SYNTHESIS AND PHARMACOLOGIAL STUDY OF DERIVATIVES OF PYRROLO[3,4-b]BENZO[1,5]DIAZEPINE

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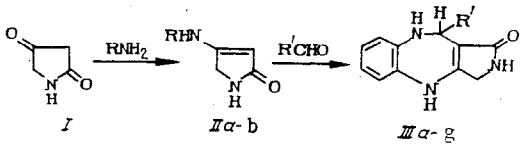
A large number of benzo[1,4]diazepines are known to exhibit biological activity; these compound include effective medicinal preparations such as chlozapid, sibazon, nozapam, diazepam, etc. [1]. Less pharmacologically active are the benzo[1,5]diazepines, nevertheless, some of these compounds do exhibit biological activity and have been shown to act as antihypertensive, and anticonvulsive, and locomotor agents [2, 3, 7, 10, 11]. This group of chemicals includes the clinically employed neuroleptic clozapine [1]. Some tricyclic compounds, containing the benzo(1,3)diazepine bicycle, have a clearly defined action on the central nervous system [9, 13]. One of the methods of synthesis of such tricyclic compounds is the reaction of a ketone with O-phenylenediamine followed by an intramolecular Mannich reaction, during which cyclization occurs to give the diazepine ring [8, 9, 16]. Based on these studies, we have studied the reaction of pyrrolidinedione-2,4 (I) with a series of compounds containing primary amino groups(aniline, phenylhydrazine, and O-phenylenediamine), and obtained the cyclic enominoamides (IIa-c). The PMR spectrum (d_6-DMSO) of the enaminoamide IIc, used for further diazepine synthesis, contained the following signals, δ, ppm: 3.94 s (CH_2), 4.90 broad s (NH_2), 4.57 s (3-H), 7.02 and 8.00 (NH-group), 6.53-7.06 (C_6H_4). The Mannich reaction between this enamine and an aromatic aldehyde proceeds with particiation of the primary o-amino group of the phenylenediamine gorup and is accompanied by cyclization to the hydrated derivative of pyrrolo [3,4-b] benzo[1,5]diazepine (III a-g).



I IIa-b IIIa-g

R=Ph (IIa), NHPh (IIb), $C_6H_4NH_2$-o (IIc);
R'=Ph (IIIa), C_6H_4OMe-p(IIIb), $C_6H_3(OMe)_2$-м, p (IIIc),
C_6H_4OH-p (IIId), C_6H_4OH-o (IIIe),
C_6H_3OMe-м-OH-p(f), C_6H_4Br-p (g).

The tricyclic compounds IIIa-g were obtained in good yield, and had very similar UV-spectra (Table 1), their structure was confirmed by PMR spectroscopy (Table 2) and mass spectral data (Table 1). In the PMR spectra (d_6-DMSO) the most characteristic signals are due to the CH_2-group protons at position 1 at ∿4 ppm.

EXPERIMENTAL (CHEMICAL)

PMR Spectra were obtained on a Varian XL-200 spectrometer, internal standard TMS. Mass spectra were taken on a Varian MAT-112 (7L eV) with direct introduction of the sample into the ion source. UV spectra were recorded on a Specord instrument using alcohol as solvent.

4-Phenylaminopyrrolidine-2-one (IIa). Aniline (0.95 g, 10 mmole) was added to a refluxing solution of pyrrolodine-2,4-dione (I) (0.99 g, 10 mmole) in MeOH (30 ml). The mixture was refluxed for 10 minutes, cooled, the residue filtered off and washed with MeOH.

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TABLE 1. Physicochemical Properties of the Compounds Synthesized

Compound	Yield, %	mp, °C (solvent)	M+	Empirical formula	UV-spectra. λ_{max} (log ε)
IIa	72	267—8, decomp. (DMFA)	174	$C_{10}H_{10}N_2O$	
IIb	31	195—7, decomp. (MeOH — DMFA, 9:1)	189	$C_{10}H_{11}N_3O$	
IIc	77	202—3 (DMFA)	189	$C_{10}H_{11}N_3O$	237(3,81); 273(3,80)
IIIa	94	242—3, decomp. (MeOH)	277	$C_{17}H_{15}N_3O \cdot H_2O$	314(3,82)
IIIb	95	247—8, decomp. (MeOH)	307	$C_{18}H_{17}N_3O_2 \cdot 0.5H_2O$	313(3,79)
IIIc	89	170—2 (MeOH — H_2O, 1:1)	337	$C_{19}H_{19}N_3O_3 \cdot 2H_2O$	313(3,79)
IIId	62	256—7, decomp. (DMFA — H_2O, 1:1)	293	$C_{17}H_{15}N_3O_2$	313(3,82)
IIIe	94	243—4, decomp. (DMFA — H_2O, 1:1)	293	$C_{17}H_{15}N_3O_2$	310(3,69)
IIIf	79	252—3, decomp. (DMFA — H_2O, 1:2)	323	$C_{18}H_{17}N_3O_3$	313(3,76)
IIIg	80	232—4 (acetone)	355 (^{79}Br)	$C_{17}H_{14}BrN_3O$	313(3,76)

TABLE 2. PMR Spectra of Compounds IIIa-g

Compound	1-CH_2	4-H	6,7,8,9-H	2,5,10 NH	R
IIIa	3,97 s	5,03* d	6,49—7,20 m	5,87 d 7,13 s 9,21 s	
IIIb	3,95 s	5,00 d	6,50—7,05 m	5,79 d 7,02 s 9,16 s	3,67 s
IIIc	3,96 s	4,98 d	6,56—6,90 m	5,81 d 7,03 s 9,17 s	3,61 s 3,63 s
IIId	3,94 d	4,95 d	6,48—6,92 m	5,81 d 7,01 s 9,14 s	9,11 s
IIIe	4,01 s	5,31 s	6,43—6,97 m	5,31 s 7,15 s 9,24 s	9,97 br.s
IIIf	4,03 s	4,95 d	6,33—6,83 m	5,74 d 7,01 s 9,13 s	3,61 s 8,65 br.s
IIIg	3,97 s	5,02 d	6,53—7,37 m	5,80 d 7,08 s 9,25 s	

*J = 4.6 Hz.

4-Phenylhydrazinoaminopyrroline-2-one (IIb). Phenylhydrazine (1.08 g, 10 mmole) was added to a refluxing solution of I (0.99 g,10 mmole) in MeOH (10 ml). The mixture was refluxed for 2 hours, cooled, the residue filtered off, and washed with MeOH.

4-(2-Aminophenyl)aminopyrroline-2-one (IIc). Compound I (9.9 g, 100 mmole) in MeOH (150 ml) was added to a refluxing solution of o-phenylenediamine (10.2 g, 110 mmole) in MeOH (40 ml). The reaction mixture was refluxed for 1 hour, cooled, the precipitated material filtered off, and washed with MeOH.

3-Oxo-4-aryl-1,2,3,4-tetrahydro-10H-pyrrolo[3,4-b]benzo[1,5]diazepine (IIIa-g). A mixture of the enamine IIc (1.89 g, 10 mmole), the corresponding aldehyde (11 mmole), alcohol (130 ml) and AcOH (5 drops) was heated until dissolved; heating was then discontinued and the reaction solution left overnight. In the case of compound IIIa-c the solvent was evaporated, water added to the residue, and the precipitate filtered off and washed with water. Compounds IIId-g separated from the reaction mixture as large heavy crystals, which were filtered off, and washed with alcohol.

EXPERIMENTAL (BIOLOGICAL)

Compounds IIIa-g were tested for sedative, anxiolytic, anti-convulsive and cardiotonic activities.

Tests were carried out on male mice weighing 18-20 g and preparations of isolated guinea-pig atria.

Sedative properties were studied by the effect on spontaneous motor activity and on the anesthetic action of thiopental sodium in mice. The effect on spontaneous motor activity was investigated using an "Opto-Varimex" (USA), motor activity was recorded over a period of 2 hours by the method described in [14]. Potentiation of the anesthetic action of thiopental sodium (30 mg/kg, intravenously) was evaluated by the length of time the animals took to recover their position when placed on their sides [17]. The myorelaxant

effect was determined by the "rotating rod" method [5], anxiolytic properties by a test in which the animals received a shock when crossing between four electrically charged plates on the floor of a chamber [12]. The anticonvulsive properties were studied on convulsions induced by corazole (125 mg/kg, subcutaneously) and by maximal electroshock [15]. Investigation of cardiotonic activity was carried out on isolated specimens of spontaneously contracting guinea pig atria by measuring the increase in the contractile amplitude [6]. Contractions were recorded using a C-2 isometric monitor (USA) on a Hugo-Zachs computer (FRG).

The acute toxicity was tested on mice, the LD_{50} was calculated by Kerber's method [4].

The test compounds were administered in doses of 3, 30, 100, 500, and 1000 mg/kg. As a comparison preparation, diazepam (seduxsen) was used in doses of 0.1, 0.5, 1, 10, and 20 mg/kg. For the in vitro study of cardiotonic activity, compounds were dissolved in 30% dimethylsulfoxide and introduced into the bath with Krebs-Genselate solution in increasing concentrations (from 10^{-7}-10^{-4} M). The activity of the test compounds was compared with that of milrinone.

Compounds IIIa-g in doses of 3, 30, or 100 mg/kg did not show any effect on the level of spontaneous motor activity, did not increase the duration of thiopental sleep, and had no myorelaxant effect on mice. In these doses the compounds IIIa-g did not increase the number of shocks from the charged plates in the chamber, and did not exhibit antagonism to the convulsive action of corazole and maximal electroshock.

Compounds IIIa-g in concentrations of 10^{-7} to 10^{-4} M did not have any effect on the contractile amplitude of isolated atria, while the known cardiotonic milrinone, starting with a concentration of 10^{-7} M, caused (depending on the dose) an increase in the amplitude and to a less extent the frequency of atrial contractions.

The acute toxicity of the compounds injected into mice was greater than 1000 mg/kg.

Based on the tests carried out, derivatives of pyrrolobenzodiazepine did not shown any effect on the central nervous system of the animals.

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