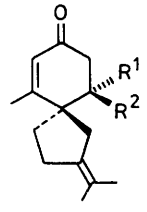
Control of Intramolecular γ-Alkylation *vs.* α-Alkylation of an αβ-Unsaturated Ketone: an Unusual Solvent Effect

By A. PETER JOHNSON* and VLATKA VAJS

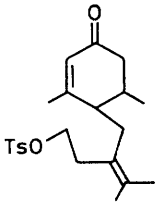
(*Department of Chemistry, Polytechnic of North London, Holloway, London* N7 8DB)

Summary Most base–solvent combinations convert (**2**) into (**3**); γ-alkylation to yield (**5**) is effected by sodium hydroxide in dimethyl sulphoxide–water mixtures in which the water content is critical.

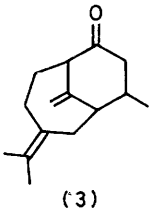
THE final step in our total synthesis of the sesquiterpene, β-vetivone (**1**),[1] requires the conversion of (**2**) into (**1**) through a base-induced, intramolecular γ-alkylation of the αβ-unsaturated ketone (**2**). Although intermolecular γ-alkylations of αβ-unsaturated ketones are rarely feasible (because of the well documented preference for α-alkylation of extended enolate anions[2]), it seemed possible that the reaction might be directed along the desired pathway under suitable conditions. In the event a variety of base–solvent combinations failed to convert (**2**) into (**1**) but instead yielded the α-alkylated product (**3**), (70% using Bu^{t}OK–Bu^{t}OH).



(1); R^1 = H, R^2 = Me
(7); R^1 = Me, R^2 = H



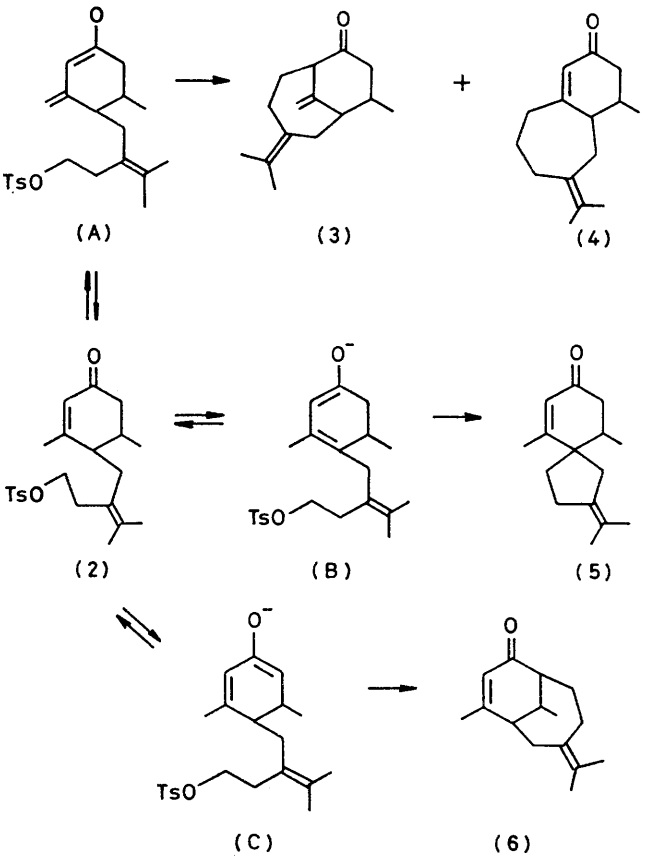
(2)
Ts = $MeC_6H_4SO_2$-*p*



(3)

The structures of the various enolate anions which might be generated by the action of base on (**2**) are depicted in the Scheme, together with structures of possible cyclisation products. The formation of (**3**) implies the intermediacy of the thermodynamically favoured enolate (A) which obviously undergoes α-alkylation rather than the alternative γ-alkylation which would yield (**4**).

Examination of the Scheme shows that the precise outcome of the base-induced cyclisation depends on the relative rates of the various reactions therein. There are two extreme situations which will give quite different



SCHEME. Ts = $MeC_6H_4SO_2$-*p*.

results: (a) step 1 is slow compared to step 2; the composition of the product mixture will reflect the composition of the mixture of enolate anions; (b) step 2 is slow compared to step 1; under these conditions the Curtin–Hammett principle might apply.† If this principle is to apply there must be an equilibrium between (A) and (B) (interconversion *via* the starting material). In this case (A) could still predominate in the equilibrium mixture, but this would not affect the product composition which would depend entirely on the relative energies of the transition states for the alternative cyclisation steps. Since five-membered rings are usually formed more rapidly than seven-membered rings, the transition state for cyclisation to give the desired product (**5**) will be lower in energy than that leading to (**3**). Hence (**5**) should predominate.

† This states that if two or more isomeric forms of a compound which are in rapid equilibrium (such as two different conformations) undergo a reaction in which each isomeric form gives rise to its own characteristic product, the ratio of products so formed is independent of the relative energy levels of the various starting forms and depends only on the relative energy levels of the transition states by which the products are formed, provided that the activation energy for the product formation is large compared to the activation energy for the interconversion of the isomeric starting materials (see E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, 'Conformational Analysis,' Wiley, New York, 1965, p. 28).

The observed formation of (**3**) through the action of Bu^tOK–Bu^tOH indicates that under these conditions situation (a) applies. In order to reverse the situation, reaction conditions which would speed up the deprotonation step were sought. Dimethyl sulphoxide was chosen as the reaction medium because of the enhanced rate of proton transfer reactions in this solvent.[3] In the event, experiments in which (**2**) was treated with sodium hydroxide in carefully degassed aqueous dimethyl sulphoxide yielded mixtures of (**3**) and (**5**) in which g.l.c. analysis showed that the proportion of (**5**) varied between 0 and 93·5%. Careful experimentation has shown that the amount of water present is the major factor which determines the ratio (**5**) : (**3**) and that high concentrations of water favour the formation of (**5**), (Table). This dramatic solvent effect is perhaps best explained by assuming that in the absence of water the deprotonation step is fast but there is no equilibrium established between (A) and (B) because of the low concentration of species such as water which can protonate (A) and hence regenerate (**2**). As the water concentration increases, the rate of this protonation also increases and so helps to establish the equilibrium between (A) and (B). It is possible that the reason why a water concentration of *ca.* 20% is required for the reaction to follow the desired path is that at lower concentrations most of the water is firmly bound to dimethyl sulphoxide by hydrogen bonding and is less available to act as a proton source.

TABLE. Cyclisation of (**2**) in aqueous Me_2SO

Solvent composition		Product composition[a]	
Me_2SO/ml	H_2O/ml	% (**5**)	% (**3**)
10·0	<0·05	0·0	100·0
9·5	0·5	14·9	85·1
9·0	1·0	23·1	76·9
8·8	1·2	50·3	49·7
8·65	1·35	68·3	31·7
8·5	1·5	83·8	16·2
8·0	2·0	92·8	7·2
7·5	2·5	93·5	6·5

[a] By g.l.c. analysis (after aqueous work-up) with a 10% Apiezon column at 225 °C.

G.l.c. analysis of (**5**) obtained using sodium hydroxide in aqueous dimethyl sulphoxide (25% H_2O) showed it to be a mixture of β-vetivone (**1**) and 10-epi-β-vetivone (**7**) in the ratio 92·6 : 7·4. (±)-β-Vetivone was crystallised as white needles, m.p. 41—44 °C (lit.[4] 43·5—44 °C). The identity of the substance was established by comparison of g.l.c. and i.r., mass, and ^1H 220 MHz n.m.r. spectra with those of an authentic sample.

We thank Dr. M. Pesaro of Givaudan Research Company Ltd. for the g.l.c. analysis, and Professor J. A. Marshall, Northwestern University, for a sample of natural β-vetivone.

(*Received, 4th June* 1979; *Com.* 584.)

[1] V. Vajs, Ph.D. Thesis, University of London, 1977.
[2] J. M. Conia and A. Sandre-Le Craz, *Tetrahedron Letters*, 1962, 505; N. W. Atwater, *J. Amer. Chem. Soc.*, 1960, **82**, 2847.
[3] D. Martin, A. Weise, and H.-J. Niclas, *Angew. Chem. Internat. Edn.*, 1967, **6**, 318.
[4] J. A. Marshall and P. C. Johnson, *J. Org. Chem.*, 1970, **35**, 192.