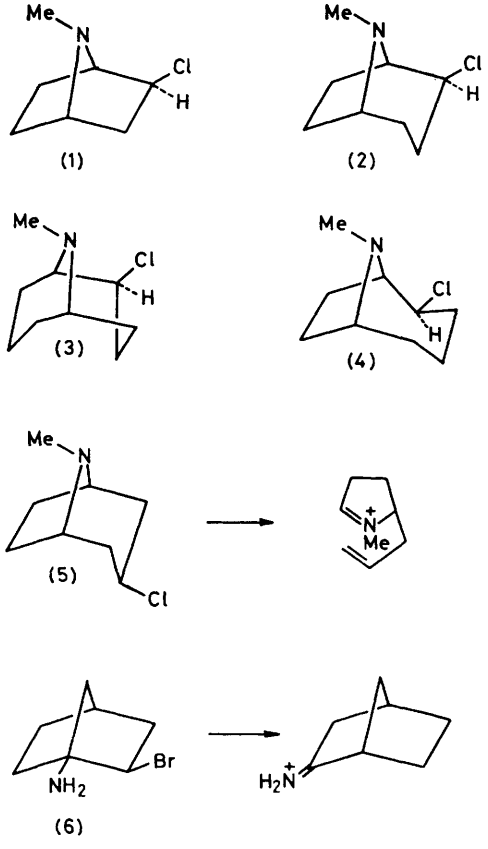
Solvolytic Rearrangements of Azabicyclic Compounds. Part 2.[1] Kinetics

By **John W. Bastable, Ian R. Dunkin,** and **John D. Hobson,*** Department of Chemistry, University of Birmingham, P.O. Box 363, Birmingham B15 2TT

Rates of solvolysis in aqueous ethanol and aqueous dioxan of three 2-*exo*-chloroazabicycloalkanes have been studied and first-order rate constants are derived and compared with published values for analogous compounds. Anchimeric assistance by the bridge N-atom is evidently not important in the rate-controlling step in these rearrangements, though it may occur to a minor extent in the case of 2-*exo*-chloro-7-methyl-7-azanorbornane. Solvolytic results for tropan-2β-yl toluene-*p*-sulphonate in aqueous ethanol and aqueous acetone mixtures are also reported and compared with literature data for the carbobicyclic and oxabicyclic analogues.

PRODUCT analysis studies on the solvolysis of the 2-*exo*-chloroazabicycloalkanes (1)—(4) described in the previous paper [1] have shown that exclusively rearranged products are formed in all cases arising from solvent capture of the corresponding cyclo-immonium cations. Comparison with the behaviour of carbocyclic [2] and oxabicyclic [3,4] analogues suggests that the nitrogen bridge has a distinctive role in determining products but the question as to whether such participation extends to assistance in the rate-controlling ionisation requires a



kinetic answer. Substantial ('frangomeric') rate acceleration, relative to the carbocyclic analogue, accompanies fragmentation of γ-aminobicycloalkyl derivatives such as (5) which possess special stereoelectronic features.[5] However, in the series of 1-substituted-2-*exo*-norbornyl bromides examined by Wilt and Wagner,[6] a study more relevant to the present work, evidence for only a modest degree of assistance was observed in solvolysis of the 1-amino-compound (6), though here also totally rearranged product was obtained.

RESULTS AND DISCUSSION

Syntheses of the 2-*exo*-azabicycloalkyl chlorides (1)—(4) have already been reported,[1,7] and isolation and characterisation of their solvolysis products in acetone and aqueous dioxan are described in the previous paper.[1] Kinetic studies of the reactions of compounds (1)—(3) † in aqueous dioxan and aqueous alcohol were carried out using the sealed ampoule technique and Volhard determination of liberated chloride; sufficient alkali was added initially to ensure that no significant N-protonation developed during solvolysis. No evidence for any significant intervention of bimolecular substitution or elimination processes were obtained from product analyses, and reactions showed good first-order behaviour during monitoring over 2—3 half-lives. Rate constants together with literature data for related compounds are presented in Table 1.

The rate constants for the three azabicyclic chlorides (1)—(3) in 50% dioxan vary over only a four-fold range. As with the corresponding carbobicyclic analogues [2] the most highly strained 7-azanorbornyl derivative (1) was the most reactive, but the data for the three do not provide evidence for any acceleration of the rate-controlling ionisation arising from the bridge N-atom. Such participation might have been expected to occur, if at all, in the case of (1), and since this study now completes published data (Table 1) for the quartet of 2-*exo*-norbornyl analogues (1), (7), (8), and (9), some general comparisons are possible.

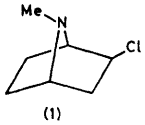
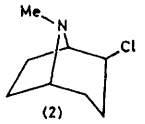
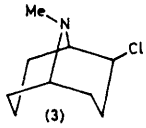
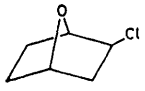
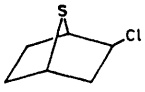
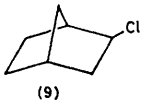
The 2 000-fold rate-retardation, relative to the carbobicyclic chloride (9), shown by the 7-oxa-compound (7), and also by its 2-*endo*-chloro-epimer,‡ was ascribed by

† The fourth compound (4) was not available in sufficient quantity for detailed study.

‡ The lack of direct *O*-3 assistance observed in the solvolysis of this compound contrasts with the strong acceleration provided by the bridge heteroatom in 2-*endo*-chloro-7-thianorbornane;[8] 2-*endo*-halogeno-derivatives of 7-azanorbornane have not yet been prepared,[9] but the much greater (*ca.* 10^5) power of NH_2, relative to OMe, as a participatory neighbouring group in the solvolysis of β-substituted ethyl derivatives [10] leads to the expectation that this type of compound would be very labile.[11]

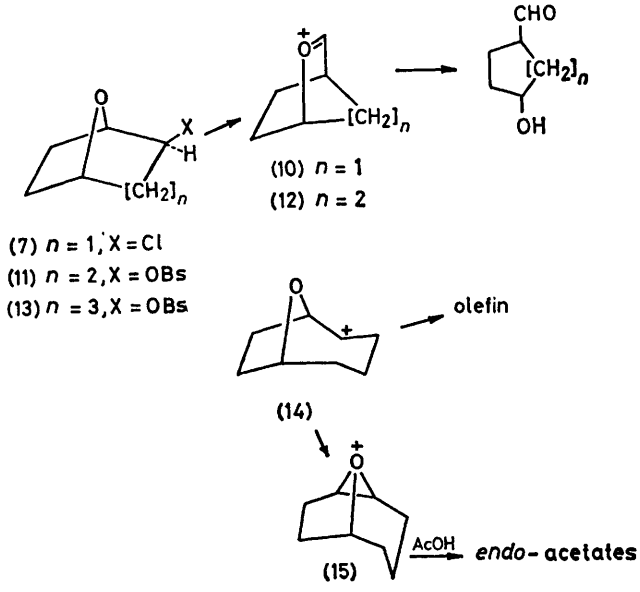
TABLE 1

Solvolysis of 2-*exo*-chloroazabicycloalkanes and related compounds

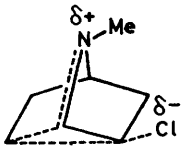
Compound [a]	Temperature (°C)	Solvent [b]	$10^5 k_1/s^{-1}$	$k_{rel.}$ 50% dioxan	$k_{rel.}$ 80% EtOH
 (1)	85.3	80% EtOH	1.58 [c]		1.00
	85.3	50% Dioxan	13.0 [c]	1.00	
 (2)	85.3	50% Dioxan	4.23 [c]	0.33	
 (3)	85.3	50% Dioxan	3.22 [c]	0.25	
 (7)	85	80% EtOH	0.001 96 [d]		0.0012
		50% Dioxan	0.0188 [d]	0.0015	
 (8)	85	50% Dioxan	0.0476 [e]	0.0037	
 (9)	85	80% EtOH	3.89 [f]		2.5
	85	50% Dioxan	35 [g]	2.7	

[a] Azabicyclic compounds >99% pure by g.l.c. Initial concentration *ca.* 0.02M. [b] Percentage ethanol–water (v/v), and percentage dioxan–water (w/w) before mixing; containing 0.04M sodium hydroxide. [c] Mean of three independent runs. [d] Ref. 3; value calculated from data obtained under other conditions. [e] Extrapolated from data obtained at higher temperatures.[8] [f] J. D. Roberts and W. Bennett, *J. Am. Chem. Soc.*, 1954, **76**, 4623. [g] Calculated from the 80% EtOH value using the Grunwald–Winstein correlation; Y (50% dioxan) = 1.36 (S. Winstein and J. H. Fainberg, *J. Am. Chem. Soc.*, 1956, **78**, 2770), m = 0.7 [on the basis of a survey of other secondary systems, a value of m of 0.5 has been considered (J. A. Berson, 'Carbonium Ion Rearrangements in Bridged Bicyclic Systems,' in 'Molecular Rearrangements,' ed. P. de Mayo, Interscience, New York, 1963, vol. 1, p. 191, footnote 155) to be appropriate in this case. However, from the data for (1) a value of 0.67 is obtained, in better agreement with m = 0.72 which can be calculated from the data reported [3] for solvolysis of the 2-*exo*-bromo-analogue of (7), in aqueous ethanol and aqueous dioxan].

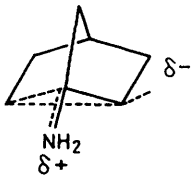
Martin and Bartlett [3] mainly to the destabilising inductive effect of the bridge oxygen atom, with no significant compensatory participation by non-bonding electrons in the transition state. Nevertheless, the heteroatom evidently has a decisive product-determining influence since 3-formylcyclopentanol, arising *via* the rearranged ion (10), was the sole product from either chloride in aqueous dioxan. Attempts to trap unrearranged intermediate with an external nucleophile (azide) were unsuccessful. The 2-*exo*-*p*-bromobenzenesulphonate (brosylate, OBs) (11) of the homologous 8-oxabicyclo[3.2.1]-octyl system showed similar behaviour, giving products derived exclusively from skeletal rearrangement to (12).[4b] In contrast, the more flexible 9-oxabicyclo[4.2.1]nonyl derivative (13) studied by Paquette and Storm [4a] showed no tendency to undergo Wagner–Meerwein rearrangement; instead the initially formed (classical) carbocation (14) either underwent elimination or was quenched internally to give the bridged oxonium ion (15), also accessible directly from the 2-*endo*-epimer of (13).



It was pointed out [3] that the rate depression shown by (7) is larger than expected from consideration of model compounds * or from calculations of dipole–dipole interaction in the transition state.[13] A comparable rate-depression has also been observed [8] for the 7-thia-analogue (8) (see Table 1) in spite of the much reduced electron-withdrawing capability anticipated for sulphur. Whatever the origin of this special effect † similar considerations might be expected to apply to the 7-aza-compound (1). However, the fact that under comparable conditions (50% dioxan) compound (1) hydrolysed faster than either the 7-oxa- or 7-thia-analogues by factors of 660 and 270, respectively, leaves some scope for a small degree of N-participation (16), almost compensating for the adverse [relative to (9)] inductive effect of the NMe bridge.‡ Any assistance to ionisation is nevertheless rather weaker than that observed ($k_{rel.}$ = 46) for 1-aminonorbornyl bromide,[6] in which the nitrogen lone pair is free to assume a more favourable disposition with respect to electron-deficiency developing at C-1 in the transition state (17).

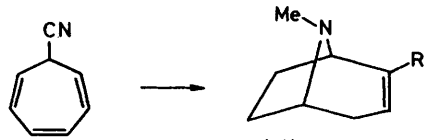


(16)

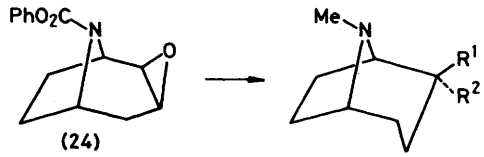


(17)

*Solvolysis of Tropan-2β-yl Toluene-*p*-sulphonate.*— Further studies of the homologous 8-azabicyclo[3.2.1]-octane system were prompted by the comparative accessibility of the tropan-2-ols, and the availability of literature data on arylsulphonate esters of the carbobicyclic and oxabicyclic analogues. Tropan-2-one (20) and the epimeric alcohols (21) and (22) have been prepared by Hofmann degradation of naturally derived [15] and synthetic [16] anhydroecgonine amide (19), the latter being obtained *via* methyl tropinone-2-carboxylate by a laborious route. In the present work the (±)-amide was obtained in 50% overall yield by reaction of 7-cyanocyclohepta-1,3,5-triene with methylamine (a procedure based on the work of Grundmann and Ottmann [17] with the corresponding carboxylate), followed by hydrolysis of the resulting nitrile (18). As reported [15] dissolving-metal reduction of the ketone (20) under equilibrating conditions afforded a mixture of alcohols rich in the axial epimer (21), from which the alcohol was obtained substantially pure by distillation. The same alcohol was also obtained by $LiAlH_4$ reduction of the 2β,3β-epoxide (24), obtained from tropidine by chloroformate demethylation [18] and trifluoroperacetic



(18) R = CN
(19) R = $CONH_2$



(24)

(20) $R^1 = R^2 = O$
(21) $R^1 = OH, R^2 = H$
(22) $R^1 = H, R^2 = OH$
(23) $R^1 = OTs, R^2 = H$

acid epoxidation (see Experimental section). Tosylation was accomplished only after conversion into the alkoxide with sodium hydride; the epimeric 2α-derivative could not be prepared at all in spite of several attempts, doubtless reflecting the strong proclivity of such compounds to undergo internally assisted solvolysis.[7,10]

The tosylate (23) behaved on solvolysis similarly to the corresponding chloride,[1] undergoing exclusive skeletal rearrangement to derivatives of the isoquinuclidine, *i.e.* 2-azabicyclo[2.2.2]octane, system. As in the case of the 8-oxa-compound (11) [4b] the relative stability of the corresponding rearranged ion (26) is evidently crucial in procuring this result, in contrast with the carbobicyclic analogue (25), which gives a mixture of [2.2.2]- and [3.2.1]-bicyclic derivatives arising from nucleophilic attack on either the bridged or classical carbonium intermediates.[2]

For the purpose of making a comparison of reactivity it is unfortunate that published data on (25) [2c] and (11) [4b] relate to solvolysis in acetic acid, a solvent in which the basic analogue (23) would be extensively protonated. Some data are available for ethanolysis of (25), [2b] but reactions of (23) in the pure solvent were somewhat slow, and it was more convenient to conduct kinetic experiments with aqueous solvents and to use the appropriate solvent polarity-rate constant correlation to compare carbobicyclic and azabicyclic systems.

In 40% aqueous ethanol the tosylate (23) had a pK_a of 7.8 at 26 °C; hence to avoid significant protonation reacting solutions were maintained at pH 10. Data were obtained for both aqueous ethanol and aqueous acetone (Tables 3 and 4; see Experimental section), reactions being monitored spectroscopically in the first

* Hydrolysis of 2-chloro-2-methoxymethylpropane relative to 2-chloro-2-methylpropane: $k_{rel.}$ = 0.0049.[12]

† Suggested [3] to arise in (7) from the fixed orientation of the C–O dipole relative to the breaking bond, together with an enhanced potential for hydrogen-bonding possessed by the bridge atom. The 100-fold rate depression shown by (11), relative to the corresponding carbobicyclic system, is notably less,[4b] but the significance of these differences is doubtful in the absence of information on the extent of internal return in both systems.

‡ A minimum estimate of this can be derived from Grob's compilation of the inductive parameters σ_I^q for various substituents and their influence on the solvolytic rate constants (80% ethanol at 70 °C) of 1-substituted-3-bromoadamantanes (ρ = 1.14).[14] Although the NMe_2 group (σ_I^q = 0.97) promotes frangomeric [5] acceleration of the ionisation, a purely inductive rate depression factor of *ca.* 0.08 can be inferred from the data.

solvent series and by automatic ' pH-Stat ' titrimetry in the second. A 21-fold increase in [OH^-] resulted in only a small (*ca.* 7%) increase in rate constant, most reasonably attributed to a salt effect; product analyses of reactions conducted under strongly alkaline conditions failed to reveal components arising from S_N2 or elimination reactions.

Grunwald–Winstein plots of first-order rate constants (Tables 3 and 4) against Y-values for the aqueous ethanol and aqueous acetone solvent series gave good, almost coincident, straight line plots. The derived m-values of 0.45 and 0.49 reflect a rather low sensitivity of the reaction towards solvent polarity, but are in the range commonly observed in solvolysis of secondary alicyclic tosylates in which the nucleophilicity of the solvent has a variable, but important role.[19,20] For the correlation of solvolytic rate constants for arenesulphonate esters in aqueous ethanol or acetone with data relating to acidic solvents, Grunwald–Winstein Y-values, based on t-butyl chloride, are inadequate. An improved scale of solvent ionising power for tosylates has recently been devised based on 2-adamantyl tosylate,[19,20] and, using these $Y_{2\text{-AdOTs}}$ values,[19] a hypothetical rate constant for the solvolysis of (23) in acetic acid can be derived from the experimental data. The resulting estimate (Table 2) must be regarded as an upper limit in the absence of an allowance for the lesser nucleophilicity of acetic acid relative to aqueous ethanol having the same Y-value,[19] but it is clear that the solvolytic reactivity of (23) is not very different from that of its carbocyclic analogue (25). The oxa-compound (11), on the other hand, shows a *ca.* 200-fold rate depression, in the range expected for inductive destabilisation of the transition state by the bridge oxygen atom. The reactivity of tropan-2β-yl tosylate (23) thus parallels that of the lower homologue and is similarly indicative of a vanishingly small degree of assistance by the bridge N-atom in the rate-controlling heterolysis of the neighbouring 2-substituent.

EXPERIMENTAL

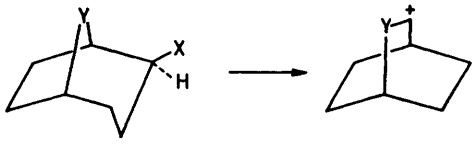
2-Cyano-8-methyl-8-azabicyclo[3.2.1]*oct-2-ene* (18).—A solution of freshly distilled methylamine (125 cm^3) and 7-cyanocyclohepta-1,3,5-triene (70.4 g, 0.60 mol) in t-butyl alcohol (250 cm^3) was heated in a closed vessel at 85 °C for 24 h. The excess of methylamine and solvent were removed *in vacuo* and the residual oil was distilled; the fraction of b.p. 115—119 °C/15 mmHg was collected (77.8 g, 87%) and shown to be 97% pure by g.l.c. On keeping the product solidified to yellow crystals, m.p. 19 °C; *m/e* 148 (M^+); $\nu_{max.}$ (film) 3 020 (=CH), 2 790 (NMe), 2 210 (CN), and 1 625 cm^{-1} (C=C); τ 3.43 (1 H, t, *J* 4 Hz), 6.60 (1 H, d, *J* 4 Hz, C-1-*H*), 6.71 (1 H, t, *J* 4 Hz, C-5-*H*), 7.63 (3 H, s, Me), and 7.1—8.8 (6 H, m, ring protons).

A solution of the nitrile (300 mg) and phenyl chloroformate (300 mg) in dichloromethane (2 cm^3) was kept at ambient temperature for 10 days. The solution was diluted with dichloromethane, washed successively with 4M-sodium hydroxide, 2M-hydrochloric acid, and water, dried and evaporated. The resulting oil crystallised under ether–light petroleum (b.p. 40—60 °C) as needles (420 mg, 82%); two recrystallisations from ethyl acetate–light petroleum gave *phenyl 2-cyano-8-azabicyclo*[3.2.1]*oct-2-ene-8-carboxylate*, m.p 91.5—5.93 °C (Found: C, 70.3; H, 5.3; N, 11.1. $C_{15}H_{14}N_2O_2$ requires C, 70.9; H, 5.6; N, 11.0%).

(±)-*Anhydroecgonine Amide* (*8-Methyl-8-azabicyclo*[3.2.1]*oct-2-ene-2-carboxamide*.—The above nitrile (18) (77.8 g) was hydrolysed by refluxing for 6 h with concentrated hydrochloric acid (500 cm^3); the hydrolysate was reduced to dryness *in vacuo*, the residue heated on a steam-bath for 2 h with thionyl chloride (500 cm^3) and the product again isolated by removal of excess of reagent and desiccation *in vacuo*. The dry residue was cooled in solid CO_2–acetone and pre-cooled aqueous ammonia (800 cm^3 of S.G. 0.880) was cautiously added with swirling. The mixture was

TABLE 2

Solvolytic data for 2-*exo*-bicyclo[3.2.1]octyl arenesulphonates



(23)
(11)
(25)

Compound	Temperature (°C)	Solvent	k/s^{-1}	$k_{rel.AcOH}$
(23; Y = NMe, X = OTs)	49.5	EtOH	8.7×10^{-6} [a]	
		AcOH	3.8×10^{-5} [b]	1
(11; Y = O, X = OBs)	49.5	AcOH	6.7×10^{-7} [c]	
(11; Y = O, X = OTs)	49.5	AcOH	2.2×10^{-7} [d]	0.0058
(25; Y = CH_2, X = OTs)	49.03	EtOH	6.6×10^{-6} [e]	
	49.03	AcOH	4.3×10^{-5} [e]	1.1

[a] Extrapolated from a plot of log *k* *vs.* $Y_{2\text{-AdOTs}}$ (slope $m = 0.57$) using data from Tables 3 and 4 (Experimental section) and ref. 19. [b] Extrapolated using $Y_{2\text{-AdOTs}} = -0.61$ for AcOH.[19] [c] Extrapolated using reported activation parameters.[4b] [d] Assuming $k_{OBs}/k_{OTs} = 3$ (D. D. Roberts, *J. Org. Chem.*, 1972, **37**, 1510). [e] Ref. 2*b*.

allowed to warm to ambient temperature during 1 h, with swirling and occasional cooling; excess of ammonia was removed by concentration *in vacuo*, potassium carbonate (400 g) was added, and the product isolated by chloroform extraction. The crude amide (67 g, 77%) had m.p. 132—140 °C, and was pure enough for subsequent conversion to tropan-2-one. Purification of a sample by four recyrstallisations from ethyl acetate gave crystals, m.p. 142—144 °C (lit.,[15] 142.5—145 °C).

Tropan-2β-ol.—(a) Anhydroecgonine amide (33.5 g) in methanol (500 cm³) was cooled to −20 °C and treated during 15 min with a mixture of 1.2M-sodium hypochlorite (130 cm³) and sodium hydroxide (10 g). The mixture was stirred vigorously and allowed to warm to ambient temperature during 1 h, and finally heated at 70 °C for 15 min. The cooled mixture was diluted with water (1 l) and the product isolated by exhaustive extraction with dichloromethane. The crude oily carbamate was refluxed with 5M-hydrochloric acid (1 l) for 1.5 h, the solution was cooled and basified by addition of 30% sodium hydroxide, and the crude ketone again isolated with dichloromethane. Distillation *in vacuo* gave tropan-2-one as a pale yellow liquid (20.0 g, 72%), b.p. 98—100 °C at 12 mmHg, shown by g.l.c. analysis to be > 98% pure. Reaction of the ketone (280 mg) with phenyl chloroformate[18] (300 mg) in dichloromethane (2 cm³) for 3 days at ambient temperature afforded N-*phenoxycarbonylnortropan-2-one*, obtained from ethyl acetate–light petroleum (b.p. 80—100 °C) as colourless needles, m.p. 108—110 °C (Found: C, 68.8; H, 5.9; N, 5.6. $C_{14}H_{15}NO_3$ requires C, 68.6; H, 6.2; N, 5.7%).

Tropan-2-one was reduced to the epimeric tropan-2-ols using the methods of Bell and Archer;[15] the 2β-ol, obtained by reduction with sodium and pentan-3-ol, was distilled *in vacuo* using a spinning-band column, and the fraction of b.p. 86—90 °C at 12 mmHg was collected and shown to be >99% pure by g.l.c. analysis.

(b) *From tropidine* (8-*methyl*-8-*azabicyclo*[3.2.1]*oct*-2-*ene*). To a cooled solution of tropidine (20.5 g) in dichloromethane (50 cm³) was added dropwise with shaking a solution of freshly distilled phenyl chloroformate (26.0 g) in dichloromethane (50 cm³). The solution was kept at ambient temperature for 24 h and then washed successively with 4M-sodium hydroxide, 2M-hydrochloric acid, and water. Evaporation of the dried solvent gave an oil which crystallised under ether; recrystallisation from ether–light petroleum (b.p. 80—100 °C) afforded *phenyl* 8-*azabicyclo*[3.2.1]*oct*-2-*ene*-8-*carboxylate* (32.8 g, 86%) as needles, m.p. 89.5—91 °C; $\nu_{max.}$ (Nujol) 3 060 (aromatic CH), 3 020 (olefinic CH), 1 710 (CO_2Ph), 1 630 (C=C stretch), and 1 590 cm⁻¹ (aromatic C=C) (Found: C, 73.4; H, 6.9; N, 6.3. $C_{14}H_{15}NO_2$ requires C, 73.3; H, 6.6; N, 6.1%).

A solution of trifluoroperacetic acid was prepared by cautious addition, during 30 min, of trifluoroacetic anhydride (27 g) to a cooled, stirred suspension of 80% hydrogen peroxide (4.4 cm³) in dichloromethane (18 cm³), followed by further stirring at 0 °C for 30 min. This was then added during 25 min to a well stirred solution of the above olefin (9.16 g) in dichloromethane (60 cm³) containing anhydrous sodium carbonate (35 g). Stirring was continued for 2.5 h, and the filtered solution was evaporated *in vacuo* and the products taken up in ether and chromatographed on alumina. Elution with ether gave successively unreacted olefin (2.25 g), *phenyl* 2α,3α-*epoxy*-8-*azabicyclo*[3.2.1]*octane*-8-*carboxylate* (0.5 g), m.p. 75—78 °C; $\nu_{max.}$ (Nujol) 1 720, 1 280—1 240, and 865—785 cm⁻¹ (Found: C, 69.2; H, 6.4; N, 5.7. $C_{14}H_{15}NO_3$ requires C, 68.6; H, 6.2; N, 5.7%); *m/e* 245 (M^+); τ ($CDCl_3$) 2.5—3.0 (5 H, m, aromatic H), 5.25 (1 H, t, *J* 6 Hz, H-1), 5.7 (1 H, br m, H-5), 6.35 (1 H, dd *J* 6 and 4 Hz, H-2β), 6.8 (1 H, t, *J* 3 Hz, H-3β), and 7.5—8.5 (6 H, m, ring protons): and *phenyl* 2β,3β-*epoxy*-8-*azabicyclo*[3.2.1]*octane*-8-*carboxylate* (2.85 g); after several recrystallisations from light petroleum (b.p. 80—100 °C) this was obtained as needles, m.p. 90.5—92 °C; $\nu_{max.}$ (Nujol) 1 720, 1 280—1 240, and 865—785 cm⁻¹ (Found: C, 68.5; H, 6.2; N, 5.7%); *m/e* 245 (M^+); τ ($CDCl_3$) 2.5—3.0 (5H, m, aromatic H), 5.58 (1 H, d, *J* 6 Hz, H-1), 5.9 (1 H, m, H-5), 6.98 (2 H, br s, H-2 and H-3), and 7.3—8.6 (6H, m, ring CH_2). This compound was obtained in rather better yield (40%) by epoxidation with benzonitrile–hydrogen peroxide in a phosphate buffer.[21]

A solution of phenyl 2β,3β-epoxy-8-azabicyclo[3.2.1]-octane-8-carboxylate (3.0 g) in anhydrous ether (70 cm³) was added with stirring and cooling during 15 min to a suspension of lithium aluminium hydride (2.0 g) in anhydrous ether (20 cm³). After stirring for 24 h, excess of reagent was destroyed by cautious addition of saturated aqueous sodium potassium tartrate (20 cm³), and the mixture was extracted with ether. The extract was washed with aqueous alkali, dried, and evaporated; the residual liquid was distilled *in vacuo* giving tropan-2β-ol (1.5 g, 87%), b.p. 88 °C at 12 mmHg; $\nu_{max.}$ (film) 3 440 (bonded OH) and 2 790 cm⁻¹ (NMe); τ ($CDCl_3$) 6.5 (2H, br, C*HOH*), 6.95 (2 H, br m, H-1, H-5), 7.82 (3 H, s, NMe), and 7.6—8.9 (8 H, m, ring CH_2).

Tropan-2β-yl Toluene-p-sulphonate (23).—A solution of tropan-2β-ol (1.0 g) in anhydrous tetrahydrofuran (6 cm³) was added with stirring under dry N_2 to sodium hydride (350 mg of 50% oil dispersion) previously washed free of oil with light petroleum. After allowing 30 min for the reaction to subside a solution of toluene-*p*-sulphonyl chloride (1.34 g) in anhydrous tetrahydrofuran (6 cm³) was added, and the mixture was stirred for 18 h. Anhydrous ether (10 cm³) was added and precipitated sodium chloride filtered off and washed with ether. Evaporation of the filtrate gave an oil which crystallised under light petroleum (b.p. 60—80 °C). Two recrystallisations from the same solvent gave the *toluene*-p-*sulphonate* (23) (750 mg, 37%), m.p. 77—77.5 °C (Found: C, 61.0; H, 7.1; N, 4.8; S, 10.9. $C_{15}H_{21}NO_3S$ requires C, 61.05; H, 7.2; N, 4.8; S, 10.9%).

Solvolysis of Azabicyclic Chlorides.—The solvents, 80% v/v ethanol–water, and 50% w/w dioxan–water, were freshly prepared from B.D.H. Ltd. AnalaR reagents. Stock solutions (25 cm³) prepared at 20 °C containing the chloride (0.5 mmol) and sodium hydroxide (40 mg) were apportioned as 2-cm³ aliquots into ampoules which were sealed under N_2 and immersed in a thermostat controlled at 85.3 ± 0.02 °C. After equilibration, ampoules were removed at regular intervals, quenched in ice-water, and liberated chloride determined by argentometric titration using the Volhard method. Reactions were followed for 2–3 half-lives, three ampoules being left for 10 half-lives to determine the infinity titre; three independent runs were made for each chloride. Rate constants were obtained by computer-assisted application of the least-squares criterion to fit the experimental data to the exponential form of the first-order rate equation, giving results (Table 1) with an average standard deviation of ±3%. Additional uncertainties arising from temperature and volume measurements lead to an estimated total standard deviation of ±7% for the values given in Table 1.

Solvolytic Rearrangement of Tropan-2β-yl Toluene-p-sulphonate (23).—A solution of the tosylate (200 mg) in 1,4-dioxan (5 cm³) and water (10 cm³) was refluxed under nitrogen for 3 h. The cooled solution was basified with 20% aqueous sodium hydroxide and the product isolated by continuous extraction with ether, giving an oil (90 mg); $\nu_{max.}$ (film) 3 400 (OH), 2 800 (MNe), and 1 720 cm^{-1} (CO). Treatment of this in ethanol–ether with 2 drops of 72% perchloric acid gave 2-methyl-2-azoniabicyclo[2.2.2]oct-2-ene perchlorate, which after recrystallisation from ethanol had m.p. 237—238 °C (lit,[22] 239 °C); $\nu_{max.}$ (Nujol) 1 690 (HC=NMe) and 1 090 cm^{-1} (ClO_4^-). The same product was obtained from solvolyses in aqueous pyridine or aqueous dioxan containing 2—3 mol equiv. sodium hydroxide; careful g.l.c. examination of crude products revealed no other volatile products. In aqueous acetone 3-acetonyl-2-methyl-2-azabicyclo[2.2.2]octane [1] was the sole isolable product.

Kinetics.—(a) *In aqueous ethanol.* *Ca.* 0.002M-solutions of the toluene-*p*-sulphonate (23) in spectroscopic ethanol–water mixtures containing 0.001M-sodium hydroxide (0.021M in one run) were placed in a thermostatted u.v. cell maintained at 49.5 ±0.1 °C and the absorbance at 262 nm ($\varepsilon_{max.}$ 622) was monitored continuously. E_∞ was obtained after 10 half-lives and at least 3 independent runs were made at each solvent composition; results are given in Table 3.

TABLE 3

Solvolytic data for tropan-2β-yl toluene-p-sulphonate in aqueous ethanol at 49.5 ± 0.1 °C

Percentage [a] EtOH–H_2O (v/v)	[NaOH]/ 10^3M	Reaction (%)	10^4k_1 [b]/s^{-1}
48	1.0	64, 65, 88	5.19 ± 0.29 [c]
57.4	1.0	71, 73, 77	3.02 ± 0.06 [c]
57.4	21.0	62	3.25
71.7	1.0	60, 80, 81	1.40 ± 0.003 [c]
76.5	1.0	70	1.03
80.0			0.83 [d]
81.5	1.0	72, 78, 50, 74	0.744 ± 0.017 [c]

[a] Percentage volumes at 20 °C before mixing. [b] Mean of number of independent runs indicated in column 3. [c] Mean deviation. [d] Interpolated from a plot of log k *vs.* $Y_{2\text{-AdOTs}}$ values derived from data given in ref. 19.

TABLE 4

Solvolytic data for tropan-2β-yl toluene-*p*-sulphonate in aqueous acetone at 49.5 + 0.1 °C

Percentage acetone–water [a]	Temperature (°C)	10^4k_1/s^{-1}
25	49.5 [c]	18.4
40	49.5	7.18
50	49.5	3.96
60	49.5	1.95
66.7	49.5	1.26
80	49.5	0.42
25 [b]	49.5	20.8
25	40.4 [c]	6.88
25	32.3 [c]	3.32

[a] Solutions pre-adjusted to, and maintained at pH 10 (except where indicated) by automatic addition of 0.1M-sodium hydroxide in the appropriate solvent. [b] Reaction maintained at pH 11. [c] Calculated activation parameters: $\Delta H^\ddagger$ 24.3 kcal mol^{-1}, $\Delta S^\ddagger$ 4.3 cal mol^{-1} K^{-1}.

(b) *In aqueous acetone.* Solvent mixtures were prepared using purified acetone and distilled water measured as percentage volumes of acetone–water at 20 °C before mixing. In a typical run, solvent (50 cm³) contained in a thermostatted (49.5 ± 0.1 °C) reaction vessel equipped with stirrer, calomel and glass electrodes, and titrant delivery tube, was adjusted to pH 10.0 by addition of the appropriate small volume of 0.1M-sodium hydroxide in the appropriate solvent. After temperature equilibration, the finely powdered tosylate (30—50 mg) was added and the solution was maintained at pH 10.0 by automatic addition of 0.1M-sodium hydroxide, the volume added being recorded as a function of time. All reactions were followed for at least 10 half-lives but the infinity titres were considered to be unreliable owing to the very small volumes involved; accordingly the data was treated by the Guggenheim method, using pairs of readings at a separation of 600 s; rate constants are listed in Table 4.

[0/722 *Received*, 16*th May*, 1980]

REFERENCES

[1] Part 1, J. W. Bastable, A. J. Cooper, I. R. Dunkin, J. D. Hobson, and W. D. Riddell, *J. Chem. Soc., Perkin Trans. 1*, preceding paper.

[2] (*a*) H. M. Walborsky, M. E. Baum, and A. A. Youssef, *J. Am. Chem. Soc.*, 1959, **81**, 4709; 1961, **83**, 988; H. M. Walborsky, *J. Org. Chem.*, 1968, **28**, 3214; H. Kwart and J. L. Irvine, *J. Am. Chem. Soc.*, 1969, **91**, 5541; (*b*) H. L. Goering and M. F. Sloan, *ibid.*, 1961, **83**, 1992; (*c*) H. L. Goering and G. N. Fickes, *ibid.*, 1968, **90**, 2862.

[3] J. C. Martin and P. D. Bartlett, *J. Am. Chem. Soc.*, 1957, **79**, 2533.

[4] (*a*) L. A. Paquette and P. C. Storm, *J. Am. Chem. Soc.*, 1970, **92**, 4295; (*b*) L. A. Paquette, I. R. Dunkin, J. P. Freeman, and P. C. Storm, *ibid.*, 1972, **94**, 8124.

[5] A. T. Bottini, C. A. Grob, E. Schumacher, and J. Zergenyi, *Helv. Chim. Acta*, 1966, **49**, 2516; C. A. Grob, *Angew. Chem. Int. Ed. Engl.*, 1969, **8**, 535.

[6] J. W. Wilt and W. J. Wagner, *J. Am. Chem. Soc.*, 1968, **90**, 6135.

[7] J. W. Bastable, J. D. Hobson, and W. D. Riddell, *J. Chem. Soc., Perkin Trans. 1*, 1972, 2205.

[8] I. Tabushi, Y. Tamaru, Z. Yoshida, and T. Sugimoto, *J. Am. Chem. Soc.*, 1975, **97**, 2886.

[9] R. R. Fraser and R. B. Swingle, *Can. J. Chem.*, 1970, **48**, 2065.

[10] B. Capon and S. P. McManus, 'Neighbouring Group Participation,' Plenum Press, New York, 1976, Vol. 1, Chap. 6.

[11] *Cf.* ref. 7, and refs. therein.

[12] M. J. Blandamer, H. S. Golinkin, and R. E. Robertson, *J. Am. Chem. Soc.*, 1969, **91**, 2678.

[13] S. Winstein, L. L. Ingraham, and E. Grunwald, *J. Am. Chem. Soc.*, 1948, **70**, 821.

[14] C. A. Grob, *Angew. Chem. Int. Edn. Engl.*, 1976, **15**, 569.

[15] M. R. Bell and S. Archer, *J. Am. Chem. Soc.*, 1958, **80**, 6147; 1960, **82**, 4642; *cf.* also W. A. M. Davies, A. R. Pinder, and I. G. Morris, *Tetrahedron*, 1962, **18**, 405.

[16] E. R. Atkinson and D. D. McRitchie, *J. Org. Chem.*, 1971, **36**, 3240.

[17] C. Grundmann and G. Ottmann, *Liebigs Ann. Chem.*, 1957, **605**, 24.

[18] J. D. Hobson and J. G. McCluskey, *J. Chem. Soc.*, 1967, 2015.

[19] F. L. Schadt, T. W. Bentley, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, 1976, **98**, 7667.

[20] T. W. Bentley and P. v. R. Schleyer, *J. Am. Chem. Soc.*, 1976, **98**, 7658; 'Advances in Physical Organic Chemistry,' Academic Press, New York, 1977, **14**, 1.

[21] Y. Ogata and Y. Sawaki, *Tetrahedron*, 1964, **20**, 2065.

[22] W. Schneider and R. Dillman, *Arch. Pharm.*, 1965, **298**, 43.