A New Bicyclic System. *N,N'*-Diaryl-2,5-diaza-3,6-dioxobicyclo[2.2.2]octanes

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The reaction of α,α'-dibromoadipic acid bisarylamides with anhydrous potassium fluoride gives a new bicyclic system, *N,N'*-diaryl-2,5-diaza-3,6-dioxobicyclo[2.2.2]octanes, together with the bisarylamides of α,α'-difluoroadipic and muconic acid. The chemical and physical properties of the bicyclic system are reported.

During our investigation of the reaction of amides of α-bromo acids with potassium fluoride,[1] it has been observed that α,α'-dibromoadipic acid dianilide is transformed in this reaction into a mixture of three substances: α,α'-difluoroadipic acid dianilide (IIIa), muconic acid dianilide (IIa), and a third substance which has the structure of *N,N'*-diphenyl-2,5-diaza-3,6-dioxobicyclo[2.2.2]octane (Ia). This is a general reaction of substituted anilides of α,α'-dibromoadipic acid with potassium fluoride (Table I).

All the substituted muconic acid dianilides (II) are insoluble in methylene chloride and can be easily separated from the reaction mixture; their structure was established by analysis and spectra. It was impossible to hydrolyze them, but their structure was proven by unequivocal syntheses from *trans,trans*-muconic acid.

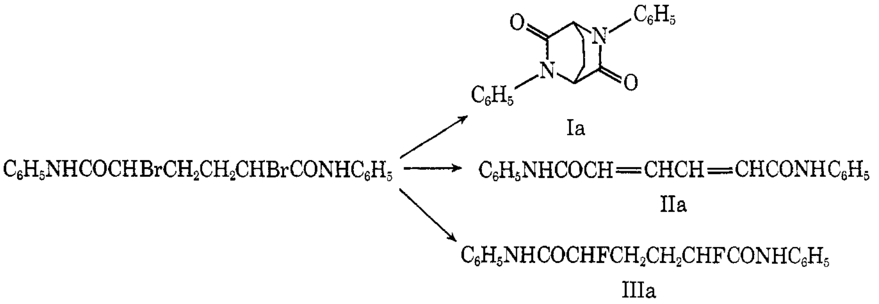
The mixtures of I and II could be separated by chromatography on alumina. The structure of compound Ia, $C_{18}H_{16}N_2O_2$, was established as follows.

(1) The uv absorption at 238 mμ (ε 1.54×10^4) is that of a *saturated* anilide [acetanilide absorbs at λ_{max}^{EtOH} 238 mμ (ε 1.05×10^4)[2]].

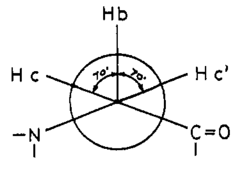
(2) In the infrared, there is no sign of the NH stretching mode; at 1700 cm^{-1} one finds the carbonyl absorption of a saturated anilide.[3]

(3) The mass spectrum shows the molecular ion *m/e* 292 and the ratio $(M + 1)^+/M^+ = 18\text{–}20\%$ corresponds well with the suggested formula. The main fragments (*m/e* 173, 172, 171, 146, 145, 144, 143, 132, 119) can be explained by Schemes I–III. The peak *m/e* 146 could represent the doubly charged ion M^{2+}; however, this possibility is ruled out by the fact that there is no peak at $(M + 1)^+/2 = 146.5$. See Figure 1.

(4) The Dreiding model of Ia shows that the molecule is symmetrical and rigid. This model is consistent with the nmr spectrum which shows three absorptions: δ (ppm) 7.40 (s, 10 aromatic H), 4.66 (broad line, 2 bridgehead H_b), 2.30 (broad line, 4 methylene H_c). The peak at δ 2.30 ppm is a narrow multiplet as can be seen clearly at a sweep width of 100 cps. Spin decoupling by irradiation at δ 4.66 ppm narrows the width at half-height of the peak at δ 2.30 ppm from 5 to 3 cps. Spin decoupling by irradiation at δ 2.30 ppm narrows the width at half-height of the peak at δ 4.66 ppm from 5 to 1.3 cps.



Newman projection of the Dreiding model of Ia at the bridgehead shows that the dihedral angle between H_b and H_c as well as between H_b and $H_{c'}$ is about 70°. There is a difference, albeit a small one, between H_c and $H_{c'}$. This is due to the fact that $H_{c'}$ is nearer to the carbonyl group, and H_c to the nitrogen atom. In any event, for such angles, Karplus' equation[4] predicts very small values for $J_{H_bH_c}$ and $J_{H_bH_{c'}}$ (about 0.7 cps), which cannot be determined in our case. It is worthy of note that Fort and Schleyer found in adamantanes (dihedral angle 60°) that $J_{vic} = 2.6 \pm 0.2$ cps while the Karplus equation gives $J_{calcd} = 1.8$ cps.[5] The other *N,N'*-diaryl-2,5-diaza-3,6-dioxobicyclo[2.2.2]octanes have very similar nmr spectra. They are summarized in Table II.



The compounds I are stable when refluxed for 72 hr with a mixture of concentrated hydrochloric and acetic acids or with a 20% solution of sulfuric acid in acetic acid. Ia and Ib can be distilled at about 240–260° (3 mm) without decomposition.

The novel cyclization appears to occur only with potassium fluoride. When potassium carbonate or triethylamine were used under similar conditions, none of the bicyclic compounds has been obtained. One might thus believe that the difluoro dianilide is formed first and assumes a conformation conducive to ring closure. The interaction of the fluorine atoms and the NH groups may play a part in this process.

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[1] I. Shahak, S. Rozen, and E. D. Bergmann, *Israel J. Chem.*, in press.

[2] H. E. Ungnade, *J. Amer. Chem. Soc.*, **75**, 432 (1953).

[3] R. E. Richards and H. W. Thompson, *J. Chem. Soc.*, 1248 (1947).

[4] M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

[5] R. C. Fort and P. v. R. Schleyer, *J. Org. Chem.*, **30**, 789 (1965); see also K. Tori, Y. Takano, and K. Kitahonoki, *Ber.*, **97**, 2798 (1964).

TABLE I

REACTION OF POTASSIUM FLUORIDE WITH $ArNHCOCHBrCH_2CH_2CHBrCONHAr$

Ar	Compound observed	Formula[a]	Yield, %	Mp, °C	Ir, cm⁻¹ (in CCl_4)	Uv λ_{max}^{EtOH}, mμ	Uv $\epsilon \times 10^4$	R_f[b]
Phenyl	Ia	$C_{18}H_{16}N_2O_2$	36.0	159[c]	1710 (C=O)	238	1.54	0.70
	IIIa	$C_{18}H_{18}F_2N_2O_2$	8.5	207[d]	3330 (NH), 1665 (C=O), 1080 (CF)			
p-Tolyl	Ib	$C_{20}H_{20}N_2O_2$	12.0	166[c]	1705 (C=O)	240	1.88	0.75
	IIb	$C_{20}H_{20}N_2O_2$	11.0	313[d,g]	3280 (NH), 1660 (C=O)	248, 302	29.00, 1.39	
	IIIb	$C_{20}H_{22}F_2N_2O_2$	7.0	210[d]	3330 (NH), 1665 (C=O) 1078 (CF)			
p-Methoxyphenyl	Ic	$C_{20}H_{20}N_2O_4$	16.0	166[c]	1705 (C=O)	243	2.00	0.60
	IIc	$C_{20}H_{20}N_2O_4$	15.0	313[e,h]	3285 (NH), 1650, 1620 (C=O)	264, 343		
	IIIc	$C_{20}H_{22}F_2N_2O_4$	5.0	229[d]	3320 (NH), 1660 (C=O) 1080 (CF)			
p-Nitrophenyl	Id	$C_{18}H_{14}N_4O_6$	18.0	268[f]	1715 (C=O)	220, 310	1.62, 2.10	0.63
p-Chlorophenyl	Ie	$C_{18}H_{14}Cl_2N_2O_2$	46.0	182[c]	1715 (C=O)	245	2.60	0.83
	IIIe	$C_{18}H_{16}Cl_2F_2N_2O_2$	8.0	221[d]	3310 (NH), 1670 (C=O), 1080 (CF)			
m-Chlorophenyl	If	$C_{18}H_{14}Cl_2N_2O_2$	57.0	199[d]	1715 (C=O)	243	2.00	0.86
2-Methyl-4-chlorophenyl	Ig	$C_{20}H_{18}Cl_2N_2O_2$	46.0	195[c]	1710 (C=O)	230	1.74	0.77
	IIg	$C_{20}H_{18}Cl_2N_2O_2$	1.0	325[e,i]	3280 (NH), 1650, 1620 (C=O)	227, 273		

[a] Satisfactory analytical values for C, H, N, and halogen as appropriate (±0.35) were reported for all compounds in the table: Ed. [b] R_f values by tlc, silica gel, 0.25-mm thickness. The developer was 5% methanol in benzene. The presence of compounds of type I was easily demonstrated by tlc since their R_f's are much larger than those of all other products present. [c] Recrystallized from benzene. [d] Recrystallized from methanol–THF. [e] Recrystallized from DMF. [f] Recrystallized from DMSO. [g] This compound is different from the independently synthesized *trans,trans*-muconic acid di-*p*-toluidide, mp 327°, from DMF. We assume cis–trans configuration: ν_{max}^{Nujol} 3290, 1640, 1600 cm⁻¹; λ_{max}^{EtOH} 233, 273, 330 mμ. [h] *trans,trans*-Muconic acid dianisidide. Comparison (mixture melting point and ir) with an authentic sample, synthesized from *trans,trans*-muconyl chloride: P. S. Bailey and J. H. Ross, *J. Amer. Chem. Soc.*, **71,** 2370 (1949). This compound is accompanied by another, more soluble isomer [mp 312° (from DMF); ν_{max}^{Nujol} 3265, 1660, 1650 cm⁻¹; λ_{max}^{EtOH} 252, 315 mμ], which is probably the cis–trans isomer. [i] The configuration has not been determined.

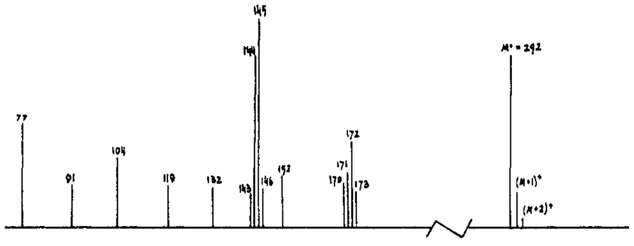


Figure 1.—The main peaks of the mass spectrum.

In the parallel reaction of potassium fluoride with α,α′-dibromoadipic acid bis-*N*-methylanilide (IV) in which an analogous cyclization is impossible, only *trans,trans*-muconic acid bis-*N*-methylanilide (V) was obtained in 45% yield. This confirms earlier results with α,α′-dibromoadipic acid bis-*N,N*-diethylamide.[1]

$$\underset{\text{IV}}{C_6H_5N(CH_3)COCHBrCH_2CH_2CHBrCO(CH_3)NC_6H_5} \xrightarrow{KF}$$

$$\underset{\text{V}}{C_6H_5N(CH_3)COCH{=}CHCH{=}CHCON(CH_3)C_6H_5}$$

V could be hydrolyzed to *trans,trans*-muconic acid by 70% sulfuric acid and was synthesized from *trans,trans*-muconyl chloride[6] and *N*-methylaniline.

Experimental Section

The melting points have been determined with a Thomas–Hoover capillary melting point apparatus. The nmr spectra were measured with a Varian T-60 instrument; the samples were dissolved in $CDCl_3$ except when otherwise indicated.

Preparation of α,α′-Dibromoadipic Acid Bisarylamides (Table III).—A mixture of 14.6 g of adipic acid (0.1 mol) and 50 g of thionyl chloride was refluxed until the acid had completely dissolved. After a further hour, 35 g of bromine (0.22 mol) was added during 2–3 hr to the boiling solution, and the heating was continued for an additional 4 hr. The excess of bromine and thionyl chloride was distilled off under reduced pressure (below 100°), and two portions (250 ml each) of toluene were added and evaporated again under reduced pressure. The crude α,α′-dibromoadipoyl chloride was diluted with 150 ml of dry benzene and used in this form.

The freshly distilled arylamine, dissolved in dry benzene (0.22 mol in 70 ml), was then added to the solution with stirring and cooling. After 1 hr at room temperature, 100 ml of cold 10% hydrochloric acid was added and the mixture was stirred for 1 hr and filtered. Thus the arylamides, which are only very sparingly soluble, were obtained in practically quantitative yields. As it is difficult to recrystallize them, they were purified by refluxing with 2% HCl for 1 hr, filtering, and drying at 100° under reduced pressure. The analytical samples were further purified by refluxing them for 30 min in THF–methanol (1:1) in which the compounds are insoluble.

The preparation of α,α′-dibromoadipic acid bis-*N*-methylanilide is slower, and the mixture of *N*-methylaniline and α,α′-dibromoadipoyl chloride had to be left at room temperature for 24 hr, yield 75%, recrystallized from methanol.

[6] P. S. Bailey and J. H. Ross, *J. Amer. Chem. Soc.*, **71,** 2370 (1949).

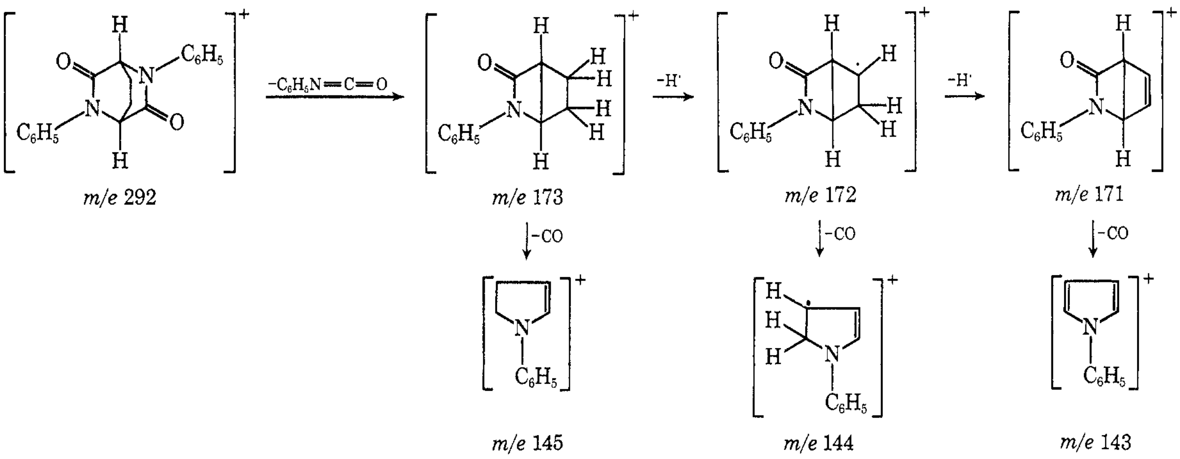
TABLE II

NMR SPECTRA OF N,N-DIARYL-2,5-DIAZA-3,6-DIOXOBICYCLO[2.2.2]OCTANES (I)

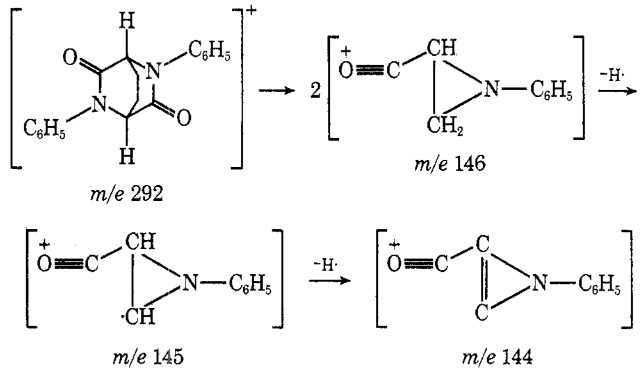
		Bridgehead hydrogen atom (H_b)			Methylene hydrogen atoms (H_c, $H_{c'}$)		
			Width at half-height (cps)			Width at half-height (cps)	
Compd	Ar[a]	Signal position (ppm)	Before irradn at H_c, $H_{c'}$	After irradn at H_c, $H_{c'}$	Signal position (ppm)	Before irradn at H_b	After irradn at H_b
Ib	p-Tolyl	4.62 (2 H)	3.5	1.7	2.31 (4H)	b	
Ic[c]	p-Methoxyphenyl	4.55 (2 H)	3.5	1.5	2.29 (4 H)	5.0	3.0
Id[d]	p-Nitrophenyl	5.12 (2 H)	4.0		2.58 (4 H)	6.0	
Ie	p-Chlorophenyl	4.63 (2 H)	5.0	2.0	2.30 (4 H)	6.0	4.0
If[e]	m-Chlorophenyl	4.70 (2 H)	5.0	2.1	2.39 (4 H)	4.5	3.0
Ig[f]	2-Methyl-4-chlorophenyl	4.34 (2 H)	6.0	2.5	2.33 (4 H)	3.5	2.0

[a] The signals for the aromatic protons were observed in the range of 7.05–7.49 ppm. In one case (I, Ar = p-nitrophenyl) an AB spectrum has been observed as follows: A = 8.33 (d, 4 H, J = 9 cps); B = 7.88 (d, 4 H, J = 9 cps). [b] The two methyl groups resonate at 2.37 ppm (s, 6 H). [c] The six methoxy protons appear as a singlet at 3.81 ppm. [d] Because of the slight solubility in $CDCl_3$, the spectrum was measured in $(CD_3)_2SO$. [e] This spectrum was determined in $CDCl_3$ and in $(CD_3)_2SO$. The chemical shifts and the widths at half-height, before and after irradiation, in the two solvents are identical. [f] The six methyl protons appear as a singlet at 2.38 ppm.

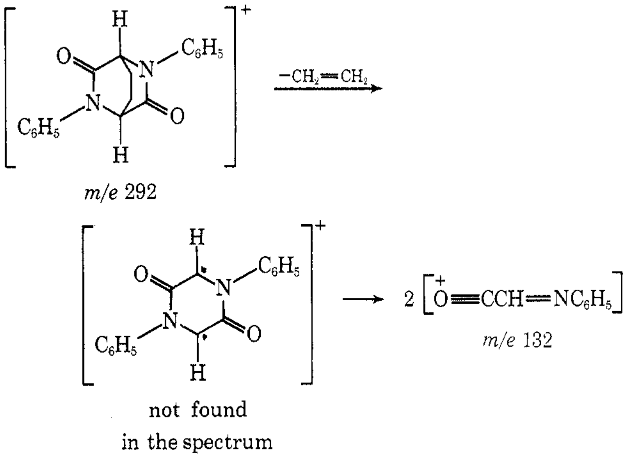
SCHEME I



SCHEME II



SCHEME III



Reaction of α,α'-Dibromoadipic Acid Bisarylamides with Potassium Fluoride.—The bisarylamide (0.15 mol) was added to a solution of 52 g (0.9 mol) of dry potassium fluoride (dried at 180° for 10 hr) in 300 ml of diethylene glycol. The mixture was heated, with stirring, at 125–130° for 2.5 hr, cooled, and poured into 3 l. of ice water. The precipitate was filtered off, washed with water, and added to 2 l. of methylene chloride. The organic phase, in which sometimes a solid was suspended, was washed three times with 200 ml of water and filtered. The insoluble phase proved always to be the substituted muconic acid bisarylamide. The filtrate was dried over anhydrous potassium carbonate and evaporated. The residue was refluxed for 30 min with 500 ml of benzene and filtered. Filtration of the mixture, while still hot, left the benzene-insoluble α,α'-difluoroadipic acid bisarylamide. The benzene filtrate was cooled, whereupon a portion of the bicyclic compound I precipitated. Concentration of the mother liquid and chromatography on alumina (Merck, neutral activity I), 2% acetone in benzene serving as eluent, gave the balance of compound I. Subsequent elution with 3% methanol in benzene gave some additional α,α'-difluoroadipic acid bisarylamide.

The reaction mixture obtained from α,α'-dibromoadipic acid p-nitroanilide behaved somewhat differently. The residue, after evaporation of the methylene chloride, was the bicyclic compound Id. It was purified by refluxing the compound with 200 ml of chloroform and filtration of the hot solution from the solid Id. No defined substance could be isolated by chromatography of the filtrate. The ir, uv, and R_f data of the compounds of type I, II, and III are included in Table I.

TABLE III

RR'NCOCHBrCH$_2$CH$_2$CHBrCONRR'

Compd	R	R'	Mp,[a] °C	Empirical formula[b]	Ir (cm^{-1})[c] NH	Ir (cm^{-1})[c] C=O
a	Phenyl	H	243	$C_{18}H_{18}Br_2N_2O_2$	3300	1660
b	*p*-Tolyl	H	236	$C_{20}H_{22}Br_2N_2O_2$	3260, 3300	1660, 1700
c	*p*-Anisyl	H	238	$C_{20}H_{22}Br_2N_2O_4$	3280, 3300	1660, 1690
d	*p*-Nitrophenyl	H	239	$C_{18}H_{16}Br_2N_4O_6$	3290, 3320	1680, 1700
e	*p*-Chlorophenyl	H	246	$C_{18}H_{16}Br_2Cl_2N_2O_2$	3270, 3300	1660, 1700
f	*m*-Chlorophenyl	H	220	$C_{18}H_{16}Br_2Cl_2N_2O_2$	3280, 3310	1660, 1700
g	2-Methyl-4-chlorophenyl	H	244	$C_{20}H_{20}Br_2Cl_2N_2O_2$	3270	1660
h	Phenyl	CH$_3$	161	$C_{20}H_{22}Br_2N_2O_2$		1670

[a] All compounds, except Ih, decompose at the melting point. [b] Satisfactory analytical values for C, H, N, and halogen as appropriate (±0.35) were reported for all compounds in the table: Ed. [c] Ir spectra in Nujol mulls.

Registry No.—Ia, 27062-59-5; Ib, 27062-60-8; Ic, 27062-61-9; Id, 27062-62-0; Ie, 27062-63-1; If, 27062-64-2; Ig, 27062-65-3; IIb, 27062-66-4; *trans,trans*-IIc, 27062-67-5; *cis,trans*-IIc, 27062-68-6; IIg, 27062-69-7; IIIa, 27062-70-0; IIIb, 27062-71-1; IIIc, 27062-72-2; IIIe, 27062-73-3. Table III—a, 27062-74-4; b, 27062-75-5; c, 27062-76-6; d, 27062-77-7; e, 27062-78-8; f, 27062-79-9; g, 27062-80-2; h, 27062-81-3.

The Synthesis and Acetolysis of 6-Oxabicyclo[3.2.1]octane-1-methyl *p*-Bromobenzenesulfonate[1]

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The intramolecular oxymercuration of 4,4-bis(hydroxymethyl)-1-cyclohexene (2) followed by sodium borohydride reduction of the chloromercurial gave 1-hydroxymethyl-6-oxabicyclo[3.2.1]octane (**4a**). The brosylate **5a** derived from this alcohol was solvolyzed in acetic acid. The products included the unrearranged acetate **6**, 4,4-bis(acetoxymethyl)-1-cyclohexene (**7a**), and the two ring-expanded bridgehead acetates **8** and **9**. Sodium borodeuteride reduction of the oxabicyclic chloromercurial gave 1-hydroxymethyl-6-oxabicyclo[3.2.1]octane-4-*d* (**4b**). The brosylate **5b** of this alcohol was also solvolyzed in acetic acid. The 4,4-bis(acetoxymethyl)-1-cyclohexene isolated from this acetolysis had lost approximately 50% of the deuterium originally located in the brosylate. The nature of the solvolytic rearrangements and the significance of the results of the deuterium experiments are discussed.

Numerous investigations of the solvolyses of bicyclic bridgehead methanol derivatives have been reported.[3-10] These studies have enhanced our understanding of bond-angle deformation and polar effects on reactivity in constrained neopentyl-type systems, particularly as regards the influence of these effects on 1,2- and 1,3-cationic rearrangements and fragmentations. The study of norbornenyl-1-carbinyl derivatives by Wilt and coworkers[8] has served to define the geometrical requirements for homoallylic delocalization. Their work in this system has provided a measure of the inductive (or field) effect of a vinyl group β to the solvolyzing center uncomplicated by homoallylic delocalization. Similar considerations led us to the investigation of the title bicyclic system in order to determine the effects of carbon–oxygen dipoles on solvolyses at the 1-carbinyl position.

In the solvolyses of compounds containing an alkoxyl group as a substituent elsewhere in the molecule, it is often difficult to assess the inductive (or field) effect of a C–O dipole on the cationic reaction center since appropriately located alkoxyl groups can facilitate solvolysis by intramolecular attack to form cyclic oxonium ions.[11-13] This competing process is eliminated in solvolyses of compounds such as **5a**. Furthermore, the precise orientation of the O–C bonds is held relatively fixed with respect to the reaction center and can be estimated with a high degree of certainty. It was also of interest to learn whether a 1,3-hydride shift from C-7 to the solvolyzing center would be observable in view of the potential cation-stabilizing effect of the ether oxygen.

Results

Syntheses.—The title brosylate **5a** and its deuterated analog **5b** were prepared using a four-step sequence

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(1) Abstracted in part from the thesis of R. A. Froehlich, submitted to San Diego State College in partial fulfillment of the requirements for M.S. Degree, Sept 1969.

(2) National Science Foundation High School Teacher Research Participant, 1967.

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