1,4-BENZDIAZEPINES AND THEIR DERIVATIVES

III. SYNTHESIS OF DERIVATIVES OF 1,3-DIHYDRO-2H-1,4-BENZDIAZEPIN-2-ONE AND CORRELATION OF STRUCTURE WITH PHARMACOLOGICAL ACTIVITY

A. V. Bogatskii, Yu. I. Vikhlyaev, S. A. Andronati, T. A. Klygul', T. K. Chumachenko, and Z. I. Zhilina

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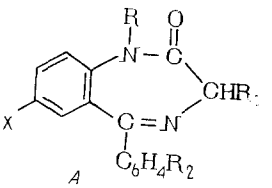
1,4-Benzdiazepine derivatives have gained expansion as minor tranquilizers[1, 2]. We have synthesized substituted 1,3-dihydro-2H-1,4-benzdiazepin-2-ones (A) including nitrazepam, oxazepam, and diazepam:



A

Compound No.	R	R_1	R_2	X
I	H	H	H	H
II	H	H	H	CH_3
III	H	H	H	Cl
IV	H	H	H	Br
V	H	H	m-NO_2	CH_3
VI	H	C_2H_5	H	Cl
VII (nitrazepam)	H	H	H	NO_2
VIII (diazepam)	CH_3	H	H	Cl
IX	CH_3	H	H	Br
X (oxazepam)	H	OH	H	Cl
XI	CH_3CO	H	H	H
XII	CH_3CO	H	H	CH_3
XIII	CH_3CO	H	H	Cl
XIV	H	C_2H_5	H	Br

The properties of these compounds and the methods for their synthesis are described in [3].

The structure of compounds A was confirmed by their IR spectra. A typical spectrum is shown in Fig. 1. This is the spectrum of compound X. Clearly shown in the spectrum are the bands of the valence vibrations of the free and associated hydroxyl groups at ν 3600—3480 cm^{-1}, the bands of the valence vibrations of the free and associated NH-groups at ν 3390—3200 cm^{-1}, the band for the valence vibrations of the carbonyl at ν 1683 cm^{-1}, and the band at ν 1594 cm^{-1} which was attributed [1] to the 1,4-benzdiazepine ring. The band for the valence vibrations of the C = N bond is clearly apparent at ν 1553 cm^{-1}. Assignment of the bands in the region ν 1400—692 cm^{-1} is, as yet, difficult in view of the small amount of data for the determination of empirical correlations.

Previously [3] we showed that substituents in position 7 of the 1,4-benzdiazepine ring display the same electronic effect as substituents of the same type in the benzene ring. It was also shown in our work [3] that 1,3-dihydro-2H-1,4-benzdiazepin-2-ones are inclined to lactam-lactim tautomerism. This cannot occur for the 1-N-substituted compounds.

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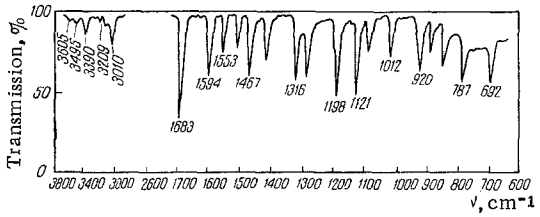


Fig. 1. IR spectrum of 7-chloro-5-phenyl-3-hydroxy-1,3-dihydro-2H-1,4-benzdiazepin-2-one (oxazepam) in chloroform.

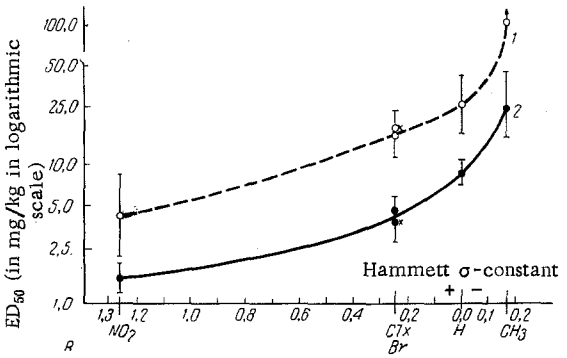


Fig. 2. Correlation of activity and Hammett σ_{para}-constant of 7-substituted 5-phenyl-1,3-dihydro-2H-1,4-benzdiazepin-2-ones (A). 1) Protection from electric shock; 2) depression of orientating reflex; vertical lines are reliability limits at P = 0.05.

Having available the collection of compounds A with various substituents X, R, R_1, and R_2, we studied the pharmacological activity of these compounds and attempted to discover a possible link between their structure and action on the central nervous system.

Study of the compounds A indicated that they all clearly acted on the central nervous system exerting a combined tranquilizing, antispasmodic, muscle-relaxing, and soporific effect which was expressed to a different degree by individual compounds. The majority of the substances evoked superficial damping and slight disturbance of motor activity and disturbance of coordination of vision and movement in animals. In greater doses individual substances evoked in animals the secondary position and sleep. Substances A displayed a significant antispasmodic activity particularly in relation to spasms caused by the action of Corazol.

Substance IX (ED_{50} = 0.03 mg/kg) possesses the greatest anti-Corazol activity, and then in decreasing order the substances are IV > VII > III > I > X > XII > XI. The ratios of the effective doses for the anti-Corazol test and for the rotating spindle test reflect not only activity but also the therapeutic latitude of the compound. The best index (80.0) was shown by compound IX. Diazepam (VIII), VII, X, III, and IV have high indexes; these are 5.1, 9.2, 10.0, 40.0, and 41.8, respectively.

On account of the ability to eliminate a maximum electrospasmodic attack compounds A are given with known antispasmodic compounds (diphenin, luminal). These substances also show a slight antagonism to the spasmodic action of strychnine.

As regards the ability to potentiate hexenal sleep the compounds may be placed in the following order of decreasing activity: VII > IV > X > IX > VIII > III > I.

The absence of parallelism in the increase or decrease of activity of individual compounds in the anti-Corazol test and in the sleep potentiation test is probably indicative of different mechanisms of action of the compounds being examined by these two characteristics.

Depression of orientating reflexes and disturbance of coordination on introducing the majority of compounds A set in only at relatively high doses.

On comparing the data on structure and effect of compounds of series A it is not difficult to arrive at a conclusion concerning the important influence of the substituent in position 7 of the 1,4-benzdiazepine ring on the activity of these compounds in the potentiation of hexenal sleep, antagonism towards electric shock and strychnine, depression of orientating reflexes, and the disturbance of coordination of vision tests.

Those compounds which have an electron-accepting substituent in position 7 prove to be most active (according to the types of action mentioned the substances with different substituents X are arranged in the series: NO_2 > Br > Cl > H > CH_3). The correlation between table values for the Hammett σ_{para}-constant of these substituents and their tranquilizing activity given in Fig. 2 is observed on attempting an approximate quantitative calculation of this effect. This correlation enables one to affirm with a high degree of authenticity, at least for one of the mechanisms of action, that the value of the relative electrophilic character of specific centers of the tranquilizer molecule plays an important role.

As regards the antagonism to Corazol this effect is rather flat and a clear correlation is absent although the replacement of the electron accepting substituents by an electron donor (CH_3) leads to a significant decrease of activity .

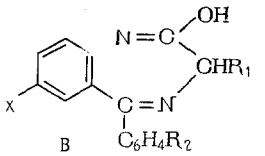
A similar evaluation of the influence of a substituent in position 1 of the 1,4-benzdiazepine ring (substituent R) is of interest. In the potentiation of hexenal sleep, antagonism to electric shock and strychnine, and lowering of orientating activity of animals and depression of their vision coordination, the substances having R = CH_3 are the most active. Then follow the substances with R = H, and least active are the compounds with R = $COCH_3$. It is possible to trace a definite agreement between these compounds and the data on the influence of substituents in position 7 on the above effects. It is easy to see that an electron-donating substituent on the N in position 1 must act in harmony with an electron-accepting substituent on the C in position 7 and increase the effect of the latter substituent.

The activity of the compounds as regards antagonism by Corazol is reduced from the analog unsubstituted on the N in position 1 to the methyl analog and to a greater degree still for the acetyl derivative. In other words, the effect of the substituent in position 1 on the anti-Corazol test is not identical with the effect of the same substituent on the series of other tests.

The effect of the substituent in position 3 is rather less specific. As regards the antagonism to Corazol and to electric shock and the depression of orientating reflexes the activity of the substances of the series A decreases in the following order: $R_1 = H > R_1 = OH > R_1 = C_2H_5$. Whereas for potentiation of hexenal sleep and effect on the disturbance of coordination the compounds with R_1 = OH proved to be most active, then followed the compounds with R_1 = H, and in the last place the compounds with $R_1 = C_2H_5$.

Finally, the introduction of a substituent into the phenyl group situated in position 5 of the system under study (compound V with a nitro group in the meta-position of the phenyl group) leads to an increase of activity as regards potentiation of hexenal sleep but has no effect on the effectiveness in the anti-Corazol test.

If the influence of the substituent for the majority of conditions of activity is determined by the effects of electron shifts then the influence of the substituent as regards the anti-Corazol test is probably associated with conformational effects. The introduction of a substituent into position 1 prevents tautomeric changes and also the formation of intermolecular associates. Whereas, compounds A, namely in the lactim form B, are able to possess a most rigid conformation with a strict fixed distance between the two nitrogen atoms and the most likelihood for forming intermolecular associates.



B

Thus, the examination of the pharmacological activity of compounds A in relation to the central nervous system enables the existence of at least two or more specific modes of action having different mechanisms to be assumed.

EXPERIMENTAL

The following are typical methods for the synthesis of compounds of type A.

7-Bromo-5-phenyl-1,3-dihydro-2H-1,4-benzdiazepin-2-one (IV). Pyridine (50 ml) was distilled off from a solution of 27 g of 5-bromo-2-aminobenzophenone and 21 g of glycine ethyl ester hydrochloride in 200 ml of anhydrous pyridine while stirring for over 12 h. Concurrently the same quantity of pyridine was added to the reaction mixture. At the end of the reaction the pyridine was distilled off under vacuum at 40-50°C. Methylene chloride and water were added to the residue. The aqueous layer was separated, made alkaline, and extracted with methylene chloride. The insoluble portion of the product was filtered off, washed with water, dried, and then dissolved in boiling benzene. On cooling crystals of substance IV separated; these were added to the main product. The solution of substance IV in methylene chloride was washed with water, dried with calcined sodium sulfate, and evaporated. The residue was crystallized from benzene. The total yield of IV was 14 g (65%) with mp 221° (from ethyl acetate). Found, %: N 8.80. $C_{15}H_{11}BrN_2O$. Calculated, %: N 8.88.

7-Chloro-5-phenyl-1-methyl-1,3-dihydro-2H-1,4-benzdiazepin-2-one (VIII). Sodium methoxide (1.08 g) was dissolved with stirring in a boiling solution of 5.4 g of compound III in 300 ml of absolute benzene. Then, 100 ml of benzene was distilled off from the solution for over 40 min while gently boiling and also stirring; after this 2.52 g of dimethyl sulfate was added dropwise to the reaction mixture. The mixture was

boiled with stirring for a further hour; then the solution was cooled to room temperature, washed with water, and dried with calcined sodium sulfate. The benzene was then distilled off in vacuum and the residue purified by crystallization from a 1 : 1 mixture of petroleum ether and diethyl ether. The yield of substance VIII was 2.9 g (50%) with mp 130° (from a mixture of petroleum ether and diethyl ether). Found, %: N 10.09. $C_{16}H_{13}ClN_2O$. Calculated, %: N 9.83.

5-Phenyl-1-acetyl-1,3-dihydro-2H-1,4-benzdiazepin-2-one (XI). Compound I (236 g) was dissolved in 150 ml of boiling absolute benzene; 0.8 g of sodium methoxide was added with stirring and the mixture was boiled until it completely dissolved. Then 50 ml of benzene was distilled off and 0.81 g of acetyl chloride was added. The solution was boiled for a further 45 min and cooled to room temperature. Then the benzene solution was washed three times with water and dried with calcined sodium sulfate. The benzene was distilled off at reduced pressure and a small quantity of boiling ethyl alcohol was added to the residue. The crystals of substance XI which separated after several hours were recrystallized from alcohol. The yield was 1.06 g (34%) with mp 142° (from ethanol). Found, %: N 10.21. $C_{17}H_{14}N_2O_2$. Calculated, %: N 10.07.

LITERATURE CITED

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3. S. A. Andronati and A. V. Bogatskii, Zh. Obshch. Khim., 39, 443 (1969).