Mass spectra were obtained through the courtesy of Dr. J. F. Siuda, University of Pittsburgh.

Analytical glpc was carried out on an F and M Model 700 using a 0.25 in. × 6 ft 10% Carbowax column. Preparative glpc was done on a 0.50 in. × 12 ft 10% SE-30 column. The percentage yields reported correspond to peak area. Nmr spectra were recorded on a Varian A-60 spectrometer using tetramethylsilane as an internal standard.

Glassware used in the handling of the mixed ketals was washed with dilute sodium hydroxide and oven dried.

exo-Norbornyl methyl ether and ethyl *exo*-norbornyl ether were prepared by the acid-catalyzed addition of methanol and ethanol, respectively, to norbornene.[11] *endo*-Norbornyl methyl ether and *endo*-norbornyl ethyl ether were prepared by the reaction of *endo*-norborneol[12] and sodium hydride in dimethoxyethane with methyl iodide and ethyl iodide, respectively.

Starting Ketals.—The dimethyl, diethyl, and diisopropyl ketals of norcamphor are most easily prepared by the acid-catalyzed reaction of norcamphor and trimethyl orthoformate, triethyl orthoformate, and triisopropyl orthoformate,[13] respectively, in the appropriate alcohol. The reaction of triisopropyl orthoformate and norcamphor was followed by the appearance of the formate hydrogen and the disappearance of the orthoformate hydrogen in the nmr. The equilibrium mixture has about one-third conversion to the product.

2-Chloronorbornyl Ethers.—The preparative procedure was to add the starting norcamphor ketal to a 5% molar excess of PCl_3 which is stirring in an ice bath. The ice bath was removed and the mixture was stirred for 1.5 hr. The mixture was distilled using an oil bath which was kept below 65°. Fractionation was accomplished by reducing the pressure of the distillation. The receiving flask was in an ice–calcium chloride slurry, and the pump was protected by a Dry Ice–acetone trap and a liquid nitrogen trap. Yields were high and free of starting ketals, but norcamphor, which appears to be a thermal decomposition product, accounts for *ca.* 10% of the products.

Mixed Ketals.—The preparation of norcamphor *exo*-ethyl *endo*-methyl ketal (**1b**) is representative and is given here. To 4.60 g (100 mmol) of ethanol, 20 ml of triethylamine, and 100 ml of diethyl ether mechanically stirred in an ice bath, 11.0 g (68 mmol) of 2-chloronorbornyl methyl ether in 20 ml of diethyl ether was added over 10 min. A thick white precipitate of triethylamine hydrochloride formed. The ice bath was removed and after 15 min 80 ml of 10% sodium carbonate was added. The ether layer was separated and washed twice with 20 ml of water. The ether was dried ($CaSO_4$), concentrated, and distilled.

When the alcohol being added was isopropyl alcohol, and particularly *tert*-butyl alcohol, a larger excess of alcohol was necessary to minimize the dehydrohalogenation product, norbornenyl methyl ether.

Distillation through a vacuum-jacketed column typically gave yields of 60–70%. Physical data for the mixed ketals is tabulated in Table II.

endo-Norbornyl isopropyl ether was collected by glpc from the hydrogenolysis reaction. *Anal.* Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.70; H, 11.62.

endo-Norbornyl *tert*-butyl ether was collected by glpc from the hydrogenolysis reaction. *Anal.* Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.39; H, 11.90.

Hydrogenolysis of Mixed Ketals.—After 0.12 g of $LiAlH_4$ had refluxed for 1 hr in 20 ml of diethyl ether, the solution was added to a solution of 1.20 g of $AlCl_3$ and 15 ml of ether in an ice bath. This yields 12.0 mmol of dichloroalane, which is stirred for 0.5 hr without the ice bath. Then 6.29 mmol of a mixed ketal (1.00 g of **1a**, 1.07 g of **1b** and **1e**, 1.16 g of **1c** and **1f**, and 1.25 g of **1d**) in 5 ml of ether was added over 5 min. After 10 min of stirring 20% NaOH was added until the ether was clear and the aluminum salts were precipitated. The products were determined by glpc and all products were collected by preparative glpc. Retention times, ir spectra, and nmr spectra were obtained for all products. A mass spectrum was obtained for the hydrogenolysis product of **1a**.

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[11] S. J. Cristol, W. K. Seifert, D. W. Johnson, and J. B. Jutale, *J. Amer. Chem. Soc.*, **84**, 3918 (1962).

[12] H. C. Brown and H. R. Deck, *ibid.*, **87**, 5620 (1965).

[13] Prepared by the distillation of methanol from an acid-catalyzed trimethyl orthoformate and isopropyl alcohol mixture. Dynamitnoble A.-G., Netherlands Appl. 6,500,507; *Chem. Abstr.*, **64**, 601g (1966).

Registry No.—**1a**, 33016-02-3; **1b**, 33016-03-4; **1c**, 33016-04-5; **1d**, 33016-05-6; **1e**, 33068-14-3; **1f**, 33016-06-7; **6f**, 33016-07-8; **7d**, 33016-08-9; $AlCl_2H$, 13497-97-7.

On the Mechanism of the Reaction of 1-*tert*-Butyl-3-azetidinyl Tosylate with Methanolic Potassium Cyanide and with Solvent[1]

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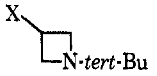
Received August 6, 1971

Recently Chen, *et al.*, described the synthesis[2] and some reactions[2,3] of 1-*tert*-butyl-3-azetidinyl tosylate (**1a**). Deyrup and Moyer[4] have determined the solvolysis rate of **1a** in ethanol and concluded that **1a** underwent assisted ionization, probably by transannular nitrogen participation forming intermediate **2**. A similar conclusion was drawn by Gaertner,[5] who studied the solvolysis of **1b** in 50% aqueous ethanol.



1a, X = OTs
b, X = Cl
c, X = CN
d, X = OMe
e, X = OH

2

As a continuation of our studies[6] of the reactions of functionally substituted azetidines, we have reexamined the solvolysis reactions of **1a**, since previous studies[4,5] have not clearly demonstrated the importance (or lack thereof) of direct nucleophilic attack on the substrate by solvent, nor have previous rate data been sufficiently precise for computation of activation parameters, which might be compared with those of the solvolysis reactions of cyclobutyl tosylates.

Results and Discussion

If it could be shown that the rate of the reaction of **1a** with nucleophiles, which are more nucleophilic than solvent, were independent of the concentration of nucleophile (and first order in substrate), it could safely be deduced that direct nucleophilic displacement of tosylate by the poorer nucleophile, solvent, was unimportant. Furthermore, except for a small "salt

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[1] Presented in part at the 80th Annual Meeting of the Nebraska Academy of Sciences, Lincoln, Nebraska, April 1970.

[2] T.-Y. Chen, T. Sanjiki, H. Kato, and M. Ohta, *Bull. Chem. Soc. Jap.*, **40**, 2401 (1967).

[3] T.-Y. Chen, H. Kato, and M. Ohta, *ibid.*, **41**, 712 (1968).

[4] J. A. Deyrup and C. L. Moyer, *Tetrahedron Lett.*, 6179 (1968).

[5] V. R. Gaertner, *J. Org. Chem.*, **35**, 3952 (1970).

[6] See, for example, (a) E. Doomes and N. H. Cromwell, *J. Heterocycl. Chem.*, **6**, 153 (1969); (b) *J. Org. Chem.*, **34**, 319 (1969); (c) R. M. Rodebaugh and N. H. Cromwell, *J. Heterocycl. Chem.*, **6**, 439 (1969); (d) **8**, 19 (1971).

effect," the first-order rate constant (k_1) for the reaction of **1a** with nucleophile should be identical with the rate of solvolysis of **1a** in the same solvent.

We chose to follow the reaction of **1a** with methanolic potassium cyanide.[2] This nucleophile and solvent were chosen because the resulting nitrile[2] has been shown to be a useful intermediate in the preparation of 3-aroylazetidines[6a,7,8] and 1-*tert*-butylazetidine-3-carboxylic acid.[2]

The reaction of **1a** with methanolic potassium cyanide yielded **1c** (determined by glc and pmr analysis of crude product); however, small quantities of **1d** and an unidentified substance were formed when the reaction mixture was injected into the glc before the reaction was complete.

The reaction of **1a** with methanolic potassium cyanide at 30° was found to be too rapid for accurate determination of cyanide ion (by titrating aliquots of the reaction mixture with silver nitrate, Liebig determination). Consequently, the reaction was followed at 0°. First-order and second-order rate constants were calculated for this reaction; see Table I. These data are clearly much more consistent with the unimolecular reaction than with the bimolecular reaction, thus supporting an ionic intermediate as was assumed by Gaertner[5] and Deyrup and Moyer.[4]

TABLE I

RATE CONSTANTS[a] CALCULATED FOR THE REACTION OF **1a** WITH METHANOLIC POTASSIUM CYANIDE AT 0°

$[\mathbf{1a}]^a \times 10^2$	$[\mathrm{CN}^-]^b \times 10^2$	k_1,[c] sec^{-1}	k_2,[d] l. $\mathrm{mol}^{-1}\,\mathrm{sec}^{-1}$
7.579	7.574	8.13×10^{-7}	1.51×10^{-5}
7.579	10.08	8.80×10^{-7}	0.94×10^{-5}
5.001	7.595	8.35×10^{-7}	1.16×10^{-5}

[a] Single determinations. [b] In mol/l. [c] For rate = $k_1[\mathbf{1a}]$. [d] For rate = $k_2[\mathbf{1a}][\mathrm{CN}^-]$.

It appeared advisable to determine the relative basicities of **1a** and the products arising from solvolysis of **1a** under the conditions of the solvolysis reaction, such that appropriate corrections could be made, if necessary, in the rate equation for protonated **1a**. The solvolysis products are substantially better bases than **1a**, indicating that the concentration of protonated **1a** is always relatively low. Furthermore, the relative basicities are reasonably independent of temperature (see Table II).

TABLE II

RELATIVE BASICITIES OF **1a** AND THE SOLVOLYSIS PRODUCTS

Temp, °C	Solvent	(K_a of **1a**/ K_a of **1d**)[a,b]	(K_a of **1a**/ K_a of **1e**)[b,c]
25	Methanol	63.5	
	60% Aqueous acetone		863
36.2	Methanol	48	
	60% Aqueous acetone		851

[a] Obtained as the antilog of differences in pK_a's of **1d** and **1a**. [b] See Experimental Section for the methods of pK_a determination. [c] Obtained as the antilog of differences in pK_a's of **1e** and **1a**.

Methanolysis of **1a**, both in the absence of and in the presence of a tenfold excess of triethylamine, yielded only **1d** (by pmr and glc); no ring contraction[5,9] or ring-opened[8] products were observed. Furthermore, no enhancement of the rate of methanolysis was observed in the presence of triethylamine; rate enhancement would be anticipated if the reaction involved direct displacement of tosylate.

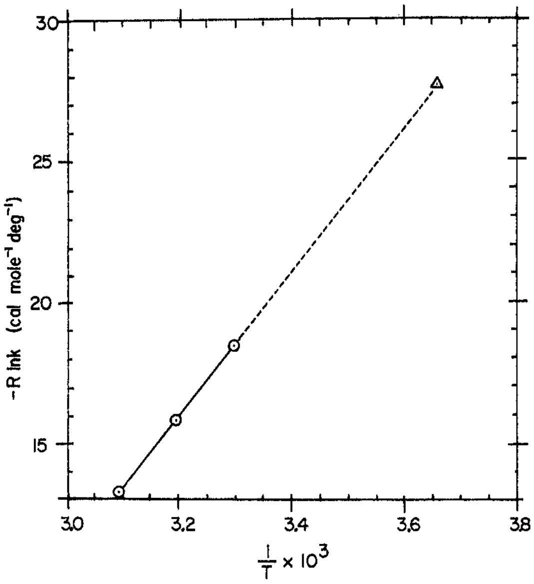
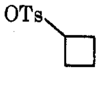


Figure 1.—Activation plot for reactions in methanol: ⊙, for solvolysis reactions; △, for reaction with methanolic potassium cyanide.

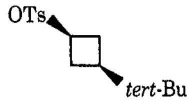
The rate of methanolysis of **1a**, at 30°, is in reasonable agreement with the qualitative estimate (6×10^{-5} sec^{-1}, see above) of the rate of the reaction of **1a** with methanolic potassium cyanide. Indeed the data for the reaction of **1a** with methanolic potassium cyanide at 0° fall on the extrapolation of the line in the activation plot (see Figure 1) for the methanolysis reaction. We feel that these facts are indicative of the similarity in rates and presumably intermediates for these reactions.

The data in Table III result from application of the simple first-order rate law (rate = $k_1[\mathbf{1a}]$). The similarity in the rates of methanolysis with and without the presence of added amine indicate that the rate expression is adequately represented by the simple first-order rate law.

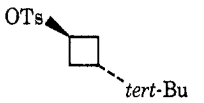
The hydrolysis of **1a** in aqueous acetone gave **1e** as the only product (by glc). The data for the hydrolysis in 60% aqueous acetone may be compared with those reported[10] for cyclobutyl tosylates (**3a–c**). A moderate



3a



3b



3c

increase in the hydrolysis rate of the heterocyclic tosylate relative to **3a**[10] or **3c**[10] (a large increase relative to **3b**[10]) is apparent. In view of the rather large uncertainty in $\Delta H^{\ddagger}$ in our investigation, it is not possible to quantitatively compare the activation parameters (or their significance) for the solvolysis reactions of **1a** and **3a–c** in 60% aqueous acetone. However, it is apparent that the enthalpies of activation for the

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(7) R. H. H., Ph.D. Dissertation, University of Nebraska, Lincoln, Nebraska, 1971.

(8) R. H. Higgins, E. Doomes, and N. H. Cromwell, *J. Heterocycl. Chem.*, in press.

(9) V. R. Gaertner, *Tetrahedron Lett.*, 5919 (1968).

(10) P. v. R. Schleyer, P. Le Perches, and D. J. Raber, *ibid.*, 4389 (1969).

TABLE III

MEAN CONDUCTIMETRIC SOLVOLYSIS RATES OF 1-*tert*-BUTYL-3-AZETIDINYL TOSYLATE

Solvent	Temp, °C	Rate, sec^{-1}	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
MeOH	30.0	$(9.09 \pm 0.39) \times 10^{-5}$		
MeOH + Et_3N[a]	30.0	$(9.00 \pm 0.17) \times 10^{-5}$	25.3 ± 1	6.3[b]
	40.0	$(3.38 \pm 0.03) \times 10^{-4}$		
	50.0	$(1.29 \pm 0.07) \times 10^{-3}$		
50% aqueous acetone	15.0	$(4.88 \pm 0.10) \times 10^{-5}$	22.8 ± 0.5	0.8
	30.0	$(3.61 \pm 0.08) \times 10^{-4}$		
	45.5	$(2.42 \pm 0.05) \times 10^{-3}$		
60% aqueous acetone	15.0	$(3.49 \pm 0.14) \times 10^{-5}$	22.05 ± 1	2.2[b]
	30.0	$(2.69 \pm 0.11) \times 10^{-4}$		
	45.5	$(1.55 \pm 0.03) \times 10^{-3}$		

[a] Contains a tenfold excess of triethylamine. [b] In view of the rather large variance in $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$ is probably valid to only ±3 eu.

solvolyses of the carbocyclic (**3a**,**b**) and heterocyclic (**1a**) tosylates are very similar in 60% aqueous acetone, and that the rate increase observed in the solvolysis of **1a** relative to **3a**–**c** is primarily due to $\Delta S^{\ddagger}$.

It is interesting that the enthalpies of activation for these tosylates compare so favorably. The enthalpy of activation for the solvolysis of **1a** may be the result of a delicate balance of inductive electron withdrawal from the cationic site by the nitrogen atom and stabilization of the cation by charge dispersal to the nitrogen atom by anchimeric assistance.[11] It seems fortuitous that $\Delta H^{\ddagger}$ for the solvolysis of **1a** and of **3a** or **3b** are identical, within experimental error, particularly in view of the uncertainty[12] surrounding the nature of the intermediate in the solvolysis of cyclobutyl tosylates.

The large values of $\Delta S^{\ddagger}$ observed in the solvolysis reactions of **1a** may be interpreted as additional support for an ionic intermediate.[13] Indeed, one is tempted to argue that the value of $\Delta S^{\ddagger}$ (in 60% aqueous acetone), relative to **3a**–**c**, is indicative of the significance of anchimeric assistance[14] by the nitrogen atom *in the transition state* involved in the solvolysis of **1a**.

The effects of substitution of C-2 on the solvolysis rates and product distribution are presently being pursued. The results of this study may give a more definitive insight into the nature of the N–C-3 bond.

Experimental Section

1-*tert*-Butyl-3-azetidinyl Tosylate (1a).—The synthesis of this compound has been described.[8]

Absolute Methanol.—Commercial absolute methanol was further dried by distillation from magnesium methoxide.[15]

Relative Basicities.—Absolute pK_a values were not determined (the null point of the pH meter being arbitrarily set at 7.07 and 7.00 for solvent at 25 and 36.25°, respectively).

The "basicity constants" of **1d** (in methanol) and **1e** (in 60% aqueous acetone) were determined by recording the "pH" of a solution of the azetidine while hydrogen chloride, in the appropriate solvent, was added at constant rate. The "pK_a" is the "pH" at the half-equivalence point.

The "basicity" constants of **1a** were determined by dissolving 1 equiv of **1a** in a solution of the appropriate solvent containing 0.5 equiv of anhydrous *p*-toluenesulfonic acid and immediately determining the "pH."

Method of Determining Remaining Cyanide.—Aliquots (5 ml) of the methanolic reaction mixture were added to *ca.* 30 ml of ice water. The resulting solution was covered with *ca.* 10 ml of ether and titrated with 0.05–0.1 *N* silver nitrate solutions (the volumes being recorded to 0.001 ml). The reaction with cyanide was followed through *ca.* one half-life; the solvolysis reactions were followed for 4–10 half-lives.

Registry No.—**1a**, 17358-65-5; methanol, 67-56-1; potassium cyanide, 151-50-8; acetone, 67-64-1; triethylamine, 121-44-8.

Acknowledgments.—The authors wish to thank Mr. Gary M. Underwood for the use of his computer program for determining solvolysis rates and Dr. C. A. Kingsbury for his valuable discussions and suggestions. This research was supported in part by Grant CA-02931 from the National Cancer Institute of the United States Public Health Service and by the University of Nebraska Damon Runyon Memorial Fund for Cancer Research.

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[11] We have no evidence for participation of nonclassical ions in the solvolysis of **1a**.

[12] See, for example, R. H. Mazur, W. N. White, D. A. Semenov, C. C. Lee, M. S. Silver, and J. D. Roberts, *J. Amer. Chem. Soc.*, **81**, 4390 (1959); R. E. Davis and A. Ohno, *Tetrahedron*, 2063 (1968).

[13] E. F. Jenny and S. Winstein, *Helv. Chim. Acta*, **41**, 807 (1958); S. Winstein and R. Heck, *J. Amer. Chem. Soc.*, **78**, 4801 (1956); D. J. Cram, *ibid.*, **86**, 3767 (1964).

[14] Anchimeric assistance, *via* phenonium ions, seems to increase the value of $\Delta S^{\ddagger}$. See the data of C. J. Kim and H. C. Brown, *ibid.*, **91**, 4287 (1969); **91**, 4289 (1969); C. J. Lancelot and P. v. R. Schleyer, *ibid.*, **91**, 4291 (1969).

[15] A. I. Vogel, "A Text-Book of Practical Organic Chemistry, 3rd ed, Wiley, New York, N. Y., 1957, p 169.

C-Alkylation of Active Methylene Compounds by Means of Alcohols. VII.[1] Synthesis of α-Substituted Phenylacetonitriles from α-Phenylacetoacetonitrile

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In a preceding paper of this series we have reported that phenylacetonitrile **1** is readily alkylated by means of four to five times the calculated amount of alcohols in the presence of metallic sodium and appropriate ester to give α-substituted phenylacetonitrile **3**. Having demonstrated that the alkylation proceeds *via* α-phenylacetoacetonitrile sodium salt **2** (Scheme I, **1** → **2** → **1** → **3**), we now wished to study the possibility that the reaction starting with **2** might be of general application for the preparation of α-substituted phenylacetonitrile **3**. By simply heating a mixture of **2** and alcohol, a series of α-substituted phenylacetonitrile

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[1] Paper VI: S. Miyano and N. Abe, *J. Org. Chem.*, **36**, 2948 (1971).

[2] To whom inquiries should be sent.