1,4-BENZODIAZEPINES AND THEIR CYCLIC HOMOLOGS AND ANALOGS

XIV.* IR AND PMR SPECTRA OF SOME 1,2-DIHYDRO-3H-1,4-BENZODIAZEPINES

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The dependence of the IR and PMR spectral characteristics of 12 compounds of the 1,2-dihydro-3H-1,4-benzodiazepine series on structural and sterochemical factors was studied. Information in favor of concepts regarding the pseudoboat conformation as the primary one for this type of 1,4-benzodiazepine derivative was obtained.

The literature contains only episodic and nonsystematized information on the IR spectra of 1,2-dihydro-3H-1,4-benzo-2-diazepinones [2-4] and only a few papers devoted to the PMR spectra of these substances. We have investigated the IR and PMR spectra of 1,4-benzodiazepines of the A type and their N_4-oxides.

*See [1] for communication XIII.

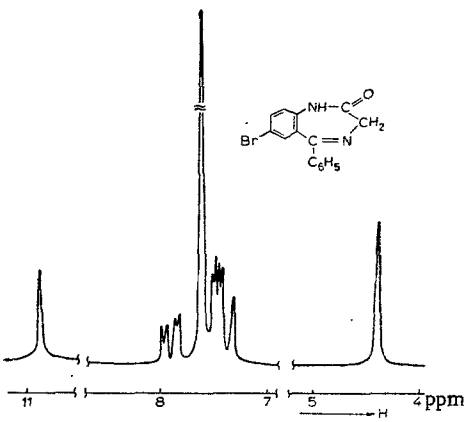

Fig. 1. PMR spectrum of 7-bromo-5-phenyl-1,2-dihydro-3H-1,4-benzo-2-diazepinone.

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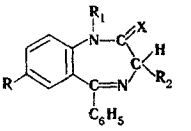
TABLE 1. Absorption Bands of Some Structural Fragments in the IR Spectra of 1,2-Dihydro-3H-1,4-benzodiazepine Derivatives

Compound No.	R	R_1	R_2	R_3	X	Solvent	Wave numbers of the stretching vibrations, cm^{-1}					
							C=O	C=N	C=C	C–H		NH
										benzene rings	CH_2	CH_3	
1	Cl	H	H	—	O	CCl_4	1694	1612	1475—1445	3090, 3035	2937, 2856		3401, 3333, 3174
2	Cl	H	H	O	O	$CHCl_3$	1696	1599	1570—1442	3070, 3030			3393
3	Cl	CH_3	H	—	O	CCl_4	1694	1612	1467, 1445	3084, 3030	2921, 2855	2988, 2955	
4	Cl	CH_3	H	—	H_2	CCl_4		1618	1480—1445	3080—3030	2900—2810	2980, 2950	
5	Cl	H	CH_3	—	O	CCl_4	1691	1612	1468—1445	3098—3040		2928, 2980	3388, 3328, 3180
6	Cl	H	C_2H_5	—	O	CCl_4	1691	1612	1465—1443	3093—3045	2873	2960, 2950	3388, 3322, 3150
7	Cl	H	H	—	S	CCl_4		1613	1462	3070—3010	2940—2860		3362, 3127

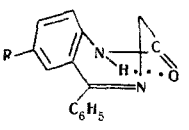


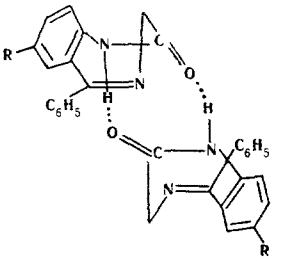
A

R=NO_2, Br, Cl, H, CH_3; R_1=H, CH_3; R_2=H, CH_3, C_2H_5, i-C_3H_7; X=O, S, H_2.

The synthesis and physical, chemical, and pharmacological properties of these substances were described in [2-4]. 7-Chloro-1-methyl-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepine (compound No. 4, medazapam) was obtained by the action of urotropin on 5-chloro-2-(2-bromoethylmethyl)aminobenzophenone in absolute ethanol [5].

The presence of absorption bands of a $C_5=N_4$ double bond at 1590-1610 cm^{-1} in their IR spectra (Table 1) is characteristic for 1,2-dihydro-3H-1,4-benzodiazepines. The assignment of this band is confirmed by its absence in the spectrum of 7-chloro-5-phenyl-1,2,3,4-tetrahydro-5H-1,4-benzo-2-diazepinone. The IR spectra of 1,2-dihydro-3H,-1,4-benzo-2-diazepinones, as already noted in [2-4], contain the absorption bands of a carbonyl group and free and associated NH groups. The most intense (at 3180 cm^{-1}) of the bands that are related to the vibrations of the NH group corresponds to the vibrations of the N–H bond of an amide group with a cis configuration [6]. The integral intensity of this band remains practically the same on dilution [4], which may attest to the presence of an intramolecular hydrogen bond between the NH group and the carbonyl group or to the formation of dimeric associates due to hydrogen bonds of the amide groups. In addition, the cis configuration of the amide group is evidence in favor of the boat conformation of the 1,2-dihydro-3H-1,4-benzo-2-diazepinone molecules.





Bands of the stretching vibrations of the carbon–carbon sesquibonds of benzene rings are presented at 1450-1550 cm^{-1} in the IR spectra of 1,2-dihydro-3H-1,4-benzodiazepines. The C–H stretching vibrations of the benzene rings of compounds A lead to the appearance of absorption bands at 3030-3100 cm^{-1}. The C–H stretching vibration of the methylene group in the 3 position of the benzodiazepine system in the absence of aliphatic substituents give two bands of asymmetrical and symmetrical vibrations at 2850-2940 cm^{-1}. When aliphatic groups are present in the 1, 3, or 7 positions, the corresponding additional bands appear in the spectra. In addition to this, a shift in the absorption bands of the methylene group is noted (in the case of 3-unsubstituted compounds).

The PMR spectra contain a multiplet signal of aromatic protons at 7.45-8.00 ppm (for solutions in d_6-dimethyl sulfoxide). The intense peak of this multiplet in the spectrum of 7-bromo-5-phenyl-1,2-dihydro-3H-1,4-benzo-2-diazepinone (compound No. 9, Fig. 1) at 7.70 ppm belongs to the protons of the 5-phenyl substitutent, judging from its chemical shift and integral intensity. The signal of the indicated protons are similarly displayed in the spectra of the other compounds (A).

TABLE 2. Chemical Shifts of the Methyl, Methylene, and Methylidyne Protons of 1,2-Dihydro-3H-1,4-benzodiazepines

Compound No.	R	R_1	R_2	R_3	X	Solvent	Concn. (%)	δ, ppm (±0.1)		
								CH_3	CH_2	CH
1	Cl	H	H	—	O	d_6-DMSO	10	—	4,41	—
2	Cl	H	H	O	O	d_6-DMSO	10	—	4,87	—
3	Cl	CH_3	H	—	O	d_6-DMSO	10	3,55	4,41	—
4	Cl	CH_3	H	—	H_2	d_6-DMSO	6	2,95	3,80	—
5	Cl	H	CH_3	—	O	d_6-DMSO	10	1,76	—	3,76
6	Cl	H	C_2H_5	—	O	d_6-DMSO	10	1,25	2,27	3,62
7	Cl	H	H	—	S	d_6-DMSO	5	—	4,83	—
8	H	H	H	—	O	d_6-DMSO	10	—	4,34	—
9	Br	H	H	—	O	d_6-DMSO	10	—	4,40	—
10	NO_2	H	H	—	O	d_6-DMSO	10	—	4,47	—
11	Cl	H	i-C_3H_7	—	O	d_6-DMSO	10	1,22	—	3,70
12	CH_3	H	H	—	O	d_6-DMSO	10	—	4,31	—
2	Cl	H	H	O	O	C_5D_5N	10	—	4,65	—
2	Cl	H	H	O	O	CD_3COOD	10	—	4,65	—
4	Cl	CH_3	H	—	H_2	C_5D_5N	6	2,17	3,08	—
4	Cl	CH_3	H	—	H_2	CD_3COOD	6	3,03	3,97	—
9	Br	H	H	—	O	C_5D_5N	10	—	4,05	—
7	Cl	H	H	—	S	C_5D_5N	5	—	4,59	—

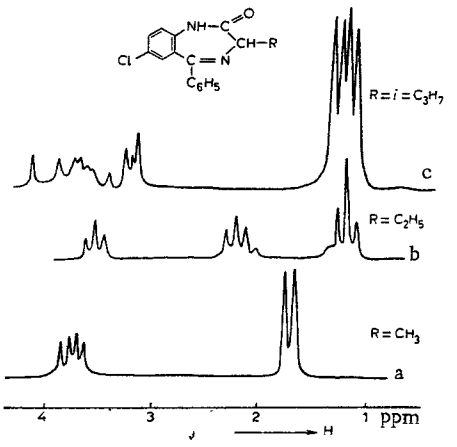


Fig. 2

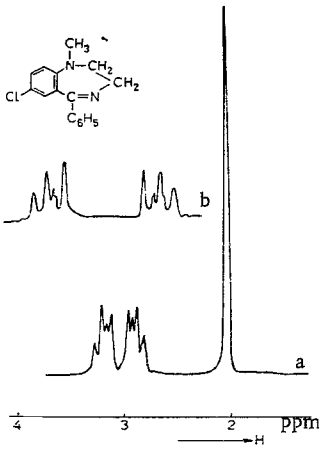


Fig. 3

Fig. 2. PMR spectra of 3-methyl- (a), 3-ethyl- (b), and 3-isopropyl-7-chloro-5-phenyl-1,2-dihydro-3H-1,4-benzo-2-diazepinones (c).

Fig. 3. PMR spectra of medazepam at: a) 60 MHz; b) 100 MHz.

The singlet (1H) at δ 10.80 ppm in this spectrum is the signal of the proton of an amide group. We note that the intensity of this signal is considerably less when the spectrum of a solution of the compound in d_6-DMSO is recorded than when the spectrum is recorded with undeuterated DMSO as the solvent.* This can be explained by deuterium exchange, i.e., by deuteration of compound No. 9 at the N_1 atom.

The chemical shifts of the protons attached to the C_3 atom and the protons of the substituents attached to the N_1 and C_3 atoms are presented in Table 2. It is seen from Table 2 that the chemical shifts of the methylene protons of compounds A differ appreciably when the spectra are recorded in different solvents (d_6-DMSO, C_5D_5N, and CD_3COOD). As in the case of other properties of compounds A, the character of substituent R has a regular effect on the chemical shifts of the protons of the methylene group. An increase in its electronegativity shifts the signal of the methylene protons to lower field; this is apparently associated with a decrease in the electron density on the C =N bond under the influence of the substituent.

The usual signals of alkyl protons are observed in the PMR spectra of 3-alkyl-substituted derivatives of the A type (Fig. 2), and diastereotopicity of the methyl groups is distinctly observed in the case of the resonance band of the isopropyl group.

*The d_6-DMSO contains up to 1% deuterium oxide, according to the manufacturer's label.

Substitution of the C_3 atom or of adjacent atoms of the heteroring has the greatest effect on the character of the resonance of the protons attached to C_3. Thus replacement of the oxygen atom attached to C_2 by sulfur and introduction of a semipolar oxygen atom in the N_4 position lead to an increase of ~0.40 ppm in the chemical shift.

Substitution at the N_1 atom by a methyl group leads to splitting of the signal of the C_3 methylene group into a quartet; this can be explained by the retarded character of ring inversion.

The resonance signal of the protons of the ring methylene groups at 2.80-3.30 ppm generates the greatest interest in the PMR spectrum of compound No. 4 (Fig. 3). As seen from the spectrum, these protons form an AA'BB' spin system and resonate as two multiplets, of which the signal of the 2-CH_2 protons evidently appear at high field, and the protons of the 3-CH_2 group appear at low field. This is apparently in good agreement with the concept of the higher basicity of the N_4 ring atom as compared with N_1. The character of the spectrum also attests that the cyclic system under consideration is quite rigid, and ring inversion is hindered at room temperature.

EXPERIMENTAL

The IR spectra of solutions of the compounds (Nos. 1-7) in CCl_4 or $CHCl_3$ were recorded with an IKS-14A spectrometer. The solution concentration was 0.01 mole and the layer thickness was 5.006 mm. The PMR spectra were recorded with a Tesla S9 487B NMR spectrometer at 80 MHz with hexamethyldisiloxane as the external standard for 5-10% solutions of compounds A in d_6-dimethyl sulfoxide, per deuteropyridine, and per deuteroacetic acid. The spectrum of compound No. 4 was also recorded with a Varian HA-100D spectrometer at 100 MHz.

1-Methyl-5-phenyl-7-chloro-1,2-dihydro-3H-1,4-benzodiazepine. A 2.8-g (8 mmole) sample of 5-chloro-2-(2-bromoethyl)methylaminobenzophenone and 2.8 g (20 mmole) of urotropin were refluxed in 50 ml of absolute ethanol for 10 h, after which the reaction mixture was vacuum evaporated, and the residue was treated with methylene chloride and water. The organic layer was separated, and the aqueous layer was made alkaline and extracted with methylene chloride. The extracts were combined and dried with calcined sodium sulfate, the methylene chloride was removed by distillation, and the residue was crystallized from ether. The yield of product with mp 100-103° (mp 102-103° [5]) was 1.8 g (83%).

LITERATURE CITED

1. Yu. I. Vikhlyaev, A. V. Bogat-skii, T. A. Klygul', S. A. Andronati, O. P. Rudenko, and P. B. Terent'ev, in: Physiologically Active Substances [in Russian], No. 6, Naukova Dumka, Kiev (1974), p. 94.
2. L. H. Sternbach, R. I. Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy, and A. Stempel, J. Org. Chem., 27, 3788 (1962).
3. A. V. Bogat-skii and S. A. Andronati, Zh. Obshch. Khim., 39, 443 (1969).
4. S. A. Andronati, A. V. Bogatskii, Yu. I. Vikhlyaev, Z. I. Zhilina, B. M. Kats, T. A. Klygul', V. N. Khudyakova, T. K. Chumachenko, and A. A. Énnan, Zh. Obshch. Khim., 40, 1881 (1970).
5. N. Blažević and F. Kajfež, J. Heterocycl. Chem., 8, 845 (1971).
6. L. Bellamy, Infrared Spectra of Complex Molecules, Methuen (1958).