Cyclobutylcarbinyl p-Bromobenzenesulfonate Solvolysis. 1-Aryl Substituent Effect

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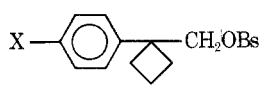
The solvolysis rates of a series of para-substituted 1-phenylcyclobutylcarbinyl brosylates has been determined in acetic acid and 2,2,2-trifluoroethanol. The data support an exclusively anchimerically assisted ionization, but the magnitude of ρ in a ρ-σ^+ plot and the value of k^{OMe}/k^{NO_2} indicate that the ability of the cyclobutane ring to compete with aryl-assisted ionization is significant.

The effect of one-ring substituents upon the rates and solvolysis products of cyclopropylcarbinyl derivatives has been the subject of considerable research.[1] In contrast, the study of one-ring substituent effects upon the rates and solvolysis products of the closely related cyclobutylcarbinyl derivatives has been the subject of only a preliminary investigation.[2] Wilt and Roberts found in their study of ring-size effects upon the acetolysis of neophyl-like substrates that 1-phenylcyclobutylcarbinyl brosylate (4-H) undergoes acetolysis (1) with only slightly faster rates than those of either cyclobutylcarbinyl or neophyl brosylate and (2) accompanied by 1,2-phenyl rearrangement rather than ring expansion.

The latter finding strongly indicates that phenyl neighboring-group participation dominates over that by the cyclobutyl group in the product-controlling step but the similar acetolysis rates for cyclobutylcarbinyl brosylate, 4-H, and neophyl brosylate (11.1×10^{-5}, 21.0×10^{-5}, and 6.84×10^{-5} sec^{-1}, respectively, at 75°[3,4]) leaves open the question as to whether anchimeric assistance to ionization by the two neighboring groups, cyclobutyl and phenyl, is similar or not provided relief of steric strain is equivalent for both substrates.[5]

In neighboring-group participation by phenyl and cycloalkyl groups under competitive circumstances, a convenient and well-established diagnostic test is the measurement of the para-substituent effect on the rate of reaction, especially in reference to some model substrate. Thus, we report in this paper the synthesis and solvolytic investigation of a series of 1-*p*-X-phenylcyclobutylcarbinyl derivatives.



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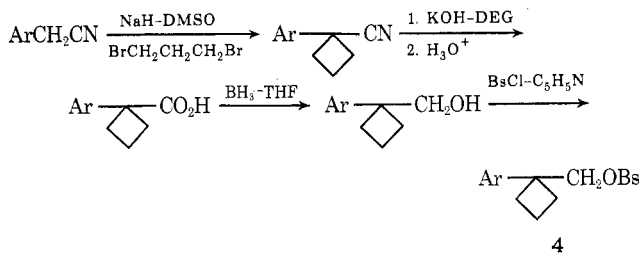
X = CH_3O, CH_3, H, Cl, NO_2

The data indicate that all substrates investigated undergo solvolysis *via* the k_Δ pathway and that the ability of the cyclobutane ring to compete with the aryl group in anchimeric assistance to the ionization of 4 is significant.

The synthesis of the 1-*p*-X-phenylcyclobutylcarbinyl brosylates was accomplished as shown in Scheme I. The key step in this synthesis scheme is the cyclization of the various para-substituted phenylacetonitriles in reasonable yield. The older, sodium amide–ether, high-dilution procedure[7] gives very low[8] yields of cyclic product, which has discouraged synthetic activity in this area. In sharp contrast, the NaH–DMSO procedure[9] affords higher yields of cyclization product than polymer.

Preparation of 1-*p*-nitrophenylcyclobutylcarbinyl brosylate was attended with special problems owing to the sensitivity of the nitro group to strongly basic conditions. Modification of a procedure[1f] used in the synthesis of 1-*p*-nitrophenylcyclopropylcarbinyl tosylate gave 1-*p*-nitrophenylcyclobutylcarbinyl brosylate as outlined in Scheme II.

Scheme I



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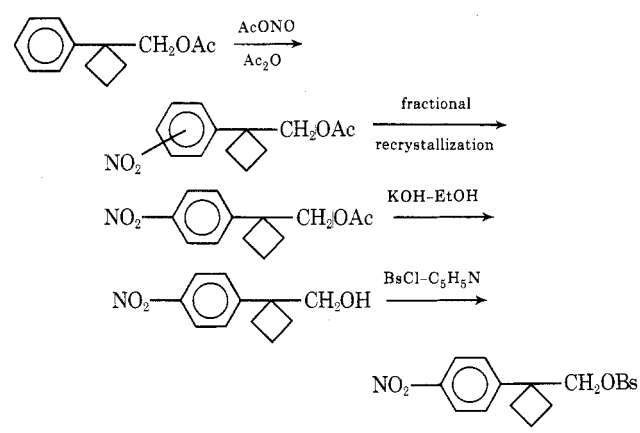
Scheme II



Results and Discussion

The kinetic data are summarized in Table I. Each of these esters was allowed to solvolyze in the indicated solvent and the course of the reaction was followed by titrating the liberated *p*-bromobenzenesulfonic acid. All reactions were strictly first order in *p*-bromobenzenesulfonic acid up to at least 80% conversion and furnished, within experimental error, 100% of the theoretical amount of acid present.

The observation[2] that 1-phenylcyclobutylcarbinyl brosylate yields exclusively rearranged products supports[10,11,12] a k_Δ pathway and is corroborated by the linear correlation (correlation coefficient 0.99) of log k_t for the 1-*p*-X-phenylcyclobutylcarbinyl brosylates with log k_t for the corresponding para-substituted neophyl brosylates (Figure 1). Both Coke[13] and Winstein[14] have demonstrated a good linear correlation between log k_t for the acetolysis of para-substituted neophyl tosylates at 75° and log k_Δ for the acetolysis of corresponding para-substituted β-arylethyl tosylates at the same temperature.

The range of ΔS^* for the acetolysis reactions recorded in Table I are also in agreement with those characteristic[15] of anchimerically assisted ionization (k_Δ). The ΔS^*

Table I
Summary of Solvolysis Rates for Para-Substituted 1-Phenylcyclobutylcarbinyl Brosylates

Registry no.	Para substituent[a]	Solvent[b]	Temp, °C	k_t, 10^5 sec^{-1}	ΔH^*, kcal/mol	ΔS^*, eu
50978-03-5	CH_3O	AcOH	45	8.8	22.0	−7
	CH_3O	AcOH	55	24.0		
	CH_3O	AcOH	65	74.4		
	CH_3O	AcOH	75	180		
	CH_3O	CF_3CH_2OH	25	25	16.7	−19
	CH_3O	CF_3CH_2OH	35	74		
	CH_3O	CF_3CH_2OH	45	183		
	CH_3O	CF_3CH_2OH	55	400		
50978-04-6	CH_3	AcOH	45	1.23	24.7	−1
	CH_3	AcOH	55	4.9		
	CH_3	AcOH	65	15.5		
	CH_3	AcOH	75	49		
	CH_3	CF_3CH_2OH	45	49	18.9	−19
	CH_3	CF_3CH_2OH	55	126		
	CH_3	CF_3CH_2OH	60	200		
	CH_3	CF_3CH_2OH	65	330		
50978-05-7	H	AcOH	45	0.62[c]	25.9	−1
	H	AcOH	55	1.97		
	H	CF_3CH_2OH	35	5.0	19.8	−19
	H	CF_3CH_2OH	45	15.5		
	H	CF_3CH_2OH	55	45.8		
	H	CF_3CH_2OH	65	107		
50978-06-8	Cl	AcOH	45	0.26	25.8	−3
	Cl	AcOH	55	0.92		
	Cl	AcOH	65	2.9		
	Cl	AcOH	75	9.5		
	Cl	CF_3CH_2OH	45	5.6	16.4	−26
	Cl	CF_3CH_2OH	55	13.7		
	Cl	CF_3CH_2OH	60	21		
	Cl	CF_3CH_2OH	65	30		
50978-07-9	NO_2	AcOH	55	0.186	27.5	0
	NO_2	AcOH	65	0.66		
	NO_2	AcOH	75	2.4		
	NO_2	CF_3CH_2OH	45	0.45	22.8	−11
	NO_2	CH_3CH_2OH	75	12.2		

[a] Initial concentration 0.015–0.030 *M*. [b] All runs in 2,2,2-trifluoroethanol buffered with urea at a concentration 10% in excess of theoretical amount of liberated *p*-bromobenzenesulfonic acid. [c] Compares with literature[2] value of 0.622×10^{-5} sec^{-1}.

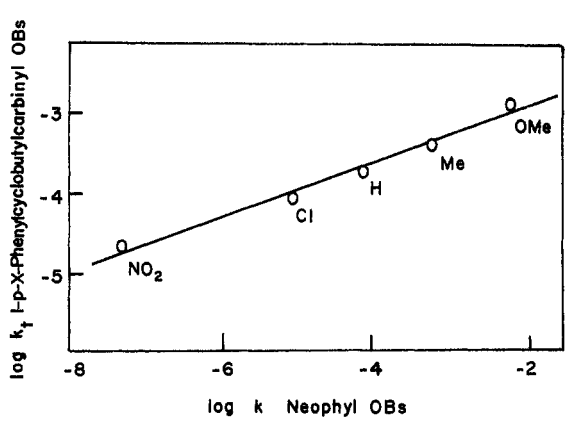


Figure 1. The linear dependence of log k_t for 1-*p*-X-phenylcyclobutylcarbinyl brosylates on log k for correspondingly para-substituted neophyl brosylates in AcOH at 75°.

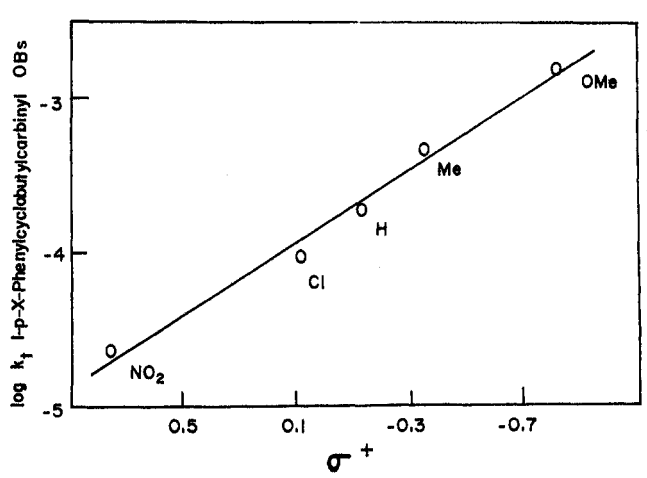


Figure 2. The linear dependence of log k_t for 1-*p*-X-phenylcyclobutylcarbinyl brosylates in AcOH at 75° on σ^+.

values for the trifluoroethanolysis reactions, on the other hand, contrast with those for acetolysis and are reminiscent of the contrasting ΔS^* values reported[1f] for 1-phenylcyclopropylcarbinyl tosylate in acetic acid and sulfolane.

A plot of log k_t for the 1-*p*-X-phenylcyclobutylcarbinyl brosylates against the Hammett σ constants[16] is nonlinear owing to greater than expected solvolysis rates for the *p*-methyl and *p*-methoxy compounds. The kinetic data are correlated (Figure 2) by use of σ^+ values,[17] the reaction constant, ρ, having a value of −1.0 (correlation coefficient 0.98). The sign of this ρ value suggests direct interaction between the para substituents and the developing cationic center in the acetolysis transition state; however, the magnitude of ρ for 4 is significantly lower than the −2.96 value of ρ reported[18] for the acetolysis of corresponding para-substituted neophyl brosylates, but quite similar in magnitude to the −0.9 value of ρ calculated[1f] for the acetolysis of corresponding para-substituted 1-phenylcyclopropylcarbinyl tosylates.

This difference in sensitivity to para substituents is conveniently analyzed by the use of the k^{OMe}/k^{NO_2} ratio data collected in Table II. As one can readily see, the ratio varies over three powers of ten, having a value of

Table II
Sensitivity of Selected Substrates to Para Substituents in Acetolysis Reactions, 75°

Compd	$k^{p\text{-OMe}}/k^{p\text{-NO}_2}$	Ref
Neophyl brosylate	80,000	18, 19
1-Phenylcyclobutylcarbinyl brosylate	75	
1-Phenylcyclopropylcarbinyl tosylate	39[a]	1f

[a] At 30°.

80,000 for the para-substituted 1-phenylcyclopropylcarbinyl tosylate series.

Since it is generally agreed[14,20] that neophyl arenesulfonates ionize exclusively with aryl assistance, and it has been clearly demonstrated[1] that the 1-phenylcyclopropylcarbinyl tosylate undergoes solvolysis without aryl assistance, the $k^{p\text{-OMe}}/k^{p\text{-NO}_2}$ ratio provides a useful scale for measuring the extent of charge dispersal into the benzene ring.

Accordingly, the low $k^{p\text{-OMe}}/k^{p\text{-NO}_2}$ ratio for the 1-phenylcyclobutylcarbinyl brosylate series indicates only a limited charge dispersal into the aryl substituent and strongly suggests that the rate acceleration[21] is due to cyclobutyl participation in the transition state leading to the first-formed cationic intermediate. This situation is very reminiscent of the solvolytic behavior of 1-phenylcyclopropylcarbinyl tosylate,[1] a first-formed intimate ion pair stabilized by cyclopropane ring σ interaction which undergoes significant orbital and structural reorganization before eventual capture by solvent.

Mechanistically these data can be discussed in terms of two reaction schemes (Scheme III and IV). Scheme III, involving an aryl-bridged species as the first-formed, rate-controlling intermediate, is considered unlikely owing to the very weak response to para substituents. Some variation of Scheme IV involving either a bisected cyclobutylcarbinyl cation, 4′, or cyclobutyl edge participation, 4″, is consistent with the experimental data. In this regard the relative rate data summarized in Table III are instructive, for they reveal that the anchimeric assistance[22] provided by the cyclobutane ring is significant—at least one-third that of the cyclopropane ring and greater than two-thirds that of the benzene ring.

While the activation entropies for the acetolysis reactions listed in Table I correlate nicely with the observation[15] that primary β-arylalkyl arenesulfonates which solvolyze *via* k_Δ typically have ΔS^* values of 0 to −10 eu, the inclusion of the activation parameters for the trifluoroethanolysis reactions (see Table I) reveals that the activation entropy correlation becomes much more complex. The dramatic and intriguing decrease in activation entropy when the ionizing medium is changed from acetic acid to trifluoroethanol can be attributed to enhanced solvation of the transition-state complex in the more strongly ionizing trifluoroethanol[25,26] rather than enhanced molecular reorganization. Although k_Δ/k_s increases with increasing solvent ionizing strength,[12,29,30] k_Δ/k_c decreases with increasing solvent ionizing strength.[31,32,33] This latter ratio, k_Δ/k_c, is a more accurate measurement of the degree of charge dispersal and accompanying molecular reorganization.

Scheme III

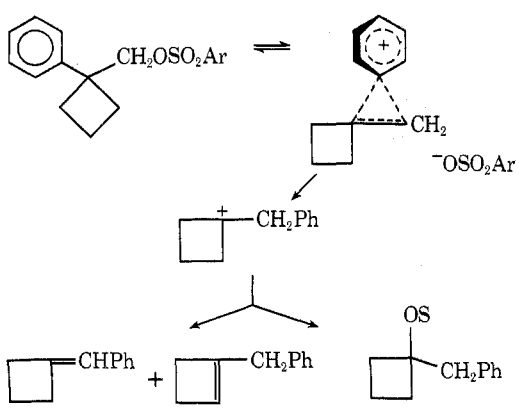
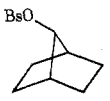
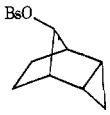
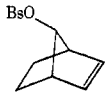
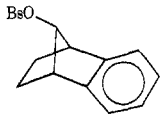
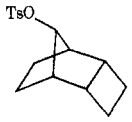
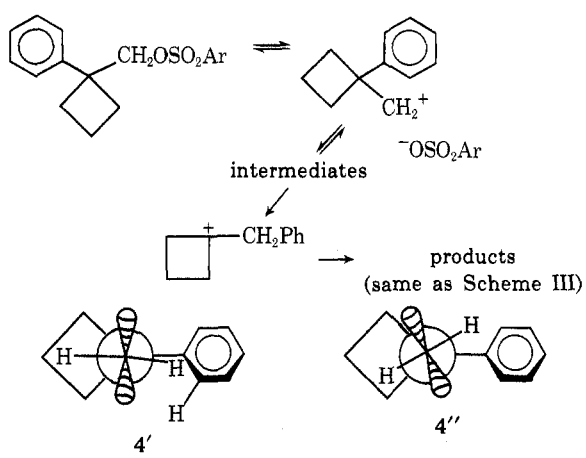


Table III
Relative Acetolysis Rates of Substituted 7-Norbornyl Derivatives

Compd	Temp, °C	Rel rate
		1
	100	10^{12}[a]
	25	10^{9}[b]
	25	$10^{5.7}$[c]
	25	$10^{4.3}$[d, e]

[a] J. S. Haywood-Farmer and R. E. Pincock, *J. Amer. Chem. Soc.*, **91**, 3020 (1969). [b] S. Winstein, M. Shatavsky, C. J. Norton, and R. B. Woodward, *ibid.*, **77**, 4183 (1955). [c] P. D. Bartlett and W. P. Giddings, *ibid.*, **82**, 1240 (1960). [d] M. Sakai, A. Diaz, and S. Winstein, *ibid.*, **92**, 4452 (1970). [e] Compared with 7-norbornyl tosylate.

Scheme IV



Experimental Section

Melting points were not corrected for stem exposure and were taken on a Mel-Temp apparatus. Infrared spectra were recorded on a Bausch and Lomb IR-270 spectrophotometer, and the ultraviolet spectra were obtained on a Beckman DK-2A spectrophotometer. A Beckman GC-4 chromatographic instrument equipped with a thermal conductivity detector and a 24 ft × 0.25 in. column of 20% Carbowax 20M on Chromosorb W, AW-DMCS (45–60 mesh) was used. All microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Table IV
1-*p*-X-Phenylcyclobutanecarboxylic Acids (2)

Registry no.	X	Mp, °C	Yield, %	Calcd, % C	Calcd, % H	Found, % C	Found, % H	Formula
	H	107–108[a]	85					
50921-37-4	MeO	106–107	65	70.25	6.35	70.41	6.54	$C_{12}H_{14}O_3$
50921-38-5	Me	115–116	86	76.20	6.88	76.01	7.01	$C_{12}H_{14}O_2$
50921-39-6	Cl	89–90	74	62.80	5.26	63.01	5.30[b]	$C_{11}H_{11}ClO_2$

[a] Lit.[35] mp 107.5–108.5°. [b] Also found: Cl, 16.69; calcd Cl, 16.80.

Table V
1-*p*-X-Phenylcyclobutylcarbinols (3)

Registry no.	X	Mp, °C	Yield, %	Calcd, % C	Calcd, % H	Found, % C	Found, % H	Formula
	H	60[a]	83					
	MeO	Oil[b]	66					
50921-40-9	Me	29–30	90	81.75	9.16	81.75	9.02	$C_{12}H_{16}O$
50921-41-0	Cl	55–56	85	67.10	6.60	67.10	6.61[c]	$C_{11}H_{13}ClO$

[a] Lit.[2] mp 60–60.5°. [b] Identified as brosylate; assigned structure consistent with ir spectrum. [c] Also found: Cl, 17.79; calcd Cl, 18.00.

Table VI
1-*p*-X-Phenylcyclobutylcarbinyl Brosylates (4)

X	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % Y	Found, % C	Found, % H	Found, % Y	Formula
MeO	75 dec	52.70	4.65	19.49[a]	52.85	4.70	19.37[a]	$C_{18}H_{19}BrO_4S$
Me	107 dec	54.70	4.84	20.22[a]	54.72	4.90	20.33[a]	$C_{18}H_{19}BrO_3S$
H	107 dec[b]							
Cl	118–119 dec	49.20	3.85	8.54[c]	49.32	3.78	8.43[c]	$C_{17}H_{16}BrClO_3S$
NO_2	123 dec	47.90	3.77	18.75[a]	48.05	3.77	18.58[a]	$C_{17}H_{16}BrNO_5S$

[a] Bromine. [b] Lit.[2] mp 108° dec. [c] Chlorine.

1-Phenylcyclobutanecarbonitrile (1-H) was prepared several times according to the method of Butler and Pollatz.[34] In a typical run, a 2-l., three-necked flask equipped with a mechanical stirrer, reflux condenser, thermometer, and pressure-equalized dropping funnel was charged under N_2 with 600 ml of dimethyl sulfoxide (purified by distillation over CaH) and 63.4 g (1.32 mol) of NaH (50% dispersion in mineral oil). After the vigorous reaction had subsided and cooling to 30° by means of an ice–water bath, a solution of benzyl cyanide (70.2 g, 0.60 mol) and 1,3-dibromopropane (133.2 g, 0.66 mol) in 400 ml of dry ether was added at a sufficient rate to maintain a 25–35° reaction temperature. The resultant thick slurry was stirred overnight and cooled in ice–water and 30 ml of 2-propanol was added dropwise followed by the addition of 500 ml of water. The mixture was then filtered through Filter-aid, the layers were separated, and the aqueous layer was extracted four times with 300-ml portions of ether. The combined ether layer and extracts were dried over $MgSO_4$, concentrated *via* rotovaporization, and distilled through a 30 × 1 cm glass helix packed column to yield 40.0 g (42%) of the nitrile 1-H, bp 80° (0.1 mm). Analysis by glpc revealed greater than 99% purity. Identity was established by conversion to the known carboxylic acid according to a published procedure.[35]

1-*p*-Chlorophenylcyclobutanecarbonitrile (1-Cl) was prepared from *p*-chlorobenzyl cyanide as described above, bp 169–170° (20 mm) [lit.[34] bp 168–169° (20 mm)]. Analysis by glpc revealed greater than 99% purity.

1-*p*-Methoxyphenylcyclobutanecarbonitrile (1-MeO) was prepared from *p*-methoxybenzyl cyanide (Research Organic/Inorganic Chemical Corp.) as described for 1-H in 42% yield, bp 117° (0.3 mm). Analysis by glpc revealed greater than 99% purity.

Anal. Calcd for $C_{12}H_{13}NO$: C, 77.00; H, 6.95; N, 7.48. Found: C, 77.30; H, 6.99; N, 7.33.

1-*p*-Methylphenylcyclobutanecarbonitrile (1-Me) was prepared from *p*-methylbenzyl cyanide (Research Organic/Inorganic Chemical Corp.) as described for 1-H in 42% yield, bp 93° (0.3 mm). Analysis by glpc revealed greater than 99% purity.

Anal. Calcd for $C_{12}H_{13}N$: C, 84.25; H, 7.64; N, 8.18. Found: C, 84.53; H, 7.54; N, 7.98.

1-*p*-X-Phenylcyclobutanecarboxylic acids (2) were prepared according to the method of Lyle[35] and the data for these acids are reported in Table IV.

1-*p*-X-Phenylcyclobutylcarbinols (3) were prepared by reduction of the acid 2 with borane in tetrahydrofuran[1b] and the data for these carbinols are given in Table V.

1-*p*-Nitrophenylcyclobutylcarbinol (3-NO_2). To a magnetically stirred solution of 1-phenylcyclobutylcarbinyl acetate (20.5 g, 0.1 mol, prepared by acetylation of 3-H) in 45 ml of acetic anhydride, a solution of fuming nitric acid (10.7 g) in 35 ml of acetic anhydride (prepared by slow addition of acid to anhydride to maintain temperature at 25°) was added at 0–3°. After stirring for 4 hr at 0° and standing overnight at room temperature, the mixture was poured onto 500 g crushed ice, and the resultant mixture was extracted three times with 80-ml portions of methylene chloride. The combined extracts were washed with cold, saturated aqueous sodium carbonate and dried over $MgSO_4$ and the solvent was removed by rotovaporization to yield 20.1 g (80%) of crude product. Analysis by glpc (220°, 75 cc/min flow rate He) revealed the absence of starting material and the presence of three peaks, A (11%), B (7%), and C (82%), with retention times of 6, 7, and 10.5 min, respectively. Recrystallization twice from 9:1 petroleum ether (bp 30–60°) yielded 14 g of pure C, mp 62°. Analysis by ir (fingerprint region) revealed the presence of a para-disubstituted benzene ring which was confirmed by uv, λ_{max} (EtOH) 280 mμ (ϵ 4820).[36] Hydrolysis of the 1-*p*-nitrophenylcyclobutylcarbinyl acetate (14 g) was accomplished by gentle reflux for 2 hr with 10.7 g of NaOH dissolved in 250 ml of 40% aqueous alcohol. After the usual work-up 9 g (80%) of 3-NO_2 was obtained, mp 70–71°. The infrared spectrum was consistent with the assigned structure.

Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.85; H, 6.31; N, 6.75.

1-*p*-X-Phenylcyclobutylcarbinyl brosylates (4) were prepared according to established procedure,[2] and the data for these esters are summarized in Table VI.

Solvents. Acetic acid solvent was prepared from 994.9 ml of glacial acetic acid (Matheson Scientific, 99.8%) and 5.1 ml of acetic anhydride. 2,2,2-Trifluoroethanol (Aldrich Chemical Co.) was redistilled just prior to use.

Rate measurements were accomplished by the usual ampoule technique.[1] Aliquots (5 ml) were sealed in each ampoule under nitrogen. The fast reactions (less than 1 hr half-life) were carried out in 25-ml volumetric flasks from which 2-ml aliquots were removed periodically. The titrating solutions were, for acetolysis,

0.050 N sodium acetate in acetic acid and, for 2,2,2-trifluoroethanolysis, 0..020 N sodium methoxide in anhydrous methanol.[37] The indicators used were Bromphenol Blue (in acetic acid) and Bromphenol Blue (in 20% aqueous alcohol), respectively.

Treatment of Kinetic Data. The thermodynamic activation parameters were obtained by IBM 1620 computer regression analysis. The correlation coefficients, R, and also the Hammett ρ value were obtained by IBM 1620 computer regression analysis.

Acknowledgment. Appreciation is expressed to Mr. Richard Chang for experimental assistance.

Registry No.—1-Phenylcyclobutanecarbonitrile, 14377-68-5; benzyl cyanide, 140-29-4; 1,3-dibromopropane, 109-64-8; 1-*p*-methoxyphenylcyclobutanecarbonitrile, 29786-45-6; *p*-methoxybenzyl cyanide, 104-47-2; 1-*p*-methylphenylcyclobutanecarbonitrile, 29786-41-2; *p*-methylbenzyl cyanide, 2947-16-7; 1-*p*-nitrophenylcyclobutylcarbinol, 50921-42-1; 1-phenylcyclobutylcarbinyl acetate, 50921-43-2.

References and Notes

(1) (a) D. D. Roberts, *J. Org. Chem.*, **29**, 294 (1964); (b) *ibid.*, **30**, 23 (1965); (c) *ibid.*, **31**, 2000 (1966); (d) *ibid.*, **33**, 2712 (1968); (e) *ibid.*, **34**, 285 (1969); (f) D. D. Roberts and T. M. Watson, *ibid.*, **35**, 978 (1970).
(2) J. W. Wilt and D. D. Roberts, *J. Org. Chem.*, **27**, 3434 (1962).
(3) D. D. Roberts, unpublished observation.
(4) A. H. Fainberg and S. Winstein, *J. Amer. Chem. Soc.*, **78**, 2763 (1956).
(5) To what extent the anchimeric assistance by the phenyl group in the ionization of neophyl tosylate may be ascribed to release of steric strain remains to be defined. However, there is some evidence[6] to indicate that it may well be significant.
(6) H. C. Brown, R. Bernheimer, and K. J. Morgan, *J. Amer. Chem. Soc.*, **87**, 1280 (1965).
(7) A. W. Weston, *J. Amer. Chem. Soc.*, **68**, 2345 (1946).
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Crystal and Molecular Structure of Cephalotaxine *p*-Bromobenzoate

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An X-ray study on the title compound verifies the constitution and relative configurations proposed for cephalotaxine and its esters, and shows for the first time the absolute configuration (5*S*). The conformation of the cephalotaxine portion of the molecule closely resembles that of the racemic methiodide, and is probably favored as well in the natural antileukemic cephalotaxine esters.

Several natural esters of cephalotaxine (I) have been found to be potent antileukemic agents, *e.g.*, homoharringtonine (II), which is undergoing preclinical testing.[1] An X-ray study has been carried out on the methiodide III, formed by reacting cephalotaxine (I, optically active) with methyl iodide at room temperature and recrystallizing from warm methanol.[2] Unexpectedly, the methiodide III was found to be racemic, indicating that the configurations at *all four* chiral centers are subject to change during the warming (no doubt *via* intermediates in which the C-9–N bond has cleaved), and thus no firm conclusions regarding the stereochemistry of cephalotaxine (I) could be drawn from the methiodide X-ray study. Two recent syntheses of racemic cephalotaxine (I), however, have lent some support to the view that its *relative* configurations are the same as those found in the racemic methiodide III.[3] We wish to report the results of an X-ray study on the title compound (IV), undertaken to check the proposed constitution and relative configurations and to establish the absolute configuration.

Experimental Section

Cephalotaxine *p*-Bromobenzoate (IV). A 2.05-g sample of *p*-bromobenzoyl chloride was added to a solution of 1.065 g of ce-