THREE-DIMENSIONAL STRUCTURES OF SOME PERHYDRO-1,4-THIAZINE DERIVATIVES

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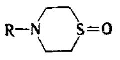
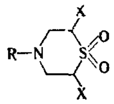
A number of perhydro-1,4-thiazine S-oxides and S,S-dioxides were synthesized. Their IR and PMR spectra were studied, and their dipole moments were determined. The latter were compared with the calculated values for the chair conformation with various orientations of the substituents. Conclusions were drawn regarding the configuration and conformation of the investigated compounds.

Despite a large number of conformational investigations devoted to sulfur- and nitrogen-containing heterocycles [1], there is no information in the literature regarding the structure of thiazan compounds. Using the method of dipole moments and IR and PMR spectroscopy, we investigated the structure of perhydro-1,4-thiazine S-oxides and S,S-dioxides (I-VII).



I-III



IV-VII

I $R=CH_3$; II $R=i\text{-}C_3H_7$; III $R=C_6H_{11}$; IV $R=CH_3$, $X=H$; V $R=C_6H_{11}$, $X=H$;
VI $R=CH_3$, $X=Br$; VII $R=C_6H_{11}$, $X=Br$

A peculiarity of I-III is the presence of two heteroatoms with unshared pairs of electrons, in connection with which, the problem regarding the relative three-dimensional orientation of the unshared pair and the substituent attached to the heteroatom arises. It seemed of interest to evaluate the inductive interactions of the dipoles for VI-VII and to compare them with the experimental results.

In view of the absence of factors that destabilize the stable chair-like conformation and promote the presence of flexible forms in the conformational equilibrium, we assumed that the chair-like conformation is the most probable ring conformation.

The dipole moments (DM) were calculated via an additive vector scheme using the bond moments, valence angles, and bond lengths presented in [2][*] and C–S 1.81 Å and CSC 99° [3] for the "nitrogen portion." The DM of the unshared pair of electrons of the sulfur atom (2.19 D) was taken into account in the calculation of the moments of S-oxides I-III, with an S=O bond moment of 3.76 D and a C–S bond moment of 0.44 D [3]. The DM of the $C-SO_2-C$ group (from the experimental DM of thiacyclohexane S,S-dioxide [4]), which is 4.44 D, was calculated for the computation of the DM of sulfones IV-VII, with $m_{C-S} = 0.66$ D.

The calculated DM for the chair conformation with axial and equatorial orientations of the substituents attached to the heteroatoms are presented in Table 1.

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[*] In view of the absence of a reliable value for the moment of the unshared pair of electrons of the nitrogen atoms, the latter was included in implicit form in the moment of the N–C bond, calculated via an additive vector scheme.

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TABLE 1. Calculated and Experimental DM of N-Alkylperhydro-1,4-thiazine S-Oxides and the Corresponding S,S-Dioxides

Compound	Calc., DM, D				Exptl. DM, D
	N—R(*a*)		N—R(*e*)		
	S=O(*a*)	S=O(*e*)	S=O(*a*)	S=O(*e*)	
I	3,90	3,35	3,75	4,5	3,60
II	3,90	3,35	3,75	4,5	3,54
III	3,90	3,35	3,75	4,5	3,76
IV	3,90		4,65		4,40
V	3,90		4,65		4,75

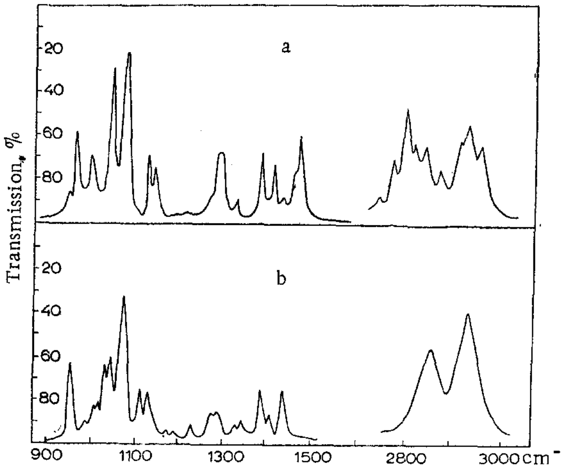

Fig. 1. IR spectra: a) N-methylperhydro-1,4-thiazine S-oxide; b) N-cyclohexylperhydro-1,4-thiazine S-oxide (0.2 M solutions in CCl_4, cuvette thickness 0.1 mm).

A study of the axial—equatorial equilibrium of the alkyl groups attached to the nitrogen atom in piperidine and piperazine systems [5, 6] demonstrated that the equatorial position is preferred for the N-alkyl group; in particular, the fraction of the equatorial conformer for the methyl group is 85 ±5%, according to the data in [6]. The predominant conformation for N-substituted perhydro-1,4-thiazines should therefore be a chair with N—R (e). A comparison of the DM calculated for the N—R (e), S=O (*a*) and N—R (e), S=O (e) forms with the experimental value makes it possible to assume that the form with an axial sulfoxide group is the most probable one.

In addition to the DM, we examined the IR spectra of I-II (Fig. 1). The very strong band at ~ 1050 cm^{-1} in the IR spectra of the sulfoxides is affiliated with the S=O stretching vibrations [7]. Our calculations of the frequencies and forms of the normal vibrations of dimethyl sulfoxide demonstrate that both the S=O bond and the SCH angles change with the vibration at 1050 cm^{-1}; i.e., this vibration is not a highly characteristic one. One may therefore fully expect that the magnitude of $\nu_{S=O}$ will change as a function of a change in the orientation of the S=O bond relative to the remaining portion of the molecule. Only the band at 1070 cm^{-1} in the IR spectrum of a solution of III in CCl_4 can be affiliated with the stretching vibrations of the S=O bond, while the weak bands at 1045 and 1035 cm^{-1} can be assigned to the vibrations of monosubstituted cyclohexane [8]. Thus the presence of conformations that differ with respect to the orientation of the S=O bond is not observed in the IR spectrum of III. Since, according to the DM data, III has the chair form with an axial orientation of the S=O bond, the strong band at 1070 cm^{-1} can be assigned to the S=O stretching vibrations.

Two very intense bands are observed at 1030 and 1070 cm^{-1} in the IR spectra of solutions of I and II in CCl_4. The ratio of the intensities of these bands does not change as the solution concentration changes from 0.1 to 0.01 M but does change as a function of the solvent polarity. The intensity of the band at 1030 cm^{-1} increases relative to the intensity of the band at 1070 cm^{-1} on passing to a more polar solvent (from n-hexane to dichloroethane). For II, transition from the liquid phase to a gas is accompanied by an increase in the intensity of the band at 1070 cm^{-1}. It seems to us most probable to interpret the presence of the intense bands at 1030 and 1070 cm^{-1} in the IR spectra of I and II as being due to the existence of an equilib-

TABLE 2. Calculated and Experimental DM of N-Methyl- and N-Cyclohexyl-3,5-dibromoperhydro-1,4-thiazine S,S-Dioxides (VI, VII)

Position of the halogen atoms	Calc. DM, D			
	N – R(*a*)		N – R(*e*)	
	disregarding induction	allowing for induction	disregarding induction	allowing for induction
aa	4,2	2,76	5,56	3,80
ee	6,34	5,15	6,70	5,53
ae	4,74	3,98	5,60	4,65
μ_{exp}, *D*	VI 4,90		VII 5,34	

TABLE 3. Perhydro-1,4-thiazine S-Oxides and S,S-Dioxides

Compound	Mp, °C	Empirical formula	Found, %			Calc., %		
			C	H	S	C	H	S
I	57—58[a]	$C_5H_{11}NOS$	45,3	8,4	23,9	45,1	8,3	24,1
II · H_2O	40	$C_7H_{15}NOS \cdot H_2O$	47,3	9,7	17,6	46,9	9,5	17,9
II	b	$C_7H_{15}NOS$	52,0	9,3	19,9	52,2	9,3	19,8
III · H_2O	70—72	$C_{10}H_{19}NOS \cdot H_2O$	54,7	9,5	14,7	54,8	9,60	14,6
III	68	$C_{10}H_{19}NOS$	59,6	9,6	16,0	59,7	9,40	15,9
IV	82[c]	$C_5H_{11}NO_2S$						
IV · HBr	150[d]	$C_5H_{11}NO_2S \cdot HBr$	25,9	5,0		26,1	5,2	
V	84—85	$C_{10}H_{19}NO_2S$	55,4	8,6	14,2	55,3	8,7	14,7
VI	130	$C_5H_9Br_2NO_2S$	19,5	3,0		19,5	2,9	
VII	103—104	$C_{10}H_{17}Br_2NO_2S$	32,1	4,4		32,0	4,5	

[a] Mp 52° [20].
[b] Bp 150° (10 mm).
[c] Mp 82° [20].
[d] With decomposition.

TABLE 4. Dipole Moments of Perhydro-1,4-thiazine S-Oxides and S,S-Dioxides

Compound	Solvent	ε_1	α	β	$P_{2\infty}$ op	DM, *D*
I	C_6H_6	2,2760	10,2441	0,1812	251,2342	3,50
II	C_6H_6	2,2860	9,3413	0,0976	256,3943	3,54
III	C_6H_6	2,2860	7,8210	0,0898	289,6080	3,76
IV	CCl_4	2,2280	25,4690	0,4858	384,392	4,40
V	C_6H_6	2,2690	12,2280	0,7890	466,9811	4,75
VI	C_6H_6	2,2720	8,5606	0,1269	487,0321	4,90
	Dioxane	2,2110	11,1386	0,3227	545,4274	5,17
VII	C_6H_6	2,2740	8,5374	0,8683	587,1130	5,36

rium between two conformations of these molecules that differ with respect to the orientation of the S=O bond. In conformity with the DM data, the existence of an equilibrium between the two chair forms with *a* and e orientations of the S=O group can be assumed for I and II. As already noted above, the band at 1070 cm^{-1} pertains to the S=O (*a*) stretching vibration, so that the band at 1030 cm^{-1} can be assigned to the S=O (e) stretching vibration. According to the DM data (Table 1), the S=O (e), N–R (e) form is more polar than the S=O (*a*), N–R (e) form, which explains the above-indicated change in the relative intensities of the bands. The IR spectra are presented in [9] along with a number of other constants of the cyclic sulfoxide under investigation, but these data are so meager that their use and comparison with our results is difficult.

The IR spectra of solid I-III and solutions in $CHCl_3$ at 1000-1100 cm^{-1} are more complex, which may be explained by the appearance of associated forms and a shift in the S=O band. It should be noted that the IR spectrum of I contains a strong band at 2805 cm^{-1}, which is absent in the IR spectra of II and III. It has been assumed [1] that this sort of absorption is characteristic for the presence of at least two C–H bonds in the trans position relative to the unshared pair of the nitrogen atom. However, the absence of a band at 2800 cm^{-1} in the IR spectra of II and III apparently does not agree with this assumption. A similar deviation was also noted for 4-methylquinolizidines [1].

The establishment of the geometry of the compounds obtained is of definite interest in studying the three-dimensional structure of the products of the addition of methylamine and cyclohexylamine to α,α'-dibromodivinyl sulfone. It is known that the DM of the bonds in molecules with several strong dipoles depends not so much on the number of bonds that separate these dipoles as much as on the mutual orientation of the dipoles in space [10]. The spatial proximity of several strong dipoles (C−Br, C−S, and S=O) should affect the DM of these bonds. The DM calculated for VI and VII with allowance for and disregarding the inductive interaction of the dipoles, which is determined by the field effect, are presented in Table 2. The C−Br bond length is 1.91 Å, and m_{C-Br} is 2.01 (from the experimental DM of cyclohexyl bromide) [4]. The induction was taken into account as in [10]. A knowledge of the localization centers of the dipole and of the center undergoing polarization is necessary for the calculation of the induced moment (m_i). We localized the point dipoles of the C−S, S=O, and C−Br bonds in accordance with [11, 12]. Proceeding from the bond refractions, we calculated the average bond polarizabilities: α_{C-Br} 3.72 [13], $\alpha_{S=O}$ 1.705 [14], and α_{C-S} (in sulfones) 0.28. (R_D of the C−S bond in sulfones is equal to R_D of the C−S bond in sulfides minus the R_D values of the unshared pair of sulfur [14].) A comparison of the experimental DM of VII (5.34 D) with the DM values calculated disregarding induction makes it possible to assume that the most probable structure is either one with a cis-diaxial orientation of the halogen or a trans-(*a*e) structure. Estimation of the dipole−dipole interaction energy from the Keesom formula [15] and taking into account the energy of the van der Waals interaction by means of the Hill method [1] for all of the possible structures demonstrate the enenergetic disadvantageousness of the diaxial conformer ($\Delta E_{aa-ee} = 5$ kcal/mole).

A comparison of the experimental DM of VII with the theoretically calculated values, with allowance for induction, confirms the impracticability of the *aa* and ee forms. The value calculated for the ee form with an equatorial orientation of the substituent attached to nitrogen proves to be closest to the experimental DM after allowance for induction. The predominant equatorial orientation of the cyclohexyl radical also follows from an analysis of the DM of IV and V (see Table 1).

Considering the preferability of the $N-CH_3$ group in the equatorial position [6], the N−R (e) form with diequatorial orientation of the halogens should also be assumed to be the most practicable form for VI. The lower experimental DM for the N-methyl derivative is apparently due to the insignificant contribution of other structures with lower DM to the conformational equilibrium.

To confirm what has been stated above, we made a thorough analysis of the PMR spectra of VI and VII. The molecular structures can be established from an examination of the spin−spin coupling constants of the vicinal protons attached to 2-C and 3-C and 6-C and 5-C, which form two ABX systems. The 3-H and 5-H protons are shifted to weak field by the effect of the C−S and C−Br bonds and represent the X portion of the ABX systems, the AB portions of which are formed by geminal protons attached to 2-C and 6-C. An analysis of the ABX system make it possible to determine $J_{ae}^{gem} = 13$ Hz, $J_{ae}^{vic} = 6.5$ Hz, and $J_{aa} = 9.5$ Hz, and also made it possible to calculate the nonequivalency of the geminal protons attached to 2-C and 6-C ($\Delta\delta = 0.18$ ppm). The magnitudes of the interaction constants correspond to the J_{AX} and J_{BX} values that are characteristic for a chair conformation with a diequatorial orientation of the halogens [16].

EXPERIMENTAL

Compounds I-VII were synthesized as in [17]. A 0.02-mole sample of the appropriate amine in 10 ml of 95% ethanol was slowly added dropwise with cooling to 0.02 mole of divinyl sulfoxide [18], divinyl sulfone [19], or α,α'-dibromodivinyl sulfone [18] in 15 ml of 95% ethanol. The reaction mixture was heated on a water bath and allowed to stand for several days. The solvent was removed, and the residue was repeatedly recrystallized from petroleum ether (I-III) or from 95% ethanol (IV-VII). The corresponding monohydrates were isolated from the reaction mixture in the case of II and III; vacuum drying for 8 h enabled us to obtain the anhydrous form. The yields of reaction products averaged ~ 50%. The physical constants of the compounds obtained and the results of analyses are presented in Table 3.

The DM were determined as in [2] at 25°. The results of the measurements are presented in Table 4, where ε_1 is the dielectric permeability of the solvent and α and β are the coefficients in the Guggenheim−Smith equation. The IR spectra were recorded with a UR-20 spectrometer. The PMR spectra were recorded with a JEOL spectrometer (60 MHz).

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