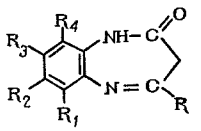
SYNTHESIS AND PHARMACOLOGY OF SOME 2,3-DIHYDRO-1H-1,5-BENZODIAZEPIN-2-ONES

A. A. Stolyarchuk, Yu. N. Furman,
V. L. Pikalov, Z. F. Solomko,
and V. S. Tkachenko

UDC 615.214.22:547.892

The pharmacological activity of 1,5-benzodiazepinones has been relatively little studied [1, 2].

Continuing our search for new biologically active compounds, we synthesized a number of 2,3-dihydro-1H-1,5-benzodiazepin-2-ones (I-VIII) from the corresponding aromatic o-diamines and β-ketoesters (Table 1):



Compounds	R	R_1	R_2	R_3	R_4
I	CH_3	H	H	H	H
II	CH_3	H	H	Cl	H
III	CH_3	H	Cl	H	H
IV	CH_3	H	H	Br	H
V	CH_3	H	CH_3	CH_3	H
VI	CH_3	H	Br	H	Br
VII	CH_3	Br	H	Br	H
VIII	C_6H_5	H	H	H	H
IX	$CH=CH-C_6H_5$	H	H	H	H

4-Styryl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (IX) was obtained by condensing diazepinone (I) with benzaldehyde [3].

The IR spectra of I-IX show a number of absorption bands. Stretching vibration bands of free and associated NH groups occur at 3400-3160 cm^{-1}, intense carbonyl absorption bands (I amide) occur at 1695-1668 cm^{-1}, and especially clear stretching-vibration bands of C=N bonds are seen at 1650-1635 cm^{-1}, which are characteristic of 1,5-benzodiazepinone systems (Table 2).

The PMR spectra of compounds II-VII, taken in trifluoroacetic acid, show methyl proton singlets (δ 2.28-3.07 ppm), methylene proton singlets (δ 3.16-4.02 ppm), and also signals of aromatic protons in the region of 7-8.2 ppm, which confirms the structures of the compounds indicated above. In compound V, protons of the two methyl groups bound to the aromatic ring show singlets at 2.82 ppm (see Table 2).

We studied the acute toxicity of the compounds, their effect on hexenal and thiopental narcosis when given at 5% of the maximum tolerable dose, and also their effect on the emotional activity of mice. The effects were compared with those of elenium and seduxen administered similarly.

The results showed that the maximum tolerable doses of the compounds for mice receiving them intragastrically were (in mg/kg): I, 500; II, 350; III, 400; IV, 400; V, 400; VI, 1000; VII, 1000; VIII, 1000; IX, 1000; elenium, 300; seduxen, 400.

Hexenal narcosis was prolonged by I, II, IV-VII, elenium, and seduxen. The latter two compounds were the most effective, while compound III had no statistically significant effect.

Vinnitsk Medical Institute. Dnepropetrovsk University. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 9, No. 8 pp. 19-21, August, 1974. Original article submitted August 19, 1974.

TABLE 1. Derivatives of 2,3-Dihydro-1H-1,5-benzodiazepin-2-ones

Compounds	Yield (%)	mp (deg)*	Found (%)			Empirical formula	Calculated (%)		
			C	H	N		C	H	N
I	72,0	148	—	—	—	$C_{10}H_{10}N_2O$	—	—	—
II	—	178	—	—	—	$C_{10}H_9ClN_2O$	—	—	—
III	89,0	140—1	57,30	4,61	13,30	$C_{10}H_9ClN_2O$	57,55	4,31	13,43
IV	77,0	202	47,41	3,49	10,98	$C_{10}H_9BrN_2O$	47,43	3,55	11,00
V	88,5	186	71,20	7,21	13,60	$C_{12}H_{14}N_2O$	71,40	6,94	13,88
VI	90,0	184	36,20	2,63	8,50	$C_{10}H_8Br_2N_2O$	36,19	2,41	8,45
VII	80,3	203	36,10	2,52	8,37	$C_{10}H_8Br_2N_2O$	36,19	2,41	8,45
VIII	45,0	206—7	—	—	—	$C_{15}H_{12}N_2O$	—	—	—
IX	—	218	—	—	—	$C_{17}H_{14}N_2O$	—	—	—

*According to the literature, the mp of I is 148°C [10]; of II, 178° [7]; of VIII, 206° [9]; and of IX, 218° [3].

TABLE 2. Spectral Characteristics of 2,3-Dihydro-1H-1,5-benzodiazepin-2-ones.

Compounds	IR spectra (cm^{-1})		PMR spectra (δ, ppm)		
	$\nu_{C=O}$	$\nu_{C=N}$	CH_3	CH_2	aromatic H's
III	1674	1639	2,87	3,83	7,10—7,60
IV	1668	1639	2,81	3,68	7,25—7,40
V	1670	1642	2,82	3,75	7,00—7,22
VI	1684	1650	3,07	4,02	7,90—8,20
VII	1690	1643	3,07	3,97	7,80—8,10

Compounds I-IV prolonged thiopental narcosis, and elenium and seduxen did so to a somewhat greater degree. Perhaps a true potentiation of narcosis is shown by the substances prolonging the effect of thiopental, inasmuch as prolongation of hexenal action may be due to inhibition of liver enzymes, thereby slowing the breakdown of the narcotic [4, 5].

Effects on emotional activity were determined by studying the fear and aggresion reactions of mice [6]. Elenium and seduxen in all cases removed both the fear and aggression reactions stimulated by mild electric shock. The benzodiazepinones removed the fear reaction from some of the animals, and compound II had no effect at all.

The aggression reaction was removed in all the animals by I, VI, VII, and IX, and the other compounds removed it only partially.

Therefore, the 1,5-benzodiazepinones studied had tranquilizing properties, although less pronounced than those of elenium and seduxen. Synthesis and pharmacological studies of other compounds of this type should be undertaken in the search for new tranquilizing and sedative preparations.

EXPERIMENTAL METHOD

IR spectra of the compounds were taken with an IKS-14 spectrophotometer; the PMR spectra were taken with a PS-60 apparatus. Hexamethyldisiloxane was used as the external standard. Compounds II-VIII were purified by crystallization from benzene. Yields and analytical data on the benzodiazepinones are given in Table 1.

4-Methyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (I). To a boiling solution of 10.8 g 1,2-phenylenediamine in 120 ml xylene was added dropwise 15.2 ml ethyl acetoacetate in 10 ml xylene. The mixture was boiled with a water trap for 30 min. After cooling, the precipitated crystals were filtered out and recrystallized from a benzene–petroleum ether mixture.

Compounds II and IV were obtained by the method of Acheson and Tully [7].

4-Methyl-7-chloro-2,3-dihydro-1H-1,5-benzodiazepin-2-one (III). To a boiling solution of 1.42 g 4-chloro-1,2-phenylenediamine in 170 ml xylene was added dropwise 1.52 ml ethyl acetoacetate in 10 ml xylene. The mixture was boiled with a water trap for 1 h. After cooling, the solution was evaporated in a vacuum. The 1.86 g of residue was purified by recrystallization.

Compound V was obtained analogously to compound III.

Compounds VI and VII were obtained by the method of Solomko et al. [8].

Compound VIII was obtained by the method of Ried and Stahlhofen [9].

LITERATURE CITED

1. G. A. Archer and L. H. Sternbach, "The chemistry of benzodiazepines," Chem. Rev., 747-784 (1968).
2. M. Protiva, "News in chemistry of psychotropic drugs in the year 1969," Act. Nerv. Sup. (Prague), 12, 193-196 (1970).
3. S. Motoki, C. Urakawa, and A. Kano, "Synthesis of benzodiazepine derivatives," Bull. Chem. Soc. Japan, 43, 808-813 (1970).
4. J. R. Boissier and E. Jacobsen, "Methods actuelles pharmacologiques des substances dites tranquillisantes," Therapies, 13, 1074-1119 (1958).
5. A. P. Kobernik, "Pharmacological study of furancarboxylic acid ureides," Author's Abstract of Candidate's Dissertation, Ivanova (1970).
6. L. Kh. Allikmets, "Correlation between the tranquilizing and sedative activities of several neuroleptics, antidepressants, and anticholinergic substances," in: Clinical Neurology and Psychiatry [in Russian], Tartu (1972), pp. 75-78.
7. R. M. Acheson, W. R. Tully, "Synthesis of some benzodiazepin-2-ones," J. Chem. Soc., C, No. 8, 1117-1121 (1970).
8. Z. F. Solomko, V. L. Pikalov, and L. V. Pribega, "Reaction of 3,5-dichloro-o-phenylenediamine with ethyl acetoacetate." Ukrain. Khim. Zh., 40, 768-769 (1974).
9. W. Ried and P. Stahlhofen, "Ueber heterocyclische Siebenringsysteme. VII. Der Reactionsverlauf zwischen o-Phenylendiamin and Alkyliden– brenztzaubensauren," Chem. Ber., 90, 828-832 (1957).
10. A. Rossi, A. Hunger, and J. Kebrie, "Benzimidazol: Derivate und verwandte Heterocyclen. V. Die Kondensation von o-Phenylendiamin mit alicyclischen Ketoestern," Helv. Chim. Acta, 13, 1298-1313 (1960).