Substituent Effects in Saturated Systems. Conformationally Transmitted Retardation of the Rates of Solvolysis of Substituted Cyclohexylphenylmethyl Chlorides

By **J. P. Coleman, F. I. Shah-Malak,** and **J. H. P. Utley,*** Department of Chemistry, Queen Mary College, London E.1

Rate coefficients at several temperatures have been measured for the solvolysis in aqueous acetone of the methyl chlorides *p*-RC_6H_4·CHCl·C_6H_{11} and *trans*-4-RC_6H_{10}·CHClPh where R = H, Me, and Bu^t. The products of solvolysis of cyclohexyl-*p*-tolylmethyl chloride have been identified and their relative proportions determined.

Alkyl substituents in the cyclohexane ring retard the rate as much as substitution in the phenyl ring increases it. Analysis of activation parameters shows that the remote t-butyl group in the alicyclic ring exerts a rate-increasing effect on the enthalpy of activation as well as an over-riding rate-decreasing effect on the entropy of activation. Both are rationalised on the basis of ring deformation by the t-butyl substituent.

It is probable that the cyclohexane ring is susceptible to distortion by alkyl group substitution and that such deformation can influence reactions, equilibria, or spectroscopic properties of other groups attached to the cyclohexane ring but remote from the alkyl group. In particular the t-butyl group may affect chemical shifts involving remote protons [1] and also the donor properties of the nitrile group in the formation of complexes with iodine monochloride.[2] These results suggest an effect on the initial state whereas reactivity phenomena may additionally or exclusively involve the remote alkyl substituent in the stabilisation or destabilisation of the transition state. The participation of vicinal carbon–hydrogen bonds in the solvolyses of cyclohexyl arenesulphonates has been demonstrated by the measurement of kinetic deuterium isotope effects [3] and the conformational dependence of the participation suggests that, for *trans*-4-t-butylcyclohexyl bromobenzene-*p*-sulphonate at least, the transition state must be in a non-chair conformation. Kinetic data on the solvolysis of 2-alkylcyclohexyl toluene-*p*-sulphonates [4] lend powerful support to this suggestion as does an analysis of the temperature-dependence of activation parameters for the acetolysis of cyclohexyl and 4-t-butylcyclohexyl toluene-*p*-sulphonates.[5] Remote alkyl substituents also cause large changes in both the enthalpy and entropy of activation for the solvolysis of 1-adamantyl bromides and 1-bicyclo[2,2,2]octyl bromobenzene-*p*-sulphonates.[6] The data for the two systems are well related in a linear free-energy plot but the anomalous position of the unsubstituted compounds points to the involvement of steric factors.

Here we describe the results of a study of the reactivity of a cyclohexane substituent that during reaction develops charge on the carbon atom attached to the ring rather than on a ring carbon atom. Reactions involving cationic transition states are known to be very susceptible to substituent effects and our aim was to observe, measure, and interpret the effect of remote alkyl substituents. To facilitate the reaction and to limit available conformations the bulky benzylic substituent, PhCHCl, was chosen. As the reaction centre is not part of the cyclohexane ring substituent effects should be transmitted through the ring rather than involve gross deformation of the chair as in previous work.

RESULTS

Kinetics.—Rate coefficients and Arrhenius parameters for the solvolysis of a series of cyclohexylphenylmethyl chlorides in 90% aqueous acetone are in Table 1. For discussion the corresponding $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values and calculated rate coefficients, all at 100°, are included.

Products.—Although not pertinent to interpretation of

[1] F. R. Jensen and B. H. Beck, *J. Amer. Chem. Soc.*, 1968, **90**, 3251; G. E. Hawkes and J. H. P. Utley, *Chem. Comm.*, 1969, 1033.

[2] F. Shah-Malak and J. H. P. Utley, *Chem. Comm.*, 1967, 69.

[3] V. J. Shiner, jun., and J. G. Jewett, *J. Amer. Chem. Soc.*, 1965, **87**, 1383; W. H. Saunders, jun., and K. T. Finley, *ibid.*, p. 1384.

[4] M. Pánková, J. Sicher, M. Tichy, and M. C. Whiting, *J. Chem. Soc.* (*B*), 1968, 365.

[5] J. L. Mateos, C. Perez, and H. Kwart, *Chem. Comm.*, 1967, 125.

[6] P. v. R. Schleyer and C. W. Woodworth, *J. Amer. Chem. Soc.*, 1968, **90**, 6528.

the kinetic results the products of one of the solvolyses were characterised. The expected course of the reaction is given in the Scheme and the results of an analysis of the products of solvolysis of cyclohexyl-*p*-tolylmethyl chloride are in Table 2. The olefins were isolated by use of preparative-scale v.p.c. and identified by n.m.r. and mass spectroscopy. Analytical v.p.c. of the products enriched with authentic methanol and methyl chloride served to identify these components.

DISCUSSION

Substitution in the Aromatic Ring.—The sensitivity of the reaction to polar effects is demonstrated by the marked increase in rate owing to alkyl substitution in the phenyl ring. It is apparent that overall this originates from a lowering of $\Delta H^{\ddagger}$. This pattern is consistent with an inductive, electron-releasing polar effect and it is interesting that although a comparison of rate coefficients at 100° would suggest the Baker–Nathan order of electron release (just), this arises from a small decrease in $\Delta S^{\ddagger}$ that overcompensates the lower $\Delta H^{\ddagger}$ value for the t-butyl *vis-à-vis* the methyl compound. If it is assumed that changes in $\Delta H^{\ddagger}$ more accurately reflect polar substituent effects it seems that electron release is really in the inductive order. However the changes in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are certainly too small to encourage dogmatism.

Substitution in the Cyclohexane Ring.—Changes in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are greater for the compounds substituted in the cyclohexyl ring. Both methyl and t-butyl provoke a lowering of $\Delta H^{\ddagger}$ (rate-increasing), the t-butyl group more than methyl. However the overall retardation of rate at 100° follows from the change to more negative $\Delta S^{\ddagger}$ values. Again the largest change follows substitution by t-butyl. Before these results can be rationalised we must consider the probable conformations of the initial and transition states.

Initial state. It is important to know the conformational preference of the PhCHCl group. The only plausible conformation with PhCHCl axial is shown in Figure 1 and it bears some resemblance to the conformation probably adopted by axial isopropyl groups. The conformational free energy of the isopropyl group [7]

TABLE 1

Rate coefficients and activation parameters for the solvolysis in 90% aqueous acetone of arylcyclohexylmethyl chlorides (I)

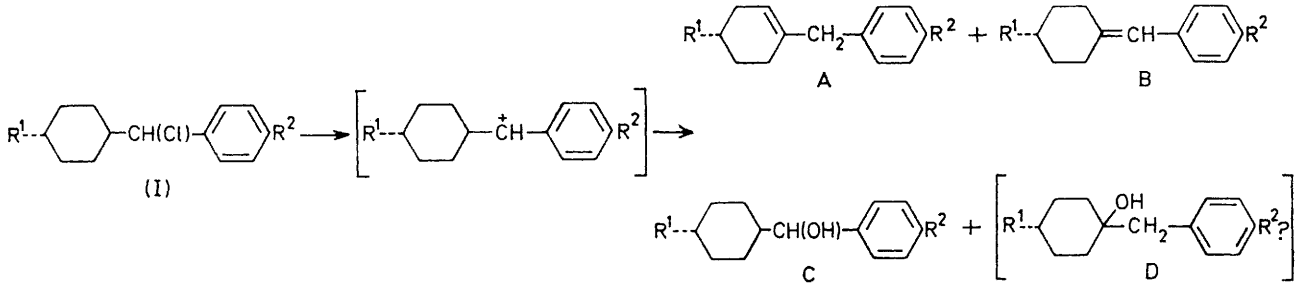
R^1	R^2	10^4k (sec.$^{-1}$); (temp.)			$E_{act.}$ (kcal. mole^{-1})	log A	10^5k † (sec.$^{-1}$)	$\Delta H^{\ddagger}$ † (kcal. mole^{-1})	$\Delta S^{\ddagger}$ † (e.u.)
H	H	2·44 (122·0°)	1·22 (110·2°)	0·490 (99·6°)	20·71	7·86	5·28	19·97	−2·49
H	Me	1·66 (89·5)	0·730 (79·4)	0·349 (70·1)	19·88	8·19	35·3	19·14	−2·34
H	Bu^t	1·44 (90·6)	0·620 (79·6)	0·294 (70·5)	19·63	7·95	28·5	18·89	−2·45
trans-Me	H	1·21 (129·7)	0·634 (119·8)	0·327 (109·6)	19·97	6·89	1·66	19·23	−2·92
trans-Bu^t	H	1·48 (129·6)	0·820 (119·4)	0·427 (109·4)	18·83	6·40	2·31	18·09	−3·16

† At 100°. $\Delta H^{\ddagger}$ considered accurate to ±0·3 kcal. mole^{-1} and $\Delta S^{\ddagger}$ to ±0·15 e.u.

TABLE 2

Major products of solvolysis of cyclohexyl-*p*-tolylmethyl chloride in 90% aqueous acetone

Product (R^1 = H, R^2 = Me)	%	Identification		
		Parent ion, *m/e*		N.m.r.
Olefin A	42	Found:	186·14109	τ 3·07 (4H,s), 4·65 (1H,m), 6·89 (2H,s), 7·70 (3H,s), 7·8—8·60 (8H, all m)
		Calc. for $C_{14}H_{18}$:	186·14085	
Olefin B	28·5	Found:	186·14068	τ 2·96 (4H,s), 3·83 (1H,s), 7·62 (3H,s), 7·42—8·60 (8H, all m)
		Calc. for $C_{14}H_{18}$:	186·14085	
Alcohol C and starting material	25			
Unidentified product	<5			



SCHEME

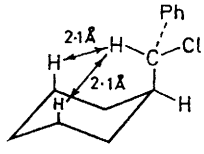


FIGURE 1

[7] J. A. Hirsch, 'Topics in Stereochemistry,' ed. E. L. Eliel, Interscience Publishers, Inc., New York, 1967, p. 199.

is in the region of 2 kcal. mole^{-1} and although a larger value would apply in our system it cannot be assumed without experimental evidence that the PhCHCl group is exclusively in the equatorial position. It is probably safe, however, to assume that the *trans*-4-methyl- and *trans*-4-t-butyl-cyclohexylmethyl chlorides are virtually entirely in the diequatorial conformation. A prominent feature of the n.m.r. spectra of the methyl chlorides is the doublet attributable to the benzylic proton.

TABLE 3

Arylcyclohexyl ketones, methanols, and methyl chlorides

Compound	Yield (%)	M.p. (or b.p.)	Analysis (%)
Ketones			
Cyclohexyl phenyl	65	54—55°	
Cyclohexyl *p*-tolyl	68	66—67 (101°/0·5 mm.)	
p-t-Butylphenyl cyclohexyl	32	(120°/1·0 mm.)	Calc.: C, 83·55; H, 9·9 Found: C, 83·3; H, 9·7
trans-4-Methylcyclohexyl phenyl	43	49—50 (94°/0·01 mm.)	Calc.: C, 83·1; H, 8·95 Found: C, 83·4; H, 9·0
trans-4-t-Butylcyclohexyl phenyl	80	82—83	Calc.: C, 83·55; H, 9·9 Found: C, 83·8; H, 9·9
Methanols			
Cyclohexylphenyl	75	49—50 (106°/0·5 mm.)	Calc.: C, 82·05; H, 9·55 Found: C, 82·2; H, 9·6
Cyclohexyl-*p*-tolyl	75	41—42 (118°/0·2 mm.)	Calc.: C, 82·3; H, 9·85 Found: C, 82·2; H, 10·0
p-t-Butylphenylcyclohexyl	90	69—71	Calc.: C, 82·85; H, 10·65 Found: C, 82·6; H, 10·6
trans-4-Methylcyclohexylphenyl	90	59—60	Calc.: C, 82·3; H, 9·87 Found: C, 82·1; H, 10·3
trans-4-t-Butylcyclohexylphenyl	90	80—81	Calc.: C, 82·85; H, 10·65 Found: C, 83·3; H, 10·6
Chlorides			
Cyclohexylphenylmethyl	78	(101°/0·5 mm.)	Calc.: C, 74·8; H, 8·2 Found: C, 74·5; H, 8·1
Cyclohexyl-*p*-tolylmethyl	86	(106°/0·01 mm.)	Calc.: C, 75·5; H, 8·6 Found: C, 75·6; H, 8·6
p-t-Butylphenylcyclohexylmethyl	85	(122°/0·1 mm.)	Calc.: C, 77·1; H, 9·5 Found: C, 77·2; H, 9·2
trans-4-Methylcyclohexylphenylmethyl	80	49—50 (87°/0·01 mm.)	Calc.: C, 75·5; H, 8·6 Found: C, 75·9; H, 8·7
trans-4-t-Butylcyclohexylphenylmethyl	79	(131°/0·05 mm.)	Calc.: C, 77·1; H, 9·5 Found: C, 77·2; H, 9·6

For *trans*-4-t-butylcyclohexylphenylmethyl chloride the doublet is centred at τ 5·53 and J 8 Hz (CCl_4, 30°). We may assume this to be characteristic of the situation with the PhCHCl group locked in the equatorial position. The coupling constant may be an averaged one owing to free rotation of the PhCHCl group although in view of the chloro-substituent the value is a little high. However, for one of the methyl chlorides with no 4-cyclohexyl substituent, cyclohexyl-*p*-tolylmethyl chloride, a virtually identical doublet was observed, (τ 5·58, J 8 Hz, CS_2, 30°). Furthermore the position of absorption and the coupling constant did not change as the temperature was lowered, eventually to −90°. Although not conclusive it is unlikely that such a result would be obtained if at room temperature the averaged spectrum included a significant contribution from the conformation with PhCHCl axial.

For PhCHCl equatorial and the shape of the phenyl substituent being ignored, the choice for the least hindered conformations lies between those shown in Figure 2. They are viewed as projections along the C(1)–substituent bond.

Conformation 2(a) embodies three significant 1,3-interactions (2 × Cl · · · H; and 1 × Ph–H). Conformation 2(b) involves a Cl · · · H and a Ph · · · H 1,3-interaction. Dreiding models show that even in these more probable conformations the rotation of the phenyl substituent is severely restricted. For instance, further consideration of conformation 2(b) suggests that the least strained modification is that shown in Figure 3. Additional sources of strain can now be seen in the form of significant interactions between the *ortho*-hydrogens of

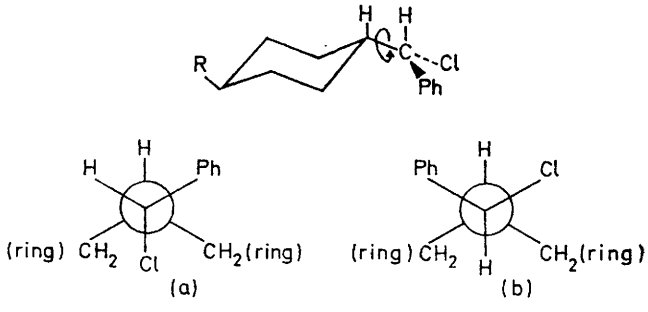


FIGURE 2

the phenyl group and the C(1) methine hydrogen and the chlorine atom. The distances quoted are for the phenyl group oriented in the plane of the C–H bond but presumably the ring would deviate from such a plane to

minimise both interactions. It is clear however that a large rotation in either direction from such a position would considerably raise the energy of the initial state. Similar considerations apply to the situation of the phenyl group in conformation 2(a).

To summarise therefore the initial state is considerably strained with the cyclohexane ring in the chair

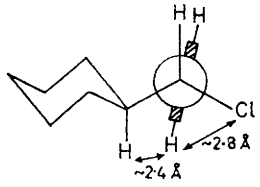


FIGURE 3

form. The *trans*-4-alkylcyclohexylphenylmethyl chlorides are assumed to be in the diequatorial conformation and, from n.m.r. spectroscopy, the corresponding conformation is probably adopted by the arylcyclohexylmethyl chlorides.

Transition state. We begin with the usual assumption that the transition state for solvolysis closely resembles the intermediate carbonium ion.

On steric grounds the least strained conformation is that shown in Figure 4(a) and such a transition state

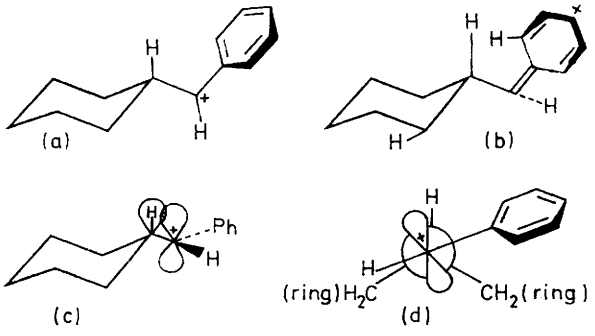


FIGURE 4

would represent a considerable relief of strain during reaction. However, stereoelectronic effects that would stabilise the carbonium ion must be accommodated in the most probable conformation. The aryl group would tend to be coplanar with the cationic centre. It cannot be so without engendering severe strain. Similarly for maximum participation of the methine hydrogen the C–H bond would need to be at right-angles to the plane of the carbonium ion to provide for maximum overlap between the C–H bond and C 2*p* orbital. The two extreme situations are featured in Figures 4(b) and 4(c) together with a suggestion for a probable compromise conformation viewed along the C^{+}–C(1) bond [4(d)].

Effect of Cyclohexane Substituents on $\Delta S^{\ddagger}$.—The entropies of activation are, as expected, negative although considerably less negative than the literature value for the solvolysis of phenethyl chloride in 80% aqueous acetone [8] ($E_{act} = 22{\cdot}2$ kcal. mole^{-1}; $\Delta S^{\ddagger} = -14{\cdot}2$ e.u.). The more positive values found for our system probably reflect the greater conformational limitations of the initial state compared with similar hindrance in the transition state. In this context, tosylates with highly hindered initial states exhibit positive entropies of activation.[9]

4-Alkyl substituents lower the entropy of activation, the t-butyl group causing the greater decrease. This may be due to a lessening of initial-state crowding or to an increase of transition-state crowding, or both. There is evidence from spectroscopic and equilibrium data [1,2] that the bulky t-butyl group causes a flattening of the cyclohexane ring. As a corollary of such opening of the internal angles of the ring the angle between the axial and equatorial positions and the ring carbon atoms will be decreased. It is therefore likely that by such deformation a bulky substituent in an equatorial position will be further removed from neighbouring hydrogen atoms. This means that the strain resulting from interaction between the equatorial substituent and the equatorial hydrogens at C(2) and C(6) would be less for 4-t-butylcyclohexylphenylmethyl chloride than for the unsubstituted compound (Figure 5).

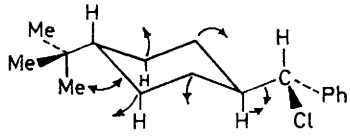


FIGURE 5

An alternative way of viewing such relief of strain is to envisage the t-butyl group ' siphoning off ' some of the strain energy imposed by the PhCHCl substituent. The t-butyl group provides additional possibilities for the spreading of angle strain between more angles. Either way the reactive substituent, PhCHCl, is granted more rotational freedom, the initial-state entropy increased, and $\Delta S^{\ddagger}$ correspondingly decreased.

Effect of Cyclohexane Substituents on $\Delta H^{\ddagger}$.—4-Alkyl substituents lower the enthalpy of activation (rate-increasing) in the order $Bu^{t} > Me$. It is highly improbable that the inductive effect of the alkyl groups is of account at a separation of five bonds. Equally improbable is the operation of an alkyl group direct field effect. As originally suggested [10] such an effect would depend on polarisation of alkyl group C–H bonds and, depending on the direction of polarisation, the groups would be either activating or deactivating in the order $Me > Bu^{t}$. We observe activation in the order $Bu^{t} > Me$. Rate enhancement resulting from a lowering of the enthalpy of activation may be explained by a polar

[8] E. Berliner and N. Shieh, *J. Amer. Chem. Soc.*, 1957, **79**, 3849.

[9] R. Baker, J. Hudec, and K. L. Rabone, *Chem. Comm.*, 1969, 197.

[10] H. Kwart and T. Takeshita, *J. Amer. Chem. Soc.*, 1964, **86**, 1161.

effect either raising the initial state energy or lowering the transition state energy. It is difficult to envisage the former in this system and we suggest that alkyl group substitution lowers the transition state energy.

Coplanarity of the phenyl group with the carbonium ion and the correct positioning of the C(1) axial hydrogen for hyperconjugation would undoubtedly be enthalpy-lowering features of a strain-free transition state. Such perfection is prevented by interaction between an *ortho* hydrogen of the phenyl group and the C(2) equatorial hydrogen [Figure 4(b)]. Ring-flattening consequent upon substitution by 4-t-butyl reduces such hindrance to coplanarity thus lowering the enthalpy of the transition state as well as raising its entropy. It is also possible that the 'pinching' of the bond angle including the C(1) axial hydrogen, C(1), and the cationic carbon atom, results in increased overlap between the C(1)–H bond and the developing $2p$ orbital of the transition state. This explanation requires steric inhibition of mesomerism to be *reduced* by 4-t-butyl substitution and it is encouraging that activation parameters for reactions involving more easily recognisable inhibition of mesomerism show the effect to be primarily on the enthalpy of activation.[11] The initial-state energy would also be raised by 4-t-butyl substitution and this could contribute to a lowering of $\Delta H^{\ddagger}$. Deformation of the cyclohexane ring therefore provides a basis for rationalisation of the substituent effects on enthalpies as well as entropies of activation.

EXPERIMENTAL

Arylcyclohexylmethyl Chlorides.—These were prepared by Friedel–Crafts reaction between the relevant cyclohexylcarbonyl chloride and benzene, toluene, or t-butylbenzene. The ketones were hydrogenated in the presence of Raney nickel to give the corresponding alcohols which were converted into the chlorides by use of thionyl chloride in dry toluene. At all stages the intermediates were carefully purified. A typical sequence of reactions is described below and the properties of the ketones, alcohols, and chlorides are summarised in Table 3.

trans-4-*t-Butylcyclohexyl Phenyl Ketone.*—*trans*-4-t-Butylcyclohexanecarbonyl chloride (15 g.) in benzene (20 ml.) was added during 30 min. to benzene (40 ml.) containing anhydrous aluminium chloride (14 g.). The mixture was stirred and kept at 60° until evolution of hydrogen chloride ceased. After cooling the mixture was poured on ice (300 g.) and hydrochloric acid (75 ml.). The organic layer was washed with aqueous sodium hydroxide (2N) and water. After drying ($MgSO_4$) benzene was removed and the residue distilled under reduced pressure to yield 15 g. (80%) of the required ketone.

G.l.c. of the product (1% Peg A/150°) showed one peak only. That epimerisation of the carbonyl chloride would be detected in this way is evident from the v.p.c. analysis of the ketones produced from benzene and *cis*-4-t-butylcyclohexylcarbonyl chloride. A mixture of products was obtained in the ratio 8 : 1, the minor product being *trans*-4-t-butylcyclohexylphenyl ketone. It seems therefore that the *cis*-isomer reacts with epimerisation whereas the *trans*-isomer preserves its configuration.

trans-4-*t-Butylcyclohexylphenylmethanol.*—The ketone (10 g.) was hydrogenated in ethanol (75 ml.) under hydrogen pressure (4 atm.) in presence of Raney nickel (5 g.). The reaction took 12 hr. and was worked up in the usual way. The methanol was subjected to v.p.c. (1% Peg A/170°) and showed one peak only. The i.r. spectrum of the product showed no olefinic or carbonyl absorption.

trans-4-*t-Butylcyclohexylphenylmethyl Chloride.*—Thionyl chloride (12 g.) was added gradually to a stirred solution of the methanol (10 g.) in dry toluene (25 ml.) at room temperature. The mixture was heated under reflux for 90 min. and then the toluene and unchanged thionyl chloride were distilled off under reduced pressure. The residue was purified by careful fractional distillation under reduced pressure.

Kinetic Measurements.—Solvent. Batches of aqueous acetone (90% v/v) were prepared by diluting CO_2-free distilled water (200 ml.) to 2 l. with AnalaR acetone.

Rate coefficients. A solution of the methyl chloride (0·02M) in 90% aqueous acetone was prepared and 5·0 ml. portions sealed in reaction bulbs. The bulbs were placed in a thermostat, removed at suitable intervals, cooled, and the contents analysed titrimetrically in the usual way. Kinetic runs had an internal accuracy always of less than $\pm 4{\cdot}5\%$ in the rate coefficient and usually in the region of $\pm 2\%$. The results presented are the means from duplicate experiments.

Products analysis. Cyclohexyl-*p*-tolylmethyl chloride (0·5 ml.) and 10·0 ml. of 90% aqueous acetone were sealed in a reaction tube and kept at 90° for *ca.* 40 hr. The contents were poured into ice-water and extracted with ether. The ether layer was washed with aqueous sodium hydrogen carbonate and water, dried ($MgSO_4$), and the ether removed. The residue was subjected to preparative-scale v.p.c. (20% Deg S/180°, Varian-Aerograph A90P), and the two low-retention time products collected. Mass spectrometry and n.m.r. spectroscopy showed these to be the expected olefins (Table 1). The relative proportions of the products were determined by v.p.c. on a Perkin-Elmer F11 instrument with a $2\frac{1}{2}\%$ silicone gum rubber column at 145° for 16 min. followed by a linearly programmed rise to 165° at 4°/min. The starting chloride and the methanol were incompletely resolved under these conditions and therefore appear together in Table 2. N.m.r. measurements were on a Varian HA100 instrument and mass measurements on an AEI MS902 machine.

One of us (J. P. C.) thanks the S.R.C. for a Research Studentship.

[9/1309 *Received, August 4th,* 1969]

[11] N. B. Chapman, 'Steric Effects in Conjugated Systems,' ed. G. W. Gray, Butterworths, London, 1958, p. 127.