Cyclisation Reactions. Part IV.[1] Stereochemistry of Cyclialkylation of 2-(2-Arylethyl)-1,3,3-trimethylcyclohexyl Cations and their Equivalents

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The stereochemistry of cyclialkylation of 2-(2-arylethyl)-1,3,3-trimethylcyclohexyl cations (I), generated from the corresponding 6-alcohols (VIII) has been studied. Whereas kinetically controlled cyclisation gives a preponderance of the *trans*-podocarpa-8,11,13-trienes (VI) to the extent of 75%, the thermodynamically controlled reaction favours the *cis*-isomers (V) almost in a reverse ratio. A qualitative estimate of the relative energies of the two isomers supports the greater stability of the *cis*. The results explain some anomalous reports in the literature.

CYCLIALKYLATION of 2-(2-arylethyl)-1,3,3-trimethylcyclohexyl cations (I), generated from a variety of precursors, is extensively used for the synthesis of octahydrophenanthrenes [(V) and (VI)].[2] Recently, Ireland and his co-workers [3] have interpreted the stereochemistry of such reactions in terms of two apparently reactant-like transition states [(II) and (III)] (the others being too unstable for steric reasons) and came to the conclusion that under kinetically controlled conditions *cis*-podocarpatrienes (V) would be the major products. The argument hinges on a delicate balance between an $A^{(1,2)}$-type strain in the transition state (II) forming the *trans*-isomer and the steric strain due to an extra axial substituent in the other transition state (III) (leading to the *cis*) after cancellation of the common interactions (one axial methyl group and the torsional strain [4]). According to these authors, the $A^{(1,2)}$-type strain is dominant and the conformation (III) is slightly more favoured. This appeared to be borne out by the cyclisation of the alcohols (VIIIc and d), which gave a preponderance of the *cis*-podocarpatrienes (Vc and d). These transition state models are evidently oversimplified (see for example, ref. 5); nevertheless they help to understand the stereochemical course of many similar reactions.[3] Our recent results of the cyclisation

[1] Part III, D. Nasipuri and S. R. Roychaudhury, *J.C.S. Perkin I*, 1975, 262.

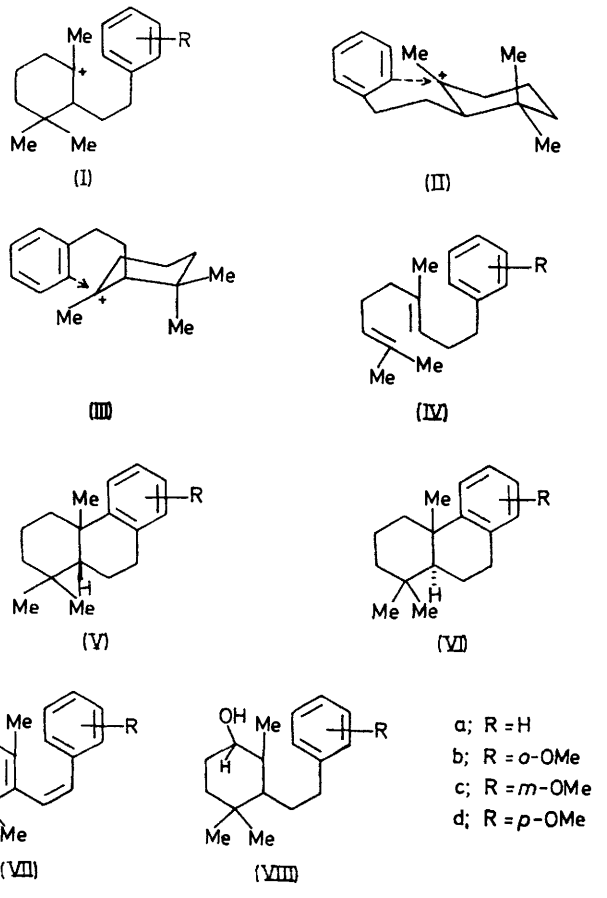
[2] L. R. C. Barclay, 'Friedel–Crafts and Related Reactions,' vol. II, part 2, ed. G. A. Olah, Interscience, New York 1964 p. 785.

[3] R. E. Ireland, S. W. Baldwin, and S. C. Welch, *J. Amer. Chem. Soc.*, 1972, **94**, 2056.

[4] M. Cherest and H. Felkin, *Tetrahedron Letters*, 1968, 2205.

[5] F. Brisse and A. Lectard, *Canad. J. Chem.*, 1974, **52**, 1123.

of the dienes (IV),[6,7] which also afford podocarpatrienes through the cyclohexyl cation intermediates,[6] and some other literature data [8] are, however, widely at variance with those of Ireland *et al.* In all these cases, the *trans*-isomers predominate. The objective of the present



ork was to carry out a systematic study of these cyclisations and to rationalise the contradictory reports.

Four substituted 3-(2-arylethyl)-2,4,4-trimethylcyclohexanols (VIII) were synthesised by a standard series of reactions [9-11] which involved condensation of substituted benzaldehydes with 3-methylbutan-2-one, a Robinson–Mannich base synthesis on the resulting 1-aryl-4-methylpent-1-en-3-ones to give 2,4,4-trimethyl-3-styrylcyclohex-2-enones (VII), and a two-step reduction. The alcohols were cyclised with polyphosphoric acid (PPA) and the products analysed by g.l.c. The results are shown in Table 1 along with some data on diene cyclisation for comparison.

The data in Table 1 establish two points: (i) contrary to the claim of Ireland *et al.*,[3] and in conformity with the work of Barltrop [8] and others,[12] these cyclialkylations yield the *trans*-podocarpatrienes (VI) as the major products; the cyclisation of the dienes (IV) also gave comparable results except in one case (IVb) where a higher temperature was used; (ii) the percentage of *cis*-isomer was higher for the methoxy-derivatives (VIIIb—d) than for the simple phenyl analogue (VIIIa)

TABLE 1

Cyclisation of alcohols (VIII) and dienes (IV) with polyphosphoric acid (90—100 °C)

Substrate	Proportions (%) of podocarpatrienes *cis*	*trans*	Ref.
Alcohol (VIIIa)	25	75 [a]	Present work
Diene (IVa)	23	77 [b]	6
Alcohol (VIIIb)	37	63	Present work
Diene (IVb)	51	49 [c]	7
Alcohol (VIIIc)	40	60 [d]	Present work
	34	66	7
Diene (IVc)	31	69	7
Alcohol (VIIId)	45	55	Present work
Diene (IVd)	48	52	7

[a] Total yield of cyclisation was 70—80%. [b] Considerable amounts of hydrophenalenes also formed.[6] [c] Polyphosphoric acid at 150 °C was used. [d] Percentage extremely susceptible to temperature and time of heating.

and increased with temperature (see later). The cyclisations of the alcohol (VIIIa) and the diene (IVa) in which the phenyl group is not activated by methoxy-substitution gave the same proportions of *cis*- and *trans*-isomers (25 : 75), which remained constant throughout a wide range of temperature (170 °C) and time. Evidently, this represents the true stereochemical course of the reaction under kinetic control. For other compounds with an activated benzene nucleus, the product possibly underwent complete or partial equilibration depending on the conditions of the reaction.

To investigate the above possibility, the products of cyclisation originally rich in the *trans*-isomer (Table 1) were further heated with PPA at 170 °C. Except for the mixture of unsubstituted podocarpatrienes (Va) and (VIa), the composition of which remained unchanged, there was a dramatic increase in the percentage of the *cis*-isomer (63—70%, Table 2). This establishes that, whereas the *trans*-isomer is the major product in a kinetically controlled cyclisation of the cations (I), the *cis* predominates under thermodynamically controlled conditions. Ireland's results showing a *cis*-preference may thus be due to equilibration of the initial product. This does not necessarily disprove the validity of their models. The so-called $A^{(1,2)}$-type strain in the transition state (II) depends on the degree of sp^2 hybridisation of the cationic centre and is reduced considerably with the loss of sp^2 character as the reactant proceeds towards the product. The relative stabilities of the two tran-

[6] D. Nasipuri, R. Bhattacharya, and C. K. Ghosh, *J. Chem. Soc.* (*C*), 1969, 782.
[7] D. Nasipuri, S. R. Roychaudhury, A. Mitra, and C. K. Ghosh, *Indian J. Chem.*, 1972, **10**, 136.
[8] J. A. Barltrop and N. A. J. Rogers, *J. Chem. Soc.*, 1958, 2566.
[9] R. F. Church, R. E. Ireland, and J. A. Marshall, *Tetrahedron Letters*, 1960, 1.
[10] D. Nasipuri and D. N. Roy, *J. Indian Chem. Soc.*, 1963, **40**, 327.
[11] D. Nasipuri and G. Pyne, *J. Chem. Soc.*, 1963, 4720.
[12] M. F. Ansell and B. Gadsby, *J. Chem. Soc.*, 1959, 2994; see also refs. 10 and 11.

sition states (II) and (III), therefore, depend on their position on the reaction co-ordinate and may well favour the former.

On the other hand, the *cis*-podocarpatriene appears to be thermodynamically more stable than the *trans*. To confirm this, an independent method of equilibration,

TABLE 2

Equilibration and attempted equilibration of the podocarpatrienes (V) and (VI)

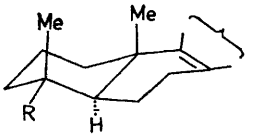
	Proportions (%) of isomers obtained by:			
	PPA at 170 °C (3h)		Palladium–charcoal (3 h)	
Compounds [a]	*cis*	*trans*	*cis*	*trans*
(Va) and (VIa)	25	75	45	65
(Vb) and (VIb)	63	37	35 [b]	75
(Vc) and (VIc)	65	35	55	45
(Vd) and (VId)	70	30	60	40
	70 [c]	30		

[a] A mixture of *cis*- and *trans*-podocarpatrienes as in Table 1 was used. [b] Pure crystalline *trans*-isomer was used. [c] Taken from ref. 3.

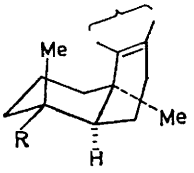
with palladium–charcoal in 2,5,8,11-tetraoxadodecane [13] was used. The results (last two columns of Table 2), however, were inconclusive. Two of the mixtures showed clear preference for the *cis* but the remaining two did not. We believe that complete equilibrium was not established in these systems. Moreover, by-products were formed which seriously interfered with the g.l.c. analysis and forbade the use of more drastic condition. In contrast, isomerisation with PPA (already well-known [14]) of the methoxy-derivatives gave a cleaner product. If we assume that the presence of the methoxy-group in the benzene ring does not substantially alter the equilibrium position, a 70 : 30 ratio of *cis* to *trans* (Table 2, last entry) may be accepted as a good measure of thermodynamic equilibrium in these compounds.

Two examples of isomerisation of analogous systems are known, wherein didehydroabietic acid (IX; R = CO_2H; only partial structure shown) [15] and the nitrile (IX; R = CN) [16] were treated with aluminium chloride to give products with *cis*-AB ring junction and loss of isopropyl group. Again, when the two *cis*-compounds (X; R = CN or CO_2Me) were in turn heated with palladium–charcoal,[13] a further reorientation took place and 5β-*trans*-isomers [as (XI)] were formed. The two isomerisations thus gave different results. The compounds, however, are not strictly comparable with podocarpatrienes (IX and X; R = Me) because in the first case (IX; R = CO_2H or CN), complex formation occurs between aluminium chloride and CO_2H(CN) and the possibility of kinetic control in bond re-formation after a reverse Friedel–Crafts ring opening cannot be wholly ignored,[16] and in the second, the antipodal *trans*-(XI; R = CO_2Me) has the Me/Me *syn*-axial interaction present in (IX) replaced by the less severe Me/CO_2Me, and may indeed be the stablest of the three (IX—XI; R = CO_2Me). This could justify the results of the above equilibrations.

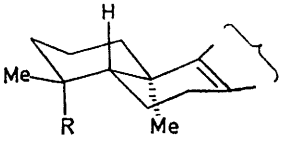
It is now well established that *cis*-podocarpatriene has a steroid-type conformation [17,18] and that both the *trans*- and the *cis*-isomers have a half-boat ring B [17]



(IX)



(X)



(XI)

(IX and X; R = Me) (this avoids the 'leaning' of the *syn*-axial methyl groups in the *trans*-isomer). The different steric interactions may be summed up as follows: for the *trans* (IX; R = Me), one Me/Me and three Me/H *syn*-axial (due to two axial Me); and for the *cis*, one Me/C=C, one C=C/H, and two Me/H *syn*-axial (due to axial Me in ring A). In addition, both have the common Me/H stern–flagpole interaction and a near Me/H *syn*-axial interaction between the equatorial Me in ring A and 6α-H. This leaves Me/Me + Me/H for the *trans*-isomer and C=C/Me + C=C/H for the *cis*, and clearly favours the *cis* since an sp^2 group interacts less than an sp^3.[19] Quantitative analysis is not possible because of the uncertainty of the conformational energy of the half-boat as well as of some of the above interactions.

EXPERIMENTAL

N.m.r. spectra were measured with a Varian T60 spectrometer for solutions in carbon tetrachloride with tetramethylsilane as internal standard. I.r. spectra were taken for solutions in chloroform. Petroleum refers to the fraction of b.p. 40—60°. 2,5,8,11-Tetraoxadodecane was purified by distillation over lithium aluminium hydride under reduced pressure. All organic solutions were dried over anhydrous sodium sulphate.

1-*Aryl*-4-*methylpent*-1-*en*-3-*ones*.—The four 1-aryl-4-methylpent-1-en-3-ones (aryl = Ph, *o*-MeO·C_6H_4, *m*-MeO·C_6H_4, or *p*-MeO·C_6H_4) were prepared by shaking an

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[14] I. Agranat and D. Avnir, *J.C.S. Chem. Comm.*, 1973, 362.
[15] W. E. Perham, E. L. Wheeler, and R. M. Dodson, *J. Amer. Chem. Soc.*, 1955, **77**, 1166.
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[17] E. Wenkert, A. Afonso, P. Beak, R. W. J. Carney, R. W. Jeffs, and J. D. McChesney, *J. Org. Chem.*, 1965, **30**, 713.
[18] A. Tahara and Ken-Ichi Hirao, *Chem. Comm.*, 1967, 326.
[19] N. L. Allinger and M. T. Tribble, *Tetrahedron Letters*, 1971, 3259.

equimolecular mixture of the appropriate benzaldehyde and 3-methylbutan-2-one with aqueous 10% sodium hydroxide (0.25 mol) in ethanolic solution. *1-Phenyl-4-methylpent-1-en-3-one* had b.p. 133° at 10 mmHg (Found: C, 82.3; H, 8.5. $C_{12}H_{14}O$ requires C, 82.8; H, 8.0%), the *o-methoxy-derivative*, b.p. 133—138° at 1 mmHg (Found: C, 76.1; H, 8.1. $C_{13}H_{16}O_2$ requires C, 76.5; H, 7.8%), the m-*methoxy-derivative*, b.p. 135—138° at 1 mmHg (Found: C, 76.0; H, 8.2%), and the p-*methoxy-derivative*, b.p. 135—140° at 1 mmHg (Found: C, 76.4; H, 7.5%).

2,4,4-Trimethyl-3-styrylcyclohex-2-enones (VII).—The methiodide of 1-*N*-diethylaminopentan-3-one was condensed with the preceding ketones as described in an earlier paper;[10] average yield 50%. The *ketone* (VIIa), b.p. 170° at 12 mmHg crystallised from ether–petroleum in light yellow needles, m.p. 74° (Found: C, 84.8; H, 8.4. $C_{17}H_{20}O$ requires C, 85.0; H, 8.3%); $\nu_{max.}$ 1 652 cm^{-1}; τ 2.70 (5 H, m, ArH), 3.40 (2 H, m, vinyl H), 7.60 (2 H, t, *J* 7 Hz, 6-H_2), 8.14 (5 H, m and s, 5-H_2 + 2-Me), and 8.79 (6 H, s, CMe_2); *dinitrophenylhydrazone* (dark red), m.p. 169—170° (Found: N, 13.1. $C_{23}H_{24}N_4O_4$ requires N, 13.3%). The *ketone* (VIIb), b.p. 180—190° at 0.5 mmHg, on chromatography afforded white crystals, m.p. 75° (Found: C, 79.8; H, 8.3. $C_{18}H_{22}O_2$ requires C, 80.0; H, 8.15%); $\nu_{max.}$ 1 650 cm^{-1}; τ 2.50—3.20 (4 H, m, ArH), 3.24 (2 H, m, vinyl H), 6.17 (3 H, s, OMe), 7.60 (2 H, t, *J* 7 Hz, 6-H_2), 8.14 (5 H, m and s, 5-H_2 + 2-Me), and 8.78 (6 H, s, CMe_2). The *m*-methoxy-ketone (VIIc) has been described elsewhere.[10] The p-*methoxy-derivative* (VIId), b.p. 180—190° at 0.5 mmHg (Found: C, 80.1; H, 8.5%) was a viscous gum; $\nu_{max.}$ 1 650 cm^{-1}. It was purified by chromatography before catalytic reduction.

3-(2-Arylethyl)-2,4,4-trimethylcyclohexanols (VIII).—The unsaturated ketones (VIIa—d) were reduced by hydrogen over 10% palladium–charcoal in ethanolic solution (uptake 2 mol. equiv. in *ca.* 4 h). The saturated ketones were all oils and were purified by distillation. *3-Phenethyl-2,4,4-trimethylcyclohexanone* had b.p. 155° at 1 mmHg (Found: C, 83.6; H, 9.6. $C_{17}H_{24}O$ requires C, 83.6; H, 9.8%); $\nu_{max.}$ 1 705 cm^{-1}; τ 2.88br (5 H, s, ArH), 7.20—8.10 (5 H, m, 2-H + 6-H_2 + $PhCH_2$), 8.20—8.70 (5 H, m, 2 × CH_2 + 3-H), 8.77 and 8.87 (3 H, d, 2-Me), and 8.97 and 9.07 (6 H, d, CMe_2). The other three ketones were characterised only by their i.r. ($\nu_{max.}$ 1 705 cm^{-1}) and n.m.r. spectra; the latter were identical with that described above except for the aromatic region and the presence of an extra peak at τ 6.28 (OMe).

The ketones were reduced by lithium aluminium hydride (excess) in ethereal solution and the crude alcohols (VIIIa—d) were checked for the complete absence of carbonyl content (i.r.) and used for the cyclisation experiments.

Cyclisation of the Alcohols (VIIIa—d).—Polyphosphoric acid was prepared by heating a mixture of phosphorus pentaoxide (65 g) and phosphoric acid (89%; 40 ml) on a steam-bath for 4 h. In a typical experiment, the alcohol (VIIIa) (3.0 g) was added to PPA (100 g) preheated to 90—100 °C and the mixture was stirred for 1 h at this temperature. Approximately half the red solution was taken out by pipette and decomposed with ice–water, and the crude product, after the usual work-up, was analysed by g.l.c. The remaining half was used for the isomerisation reaction (see later).

The crude product was distilled and the distilled mixture used for the equilibration reaction with palladium–charcoal (see later). Two pure *trans*-podocarpatrienes were isolated in crystalline form: *trans*-14-methoxypodocarpatriene (VIb), m.p. 117—118° (lit.,[20] 117—118°), τ 2.90—3.65 (3 H, m, ArH), 6.25 (3 H, s, OMe), 7.32 (2 H, m, 7-H_2), 7.60—8.80 (9 H, 4 × CH_2 + 5-H), 8.81 (3 H, s, 10-Me), and 9.04 (6 H, d, CMe_2); and *trans*-13-methoxypodocarpatriene (VIc),[10] m.p. 88°. These were used as reference compounds in g.l.c. N.m.r. spectra of the mixtures obtained in the above cyclisation were more complex than that of the pure *trans*-isomer. A 40 : 60 *cis–trans*-mixture of 12-methoxypodocarpatriene showed peaks at τ 2.90—3.65 (3 H, m, ArH), 6.32 (3 H, s, OMe), 7.32 (2 H, m, 7-H_2), 7.62—8.80 (9 H, m, 4 × CH_2 + 5-H), 8.85 (3 H, s, 10-Me), and 9.1 (6 H, m, CMe_2).

Gas Chromatography.—G.l.c. was carried out with a column (6 ft × ¼ in) of 10% polyester of diethylene glycol adipate (DEGA) and succinate (DEGS) supported on GasChrom-Z or a column of Carbowax 20M on Chromosorb with nitrogen as carrier gas. The oven temperature was usually kept at 150 °C for (Va) and (VIa) and at 180 °C for the others. *trans*-Podocarpatriene was always preceded by the *cis* in a series and was followed by a small peak of an unknown compound.[7] The crystalline *trans*-isomers (VIb and c) were used as reference compounds. For others, authentic samples from previous work[6,7] were used as standards. Mixed chromatograms were obtained at different temperatures and on different columns.

Equilibration Experiments.—(a) *With polyphosphoric acid.* The residual mixtures after the removal of samples in the cyclisation reactions already described were heated for an additional 3 h at 170 °C. The products were worked up in the usual way and analysed by g.l.c.

(b) *With palladium–charcoal.* A mixture of *cis*- and *trans*-podocarpatriene (composition as given in Table 1) (120 mg), 10% palladium–charcoal (120 mg), and 2,5,8,11-tetraoxadodecane (1.5 ml) were heated under reflux for 3 h. The product was taken up in petroleum and the solution filtered. The filtrate was repeatedly washed with water to remove the tetraether, dried, and evaporated. The residue was analysed by g.l.c. Considerable amounts of unidentified by-products were formed, conceivably owing to decomposition (possibly aromatisation) of the original mixture.

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