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STUDIES ON BICYCLO[3.3.1]NONANES—I

THE ACETOLYSIS OF 4-CYCLOOCTENYLMETHYL TOLUENE-*p*-SULPHONATE

K. H. Baggaley, J. R. Dixon, J. M. Evans and S. H. Graham
The Edward Davies Chemical Laboratory, Aberystwyth

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Abstract—The acetolysis of 4-cyclooctenylmethyl toluene-*p*-sulphonate gives rise to bicyclo[4.2.1]non-2-ene, and bicyclo[3.3.1]non-2-ene. The chemistry of the epimeric bicyclo[3.3.1]nonan-2-ols is discussed.

FORMATION of bicyclic structures as a result of π-electron participation in solvolytic processes has been reported by Le Ny,[1] who obtained a 2-acetoxybicyclo[3.2.1]octane as the main product from the acetolysis of 4-cycloheptenylmethyl tosylate. Hanack and Kaiser[2] in a brief communication reported the formation from 4-cyclooctenylmethyl tosylate (I) of a mixture of olefins and of two acetate esters which latter were converted to a mixture of bicyclo[3.3.1]nonan-2-one, and a second ketone presumed to be bicyclo[4.2.1]nonan-2-one. The preparation of this last compound has been more recently described by Hartmann,[3] but its identity with the ketone of Hanack and Kaiser was not positively established. From the solvolysis of the corresponding brosylate ester Cope[4] obtained only one olefin but three acetate esters, two of which were identified as the epimeric bicyclo[3.3.1]non-2-yl acetates, and the third presumed to be a bicyclo[4.2.1]non-2-yl acetate. When this publication appeared our own investigation was well advanced and we now report the results thereof.

We carried out the acetolysis of I both at 60° for 48 hr, and at 80–90° for 6 hr, and obtained the same results in both cases. Distillation readily separated the product into olefin and ester fractions, recrystallization of the epoxide prepared from the former gave bicyclo[3.3.1]nonan-$2\beta,3\beta$-oxide. Hydrogenolysis of the ester fraction (LAH) and recrystallization of the resulting mixture of alcohols gave almost pure bicyclo[3.3.1]nonan-2α-ol (IIIa), m.p. 178° (a sample of pure alcohol had m.p. 182°).

Gas chromatographic analysis of the olefin and alcohol fractions (the acetates IIIb and IVb could not be resolved on the stationary phases investigated, as reported by Cope[4]) gave the following composition for the solvolysis products bicyclo[3.3.1]non-2-ene (II) 10·9%, bicyclo[4.2.1]non-2-ene (V) 0·6%, 2α-acetoxy bicyclo[3.3.1]nonane (IIIb) 67·6%, 2β-acetoxybicyclo[3.3.1]nonane (IVb) 2·6%, 2-acetoxybicyclo[4.2.1]nonane (VI) 18·3%. Apart from the presence of the second olefin these results are in complete agreement with those of Cope.[4] It seems probable that this product was overlooked in the earlier work as a result of the GLC analyses being run at too high a temperature, in our own experiments we noticed that the two peaks merged as the column temperature was raised.

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[1] G. Le Ny, *C.R. Acad. Sci., Paris* **251**, 1526 (1960).

[2] M. Hanack and W. Kaiser, *Angew. Chem.* (*English Edition*) **3**, 583 (1964).

[3] M. Hartmann, *Z. Chem.* 457 (1964).

[4] A. C. Cope, D. L. Nealy, P. Scheiner and G. Wood, *J. Amer. Chem. Soc.* **87**, 3130 (1965).

Authentic samples of all three acetates were prepared by unambiguous routes. Peracid oxidation of II gave a single oxide, which must therefore be the 2*β*,3*β*-oxide, formed by attack from the less hindered side of the molecule. Reduction (LAH) gave pure bicyclo[3.3.1]nonane-2*β*-ol (IVa). The 2*α*-ol was prepared from 2-pyrrolidylbicyclononane by oxidation (mercuric acetate[5]) and hydrolysis to the 2-one followed by reduction (LAH) to IIIa together with 1% of IVa. (Reduction with borohydride gave 5% of IVa.) There are widely discrepant values reported for the m.p. of the 2-one, 128·5–130·5°,[4] 135°,[6] and 150°:[7] we recorded the m.p. 126°. Cope had allocated configurations to the bicyclo[3.3.1]nonan-2-ols on the basis of their spectra and a reasonable assumption about the conformation of the carbon skeleton. The above synthesis of IVa furnishes a more direct proof of these configurations. The PMR spectra of IIIa and IVa show, from the band widths of the *α*-protons of the alcoholic groups, that the hydroxyl groups are equatorial and axial respectively, confirming that the substituted ring is a chair in each case.

The sample of IVa prepared by reduction of the epoxide was completely free from the epimer IIIa. It has been reported that reduction of *trans*-4-t-butylcyclohexene oxide gives 10% of *cis*-3-t-butylcyclohexanol and 90% of *trans*-3-t-butylcyclohexanol: similarly reduction of the *cis*-oxide gives only 4-t-butylcyclohexanol, 90% *cis* and 10% *trans*. The formation of the minor product in each case has been ascribed to the production of ketone by hydride abstraction (by AlH_3) from the alkoxide ion formed when hydride ion (from AlH_4^-) opens the epoxide ring. The absence of IIIa from the reduction product of the oxide of II is presumably because the C_8 methylene would inhibit such attack by AlH_3 on the C_2 *α*-proton.

The formation of only 1% of IVa by reduction of the 2-one is striking. Formation of equatorial alcohols in hydride reductions of ketones is usually regarded as a consequence of thermodynamic control,[9] but on this basis a much higher proportion of IVa would have been expected, for while the 2*β*-ol has two diaxial repulsions between hydroxyl and hydrogen, the 2*α*-ol has one such repulsion (between the hydroxyl group and the 8*α*-proton), and the free energy difference between the epimers should be approximately half that between the equatorial and axial conformers of cyclohexanol.[10] We have measured this equilibrium, approaching it from each side and using isopropoxide as catalyst in the usual way. The equilibrium composition (32% IVa; 68% IIIa) gives a ΔF_{88° of 559 cal which agrees reasonably with the values for $\Delta F_{(e \rightarrow a)}$ recently reported by Eliel for cyclohexanol.[10] The formation of so high a proportion of the equatorial alcohol therefore is not due to thermodynamic control. That this is so was confirmed by the results obtained by hydrogenation of the 2-one over platinum: in acetic acid 96% IIIa and 4% IVa were formed, while the slower hydrogenation in ethanol gave 81% and 19% respectively of the two epimers. These results are best explained by steric hindrance to approach of reagent by the C_8 methylene, in accordance with the views of Richer.[11] An alternative explanation would be that reduction

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[5] N. J. Leonard and F. P. Hauck, *J. Amer. Chem. Soc.* **79**, 5279 (1957).

[6] J. P. Ferris and N. C. Miller, *J. Amer. Chem. Soc.* **85**, 1325 (1963).

[7] H. Meerwein, F. Kiel, G. Klosgen and E. Schoh, *J. Prakt. Chem.* [2] **104**, 161 (1922).

[8] B. Rickborn and J. Quartucci, *J. Org. Chem.* **29**, 3185 (1964).

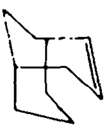
[9] W. G. Dauben, G. J. Funken and D. S. Noyce, *J. Amer. Chem. Soc.* **78**, 2579 (1956).

[10] E. L. Eliel and S. H. Schroeter, *J. Amer. Chem. Soc.* **87**, 5031 (1965).

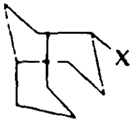
[11] J. C. Richer, *J. Org. Chem.* **30**, 324 (1965).

of the 2-one involves addition to the conformer with a boat cyclohexanone ring, which would naturally give exclusively 2α-ol as a result of steric approach control. This explanation is unlikely to be correct, however, as although such a conformation might be populated to an appreciable extent,[12] the transition state leading from it to the 2α-ol would be subject to serious steric interactions.

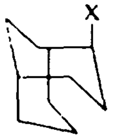
By contrast, the case of the bicyclo[3.2.1]octan-2-ols would appear to be quite different. It has been reported that the equilibrium mixture of the two epimers contains 95% of equatorial alcohol[13] (very nearly the same proportion is formed in the reduction by LAH of the 2-one). Here the 7-methylene is somewhat rotated so as to reduce its interaction with a 2α-substituent, and this seems to result in a lowering of the energy of the 2α-ol. (Some reduction in the energy of the 2β-ol also might well be expected in this case as a result of the "reflex effect",[14] but apparently on balance this is less significant.)



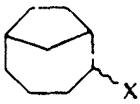
II



III a, X = OH
b, X = OAc

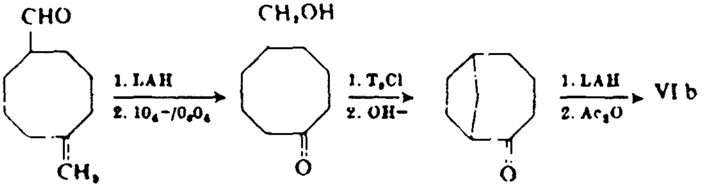


IV a, X = OH
b, X = OAc



VI a, X = OH
b, X = OAc.

Bicyclo[4.2.1]non-2-yl acetate (VIb) was synthesised from 5-formylmethylenecyclooctane[15] by the route shown. It was observed that the cleavage of the exocyclic double bond was more cleanly effected by the use of the osmic acid-periodate reagent,[16] than by ozonolysis. There is no proof of the geometry of the acetoxy group, reduction of the 2-one would probably, by analogy with the formation of IIIa, give the 2α-ol.



Bicyclo[3.3.1]non-2-ene (II) was synthesised by Wolff-Kishner reduction of bicyclo-[3.3.1]non-2-en-9-one.[17] The pure bicyclo[4.2.1]non-2-ene was not prepared, but a mixture of it and II was obtained by pyrolysis of the acetate fraction of the solvolysis products of I. This gave two olefins in the ratio of 9 to 1, and the minor component had the same retention time on gas chromatography as the second olefin formed in the solvolysis.

It is noteworthy that the ratio of acetate to olefin is much greater within the [4.2.1] series (30·5 : 1) than within the [3.3.1] series (6·35 : 1). This implies that although ideal

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[12] R. A. Appleton and S. H. Graham, to be published.
[13] R. A. Youssef, M. E. Baum and H. M. Walborsky, *J. Amer. Chem. Soc.* **81**, 4709 (1959).
[14] G. Ourisson and B. Waegall, *Bull. Soc. Chim. Fr.* 495 (1963).
[15] K. H. Baggaley and S. H. Graham, to be published.
[16] R. Pappo, D. S. Allen Jr., R. U. Lemieux and W. S. Johnson, *J. Org. Chem.* **21**, 478 (1956)
[17] S. Foote and R. B. Woodward, *Tetrahedron* **20**, 687 (1964).

geometry for both substitution (solvent attack on C_2), and for elimination (solvent attack on the C_3 proton) may be attained within the [3.3.1] series, the correct geometry for elimination is not readily attainable within the [4.2.1] series. Examination of Dreiding models shows that while for the [3.3.1] skeleton, suitable geometry for both processes is obviously attainable, there are conformations for the [4.2.1] skeleton which would seem to favour just as ready formation of olefin. Such conformations, for reasons not apparent in the models, cannot contribute to the transition state.

EXPERIMENTAL

5-Toluenesulphonyloxymethylcyclooctene (I). 5-Methoxycarbonylcyclooctene[18] was reduced with LAH to give the alcohol (71%) b.p. 116–118°/18 mm. Toluene-*p*-sulphonyl chloride (57 g) in dry pyridine (100 ml) was added to a soln of the alcohol (27 g) in dry pyridine (50 ml) at 0°. The mixture was kept in the refrigerator for 36 hr, then poured into 1 l. ice water containing conc HCl (40 ml). The oil which separated was ether extracted, the extracts washed with 2N HCl, water and $NaHCO_3$aq, and dried ($MgSO_4$). Removal of solvent left a viscous yellow oil (51 g, 90%) which was used without further purification.

Acetolysis of 5-toluenesulphonyloxymethylcyclooctene. The tosylate (25 g) and AcONa (16 g) were dissolved in glacial AcOH (50 ml) and stirred in an atm of N at 80° for 6 hr, then poured into water and the oil which separated was ether extracted. Removal of ether after washing (water and $NaHCO_3$aq) and drying the extracts gave a pale yellow liquid (13 g) which contained two fractions (GLC on silicone oil at 120°). Distillation at 0·5 mm gave a sticky white solid, much of which could be condensed only in liquid air traps (1·4 g) and a colourless liquid (10·5 g) b.p. 64–68°. Similar results were obtained when the acetolysis was run at 60° for 48 hr.[8] VPC of the olefinic (lower boiling) fraction tricyanoethoxypropane at 90°) showed it to consist of II (95%) and V (5%): similar analysis of the acetate fraction (T.C.E.P. at 120°) showed only two peaks: one of these (21%) was shown to correspond to VIb and the other (79%) consisted of IIIb and IVb, since both the alcohols IIIa and IVa could be identified in the analysis of the acetate hydrolysis products.

Bicyclic alcohols from the acetate fraction

(a) *By hydrogenolysis.* The mixed acetates (4 g) in dry ether (50 ml) were added to LAH (0·6 g) in dry ether (50 ml) with stirring, and the mixture refluxed for 4 hr. After the usual work-up, removal of solvent left a white sticky solid (3 g).

(b) *By hydrolysis.* The mixed acetates (4 g) were refluxed with KOH (10 g) in EtOH (50 ml) for 6 hr, the greater part of the EtOH was distilled off and the residue partitioned between water and ether. Removal of ether after washing and drying gave a white sticky solid (3 g).

VPC (tritolyl phosphate at 120°) showed both samples to consist of IIIa, VIa and IVa. The first two were not well-resolved and together constituted 96% of the mixture, alcohol IVa comprising 4%. Recrystallization from petrol gave bicyclo[3.3.1]nonan-2-ol m.p. 179° (lit.[7] 185°). (Found: C, 76·88; H, 11·32. Calc. for $C_9H_{16}O$: C, 7 7·14; H, 11·43%.)

Oxidation of bicyclo[3.3.1]*nonan-2-ol.* Sodium dichromate (12 g) in 8% H_2SO_4 (100 ml) was slowly added to a solution of IIIa (4 g) in ether (100 ml) with stirring. Stirring was continued for 4 hr after addition was complete, the layers were separated and the aqueous layer ether extracted. The combined extracts were washed (water, $NaHCO_3$aq), dried, and evaporated. Sublimation of the residue (bath temp 70–80°/10 mm) gave bicyclo[3.3.1]nonan-2-one (2·9 g, 71%), m.p. 123–126° (lit., 128·5-130·5°[4], 135°[6], 150°[7], and 126°[19]). (Found: C, 78·06; H, 9·95. Calc. for $C_9H_{14}O$: C, 78·25; H, 10·14%.)

2-(N-*pyrrolidinyl*) *bicyclo*[3.3.1]*nonane.* To a soln of Na (6 g) in diethyleneglycol (100 ml) was added 2-(N-pyrrolidinyl)bicyclo[3.3.1]nonan-9-one[19] (32 g) and 99% hydrazine hydrate (18 ml). The mixture was refluxed for 4 hr, cooled and added to water (1200 ml). Ether extraction, washing, drying and removal of ether gave the *amine* (19 g, 64%), b.p. 96–98°/0·5 mm, n^{24} 1·5025. (Found: C, 80·42; H, 11·90; $C_{13}H_{23}N$ requires: C, 80·83; H, 11·91%.)

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[18] G. Stork and H. K. Landesman, *J. Amer. Chem. Soc.* **78**, 5129 (1956).

[19] Present work.

Bicyclo[3.3.1]*nonan-2-one*. The above amine (19 g) was added to a soln of mercuric acetate (80 g) in 5% AcOH (400 ml), and stirred at 100° for 2·5 hr, pptn of mercurous acetate commenced after 10 min. After cooling, the pptd salt was filtered off, the ppt washed twice with 5% AcOH (50 ml), the combined filtrates and washings saturated with H_2S, and the HgS filtered off. The sulphide ppt was washed with acetone, the acetone washings concentrated to small bulk and added to the aqueous filtrate. To the aqueous soln was added 2N HCl (60 ml) and the mixture boiled for 30 min: ether extraction of the cooled mixture, and evaporation of the washed and dried extract, followed by sublimation (75–80°/12 mm) gave the ketone (2·5 g 37%), m.p. 126–128°, undepressed on admixture with the ketone obtained by oxidation of the major solvolysis alcohol. Both samples had identical IR spectra.

Bicyclo[3.3.1]*nonan-2α-ol* (IVa). Bicyclo[3.3.1]nonan-2-one (0·2 g) in dry ether (15 ml) was added to LAH (0·05 g) in dry ether (50 ml with stirring, and the mixture refluxed for 4 hr. The normal work-up gave a white solid (0·18 g, 85%), which consisted of IVa (99%) and IIIa (1%) (GLC on tritolyl phosphate at 120°). Recrystallization from petrol gave pure bicyclo[3.3.1]nonan-2α-ol m.p. 182° (lit.[7] 185°), not depressed on admixture with the alcohol m.p. 179° obtained from acetolysis products of I. Use of sodium borohydride in EtOH gave IVa (95%) and IIIa (5%). In the PMR spectrum, the resonance of the C*H*OH proton appeared as a broad unresolved multiplet centred on τ 6·3: the band width (15 c/s) was consistent only with an axial proton.

Bicyclo[3.3.1]*nonan-2β,3β-oxide*. To the olefin II (10 g) in chf (20 ml) was added an ice-cold 5·8% soln of perbenzoic acid in chf (240 ml). After being kept in the refrigerator for 2 days the soln was washed with water and $NaHCO_3$aq, and dried. Removal of solvent, and sublimation (65–70°/9 mm), followed by recrystallization from MeOH–water (1:1) gave the *oxide* as a white powder (8 g, 71%), m.p. 164°. (Found: C, 78·30; H, 10·34. $C_9H_{14}O$ requires: C, 78·25; H, 10·14%.)

Bicyclo[3.3.1]*nonan-2β-ol* (IIIa). The above oxide (1 g) and LAH (0·2 g) in THF (50 ml) were refluxed for 3 hr with stirring. Evaporation of the greater part of the solvent, addition of water and the usual work-up with ether extraction gave the *alcohol* (IVa; 0·74 g, 73%) as a white powder, m.p. 171°. (Found: C, 77·21; H, 11·49. $C_9H_{16}O$ requires: C, 77·14; H, 11·43%.) The PMR spectrum of this alcohol showed the resonance of the C*H*OH proton as an unresolved multiplet, centred on τ 6·3, with band width at half height of 7·5 c/s, consistent only with e,a and e,e couplings.

Equilibration of the stereoisomeric bicyclo[3.3.1]*nonan-2-ols*. Runs were made starting both with pure 2α-ol and pure 2β-ol. Acetone was refluxed over and distilled from K_2CO_3; isopropanol was refluxed over and distilled from CaO. The alcohol (IIIa or IVa; 0·5 g) redistilled aluminium isopropoxide (0·5 g), and acetone (0·6 ml) were dissolved in isopropanol (15 ml) and refluxed for 7 days. After cooling, the reaction mixtures were poured into water (80 ml) and 10N HCl (5 ml) and twice extracted with ether (50 ml). The ether extracts were washed (water and $NaHCO_3$aq) and dried. The crude soln were immediately analysed by VPC (tritolyl phosphate at 120°). Starting from IVa the equilibrium mixture contained IIIa, 70·5% and IVa 29·5%: starting from IIIa the figures were IIIa, 67·5% and IVa 32·5%.

5-Hydroxymethylmethylenecyclooctane. To LAH (260 mg) in ether (50 ml) was added 5-formylmethylenecyclooctane[15] (3·4 g) in ether (50 ml), and the mixture was refluxed for 1 hr. After cooling, the excess of hydride was decomposed with AcOEt, water added, and the mixture extracted continuously with ether for 6 hr. After drying ($MgSO_4$), the ether was evaporated, and the residue distilled to give the *alcohol* as a colourless viscous oil. (3·3 g, 90%), b.p. 85·87°/1·5 mm, n^{24} 1·4969. (Found: C, 77·68; H, 11·86. $C_{10}H_{18}O$ requires: C, 77·87; H, 11·76%.) *Naphthylurethane*, fluffy white needles from petrol, m.p. 116–118. (Found: C, 77·97; H, 7·82; N, 4·30. $C_{21}H_{25}NO_2$ requires: C, 78·02; H, 7·74; N, 4·33%.)

5-Hydroxymethylcyclooctanone. A mixture of the above alcohol (4·6 g), pure THF (50 ml), OsO_4 (250 mg), and water (80 ml) was stirred at room temp for 15 min, then sodium metaperiodate (14·5 g) was added in portions over 30 min and stirring continued till the brown colour of the mixture changed to yellow (approx. 1 hr). Solids were filtered off and washed with ether (50 ml), the combined filtrates concentrated under red press, the residue basified with 2N NaOH, and extracted with CA_2Cl_2 (3 × 20 ml). After water washing, drying ($MgSO_4$), and evaporation of solvent the hydroxyketone was distilled as a colourless viscous oil (2·9 g, 62%), b.p. 109–110°/0·6 mm. The IR spectrum showed a single carbonyl frequency at 1724 cm^{-1}. The once-distilled alcohol was not further purified but was immediately converted in the usual way to the *tosylate* (78% yield) cream plates from CCl_4–petrol, m.p. 124·5–126°. (Found: C, 61·80; H, 7·20: S, 10·49. $C_{16}H_{22}SO_4$: requires: C, 61·88; H, 7·09; S, 10·34%.)

Bicyclo[4.2.1]*nonan-2-one*. The above tosylate (1 g) was refluxed with NaOH (0·2 g) in 50% aqueous MeOH (50 ml) for 14 hr. After cooling, the reaction mixture was just acidified to congo red with 2N HCl, and ether extracted. The extracts were washed (water, $NaHCO_3$aq), dried ($MgSO_4$) and evaporated. The residue of crude ketone was immediately converted to its *semicarbazone*, white prisms from EtOH, m.p. 197–198°. (Found: C, 61·23; H, 8·48; N, 21·15. $C_{10}H_{17}N_3O$: requires: C, 61·49; H, 8·78; N, 21·52%.) Hydrolysis gave pure *ketone*, purified by sublimation, m.p. 91–92° (Hartmann quotes 95–96°[9]).

2-*Acetoxybicyclo*[4.2.1]*nonane* (VIb). Reduction of the above ketone (1·3 g) with LAH (0·25 g) in the usual way, gave VIa (1·2 g, 91%) purified by sublimation at 10 mm, m.p. 130–131°. (Found: C, 77·19; H, 11·20. $C_9H_{16}O$ requires: C, 77·11; H, 11·50%.) This alcohol (1·1 g), AcONa (0·5 g), and Ac_2O (2 ml) were refluxed for 2 hr, cooled and poured into water. Ether extraction of the oil, followed by the usual washing and drying gave the *ester* (VIb; 1·4 g, 98%), b.p. 65°/0·5 mm, n^{20} 1·4780. (Found: C, 72·87; H, 10·16. $C_{11}H_{18}O_2$ requires: C, 72·47; H, 9·95%.) This ester was homogeneous (GLC on tritolyl phosphate at 120°.)

Bicyclo[3.3.1]*non-2-ene*. Bicyclo[3.3.1]non-2-en-9-one was prepared by pyrolysis of the oxide of 2-pyrrolidylbicyclo[3.3.1]nonane-9-one:[17] together with the ketone (27% yield) was obtained an acid (3·5% yield) which was identified as 5-hydroxycarbonylcyclooctene on the basis of its IR spectrum. (We are informed by Mr. C. S. Dean that he has confirmed the identity of this acid by mixed m.p. measurement on its *p*-bromophenacyl ester.) The ketone (18 g) and 99% hydrazine hydrate (14·5 g) were added to a soln of Na (4·7 g) in diethylene glycol (300 ml) and the whole refluxed for 8 hr. (The addition of a few ml of diethyl ether prevented accumulation of sublimate in the reflux condenser.) The mixture was then distilled while mainly solid material passed over, till the temp reached 200°. The distillate was then taken up in ether, and the soln washed (water) and dried. Evaporation of solvent left the *olefin* (13·5 g, 84%), m.p. 94°, which could be purified by sublimation at 10 mm. (Found: C, 88·45; H, 11·55. C_9H_{14} requires: C, 88·14; H, 11·62%.)

Pyrolysis of acetate mixture from acetolysis. The mixed acetates (10 g) were pyrolysed at 480° in a tube furnace packed with Fenske helices, in a stream of N. The pyrolysate was taken up in ether, washed (water, $NaHCO_3$aq) and dried. Removal of solvent left a white semisolid (5·5 g, 98%) which was analysed by VPC (on tritolyl phosphate at 90°) and was a mixture of the two compounds which constituted the olefinic fraction from the acetolysis experiment in the ratio 9:1.

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