 Hz). In conformation (B) H_a and H_b are accidentally equivalent, otherwise each methylene pair gives rise to an AB or AX quartet. We may assume that in each case the methylene pair *syn* to the carbonyl group shows the large chemical shift difference.[40] However, so far the two separated spectra have been *arbitrarily* assigned to conformations (A) and (B); *i.e.* we do not know whether, for instance, the signal at τ 6·40 in Figure 1(a) represents protons a and b (as shown) or c and d. This ambiguity can be resolved by reference to the

[32] A. Maccoll, *Adv. Phys. Org. Chem.*, 1965, **3**, 91.
[33] S. W. Pelletier, *Tetrahedron*, 1961, **14**, 76.
[34] W. B. Whalley, *Tetrahedron*, 1962, **18**, 43.
[35] D. Dvornik and O. E. Edwards, *Canad. J. Chem.*, 1964, **42**, 137.
[36] M. Gotz and K. Wiesner, *Tetrahedron Letters*, 1969, 4369; F. Brisse, *ibid.*, p. 4373.
[37] L. H. Wright, M. G. Newton, S. W. Pelletier, and N. Singh, *Chem. Comm.*, 1970, 359.
[38] See (*a*) J. A. Pople, W. G. Schneider, and H. J. Bernstein, 'High Resolution Nuclear Magnetic Resonance,' McGraw-Hill, New York, 1959; (*b*) L. M. Jackman and S. Sternhell, 'N.M.R. Spectroscopy in Organic Chemistry,' Pergamon, Oxford, 1969.
[39] S. W. Pelletier and T. N. Oeltmann, *Tetrahedron*, 1968, **24**, 2019.
[40] A. H. Lewin, M. Frucht, and F. A. Bovey, *Tetrahedron Letters*, 1970, 1083; A. H. Lewin, *ibid.*, 1971, 3583.

spectrum [Figure 1(b)] of the acetamide (19). Models show that in this substance H_a will be appreciably shielded by the olefinic bond. In fact there is a substantial upfield shift for only one of the four protons when the spectra of (21) and (19) are compared (τ 6·40 ⟶ 6·76 CO *anti*; τ 6·94 ⟶ 7·24 CO *syn*). The other three signals shift less than 0·5 Hz between the two spectra, so that the signals showing the large shift must correspond to H_a in the four cases, thus establishing conformations A and B as shown.

Heating the acetamide (21) in tetrachloroethane caused the signals of the CH_2·N·CH_2 protons to broaden and finally to collapse (at 115°). At 160° the spectrum had simplified to the four expected doublets (J 14 Hz) centred at τ 5·95 (H_b), 6·43 (H_d), 6·68 (H_a), and 7·10 (H_c). The coalescence temperature (80°) for the acetyl methyl signal and its separation (4 Hz) at 20° leads [41,42] to a rough estimate for the barrier to rotation ($\Delta G^{\ddagger}$) of 19 kcal mol^{-1}, which agrees surprisingly well with the accurate values [43] of 18·2 (neat liquid) and 18·6 kcal mol^{-1} [in $(CD_3)_2SO$] for *NN*-dimethyl[$^2H_3$]-acetamide.

EXPERIMENTAL

The following instruments were used: i.r. Perkin-Elmer 237, Unicam SP 100; u.v. Unicam SP 800; n.m.r. Perkin-Elmer R10, Varian T60, Varian HA100 (double irradiation and variable temperature); mass spectrometry A.E.I. MS9 and MS12; g.l.c. Pye–Argon and Perkin-Elmer F 11; g.l.c.–mass spectrometry LKB 9000A. The following solvents were used, unless otherwise specified: i.r. carbon tetrachloride; u.v. ethanol; n.m.r. [^{2}H]chloroform. Values of $[\alpha]_D$ were recorded for solutions in chloroform with a Hilger–Watts photoelectric polarimeter. Merck Kieselgel G was used for analytic and preparative t.l.c., and Woelm alumina, deactivated to the appropriate Brockmann grade, for column chromatography. Micro-analyses were performed by Mr. J. M. L. Cameron and his staff.

Atisine (1).—Atisine was extracted from *Aconitum heterophyllum* roots as described by Edwards [44] and converted into the hydrochloride, needles, m.p. 310—311°, $[\alpha]_D$ +24° (*c* 0·86 in H_2O) [lit.,[44] m.p. 303° (decomp.)].

Atisinium Chloride Diacetate (52).—This was obtained from atisinium chloride (90% yield) as needles, m.p. 240—243° (lit.,[16] 242·5—245°).

The Amine Acetate (54).—Atisinium chloride diacetate was converted into the azomethine acetate (53) (74% yield); this, without purification was reduced with sodium borohydride to the amine acetate (54) (92%), m.p. 167—168° (lit.,[16] 168—169°).

The Amide Acetate (55).—Obtained from the foregoing amine acetate by treatment with acetic anhydride–pyridine (96% yield), this crystallised from acetone–light petroleum in needles, m.p. 152—154° (lit.,[45] blades from ether, m.p. 167—170°).

The Acetamido-alcohol (21).—Obtained from the foregoing *NO*-diacetate (78% yield), this had m.p. 224—226° (lit.,[45] 222—225°).

The Enone (22).—(*a*) The acetamido-alcohol (21) (0·215 g, 0·63 mmol) and chromic oxide (70 mg) in dimethylformamide (5 ml) containing conc. sulphuric acid (2 drops) were kept for 60 h at 20°. Extraction as usual, and preparative t.l.c. [ethyl acetate–light petroleum (4 : 1)] of the oily product, afforded the enone (22) (130 mg, 60%), prisms (from acetone), m.p. 140—145° (lit.,[16] 143—150° depending on rate of heating).

(*b*) Sarett oxidation afforded the enone (22) in 60% yield.

(*c*) Oxidation with activated manganese dioxide in chloroform at a reflux afforded *ca.* 10% (by i.r. spectroscopy) of the enone (22).

Reduction of the Enone (22) *with Sodium Borohydride.*—Sodium borohydride (250 mg) was added to a solution of the enone (194 mg, 0·571 mmol) in cooled methanol (10 ml). After 6 h at 20° the solvent was removed *in vacuo*. The chloroform-soluble residue (180 mg) consisted of three components [t.l.c. in ethyl acetate–light petroleum (4 : 1)]. These were separated by preparative t.l.c. in the same solvent system, furnishing a mixture of saturated alcohols (15 mg) ($\nu_{max.}$ 3612 and 1645 cm^{-1}), the acetamido-alcohol (21) (82 mg, 42%), and its epimer (23) (75 mg, 38%), m.p. 178—179° (lit.,[16] 176—177°).

The Hydroxy-ketones (17) *and* (18).—(a) *Osmylation and periodate oxidation of the amide acetate* (55). (i) The amide acetate (55) (30 mg, 0·078 mmol) [prepared as already described from the amine acetate (54) or by acetylation of the alcohol (21)] and osmium tetroxide (30 mg) were kept in dry ether (15 ml) and pyridine (0·5 ml) for 24 h at 20° in the dark. Replacement of the ether with benzene, saturation with hydrogen sulphide gas, filtration through Celite, and removal of solvent afforded a gum (32 mg), consisting (t.l.c.) of the two epimeric dihydroxy-acetate ($\nu_{max.}$ 3450br), 1734, 1646, 1233, 1044, and 1031 cm^{-1}). This was oxidised without further purification as follows. The mixture (30 mg, 0·071 mmol) in methanol (10 ml) was mixed with sodium periodate (100 mg) in water (10 ml) and kept at 20° for 48 h. Removal of solvent *in vacuo* and partition between ethyl acetate and water gave, on preparative t.l.c. [chloroform–methanol (19 : 1)] of the ethyl acetate-soluble fraction, the *keto-acetate* (25), needles (24 mg, 87%), m.p. 199—200° (from acetone–light petroleum), $[\alpha]_D$ −123° (*c* 1·30) $\nu_{max.}$ 1758, 1743, 1647, 1226, 1063, and 1045 cm^{-1}, τ 9·09 (3H, s), 7·88 (3H, d), 7·80 (3H, s), 5·15 (1H, s), and 5—7 (4H, complex m) (Found: C, 71·45; H, 8·65, N, 3·6; $C_{23}H_{33}NO_4$ requires C, 71·3; H, 8·6; N, 3·6%).

(ii) The amide acetate (55) (50 mg, 0·130 mmol) and osmium tetroxide (5 mg) in aqueous dioxan (5 ml) were stirred at 20° for 5 min, during which the solution turned dark brown. Sodium periodate (50 mg) was added and stirring was continued for 18 h. The white precipitate was filtered off and the filtrate partitioned between ethyl acetate and water. Work-up as before gave the keto-acetate (25) as an oil (35 mg) which spontaneously solidified and was identical in all respects with material prepared in (i).

The hydroxy-ketone (17). A solution of the keto-acetate (25) (50 mg, 0·129 mmol) in methanol (5 ml) and water (0·5 ml) was saturated with solid sodium carbonate and

[41] Ref. 38*a*, p. 223.
[42] A. Allerhand, H. S. Gutowsky, J. Jonas, and R. A. Meinzer, *J. Amer. Chem. Soc.*, 1966, **88**, 3185.
[43] R. C. Neuman and V. Jonas, *J. Amer. Chem. Soc.*, 1968, **90**, 1970.
[44] O. E. Edwards, *Canad. J. Chem.*, 1954, **32**, 465.
[45] S. W. Pelletier and W. A. Jacobs, *J. Amer. Chem. Soc.*, 1956, **78**, 4139, 4144.

stirred at 20° for 24 h. Work-up afforded an oil (40 mg), from which the *hydroxy-ketone* (17) (20 mg, 45%) was obtained by preparative t.l.c. [methanol–chloroform (2 : 98)]; m.p. 213—218° (depending on rate of heating) [from acetone–chloroform (trace)], $[\alpha]_D$ −93° (*c* 1·07), $\nu_{max.}$ 3250, 1730, 1645, 1284, 1271, 1215, 1105, 1084, and 1041 cm^{-1}, τ 9·13 (3H, s), 7·93 (3H, d), 6·56 (1H, s), and 5—7 (4H, complex m) (Found: C, 73·05; H, 8·95; N, 4·0. $C_{21}H_{31}NO_3$ requires C, 73·0; H, 9·05; N, 4·05%).

The keto-toluene-p-*sulphonate* (28). The hydroxy-ketone (17) (200 mg, 0·580 mmol) and recrystallised toluene-*p*-sulphonyl chloride (300 mg) in anhydrous pyridine (10 ml) were kept at 0° for 4 days. Solvent extraction and preparative t.l.c. [methanol–chloroform (2 : 98)] afforded the *keto-toluene*-p-*sulphonate* (28) (250 mg, 86%), needles (from acetone–ether), m.p. 197—198° $[\alpha]_D$ −112° (*c* 1·10), $\nu_{max.}$ 1747, 1645, 1373, 1188, 1176, 1030, 985, and 860 cm^{-1}, τ 9·12 (3H, s), 7·91br (3H, s), 7·56 (3H, s), 5·61 (1H, s), 2·34 (4H, q), and 5—7 (4H, complex m) (Found: C, 67·3; H, 7·45; N, 2·7. $C_{28}H_{37}NO_5S$ requires C, 67·3; H, 7·45; N, 2·8%).

Ozonolysis of the amide acetate (26). The amide acetate (26) was obtained from the alcohol (23) by the usual method. It was homogeneous on t.l.c. but remained amorphous; $\nu_{max.}$ 3088, 3070, 3036, 1739, 1644, 1236, and 1027 cm^{-1}, τ 9·14 (3H, s), 7·92 (6H, d), 7·64 (1H, m), 5·13 (1H, s), 4·95 (2H, d), and 5—7 (4H, m).

A solution of the amide acetate (30 mg, 0·078 mmol) in ethyl acetate (20 ml) was saturated with ozonised oxygen at −60° during 3 h. Reductive decomposition of the ozonide with zinc and acetic acid afforded an oil consisting of two components which were separated by preparative t.l.c. [(chloroform–methanol) (19 : 1)]. This gave the more mobile *keto-acetate* (27) (15 mg, 53%), m.p. 219—222° (from acetone–light petroleum), $[\alpha]_D$ +23° (*c* 1·22), $\nu_{max.}$ 1755, 1740, 1646, 1226, and 1048 cm^{-1}, τ 9·11 (3H, s), 7·88 (3H, d), 7·86 (3H, s), 5·16 (1H, s), and 5—7 (4H, m) (Found: C, 71·4; H, 8·65; N, 3·85. $C_{23}H_{33}NO_4$ requires C, 71·3; H, 8·6; N, 3·6%).

The i.r. spectrum of the more polar product (very similar except for less intense 1646 cm^{-1} peak), suggested that further oxidation of the amide function had occurred.

The hydroxy-ketone (18). The keto-acetate (27) was hydrolysed as for the epimeric compound (25), furnishing the *hydroxy-ketone* (18), m.p. 210—216° (depending on rate of heating) [from acetone–chloroform (trace)], $[\alpha]_D$ +7° (*c* 0·87), $\nu_{max.}$ 3535, 1730, 1645, 1279, 1268, 1196, 1101, and 1053 cm^{-1}, τ 9·11 (3H, s), 7·88 (3H, d), 7·55 (1H, m), 6·61 (1H, s), and 5—7 (4H, m) (Found: C, 72·9; H, 9·05; N, 4·1. $C_{21}H_{31}NO_3$ requires C, 73·0; H, 9·05; N, 4·05%).

The keto-toluene-p-*sulphonate* (29). Toluene-*p*-sulphonation of the hydroxy-ketone (18) (180 mg, 0·360 mmol) as for the epimeric hydroxy-ketone (17) afforded (by preparative t.l.c.) the keto-toluene-*p*-sulphonate (29) (177 mg 68%), which did not crystallise satisfactorily; $\nu_{max.}$ 1746, 1646, 1373, 1190, 1179, 1023, 991, 968, 920, and 873 cm^{-1}, τ 9·10 (3H, s), 7·89 (3H, s), 7·53 (3H, s), 5·58 (1H, s), 2·31 (4H, q), 5—7 (4H, m).

(b) *The hydroxy-acetal* (30). (i) The hydroxy-ketone (17) (30 mg, 0·087 mmol) and toluene-*p*-sulphonic acid (8 mg) were refluxed in dry benzene (15 ml) and dry ethylene glycol (0·5 ml) during 18 h, under a Dean–Stark separator. Partition of the product between ethyl acetate and aqueous sodium hydrogen carbonate afforded an oil (40 mg), from which the *hydroxy-acetal* (30) (27 mg, 80%) was obtained by preparative t.l.c. [chloroform–methanol (98 : 2)] as prisms, m.p. 182—183° (from acetone), $[\alpha]_D$ −39° (*c* 1·50), $\nu_{max.}$ 9·16 (3H, s), 7·90 (3H, d), 6·97 (1H, s), 6·98br (1H, s, D_2O-exchangeable), 6·02 (4H, s), and 5—7 (4H, m) (Found: C, 71·05; H, 9·05; N, 3·45. $C_{23}H_{35}NO_4$ requires C, 70·9; H, 9·05; N, 3·6%).

(ii) Acetalisation of the keto-acetate (25), as for the hydroxy-ketone (17), afforded the acetoxy-acetal (30a) as an oil, $\nu_{max.}$ 1741, 1645, 1241, 1179, 1114, 1044, and 1031 cm^{-1}, τ 9·15 (3H, s), 7·90 (3H, d), 7·85 (3H, s), 6·13 (4H, m), 5·70 (1H, s), and 5—7 (4H, m).

The acetoxy-acetal was hydrolysed either with sodium carbonate in methanol–water (5 : 1) at 20°, or with 2·5% potassium hydroxide in methanol–water (10 : 1) under reflux for 30 min, affording in 85% yield the hydroxy-acetal (30). Preparative t.l.c. was required in the latter method.

The oxo-acetal (31). The hydroxy-acetal (30) (200 mg, 0·513 mmol) in dry pyridine (2 ml) was cautiously added to the Sarett complex prepared from chromium trioxide (300 mg) and pyridine (3 ml), and stirring was continued for 48 h at 20°. Work-up and preparative t.l.c. [chloroform–methanol (98 : 2)] afforded the *oxo-acetal* (31) (105 mg, 75%), rods, m.p. 211—211·5° (from acetone), $[\alpha]_D$ +6° (*c* 0·76), $\nu_{max.}$ 1736, 1646, 1171, 1040, 1027, and 1018 cm^{-1}, τ 9·16 (3H, s), 7·94 (3H, d), 5·89 (4H, A_2B_2m), and 5—7 (4H, m) (Found: C, 71·1; H, 8·6; N, 3·55. $C_{23}H_{33}NO_4$ requires C, 71·3; H, 8·6; N, 3·6%).

Reduction of the oxo-acetal (31) *with sodium borohydride and deacetalisation of the product.* The oxo-acetal (31) (65 mg, 0·168 mmol) in methanol (5 ml) was reduced with sodium borohydride (300 mg) in the usual way. Analytical t.l.c. [chloroform–methanol (98 : 2)] revealed two equally intense, partly overlapping spots; the less polar was identified by comparison with a previously prepared sample as the hydroxy-acetal (30).

The mixture was deacetalised as follows:

(i) The acetal mixture (65 mg, 0·167 mmol) was kept with toluene-*p*-sulphonic acid (10 mg) in acetone (10 ml) for 60 h at 20°. Work-up afforded an oil (60 mg), which was separated by preparative t.l.c. [chloroform–methanol (98 : 2)] into the hydroxy-ketones (17) and (18) (5 mg each) and two more polar products (20 mg each). The similarity of their i.r. and n.m.r. spectra to those of the hydroxy-ketones suggested that they were masked acetal dimers [as (56)]. Essentially the same product mixture was obtained from the same reaction at reflux.

(ii) The acetal mixture (1·0 g, 2·571 mmol) was refluxed in 75% aqueous acetic acid for 30 min. The products, recovered by preparative t.l.c. [chloroform–methanol (19 : 1)] were the hydroxy-ketones (17) (320 mg, 36%) and (18) (280 mg, 32%). The dimers (?) obtained in (i) were under these conditions quantitatively converted into the hydroxy-ketones (17) and (18).

(iii) The acetal mixture (10 mg, 0·026 mmol) was dissolved in chloroform and 10% hydrochloric acid (5 drops) was added. The solution was made homogeneous by dropwise addition of methanol and then kept at 20° for 18 h. Analytical t.l.c. showed a mixture consisting (>85%) of the hydroxy-ketones (17) and (18).

Attempts to Obtain the α-Hydroxy-ketone (18) *by Equilibration Procedures.*—(a) *Attempted epimerisation of the hydroxy-ketone* (17). Compound (17) (5 mg, 0·015 mmol) and toluene-*p*-sulphonic acid (2 mg) in chloroform (10 ml) were refluxed under nitrogen for 4 h. T.l.c. [chloroform–

methanol (98 : 2)] showed two products which were less polar than the starting acetal and these were not further investigated.

(b) *Reaction of the tosyloxy-ketone* (28) *with dimethylformamide.* The tosyloxy-ketone (30 mg, 0·060) in dimethylformamide (1·2 g) was heated at 78° in a sealed glass ampoule for 24 h. The product, obtained as usual, was dissolved in dry benzene–ether (1 : 1) and passed through an alumina (grade III, neutral) column to hydrolyse formates. Analytical t.l.c. [chloroform–methanol (98 : 2)] revealed at least six products, including *ca.* 30% starting ketone, but only minor amounts (<5%) of the hydroxy-ketones (17) and (18). The yield was not improved by variations in the time and temperature of reaction.

(c) *Attempted equilibration of the hydroxy-acetal* (30). (i) The hydroxy-acetal (8 mg, 0·21 mmol), aluminium isopropoxide (5 mg, 0·03 mmol), acetone (1·5 ml), and propan-2-ol (0·3 ml) were kept in a sealed ampoule at 100° for 4 days. The neutral product, recovered as usual, consisted entirely of the hydroxy-acetal (30).

(ii) The hydroxy-acetal (30) (10 mg, 0·026 mmol), sodium (5 mg), fluorenone (10 mg), and dry toluene (2 ml) were kept in a sealed glass ampoule at 100° for 90 h. The product, deacetalised as previously with toluene-*p*-sulphonic acid in acetone, consisted entirely (t.l.c.) of the starting hydroxy-acetal.

*Acetolysis Experiments.—Acetolysis of the keto-toluene-*p*-sulphonate* (28). Compound (28) (20 mg, 0·040 mmol), sodium acetate (8 mg), and anhydrous acetic acid (2·5 ml) were kept in a sealed glass ampoule at 150° for 48 h. The ampoule contents were then neutralised with aqueous sodium hydrogen carbonate, extracted into ethyl acetate, and separated by preparative t.l.c. [chloroform–methanol (98 : 2)], affording the rearranged olefin (19) (11 mg, 83%), which was not obtained crystalline; M^+ 327, $\nu_{max.}$ 1760, 1647, 1270, 1196, 1149, and 1033 cm^{-1}, no olefinic H signals in the n.m.r. spectrum, g.l.c. R_t (5% SE30 at 225°) 1·87 (relative to n-hexacosane).

A similar experiment carried out at 55° afforded only unchanged starting material. Substitution of urea for sodium acetate at 150° gave an identical product.

*Acetolysis of the keto-toluene-*p*-sulphonate* (29). (*a*) Compound (29) (90 mg, 0·180 mmol) was acetolysed as for the epimer (28). The product (65 mg), essentially homogeneous by t.l.c., was identical (t.l.c., g.l.c., mass, i.r., and n.m.r. spectra) with the rearranged olefin (19) obtained from (28).

(*b*) The toluene-*p*-sulphonate (50 mg, 0·100 mmol), urea (15 mg), and sodium perchlorate (28 mg) in anhydrous acetic acid (1 ml) at 150° for 48 hr, afforded almost entirely the olefin (19) as in (*a*).

(*c*) The toluene-*p*-sulphonate (10 mg, 0·020 mmol), urea (10 mg), trifluoroacetic acid(1 ml), and trifluoroacetic anhydride (2 drops) at reflux for 48 h afforded only unchanged starting material.

(*d*) The toluene-*p*-sulphonate (6 mg, 0·012 mmol) and fused sodium acetate (30 mg) in anhydrous acetic acid (3 ml) were heated under reflux (*ca.* 118°). Samples (2 ml) were removed by pipette after the intervals stated and worked-up with sodium hydrogen carbonate and ethyl acetate as before:

(i) 30 min: t.l.c. and i.r. showed only starting toluene-*p*-sulphonate ($\nu_{max.}$ 1745, 1644, 1372, 1188, and 1178 cm^{-1}); (ii) 3·5 h: t.l.c. showed presence of compound (29) (70%) and the epimeric (28) (30%), i.r. spectrum similar to that of product from (i) but additional bands (968 and 1023 cm^{-1}) revealed presence of (28); (iii) 25 h: t.l.c. showed three components: (A) rearranged olefin (19) (>50%), (B) compound (28) (*ca.* 20%), and (C) compound (29) (*ca.* 20%), $\nu_{max.}$ 1759, 1646, 1371, 1189, 1178, and 1032 cm^{-1} [bands at 1371, 1189, and 1178 cm^{-1} (toluene-*p*-sulphonate) were much reduced in relative intensity].

(*e*) The toluene-*p*-sulphonate (29) (10 mg, 0·020 mmol), fused sodium acetate (30 mg), acetic anhydride (3 ml), and deuterium oxide (0·5 ml) were refluxed for 48 h. The olefin, obtained as before, was analysed for deuterium by mass and n.m.r. spectroscopy. The former revealed $^2H_0$ 23%, $^2H_1$ 35%, $^2H_2$ 27%, $^2H_3$ 11%. The latter showed that deuterium had been incorporated into the *N*-acetyl group.

Acetolysis of the keto-acetate (25). Compound (25) (10 mg, 0·026 mmol), fused sodium acetate (10 mg), toluene-*p*-sulphonic acid (5 mg), and anhydrous acetic acid (2 ml), were heated at 150° for 48 h as before. Analytical t.l.c. of the product showed the presence of the keto-acetates (25) and (27) (40% each), confirmed by i.r. comparison with authentic specimens. One minor product (<10%) was the unsaturated ketone (19); the other was not identified. Hydrolysis of the reaction product with sodium carbonate in aqueous methanol afforded mainly the hydroxy-ketones (17) and (18), which were separated by preparative t.l.c.

Acetalisation of the Keto-olefin (19) *and Reduction of the Product.—The amine salts* (34) *and* (35). Compound (19) (20 mg, 0·061 mmol), toluene-*p*-sulphonic acid (10 mg), ethylene glycol (0·5 ml), and dry benzene (10 ml) were refluxed for 18 h with azeotropic removal of water. The oily product (20 mg, 88%) was homogeneous on t.l.c. and was reduced without purification.

The acetal (20 mg, 0·054 mmol) in dry tetrahydrofuran was reduced with lithium aluminium hydride (50 mg). Work-up and preparative t.l.c. [diethylamine–light petroleum (1 : 9)] afforded the oily amino-acetal (14 mg, 73%), $\nu_{max.}$ 2745—2795, 1200, 1150, 1108, 1087, and 1047 cm^{-1}. Dissolution in methanol and careful neutralisation with dilute hydriodic acid furnished the hydriodide (34), m.p. 228—232°, rosettes from methanol–ether. The hydrobromide, m.p. 245° (sublimes), was formed similarly.

Borohydride Reduction of the Keto-olefin (19).—Compound (19) (10 mg, 0·031 mmol) in methanol (2 ml) was reduced with sodium borohydride (20 mg). Work-up and preparative t.l.c. [chloroform–methanol (98 : 2)] afforded the unsaturated alcohol (36), which was homogeneous on t.l.c, and g.l.c.; $\nu_{max.}$ (0·03M in CCl_4) 3573, 1646, 1268, 1100. 1089, and 1037 cm^{-1}.

Attempted Acid-Catalysed Cleavage of the Keto-olefin (19).—(*a*) A solution of compound (19) (10 mg, 0·031 mmol) in methanol (4 ml), sulphuric acid (0·4 ml), and water (0·2 ml) was refluxed under nitrogen for 48 hr. Extraction and preparative t.l.c. [chloroform–methanol (98 : 2)] afforded the oily dimethoxy-acetal (5 mg), $\nu_{max.}$ 1646, 1269, 1204, 1120, 1111, and 1062 cm^{-1}, τ 9·13 (3H, s), 7·94br (3H, s), and 6·78 (6H, s). With toluene-*p*-sulphonic acid in acetone at 20° for 18 h this was quantitatively reconverted into the unsaturated ketone (19).

(*b*) Refluxing the unsaturated ketone (10 mg, 0·031 mmol) in hydrochloric acid (1 ml) and glacial acetic acid (3 ml) for 24 h under nitrogen gave only unchanged starting material.

Pyrolysis Experiments.—G.l.c. experiments. The keto-toluene-*p*-sulphonates (28) and (29) were separately injected in chloroform on to a 5% SE30 column at 225°.

The traces obtained are shown in Figures 2 and 3. Cross-injection demonstrated identity of the pairs **1** and **5**, **2** and **6**, and **4** and **7**. Compounds **1** and **5** had the same retention time as the olefinic ketone (19). The ratios were: **1** : (**2** + **3**) : **4** ≡ 19 : 37 : 44; **5** : **6** : **7** ≡ 61 : 17 : 22.

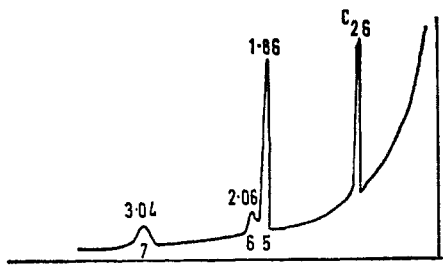


FIGURE 2 G.l.c. of the keto-toluene-*p*-sulphonate (28) at 225°

Pyrolysis of the keto-toluene-p-*sulphonate* (29). (*a*) The keto-toluene-*p*-sulphonate (29) (10 mg, 0·020 mmol), heated in a sealed tube at 180° for 30 min, afforded only starting material on work-up. At 300° for 1 h a dark, insoluble resin was produced, lacking the amide i.r. band at 1646 cm^{-1}.

(*b*) The keto-toluene-*p*-sulphonate (29) (10 mg) was sublimed in a glass tube at 0·1 mmHg and 300°. The neutral portion of the oily sublimate showed on t.l.c. some unchanged starting material. G.l.c. as before showed the same three peaks [1 : (2 + 3) : 4 in the ratios 49 : 33 : 18]. Thus the unsaturated ketone (19) constituted almost 50% of the product.

(*c*) Heating compound (29) in refluxing collidine for 18 h afforded only starting material. At 300° in a sealed tube a complex mixture resulted.

(*d*) A solution of the keto-toluene-*p*-sulphonate (29) (15 mg) in chloroform (5 ml) was thoroughly mixed with 1% SE30 g.l.c. packing (125 mg) and the solvent was removed *in vacuo*. The residue was heated in a sealed tube at 300°

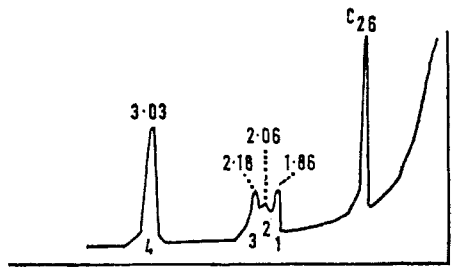


FIGURE 3 G.l.c. of the keto-toluene-*p*-sulphonate (29) at 225°

for 15 min. The ethyl acetate-soluble product (11 mg) showed i.r. bands at 1760, 1646, 1260, and 1080—1010 cm^{-1}. Rearranged, unsaturated ketone ($\nu_{max.}$ 1760 cm^{-1}) appeared to be the main product, the reduced intensity of the band at 1646 cm^{-1} indicating loss of amide. G.l.c. as before showed three components with, R_t 0·63 (50%; corresponds to loss of acetamide in i.r.), 1·85 (40%), and 2·18 (10%) (relative to n-hexacosane on 5% SE30 at 225°).

(*e*) The apparatus used for gas-phase pyrolysis is illustrated in Figure 4. The silica pyrolysis tube was electrically heated. A nitrogen pressure of 0·3—0·5 mmHg was maintained throughout the experiment. The compound to be pyrolysed was injected as a solution in a suitable solvent from a hypodermic syringe through the rubber septum, the needle being long enough to project into the heated zone. The pyrolysate was recovered from the cold zone of the pyrolysis tube emerging from the furnace and from the cold trap.

In a typical experiment the keto-toluene-*p*-sulphonate (29) (470 mg, 0·940 mmol) in acetone (2 ml) was injected at a furnace temperature of 600 ± 10°. The pyrolysate (400 mg), condensed almost at once at the exit end of the tube and in the cold trap, was collected with chloroform. I.r. spectroscopy showed this to contain about 50% unchanged tosylate, which was absent when the total pyrolysate had been pyrolysed twice more. The oily product (250 mg) then showed i.r. bands at 1759, 1743, 1646, 1270, 1235, 1214, 1189, and 1047 cm^{-1} (absence of tosylate bands at 1370, 1190, and 1178 cm^{-1}). Preparative t.l.c. on silver nitrate–silica gel (repeated elution with ethyl acetate) then afforded the keto-olefin mixture (105 mg) consisting of

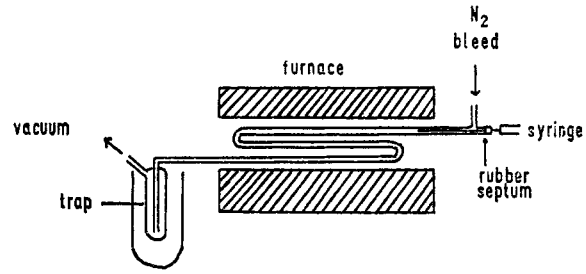


FIGURE 4 Apparatus for gas-phase pyrolysis

compounds (20) (95%) and (19) (5%); M^+ 327, $\nu_{max.}$ 1760, 1648, 1270, 1188, and 1036 cm^{-1}, τ 9·08 (s), 9·12 (s), 7·92br (3H, s), 4·80 (1H, diffuse m), and 5—7 (4H, complex m). G.l.c. (5% SE30 at 225°) showed two peaks, R_t 2·17 (95%) and 1·85 (5%) (relative to n-hexacosane).

Attempted Isomerisation of the Olefin (20).—The olefin (20) (2 mg) obtained in experiment (*e*) was kept in chloroform (2 ml) saturated with hydrogen chloride gas at 20° for 20 h. Only unchanged starting material was obtained (g.l.c.).

Acetalisation of the Olefin (20).—The crude product (40 mg) from gas-phase pyrolysis of compound (29) [see (*e*)] was acetalised with toluene-*p*-sulphonic acid (20 mg), redistilled ethylene glycol (1 ml), and dry benzene (20 ml) by the usual method. Preparative t.l.c., first on Kieselgel G, then on silver nitrate-treated Kieselgel G (ethyl acetate), afforded the *unsaturated acetal* (57) (9 mg) as an oil, M^+ 371, $\nu_{max.}$ 1646, 1353, 1269, 1121, and 1041 cm^{-1}, τ 9·08 (3H, s), 7·93 (3H, d), 6·02 (4H, s), 4·75 (1H, m), and 5·8—7·5 (4H, complex m), R_t (1% SE30 at 225°) 1·79 (relative to n-C_{28}) or 5·96 (rel. to n-C_{24})]. Deacetalisation of the acetal (57) (2 mg) with toluene-*p*-sulphonic acid and acetone, as before, furnished a product ($\nu_{max.}$ 1760 and 1646 cm^{-1}) which g.l.c. (1% QF1 at 225°) showed to consist of the keto-olefin (20) (80%) (R_t rel. to n-C_{34} 6·64) and the starting acetal (20%).

Reduction of the Amido-acetal (57) *to the Amino-acetal* (58).—The amido-acetal (57) (50 mg, 0·135 mmol) in dry tetrahydrofuran (5 ml), was added dropwise to a stirred suspension of lithium aluminium hydride (60 mg) in dry tetrahydrofuran (10 ml) at 20°. The resultant suspension was stirred under reflux for 4 h and then at 20° for 16 h more.

Preparative t.l.c. of the product [eluant diethylamine–cyclohexane (1 : 9)] afforded the oily *amino-acetal* (58) (35 mg, 73%), M^+ 357, $\nu_{max.}$ 2755—2800, 1450, 1350, 1327, 1169, 1120, 1099, 1057, and 1044 cm^{-1}, τ 9·19 (3H, s), 9·00 (3H, t, J_{AX} 7 Hz), 6·06 (4H, s), and 4·79 (1H, m), R_t (1% SE30 relative to n-C_{24}) 1·65 at 200°, 1·73 at 225°.

The Hydriodide (48) *and Hydrobromide* (49).—The amino-acetal (58) (5 mg, 0·14 mmol) in methanol (few drops) was carefully neutralised with dilute hydrogen iodide in methanol (2 drops conc. HI in 2 ml MeOH). A very slight excess of acid was added, then ether in excess, and the separated salt was filtered off rapidly. Several fast crystallisations from the same solvent pair and a final slow crystallisation afforded the hydriodide (48) as rods, m.p. 240—243·5°, suitable for *X*-ray crystallography.

The hydrobromide similarly formed needles, m.p. 250° (sublimes) (from the same solvent pair).

Attempts to convert the amido-acetal (57) into crystalline adducts of the derived osmate with pyridine and β-picoline, suitable for *X*-ray analysis, were unsuccessful.

Pyrolysis of the Keto-toluene-p-*sulphonate* (28).—Compound (28) (20 mg, 0·040 mmol) in carbon tetrachloride (1 ml) was pyrolysed as in method (*e*) at a furnace temperature of 500°. The product (15 mg), recovered as before, consisted mainly of the unsaturated ketone (19) and unchanged tosylate (28), as judged by analytical t.l.c.; $\nu_{max.}$ 1759, 1745sh, 1646, 1373, 1270, 1191, 1180, and 1033 cm^{-1}. The tosylate bands were weak [<50% compared with pure (28)]. The g.l.c. trace (1% SE30 at 225°) was almost identical with that previously obtained from injection of (28) on to a 1% SE30 column at 225°.

Attempted Pyrolysis of the Keto-acetate (27).—Treatment of the keto-acetate (27) (20 mg, 0·052 mmol) at 600° under the conditions used for the toluene-*p*-sulphonates afforded only starting acetate [i.r. spectrum, t.l.c., and g.l.c. (R_t rel. to n-hexacosane 3·39 on 5% SE30 at 225°)].

We thank the Carnegie Trust for the Universities of Scotland for scholarship support (to J. P. J.).

[1/2401 *Received*, 15*th December*, 1971]