Anal. Calcd for $C_8H_4S_3Br_2$: C, 26.98; H, 1.13; S, 27.01; Br, 44.88. Found: C, 27.24; H, 1.22; S, 27.35; Br, 44.72.

On oxidation of the aqueous layers with 40 g of $K_3Fe(CN)_6$ as described for the synthesis of **12**, 12.2 g (85%) of the disulfide **12** could be reobtained, mp 66–68°.

Dithieno[2,3-*b*:3′,4′-*d*]thiophene (4).—Starting from 13.4 g (0.038 mol) of **13** and 50 ml of a 1.5 *N* ethereal *n*-BuLi solution, the dilithio derivative was prepared at −70°. The usual oxidative ring closure with 13 g (0.08 mol) of anhydrous $CuCl_2$ yielded a yellow oil, which on distillation furnished a solid, which was recrystallised from ether–pentane 1:3, giving 2.1 g (29%) of **4** as colorless needles: bp 114–116° (0.07 mm); mp 76–77°; nmr (CD_3COCD_3) δ 7.17 (d, 2, *J* = 5.5 Hz), 7.33 (d, 2, *J* = 5.5 Hz), 7.25 (d, 2, *J* = 2.6 Hz), 7.31 (d, 2, *J* = 2.6 Hz).

Anal. Calcd for $C_8H_4S_3$: C, 48.95; H, 2.06; S, 48.99. Found: C, 48.67; H, 2.14; S, 48.92.

Dithieno[3,2-*b*:2′,3′-*d*]thiophene 4,4-Dioxide[4] (15).—From 196 mg (1 mmol) of **1** dissolved in 15 ml of acetic acid and 3 ml of 30% H_2O_2, 130 mg (57%) of **15** was obtained after stirring for 30 hr at room temperature: mp 248–249° (lit.[4] mp 251.5–253°); uv max (EtOH) 236 mμ (log ε 4.06), 243 (4.06), 354 (3.78); nmr (CD_3COCD_3) δ 7.37 (d, 2, *J* = 5.0 Hz), 7.73 (d, 2, *J* = 5.0 Hz); ir (KBr) 1130, 1285 cm^{-1} (SO_2).

Dithieno[3,4-*b*:3′,4′-*d*]thiophene 4,4-Dioxide (16).—In 50 ml of dry dichloromethane 588 mg (3 mmol) of **3** and 1.20 g (7 mmol) of *m*-chloroperbenzoic acid were dissolved. The mixture was allowed to stand 14 hr at −10°, the solvent was evaporated, and the solid residue was washed with 10 ml of a saturated $NaHCO_3$ solution. After the residue was recrystallized from dioxane–water 1:1, 500 mg (70%) of **16** was obtained as long white needles: mp 239–240°; uv max (EtOH) 226 mμ (log ε 4.40), 234 (4.41), 243 (4.39), 271 (3.86), 294 (3.69); nmr (CD_3COCD_3) δ 7.77 (d, 2, *J* = 2.4 Hz), 8.13 (d, 2, *J* = 2.4 Hz); ir (KBr) 1130, 1290 cm^{-1} (SO_2).

Anal. Calcd for $C_8H_4S_3O_2$: C, 42.08; H, 1.76; S, 42.13. Found: C, 42.03; H, 1.84; S, 42.35.

Dithieno[2,3-*b*:3′,2′-*d*]thiophene 7,7-Dioxide (17).—From 588 mg (3 mmol) of **2** and 1.20 g (7 mmol) of *m*-chloroperbenzoic acid the procedure described for the preparation of **16** afforded 342 mg (50%) of the sulfone **17** as white needles from methanol: mp 193–195°; uv max (EtOH) 223 mμ (log ε 4.31), 285 (3.91), 335 (2.99); nmr (CD_3COCD_3) δ 7.38 (d, 2, *J* = 5.0 Hz), 8.00 (d, 2, *J* = 5.0 Hz); ir (KBr) 1150, 1305 cm^{-1} (SO_2).

Anal. Calcd for $C_8H_4S_3O_2$: C, 42.08; H, 1.76; S, 42.13. Found: C, 42.68; H, 2.00; S, 42.54.

Dithieno[2,3-*b*:3′,4′-*d*]thiophene 7,7-Dioxide (18).—By the method described for the preparation of **16**, from 500 mg (2.55 mmol) of **4** and 1.1 g (6.4 mmol) of *m*-chloroperbenzoic acid 370 mg (64%) of **18** was obtained as white needles from dioxane–water 1:1: mp 210–211°; uv max (EtOH) 236 mμ (log ε 4.24), 256 (4.00), 264 (4.16), 304 (3.08); nmr (CD_3COCD_3) δ 8.15 (d, 2, *J* = 2.4 Hz), 7.68 (d, 2, *J* = 2.4 Hz), 7.80 (d, 2, *J* = 5.0 Hz), 7.62 (d, 2, *J* = 5.0 Hz); ir (KBr) 1140, 1290 cm^{-1} (SO_2).

Anal. Calcd for $C_8H_4S_3O_2$: C, 42.08; H, 1.76; S, 42.13. Found: C, 42.07; H, 1.84; S, 42.08.

Dithieno[3,4-*b*:3′,4′-*d*]thiophene 4-Oxide (19).—To a solution of 196 mg (1 mmol) of **3** in 20 ml of acetic acid was added 2 ml of a 30% H_2O_2 solution. After the solution was stirred at room temperature for 5.5 hr, 40 ml of water was added, and the crystalline material was filtered and recrystallized from methanol yielding 160 mg (75%) of **19** as white needles: mp 203–204°; uv max (EtOH) 220 mμ (log ε 4.41), 242 (4.40), 248 (4.41), 268 (3.88), 278 (3.84), 298 (3.47); nmr (CD_3COCD_3) δ 7.71 (d, 2, *J* = 2.4 Hz), 8.18 (d, 2, *J* = 2.4 Hz); ir (KBr) 1030 cm^{-1} (S=O).

Anal. Calcd for $C_8H_4S_3O$: C, 45.26; H, 1.89; S, 45.31. Found: C, 45.08; H, 2.02; S, 44.87.

Registry No.—**1**, 3593-75-7; **2**, 236-63-5; **3**, 13090-49-8; **4**, 28504-79-2; **9**, 28504-80-5; **11**, 28504-81-6; **12**, 28504-82-7; **13**, 28504-83-8; **15**, 3807-53-2; **16**, 28504-85-0; **17**, 28504-86-1; **18**, 28504-87-2; **19**, 28504-88-3.

Solvolyses of 2α,5-Epithio-5α- and -Epoxy-5α-cholestane Derivatives. A Reactivity Factor of 10^{11} Due to Sulfur Participation in a 7-Thiabicyclo[2.2.1]heptane Derivative

TERUJI TSUJI, TAICHIRO KOMENO, HIKARU ITANI, AND HIROSHI TANIDA*

Shionogi Research Laboratory, Shionogi & Co., Ltd., Fukushima-ku, Osaka, Japan

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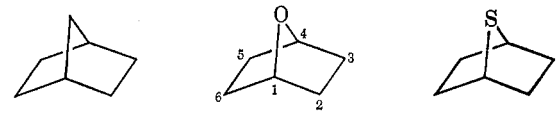
Solvolysis reactions of 2α,5-epithio-5α-cholestanes, a corresponding sulfoxide, and 2α,5-epoxy-5α-cholestanes bearing a bromo or methanesulfonyloxy group at the C-3 exo (α) or endo (β) reaction site were investigated in aqueous dioxane and compared with the solvolyses of *exo*- and *endo*-2-norbornyl methanesulfonates (**12** and **13**). Rates of exo derivatives of the epithiocholestane (**6**), the epoxycholestane (**9**), and 7-oxabicyclo[2.2.1]heptane (**1**) are of the same order of magnitude and about 10^3 times less than that of **12**. The products were those expected to result from Wagner–Meerwein rearrangement of the C(1)-C(2) bond, the hemithioacetal **14** (formed by cyclization of a *cis*-mercaptoaldehyde) from **6** and the *cis*-hydroxyaldehyde **16** from **9**. The small reactivities of **6** and **9** relative to **12** are considered to arise from the inductive effect of the oxygen or the sulfur bridge and the effects of bridging C-5 with C-10 (exo) by the B ring are indicated to be unimportant. The *endo*-epithiocholestane (**5**) solvolyzes with a very fast rate which is, in 70% dioxane, 1.1×10^{10} times the rate of *endo*-epoxycholestane (**8**) and 1.2×10^8 times that of **6**. A product of retention of configuration is exclusively formed from **5**. The results are interpreted in terms of participation of the sulfur atom, greatly enhanced by its geometric situation in the steroidal [2.2.1] system. Conversion of **5** to its sulfoxide **7** results in a disappearance of the sulfur participation. Whereas the *endo*-7-oxabicyclo[2.2.1]heptane (**2**) undergoes a Wagner–Meerwein rearrangement, **8** produces mainly a product of retention of configuration. This retention is discussed as being indicative of a small degree of participation of oxygen.

The ring system most extensively studied in connection with the interest in the role of neighboring group participation in carbonium ion reactions is the bicyclo[2.2.1]heptane system.[1] Effects of the replacement of the 1,4-methylene bridge in this system by

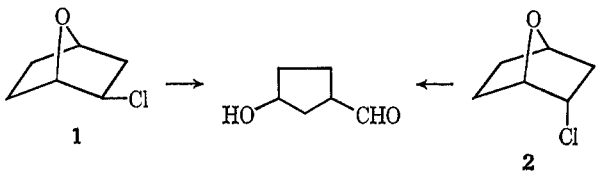


an oxygen bridge were first investigated by Martin and Bartlett[2] by the solvolyses of 7-oxabicyclo[2.2.1]-hept-2(*exo* and *endo*)-yl chlorides (and bromides).

(1) (a) P. D. Bartlett, "Nonclassical Ions," W. A. Benjamin, New York, N. Y., 1965; (b) J. A. Berson, "Molecular Rearrangements," Vol. 1, P. de Mayo, Ed., Interscience, New York, N Y., 1963, Chapter 3; (c) C. D. Sargent, *Quart. Rev.* (*London*), **20**, 301 (1966).

(2) J. C. Martin and P. D. Bartlett, *J. Amer. Chem. Soc.*, **79**, 2533 (1957).

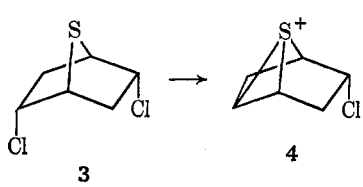
They found that the exo chloride **1** is less reactive than *exo*-2-norbornyl chloride by a factor of approxi-



1 **2**

mately 2000 and that the endo chloride **2** solvolyzes 160 times more slowly at 140° than **1**. In either case, the solvolysis product was that expected to result from rearrangement, 3-formylcyclopentanol. These workers' interpretation of the results was that the replacement of the methano bridge by the oxygen bridge causes the adverse inductive effect by the oxygen atom, with no capability for participation by the oxygen atom, and that the anchimeric assistance of ionization, as proposed for *exo*-2-norbornyl chloride, is not greatly affected by the replacement.

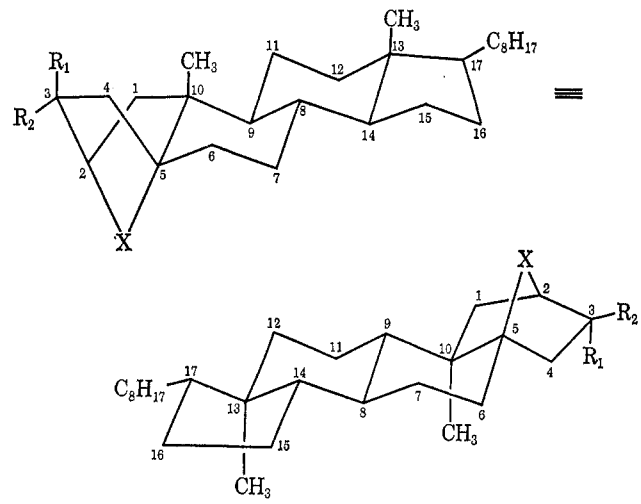
A neighboring sulfur atom has long been known as a very effective participating group[3] and, in appropriate cases, participation by sulfur has been found to be much greater than that by oxygen.[4] However, recent evidence in some bridged polycyclic systems demonstrates that the ability of sulfur to participate is greatly influenced by the stereochemistry of the leaving group and the internuclear distance from the developing electron-deficient center.[5,6] For these reasons, we have been interested in the solvolysis of 7-thiabicyclo[2.2.1]heptane derivatives, in which the methylene bridge in bicyclo[2.2.1]heptane is replaced by the sulfur bridge. Corey and Block[7] succeeded in a convenient synthesis of 7-thiabicyclo[2.2.1]heptanes and found that one of these compounds, 2,5-bis-*endo*-dichloro-7-thiabicyclo[2.2.1]heptane (**3**), solvolyzed with a very fast rate and gave a stereospecific product. Although they suggested that these results were indicative of intervention of a sulfonium ion intermediate (**4**), since their research was directed toward



3 **4**

the development of synthetic methods, they reported neither the kinetic data on **3** nor the solvolytic behavior of the exo counterpart.

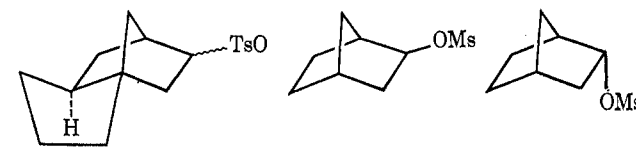
Recently, 2α,5-epithio-5α-cholestanes (**5** and **6**) and the related sulfoxide (**7**), and 2α,5-epoxy-5α-cholestanes (**8**, **9**, and **10**) bearing groups suitable for solvolysis, bromo or methanesulfonyloxy, at C-3, became available in our laboratory.[8] These steroidal compounds have the 7-thia- or 7-oxabicyclo[2.2.1]heptane system in the A ring and the substituents at C-3 make sets of exo (α) and endo (β) epimers. Corrections due only to the difference between the leaving bromo and methanesulfonyloxy groups will be needed for discussion of the relative reactivities. Furthermore, the



5, X = S; R_1 = Br; R_2 = H
6, X = S; R_1 = H; R_2 = OSO_2CH_3
7, X = SO; R_1 = Br; R_2 = H
8, X = O; R_1 = OSO_2CH_3; R_2 = H
9, X = O; R_1 = H; R_2 = OSO_2CH_3
10, X = O; R_1 = H; R_2 = Br

(R_1, β or endo; R_2, α or exo)

bridgehead C-5 and the C-10 exo (or α) positions in the [2.2.1] moiety are linked by the four-carbon chain of the B ring. Interest in such a linkage in the [2.2.1] system was exemplified by Corey and Glass[9] by the solvolysis of *exo*- and *endo*-4,5-*exo*-trimethylene-2-norbornyl tosylates (**11**), in which a trimethylene chain connects the corresponding C-4 bridgehead and the C-5 exo positions. Therefore, to investigate the effect of the B ring on the solvolysis of the steroids would be also of considerable interest. These considerations led us to initiate the present work.



11e, *exo*-TsO
11n, *endo*-TsO

12

13

Results

Solvolysis Rates.—Rates of hydrolysis of the steroids **5**–**10** and, as reference compounds, *exo*- and *endo*-norbornyl methanesulfonates (mesylates) (**12** and **13**) were measured in aqueous dioxane containing varying amounts of water and 1.1 equiv of sodium acetate, by titrating at intervals the methanesulfonic acid or the hydrobromic acid liberated during the reaction. The observed kinetics were first order in all cases, and the experimental infinity titers at about ten half-lives corresponded to the calculated values. Since we failed to prepare the epithio β-mesylate (X = S, R_1 = OSO_2CH_3, R_2 = H), the solvolyses of the less reactive bromides (**5** and **7**) were carried out. Rate constants

(3) (a) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill, 1962, pp 108–110; (b) B. Capon, *Quart. Rev., Chem. Soc.*, **18**, 45 (1964).

(4) For example, M. Hojo, T. Ichi, Y. Tamaru, and Z. Yoshida, *J. Amer. Chem. Soc.*, **91**, 5170 (1969).

(5) R. E. Ireland and H. A. Smith, *Chem. Ind. (London)*, 1252 (1959).

(6) L. A. Paquette, G. V. Meehan, and L. D. Wise, *J. Amer. Chem. Soc.*, **91**, 3231 (1969).

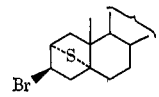
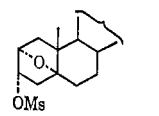
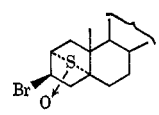
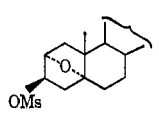
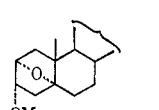
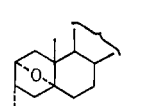
(7) E. J. Corey and E. Block, *J. Org. Chem.*, **31**, 1663 (1966).

(8) (a) T. Komeno and H. Itani, *Chem. Pharm. Bull.*, **18**, 608 (1970); (b) T. Komeno, H. Itani, H. Iwakura, and K. Nabeyama, *ibid.*, **18**, 1145 (1970); (c) Y. Komeno, M. Kishi, and K. Nabeyama, *Tetrahedron*, in press; T. Komeno and M. Kishi, to be published.

(9) E. J. Corey and R. S. Glass, *J. Amer. Chem. Soc.*, **89**, 2600 (1967).

TABLE I

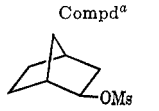
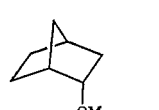
SOLVOLYSIS OF 2α,5-EPITHIO-5α- AND -EPOXY-5α-CHOLESTANE DERIVATIVES IN AQUEOUS DIOXANE

Compd[a]	Vol % of dioxane[b]	Temp, °C	k, sec^{-1}	Calcd at 25°: $\Delta H^{\ddagger}$, kcal	Calcd at 25°: $\Delta S^{\ddagger}$, cal/deg	Calcd at 25°: k, sec^{-1}
 5	90	5.0	2.39×10^{-5}	17.30	−17.4	2.04×10^{-4} [c]
	90	15.0	6.82×10^{-5}			
	90	25.0	2.09×10^{-4}			
	80	5.0	5.34×10^{-4}			
	70					4.12×10^{-2} [d]
 6	90	119.5	2.35×10^{-5}	27.50	−10.2	2.60×10^{-10}
	90	151.2	3.46×10^{-4}			
	70	90.7	3.17×10^{-5}	25.70	−8.9	1.05×10^{-8}
	70	119.5	4.56×10^{-4}			
	60					3.82×10^{-8} [d]
 7	60	130.2	2.02×10^{-5}	21.92	−26.2	1.00×10^{-9}
	60	160.3	1.42×10^{-4}			
 8	70	119.8	2.99×10^{-5}	30.07	−3.2	1.14×10^{-10}
	70	149.9	4.89×10^{-4}			
 9	90	119.3	7.78×10^{-5}	25.93	−11.8	1.66×10^{-9}
	90	149.0	8.52×10^{-4}			
	70	80.2	4.35×10^{-5}	22.64	−14.7	9.50×10^{-8}
	70	109.7	5.56×10^{-4}			
	80					1.78×10^{-8} [d]
 10	80	157.2	4.24×10^{-4}	25.39	−15.6	5.98×10^{-10}
	80	127.7	4.53×10^{-5}			

[a] [R—X] = 4.0×10^{-3} *M*. [b] Containing 1.1 equiv of CH_3COONa. [c] Calculated from the observed rates using the least-squares method. [d] Extrapolated by the Grunwald-Winstein equation, $\log k/k_0 = mY$. We obtained the following m values: for **5**, 1.13 at 5°; for **6**, 0.79 at 25°; for **9**, 0.86 at 25°.

TABLE II

SOLVOLYSIS OF 2-NORBORNYL METHANESULFONATE IN AQUEOUS DIOXANE

Compd[a]	Vol % of dioxane[b]	Temp, °C	k, sec^{-1}	Calcd at 25°: $\Delta H^{\ddagger}$, kcal	Calcd at 25°: $\Delta S^{\ddagger}$, cal/deg	Calcd at 25°: k, sec^{-1}	*exo/endo* rate ratio
 12	90	80.1	5.07×10^{-4}	21.15	−14.2	1.68×10^{-6}	180
	90	50.2	2.91×10^{-5}				(90% dioxane)
	70	25.0	1.21×10^{-4}			1.21×10^{-4}	880
							(70% dioxane)
 13	90	129.9	3.69×10^{-4}	23.53	−16.5	9.42×10^{-9}	
	90	100.0	3.32×10^{-5}				
	70	100.0	7.08×10^{-4}	24.64	−7.5	1.38×10^{-7}	
	70	69.9	3.60×10^{-5}				

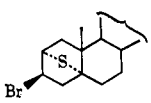
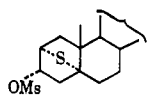
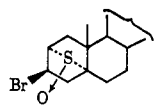
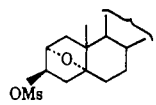
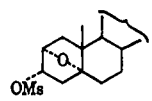
[a] [R—X] = 8.0×10^{-3} *M*. [b] Containing 1.1 equiv of CH_3COONa.

thus obtained for the steroids are summarized in Table I and those of **12** and **13** in Table II. For comparison of the relative reactivities, the rate constants were extrapolated to 25° by the Arrhenius equation, the rate of **5** in 70% aqueous dioxane and that of **6** in 60% aqueous dioxane were calculated by the Grunwald–Winstein equation, $\log k/k_0 = mY$,[10] and the rate factor, $k_{OSO_2CH_3}/k_{Br} = 30$, obtained from the hydrolyses of **9** and **10** in 80% aqueous dioxane, was used for correction of the leaving group effects. Table III lists the relative reactivities choosing that of **6** as unity.

For product determination, the hydrolyses were carried out for ten half-lives under the same conditions as used for the rate studies. Hydrolysis of **5** in 90% dioxane at a room temperature was found to give the product of retention of configuration, the endo alcohol and its acetate, without any other detectable compound. Hydrolysis of **6** in 70% dioxane caused rearrangement forming mainly a hemithioacetal, for which the structure **14** was assigned. The nmr spectrum shows a doublet at τ 5.25 (J = 1.6 Hz), assignable to a proton attached to the carbon bearing the

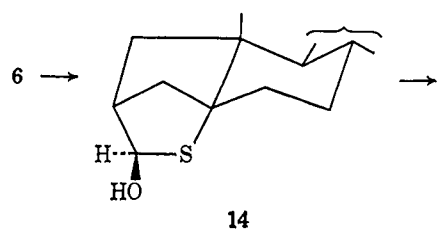
(10) J. F. Bunnett, "Technique of Organic Chemistry," Vol. 8, part 1, S. L. Friess, E. S. Lewis, and A. Weissberger, Ed., Interscience, New York, N. Y., 1961, Chapter 6, pp 240–245.

TABLE III
RELATIVE REACTIVITY AT 25°

Vol % of dioxane	 5[a]	 6	 7[a]	 8	 9
90	2.3×10^7	1.0			6.4
70	1.2×10^8	1.0		0.011	9.0
60		1.0	0.79		

[a] The rate for the corresponding methanesulfonate was estimated by use of the factor, methanesulfonate; bromide = 30, obtained from the solvolysis of the epoxy α derivatives (9 and 10).

hydroxyl group, and a broad doublet at τ 7.44 (J = 6.0 Hz), assignable to the bridgehead proton. Vicinal coupling constants in the bicyclo[2.2.1]heptane system have been well investigated.[11] The constants between the C-1 bridgehead proton and the C-2 (endo) proton in this system are usually found in the range 0–2 Hz, while those between the bridgehead proton and the C-2 (exo) proton in the range 3–6 Hz. On the basis of these data, the hydroxyl group in **14** was determined as the exo orientation. Oppenauer oxidation of **14** gave a bridged γ-thiolactone **15**, whose CD curve exhibits a negative sign of the n–π* Cotton effect at 280 mμ.[12]



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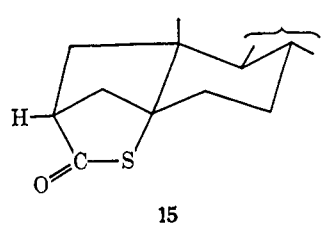

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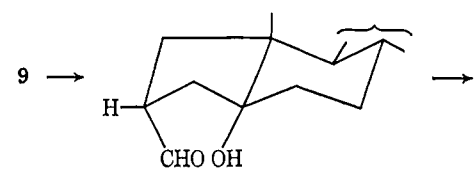
The products from the sulfoxide **7** were not investigated in detail because of their apparent complexity.

Hydrolysis of **8** in 70% dioxane led to three products, separable by preparative layer chromatography, whose yields were determined as 86.8, 1.8, and 0.9%, respectively. The structures for the 86.8% and 0.9% products were determined to be, respectively, the alcohol of retention (R_1 = OH in **8**) and the alcohol of inversion (R_2 = OH in **9**). The structure of the product of 1.8% yield was found to be identical with the predominant product from **9**, mentioned next. Hydrolysis of **9** in 70% dioxane fromed a rearranged product in 80% yield, whose structure was assigned as the *cis*-hydroxyaldehyde (**16**) by spectral data. The nmr spectrum shows a doublet due to the secondary aldehyde proton at τ 0.26 (J = 2.0 Hz). The orientation of the aldehyde group was demonstrated by the fact that oxidation of **16** with Jones reagent in acetone gave a bridged γ lactone (**17**), showing an infrared carbonyl band at 1784 cm^{-1} and a negative n–π* Cotton effect curve ([θ] −1490 at 219 mμ), as predicted from the lactone sector rule.[13]



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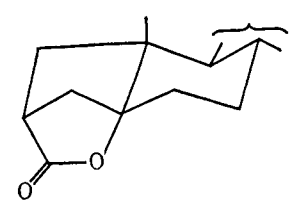

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Discussion

First, the reactivities of the exo compounds are discussed. In Table I the rates of the epithio exo (**6**) and the epoxy exo (**9**) compounds are found to be of the same order of magnitude, so that replacement of the oxygen bridge by the sulfur bridge in these steroidal C-3 exo systems is unimportant in solvolysis. The chloride **1** was reported to be 2000 times less reactive than *exo*-2-norbornyl chloride and comparison of the data in Tables I and II indicates that **9** is less reactive than **12** in 70% dioxane by approximately the same factor, 1300. In addition, nearly identical reactivities were predicted for 7-oxabicyclo[2.2.1]hept-2(*exo*)-yl bromide and **10** by a rough calculation based on available rate constants: for the former bromide, $k_1 = 7.4 \times 10^{-9}$ sec^{-1} at 25° in 50% dioxane[2] (the reported data were extrapolated to 25°); for **10**, $k_1 = 5.98 \times 10^{-10}$ sec^{-1} at 25° in 80% dioxane.[14] It is, therefore, suggested that a factor(s) responsible for the diminished reactivity of the **1** derivatives relative to the *exo*-2-norbornyl derivatives is also effective for **9** and **10** and that the B ring connecting the C-5

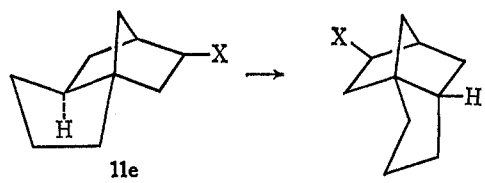
(11) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, New York, N. Y., 1969, pp 288–289; J. I. Musher, *Mol. Phys.*, **6**, 93 (1963); J. E. Franz, C. Osuch, and M. W. Dietrich, *J. Org. Chem.*, **29**, 2922 (1964).

(12) (a) K. Kuriyama, K. Komeno, and K. Takeda, *Shionogi Kenkyusho Nempo*, **17**, 66 (1967); (b) K. Takeda, K. Kuriyama, T. Komeno, D. A. Lightner, R. Records, and C. Djerassi, *Tetrahedron*, **21**, 1203 (1965).

(13) J. P. Jennings, W. Klyne, and P. M. Scopes, *Proc. Chem. Soc., London*, 412 (1964); *J. Chem. Soc.*, 7211 (1965).

(14) Since, for 7-oxabicyclo[2.2.1]hept-2(*exo*)-yl bromide, the rate constants at 85° of 8.58×10^{-7} sec^{-1} in 80% ethanol and 8.24×10^{-6} sec^{-1} in 50% dioxane have been reported,[2] an application of the Grunwald–Winstein equation gives m = 0.725. Assuming that m is independent of reaction temperature, this m value and the rate in 50% dioxane give a rate constant of 1.95×10^{-10} sec^{-1} at 25° in 80% dioxane. Therefore, the relative reactivities for 7-oxabicyclo[2.2.1]hept-2(*exo*)-yl bromide and **10** are 1 to 3.

bridgehead with the C-10 exo position is not a significant factor in the present steroidal oxa system. For the diminished reactivity of the oxa compounds, the inductive effect of the oxygen atom seems to be the most important, as postulated by Martin and Bartlett.[2] The large rate decrease and the inhibition of Wagner–Meerwein rearrangement (**11e** → **18**) resulting from the trimethylene linkage in **11e**[9] is in sharp contrast

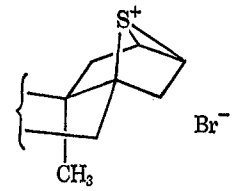


11e **18**

with the absence of such effects in the case of bridging due to the B ring. It has been proposed that, in the case of **11e**, the Wagner–Meerwein rearrangement accompanying the solvolysis steadily increases strain energy and also that such an increase of strain would be diminished to a small value when the number of bridge atoms is large (longer than a trimethylene chain).[9] Although it is not simple in such complex molecules as the present steroids to estimate the difference in strain between the starting compound and the product formed with Wagner–Meerwein rearrangement, inspection of Fieser–Dreiding molecular models suggests that the strain difference is not serious, in accord with our observations.

The formation of products in the exo solvolysis is mechanistically uniform; the occurrence of Wagner–Meerwein rearrangement was observed in all cases and, as a result, the hemithioacetal **14** and the *cis*-hydroxyaldehyde **16** were formed from **6** and **9**, respectively. These results are similar to that from **1**.

The epithio endo compound **5** is enormously more reactive than the exo counterpart **6** and the oxa analog **8**. After correction for the difference of leaving groups (Br *vs.* OSO_2CH_3), the endo/exo reactivity ratio is 2.3×10^7 in 90% dioxane and 1.2×10^8 in 70% dioxane and the reactivity ratio of **5** to **8** is 1.1×10^{10} in 70% dioxane (Table III). In the oxa-bridged series the exo isomer **9** hydrolyzes in 70% dioxane 820 times faster than the endo isomer **8**. It is noted that this exo/endo rate ratio is quite comparable to that found in the norbornyl system (880 in the same solvent). Since it can be considered that the rate for **6** involves an acceleration by C(1)–C(2) bond participation [equivalent to C(1)–C(6) bond participation in the norbornyl system], to a degree indicated by the exo/endo rate ratio, a real rate enhancement in **5** may amount to a huge factor of $\sim 10^{11}$ correcting the apparent factor of 1.2×10^8 in 70% dioxane for the exo/endo rate ratio. Furthermore, the high reactivity of **5** completely vanishes on transformation of **5** into the sulfoxide **7**. Therefore, it is apparent that the sulfur atom in **5** exerts a remarkable driving force during ionization of the C–Br bond. The solvolysis process of **5** can be formulated as involving direct interaction of the lone pair electrons on the sulfur with the developing cationic center at C-3 to stabilize the transition state and thereby would lead directly to such a three-membered sulfonium ion as **19**. Such participation of the



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sulfur agrees with the observed exclusive formation of the retained product in a stereospecific manner.

The steroidal epoxy endo **8** is less reactive than the *endo*-norbornyl **13** by a factor of 1200 in 70% dioxane. The exo/endo rate ratios are 820 in the steroidal epoxy system, 880 in the norbornyl system, and 160 in the 7-oxabicyclo[2.2.1]heptyl system [although in the last system the leaving group, the reaction solvent, and the temperature used (140°) were different]. All the ratios are of the same order of magnitude. However, whereas the products from the 7-oxa[2.2.1] **2** and the norbornyl **13** involve Wagner–Meerwein rearrangement, the hydrolysis of **8** resulted mainly in formation of the retained product. A possible explanation is that the retention of configuration from **8** is a result of participation of the oxygen. Although the major factor influencing the observed reactivities of **8** and the exo counterpart **9** is the great rate-retarding inductive effect of the oxygen, both these reactions are affected additionally by much smaller rate-accelerating factors, oxygen participation in the case of **8** and rearrangement to an alkoxycarbonium ion with **9**. The "normal" exo/endo rate ratios for the above 7-oxa compounds might result from cancellation of these two rate-accelerating factors. The geometric constraints in **8** imposed by its fused steroidal skeleton prevent rearrangement to the alkoxycarbonium ion and result in retention of configuration, while **2** is not geometrically restrained from rearrangement to a stable alkoxycarbonium ion. Nevertheless, if the oxygen exerts a significant product control after an unassisted ionization, the present results from **8** can be accommodated without the proposal of oxygen participation. A classical cation with a charge situated at the C-3 position could not be transformed into the alkoxycarbonium ion due to the geometric constraints.

Experimental Section

All melting points were taken on a Kofler hot-stage and are uncorrected. Optical rotations were determined with a Perkin-Elmer polarimeter, type 141, in chloroform containing 1% of ethanol. Ir spectra in Nujol mulls were measured by use of a Koken DS-201B spectrophotometer. CD and ORD curves were determined with a Jasco Model ORD/UV-5 equipped with CD. All nmr spectra were run in deuteriochloroform solutions with a Varian A-60 spectrometer, using tetramethylsilane as an internal standard. For preparative tlc, silica gel G (E. Merck Co.) was used as an adsorbent.

Materials.—Preparation and structural elucidation of the materials (**5**–**10**) used for hydrolysis were reported elsewhere.[8] The physical properties and elementary analyses are listed in Table IV.

***exo*-2-Norbornyl Mesylate (12).**—*exo*-2-Norbornanol[15] was dissolved in cold pyridine, treated with a slight excess of mesyl chloride, and allowed to stand in a refigerator overnight. After being poured into cold water, the reaction mixture was extracted with ether, washed successively with dilute sulfuric acid, sodium carbonate solution, and water, and dried over sodium

(15) H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, **81**, 4106 (1959).

TABLE IV

Compd	Mp, °C	[α]D, deg (°C)[a]	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found	S or Br, % Calcd	S or Br, % Found
5	88–89	+43.1 (24)	$C_{27}H_{45}BrS$	67.33	67.34	9.42	9.44	16.59[b]	16.62
6	120–121.5	−24.9 (21)	$C_{28}H_{48}O_3S_2$	67.69	67.46	9.74	9.67	12.91	12.81
7	94–95	+79.9 (22)	$C_{27}H_{45}OSBr$	65.17	65.08	9.12	9.14	16.06[b]	15.98
8	128–129.5	+28.7 (23)	$C_{28}H_{48}O_4S$	69.95	69.97	10.06	10.13	6.70	6.80
9	116–118	+13.2 (19)	$C_{28}H_{48}O_4S$	69.95	70.05	10.06	10.02	6.70	6.78
10	122–124	+23.6 (22)	$C_{27}H_{45}OBr$	69.66	69.66	9.74	9.69	17.17[b]	17.35

[a] Measured in chloroform solution containing 1% ethanol. [b] Calculated value for bromine.

sulfate. Evaporation of the ether under reduced pressure gave **12** as an oil, which was used for hydrolysis at once, $n^{25}D$ 1.4766.

Anal. Calcd for $C_8H_{14}O_3S$: C, 50.50; H, 7.42; S, 16.86. Found: C, 50.56; H, 7.49; S, 16.50.

endo-**2-Norbornyl Mesylate** (**13**).—According to the same procedure, **13** was obtained as an oil from *endo*-2-norbornanol,[16] $n^{25}D$ 1.4802.

Anal. Calcd for $C_8H_{14}O_3S$: C, 50.50; H, 7.42; S, 16.86. Found: C, 50.22; H, 7.38; S, 17.08.

Hydrolysis of 3β-Bromo-5α-cholestane 2α,5-Episulfide (**5**).—A solution of 100 mg (0.21 mmol) of **5** in 53 ml of 90% aqueous dioxane containing 0.23 mmol of sodium acetate was allowed to stand overnight at room temperature. The reaction mixture was concentrated under reduced pressure, diluted with water, and extracted with methylene dichloride, and the methylene dichloride solution was dried over sodium sulfate. After removal of the solvent, the residue, which exhibited two spots on tlc, was separated by preparative tlc with cyclohexane–ethyl acetate (3:1) to yield 40 mg (41.8%) of **5**-OAc, mp 120.5–121°, and 36 mg (41.4%) of **5**-OH, mp 149–150°, the properties of which were identical with the reported data.[8c]

Hydrolysis of 3α-Mesyloxy-5α-cholestane 2α,5-Episulfide (**6**).—A mixture of 900 mg (1.81 mmol) of **6** in 70 ml of dioxane and 364 mg (4.44 mmol) of sodium acetate in 30 ml of water was heated in a sealed tube at 90° for 61 hr. The work-up as used for **5** afforded 800 mg of crude products, which were chromatographed over 80 g of silica gel. The fractions eluted with benzene–ether (9:1) gave 396 mg of the hemithioacetal **14** as colorless crystals in a yield of 52.2%. Recrystallization from acetone afforded a pure sample, mp 145–146°, $[\alpha]^{23}D$ −52.3 ± 1.8° (*c* 0.524).

The infrared absorptions due to OH appeared at 3598, 3450, 1040, 1030, and 1015 cm^{-1}. The nmr spectrum showed τ 9.33 (s, 3 H of 13-CH_3), 9.04 (s, 3 H of 10-CH_3), 7.44 (d, J = 6.0 Hz, 1 H of 2β-H), and 5.25 (d, J = 1.6 Hz, 1 H of SCH).

Anal. Calcd for $C_{27}H_{46}OS$: C, 77.45; H, 11.07; S, 7.66. Found: C, 77.29; H, 11.10; S, 7.65.

5-Mercapto-*A*-nor-5α-cholestane-2α-carboxylic Acid Lactone (**15**).—A mixture of 150 mg (0.359 mmol) of **14**, 72 mg (0.353 mmol) of aluminum isopropoxide, and 1.2 ml (11.4 mmol) of cyclohexanone in 15 ml of dry benzene was heated under reflux for 1 hr. After addition of an aqueous solution of sodium potassium tartrate tetrahydrate, the reaction solution was extracted with methylene dichloride. The methylene dichloride extract was washed with water and dried over sodium sulfate. After evaporation of the solvent, the residue was subjected to preparative tlc, developing with cyclohexane–ethyl acetate (4:1). The less mobile fraction gave 30 mg (20%) of the starting material **14**. The more mobile fraction afforded 110 mg of γ-thiolactone **15** in a yield of 72.9%, which was recrystallized from acetone yielding a pure sample: mp 126–127°; $[\alpha]^{23}D$ +41.0 ± 1.5° (*c* 0.524); CD (isooctane) $[\theta]_{280}$ −4377, $[\theta]_{272}$ −4445, $[\theta]_{237}$ +36560, $[\theta]_{218}$ −14510, $[\theta]_{205}$ +6890; ORD (isooctane) $[\phi]_{400}$ +440, $[\phi]_{350}$ +684, $[\phi]_{300}$ +646, $[\phi]_{247}$ +28750, $[\phi]_{226}$ −37380, $[\phi]_{205}$ +11710. The infrared spectrum showed an absorption of CO at 1706 cm^{-1}. The nmr spectrum showed τ 9.31 (s, 3 H of 13-CH_3), 8.91 (s, 3 H of 10-CH_3), and 7.16 (m, 1 H of 2β-H).

Anal. Calcd for $C_{27}H_{44}OS$: C, 77.63; H, 10.62; S, 7.67. Found: C, 77.24; H, 10.58; S, 7.74.

Hydrolysis of 3β-Mesyloxy-5α-cholestane 2α,5-Epoxide (**8**).—To a solution of 1.0 g (2.08 mmol) of **8** in 70 ml of dioxane was added a solution of 264 mg (3.22 mmol) of sodium acetate in 30 ml of water, and the mixture was heated in a sealed tube at 120° for 64 hr. After the usual work-up, 864 mg of crystalline products obtained were chromatographed through 85 g of silica gel using a fraction collector. Elution with chloroform–ethyl acetate (9:1) gave four kinds of products roughly separated, which were further purified by preparative tlc to yield 15 mg (1.8%) of the hydroxyaldehyde **16**, 27 mg (2.5%) of the starting mesylate **8**, 7 mg (0.9%) of **9**-OH, and 727 mg (86.8%) of the retained alcohol **8**-OH.

Hydrolysis of 3α-Mesyloxy-5α-cholestane 2α,5-Epoxide (**9**).—Hydrolysis of 1.0 g (2.08 mmol) of **9** was carried out (80°, 45 hr) similarly as described for **8**, furnishing 840 mg of a crude material. This material was purified by chromatography over 84 g of silica gel. The fractions eluted with benzene–ether (9:1) gave 661 mg of the hydroxyaldehyde **16** in a yield of 79%, which was recrystallized from acetone yielding a pure sample, mp 112–114°, $[\alpha]^{23}D$ +11.5 ± 0.6° (*c* 0.989). The infrared spectrum showed absorption of OH at 3524 and 3470 cm^{-1}, C=O at 2720, 1717, and 1706 cm^{-1}. The nmr spectrum showed τ 9.33 (s, 3 H of 13-CH_3), 9.09 (s, 3 H of 10-CH_3), 6.90–7.40 (broad m, 1 H of 2β-H), and 0.26 (d, J = 2.0 Hz, 1 H of CHO).

Anal. Calcd for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52. Found: C, 80.56; H, 11.44.

5-Hydroxy-*A*-nor-5α-cholestane-2α-carboxylic Acid Lactone (**17**).—To a solution of 50 mg of **16** in 0.5 ml of acetone was added 0.05 ml of 8 *N* Jones reagent, and the mixture was stirred for 10 min at room temperature. The reaction solution was poured into ice–water and extracted with ether. The ether extract was washed with sodium carbonate, dried over sodium sulfate, and then evaporated to dryness giving 30 mg of **17** as colorless crystals in a yield of 60%. These were recrystallized from ether–methanol: mp 145–147°; $[\alpha]^{23}D$ 0 ± 0.4°; $[\alpha]_{436}$ −51.8 ± 4.0°; $[\alpha]_{365}$ −186.8° (*c* 0.985); CD (isooctane) $[\theta]_{255}$ 0, $[\theta]_{219}$ −14690, $[\theta]_{210}$ −9770; ORD (isooctane) $[\phi]_{235}$ −6765, $[\phi]_{207}$ +15650. The infrared spectrum showed an absorption of C=O at 1784 cm^{-1}. The nmr spectrum gave τ 9.18 (s, 3 H of 13-CH_3), 8.93 (s, 3 H of 10-CH_3), and 7.27 (m, 1 H of 25-H).

Anal. Calcd for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 80.87; H, 11.00.

Kinetic Measurements.—The dioxane was treated by the procedure of Fieser,[17] distilled from sodium, and stored under nitrogen. Perchloric acid standard solution was prepared by diluting 0.85 ml of reagent grade 70% perchloric acid with the above dioxane to 100 ml of the total volume, followed by further dilution fifty times with dioxane; the concentration was approximately 0.002 *N*. Samples of the mesylates and the bromides (*ca.* 0.08 mmol) were weighed into a 20-ml volumetric flask and dissolved with a constant volume of the dioxane, followed by addition of purified water containing 0.088 mmol of sodium acetate to the total volume of 20 ml. Aliquots, nine 2-ml portions, were pipetted from the flask into ampoules. The sealed ampoules were placed in the constant temperature bath and then plunged into 10 ml of the dioxane. In the case of **5**, aliquots were pipetted directly from the volumetric flask maintained at the reaction temperature into 10 ml of cooled acetone and titrated. "Infinity" ampoules were removed after ten half-lives and usually two were taken for each run. The sodium acetate decrease on the formation of methanesulfonic acid or hydrobromic acid was titrated with the standard perchloric acid solution using a Metrohm potentiograph E336. Rate constants were determined by the infinity titer method.

Registry No.—**5**, 28627-71-6; **6**, 28627-72-7; **7**, 28627-73-8; **8**, 27948-66-9; **9**, 26519-23-3; **10**, 27948-63-6; **12**, 28627-77-2; **13**, 28627-78-3; **14**, 28627-79-4; **15**, 28627-81-8; **16**, 28627-82-9; **17**, 28627-83-0.

(16) S. Winstein and D. Trifan, *J. Amer. Chem. Soc.*, **74**, 1147 (1952).

(17) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath, Boston, Mass., 1957, p 284.