Synthesis and Solvolysis of 4-Substituted Nortricyclenes

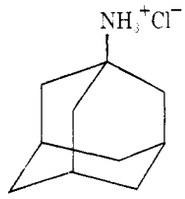
Philip J. Chenier,* James R. McClure, and David J. Golembeski

Department of Chemistry, University of Wisconsin-Eau Claire, Eau Claire, Wisconsin 54701

Received March 28, 1978

A number of 4-substituted nortricyclenes (**2**) have been synthesized, including 4-aminonortricyclene hydrochloride (**2a**), nortricyclyl-4-carbinol (**2f**), and its tosylate (**2e**). The synthesis of these compounds is discussed. Amine hydrochloride **2a** was synthesized because of its similarity in structure to 1-aminoadamantane hydrochloride (**1**), which has antiviral properties against certain influenzas. Tosylate **2e** was solvolyzed in acetic acid; the pK_a of nortricyclene-4-carboxylic acid (**2c**) was determined in 50% ethanol. These results measure a substantial inductive withdrawal by the cyclopropane ring when compared to the 1-norbornylcarbinyl system. This inductive effect for a cyclopropane ring has not previously been measured completely free of other effects such as ring strain or π participation. These studies require a reinterpretation of the extreme slowness of 4-nortricyclyl bridgehead solvolyses compared to the 1-norbornyl bridgehead system, which in the past was explained solely on the basis of an increase in ring strain, but now must include an inductive effect.

In 1964 it was announced that 1-aminoadamantane hydrochloride (**1**) would be marketed as an antiviral agent



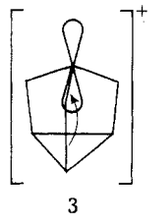
1

against certain influenza viruses.[1,2] It appears to act by interfering with the penetration of the host cell by the virus. Its chief limitations are that protection stops shortly after daily dosage is terminated and it does not extend to all viral types. Early in 1966 one of us began working in another laboratory[3] on the synthesis of 4-substituted nortricyclenes (**2**), especially

2a, X = $NH_3^+Cl^-$
b, X = Cl
c, X = COOH
d, X = OTf
e, X = CH_2OTs
f, X = CH_2OH
h, X = OTs

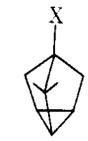
4-aminonortricyclene hydrochloride (**2a**), which is very similar in structure to **1**. Both have a bulky but symmetrical ring structure linked to a polar functional group. The hydrochloride salt is used because of its desirable solubility. The only difference in the two is that in **2a** the bridgehead amino group is joined to a cyclopropane ring by three bridging methylene groups, while in **1** the bridgehead amino group is joined to a cyclohexane ring by three bridging methylene groups.

A second purpose of the research was to measure the effect of the face of a cyclopropane ring on stabilization of a positive charge at the bridgehead position above its middle, as in ion **3**.



3

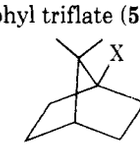
4-Chloronortricyclene (**2b**)[3] and 4-chlorotricyclene (**4b**)[4] were synthesized, and their reactivity was studied. Extensive testing with **4b** showed it to be nearly if not completely inert



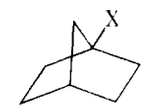
4

to silver ion even under the most strenuous conditions.[3] Consequently, this research was terminated.

In 1967 the synthesis of 4-chloronortricyclene (**2b**) and nortricyclene-4-carboxylic acid (**2c**) was published.[5] Three years later the solvolyses of 4-nortricyclyl and 4-tricyclyl triflates (**2d** and **4d**) were reported.[6] These studies showed, as we had found earlier, that there was no stabilization of the bridgehead carbonium ion **3** by the cyclopropane ring. In fact, 1-apocamphyl triflate (**5d**) reacts 28 400 times faster than **4d**



5



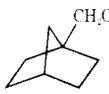
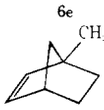
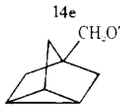
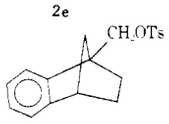
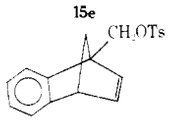
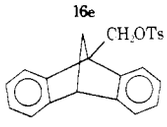
6

in 60% ethanol at 25 °C, and 1-norbornyl triflate (**6d**) is some 174 000 times faster than **2d** in 50% ethanol at 100 °C. There is thus a very dramatic *de*stabilization of the bridgehead carbonium ions in cyclopropyl systems **2** and **4**. Of the two possible reasons for this inertness, i.e., the electron-withdrawing inductive effect of the cyclopropane ring and the increased ring strain of the nortricyclyl and tricyclyl systems, the latter viewpoint has been favored.[6] The basis for this preference lies in results of strain energy calculations,[6,7] but not on experimental data. We are of the opinion that the former effect is also operating.

There are two alternative ways of determining if the inductive effect of the cyclopropane ring is operating in 4-substituted nortricyclenes. One method involves a study of the solvolysis of the bridgehead carbinyl tosylates **2e** vs. **6e**. If **2e** is slower than **6e** in solvolysis, it would be due to the electron-withdrawing inductive effect of the cyclopropane ring. Although increased ring strain is a possible factor in bridgehead ion stability, it cannot be an important factor in bridgehead carbinyl ion stability. Furthermore, if **2e** is slower than **6e** by this inductive withdrawal, then most certainly at least part of the solvolytic deceleration of **2d** vs. **6d** is due to this same effect since the developing positive charge is one carbon closer to the cyclopropane ring and inductive effects increase dramatically with decreasing distance between interacting centers.

0022-3263/78/1943-4306$01.00/0

Table I. Acetolysis Rates at 130.4 °C

tosylate	ref	10^5k, s^{-1}	k_{rel}
 6e	*a,b*	21.5	1400
 14e	*b,c*	5.9	390
 2e	*d*	0.82	55
 15e	*a,b*	0.65	43
 16e	*b,e*	0.050	3.3
 17e	*b,e*	0.015	1.0

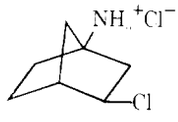
[a] Reference 10. [b] Extrapolation from data at other temperatures. [c] Reference 14. The rate constant for the brosylate was assumed to be 2.9 times the rate of the corresponding tosylate. [d] This work. Our results give a rate constant of (0.820 ± 0.030) × 10^{-5} s^{-1} at the 95% confidence level. [e] Reference 16. The rate constant for the triflate was assumed to be 1.34 × 10^4 times the rate of the corresponding tosylate.

A second accepted method of determining inductive effects of molecules is measurement of acidity constants. If acid **2c** was found to be stronger than **6c**, it would be due to an inductive effect of the cyclopropane ring, withdrawing electron density and stabilizing the anion of **2c** relative to **6c**.

Results

For these reasons we reopened our earlier investigation of the 4-nortricyclyl system and set out to synthesize amine hydrochloride **2a** for its possible antiviral activity and tosylate **2e** and acid **2c** for their theoretical significance. Acid **2c** was synthesized by the published method,[5] and the acid chloride was obtained by standard procedures. The Curtius reaction,[8] with sodium azide in aqueous acetone followed by heating in benzene, gave the rearranged isocyanate, which was hydrolyzed with dilute hydrochloric acid at room temperature to give the desired amine salt **2a** in 54% yield overall from the acid. Its structure was proven by spectral and elemental analyses. Detailed antiviral studies are now being conducted in other laboratories and are not reported here.

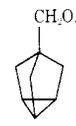
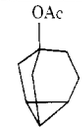
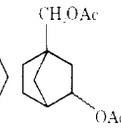
The use of higher temperatures or more concentrated acid to hydrolyze the isocyanate gave none of the desired amine hydrochloride. A complete analysis of the side product was not undertaken, but it appears to be **7**, formed by opening of the cyclopropane ring with hydrochloric acid.



7

Acid **2c** was reduced to the alcohol **2f** with lithium aluminum hydride and tosylate **2e** was made in normal fashion. The acetolysis of **2e** was run at 130.4 °C and contrasted with previous kinetic data available, especially for tosylate **6e**.[9,10] Table I gives the rate constants for appropriate tosylates in acetolysis at 130.4 °C.

Table II. Percentages of Acetolysis Products

temp, time	products, %			
	 8	 9	 10	**11, 12, or 13**
120 °C, 6 days[a]	9.2	25.1	48.4	17.2
	34.3		65.6	
137 °C. 13 days[b]	4.4	5.7	49.5	40.4
	10.1		89.9	

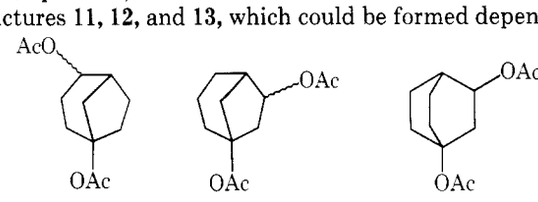
[a] Total ring expansion under these conditions (**9** + **11**) is 42.3%. [b] Total ring expansion is 46.1%.

Table III. pK_a Values

carboxylic acid	ref	pK_a
benzoic	*a*	5.35
	b	5.50
	c	5.55
	d	5.58
norbornane-1 (**6c**)	*b*	6.37
norbornene-1 (**14c**)	*b*	5.98
nortricyclene-4 (**2c**)	*a*	5.89
benzonorbornene-1 (**15c**)	*b*	5.88
benzonorbornadiene-1 (**16c**)	*c,d*	5.45
dibenzonorbornadiene-1 (**17c**)	*c*	5.50

[a] This work. [b] Reference 10. [c] Reference 16. [d] Reference 15.

A product study on a sample heated in acetic acid for a long period of time (120 °C, 6 days) showed the presence of two isomers of very short retention times and two isomers with long retention times. When the solvolysis was allowed to proceed at a higher temperature and a much longer time (137 °C, 13 days), the percentages of the products of short retention times became very low while the longer retained compounds increased in percentage. Unrearranged acetate **8** and ring-expanded acetate **9** were identified as the two isomers with short times. Unrearranged but cyclopropane ring-opened diacetate **10** was identified as a product with long retention time. The second diacetate is a ring-expanded and ring-opened product, but our data does not differentiate between structures **11**, **12**, and **13**, which could be formed depending



11 12 13

on which bond is broken in the ring opening of acetate **9** and the orientation of addition of acetic acid.

Table II gives the products and percentages under different conditions. Note that the total percentage of acetates formed (34.4%) under less stringent conditions is much larger than that produced (10.1%) when the reaction is forced with higher temperature and longer time. The solvolysis of the tosylate therefore is occurring first followed by subsequent ring opening with acetic acid.

The pK_a of acid **2c** was determined in 50% aqueous ethanol. A summary of these results and data from other appropriate acids are given in Table III for 23–25 °C.

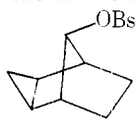
Discussion

The electron-withdrawing inductive effect of a double bond or aromatic ring is well established. The most common range of values is 5- to 10-fold for a homoallylically (γ) positioned double bond. Although usually accompanied by a rate acceleration caused by π participation of the double bond or aromatic ring in solvolysis, in one study not complicated by this participation Wilcox and Chibber[11] found that δ-unsaturated substrates solvolyze 2.5–4 times slower than their saturated counterparts. A movement of the double bond from the δ to the γ (homoallylic) position should increase the inductive effect by a factor of 2.8.[12] This same homology factor is also obtained for other series, i.e., $ClCH_2$– vs. $ClCH_2CH_2$– and CH_3CO– vs. CH_3COCH_2–, where an extra methylene group is interposed. An inductive similarity between vinyl and phenyl groups has been reported.[13]

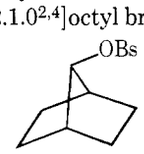
The best measure of the isolated inductive effect of the vinyl and phenyl groups is exemplified by the data summarized in Tables I and III. Norbornenyl-1-carbinyl tosylate (**14e**) has been found to be about 3.6 times slower than its saturated analogue norbornyl-1-carbinyl tosylate (**6e**),[14] and benzonorbornenyl-1-carbinyl tosylate (**15e**) is 33 times slower.[10] Our group[15] and others[16] have found that the concurrent presence of both a homoallylic vinyl and phenyl group as in benzonorbornadienyl-1-carbinyl tosylate (**16e**) retards the rate by a factor of 430 compared to the saturated system **6e** and a factor of 13–120 compared to the monounsaturated effects seen in **15e** and **14e.** Likewise, a recent study of dibenzonorbornadienyl-1-carbinyl tosylate (**17e**)[16] showed a rate deceleration of 1400 compared to **6e** and 43–390 compared to unsaturated systems **15e** and **14e.** These solvolytic studies prove the inductive withdrawal of the vinyl group, the somewhat larger but similar effect of a phenyl group, and the additivity of the effects.

The data in Table III indicate a similar conclusion by measurement of a different phenomenon entirely, that of the acidity of the corresponding acids. The only substantial difference in the two studies is the relative degrees of inductive withdrawal for vinyl and phenyl groups. In stabilizing carboxylate anions by inductive withdrawal, these two groups are quite similar. In fact, the stabilization by one vinyl and one phenyl group in **16c** seems to be slightly greater than that for two phenyl groups in **17c.**

Experimental evidence for the inductive withdrawal by cyclopropane rings before this study has been scarce. The acetolysis of *exo-anti*-8-tricyclo[3.2.1.$0^{2,4}$]octyl brosylate (**18**)

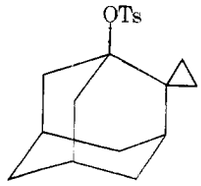


18

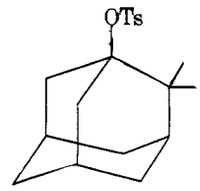


19

is slower by a factor of 3 than the acetolysis of 7-norbornyl brosylate (**19**).[17] This has been explained as either steric interference or electron withdrawal by the cyclopropane ring. The exo cyclopropane ring cannot participate in the solvolysis. Similarly, the adamantyl derivative **20** undergoes acetolysis



20



21

at 45 °C 350 times slower than its dimethyl analogue **21.**[18] The chloride corresponding to tosylate **20** is 625 times slower than 1-adamantyl chloride in 50% ethanol at 25 °C.[19] Since there is no appreciable steric difference between **20** and **21** and a good Hammett–Taft correlation exists for these systems, the results were originally interpreted in terms of an inductive withdrawal by the cyclopropane ring,[18–20] although some of this effect may be due to increased ring strain in **20.** These results have recently been reinterpreted solely in terms of a ring strain argument to the exclusion of any inductive effect.[6b]

Mentioned earlier was the work on 4-nortricyclyl (**2d**) and 4-tricyclyl triflate (**4d**)[6] and the very dramatic decelerating effect of the cyclopropane ring compared to 1-norbornyl (**6d**) and 1-apocamphyl (**5d**) triflate, interpreted by Schleyer[6a] and Bergman[6b] to be caused by ring strain, with the inductive effect of the cyclopropane ring playing little or no role in retarding ionization in these systems. No experimental evidence for one theory over the other was presented.

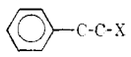
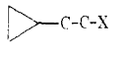
We believe that we have for the first time isolated the inductive withdrawal of the cyclopropane ring from any possible ring strain effect or π participation and have provided experimental evidence for its magnitude. The nature of the nortricyclyl-4-carbinyl system makes these two other phenomena impossible. Yet our results of the acetolysis of tosylate **2e** and of the acidity of **2c,** when compared with other bridgehead carbinyl systems, show that the cyclopropane ring of system **2** is nearly equal to the phenyl group of **15** in its well-documented inductive withdrawal. In acetolysis, **2e** solvolyzes 26 times slower than norbornyl-1-carbinyl tosylate (**6e**), compared to a decelerating effect of 33 for the phenyl group. The cyclopropyl ring in **2e** has a much stronger decelerating effect than the vinyl group of norbornenyl-1-carbinyl tosylate (**14e**), which is only 3.6 times slower than its saturated analogue **6e.**

Similarly, the acidity of nortricyclene-4-carboxylic acid (**2c**) is close to the two unsaturated acids **14c** and **15c** and, because of inductive withdrawal, is much more acidic than the saturated acid **6c.**

The only reasonable explanation of these results lies in assuming a strong inductive withdrawal of the cyclopropane ring. It should be noted that the cyclopropane ring in **2e** is actually one carbon further removed from the reaction site than the vinyl and phenyl groups of **14e** and **15e.** If we apply the factor of 2.8 mentioned by Taft[12] as the value of the inductive effect of many groups when placed one carbon closer to the reaction site, then the cyclopropyl inductive effect would be 2.8 times greater if it were present at the homocyclopropylcarbinyl (γ) position instead of the δ position. Based on the acetolysis data in Table I and the Taft homology factor, Table IV compares the pure inductive effect of the three groups under discussion at equal distances from the reaction site. The decelerating effect of the cyclopropane ring at the δ position, 26 as calculated from Table I for k_{6e}/k_{2e}, multiplied by the homology factor (2.8), gives 73 for the isolated inductive effect of a homocyclopropylcarbinyl (γ) system as in tosylate **2h.** In view of the fact that each carbon of the cyclopropane ring is connected to the reacting site by one of three carbon bridges, this type of system might be more accurately described as a tris(homocyclopropylcarbinyl) system. Although the homocyclopropylcarbinyl deceleration effect in **2h** is 73, it may be considerably less in a normal mono(homocyclopropylcarbinyl) system, perhaps one-third of this value if the entire effect is being transmitted through bonds and not through space. The present study in no way attempts to differentiate between through-bond and through-space effects.

If we correct the reported rate of 4-nortricyclyl triflate **2d**[6a] for temperature differences, a leaving group change (assum-

Table IV. Isolated Inductive-Withdrawing Effects in Acetolysis

name	structure	deceleration effect
saturated	C-C-C-C-X	1.0
homoallyl	C=CCC—X	3.6
homobenzyl		33
homocyclopropylcarbinyl		73

ing[16] k_{OTf}/k_{OTs} is 1.34×10^4), and a solvent change (assuming[6a] k in 50% ethanol/k in acetic acid is 185 at 130.4 °C), then the relative rates of 4-nortricyclyl tosylate (**2h**) and 1-norbornyl tosylate (**6h**) can be calculated for acetolysis at 130.4 °C. These values are given in Table V.

It appears that of the 10^5 factor which separates these two bridgehead systems in solvolytic rate, a factor of 73 or about 10^2 of this can be explained by inductive withdrawal of the homocyclopropylcarbinyl (γ) group present in tosylate **2h** and triflate **2d.** Therefore, on the basis of studies of the nortricyclyl-4-carbinyl system, we cannot agree with those who say that for the tricyclyl and nortricyclyl bridgehead solvolysis "... the inductive effect of the cyclopropane ring plays little or no role in retarding ionization in this system," [6b] or that "The slow rates of solvolysis are accounted for completely by the 'stiff' potential function which describes the deviation of C-4 from planarity, and the distortion of the C–C–C angle at the methylene carbons caused by the partial flattening of C-4 which does occur." [6b] We believe that a substantial portion of the bridgehead reactivity difference between **2** and **6** is due to the inductive withdrawal of the cyclopropane ring situated at a position that is γ to the reaction site.

Experimental Section

Melting and boiling points are uncorrected. The melting points were taken by capillary in a Thomas-Hoover apparatus. The following instruments were used: a Varian T-60 NMR spectrometer, Perkin-Elmer 727 and 283 infrared spectrophotometers, and Varian Aerograph A-90-P and 700 Autoprep gas chromatographs. NMR data are given in parts per million (δ) relative to internal Me_4Si. Only significant IR absorptions are listed in cm^{-1}. Gas chromatography was performed on SE-30 and QF-1 columns with helium carrier gas. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill. High-resolution mass spectral analyses and ^{13}C NMR spectra were done at the Department of Chemistry, University of Minnesota, Minneapolis, Minn.

Nortricyclene-4-carboxylic Acid (2c). This acid was prepared by the published procedure[5] starting from 4-chloronorcamphor, which is synthesized from norcamphor[21] or norbornene.[22]

4-Aminonortricyclene Hydrochloride (2a). A mixture of 4.47 g (0.0324 mol) of acid **2c**, 6 mL (0.08 mol) of thionyl chloride, and 6 mL of benzene (dried by calcium chloride) was refluxed for 2 h. The excess benzene and thionyl chloride were rotary evaporated in vacuo, and the residue was distilled to give 4.18 g (0.0267 mol, 82%) of the acid chloride: bp 80–83 °C (10 mm); IR (neat) 3068 (cyclopropyl C–H), 2940 and 2868 (C–H), 1789 (C=O), 1275, 1270, 1143, 941, 797, 751 cm^{-1}.

The acid chloride in 9 mL of reagent acetone was added dropwise to a stirred solution of 2.43 g (0.0374 mol) of sodium azide in 9 mL of distilled water below 10 °C. The addition required 0.5 h, and the mixture was stirred an additional 1.5 h. The sweet odor of the azo ketone was readily detectable. The layers were separated, and the top layer was added dropwise to 27 mL of warm dry benzene while being stirred magnetically. The addition took 0.5 h with a slow evolution of nitrogen. The mixture was refluxed for 2 h. The lachrymatory isocyanate was apparent.

The cooled benzene solution was added to 111 mL (0.0267 mol) of 2% hydrochloric acid (98:2 water–concentrated acid), and the two layers were stirred at room temperature for 4 days. The layers were separated, and the bottom aqueous layer was filtered and evaporated at <1 mm from a warm water bath while being stirred. The solid was dried in vacuo overnight to give 2.55 g (0.0175 mol, 54%) of hydrochloride **2a** as a white powder: IR (KBr) 3440 (N–H), 3082 (cyclopropyl C–H), 2400–2600 (NH^+Cl^-), 2005 (NH^+Cl^-), 1498 (N–H), 1353, 1297, 1248, 801, 792 cm^{-1}; NMR (D_2O, external Me_4Si) δ 4.70 (s, H_2O and NH), 1.65 (s, 6, CH_2), 1.37 (s, 3, CH); ^{13}C NMR (D_2O, TSP-d_4) 54.78 (CN^+), 35.55 (CH_2), 11.61 (CH) ppm. Mass spectral analysis showed a molecular ion with loss of HCl at m/e 109. Exact mass calcd for $C_7H_{11}N$, 109.0891; found, 109.0892. Exact mass calcd for $C_7H_{10}N$, 108.0813; found, 108.0820.

A pure sample was obtained by three recrystallizations from methanol–ether: white plates; mp >275 °C. Anal. Calcd for $C_7H_{12}NCl$: C, 57.73; H, 8.31. Found: C, 57.50; H, 8.22.

When refluxing concentrated hydrochloric acid was used to hydrolyze the isocyanate, a different product was obtained, mp 227–229 °C. It was partially characterized as being an amine hydrochloride [IR (KBr) 2000 cm^{-1} (NH^+Cl^-)], but its NMR spectrum (D_2O) showed a small multiplet at δ 4.0–4.4 (CHCl) and a large complex pattern at δ 1.4–2.8. This compound is believed to be *exo*-3-chloro-1-aminonorbornane hydrochloride (**7**).

Nortricyclyl-4-carbinyl Tosylate (2e). Alcohol **2f** was formed by treating 2.5 g (0.018 mol) of acid **2c** with 1.5 g (0.040 mol) of lithium aluminum hydride in 80 mL of dry ether under reflux for 2 h in normal fashion.[23] The product had bp 82–84 °C (6.0 mm) and was obtained in a good yield of 2.0 g (0.016 mol, 89%): IR (neat) 3340 (O–H), 3070 (cyclopropyl C–H), 2940 and 2870 (C–H), 1250, 1160, 1040 (C–O), 1000, 810 cm^{-1}; NMR (CCl_4) δ 4.40 (s, 1, OH), 3.68 (s, 2, CH_2O), 1.20 (s, 6 CH_2), 1.08 (s, 3, CH).

Alcohol **2f** was converted into the tosylate **2e** without further purification. In the usual manner,[24] 1.80 g (0.0145 mol) of **2f** was treated with 6.15 g (0.0323 mol) of tosyl chloride in pyridine at 0 °C for 72 h to give 2.20 g (0.00791 mol, 54%) of **2e:** IR (melt) 3070 (cyclopropyl C–H), 3050 (Ar–H), 2940 and 2860 (C–H), 1600 (C=C), 1355 and 1165 (S=O), 1245, 1100, 975, 960, 855, 845, 820, 800, 660 cm^{-1}; NMR (CCl_4) δ 7.1–7.8 (AA'XX', 4, ArH), 4.07 (s, 2, CH_2O), 2.37 (s, 3, CH_3Ar), 1.17 (s, 6, CH_2), 1.03 (s, 3, CH).

Tosylate **2e** was purified for analysis by seven recrystallizations from 30–60 °C petroleum ether, mp 74.5–76.0 °C. Anal. Calcd for $C_{15}H_{18}SO_3$: C, 64.72; H, 6.52. Found: C, 64.89; H, 6.57.

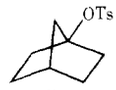
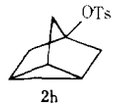
Kinetic Studies. Standard procedures were followed for the acetolysis studies. Standardized 0.04 M sodium acetate in redistilled glacial acetic acid containing 0.3% acetic anhydride was the solvent, with a tosylate concentration of 0.025 M. Aliquots (2 mL) were sealed in ampules and heated to the reaction temperature. The excess sodium acetate was back-titrated in the ampule with standard 0.014 *p*-toluenesulfonic acid in acetic acid using bromophenol blue indicator (yellow to colorless end point). The first-order plot of **2e** was linear to 79% completion. The infinity titre was calculated to be 96%. Results are given in Table I.

Acetolysis Products. To 10 mL of acetic acid containing 0.3% acetic anhydride was added 0.287 g (1.03 mmol) of tosylate **2e** and 0.17 g (2.07 mmol) of anhydrous sodium acetate. The mixture was refluxed at 120 °C for 138 h. The solution was cooled, diluted with 125 mL of water, and extracted with four portions of 30 mL of ether. The ether layers were combined and washed twice with 50 mL of 10% sodium bicarbonate, once with 35 mL of water, and once with 25 mL of brine. The organic layer was dried over anhydrous magnesium sulfate and filtered, and the solvent was distilled at atmospheric pressure from a water bath.

Gas chromatographic analysis (14 ft, 10% SE-30, 166 °C) showed the presence of four products at 9, 11, 26, and 28 min. The two products of short retention times were collected separately at 141 °C with retention times of 19 and 23 min and were determined by NMR analysis to be **8** and **9**, respectively. NMR of **8**: (CCl_4) δ 4.17 (s, 2, CH_2O), 1.93 (s, 3, CH_3CO), 1.22 (near s, 6, CH_2), 1.07 (near s, 3, CH). NMR of **9**: (CCl_4) δ 1.6–2.2 (m, 8, CH_2), 1.87 (s, 3, CH_3CO), 1.1–1.4 (d of m, J = 7 Hz, 2, CH), 0.5–0.8 (m, 1, CH).

Acetates **8** and **9** were recollected together for analysis. Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.94; H, 8.34.

Table V. Acetolysis Rates at 130.4 °C

tosylate	k, s^{-1}	k_{rel}
 **6h**	2.97×10^{-9}	1.5×10^5
 **2h**	2.01×10^{-14}	1.0

The two products of longer retention times were collected separately at 155 °C with retention times of 52 and 55 min and were determined by NMR analysis to be **10** and **11, 12,** or **13,** respectively. The NMR data is given below.

In a second product study, 1.00 g (3.60 mmol) of tosylate **2e** and 0.59 g (7.20 mmol) of anhydrous sodium acetate in 30 mL of acetic acid containing 0.3% acetic anhydride were heated in a pressure bottle at 133–141 °C for 13 days. A workup analogous to the first product study gave 0.70 g of crude product mixture: IR (neat) 2950 and 2870 (C–H), 1732 (C=O), 1250 (asymmetric C–O), 1030 (symmetric C–O) cm^{-1}.

Gas chromatographic analysis (20 ft, 15% SE-30, 201 °C) showed the presence of four products at 10, 12, 26, and 28 min. With another column (QF-1, 198 °C), the order of the two diacetate products was reversed with 15- and 17-min retention times. The two diacetates were separated and collected (QF-1, 165 °C) with retention times of 17 and 23 min and were determined to be **11, 12,** or **13** and **10,** respectively.

NMR of **10:** (CCl_4) δ 4.5–4.7 (m, 1, CHO), 4.13 (s, 2, CH_2O), 2.2–2.4 (m, 1, bridgehead), 2.00 (s, 3, CH_3CO), 1.93 (s, 3, CH_3CO), 1.1–2.0 (m, 8, CH_2). Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.40; H, 8.07.

NMR of the ring-expanded, ring-opened diacetate **11, 12,** or **13:** (CCl_4) δ 4.4–4.8 (m, 1, CHO), 2.00 (s, 3, CH_3CO), 1.92 (s, 3, CH_3CO), 1.3–2.4 (m, 11, CH_2 and CH). Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.58; H, 8.08.

The percentages of products for both studies are given in Table II.

pK_a of Nortricyclene-4-carboxylic Acid (2c). The pK_a of acid **2c** was taken by dissolving 41.4 mg (0.300 mmol) in 50% ethanol (50 mL, 1:1 absolute ethanol–distilled water by volume) and titrating with 0.0529 N aqueous sodium hydroxide at ambient temperature while the pH was measured with a Corning Model 7 pH meter. The pK_a was obtained from the pH at the half-neutralization point. Benzoic acid was run as a control.

Acknowledgment. The authors wish to express their sincere thanks to the Wolcott Gibbs Fund of the National Academy of Sciences and the University of Wisconsin-Eau Claire Faculty Research Fund for grants in partial support of this investigation. We also thank Professor James W. Wilt, Loyola University of Chicago, for helpful discussions in the early stages of the research and Ms. Irene Gennick, University of Minnesota, for running the ^{13}C NMR spectrum of amine hydrochloride **2a.**

Registry No.—**2a,** 67393-42-4; **2a** free base, 67393-43-5; **2c,** 17294-83-6; **2c** acid chloride, 67393-44-6; **2e,** 67393-45-7; **2f,** 67393-46-8; **2h,** 67393-47-9; **6h,** 33175-47-2; **7,** 15023-54-8; **8,** 67393-48-0; **9,** 67393-49-1; **10,** 67393-50-4.

References and Notes

(1) For a nontechnical discussion of the pharmaceutical effectiveness of this drug, see the following references; (a) W. L. Davies, R. R. Grunert, R. F. Hoff, J. W. McCahen, E. M. Neumayer, M. Paulshock, J. C. Watts, T. R. Wood, E. C. Hermann, and C. E. Hoffmann, *Science,* **144,** 862 (1964); (b) *Chem. Eng. News,* **44** (44), 26 (1966); (c) *ibid.,* **45** (45), 22, 23 (1967); (d) *ibid.,* **46** (39), 13, 14 (1968); (e) *ibid.,* **46,** (42), 18 (1968); (f) *ibid.,* **48** (24), 13 (1970).
(2) For pertinent patents in this area, note the following: (a) U.S. Patent 3 274 274, 1966; (b) U.S. Patent 3 283 001, 1965; (c) British Patent 1 006 885, 1965; (d) Netherlands Patent 6 414 720, 1965; (e) Netherlands Patent 6 511 537, 1966; and (f) U.S. Patent 3 504 030, 1970.
(3) J. W. Wilt and P. J. Chenier, unpublished work, Loyola University, Chicago, Ill. We thank Professor Wilt for allowing us to continue this work at the University of Wisconsin-Eau Claire. A preliminary account of this paper was given at the Joint Central-Great Lakes Regional American Chemical Society Meeting, Indianapolis, Indiana, May 24–26, 1978, No. ORGN 43.
(4) H. Meerwein and R. Wortmann, *Justus Liebigs Ann. Chem.,* **435,** 190 (1924); J. Houben and E. Pfankuch, *ibid.,* **501,** 219 (1933); **489,** 193 (1931); **507,** 37 (1933); H. L. Hoyer, *Chem. Ber.,* **87,** 1849 (1954).
(5) R. R. Sauers and R. J. Kiesel, *J. Am. Chem. Soc.,* **89,** 4695 (1967). We thank Professor Sauers for providing us with details of some of these steps.
(6) (a) R. C. Bingham, W. F. Sliwinski, and P. v. R. Schleyer, *J. Am. Chem. Soc.,* **92,** 3471 (1970); (b) S. A. Sherrod, R. G. Bergman, G. J. Gleicher, and D. G. Morris, *ibid.,* **92,** 3469 (1970); **94,** 4615 (1972).
(7) G. J. Gleicher and P. v. R. Schleyer, *J. Am. Chem. Soc.,* **89,** 582 (1967); V. R. Koch and G. J. Gleicher, *ibid.,* **93,** 1657 (1971); R. C. Bingham and P. v. R. Schleyer, *ibid.,* **93,** 3189 (1971).
(8) C. F. Allen and A. Bell, "Organic Syntheses", Collect. Vol. 3, Wiley, New York, N.Y., 1955, p 846. We thank Ms. Marie Ah-King for testing this procedure with cyclohexanecarboxylic acid.
(9) J. W. Wilt, C. T. Parsons, C. A. Schneider, D. G. Schultenover, and W. J. Wagner, *J. Org. Chem.,* **33,** 694 (1968).
(10) J. W. Wilt, H. F. Dabek, Jr., J. P. Berliner, and C. A. Schneider, *J. Org. Chem.,* **35,** 2402 (1970).
(11) C. F. Wilcox, Jr., and S. S. Chibber, *J. Org. Chem.,* **27,** 2332 (1962).
(12) R. W. Taft, Jr., "Steric Effects in Organic Chemistry", M. S. Newman, Ed., Wiley, New York, N.Y., 1956, p. 592.
(13) R. S. Bly and R. T. Swindell, *J. Org. Chem.,* **30,** 10 (1965).
(14) R. S. Bly and Q. E. Cooke, Abstracts, 148th National Meeting of the American Chemical Society, Chicago., Ill., Sept 1964, No. 80-S; R. S. Bly and E. K. Quinn, Abstracts, 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967, No. 91-O.
(15) P. J. Chenier, S. R. Jensen, D. A. Jess, and B. B. Rosenblum, *J. Org. Chem.,* **38,** 4350 (1973).
(16) T. Irie and H. Tanida, *J. Org. Chem.,* submitted for publication. We thank Professor Tanida for providing us with a preprint before publication.
(17) J. Haywood-Farmer, R. E. Pincock, and J. I. Wells. *Tetrahedron,* **22,** 2007 (1966).
(18) B. R. Ree and J. C. Martin, *J. Am. Chem. Soc.,* **92,** 1660 (1970).
(19) P. v. R. Schleyer and V. Buss, *J. Am. Chem. Soc.,* **91,** 5880 (1969).
(20) V. Buss, R. Gleiter, and P. v. R. Schleyer, *J. Am. Chem. Soc.,* **93,** 3927 (1971).
(21) K. B. Wiberg, B. R. Lowry, and T. H. Colby, *J. Am. Chem. Soc.,* **83,** 3998 (1961).
(22) D. C. Kleinfelter and P. v. R. Schleyer, *Org. Synth.,* **42,** 79 (1962).
(23) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, Wiley, New York, N.Y., 1967, pp 581–595.
(24) Reference 23, pp 1179–1185.