1,4-BENZODIAZEPINES AND THEIR CYCLIC HOMOLOGS AND ANALOGS

XV.* SYNTHESIS AND PROPERTIES OF A NEW HETEROCYCLIC SYSTEM – 1-[γ-(10-PHENOTHIAZINYL)PROPYL]-1,2-DIHYDRO-3H-1,4-BENZODIAZEPIN-2-ONES

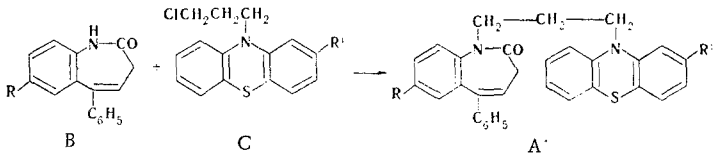
A. V. Bogat-skii, S. A. Andronati, S. N. Bogina, A. N. Gritsenko, Yu. I. Vikhlyaev, and T. A. Klygul'

UDC 547.892'869.2.07:543.422

A new heterocyclic system of the dumbbell type – 1-[γ-(10-phenothiazinyl)propyl]-1,2-dihydro-3H-1,4-benzodiazepin-2-one – was synthesized; nine compounds of this type, which have the properties of minor tranquilizers, were synthesized.

It is known that substitution in the 1-position of the 1,4-benzodiazepine ring leads to preparations that have extremely interesting pharmacological properties [2, 3]. The preparation of 1-[γ-(10-phenothiazinyl)-propyl]-1,2-dihydro-3H-1,4-benzodiazepin-2-ones (A), compounds that combine in one molecule the fragments of neuroleptics and minor tranquilizers, seemed especially interesting from this point of view. Compounds of the A type have not yet been described. The proposed synthesis therefore seemed of interest for the further development of the chemistry of heterocycles: it was a question of the preparation of a new heterocyclic system of the "dumbbell" type. Considering the above, we undertook the present study.

Substances of the A series were obtained by reaction of N-(γ-chloropropyl)phenothiazines (C) with 1,2-dihydro-3H-1,4-benzodiazepin-2-ones (B) in anhydrous dimethylformamide (DMFA) in the presence of sodium hydride. Their properties are described in Table 1. Despite the relative triviality of the synthetic method [4], the preparation of compounds of the A series requires modification of the general method and strict observance of the reaction conditions.



B C A

The IR spectrum of I presented in Fig. 1 is typical for substances of the A series. The most intense band in the spectrum of I is the band of stretching vibrations of the carbonyl group at 1670 cm^{-1}. The band at 1610 cm^{-1} corresponds to the stretching vibrations of the C=N bond. The presence of absorption in the region of the stretching vibrations of the C–H bonds of alkyl groups at 2800-2900 cm^{-1} is characteristic for the spectrum.

The UV spectra of compounds of the A series are characterized by the presence of three absorption maxima (Fig. 2). The first (at 230-240 nm) is peculiar to 1,2-dihydro-3H-1,4-benzodiazepin-2-ones [4],

* See [1] for communication XIV.

I. I. Mechnikov Odessa State University. Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1261-1264, September, 1974. Original article submitted October 30, 1973.

TABLE 1. 1-[γ-(10-Phenothiazinyl)propyl]-1,2-dihydro-3H-1,4-benzodiazepin-2-ones

Compound	R	R'	mp, °C	Empirical formula	Found, %			Calc., %			Yield, %
					C	H	N	C	H	N	
I	Cl	H	178—179	$C_{30}H_{24}ClN_3SO$	70,7	4,8	8,4	70,7	4,7	8,2	39
II	Br	H	186—187	$C_{30}H_{24}BrN_3SO$	64,8	4,4	7,8	64,9	4,3	7,6	45
III	CH_3	H	161	$C_{31}H_{27}N_3SO$	76,1	5,9	8,5	76,0	5,8	8,6	35
IV	Cl	Cl	206—207	$C_{30}H_{23}Cl_2N_3SO$	66,3	4,3	7,7	66,2	4,2	7,7	50
V	Br	Cl	217—218	$C_{30}H_{23}ClBrN_3SO$	61,2	3,8	7,3	61,1	3,9	7,1	58
VI	CH_3	Cl	188—189	$C_{31}H_{26}ClN_3SO$	71,0	4,2	8,2	71,1	4,0	8,0	46
VII	Cl	CF_3	157—158	$C_{31}H_{23}ClF_3N_3SO$	64,6	3,9	7,4	64,5	4,0	7,3	60
VIII	Br	CF_3	168—169	$C_{31}H_{23}BrF_3N_3SO$	59,7	3,9	6,7	59,6	3,7	6,7	68
IX	CH_3	CF_3	158	$C_{32}H_{26}F_3N_3SO$	68,8	4,6	7,3	68,9	4,7	7,5	59

TABLE 2. Absorption Bands in the UV Spectra of 1-[γ-(10-Phenothiazinyl)propyl]1,2-dihydro-3H-1,4-benzodiazepin-2-ones

R	R'	λ_{max}, nm	lg ε
CH_3	Cl	235	4,58
		258	4,58
		313	3,75
Cl	Cl	237	4,59
		257	4,64
		315	3,77
Br	Cl	235	4,51
		257	4,55
		317	3,66

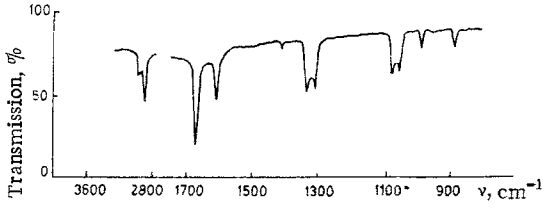
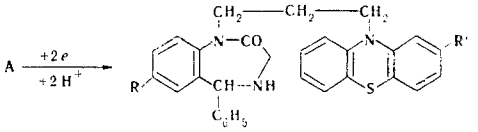


Fig. 1. IR spectrum of I.

while the second (at 260 nm) is peculiar to the phenothiazine chromophore [5], and the third (315 nm) is usually characteristic for both substances of the B class and for phenothiazine derivatives [4, 5]. It is apparent from Table 2 that the effect of substituent R on the position of the absorption maxima is small. The information obtained in the course of a study of the UV spectra does not leave any doubt as to the structure of I-IX.

Substances of the A series are reduced polarographically and give one polarographic wave (Fig. 3). This might have been expected considering the data in [6, 7]. In fact, only the azomethine group in structure A should be reduced polarographically:



Consequently, the development of one polarographic wave in the experiment can be considered as proof of the structure of the substances of the A series. It should be noted that compounds of the A series are reduced at more negative polarographic half-wave potentials than substances of the B series and their 1-methyl derivatives; this is due to the inductive and, perhaps, steric effect of the phenothiazinylalkyl substituent.

A pharmacological examination of substances of the A series showed that they have pronounced tranquilizing properties (ED_{50} ranges from 22 to 250 mg per kg of animal weight) and extremely low toxicities (LD_{50} ranges from 1000 to 1500 mg per kg of animal weight). At the same time, compounds of the A series do not display neuroleptic and analgesic properties. Data from a detailed study of the pharmacology of substances of the A series will be published in the subsequent communications of this series.

EXPERIMENTAL

The IR spectra of 0.01 M solutions of substances of the A series in $CHCl_3$ and mineral-oil suspensions of them were recorded with an IKS-14-A spectrometer at a layer thickness of 5.006 mm. The UV

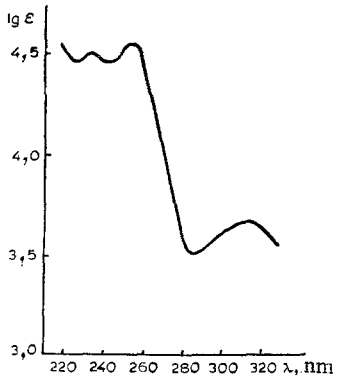


Fig. 2. UV spectrum of I.

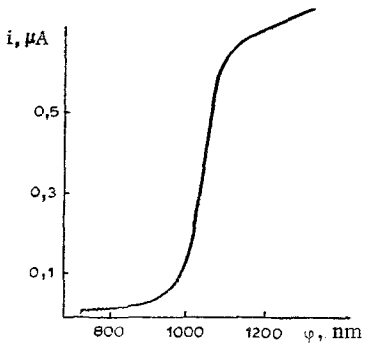


Fig. 3. Polarogram of I.

spectra of solutions of substances of the A series in ethanol ($2.5 \cdot 10^{-2}$ mole) were recorded with an SF-16 spectrophotometer at a layer thickness of 0.0107 cm. Polarographic reduction was accomplished with a polarograph of the ORION 7-77-4c type with an acetate-buffer base electrolyte in an aqueous alcohol medium; the measuring electrode was a dropping mercury electrode, the comparison electrode was a saturated calomel electrode, and the depolarizer concentration was 0.0012 mole. The pharmacological tests were made on male white mice under the conditions described in [9].

We obtained starting substances B and C by the method in [4, 8]; their physical constants were in agreement with the literature data.

1-[γ-(2-Chloro-10-phenothiazinyl)propyl]-5-phenyl-7-chloro-1,2-dihydro-3H-1,4-benzodiazepin-2-one (IV). A solution of 0.95 g of 5-phenyl-7-chloro-1,2-dihydro-3H-1,4-benzodiazepin-2-one in 5 ml of anhydrous dimethylformamide (DMFA) was added dropwise to a suspension of 0.085 g of sodium hydride in 3.5 ml of DMFA, and the mixture was stirred at room temperature for 1 h, after which it was heated to 60°. A 1.1-g sample of 2-chloro-10-(γ-chloropropyl)phenothiazine in 2.5 ml of DMFA was added to the mixture, and the resulting mixture was maintained at 60° with constant stirring for 2 h, after which it was poured into cold ice water. Compound IV was extracted from the mixture with methylene chloride, the extract was dried, the solvent was removed by distillation, and the residue was purified by crystallization to give 0.85 g (50%) of IV. As in the case of other substances of the A series, the properties of IV synthesized under similar conditions are described in Table 1.

LITERATURE CITED

1. A. V. Bogat-skii, S. A. Andronati, Yu. Yu. Samitov, A. I. Galatina, E. V. Konovalov, E. I. Saenko, and S. G. Soboleva, Khim. Geterotsikl. Soedin., 838 (1974).
2. A. V. Bogat-skii and S. A. Andronati, Usp. Khim., 39, 2217 (1970).
3. M. Negwer, Organischen Chemischen Arzneimittel und Ihre Synonyma, Akademie-Verlag, Berlin (1971).
4. A. V. Bogat-skii and S. A. Andronati, Zh. Obshch. Khim., 39, 443 (1969).
5. S. V. Zhuravlev and V. A. Skorodumov, Khim. Geterotsikl. Soedin., 1333 (1970).
6. H. Oelschläger, J. Volke, and E. Kurek, Arch. Pharmaz. und Deutsche Pharm. Ges., 297, 431 (1964).
7. A. V. Bogat-skii, S. A. Andronati, V. P. Gul'tyai, A. F. Galatin, Z. I. Zhilina, and T. A. Klygul', Zh. Obshch. Khim., 41, 1358 (1971).
8. S. V. Zhuravlev, A. N. Gritsenko, and Z. I. Ermakova, Zh. Obshch. Khim., 32, 1912 (1962).
9. Yu. I. Vikhlayaev, T. A. Klygul', A. V. Bogat-skii, S. A. Andronati, Z. I. Zhilina, and T. K. Chumachenko, Physiologically Active Substances, Collection 3 [in Russian], Naukova Dumka, Kiev (1971), p. 265.