Conformational Analysis. 47.[1a] The Stereochemistry of Sulfur Organic Compounds. 21.[1b] The Conformation of Oxanes with Sulfur Substituents

José Luis García Ruano,[2a] Jesus Rodríguez,[2a] Felipe Alcudia,[2b] José Manuel Llera,[2b] Edward M. Olefirowicz,[2c] and Ernest L. Eliel*[2c]

Department of Organic Chemistry, Universidad Autónoma, Madrid, Spain, Department of Organic Chemistry, School of Pharmacy, Seville, Spain, and W.R. Kenan Laboratories, University of North Carolina, Chapel Hill, North Carolina 27514

Received February 9, 1987

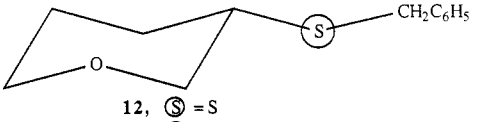
The energy difference between equatorial and axial sulfur functions at C(3) in oxane has been determined in various solvents by low-temperature ^{13}C NMR spectroscopy. The values in CD_2Cl_2 are as follows: MeS, −1.21 ± 0.11 kcal/mol; SOMe, more polar isomer, −0.10 ± 0.05 kcal/mol, less polar isomer, −0.43 ± 0.13 kcal/mol; SO_2Me, ca. −1.45 kcal/mol; Me_2S^+, 0.55 kcal/mol; HS, −1.1 ± 0.1 kcal/mol (negative values meaning preference for the equatorial conformer). The configurations of the two sulfoxides were determined by a combination of X-ray crystallography and proton and ^{13}C NMR spectroscopy. In the case of MeS, $-\Delta G°$ is close to the average of the corresponding conformational free energy differences in cyclohexane and dioxane (at C-5). For MeSO the same is true for the mean $-\Delta G°$ of the two sulfoxides but not for the individual values. In the case of $MeSO_2$, the experimental value of $-\Delta G°$ is much larger than the above average, supporting an earlier hypothesis that in 1,3-dioxan-5-yl methyl sulfone the methyl group is turned into the ring. In the methyl 3-tetrahydropyranyl sulfone, this would produce serious steric compression with the axial hydrogen at C(5).

In previous publications we have discussed conformational equilibria of oxanes substituted with nonpolar (methyl) groups,[3] of thianes and their sulfoxides, and sulfones substituted with hydroxy, alkoxy, and acetoxy groups,[1a] as well as conformational properties of acyclic compounds with vicinal oxygen and sulfur functions.[4] The present work deals with oxanes substituted in position 3 with sulfide, sulfoxide, sulfone, and sulfonium functions and serves as a check for the magnitudes of pertinent sulfur/oxygen gauche interactions; it also points to some characteristic differences in conformational equilibria of sulfur-substituted cyclohexanes and corresponding 1,3-dioxanes (substituent in 5) on one hand and 3-substituted oxanes on the other. In contrast to the conformational energies of nonpolar substituents in oxanes,[3] the $\Delta G°$ values for polar substituents are *not* necessarily midway between those in cyclohexanes and those in 1,3-dioxanes.

Synthesis and Configurational Assignment. Compounds in the 3-substituted oxane series were synthesized as shown in Scheme 1, R = H. Free radical catalyzed addition of thiolacetic acid to dihydropyran followed by saponification to mercaptide and methylation gave the methylthio ether **1**, which was oxidized with 1 equiv of sodium periodate to a diastereomer mixture of sulfoxides **2** and **3**, which were separated by chromatography. Oxidation of **1** with excess periodate gave the sulfone **4**; sulfonium salt **5** was prepared from **1** and methyl *p*-toluenesulfonate. Acidification of the solution of mercaptide (vide supra) gave thiol **6**.

We also prepared the corresponding cis- and trans-6-methyl compounds (Scheme I, R = CH_3) by starting from 6-methyldihydropyran[5] in place of dihydropyran. The diastereomeric 2-methyl-5-(methylthio)oxanes (**7**) were separated by chromatography and the cis isomer was further oxidized to sulfoxides *cis*-**8** and -**9** (separated by chromatography). Both isomers of **7** were converted to sulfones **10** and sulfonium salts **11**. The cis (equatorial–axial) isomer **7** was readily distinguished from the diequatorial trans by the higher field position of most of its signals in the ^{13}C NMR spectrum and by its much larger (diaxial) proton coupling constant between $H_a(2)$ and H(3) ($J_{1,3}$ in Table III); the latter criterion also applies to the diastereomers of **10** and **11**.

For the purpose of conformational analysis, it was essential to know the configurations of the diastereomeric sulfoxides **2** (more polar isomer, lower R_f in chromatography) and **3** (less polar isomer, higher R_f). Since both **2** and **3** are liquids, direct assignment by X-ray diffraction was not feasible, but such an assignment could be made (see Experimental Section) for the less polar, crystalline benzyl sulfoxide **14** obtained (along with its more polar diastereomer **13** from which it was separated by chromatography) by substituting benzyl bromide for methyl iodide in the synthetic sequence shown in Scheme I, R = H. (Sulfide **12** was an intermediate in this synthesis and sulfone **15** was produced by vigorous oxidation.) The



12, Ⓢ = S
13, Ⓢ = SO, more polar isomer
14, Ⓢ = SO, less polar isomer
15, Ⓢ = SO_2

correlation between the methyl sulfoxides **2** and **3** and the benzyl sulfoxides **13** and **14** rests not only on their relative polarity but also, as will be seen in the sequel, on their ^{13}C NMR spectra and their conformational behavior. The combination of the X-ray crystallography of **14** and the comparison of **13** and **14** with **2** and **3** demonstrates conclusively that **14** (and therefore **3**) has the *RR,SS* (or *R*R**) configuration; the configuration of **13** and **2** is therefore *RS,SR* (or *R*S**). Confirmation of this conclusion comes from the proton and ^{13}C NMR spectra of the 6-methyl derivatives **8** and **9** and their comparison with **2** and **3**, as will be explained in the next section.

NMR Spectroscopy. The ^{13}C chemical shifts for the parent *S*-methyl compounds **1**–**6**, the *cis*-6-methyl derivatives *cis*-**7**–**11**, the trans isomers *trans*-**7**, -**10**, and -**11**, and the *S*-benzyl analogues **12**–**15** are shown in Table I; the

(1) (a) Part 46: Brunet, E.; Eliel, E. L. *J. Org. Chem.* **1986**, *51*, 677. (b) Part 20: Brunet, E.; Gallego, M. T.; García Ruano, J. L. *Tetrahedron* **1986**, *42*, 1423.

(2) (a) Departamento de Química Orgánica, Universidad Autónoma de Madrid, Canto Blanco 2809, Madrid, Spain. (b) Departamento de Química Orgánica, Universidad de Sevilla, Facultad de Farmacia, Apartado de Correos 874, Seville, Spain. (c) Department of Chemistry 045A, University of North Carolina, Chapel Hill, NC 27514.

(3) Eliel, E. L.; Hargrave, K. D.; Pietrusiewicz, K. M.; Manoharan, M. *J. Am. Chem. Soc.* **1982**, *104*, 3635.

(4) Carretero, J. C.; García Ruano, J. L.; Martínez, M. C.; Rodríguez, J. H.; Alcudia, F. *Tetrahedron* **1985**, *41*, 2419 and references cited therein.

(5) Zelinski, R.; Eichel, H. J. *J. Org. Chem.* **1958**, *23*, 462. Eliel, E. L.; Giza, C. A. *Ibid.* **1968**, *33*, 3754.

0022-3263/87/1952-4099$01.50/0

Scheme I

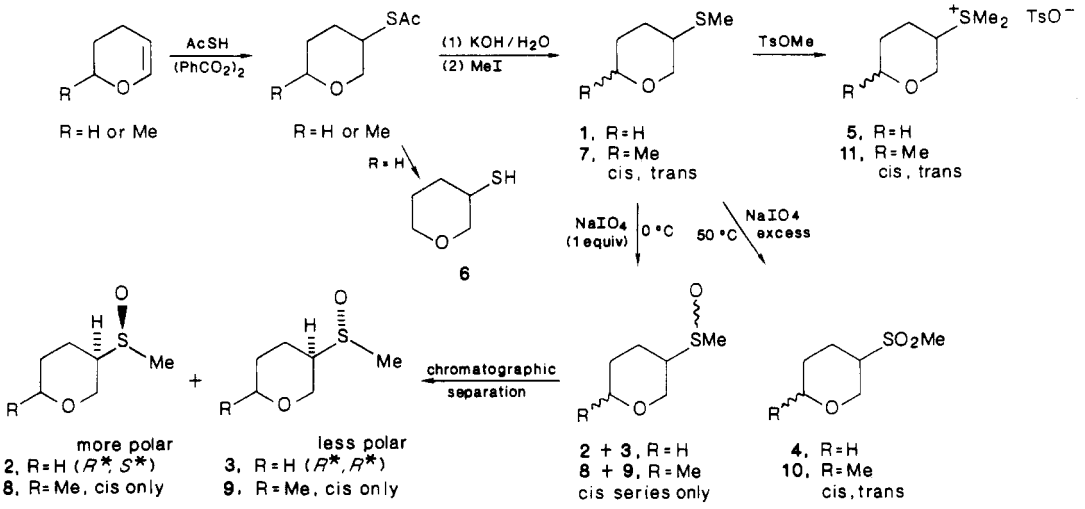


Table I. Room Temperature ^{13}C NMR Chemical Shifts[a]

subst (compd)	C(2)	C(3)	C(4)	C(5)	C(6)	S*Me*	C*Me*
3-SMe (1)	72.2	42.6	30.0	26.3	67.9	13.4	
3-SOMe, more polar isomer (2)	65.7	58.8	23.5	24.4	67.5	36.3	
3-SOMe, less polar isomer (3)	66.6	58.1	20.5	24.0	67.9	35.9	
3-SO_2Me (4)	65.8	59.3	22.6	24.3	67.7	39.0	
3-$^+SMe_2$ (5)	65.8	52.0	24.0	22.3	67.7	22.3, 22.6	
3-SH[g] (6)	75.3	36.0	34.7	26.6	67.7		
cis-6-Me-3-SMe[b,c] (7)	70.1	43.7	28.1	29.2	74.0	14.9	21.6
cis-6-Me-3-SOMe,[b,c] more polar isomer (*cis*-8)	64.5	60.7	23.6	29.7	74.1	37.6	21.8
cis-6-Me-3-SOMe,[b,c] less polar isomer (*cis*-9)	66.4	60.7	22.1	29.2	74.4	37.4	21.7
cis-6-Me-3-SO_2Me[b,c] (*cis*-10)	64.8	59.2	22.2	28.8	73.7	41.9	21.4
cis-6-Me-3-$^+SMe_2$[b] (*cis*-11)	66.1	53.8	24.7	28.4	74.6	*d*	*d*
3-SCH_2Ph (12)[b]	72.8	41.2	30.7	26.7	68.2	35.4[e]	
3-$SOCH_2Ph$, more polar isomer[b] (13)	66.0	55.8	(24.7)	(24.1)	68.2	56.1[e]	
3-$SOCH_2Ph$, less polar isomer[b] (14)	67.6	55.5	20.9	24.9	68.4	56.3[e]	
3-SO_2CH_2Ph (15)	65.7	56.8	22.6	24.5	67.5	58.3[e]	
trans-6-Me-3-SMe[c] (*trans*-7)	72.2	42.0	30.5	34.0	73.5	13.3	21.6
trans-6-Me-3-SO_2Me[c] (*trans*-10)	65.7	59.1	23.0	31.8	73.5	38.8	21.2
trans-6-Me-3-SMe_2^+ (*trans*-11)	66.1	49.4	25.0	32.0	73.5	*f*	*f*

[a] In ppm from Me_4Si in $CDCl_3$ unless otherwise indicated. Entries in parenthese are uncertain as to assignment and may have to be reversed. An expanded Table Ia, including data in CD_2Cl_2, CD_3OD, and CD_3COCD_3 is included in the supplementary material. [b] In CD_2Cl_2. [c] The correct position numbering for these compounds is 2-Me-5-SXMe. The alternate numbering system was chosen to preserve analogy of positions in Table I. [d] Signals at 23.5, 22.5, 21.5, and 21.2 ppm belong to the two $^+SMe_2$ groups, the CMe group, and the *p*-toluenesulfonate gegenion, the exact assignment being uncertain. [e] CH_2Ph. [f] Signals at 23.0, 22.3, 21.2, and 20.9 ppm belong to the two $^+SMe_2$ groups, the CMe group, and the *p*-toluenesulfonate gegenion, the exact assignment being uncertain. [g] In CD_2Cl_2, 3.8 M.

Table II. Effects of Various Sulfur Functions in Axial and Equatorial 3-Positions in Oxane on ^{13}C Chemical Shifts

	induced shift (ppm) at position indicated				
subst	C-2(β)	C-3(α)	C-4(β)	C-5(γ)	C-6(δ)
SMe					
axial	+1.7	+17.6	+4.3	−4.7	+0.1
equatorial	+3.8	+15.9	+6.7	+0.1	−0.4
SOMe (more polar; *RS,SR*; axial)	−3.9	+34.6	−0.2	−4.2	+0.2
SOMe (less polar; *RR,SS*; axial)	−2.0	+34.6	−1.7	−4.7	+0.5
SO_2Me					
axial	−3.6	+33.1	−1.6	−5.1	−0.2
equatorial	−2.7	+33.0	−0.8	−2.1	−0.4
$^+SMe_2$					
axial	−2.3	+27.7	+0.9	−5.5	+0.7
equatorial	−2.3	+23.3	+1.2	−1.9	−0.4
CH_3					
axial[a]	+4.6	+2.1	+5.6	−5.3	+0.3
equatorial[a]	+6.3	+4.8	+9.0	0.0	−0.4

[a] Value included for comparison; from ref 7.

spectra of compounds **1–5** were recorded in several different solvents. The room temperature spectra of **1–5** are straightforward as to assignment, given what is known about oxane spectra.[3,6,7] C(4) and C(5) in **1** and **3–5** were initially assigned from the near-invariability of C(5) compared to the variance of C(4) (see below), and all assignments are confirmed by DEPT and ^1H–^{13}C 2-D experiments (see below for discussion of proton spectra).

(6) Eliel, E. L.; Pietrusiewicz, K. M. *Top. Carbon-13 NMR Spectrosc.* **1979**, *3*, 171.

(7) Eliel, E. L.; Manoharan, M.; Pietrusiewicz, K. M.; Hargrave, K. D. *Org. Magn. Reson.* **1983**, *21*, 94.

Table III. Low-Temperature ^{13}C Chemical Shifts of Compounds 1-6 and 12-14[a]

subst (compd)	isomer[b]	C(2)	C(3)	C(4)	C(5)	C(6)	SC
3-SMe (1)	A	72.4	42.2	29.8	26.9	68.0	14.2
	B	70.2	43.8	27.3	21.7	68.9	15.2
3-SOMe (2)	A	66.9	57.8	(23.6)	(25.2)	67.9	36.2
(more polar isomer)	B	64.7	60.6	(23.3)	(22.5)	68.6	37.3
3-SOMe (3)	A	67.3	56.0	19.4	25.1	68.0	35.4
(less polar isomer)	B	66.7	60.7	21.8	21.8	69.0	37.4
3-SO_2Me (4)	S	65.7	58.5	22.2	24.6	67.9	38.3
3-$^+SMe_2$ (5)	A	66.1	54.0	c	c	69.0	c
	B	66.7	49.0	c	c	68.0	c
3-SH (6)[d,e]	A	74.5	35.1	34.0	26.4	66.6	
	B	72.8	35.5	30.5	19.6	67.9	
3-SCH_2Ph (2)	A	72.4	38.9	29.7	26.7	67.9	34.3
	B	70.5	39.5	27.1	21.8	68.9	34.6
3-$SOCH_2Ph$ (13)[f]	A	66.9	c	22.5	25.1	68.0	54.3
(more polar isomer)	B	64.7	c	23.7	22.8	68.6	c
3-$SOCH_2Ph$ (14)	A	67.5	53.0	19.2	25.1	68.0	54.2
(less polar isomer)	B	66.5	c	(21.8)	(22.1)	68.9	c

[a] In ppm downfield from Me_4Si, in CD_2Cl_2 at 173 K. A more extensive Table 3a with data in $(CD_3)_2CO$ and CD_3OD as well as CD_2Cl_2 is included in the supplementary material. [b] A: major conformer. B: minor conformer. S: sole isomer seen. [c] Signal not seen. [d] 3.8 M in CD_2Cl_2. [e] At 183 K. [f] At 163 K.

The shifts of *cis*-7–11 were also readily assigned except for C(4) and C(5). From the known[7] spectrum of 2-methyloxane and the shifts for *cis*-7–11 in Table I and assuming that *cis*-7–11 exist very largely with equatorial Me ($\Delta G°_{Me-2}$ = −2.87 kcal/mol[7]) one can calculate the shift parameters for axial SMe, SOMe (both isomers) SO_2Me, and $^+SMe_2$ substituents at various position in oxane; these parameters are summarized in Table II, with the corresponding parameters for methyl[7] included for comparison. The α_a effects for all the sulfur functions are very much larger than the corresponding effect for methyl, the increase being beyond what would be expected of the additional β effect from the R group in SR. A similarly large α_a effect (+17.4 ppm) had previously been seen[8] for an axial MeS group in (methylthio)cyclohexane and, similarly as shown in Table II for 3-(methylthio)oxane, the effect increased to +34.6 ppm in the axial sulfoxide and +30.9 ppm in the sulfone derived from 3-(methylthio)cyclohexane.[8] The β_a effect at C(4) is also quite different from that for a methyl group but similar to that of corresponding sulfur functions in cyclohexane:[8] MeS, +3.7; MeSO, −0.2; $MeSO_2$, −2.3. However, a less positive (or more negative) β_a effect is seen (Table II) at the C(2) position (the one next to the ring oxygen). The (upfield shifting) γ_a effects and the (very small) δ_a effects are similar to those of a methyl group (Table II) and to the corresponding effects in cyclohexane.[8]

A salient difference between C(4) and C(5) in thioether **1**, sulfoxides **2** and **3**, sulfone **4**, and sulfonium salt **5** relative to mercaptan **6** is that C(4) is γ to the substituents on sulfur (O, Me) whereas C(5) is δ to these substituents; thus the substituents should have an upfield shifting effect at C(4) but small effects at C(5). Table I shows that (with the assignments there) this is indeed so for the thioether, sulfoxides, and sulfone (less clearly for the sulfonium salt)—suggesting that the C(4) shifts have been correctly assigned. Similar shift differences are seen in compounds *cis*-**8**–**11** relative to thioether *cis*-**7**, in *trans*-**10** and **-11** relative to *trans*-**7**, and in **13**–**15** relative to **12**.

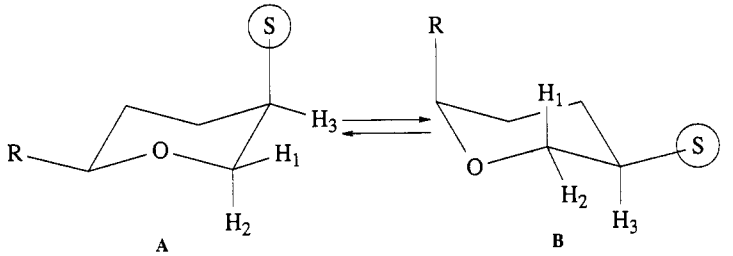
Also shown in Table II are the shift parameters for the equatorial MeS, $MeSO_2$, and Me_2S^+ substituents in the (diequatorial) trans isomers *trans*-**7**, **-10**, and **-11**. The β effects are, as expected, more positive (or less negative) than those for the corresponding axial substituents. The α effects, however, are less positive for the methyl sulfide and dimethylsulfonium salt and are the same for the two epimeric sulfones. This situation is different from that in the cyclohexane analogues;[8] on the other hand the γ_e effect which is negligible in the methyl sulfide but appreciably negative for the sulfone and sulfonium salt has its parallel in the carbocyclic series.

The shifts of the ring carbons in the benzyl compound **12** are very similar to those of the methyl analogue **1**. It therefore seems reasonable to use the sizeable difference in the C(4) shifts between **2** and **3** as well as **13** and **14** to correlate these pairs: on that basis, the configuration of the more polar **2** is the same as that of the more polar **13**, i.e., *R*S**, and that of the less polar isomer **3** agrees with that of the less polar **14**, i.e., *R*R**. The relative shifts at C(2) are in accord with this assignment (less polar isomer downfield in both *S*-methyl and *S*-benzyl series). Low-temperature spectra (Table III) further strengthen the argument in that only conformer A in the less polar sulfoxides **3** and **14** shows a consistently large difference in shift between C(4) and C(5). We shall return to this point later. The relatively larger difference between the C(4) and C(5) shifts in the less polar sulfoxide isomers persists at room temperature (compare the pertinent shifts in Table I) for **2**/**3** and **13**/**14** but is not evident in the pair **8**/**9**. Since in compounds *cis*-**7**–**11** the conformation with equatorial methyl (and hence axial sulfur functions) predominates by far (vide supra), it must be the other conformation—i.e., the one with equatorial sulfoxide—which is mainly responsible for the differences between **2** and **3** as well as **13** and **14**. Thus it appears that conformer A of compounds **3** (and **14**) (cf. Table III) is the equatorial conformer. Confirmation of this hypothesis will be adduced later.

The proton NMR shifts shown in Table IV provide additional evidence for the configurational assignment of **8** and **9** and thereby indirectly **2** and **3**. The triad H(1)–H(2)–H(3)—protons adjacent to heteroatoms—is relatively easily identified and analyzed, either as a near-first-order ABX spectrum or by the program PANIC of the Aspect 2000 computer (see footnotes to Table IV). The shifts of H(1) in **8** and **9** are particularly revealing. For reasons already discussed, these compounds exist entirely in conformation A (top of Table IV); indeed, low-temperature ^{13}C NMR spectroscopy of *cis*-**7**–**11** shows only single conformers whose chemical shifts—close to the room temperature shifts in Table I—are in accord with equatorial methyl and axial sulfur functions. Now, if the axial conformer of the sulfoxide (Scheme II) exists very pre-

(8) Eliel, E. L.; Kandasamy, D. *J. Org. Chem.* **1976**, *41*, 3899.

Table IV.[a] Proton NMR Signals of Compounds 1–11 at Ambient Temperature (in ppm from Me_4Si)

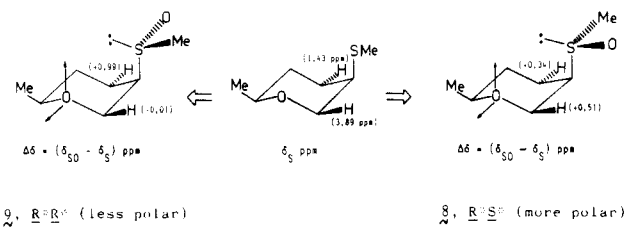


A B

subst (compd)	H(1)	H(2)	H(3)	$J_{1,2}$	$J_{1,3}$	$J_{2,3}$
3-SMe[b] (1)	4.03	3.27	2.56	−11.2	4.2	10.2
3-SOMe,[c] more polar isomer (2)	4.16	3.87	2.77	−11.8	3.9	8.3
3-SOMe,[c] less polar isomer (3)	4.02	3.64	2.71	−11.8	3.8	8.6
3-SO_2Me[b] (4)	4.27	3.65	3.15	−11.4	4.1	10.9
3-$^+SMe_2$[c] (5)	3.97	3.84	4.21	−13.3	3.9	2.5
3-SH[b,e,f] (6)	3.17	3.91	2.85	−11.1	9.8	4.1
cis-6-Me-3-SMe[c,h] (*cis*-7)	3.89	3.73	2.77	−12.0	2.3	2.5
trans-6-Me-3-SMe	3.25	4.06	2.65	−11.0	11.0	4.3
cis-6-Me-3-SOMe,[b,e,i] more polar isomer (8)	4.40	3.65	2.56	−12.7	2.0	2.4
cis-6-Me-3-SOMe, less polar isomer[e,j] (9)	3.88	3.83	2.62	−13.3	2.0	2.5
cis-6-Me-3-SO_2Me[e,k] (*cis*-10)	4.46	3.81	2.86	−13.2	2.0	3.8
trans-6-Me-3-SO_2Me (*trans*-10)	3.62	4.33	2.15	−11.0	10.9	4.0
cis-6-Me-3-$^+SMe_2$[e,l] (*cis*-11)	4.15	3.76	4.24	−14.0	1.6	1.8
trans-6-Me-3-SMe_2[m] (*trans*-11)	3.50	4.19	3.83	−10.9	10.9	4.0

[a] A more extensive Table 4a, with data in CD_2Cl_3, CD_3COCD_3, and CD_2Cl_2 as well as $CDCl_3$, is included in the supplementary material. All J are in Hz. [b] Analyzed as first-order ABX spectrum. [c] Computer-optimized spectrum. [d] Approximate analysis. [e] In CD_2Cl_2. [f] 0.095 M. [g] $J_{H(3)SH}$ = 8.4 Hz. [h] $J_{5a,6}$ = 9.7 Hz, $J_{5e,6}$ = 2.8 Hz. $H_e(4)$ 1.43 ppm, $H_a(4)$ 1.65 ppm. [i] $J_{5a,6}$ = 10.0 Hz, $J_{5e,6}$ = 2.9 Hz. $H_e(4)$ 1.77 ppm, $H_a(4)$ 2.05 ppm. [j] $J_{5a,6}$ = 10.5 Hz, $J_{5e,6}$ = 2.3 Hz (in benzene-d_6). $H_e(4)$ 2.42 ppm, $H_a(4)$ 1.88 ppm. [k] $J_{5a,6}$ = 9.8 Hz, $J_{5e,6}$ = 2.7 Hz. $H_e(4)$ 2.42 ppm, $H_a(4)$ 2.06 ppm (in benzene-d_6). [l] $J_{5a,6}$ = 10.7 Hz, $J_{5e,6}$ = 2.6 Hz. [m] $J_{5a,6}$ = 11.0 Hz, $J_{5e,6}$ = 2.0 Hz. $H_e(4)$ 2.33 ppm.

Scheme II



9, R*R* (less polar) 8, R*S* (more polar)

dominantly with the pair toward the inside of the ring,[9] the sulfoxide oxygen will be parallel (syn-axial) with the equatorial H(4) in the *R*R** isomer. This should lead to a downfield shift of H(4) in sulfoxide **9** relative to the corresponding proton in the parent sulfide *cis*-**7** whereas in sulfoxide **8** the downfield shift should affect $H_e(2)$.[10] The numbers in Scheme II indicate that the situation for $H_e(2)$ is very clear-cut: the more polar isomer is *R*S**, the less polar *R*R**. (The shifts for $H_e(4)$ support this assignment.) The correlation with relative polarity is the same as in **2**/**3** and **13**/**14** (vide supra). This assignment is in accord with expectation: if one resolves the dipole of the ether function of the oxanes **8** and **9** into equatorial and axial components (cf. the arrows in Scheme II) the equatorial component in **9** is opposed to the sulfoxide S–O bond moment in **9** but partially aligned with it in **8**, making the overall moment of the latter larger. (The axial components make equal contributions in both isomers.)

Conformational Analysis and Discussion. The low-temperature ^{13}C spectra for compounds **1**–**6** and **12**–**14** are shown in Table III. In contrast to the spectra of the essentially conformationally homogeneous compounds *cis*-**7**–**11** and *trans*-**7**–**11**, the spectra of **1**–**3**, **5**, and **12**–**14** decoalesced on cooling and showed the presence of two,

Table V. $\Delta G°$ Values Obtained from ^{13}C NMR Signal Intensity

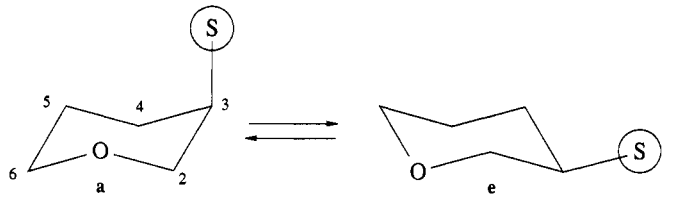
compd (subst)	solv	T, K	$\Delta G°_{a=e}$, kcal/mol
1 (SMe)	CD_2Cl_2	173	−1.21 ± 0.11
	$(CD_3)_2CO$	178	−1.30 ± 0.19
	CD_3OD	173	−1.36 ± 0.09
2 (SOMe), more polar	CD_2Cl_2	173	−0.10 ± 0.05
isomer	$(CD_3)_2CO$	173	−0.01 ± 0.04
	CD_3OD	173	+0.15 ± 0.08
3 (SOMe), less polar	CD_2Cl_2	173	−0.43 ± 0.13
isomer	$(CD_3)_2CO$	173	−0.42 ± 0.05
	CD_3OD	173	−0.26 ± 0.03
4 (SO_2Me)[a]	CD_2Cl_2, CD_3OD	173	<−1.4[a]
5 ($^+SMe_2$)	CD_2Cl_2	173	+0.55[b]
	CD_3OD	173	+0.34[b]
6 (SH)	CD_2Cl_2		
	3.8 M	183	−1.04 ± 0.05
	0.95 M	183	−1.20 ± 0.05
	0.095 M	183	−1.07 ± 0.05
12 (SCH_2Ph)	CD_2Cl_2	173	−1.08 ± 0.06
13 ($SOCH_2Ph$), more polar	CD_2Cl_2	163	−0.07 ± 0.03
isomer	CD_3OD	173	+0.05 ± 0.04
14 ($SOCH_2Ph$), less polar	CD_2Cl_2	173	−0.50 ± 0.02
isomer	CD_3OD	173	−0.24 ± 0.05

[a] See section on conformational analysis. [b] Too few signals integrable to warrant indication of an error limit.

well-resolved conformers at −90 to −100 °C. From the areas of the pertinent signals, the free-energy differences tabulated in Table V were computed.[11] These values refer to the equilibrium from the axial toward the equatorial conformer; i.e., negative numbers imply that the equatorial

(9) Cf.: Kaloustian, M. K.; Dennis, N.; Mager, S.; Evans, S. A.; Alcudia, F.; Eliel, E. L. *J. Am. Chem. Soc.* **1976**, *98*, 956.
(10) Cf.: Lambert, J. B.; Keske, R. G. *J. Org. Chem.* **1966**, *31*, 3429.
(11) Concerning the validity of this procedure (with respect to possible perturbations resulting from differences in nuclear Overhauser effects and relaxation times), cf. (specifically, p 3700 column 2): Eliel, E. L.; Kandasamy, D.; Yen, C.-y.; Hargrave, K. D. *J. Am. Chem. Soc.* **1980**, *102*, 3698.
(12) The effective polarity of benzene is appreciably greater than its dielectric constant might indicate, e.g.: Eliel, E. L.; Hofer, O. *J. Am. Chem. Soc.* **1973**, *95*, 8041.

Table VI. Experimental Values (CD_2Cl_2 at Low Temperature) and Calculated Values (in Parentheses) of ^{13}C NMR Chemical Shifts for Compounds 1–5 (Axial Conformers)



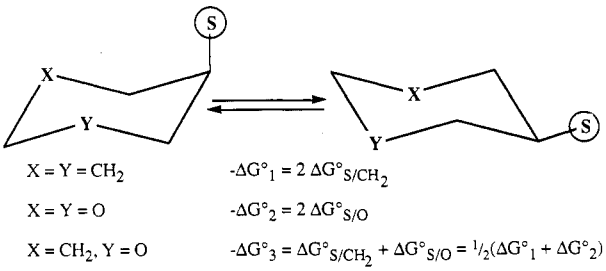
subst (compd)		C-2	C-3	C-4	C-5	C-6
SMe (1)	a[a]	70.2	43.8	27.3	21.7	68.9
		(70.2)	(44.3)	(27.9)	(22.0)	(68.6)
	e[b]	72.4	42.2	29.8	26.9	68.0
		(72.3)	(42.6)	(30.3)	(26.8)	(68.1)
SOMe (2)[c,d]	a[a]	64.7	60.6	23.3	22.5	68.6
		(64.6)	(61.3)	(23.4)	(22.5)	(68.7)
	e[b]	66.9	57.8	(23.6)	(25.2)	(67.9)
SOMe (3)[d,e]	a[a]	66.7	60.7	21.8	21.8	69.0
		(66.4)	(61.2)	(21.8)	(21.8)	(69.0)
	e[b]	67.3	56.0	19.4	25.1	68.0
SO_2Me (4)	a	*f*	*f*	*f*	*f*	*f*
		(64.9)	(69.8)	(22.0)	(21.6)	(68.3)
	e	65.7	58.5	22.2	24.6	67.9
		(65.8)	(59.7)	(22.8)	(24.6)	(68.1)
$^+SMe_2$ (5)	a[b]	66.1	54.0	*g*	*g*	69.0
		(66.2)	(54.4)	(24.5)	(21.2)	(68.8)
	e[a]	66.7	49.0	*g*	*g*	68.0
		(66.2)	(50.0)	(24.8)	(24.8)	(68.1)

[a] Isomer B, Table III. [b] Isomer A, Table III. [c] More polar isomer. [d] Calculated shifts for equatorial conformer not available. [e] Less polar isomer. [f] Signals for this isomer not seen. [g] Signals not observed.

isomer is the more stable whereas positive numbers mean that the axial conformer is favored at equilibrium at the temperature of measurement in the solvent indicated. To obtain the algebraic values of $\Delta G°$, one must determine whether the more stable isomer A in Table III corresponds to the axial or equatorial conformer. For compounds **1–5** this was done by adding the substituent parameters in Table II to the base value of oxane[7] [C(2,6), δ 68.5; C(3,5), δ 26.7; C(4), δ 23.6] to obtain the shift values for the axial conformers, as well as, in the case of the sulfide, sulfone, and sulfonium salt, the equatorial ones. The results (comparison of calculated with experimental values, the latter at ca. −100 °C) are shown in Table VI. They are in very good agreement especially considering that the calculated values refer to room temperature and that the base values are in $CDCl_3$. In view of the fact that there are sizeable differences for at least some carbon shifts in each pair of conformers (cf. Table III), the assignment of the major conformer on the basis of the calculated shifts in Table VI also appears entirely secure. In the case of sulfone **4**, it is evident, on the basis of the observed shifts for C(3) and C(5), that the sole conformation found for this compound is the equatorial one. Incidentally, the fact that the calculated shifts for **2** and **3** (isomer B) are in good agreement with the experimental ones constitutes a correlation of configuration of **2** with **8** and **3** with **9** (inasmuch as the calculated shifts for **2** and **3** in Table VI are based on the experimental ones for **8** and **9**—whose configurational assignment, based on proton NMR spectra, was discussed earlier). It is clear from Table VI that reversal of the configurational assignment of **2** and **3** (equivalent to an interchange of the formula numbers in Table VI) would give considerably less satisfactory agreement between calculated and observed shifts at all positions, but especially at C(2) and C(4).

As a first approximation, one might expect the axial–equatorial energy differences in 3-substituted oxanes to be midway between (i.e., the arithmetic mean of) corresponding interactions in cyclohexanes on one hand and

Scheme III



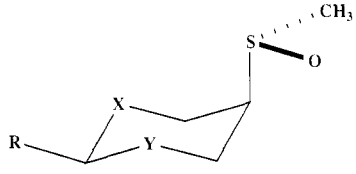
5-substituted 1,3-dioxanes on the other (Scheme III); this is, in fact, nearly true for methyl substituents.[3] For SCH_3, $-\Delta G_1° = 1.0 \pm 0.05$ kcal/mol,[8] $-\Delta G_2° = 1.73 \pm 0.02$ (in diethyl ether)[9] or 1.55 ± 0.02 kcal/mol (in benzene), hence $-\Delta G_3°_{calcd} = 1.28$ or 1.37 ± 0.03 kcal/mol vs. $-\Delta G_3°_{exptl} = 1.21 \pm 0.11$ kcal/mol (in CD_2Cl_2). In view of the fact that the effective polarities of benzene and of ether differ somewhat from that of CD_2Cl_2, agreement is satisfactory within the error limits of the determinations. That $-\Delta G°$ is larger in the substituted oxane (and still larger in the corresponding dioxane) than in cyclohexane has been explained in terms of a repulsive S/O gauche effect.[13,14] It is somewhat surprising that whereas $-\Delta G_2°$ (in 5-(methylthio)-1,3-dioxane) diminishes with increasing solvent dielectric (as might be expected of the S/O interaction which includes an electrostatic repulsion), $-\Delta G_3°$ (in 3-(methylthio)oxane) seems to display the opposite trend; however, the effect is not outside the limits of experimental error.

For $OSCH_3$, $-\Delta G_1° = 1.20 \pm 0.05$ kcal/mol[8] and $+\Delta G_2° = 0.82 \pm 0.11$ kcal/mol[9] (in $CHCl_3$) whence the calculated

(13) E.g.: Zefirov, N. S.; Gurvich, L. G.; Shaskov, A. S.; Krimer, M. Z.; Vorob'eva, E. A. *Tetrahedron* **1976**, *32*, 1211 and earlier references there cited.

(14) See also: Eliel, E. L.; Juaristi, E. *J. Am. Chem. Soc.* **1978**, *100*, 6114.

$-\Delta G_3°$ is −0.19 ± 0.06 kcal/mol; again there is some uncertainty in the comparison with the experimental value (Table V) because of differences in solvent. However, it is clear from Table V that the $-\Delta G_3°$ values for the two sulfoxides **2** and **3** are not the same; that for **2** is less than the calculated value, and that for **3** is greater. A careful inspection of the axial sulfoxide **16** in the 1,3-dioxane series makes it clear that it is in fact not proper to divide the sulfoxide interaction in half (to obtain the interaction with each individual ring oxygen) because the sulfoxide function lacks a local symmetry plane. The interaction with one



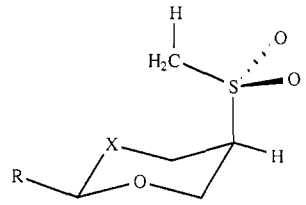
16, X = Y = O
17, X = Y = CH_2

oxygen is an O–CH_2–CH–S–O and that with the other an O–CH_2–CH–S–Me interaction; these two interactions are not the same. Reference to Scheme II (methyl homologues) shows that the more polar isomer has an O–CH_2–CH–S–O (plus a CH_2–CH_2–CH–S–Me) interaction, whereas the less polar has an O–CH_2–CH–S–Me (plus a CH_2–CH_2–CH–S–O) interaction. It is significant that the sum of these interactions (O–CH_2–CH–S–O + O–CH_2–CH–S–Me + CH_2–CH_2–CH–S–O + CH_2–CH_2–CH–S–Me) should be equal to the total axial interaction in the 1,3-dioxane plus the total axial interaction in the cyclohexane **17**. Experimentally the sum for **2** and **3** is −0.53 ± 0.14 kcal/mol, and the sum for **16** and **17** is −0.38 ± 0.12 kcal/mol; the two sums agree within limits of experimental error (and considering the variations in solvent).

It is perhaps surprising that equilibrium in the more polar isomer **2** favors the equatorial conformation less ($-\Delta G°$ is smaller) than that in the less polar isomer **3**. Reference to Scheme II might suggest that with steric effects being approximately equal, the more unfavorably oriented dipole in **2** (lower homologue of **8**) might destabilize the axial conformer of **2** relative to that of **3** (lower homologue of **9**). A possible explanation as to why the contrary is true has been given before.[15] In **8** there is possibility of overlap of an unoccupied sulfur d orbital with an occupied p orbital of the ring oxygen; in contrast, in **9** the d orbital properly disposed for such overlap is tied up by overlap with one of the p electron pairs of sulfoxide oxygen (for details see Figure 3 in ref 15). An alternative explanation in terms of electrostatics is based on the fact that the equatorial H(2) is more electropositive (by virtue of its proximity to O(1)) than the equatorial H(4), and thereby the axial sulfoxide conformation in which the sulfoxide oxygen is close to H(2), i.e., **8**, may be preferred. The solvent effects in **2** and **3** are small (similarly as in **16**[9]) except for the hydrogen-bonding solvent CD_3OD, which favors the axial conformers (for a similar observation, see ref 14).

The situation in the sulfonium salt **5** and the sulfone **4** is less transparent because some of the interactions involved in the calculations for these species are too large to measure. The equilibrium for **5** is quite accessible (electrostatic attraction is dominant to the point where the axial conformer clearly predominates in both methanol and methylene chloride). But the average between the corresponding cyclohexyl compound (for which $-\Delta G°$ was determined, in the course of this work, to be −1.09 kcal/mol; i.e., the values for SMe_2^+ and SMe are virtually the same) and the 5-substituted 1,3-dioxanyl compound cannot be computed because $\Delta G°$ for the latter was too large to measure.[9] All one can say is that the calculated average, $-{}^1/_2(\Delta G_1° + \Delta G_2°)$ is in excess of +0.46 kcal/mol, which is at least not in contradiction with the experimental value (Table V) of +0.55 kcal/mol.

Scheme IV



cis-**10** R = $(CH_3)_2CH$-, X = O, ^4J = 1.14 Hz
cis-**10** R = CH_3-, X = CH_2, ^4J = 0.8 Hz

$-\Delta G°$ for sulfone **4** was too large to measure directly; at low temperature only one set of peaks, assigned (vide supra) to the equatorial isomer, was seen, implying $-\Delta G° >$ 1.4 kcal/mol. However, an upper limit to this value was obtained by observing that sulfone *cis*-**10** (Scheme IV) also remained conformationally homogeneous at −100 °C; at least no peaks corresponding to the minor conformer could be detected in the ^{13}C NMR spectrum. This implies $-\Delta G° >$ 1.4 kcal/mol in favor of axial sulfone, and since $-\Delta G°_{Me(2)}$ in tetrahydropyran is 2.86 kcal/mol,[3] $-\Delta G°_{SO\text{-}Me(3)}$ cannot exceed 1.5 kcal/mol or else signals for the minor conformer (equatorial sulfone) should have been seen. This places $-\Delta G°_{SO\text{-}Me(3)}$ in the 1.4–1.5 kcal/mol range. Clearly this value is significantly greater than the average—${}^1/_2(2.5 - 1.19)$ = 0.65 kcal/mol—of the values of 2.5 and −1.19 kcal/mol of the conformational energies of SO_2Me in cyclohexane[8] and at C(5) in 1,3-dioxane (in solvent chloroform),[9] respectively.

The reason for this large discrepancy is not difficult to see. In 1,3-dioxane, evidence has been adduced that the methyl sulfone group at C(5), when axial, turns its methyl substituent inside the ring with the sulfonyl oxygens pointing to the outside.[9] This results from a combination of a relatively small Me/O/O steric repulsion (with Me inside) as against a potentially rather destabilizing dipolar O/O/O interaction (were oxygen inside). In the conformer of oxane **4** with axial SO_2Me, the methyl sulfone group finds itself in a dilemma: If the methyl substituent turns into the ring, there is a severe clash with the axial hydrogen at C(5) whereas turning the oxygen into the ring causes a serious repulsive polar interaction with the ring oxygen. Thus the axial SO_2Me group is comfortable in neither rotameric form and its conformational energy is much greater than the average of the values in cyclohexane and 1,3-dioxane. The H_3C–$S(O_2)$–C–*H* long-range coupling constant in *cis*-**10**, ^4J = 0.8 ($CDCl_3$) or 1.0 Hz (C_6D_6), is larger than that in the equatorial isomer, *trans*-**10** (0.5 Hz); corresponding values in the 1,3-dioxane series[9] are 1.14 and 0.39 Hz. Assuming that the equatorial coupling constants reflect conformational averaging, the larger one for the axial isomer suggests considerable preference for the *W* conformation which requires the methyl group to point inside the ring (Scheme IV). That the long-range coupling constant in the (methylsulfonyl)oxane is somewhat smaller than in the corresponding 1,3-dioxane (Scheme IV) may be due to one of two causes: Either there is some contribution from the O-inside rotamer (i.e., its conformational energy is only slightly higher than that of the Me-inside one) or the axial sulfone group is not perfectly staggered

(15) Brunet, E.; García Ruano, J. L.; Martínez, M. C.; Rodríguez, J. H. *Tetrahedron* **1984**, *40*, 2023.

with respect to the ring bonds. In any case, since the ring-O/CH_3SO_2 interaction in the dioxane is attractive by about 0.6 kcal/mol, the ring-CH/CH_3SO_3 repulsion must amount to ca. 1.45 + 0.6 or 2.05 kcal/mol, considerably more than the ring-CH/O_2SCH_3 interaction in an axially substituted cyclohexyl methyl sulfone (1.25 kcal/mol). Moreover, since the O-inside conformation in *cis*-**10** is disfavored, the ring-O/O_2SCH_3 repulsion must exceed 1.45–1.25 or 0.2 kcal/mol.

In the case of the SH compound (**6**) a comparison with the corresponding 1,3-dioxane is not possible because the $-\Delta G°$ value for HS(5) in the latter compound is unknown. However, low-temperature NMR (Table V) leads to a $-\Delta G°$ a value of 1.1 ± 0.1 kcal/mol, i.e., the SH function prefers the equatorial conformation almost by as much as in cyclohexane ($-\Delta G°$ = 1.2 kcal/mol[16,17]). Evidently the dominating factor in the SCH_3 compound—O/S polar repulsion—persists in the SH compound and is not appreciably offset by intramolecular S–H···O hydrogen bonding in the axial conformer.

Experimental Section

Melting points were determined on an electrothermal apparatus in open capillary tubes and are uncorrected. Elemental analyses were performed by the Instituto de Química Orgánica (CSIC) in Madrid with a Perkin-Elmer model analyzer. Mass spectra (supplementary material) were recorded on an AEI Model MS-30 spectrometer at 70 eV. IR spectra (supplementary material) were obtained with a Perkin-Elmer Model 1310 spectrometer. Proton and carbon NMR spectra were recorded on a Bruker WM-200-SY or a Bruker WP-80-SY instrument. Shifts are reported in ppm downfield from internal Me_4Si. The silica gel used in chromatography was Merck F-254 (TLC) or 60 (70–230 mesh) (column).

Compounds **1**, **6**, and **12** have been previously described.[18]

3-(Methylsulfinyl)tetrahydropyran (2 and 3). To an ice-cooled solution of 1.283 g (6 mmol) of sodium metaperiodate in 10 mL of water was added 0.793 g (6 mmol) of **1**[18] dissolved in 3 mL of ethanol. The mixture was stirred at 0 °C for 4 h and was then allowed to stand overnight at room temperature. The reaction mixture was concentrated to dryness, and the resulting material was extracted several times with methylene dichloride. The extracts were dried (Na_2SO_4) and concentrated (rotary evaporator) to afford 0.863 g (97%) of the two diastereometric sulfoxides as a colorless oil. Separation of the isomers **2** and **3** was carried out by column chromatography (CCl_4/*i*-PrOH, 19:1).

More polar diastereomer (**2**): R_f (CCl_4/*i*-PrOH, 9:1) 0.20; ^1H NMR ($CDCl_3$) δ 4.16 (ddd, 1 H, J = −11.8, 3.9, and 1.5 Hz, H_{2_e}), 3.86 (dd, 1 H, J = −11.8 and 8.3 Hz, H_{2_a}), 3.83 (m, 1 H, H_{6_e}), 3.58 (m, 1 H, H_{6_a}), 2.76 (m, 1 H, H_3), 2.61 (s, 3 H, SOMe), 2.00 (m, 1 H, H_{4_e}), 1.86–1.56 (m, 3 H, H_{5_e}, H_{4_a}, H_{5_a}).

Less polar diastereomer (**3**): R_f (CCl_4/*i*-PrOH, 9:1) 0.23; ^1H NMR ($CDCl_3$) δ 4.03 (ddd, 1 H, J = −11.8, 3.9 and 1.4 Hz, H_{2_e}), 3.84 (m, 1 H, H_{6_e}), 3.64 (dd, 1 H, J = −11.8 and 8.7 Hz, H_{2_a}), 3.56 (m, 1 H, H_{6_a}), 2.82 (m, 1 H, H_3), 2.59 (s, 3 H, SOMe), 2.16–1.65 (m, 4 H, H_{4_e}, H_{4_a}, H_{5_e}, H_{5_a}).

3-(Methylsulfonyl)tetrahydropyran (4). To a solution of 1.45 g (6.78 mmol) of sodium metaperiodate in 20 mL of water was added 0.397 g (3 mmol) of the sulfide **1**. The solution was warmed at 50 °C for 8 h. The reaction mixture was then evaporated to dryness, and the residue was extracted several times with methylene chloride. The extracts were dried (Na_2SO_4) and concentrated to give 0.439 g (89%) of **4**. It was crystallized from carbon tetrachloride: mp 53–54 °C; ^1H NMR ($CDCl_3$) δ 4.27 (ddd, 1 H, J = −11.4, 4.2, and 2.2 Hz, H_{2_e}), 3.92 (dddd, 1 H, J = −11.2, 3.9, 2.7, and 1.3 Hz, H_{6_e}), 3.65 (dd, 1 H, J = −11.4 and 10.0 Hz, H_{2_a}), 3.43 (ddd, 1 H, J = −11.2, 10.7, and 3.0 Hz, H_{6_a}), 3.15 (tt, 1 H, J = 10.5 and 4.1 Hz, H_3), 2.88 (d, 3 H, J = 0.5 Hz, SO_2Me), 2.29 (m, 1 H, H_{4_e}), 2.02–1.67 (m, 3 H, H_{4_a}, H_{5_e}, H_{5_a}). Anal. Calcd for $C_6H_{12}SO_3$: C, 43.88; H, 7.37; S, 19.53. Found: C, 43.69; H, 7.50; S, 19.77.

Dimethyl-3-tetrahydropyranylsulfonium *p*-Toluenesulfonate (5). A mixture of **1** (1 g, 7.56 mmol) and methyl *p*-toluenesulfonate (3.239 g; 17.4 mmol) was stirred at 30 °C for 48 h. The reaction mixture was washed with anhydrous ether and filtered to afford 2.134 g (88.6%) of **5**. It was crystallized from anhydrous acetone: mp 104–105 °C; ^1H NMR ($CDCl_3$) δ 7.74–7.14 (AA'BB' system, 4 H, C_6H_4), 4.21 (m, 1 H, H_{3_e}), 3.97 (ddd, part A of an AMX system, 1 H, J = −13.2, 3.9, and 1.6 Hz, H_{2_e}), 3.84 (dd, part M of an AMX system, 1 H, J = −13.2 and 2.5 Hz, H_{2_a}), 3.81 (m, 1 H, H_{6_e}), 3.57 (ddd, 1 H, J = −12.6, 9.4, and 3.3 Hz, H_{6_a}), 3.21 (s, 3 H, SMe), 3.18 (s, 3 H, SMe), 2.34 (s, 3 H, $ArCH_3$), 2.25–1.54 (m, 4 H, H_{4_e}, H_{4_a}, H_{5_e}, H_{5_a}). Anal. Calcd for $C_{14}H_{22}S_2O_4$: C, 52.80; H, 6.96; S, 20.14. Found: C, 52.86; H, 6.68; S, 20.02.

***cis*- and *trans*-5-Thioacetyl-2-methyltetrahydropyran.** To a solution of 3.12 mL (3.335 g; 43.8 mmol) of thiolacetic acid and 220 mg of benzoyl peroxide, cooled to 0 °C, was added 4.3 g (43.8 mmol) of 2-methyl-3,4-dihydro-2*H*-pyran.[5] The mixture was allowed to stand overnight and then was treated with aqueous 10% sodium bicarbonate and extracted with ether. The organic layer was dried (Na_2SO_4) and evaporated to give 6.909 g (90.5%) of the thioacetates as a cis–trans mixture (66:34), which was used in the following reaction without prior purification: IR (film) ν_{max} 1690 ($SCOCH_3$) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.32 (s, 1.98 H, $SCOCH_3$, cis), 2.30 (s, 1.02 H, $SCOCH_3$, trans).

***cis*- and *trans*-5-(Methylsulfenyl)-2-methyltetrahydropyran (*cis*- and *trans*-7).** The above cis–trans mixture (6 g; 34.4 mmol) of thioacetates, 50 mL of aqueous 20% potassium hydroxide, and 25 mL of methanol were refluxed 1 h. Then 4.3 mL (9.774 g; 68.7 mmol) of methyl iodide was added and refluxing continued for 30 min. The reaction mixture was extracted with ether, dried (Na_2CO_3), and concentrated to yield 4.31 g (85.6%) of cis–trans thioethers in a 66:34 ratio (^1H NMR). The isomers were separated by column chromatography (ether/hexane, 1:29).

Cis isomer: R_f (ether/hexane, 1:9) 0.29; ^1H NMR ($CDCl_3$) δ 3.95 (dt, part A of an AMX system, 1 H, J = −12.0 and 2.3 Hz, H_{6_e}), 3.88 (m, 1 H, H_{2_a}), 3.75 (dd, part M of an AMX system, 1 H, J = −12.0 and 2.5 Hz, H_{6_a}), 2.80 (m, 1 H, H_5), 2.11 (m, 3 H, SMe), 1.91 (m, 2 H, H_{4_e}, H_{4_a}), 1.80–1.30 (m, 2 H, H_{3_e}, H_{3_a}); 1.20 (d, 3 H, J = 6.3 Hz, CCH_3).

Trans isomer: R_f (ether/hexane, 1:9) 0.40; ^1H NMR ($CDCl_3$) δ 4.06 (ddd, 1 H, J = −11.0, 4.3, and 2.3 Hz, H_{6_e}), 3.55–3.20 (m, 1 H, H_{2_a}), 3.25 (t, 1 H, J = 11.0 Hz, H_{6_a}), 2.65 (m, 1 H, H_5), 2.20–1.05 (m, 4 H, H_{4_e}, H_{3_e}, H_{3_a}, H_{4_a}); 2.09 (s, 3 H, SMe), 1.16 (d, 3 H, J = 6.2 Hz, CCH_3).

***cis*-5-(Methylsulfonyl)-2-methyltetrahydropyran (*cis*-10).** The thioether *cis*-**7** was oxidized with sodium metaperiodate as indicated above for **4** (quantitative yield). It was crystallized from benzene-hexane (1:3): mp 51–52 °C; ^1H NMR (CD_2Cl_2) δ 4.66 (dt, 1 H, J = −13.2 and 2.0 Hz, H_{6_e}), 3.82 (dd, 1 H, J = −13.2 and 3.8 Hz, H_{6_a}), 3.52 (dqd, 1 H, J = 9.8, 6.2, and 2.7 Hz, H_2), 2.94 (d, 3 H, J = 0.7 Hz, SO_2Me), 2.86 (m, 1 H, H_5), 2.42 (m, 1 H, H_{4_e}), 2.06 (m, 1 H, H_{4_a}), 1.61 (m, 2 H, H_{3_e}, H_{3_a}), 1.18 (d, 3 H, J = 6.2 Hz, CCH_3). Anal. Calcd for $C_7H_{14}SO_3$: C, 47.17; H, 7.92; S, 17.99. Found: C, 47.13; H, 7.73; S, 17.95.

***cis*-5-(Methylsulfinyl)-2-methyltetrahydropyrans (8 and 9).** The mixture of isomers was obtained by oxidation of **7** with sodium metaperiodate as described for the **2** + **3** mixture: yield, 93%. The isomers were separated by column chromatography (CCl_4/*i*-PrOH, 14:1). Both epimers are hygroscopic liquids.

More polar diastereomer (**8**): R_f (CCl_4/*i*-PrOH, 9:1) 0.20; ^1H NMR (CD_2Cl_2) δ 4.40 (dt, 1 H, J = −12.7 and 2.0 Hz, H_{6_e}), 3.65 (dd, 1 H, J = −12.7 and 2.4 Hz, H_{6_a}), 3.16 (m, 1 H, H_2), 2.54 (s, 3 H, SOMe), 2.56 (m, 1 H, H_5), 2.14–1.96 (m, 1 H, H_{4_a}), 1.84–1.70 (m, 1 H, H_{4_e}), 1.55–1.34 (m, 2 H, H_{3_e}, H_{3_a}), 1.14 (d, 3 H, J = 6.2 Hz, CCH_3).

Less polar diastereomer (**9**): R_f (CCl_4/*i*-PrOH, 9:1) 0.26. ^1H NMR (C_6D_6) δ 3.50 (dt, 1 H, J = −13.2 and 2.0 Hz, H_{6_e}), 3.22 (dd, 1 H, J = −13.2 and 2.6 Hz, H_{6_a}), 3.14–3.00 (m, 1 H, H_2), 2.59–2.46 (m, 1 H, H_{4_e}), 2.00 (m, 1 H, H_5), 1.94 (s, 3 H, SOMe), 1.66–1.19 (m, 3 H, H_{4_a}, H_{3_e}, H_{3_a}), 1.01 (d, 3 H, J = 6.1 Hz, CCH_3).

Dimethyl(*cis*-2-methyltetrahydropyran-5-yl)sulfonium *p*-toluenesulfonate (*cis*-11) was prepared from *cis*-**7** following

(16) Schneider, H.-J.; Hoppen, V. *J. Org. Chem.* **1978**, *43*, 3866.
(17) Jensen, F. R.; Bushweller, C. H. *Adv. Alicycl. Chem.* **1971**, *3*, 139.
(18) Martin, M.; Bassery, L.; Leroy, C. *Bull. Soc. Chim. Fr.* **1972**, 4763.
(19) Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr., Sect. A* **1971**, *A27*, 368.

Table VII. ^{13}C NMR Chemical Shifts (Intensity) [in ppm]

solv	T, K	C(1)	C(2,6)	C(3,5)	C(4)	C*Me*	S*Me*
CD_3OD	300	57.1	25.7	30.9	30.9	20.7	23.2
CD_3OD[a]	183	56.8 (5.19)	27.0	30.3 (4.73)	33.0	*e*	22.9
CD_3OD[b]	183	54.7 (1.00)	22.2	31.3 (1.00)	*e*	17.0	*e*
CD_2Cl_2[c]	183	54.8	26.4	29.2 (6.08)	32.0	*e*	22.5
CD_2Cl_2[d]	183	53.2	21.8	30.1 (1.00)	*e*	16.7	*e*

[a] Conformer with axial $^+SMe_2$. [b] Conformer with equatorial $^+SMe_2$, $\Delta G°_{e\rightleftharpoons a} = -0.65 \pm 0.01$ kcal/mol. [c] Conformer with axial $^+SMe_2$. [d] Conformer with equatorial $^+SMe_2$, $\Delta G°_{e\rightleftharpoons a} = -0.58 \pm 0.02$ kcal/mol. [e] Not observed.

the procedure described in the synthesis of **5**: reaction time, 1 day: yield, 91%; crystallized from anhydrous acetone, mp 156–157 °C; ^1H NMR ($CDCl_3$) δ 7.74–7.14 (AA′BB′ system, 4 H, C_6H_4), 4.24 (m, 1 H, H_5), 4.14 (d, 1 H, $J = -14.1$ Hz, H_{6_e}), 3.76 (dd, 1 H, $J = -14.1$ and 1.8 Hz, H_{6_a}), 3.51 (m, 1 H, H_2), 3.20 (s, 3 H, SMe), 3.16 (s, 3 H, SMe), 2.34 (s, 3 H, $ArCH_3$), 2.14 (m, 1 H, H_{4_e}), 1.67–1.36 (m, 3 H, H_{4_a}, H_{3_e}, H_{3_a}), 1.16 (d, 3 H, $J = 6.2$ Hz, CCH_3). Anal. Calcd for $C_{15}H_{24}S_2O_4$: C, 54.19; H, 7.28; S, 19.29. Found: C, 53.85; H, 7.05; S, 19.27.

3-(Benzylsulfinyl)tetrahydropyran (13 and 14) was prepared from **12**[18] as described for the sulfoxides **2** and **3**: yield, 84%. The separation of the isomers was carried out by column chromatography (CCl_4/*i*-PrOH, 19:1).

More polar diastereomer (**13**): R_f (CCl_4/*i*-PrOH, 9:1) 0.42; crystallized from carbon tetrachloride, mp 91–92 °C; ^1H NMR ($CDCl_3$) δ 7.46–7.27 (m, 5 H, C_6H_5), 4.14 (ddd, 1 H, $J = -11.8$, 4.0, and 1.4 Hz, H_{2_e}), 4.11–3.90 (AB system, 2 H, $J = -13.2$ Hz, $SOCH_2Ph$), 3.91 (dd, 1 H, $J = -11.8$ and 8.3 Hz, H_{2_a}), 3.81 (m, 1 H, H_{6_e}), 3.55 (m, 1 H, H_{6_a}), 2.77 (m, 1 H, H_3), 2.03–1.51 (m, 4 H, H_{4_e}, H_{4_a}, H_{5_e}, H_{5_a}). Anal. Calcd for $C_{12}H_{16}SO_2$: C, 64.25; H, 7.19; S, 14.29. Found: C, 64.21; H, 7.17; S, 13.96.

Less polar diastereomer (**14**): R_f (CCl_4/*i*-PrOH, 9:1) 0.47; crystallized from carbon tetrachloride, mp 105–106 °C; ^1H NMR ($CDCl_3$) δ 7.44–7.22 (m, 5 H, C_6H_5), 4.00 (s, 2 H, $SOCH_2Ph$), 3.91 (ddd, 1 H, $J = -11.7$, 9.2, and 4.0 Hz, H_{2_e}), 3.83 (dt, 1 H, $J = -11.4$ and 4.2 Hz, H_{6_e}), 3.61 (dd, 1 H, $J = -11.7$ and 9.2 Hz, H_{2_a}), 3.51 (ddd, 1 H, $J = -11.4$, 9.6, and 3.1 Hz, H_{6_a}), 2.71 (m, 1 H, H_3), 2.13–1.59 (m, 4 H, H_{4_e}, H_{4_a}, H_{5_e}, H_{5_a}). Anal. Calcd for $C_{12}H_{16}SO_2$: C, 64.25; H, 7.19; S, 14.29. Found: C, 64.50; H, 7.38; S, 13.90.

3-(Benzylsulfonyl)tetrahydropyran (15) was obtained from **12** following the procedure described for **4**: yield, 88%; crystallized from carbon tetrachloride, mp 138–139 °C; ^1H NMR ($CDCl_3$) δ 7.42 (s, 5 H, C_6H_5), 4.20 (AA′ system, $J = -14.0$ Hz, SO_2CH_2Ph), 4.14 (ddd, 1 H, $J = -11.4$, 4.1, and 2.1 Hz, H_{2_e}), 3.88 (m, 1 H, H_{6_e}), 3.60 (dd, 1 H, $J = -11.4$ and 10.3 Hz, H_{2_a}), 3.37 (td, 1 H, $J = -11.4$ and 2.8 Hz, H_{6_a}), 3.05 (ddt, 1 H, $J = 10.9$, 10.3, and 4.1 Hz, H_3), 2.19 (m, 1 H, H_{4_e}), 2.01–1.50 (m, 3 H, H_{5_e}, H_{4_a}, H_{5_a}). Anal. Calcd for $C_{12}H_{16}SO_3$: C, 59.97; H, 6.71; S, 13.34. Found: C, 60.09; H, 6.77; S, 13.55.

***trans*-5-(Methylsulfonyl)-2-methyltetrahydropyran (*trans*-10).** The thioether *trans*-**7** was oxidized with sodium metaperiodate as indicated for **4** (quantitative yield). It was crystallized from benzene/hexane (1:3): mp 66.5–67.5 °C; ^1H NMR ($CDCl_3$) δ 4.33 (ddd, 1 H, $J = -11.0$, 4.0, and 2.3 Hz, H_{6_e}), 3.62 (dd, 1 H, $J = -11.0$ and 10.9 Hz, H_{6_a}), 3.60–2.90 (m, 1 H, H_2), 2.84 (s, 3 H, SO_2Me), 2.15 (m, 1 H, H_5), 2.00–1.20 (m, 4 H, H_{4_e}, H_{4_a}, H_{3_e}, H_{3_a}), 1.20 (d, 3 H, $J = 6.2$ Hz, CCH_3). Anal. Calcd for $C_7H_{14}SO_3$: C, 47.17; H, 7.92; S, 17.99. Found: C, 46.89; H, 7.60; S, 17.76.

Dimethyl(*trans*-2-methyltetrahydropyran-5-yl)sulfonium *p*-toluenesulfonate (*trans*-11) was prepared from *trans*-**7** following the procedure above described for the synthesis of **5**: reaction time, 1 day; yield, 81%; crystallized from ethanol/hexane (1:3), mp 171–172 °C; ^1H NMR ($CDCl_3$) δ 7.80–7.10 (AA′BB′ system, 4 H, C_6H_4), 4.19 (ddd, 1 H, $J = -10.9$, 4.0, and 2.4 Hz, H_{6_e}), 3.83 (m, 1 H, H_5), 3.50 (t, 1 H, $J = 10.9$ Hz, H_{6_a}), 3.43 (m, 1 H, H_2), 3.20 (s, 3 H, ^+SMe), 3.19 (s, 3 H, ^+SMe), 2.34 (s, 3 H, $ArCH_3$), 2.33 (m, 1 H, H_{4_e}), (d, 3 H, $J = 6.2$ Hz, CCH_3).

Anal. Calcd for $C_{15}H_{24}S_2O_4$: C, 54.19; H, 7.28; S, 19.29;. Found: C, 53.98; H, 7.10; S, 19.13.

Crystal Structure of (*R*R)-3-(Benzylsulfinyl)oxane.** A single colorless crystal (0.49 × 0.57 × 0.02 mm) of (*R*R**)-3-(benzylsulfinyl)oxane (**14**) was found to be monoclinic, space group *Ia*, with $a = 8.824$ (10) Å, $b = 5.428$ (3) Å, $c = 24.331$ (6) Å, $\beta = 95.99$ (8)°, volume = 1159 (2) Å^3, $Z = 4$, $D_{calcd} = 1.285$, and $D_{obsd} = 1.21$ (6) g cm^{-3} (flotation in aqueous sodium bromide). The structure was refined to a final value of the weighted R factor of 0.075 based on 726 intensities. Data were collected on Enraf-Nonius CAD-4/SDP diffractometer by using Mo Kα radiation and a graphite monochromator. Absorption corrections were not applied.

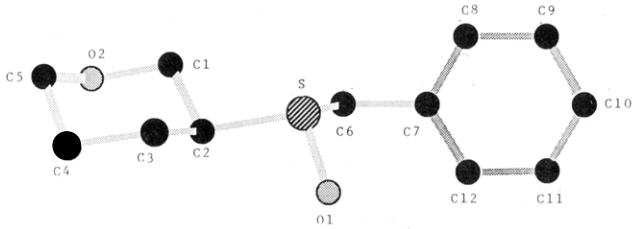


Figure 1. Numbering scheme for structure **14**.

Table VIII. Atomic Positional Parameters for 14

atom	*X*	*Y*	*Z*
S	0.2559 (0)	0.8312 (6)	0.1840 (0)
O1	0.240 (1)	1.100 (1)	0.1707 (3)
O2	0.539 (1)	0.582 (2)	0.3143 (3)
C1	0.442 (1)	0.572 (3)	0.2632 (5)
C2	0.389 (1)	0.830 (2)	0.2475 (4)
C3	0.291 (1)	0.923 (2)	0.2937 (5)
C4	0.404 (1)	0.919 (2)	0.3479 (4)
C5	0.455 (2)	0.657 (3)	0.3586 (5)
C6	0.371 (2)	0.697 (2)	0.1375 (5)
C7	0.306 (1)	0.716 (2)	0.0788 (4)
C8	0.344 (1)	0.911 (2)	0.0451 (5)
C9	0.276 (2)	0.929 (3)	−0.0083 (5)
C10	0.175 (2)	0.758 (2)	−0.0278 (5)
C11	0.134 (2)	0.566 (3)	0.0038 (6)
C12	0.206 (1)	0.542 (2)	0.0576 (5)

The structure was solved by direct methods using MULTAN.[19] Since the crystal was of poor quality (very thin), hydrogens were placed in calculated positions and not refined. The atomic positional parameters of **14** derived from the final least-squares refinements are listed in Table VIII.

The structure (represented for the *S,S* isomer) is depicted in Figure 1.

***cis*-(4-Methylcyclohexyl)dimethylsulfonium *p*-toluenesulfonate** was prepared from *cis*-4-methylcyclohexyl methyl sulfide[8] and methyl *p*-toluenesulfonate following a previously described method,[20] mp 156–157 °C. The starting material, *cis*-4-methylcyclohexyl methyl sulfide, was obtained by treatment of *trans*-4-methylcyclohexyl *p*-toluenesulfonate[21] (0.7 g; 2.6 mmol) with 2 g (5 mmol) of an 18% solution of sodium methyl sulfide in anhydrous methanol at 80 °C overnight. Workup of the reaction mixture and purification by flash chromatography (hexanes/ethyl acetate, 9:1) yielded 88 mg of pure sulfide, whose ^1H NMR data agree with those reported:[8] IR (Nujol) ν_{max} 1190, 1120, 1033, 1007, 811, 676 cm^{-1}; ^1H NMR (CD_3OD) δ 0.95 (d, 3 H), 1.33 (m, 2 H), 1.66 (m, 3 H), 1.95 (m, 4 H), 2.36 (s, 3 H), 2.87 (2, 6 H), 3.60 (m, 1 H), 7.24 (d, 2 H), 7.71 (d, 2 H); ^{13}C NMR data are shown in Table VII.

Since $\Delta G°_{e\rightleftharpoons a}$ for CH_3 is 1.74 ± 0.06 kcal/mol, $\Delta G°_{e\rightleftharpoons a}$ for SMe_2^+ (assuming additivity) is 1.16 ± 0.07 kcal/mol in CD_2Cl_2 or 1.09 ± 0.07 kcal/mol in CD_3OD.

(20) Brunet, E.; Carreño, M. C.; Gallego, M. T.; García Ruano, J. L. Alcudia, F. *J. Chem. Soc., Perkin Trans. 2* **1983**, 937.
(21) Eliel, E. L.; Ro, R. S. *J. Am. Chem. Soc.* **1957**, *79*, 5995.

Acknowledgment. This work was supported by U. S.–Spain Collaborative Grant INT-8412811 (Conjunto Hispano-Norteamericano Grant 84020061), by C.A.C.Y.T. Grant 0352-84, and by NSF Grant NSF CHE-8314169. We are grateful to Professor Derek J. Hodgson and Dr. Y. Yokomori for help with the unexpectedly difficult X-ray structure determination and to Dr. Ernesto Brunet Romero for determining the conformational energy of the SMe_2^+ group in the cyclohexyl system and for helpful discussions.

Registry No. (±)-1, 109392-49-6; (±)-2, 109392-50-9; (±)-3, 109392-51-0; (±)-4, 109392-52-1; (±)-5, 109392-54-3; (±)-*cis*-7, 109392-57-6; (±)-*trans*-7, 109392-58-7; (±)-8, 109392-60-1; (±)-9, 109392-61-2; (±)-*cis*-10, 109392-59-8; (±)-*trans*-10, 109392-68-9; (±)-*cis*-11, 109392-63-4; (±)-*trans*-11, 109392-70-3; (±)-12, 109392-64-5; (±)-13, 109392-65-6; (±)-14, 109392-66-7; (±)-15, 109392-67-8; (±)-2-methyl-3,4-dihydro-2*H*-pyran, 75795-70-9; (±)-*cis*-thioacetyl-2-methyltetrahydropyran, 109392-55-4; (±)-*trans*-thioacetyl-2-methyltetrahydropyran, 109392-56-5.

Supplementary Material Available: Tables 1a, 3a, and 4a (expanded versions of Tables 1, 3, and 4), Tables S1 (bond lengths), S2 (bond angles), S3 (torsion angles), and S4 (anisotropic thermal parameters), infrared data for compounds **2–5**, *cis*- and *trans*-**7**, **8**, **9**, *cis*- and *trans*-**10**, *cis*- and *trans*-**11**, and **13–15**, and mass spectral data for compounds **2–4**, *cis*- and *trans*-**7**, **8**, **9** (14 pages); Table S5 (observed and calculated structure amplitudes) (7 pages). Ordering information is given on any current masthead page.

Notes

New Routes to 1,2-Diazetidin-3-ones

Edward C. Taylor* and Jeffery S. Hinkle†

Department of Chemistry, Princeton University, Princeton, New Jersey 08544

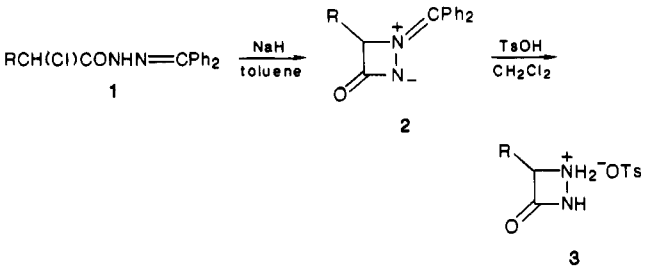
Received February 12, 1987

In a series of recent papers we have described the preparation and properties of both monocyclic and bicyclic 1,2-diazetidin-3-ones, which were prepared as highly strained bridgehead aza analogues of the carbapenem and carbacephem β-lactam antibiotics.[1-9] Our preferred route to the parent 1,2-diazetidin-3-one system has involved intramolecular dehydrohalogenation of α-chloroacyl hydrazones of diaryl ketones to generate ylides of type **2**, which were then hydrolyzed to the *p*-toluenesulfonate salts of 1,2-diazetidin-3-ones (Scheme I).[7-9] Methods for the subsequent conversion of these key intermediates to target aza β-lactams have been described.[1-3,6] A number of alternate routes to 1,2-diazetidin-3-ones are also known;[4] they range from the cycloaddition of ketenes with azines[10] (which is only of historical interest, since its applicability is severely limited by lack of regioselectivity, low yields and inaccessibility of reaction partners with appropriate functionality) to a recently described and potentially versatile carbene coupling of (α-azoacyl)hydrazines.[11]

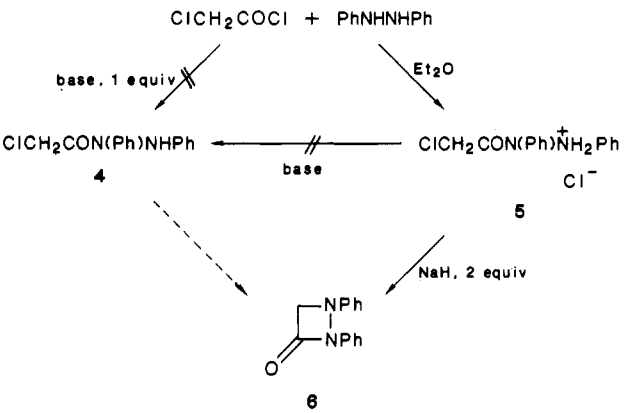
We describe in this paper several additional synthetic routes to 1,2-diazetidin-3-ones. We were motivated in this investigation by considerable difficulties which we have encountered in directly introducing appropriate substituents at N-1, N-2, and/or C-4 on preformed 1,2-diazetidin-3-ones, as well as difficulties experienced in further modifying substituents on this fragile ring system. It would obviously be attractive to have in hand a synthetic procedure which would make it possible to introduce desired substituents at a stage prior to formation of the diazetidinone ring.

The first route explored is outlined in Scheme II and involves intramolecular alkylation of an (α-haloacyl)-hydrazine precursor. The feasibility of this concept for direct diazetidinone synthesis was explored with (α-chloroacetyl)-1,2-diphenylhydrazine. Stirring 1,2-diphenylhydrazine with chloroacetyl chloride in ether at 0

Scheme I



Scheme II



†Ortho Pharmaceutical Corporation, Raritan, NJ 08869-0602.

(1) Taylor, E. C.; Davies, H. M. L. *J. Org. Chem.* **1986**, *51*, 1537.
(2) Taylor, E. C.; Davies, H. M. L.; Hinkle, J. S. *J. Org. Chem.* **1986**, *51*, 1530.
(3) Taylor, E. C.; Davies, H. M. L. *J. Org. Chem.* **1984**, *49*, 4415.
(4) Taylor, E. C.; Davies, H. M. L.; Lavell, W. T.; Jones, N. D. *J. Org. Chem.* **1984**, *49*, 2204.
(5) Taylor, E. C.; Davies, H. M. L. *J. Org. Chem.* **1984**, *49*, 113.
(6) Taylor, E. C.; Clemens, R. J.; Davies, H. M. L. *J. Org. Chem.* **1983**, *48*, 4567.
(7) Taylor, E. C.; Haley, N. F.; Clemens, R. J. *J. Am. Chem. Soc.* **1981**, *103*, 7743.
(8) Taylor, E. C.; Davies, H. M. L.; Clemens, R. J.; Yanagisawa, H.; Haley, N. F. *J. Am. Chem. Soc.* **1981**, *103*, 7660.
(9) Taylor, E. C.; Clemens, R. J.; Davies, H. M. L.; Haley, N. F. *J. Am. Chem. Soc.* **1981**, *103*, 7659.
(10) Staudinger, H. *Die Ketene*; F. Enke: Stuttgart, 1912; p 91.

0022-3263/87/1952-4107$01.50/0