decreases under the influence of the drug after 18 h by a factor of more than three. The SOG-4 sharply potentiates the 5-HTP hyperkinesis caused by the administration of 5-HTP (Table 3). The antimonoamine oxidase activity of SOG-4 is manifested distinctly after both 2 and 18 h in liver and brain of rats (Table 3).

Thus, with respect to reserpine antagonism, potentiation of 5-HTP hyperkinesis, and antimonoamine oxidase activity, SOG-4 is not inferior to nialamide, and in certain tests it is even superior to it (the reserpine hypothermia, antimonoamine oxidase activity in brain). It also has a fairly broad therapeutical activity.

The drug is interesting because in the absence of nialamide and other monoamine oxidase inhibitors [5], it does not prolong medicated sleep, but increases the motor activity, and decreases the body temperature.

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SYNTHESIS AND PHARMACOLOGICAL STUDY OF 10H-PYRIDAZINO [4, 5-b]-BENZOXAZINES [1, 4] (2, 3-DIAZAPHENOXAZINES)

II. SYNTHESIS AND PHARMACOLOGICAL STUDY OF DERIVATIVES OF 7-NITRO-, 7-DIMETHYLSULFAMYL-, 7-ACETYL-, AND 7-CHLORO-2,3-DIAZAPHENOXAZINES

N. V. Savitskaya, T. V. Gorminskaya, V. G. Nyrkova, I. N. Fedorova, A. I. Polezhaeva, and M. D. Mashkovskii

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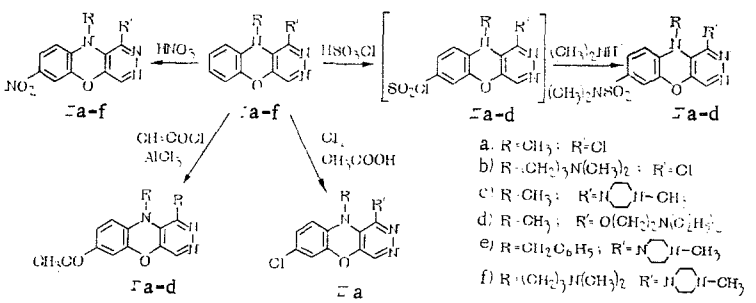
To investigate the relationship between the psychotropic activity of some 2,3-diazaphenoxazines and the nature of the substituent in the benzene ring, 1,10-disubstituted derivatives were prepared with a nitro, a dimethylsulfamyl, an acetyl group, and a chlorine atom in the 7 position. Nitration with nitric acid



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0091-150X/77/1107-0889$07.50

TABLE 1. 1,7,10-Trisubstituted 2,3-Diazaphenoxazines

Compound	Yield, %	Melting point, deg.	Found, %					Empirical formula	Calculated, %				
			C	H	Cl	N	S		C	H	Cl	N	S
IIa	91,5	289—290 decomp.	47,58	2,60	12,86	—	—	$C_{11}H_7ClN_4O_3$	47,41	2,53	12,73	—	—
IIb	80	144—145	51,03	4,43	9,74	20,10	—	$C_{15}H_{16}ClN_5O_3$	51,50	4,61	10,14	20,03	—
	—	266—268 decomp.	—	—	24,03	—	—	$C_{15}H_{16}ClN_5O_3 \cdot 2HCl \cdot H_2O$*	—	—	24,13	—	—
IIc	78,7	231—233	56,04	5,27	—	24,80	—	$C_{16}H_{18}N_6O_3$	56,13	5,27	—	24,55	—
	—	Did not melt below 335	—	—	17,09	20,21	—	$C_{16}H_{18}N_6O_3 \cdot 2HCl$	—	—	17,07	20,20	—
IId	79,5	136—137,5	55,03	6,02	—	19,16	—	$C_{17}H_{21}N_5O_4 \cdot 0,5H_2O$*	55,42	6,02	—	19,01	—
	—	Did not melt below 330	—	—	15,69	15,83	—	$C_{17}H_{21}N_5O_4 \cdot 1,9HCl$	—	—	15,71	16,34	—
IIe	63,5	170—172	60,85	5,30	—	19,65	—	$C_{22}H_{22}N_6O_3 \cdot {}^3/_4H_2O$*	61,17	5,48	—	19,46	—
	—	243—245 decomp.	—	—	13,98	16,48	—	$C_{22}H_{22}N_6O_3 \cdot 2HCl \cdot H_2O$*	—	—	13,92	16,50	—
IIf	—	207—209	58,08	6,35	—	23,60	—	$C_{20}H_{27}N_7O_3$	58,09	6,58	—	23,71	—
	—	267—269 decomp.	—	—	20,38	—	—	$C_{20}H_{27}N_7O_3 \cdot 3HCl$	—	—	20,34	—	—
IVa	80	252—254	—	—	10,19	16,45	9,16	$C_{18}H_{13}ClN_4O_2S$	—	—	10,40	16,44	9,41
IVb	72,5	143—145	49,69	5,24	—	—	7,61	$C_{17}H_{22}ClN_5O_2S$	49,57	5,38	—	—	7,79
	—	244—246 decomp.	—	—	21,53	—	6,48	$C_{17}H_{22}ClN_5O_2S \cdot 2HCl$	—	—	21,90	—	6,61
IVc	68,2	235—237	53,22	5,87	—	20,61	7,90	$C_{18}H_{24}N_6O_2S$	53,44	5,98	—	20,78	7,93
	—	247—248 decomp.	—	—	15,28	—	6,34	$C_{18}H_{24}N_6O_2S \cdot 2HCl$	—	—	14,85	—	6,72
IVd	72	120—121	54,26	6,47	—	16,50	7,14	$C_{19}H_{27}N_5O_4S$	54,14	6,46	—	16,62	7,61
	—	294—296	—	—	13,89	—	6,53	$C_{19}H_{27}N_5O_4S \cdot 2HCl$	—	—	14,34	—	6,49
Va	72	235—236	56,77	3,48	12,27	15,22	—	$C_{13}H_{10}ClN_3O_2$	56,64	3,66	12,86	15,24	—
Vb	62	155—156	58,47	5,57	10,09	15,87	—	$C_{17}H_{19}ClN_4O_2$	58,87	5,52	10,22	16,15	—
	—	205—208	—	—	23,95	13,80	—	$C_{17}H_{19}ClN_4O_2 \cdot 1,75HCl$	—	—	23,74	13,64	—
Vc	41	264—265 decomp.	—	—	18,36	16,00	—	$C_{18}H_{23}N_5O_2 \cdot 2,25HCl \cdot 1,25H_2O$*	—	—	17,96	15,78	—
Vd	50	130—132	63,93	6,68	—	15,54	—	$C_{19}H_{24}N_4O_3$	64,02	6,79	—	15,72	—
VIa	58,8	222—223	48,71	2,80	26,48	15,74	—	$C_{11}H_6Cl_2N_2O_3$	49,28	2,63	26,45	15,67	—
VII	65	220—222	—	—	9,36	18,03	8,14	$C_{15}H_{18}ClN_5O_3S$	—	—	9,24	18,25	8,38
VIII	32,7	170—171	—	—	10,70	20,89	—	$C_{16}H_{18}ClN_5O$	—	—	10,69	21,11	—
	—	307—308 decomp.	—	—	25,75	17,28	—	$C_{16}H_{18}ClN_5O \cdot 2HCl$	—	—	26,28	17,31	—
IX	42,6	250—251	55,42	5,75	10,09	—	—	$C_{16}H_{20}ClN_5O_2$	54,93	5,76	10,13	—	—
X	70,8	107—108	44,78	3,40	34,78	13,65	—	$C_{15}H_{12}Cl_4N_4O$	44,54	3,46	34,75	13,73	—

* Amount of water was determined analytically.

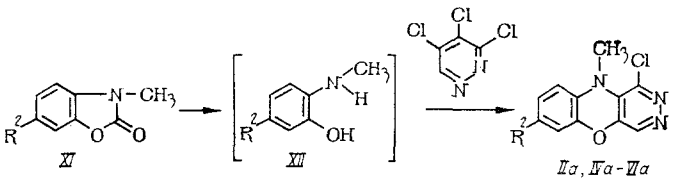
Note. Compounds IIa, IVa, Va, VIa, VII, and IX were recrystallized from DMFA; compounds IIb, IVb, Vb, Vd, and VIII from ethyl acetate; IIc, IIe from alcohol; IId from aqueous methanol; IIf, IVc from benzene, and IVd, X from heptane.

(d = 1.4) of the 1,10-disubstituted 2,3-diazaphenoxazines (Ia-e) [1] gave the 7-nitro-1,10-disubstituted 2,3-diazaphenoxazines (IIa-e; see Table 1). Chlorosulfonation of compounds Ia-d gave 7-sulfochlorido-2,3-diazaphenoxazines (IIIa-d), which were not isolated but were converted to 7-dimethylsulfamyl-1,10-disubstituted 2,3-diazaphenoxazines (IVa-d; see Table 1) by treatment with dimethylamine. Compounds IVc and IVd were also obtained by substituting the chorine atom in IVa with a methylpiperazine group and a diethylaminoethoxy group respectively. The reaction of IIIb with ammonia gave the 7-sulfamyl derivative (VII; see Table 1).

Friedel–Crafts acetylation of Ia-d gave 7-acetyl-1,10-disubstituted 2,3-diazaphenoxazines (Va-d; see Table 1). The IR spectra of compounds Va-d which have an acetyl group in the 7 position have absorption bands in the region 1670-1680 cm^{-1} characteristic of the CO group.

Chlorination of Ia with twice the theoretical quantity of chlorine gave 1,7-dichloro-10-methyl-2,3-diazaphenoxazines (VIa), which on treatment with N-methylpiperazine was converted to 1-(4-methylpiperazinyl-1)-7-chloro-10-methyl-2,3-diazaphenoxazine (VIII; see Table 1). The latter with alcoholic potassium hydroxide gave 3-(4-methylpiperazinyl-1)-4-[(2-hydroxy-4-chorophenyl)-N-methylamino]-pyridazone-5 (IX; see Table 1).

Chlorination with a large excess of chlorine gives polyhalogen compounds. Thus, the product from compound Ib contained four chlorine atoms (X), two of which are in positions 1 and 7; the positions of the remaining chlorine atoms were not determined. The position of the substituents in the benzene ring was confirmed by the following alternative syntheses:



XI XII IIa, IVa-VIa

R^2 = NO_2; $(CH_3)_2NSO_2$; $COCH_3$; Cl

3-Methylbenzoxazolones (XI, R^2 – NO_2, $COCH_3$, Cl), containing a nitro, dimethylsulfamyl, acetyl group or chlorine atom in the 6 position were synthesized [2-4]; 3-methyl-6-dimethylsulfamylbenzoxazolone (XI, R^2 = $(CH_3)_2NSO_2$) was obtained from the reaction between dimethylamine and 3-methyl-6-sulfochloridobenzoxazolone [5]. 4-Substituted 2-hydroxy-N-methylaniline (XII) was obtained by alkaline hydrolysis of XI, and without isolation was condensed with 3,4,5-trichloropyridazine to give the corresponding 7-substituted 10-methyl-1-chloro-2,3-diazaphenoxazines (IIa, IVa-VIa); the IR spectra of samples of compounds IIa, IVa-VIa obtained by the alternative synthesis and by electrophilic substitution were identical.

It should be noted that salts of many of the prepared bases contained different amounts of water of crystallization (see Table 1); these salts are easily isolated in the anhydrous state. The quantity of hydrogen chloride in the hydrochlorides also varies.

Experimental

The IR spectra were taken in mineral oil on a UR-10 spectrophotometer.

1-Chloro-7-nitro-10-methyl-2,3-diazaphenoxazine (IIa). A. Compound Ia (5 g; 0.021 mole) was added to nitric acid (11 ml; d = 1.4) at 5-10°C, the mixture was maintained at 20-25° for 1 h, poured onto ice, and made alkaline. The precipitate was filtered off, washed with water, and dried. Yield, 5.5 g of IIa. Compounds IIb-f are prepared by the same method (see Table 1).

The hydrochlorides of IIa-e were prepared by treating a solution of the corresponding base in absolute alcohol (IIc,e), or ethyl acetate (IIb, d), or chloroform (IIf) with a solution of hydrogen chloride in absolute ethanol (see Table 1).

B. A solution of potassium hydroxide (5.05 g; 0.09 mole) in water was added to XI (R^2 = NO_2) (5.8 g; 0.03 mole) and the mixture was refluxed for 1.5 h. It was then diluted with alcohol (50 ml) and refluxed for a further 30 min. A solution of 3,4,5-trichloropyridazine (7.3 g; 0.04 mole) in alcohol (14 ml) was slowly added to the hot reaction mixture and the whole refluxed for 6 h and then cooled. The precipitate was filtered off, washed with alcohol and water, and dried. Yield, 6.8 g (81%) of IIa, mp 289-290° (from DMFA). Found, %: C 47.66, H 2.80, Cl 12.70. $C_{11}H_{17}ClN_4P_3$. Calculated, %: see Table 1. The IR spectra of samples of Ia obtained by methods A and B were identical.

1-Chloro-7-dimethylsulfamyl-10-methyl-2,3-diazaphenoxazine (IVa). A. Compound Ia (4 g; 0.017 mole) was added slowly with mixing to 95.5% chlorosulfonic acid (21 g; 0.17 mole) at 5-10°, and mixing was continued for 30 min at 20-25° and then for 2 h at 60-65°. The reaction mixture was cooled, poured into an aqueous solution of dimethylamine (75 ml; 33%), cooled to 0°, the precipitate filtered off, washed with water, and dried. Yield, 4.7 g of IVa. Compounds IVb-d were prepared by the same method (see Table 1).

The hydrochlorides of IVb-d were obtained by treating solutions of the corresponding bases in absolute alcohol (IVb), chloroform (IVc) or ethyl acetate (IVd) with a solution of hydrogen chloride in absolute alcohol (see Table 1).

B. A solution of 84% potassium hydroxide (6 g; 0.09 mole) in water (11 ml) was added to XI [$R^2 = SO_2N(CH_3)_2$] (7.7 g; 0.03 mole), the mixture refluxed for 1 h, diluted with alcohol (70 ml) and refluxed for a further 15 min. A solution of 3,4,5-trichloropyridazine (7.3 g; 0.04 mole) in alcohol (14 ml) was added gradually and the mixture refluxed for 5 h, and then cooled. The precipitate was filtered off and washed with alcohol and water. Yield, 5.5 g (54%) of IVa, mp 252-254° (from DMFA); the melting point was not depressed by the addition of a sample of IVa prepared by method A.

1-(4-Methylpiperazinyl-1)-7-dimethylsulfamyl-10-methyl-2,3-diazaphenoxazine (IVc). A mixture of IVa (4 g; 0.012 mole) and N-methylpiperazine (3.3 g; 0.033 mole) in cyclohexanol (40 ml) was refluxed for 6 h, the cyclohexanol distilled off with water, and residue triturated with alcohol and the precipitate filtered off. Yield, 2.3 g (49%) of IVc, mp 235-237° (from benzene); the melting point was not depressed by the addition of a sample of IVc obtained by method A.

1-Diethylaminoethoxy-7-dimethylsulfamyl-10-methyl-2,3-diazaphenoxazine (IVd). A mixture of IVa (4.2 g; 0.012 mole) and a solution of sodium (0.28 g; 0.012 g-atom) and diethylaminoethanol (2.8 ml) in toluene (19 ml) was refluxed for 2 h and the toluene and diethylaminoethanol then distilled off. The residue was dissolved in toluene, the solution washed several times with water, and treated with 10% hydrochloric acid. The hydrochloric acid solution was made alkaline and extracted with ethyl acetate, the ethyl acetate solution washed with water, dried with magnesium sulfate and the residue obtained after removal of the ethyl acetate recrystallized from heptane. Yield, 2.5 g (49.5%) of IVd, mp 120-121° (from heptane); the melting point was not depressed by the addition of a sample of IVd obtained by method A.

1-Chloro-7-sulfamyl-10-dimethylaminopropyl-2,3-diazaphenoxazine (VII). This was prepared by the same method as compound IVa, from Ib (6 g; 0.02 mole) and 95.5% chlorosulfonic acid (14 ml). The reaction mixture was poured into a cooled solution of 24% aqueous ammonia, yield, 4.9 g of VII (see Table 1).

1-Chloro-7-acetyl-10-methyl-2,3-diazaphenoxazine (Va). A. Acetyl chloride (10 ml) was gradually added with cooling and mixing to a mixture of Ia (10 g; 0.042 mole) and anhydrous aluminum chloride (22 g), and this was then heated for 4.5 h at 55-60°. The reaction mixture was cooled and decomposed with ice and hydrochloric acid (~50 g ice and 5 ml concentrated hydrochloric acid), stirred for 30 min, and made alkaline. The precipitate was filtered off and washed with water. Yield, 8.5 g of Va (see Table 1). IR spectrum, cm^{-1}: ν_{CO} 1680. Compounds Vb-d were prepared by the same method (see Table 1).

The hydrochlorides of Vb and d were prepared by treating solutions of the bases in ethyl acetate (Vb) or chloroform (Vd) with a solution of hydrogen chloride in absolute alcohol (see Table 1).

B. A solution of 84% caustic potash (10 g; 0.15 mole) in water (9 ml) and XI ($R^2 = COCH_3$) were refluxed for 1.5 h; alcohol (125 ml) was added and the mixture refluxed for a further 15 min. A solution of 3,4,5-trichloropyridine (10 g) in alcohol (35 ml) was added and refluxing continued for 5 h. The precipitate which formed on cooling was filtered off and washed with alcohol and water. Yield, 7 g (50.5%) of Va, mp 243-236°; the melting point was not depressed by the addition of a sample of Va obtained by method A.

1,7-Dichloro-10-methyl-2,3-diazaphenoxazine (IVa). A. Chlorine was passed into a solution of Ia (5 g; 0.021 mole) in glacial acetic acid (50 ml) containing catalytic amounts of $FeCl_3$ and iodine at 60°. The passage of chlorine was stopped after absorption of 3 g (0.043 mole) of the gas, and the reaction mixture left overnight at 20°. The precipitate was filtered off and washed with water. Yield, 3.4 g of VIa (see Table 1).

B. A solution of 84% caustic potash (6 g; 0.09 mole) in water (6 ml) and XI ($R^2 = Cl$) (5.5 g; 0.03 mole) was refluxed for 40 min; alcohol (50 ml) was added, and refluxing continued for a further 30 min. A solution of 3,4,5-trichloropyridazine (7.3 g; 0.04 mole) in alcohol (14 ml) was added and this was refluxed for 4 h and then cooled. The precipitate was filtered off, washed with alcohol, and water, and dried. Yield, 5.4 g (66.5%) of VIa, mp 222-223° (from DMFA); the melting point was not depressed by the addition of a sample of VIa obtained by method A.

1-(4-Methylpiperazinyl-1)-7-chloro-10-methyl-2,3-diazaphenoxazine (VIII). This was prepared in the same way as compound IVb from VIa (8 g; 0.03 mole) and N-methylpiperazine (9 g; 0.09 mole) in cyclohexanol (35 ml).

The hydrochloride of VIII was obtained by treatment of an ethyl acetate solution of the base with hydrogen chloride in alcohol (see Table 1).

3-(4-Methylpiperazinyl-1)-4-[(2-hydroxy-4-chlorophenyl)-N-methylamino]-pyridazone-5 (IX). A mixture of the hydrochloride of VIII (2.2 g), 84% potassium hydroxide (2.2 g) and alcohol (22 ml) was heated on a water bath at 160-170° for 8 h, cooled, the alcohol removed, and the residue dissolved in water and acidified to pH 7.0. The precipitate was filtered off and washed with water. Yield, 0.78 g of IX (see Table 1). IR spectrum, cm^{-1}: ν_{CO} 1670.

1,7,x,x-Tetrachloro-10-dimethylaminopropyl-2,3-diazaphenoxazine (X). This was prepared in the same way as compound VIa from Ib (4 g; 0.013 mole) in glacial acetic acid (40 ml). The amount of chlorine absorbed was 9 g. Yield 3.8 g of X (see Table 1).

3-Methyl-6-dimethylsulfamylbenzoxazolone [XI, $R^2 = SO_2N(CH_3)_2$]. This was prepared in the same way as compound IVa, from 3-methylbenzoxazolone (11.2 g; 0.075 mole) and chlorosulfonic acid (26 ml). Yield, 14.4 g (74.5%) XI, m.p. 216-218° (from alcohol). Found, %: C 47.04, H 4.76, N 10.36, S 12.49. $C_{10}H_{12}N_2O_4S$. Calculated, %: C 46.84, H 4.72, N 10.94, S 12.52. IR spectrum, cm^{-1}: ν_{CO} 1785.

EXPERIMENTAL

A pharmacological study was carried out on compounds IIb-f, IVc, d, Vb-d, and VIII.

The same methods were used as had previously been used to study the neurotropic and antidepressant properties of the 2,3- and 3,4-diazaphenoxazine derivatives.

The overall action of the compounds was studied using white mice; the effect on the hyperthermic action of amphetamine (10 mg kg), on the "group" toxicity of amphetamine and, on hypothermia and blepharoptosis caused by reserpine (2 mg/kg, subcutaneously) was studied. The effect on catalepsy caused by triftazin (6 mg/kg intraperitoneally) was studied on rats. The effect on the central n-cholinoreactive (nicotine 1) mg/kg subcutaneously) and m-cholinoreactive (arecoline 15 mg/kg subcutaneously)systems was studied using mice. The effect on the peripheral region of the nervous system was studied using urethane-narcotized cats. The LD_{50} was determined by subcutaneous injection into mice.

It was found that none of the compounds when injected subcutaenously into mice or rats in doses of 25-100 mg/kg caused hypothermia, blepharoptosis, loss of locomotion, catalepsy, i.e., any of the phenomena characteristic of neurotropic substances.

Some of the compounds, however, displayed some antidepressant action.

Compounds IIb, e, and f when injected subcutaenously in doses of 25 and 50 mg/kg prolonged the hyperthermic action of amphetamine. Injection of amphetamine (10 mg/kg subcutaneously) into a control group of mice caused a maximum increase in the body temperature of $1.5 \pm 0.24°$. Restoration of the initial temperature occurred after 120-150 min. After injection of the compounds under investigation, the body temperature of the mice was 1-2° higher than after injection of amphetamine alone. Prolongation of the hyperthermic effect also occurred in the majority of cases.

Compounds IIb, e, and f increased the group toxicity of amphetamine. Thus, amphetamine injected subcutaneously in a dose of 10 mg/kg destroyed 20% of the mice, whereas when compound IIe (50 mg/kg subcutaneously) was injected simultaneously with amphetamine, death occurred in 70% of cases (χ^2 with $P < 0.01$), and for compounds IIb and f, in 40-60% of cases (χ^2 with $P < 0.05$). The remaining compounds were either less active (IIc, d, Vb), or did not display any of this type of activity (IVc, IVd, Vc, Vd, VIII).

Compounds IIb and IIe decreased the depressing effect of reserpine. Blepharaptosis was reduced by 25-30% under the influence of these compounds (25-50 mg/kg subcutaneously) and the hypothermic action of reserpine was decreased by 1.5-2°. The remaining compounds displayed no noticeable effect on the action of reserpine.

None of the compounds on subcutaneous injection in doses of 25-50 mg/kg decreased triftaxin-induced catalepsy in mice.

In tests on mice (25-50 mg/kg subuctaneously) none of the compounds displayed central cholinolytic activity, and in tests on urethane-narcotized cats (1-5 mg/kg) they showed no peripheral cholinolytic activity. In these doses the compounds showed no adrenomimetic or adrenolytic effect.

The LD_{50} for injection under the skin was 500 mg/kg for IIb, 230 mg/kg for IIc, 270 mg/kg for IId, 210 mg/kg for IIe, 500 mg/kg for IIf, 1020 mg/kg for IVc, 1050 mg/kg for IVd, 520 mg/kg for Vb, 320 mg/kg for Vc, 235 mg/kg for Vd, and 260 mg/kg for VIII.

Thus, none of the compounds possessed any neurotropic activity. Compounds with a nitro group in the 7 position in the diazaphenoxazine ring displayed some antidepressant activity. When an acetyl or sulfamyl group is introduced into the 7 position, this activity is weakened or lost.

The same relationship between chemical structure and pharmacological activity was found during a study of the derivatives of 3,4-diazaphenoxazine [5].

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