ANXIOLYTIC ACTIVITY OF DERIVATIVES OF 1-(2-PYRIMIDINYL)PIPERAZINE

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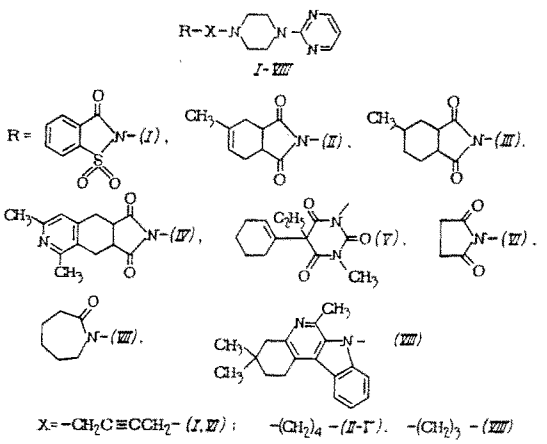
UDC 615.214.3:547.861.3]076.9

1-(2-Pyrimidinyl)piperazine (PP) is an active metabolite of buspirone in the rat and man [8]. Buspirone – 8]{-4-[4-(2-pyrimidinyl)-piperazinyl]bityl}-8-azaspiro[4, 5]decane-7,9-dione dihydrochloride – belongs to a new generation of anxiolytics. It differs from benzodiazepine tranquilizers in that it exhibits weak sedative, muscle-relaxant, and narcosis-potentiating properties and also by its mechanism of action [7, 9]. Some structural analogs of buspirone, being derivatives of PP, also possess anxiolytic activity [11]. The anxiolytic properties not only of buspirone, but also of ipsapirone and hepirone, have been sufficiently well studied in many experimental models of anxiety states [13].

In the present work we describe the synthesis and pharmacologic activity of structural analogs of bispirone, 1-(2-pyrimidinyl)piperazine, and its derivatives.

1-(2-Pyrimidinyl)piperazine, synthesized by a method described in [10], served as the starting material for the synthesis of all the rest of the derivatives. The synthesis of II-V was accomplished by alkylation of the corresponding imides, as well as hexenal, with 8-aza-5-azoniaspiro[4,5]decane bromide, by a method analogous to the synthesis of buspirone [12].



Butynyl derivatives I, VI, and VII were obtained by the Mannich reaction from PP, paraform, and the propargyl derivatives of saccharin, succinimide, and caprolactam respectively.

The starting imides were obtained by the reaction of methyltetrahydro- and methylhexahydrophthalic anhydrides or 1,3-dimethyl-6,7-anhydridodicarboxy-5,6,7,8-tetraphydrobenzo[c] pyrilium perchlorate with aqueous ammonia, and subsequent thermal cyclization of the ammonium salt of the acid amides at 250°C.

Compound VIII was synthesized from 3,3,6-trimethyl-1,2,3,4-tetrahydroindolo[2,3-c]-quinoline [2], which was alkylated with 1-chloro-3-bromopropane, after which the resulting chloropropyl derivative was treated with PP.

M. Gorkii Medical Institute. Institute of Physical Organic Chemistry and Coal Chemistry, Academy of Sciences of the Ukrainian SSR, Donetsk. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 25, No. 3, pp. 40-42, March, 1991. Original article submitted May 31, 1989.

0091-150X/91/2503-0193$12.50

TABLE 1. Derivatives of 1-(2-Pyrimidinyl)-piperazine

Compound	Yield, %	mp, °C	Empirical formula
I	89	118—119	$C_{14}H_{19}N_5O_3S$
II*	54	157—158	$C_{21}H_{31}Cl_2N_5O_2$
III*	55	169—170	
IV**	54	175—176	$C_{21}H_{33}Cl_2N_5O_2$
V*	35	70—72	$C_{25}H_{35}Cl_3N_6O_2$
VI	76	128—129	$C_{25}H_{38}Cl_2N_6O_3$
VII	73	liquid	$C_{16}H_{29}N_5O_2$
VIII***	77	283—285 (dec.)	$C_{18}H_{25}N_5O$
			$C_{29}H_{39}Cl_3N_6 \cdot 2C_2H_5OH$

*Dihydrochloride.
**Trihydrochloride.
***Crystalloalcoholate trihydrochloride.

Compounds I, VI, and VII were characterized as the free bases, the others as the hydrochlorides. Buspirone and ipsapirone were obtained from the firm Troponwerke (Germany).

EXPERIMENTAL (CHEMISTRY)

The properties of the synthesized analogs of buspirone are given in Table 1. The structures and compositions of the synthesized compounds were confirmed by IR and PMR spectroscopy as well as by elemental analysis, the results of which agreed with calculated values.

4-Methyl-1,2,3,6-tetrahydrophthalimide. A 9-g (0.054 moles) portion of methyltetrahydrophthalic anhydride was dissolved in 27 ml of 25% aqueous ammonia, the solution was evaporated, and the residue was heated to 240-245°C and kept at this temperature for 2 h. The impure imide was crystallized first from aqueous ethanol with activated charcoal, then from benzene. Yield 5.9 g (66%). mp 98-99°C. $C_9H_{11}NO_2$.

4-Hexahydrophthalimide was obtained analogously. Yield 75%. mp 78-79°C. $C_9H_{11}NO_2$.

1,3-Dimethyl-5,5a,6,8,8a,9-hexahydropyrrolo[3,4-g]isoquinoline-6,8-dione. A 7.5-g portion of the ammonium salt of the acid amide, obtained as in [1], was heated to 250°C for 2 h. The salt first melted, giving off water and ammonia vapors, and then hardened. The resulting imide was crystallized from DMFA. Yield 4.1 g (63%); mp 267-268°C. $C_{13}H_{14}N_2O_2$.

General Method for Synthesis of I, VI, and VII. A 0.01-mole portion of the starting propargyl compound, 0.3 g (0.01 mole) paraform, 1.37 g (0.01 mole) PP, and 0.01 g CuCl were boiled in 20 ml dioxane for 2 h, diluted with 100 ml water, and acidified with HCl to pH 2. After distillation of chloroform, compounds I and VI were crystallized from a mixture of benzene—hexane; compound VII was purified from the admixture of starting propargylcaprolactam by heating to 120°C in a vacuum of 0.5 mm Hg for 2 h; I and VI were converted to the hydrochlorides.

3,3,6-Trimethyl-1,2,3,4-tetrahydroindolo[2,3-c]quinoline was obtained by Kishner reduction of 1-oxo-3,3,6-trimethyl-1,2,3,4-tetrahydroindolo[2,3-c]quinoline [2] in 95% yield; mp 245-247°C. $C_{18}H_{20}N_2$.

3,3,6-Trimethyl-7-(3-chloropropyl)-1,2,3,4-tetrahydroindolo[2,3-c]quinoline. To a solution of 2.64 g (0.01 mole) 3,3,6-trimethyl-1,2,3,4-tetrahydroindolo[2,3-c]quinoline in 35 ml dry dimethyl formamide was gradually added 0.26 g (0.11 mole) sodium hydride. The mixture was stirred for 1 h at 50°C, cooled to room temperature, added over 15 min to a solution of 1.9 g (0.013 mole) chlorobromopropane, and left overnight. The reaction mass was diluted with 200 ml water and extracted with ether. The ethereal extract was washed with water, dried with sodium sulfate, and evaporated.

The residue was crystallized from hexane. Yield 2.56 g (75%); mp 119-121°C.

3,3,6-Trimethyl-7-(3-[4-(2-pyrimidinyl)-1-piperazinyl]-propyl)-1,2,3,4-tetrahydroindolo[2,3-c]quinoline (VIII). A mixture of 0.8 g (2.35 mmoles) 3,3,6-trimethyl-7-(3-chloropropyl)-1,2,3,4-tetrahydroindolo[2,3-c]quinoline, 0.38 g (2.35 mmoles) PP, 0.69 g (5 mmoles) potassium carbonate, 0.08 g (0.5 mmole) potassium iodide, and 20 ml acetonitrile was boiled with

TABLE 2. Pharmacologic Activity of 1-(2-Pyrimidinyl)piperazine and Its Derivatives

Compound	Anxiolytic activity (MED), mg/kg, in tests			General depressant activity ($ED_{50} \pm S_x$)					Toxicity, mg/kg
	conflicting situations	threatening situations	avoiding lighted areas	depression of locomotion	depression of orientating behavior	myorelaxation	potentiation of effect of hexenal	anticorazole activity	
PP	>20	10	>10	15,2±2,5	11,8±1,9	48,6±5,4	43,8±6,7	>60	130±11
Buspirone	3	10	3	8,7±1,8	7,6±1,9	54,2±8,1	8,2±2,4	>60	140±20
Ipsapirone	10	10	10	6,9±2,4	6,7±2,2	>80	8,8±2,7	>100	105±12
I	20	>10	10	20,5±3,4	25,5±3,5	>100	41,3±7,1	>100	105±12
II	10	10	10	8,6±1,5	7,5±1,0	35,0±6,1	34,8±6,2	>100	265±36
III	10	3	10	7,5±1,1	12,0±1,2			>100	240±26
IV	20	>20	20	13,3±3,0	18,1±3,0	50,0±5,9	21,4±3,8	>60	167±19
V	>20	20	>20	17,5±3,7	14,7±2,3	>60	29,2±8,1	>60	75±19
VI	20	>20	20	16,7±3,5	13,0±3,3	149±19	83,6±9,2	>100	257±33
VII	10	3	10	22,9±3,4	24,2±3,6	121±9,1	22,1±5,1	>100	>320
VIII	>20	20	10	15	15	30,0±5,1	30	>80	88±9 N
Diazepam	1	1	1	0,63±0,14	0,63±0,14	2,13±0,14	0,33±0,11	1,25±0,77	110±20

Note. Anxiolytic activity of compounds was studied in rats, general depressant activity in mice.

stirring for 10 h, filtered, and the residue washed with hot acetonitrile. The filtrate was evaporated, and the residue was dissolved in acetone and added to an ethereal solution of hydrogen chloride. Yield of trihydrochloride VIII was 1.05 g (77%). Following recrystallization from absolute ethanol, the material contained 2 molecules ethanol of crystallization.

EXPERIMENTAL (PHARMACOLOGICAL)

The anxioloytic activity of the compounds was studied on mongrel white rats weighing 260 ± 30 g, using the method of conflicting situations, of avoiding lighted areas and threatening situations. In the first case was registered the number of punishments by voluntary electric shock on taking water, along with the rat's attempts to drink under water deprivation; in the second case, the time the rat stayed in a lighted area before going into a dark chamber; and in the third case, the time the rat stayed in a lighted compartment when being voluntarily electrically shocked by a "rat sacrificer," with separation by transparent partition from the experimental. At the same time, the motor activity of the animals was measured (number of horizontal excursions). The substance under investigation was given in doses of 1, 3, 10, and 20 mg/kg intraperitoneally 20-30 min before the experiment, to determine the minimal effective dose (MED). In the control series, a corresponding volume of distilled water was given.

In experiments on mice weighing 20 ± 3 g, the sedative activity (ED_{50}) was assessed, by the ability of the substance to decrease the horizontal excursions by half and more, and to depress the orientational-investigatory activity of the animals. Myorelaxant activity was studied by the method of rotational pivoting. The narcosis-potentiating properties were determined as the dose (ED_{50}) against a background of which hexenal, in a nonnarcotizing dose (35 mg/kg, intraperitoneally), caused prolonged rolling posture in less than 5 min. Anticonvulsive activity was determined by the ability to prevent clonic-component convulsions caused by injecting corazole at the ED_{50} (85 mg/kg), and the error of the mean was found by probit analysis [4]. Also studied was the effect of the substance on phenamine stereotypy in the rat [6], and the antidepressant activity of the compound was determined by the swimming test [5].

It was found that under the conditions of the method of conflicting situations, PP, V, and VIII, in doses from 3-20 mg/kg, were not observed to have anxiolytic activity (Table 2). At the same time, buspirone, at a dose of 1 mg/kg, increased the number of approaches to drink, and at 3 mg/kg increased approaches to drink, as well as the number of punishments on taking water, without changing the motor activity of the animals. Ipsapirone exhibited a similar effect only at a dose of 10 mg/kg; its butynyl analog did not show anxiolytic activity at this dose. However, compound I at a dose of 20 mg/kg, and other butynyl derivatives of PP (VI and VII) in doses of 20 and 10 mg/kg, altered the behavior of the animals

under the conditions of the method of conflicting situations, increasing the number of punishments on taking water and the approaches to drink (Table 2). All substances studied showed less activity than buspirone, but the anticonflict activity of compounds II, III, and VII was comparable to that of ipsapirone (Table 2).

All compounds tested showed activity in the test of avoiding lighted areas, and many of them (except for I, IV, and VI) under the conditions of the method of threatening situations, as well. Of the compounds which were not found to be anxiolytically active in the conditions of the method of conflicting situations, PP (10 mg/kg) and V (20 mg/kg) exhibited activity under the conditions of the method of threatening situations, and VIII (10 mg/kg) also in the test of avoiding lighted areas.

All compounds studied depressed spontaneous motor activity and orientational-investigatory behavior in mice in doses of 6.7-24.2 mg/kg, at or near the dose of buspirone, but substantially grater (by 10.6-38 times) than the corresponding dose of diazepam. Myorelaxant activity of buspirone and its structural analogs was exhibited in doses 15-70 fold greater than that of diazepam, and narcotizing properties in doses 25-250 fold greater than that of diazepam. In contrast to the above, buspirone and its analogs did not possess anti-corazole activity (see Table 2).

The majority of the compounds studied did not alter the duration of phenamine stereotypy in rats. An exception is compound VII, which prolonged phenamine stereotypy (137% of control, $t = 3.22$ for $n = 8$) and shortened the duration of immobilization (64% of control, $t = 3.36$ for $n = 8$) in the forced swimming test. The other compounds tested did not change or significantly increased (PP, VI) the duration of immobilization of mice.

Thus, all compounds studied were observed to have anxiolytic activity, though not necessarily in all three models of anxiety states. In contrast to the equal effectiveness in all models of anxiety of diazepam, some of the compounds studied are more active in conflicting situations and in the test of staying in a lighted area (buspirone, IV, VI), others in models of threatening situations (V, VII). In anxiolytic activity, the derivatives of PP are inferior to diazepam by 3-10 fold. Derivatives of 2-alkyl-1-(2-pyrimidinyl)piperazine expressing anxiolytic activity include not only the imide derivatives, but also its lactam VII. The general depressant effect of PP and its derivatives on the CNS is weaker than that of diazepam by at least 3-10 times. The butynyl derivatives of PP are practically devoid of myorelaxant activity.

LITERATURE CITED

1. V. I. Dulenko, V. M. Golyak, N. I. Alekseev, and N. F. Gorenko, Khim. Geterotsikl. Soedin., No. 10, 1318-1321 (1984).
2. V. I. Dulenko, V. I. Luk'yanenko, A. V. Kibal'nyi, et al., ibid., No. 3, 363-366 (1985).
3. T. A. Klygul' and V. A. Krivolapov, Farmakol. Toksikol., 29, No. 2, 241-244 (1966).
4. V. P. Prozorovski, ibid, 25, No. 1, 115-120 (1962).
5. D. Yu. Rusanov and A. V. Val'dman, ibid., 46, No. 5, 107-111 (1978).
6. E. L. Shchelkunov, ibid., 27, No. 5, 628-633 (1964).
7. A. S. Eison and D. L. Temple, Am. J. Med., 80, No. 3B, 1-9 (1986).
8. R. E. Gammans, R. F. Mayol, and J. A. Labudde, ibid., 41-51.
9. K. Goa and A. Ward, Drugs, 32, No. 2, 114-129 (1986).
10. K. L. Howard, H. W. Stewart, E. A. Conroy, and J. J. Denton, J. Org. Chem., 18, No. 11, 1484-1488 (1953).
11. J. S. New, J. P. Jevich, M. S. Eison, et al., J. Med. Chem., 29, No. 8, 1476-1482 (1986).
12. J. C. Simms, U.S. Patent 4,351,939 (1982).
13. J. Traber and T. Glaser, Trends Pharmacol. Sci., 8, No. 11, 432-437 (1987).