REACTIONS OF AZIRINES WITH SULFUR NUCLEOPHILES.

3.* A NEW METHOD FOR THE SYNTHESIS OF 2,2-DISUBSTITUTED THIOMORPHOLINES

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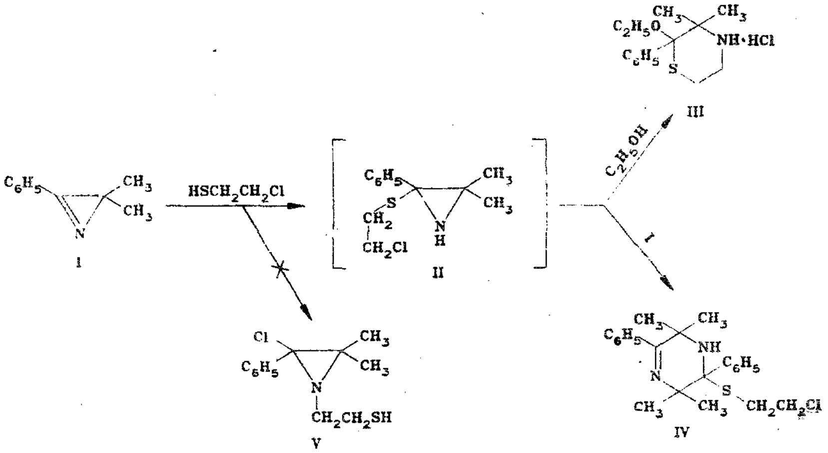
A new method has been found for the preparation of 2,2-disubstituted thiomorpholines by the reaction of 2,2-dimethyl-3-phenylaziridine with 2-chloroethanethiol.

In a study of the reactivity of 2,2-dimethyl-3-phenylaziridine (I) relative to sulfur nucleophiles, we discovered that the presence of nucleophilic substitutents in the β-position relative to the sulfide group facilitates intramolecular cyclization of the initially formed aziridinyl alkyl sulfides to give cyclic sulfides [1]. We thus found interest in studying the reaction of aziridine I with 2-chloroethanethiol which is a compound capable of reacting with the electrophilic (C) and nucleophilic (N) sites of aziridine I to form either the corresponding aziridinyl alkyl sulfide or aziridinylethanethiol (or the products of their decomposition or rearrangement).

These studies showed that the reaction of aziridine I with 2-chloroethanethiol in ethanol leads to the formation of III and IV in 57 and 13% yield, respectively. The vibrational spectrum of III shows an NH_2^+ stretching band at 2405-2700 cm^{-1} and an NH_2^+ group deformation band at 1565 cm^{-1}. The PMR spectrum of this compound (Table 1) has multiplets of the inequivalent protons of the α- and β-methylene groups of the 2-chloroethanethiol fragment, which is possible only in the case of a cyclic structure for reaction product III, and also characteristic signals for the protons of an ethyl group, phenyl ring and two broad singlets for the NH_2^+ group protons at 8.57 and 9.88 ppm with 1H intensity each. Its PMR spectrum has nonequivalent resonance signals for the gem-methyl groups, which also indicates the formation of a cyclic structure. On the basis of the spectral and analytical data, we concluded that the reaction of azirine I with 2-chloroethanethiol in ethanol gives 2-ethoxy-3,3-dimethyl-2-phenylthiomorpholine hydrochloride (III) as the major product:



The mass spectrometric analysis of II showed the presence of the $M^+ - HCl$ ion (215).

An interesting feature of the PMR spectrum of thiomorpholine III is the nonequivalence of the ammonium group protons which give two broad singlets. The difference in the shielding of the NH_2^+ group protons is presumably the result of the participation of one of the hydrogen

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*For Communication 2, see [1].

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TABLE 1. PMR Spectral Parameters of Thiomorpholine III

Proton	δ, ppm	J, Hz
5-H_a	3,37	
5-H_e	3,30	
6-H_e	2,82	$^2J_{66}=14{,}0$; $^3J_{5a6e}={}^3J_{5e6e}=2{,}8$
6-H_a	2,92	$^3J_{5a6a}=11{,}7$; $^3J_{5e6a}=4{,}0$
NH_a	8,57	$^3J_{4a5a}=11$; $^3J_{4a5e}=0$
NH_e	9,88	$^2J_{44}=11$; $^3J_{e,1}\simeq{}^3J_{e,2}\simeq 0$; $^3J_{4e5a}={}^3J_{4e5e}=0$
3-CH_3	2,38; 2,23	
CH_2	3,61; 3,22	$^2J=9{,}5$; $^3J=7{,}0$
CH_3	2,32	
C_6H_5	7,3—7,5	

atoms in intramolecular hydrogen bonding with the ethoxy group oxygen atom. The Dreiding model for III confirms the possibility of the formation of such a bond if the thiomorpholine ring has chair form with extrusion of the sulfur and nitrogen atoms from the plane in opposite directions and mutual cis-orientation of one of the NH_2^+ group protons and the ethoxy group.

The molecular and crystal structure thiomorpholine III was determined in order to establish its three-dimensional structure. The molecular structure with bond lengths (Å) and angles (deg) is given in Fig. 1. The thiomorpholine right has chair conformation. The S and $N_{(4)}$ atoms extrude from the $C_{(2)}$—$C_{(3)}$—$C_{(5)}$—$C_{(6)}$ plane in opposite direction by 0.956(1) and 0.636 (4) Å, respectively. The dihedral angles formed by the $C_{(2)}$—$S_{(1)}$—$C_{(6)}$ and $C_{(3)}$—$N_{(4)}$—$C_{(5)}$ corners and the $C_{(2)}$—$C_{(3)}$—$C_{(5)}$—$C_{(6)}$ plane are 53.1 and 55.3°, respectively. The angle between the rigorously planar phenyl ring (±0.006 Å) and the mean plane of the thiomorpholine ring is 64.7°. The phenyl ring has equatorial orientation relative to the thiomorpholine ring. The mean C—S bond lengths in the thiomorpholine ring [1.823(5) Å] is close to the standard value (1.817 Å [2]). The extension of the $C_{(2)}$—$C_{(3)}$ [1.572 (6) Å] and $C_{(3)}$—$N_{(4)}$ bonds [1.513(6) Å] relative to the standard values (1.537 and 1.479 Å [2], respectively) is apparently related to the inductive effect of the two methyl groups (σ-electron donors) at $C_{(3)}$. The $N_{(4)}$ atom is protonated and has tetrahedral coordination. Figure 2 gives the projection of the crystal structure onto the ac plane. The molecules in the crystal are connected into centrosymmetric pairs by means of two hydrogen bonds with the chlorine atoms [N...Cl = 3.109 (4), $H_{(1)}$...Cl = 2.21 (7) Å ∠ N—$H_{(1)}$...Cl = 154(5)° and N...Cl = 3.804(4), $H_{(2)}$...Cl = 2.02 (7) Å, ∠ N—$H_{(2)}$...Cl = 174(5)°]. The molecule has a short intramolecular contact, $H_{(1)}N_{(4)}$... O = 2.47(6) Å.

(3,3,6,6-Tetramethyl-2,5-dipenyl-1,2,3,6-tetrahydropyrazinyl-2)-2-chloroethyl sulfide (IV) is also formed in addition to thiomorpholine III in the reaction of azirine I with 2-chlorethanethiol (see Experimental). The formation of tetrahydropyrazine systems such as IV is extremely characteristic for the addition reactions of azirines when the reaction of an additional azirine molecule with the addition product leads to the formation of tetrahydropyrazine derivatives. It is precisely the isolation of tetrahydropyrazine IV which permits us to conclude that the reaction of azirine I with 2-chloroethanethiol proceeds initially at the sulfhydryl group of the thiol to form aziridinyl alkyl sulfide II. Then, II apparently undergoes expansion of the aziridine ring with breakage of the 1,2-ring bond and formation of thiomorpholine III and also reacts with an additional molecule of azirine I leading to tetrahydropyrazine IV . In the opposite case, if we assume that the electrophilic addition of 2-chloroethanethiol to azirine I results initially in the formation of 1-(2-mercaptoethyl)-2-chloro-3,3-dimethyl-2-phenylazirine (V) by analogy to the reaction of aryl halides with 3-dimethylamino-2,2-dimethylazirine [3], the formation of tetrahydropyrazine IV would be impossible.

EXPERIMENTAL

The IR spectra were taken in Nujol mull and neat on a Perkin-Elmer 580B spectometer. The PMR spectra were taken on Bruker WH-90 and Bruker WH-360 spectrometers for 5% solutions and TMS as the internal standard (one drop of trifluoroacetic acid was added to the 5% solution of III in DMSO-d_6). The mass spectrum was taken on an MS-905 spectrometer at 70 eV.

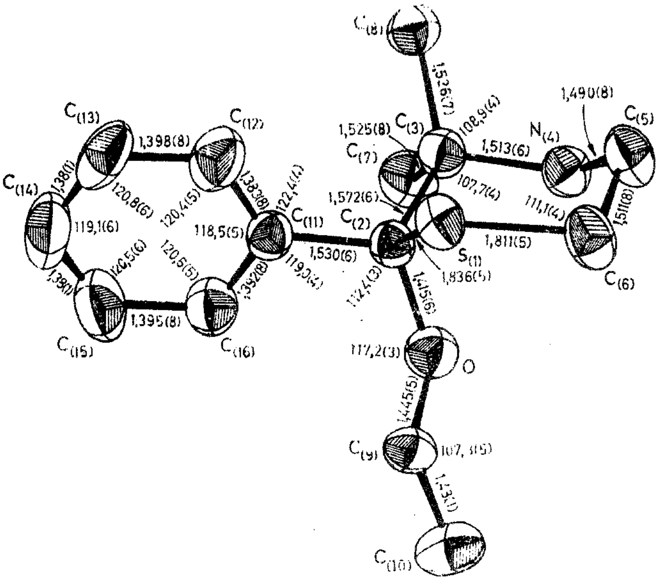

Fig. 1. Structure of thiomorpholine III:
$C_{(2)}-S_{(1)}-C_{(6)}$ = 97.4(2) $O-C_{(2)}-C_{(3)}$ = 103.4(3) $N_{(4)}-C_{(3)}-C_{(7)}$ = 105.4(4)
$S_{(1)}-C_{(2)}-O$ = 111.4(3) $C_{(3)}-C_{(2)}-C_{(11)}$ = 111.3(4) $C_{(7)}-C_{(3)}-C_{(8)}$ = 109.9(4)
$S_{(1)}-C_{(2)}-C_{(3)}$ = 110.8(3) $C_{(2)}-C_{(3)}-C_{(7)}$ = 111.1(4) $C_{(3)}-N_{(4)}-C_{(5)}$ = 118.2(4)
$S_{(1)}-C_{(2)}-C_{(11)}$ = 107.5(3) $C_{(2)}-C_{(3)}-C_{(8)}$ = 113.5(4) $N_{(4)}-C_{(5)}-C_{(6)}$ = 112.0(4)

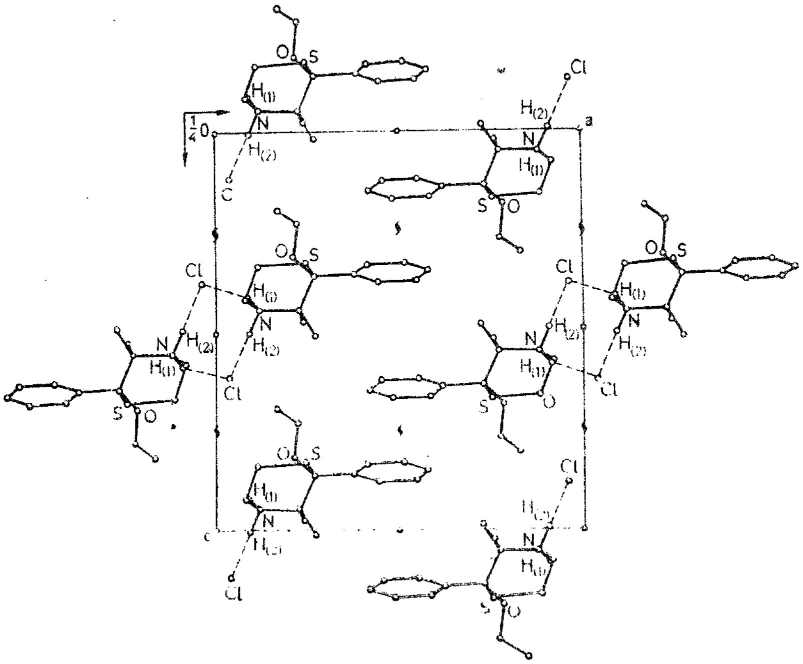

Fig. 2. Projection of the crystal structure of thiomorpholine III on the ac plane.

Single crystals of III were grown from 1:3 ethanol—ether. The unit cell parameters of the monoclinic crystals of $C_{14}H_{21}NOS{\bullet}HCl$ are as follows: a = 13.724 (4), b = 6.508 (1), c = 16.727 (3) Å, β = 90.25 (2)°, V = 1494.0 Å^3, M = 287.88, d_{calc} = 1.28 g/cm^3, $\mu(CuK_\alpha)$ = 34.2 cm^{-1}, Z = 4, space group $P2_1/c$, F_{000} = 616.

The intensities of 2131 independent reflections were measured on a Syntex $P2_1$ diffractometer using CuK_α radiation and a graphite monochromator by $\theta/2\theta$ scan to $2\theta_{max}$ = 150°. A total of 1814 reflections with $I \geqslant 2\sigma_I$ was used in the calculations. The structure was

TABLE 2. Atomic Coordinates ($\times 10^4$, $\times 10^3$ for H)

Atom	x	y	z	Atom	x	y	z
$S_{(1)}$	7543(1)	4411(2)	1687(1)	$H_{(1)}C_{(5)}$	995(4)	366(9)	74(4)
Cl	10394(1)	−1221(2)	1184(1)	$H_{(2)}C_{(5)}$	893(4)	480(9)	31(3)
O	7830(2)	329(5)	1836(2)	$H_{(1)}C_{(6)}$	910(4)	332(9)	204(3)
$N_{(4)}$	8799(3)	1725(7)	523(2)	$H_{(2)}C_{(6)}$	908(4)	569(10)	170(4)
$C_{(2)}$	7306(3)	1760(8)	1364(2)	$H_{(1)}C_{(7)}$	787(5)	−103(10)	−26(4)
$C_{(3)}$	7709(3)	1386(8)	498(2)	$H_{(2)}C_{(7)}$	685(5)	−126(10)	20(4)
$C_{(5)}$	9167(4)	3785(9)	767(3)	$H_{(3)}C_{(7)}$	785(5)	−178(10)	61(4)
$C_{(6)}$	8858(4)	4340(11)	1606(3)	$H_{(1)}C_{(8)}$	657(5)	244(11)	−24(4)
$C_{(7)}$	7574(4)	−848(9)	247(3)	$H_{(2)}C_{(8)}$	764(5)	254(10)	−62(4)
$C_{(8)}$	7262(4)	2808(10)	−129(3)	$H_{(3)}C_{(8)}$	736(5)	422(11)	2(4)
$C_{(9)}$	7745(4)	511(10)	2694(3)	$H_{(1)}C_{(9)}$	710(4)	53(9)	283(3)
$C_{(10)}$	8309(5)	1196(13)	3053(4)	$H_{(2)}C_{(9)}$	802(4)	194(9)	286(3)
$C_{(11)}$	6204(3)	1413(8)	1399(3)	$H_{(1)}C_{(10)}$	836(4)	−110(9)	364(4)
$C_{(12)}$	5540(4)	2933(11)	1205(3)	$H_{(2)}C_{(10)}$	803(5)	−251(11)	294(4)
$C_{(13)}$	4540(4)	2549(13)	1251(4)	$H_{(3)}C_{(10)}$	896(5)	−118(10)	289(4)
$C_{(14)}$	4197(4)	664(13)	1495(4)	$HC_{(12)}$	577(4)	430(9)	107(3)
$C_{(15)}$	4854(4)	−861(13)	1685(4)	$HC_{(13)}$	413(5)	366(9)	108(4)
$C_{(16)}$	5854(4)	−499(10)	1634(3)	$HC_{(14)}$	344(5)	40(10)	155(4)
$H_{(1)}N_{(4)}$	912(5)	63(10)	81(4)	$HC_{(15)}$	466(5)	−216(10)	189(4)
$H_{(2)}N_{(4)}$	908(5)	143(10)	−6(4)	$HC_{(16)}$	632(4)	−159(9)	180(3)

solved by the direct method using the XTL programs and refined by the method of least squares in the full-matrix anisotropic approximation with the weighting scheme $1/W = \sigma^2 + (0.025F)^2$. Absorption was not considered. The hydrogen atoms whose positions were found in the difference map were refined isotropically. The final R value was 0.030. The atomic coordinates are given in Table 2.*

2-Ethoxy-3,3-dimethyl-2-phenylthiomorpholine Hydrochloride (III). A sample of 2.92 g (0.03 mole) 2-chloroethanethiol [4] was added dropwise to a solution of 4.74 g (0.03 mole) azirine I [3] in 25 ml ethanol and stirred for 3 h at 70°C. The precipitate was filtered off and recrystallized from 1:3 ethanol—ether to give 4.9 g (57%) III, mp 215-216°C. Found: C, 66.6; H, 8.1; N, 5.4; S, 12.6%. Calculated for $C_{14}H_{21}NOS \cdot HCl$: C, 66.9; H, 8.4; N, 5.6; S, 12.8%.

After the separation of thiomorpholine III, the filtrate was evaporated and the residue was distilled to yield 1.6 g (13%) (3,3,6,6-tetramethyl-2,5-diphenyl-1,2,3,6-tetrahydropyrazinal-2)-2-chloroethyl sulfide (IV) bp 40-42°C (4 hPa). IR spectrum (neat): 1680 (C = N), 3300 cm^{-1} (NH). PMR spectrum ($CDCl_3$): 1.17, 1.26, 1.37, 1.53 (12H, s, CH_3), 1.76 (1H, s, NH), 3.02 (2H, t, $S-CH_2$), 3.75 (2H, t, CH_2Cl), 7.42 (6H, m, H_m and H_p), 7.66 (2H, m, H_o), 7.89 ppm (2H, m, H_o). Found: C, 68.1; H, 6.8; N, 7.0; S, 8.0%. Calculated for $C_{22}H_{27}ClN_2S$: C, 68.3; H, 7.08; N, 7.2; S, 8.3%.

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*The anisotropic temperature factors may be obtained from the authors.