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

VIII. SYNTHESIS AND PHARMACOLOGICAL STUDY OF DERIVATIVES OF 7-ACETYL, 7-ALKOXY-, AND 7-CHLORO- OR 8-CHLORO-3,4-DIAZAPHENOXAZINES

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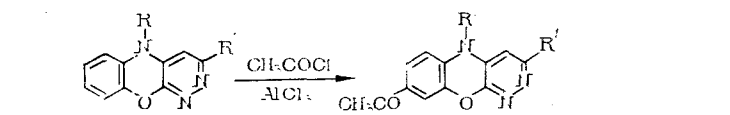
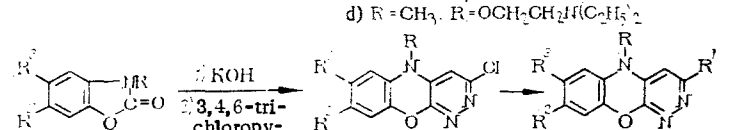
The synthesis of 2,10-disubstituted 7-acetyl-, 7-alkoxy-, and 7-chloro- or 8-chloro-3,4-diazaphenoxazines has been effected with the aim of studying the dependence of psychotropic activity on the character of the substituents in the benzene ring of 3,4-diazaphenoxazine.

7-Acetyl-2,10-disubstituted 3,4-diazaphenoxazines (IIa-d, Table 1) were obtained by the Friedel–Crafts acetylation of 2,10-disubstituted 3,4-diazaphenoxazines (I) which were themselves synthesized by a method described previously [1].



Ia-d IIa-d

where a) R = CH_3, R' = Cl
b) R = $(CH_2)_3N(CH_3)_2$, R' = Cl
c) R = CH_3, R' = N(CH$_2$CH$_2$)$_2$N–CH_3
d) R = CH_3, R' = $OCH_2CH_2N(C_2H_5)_2$



IIIa-g IVa-g Va-g where R^2 = H

IIIa) R = CH_3, R^2 = CH_3O, R^5 = H
b) R = CH_3; R^2 = C_2H_5O; R^5 = H
c) R = $(CH_2)_3N(CH_3)_2$; R^2 = C_2H_5O; R^5 = H
d) R = H; R^2 = Cl; R^5 = H
e) R = CH_3; R^2 = Cl, R^5 = H
f) R = $(CH_2)_3N(CH_3)_2$; R^2 = Cl; R^5 = H
g) R = $(CH_2)_3N(CH_3)_2$; R^2 = H, R^5 = Cl

IVa) R = CH_3; R = N(CH$_2$CH$_2$)$_2$N–CH_3, R^2 = CH_3O
b) R = CH_3; R = N(CH$_2$CH$_2$)$_2$N–CH_3; R^2 = C_2H_5O
c) R = CH_3; R = N(CH$_2$CH$_2$)$_2$N–CH_3; R^2 = Cl
d) R = CH_3; R = $OCH_2CH_2N(C_2H_5)_2$; R^2 = Cl
e) R = $(CH_2)_3N(CH_3)_2$; R = N(CH$_2$CH$_2$)$_2$N–CH_3; R^2 = Cl
f) R = $(CH_2)_3N(CH_3)_2$; R = $OCH_2CH_2N(C_2H_5)_2$, R^2 = Cl

*Deceased.

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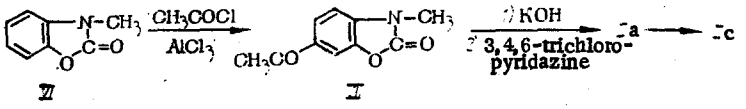
The synthesis of IIa was carried out from 3-methylbenzoxazolone (VI) by the following scheme in order to confirm the position of the acetyl group:



VI VII

6-Acetyl-3-methylbenzoxazolone (VII), which is not described in the literature, was obtained by the Friedel–Crafts acetylation of VI [1]. According to PMR data [doublet at δ = 7.24 ppm with SSIC* J = 8.5 Hz (4H), 7.86 ppm J = 1.8 Hz (7H) and quartet at δ = 7.98 ppm J_1 8.5 Hz, J_2 = 1.8 Hz] the acetyl group in VII is in position 5 or 6. Since the melting point of VII (166-168°) is different from the melting point of 5-acetyl-3-methylbenzoxazolone (132°) given in literature [2] it may be taken that acetylation of VII goes in the 6 position.

2-Methylamino-5-acetylphenol was obtained by the alkaline hydrolysis of VII and without isolation was subjected to condensation with 3,4,6-trichloropyridazole in alcoholic alkaline solution. Compound IIa obtained was converted into IIc for convenience of identification.

On interaction of IIa or IIb with hydroxylamine the corresponding oximes VIII and IX were obtained (see Table 1). By treating IIa with sodium butylate 2-butoxy-7-acetyl-10-methyl-3,4-diazaphenoxazine X was isolated (see Table 1).

Derivatives of 7-alkoxy-2-chloro-, 2,7-dichloro-, or 2,8-dichloro-3,4-diazaphenoxazines (IVa-g, Table 2) were synthesized by an analogous method from derivatives of 6-alkoxy-, 6-chloro-, or 5-chloro-benzoxazines (IIIa-g) [3] and, by treatment with N-methylpiperazine or sodium diethylaminoethylate, were converted into the corresponding derivatives containing an N-methylpiperazine residue or a diethylaminoethoxy group in the 2 position (Va-f, Table 2).

3-Methyl-6-methoxy- and 3-methyl-6-ethoxybenzoxazolones (IIIa and IIIb) were synthesized from the corresponding ethers of 2-nitrosoresorcinol by the method described in [4]. Compounds IIId-e were obtained from benzoxazolone by a known method. Compounds IIIc, f, g, which are not described in the literature, were obtained by the method developed by us [1] by the interaction of 6-ethoxy-, 6-chloro-, or 5-chlorobenzoxazolone with 3-dimethylaminochloropropane. In this way the first two compounds (IIIc, f) were subjected to further conversion without isolation, the third (IIIg) was isolated in pure form.

On chlorination of 2-chloro-10-methyl-3,4-diazaphenoxazine (Ia) with chlorine in acetic acid at room temperature a derivative of 3,4-diazaphenoxazine containing three atoms of chlorine in the molecule was obtained (XI). To confirm the position of two chlorine atoms in XI, chlorination of 2,7-dichloro-10-methyl-3,4-diazaphenoxazine (IVe) was carried out with sulfuryl chloride in dimethylformamide. In this way a substance was isolated which had the same elemental composition as XI, and in mixing test with the latter no depression of melting point was given. The absence of a singlet for the 1H proton in the PMR spectrum and also the presence of two doublet signals at δ = 7.03 ppm (9H) with J = 8.5 Hz and 7.08 ppm (6H) with J = 1.8 Hz and a quartet at δ = 7.25 ppm with J_1 = 8.5 Hz and J_2 = 1.8 Hz confirmed that chlorine had entered into position 1.

In order to establish the significance of the chlorine atom in 2-chloro-10-γ-dimethylaminopropyl-3,4-diazaphenoxazine for the psychotropic activity of this compound a stubstance was obtained in which the chlorine atom was substituted by a methyl group, viz., 2-methyl-10-γ-dimethylaminopropyl-3,4-diazaphenoxazine (XII). This compound was synthesized by the interaction of 3-γ-dimethylaminopropylbenzoxazolone [5] with 4-methyl-3,6-dichloropyridazine. The latter was obtained from 4-amino-1,2,4-triazole and acetoacetic ester through a series of steps [6, 7].

EXPERIMENTAL

Chemistry

IR spectra were taken on a UR-10 spectrophotometer in Nujol, UV spectra on a Hitachi instrument in alcohol, and PMR spectra on an INM-4H-100 instrument, the internal standard being tetramethylsilane.

2-Chloro-7-acetyl-10-methyl-3,4-diazaphenoxazine (IIa). a). Acetyl chloride (4.5 g: 0.056 mole) was added gradually with stirring and cooling to Ia (5 g: 0.021 mole) and anhydrous aluminum chloride (11.25 g: 0.084 mole) and the mixture was heated at 60° for 3.5 h. After cooling, 10% hydrochloric acid (8 ml) and ice

*Spin–spin interaction constant.

(25 g) were added, the mixture stirred for 1 h, then made alkaline. The precipitate was filtered off, washed with water, and dried. Compound IIa (4.6 g) was obtained (see Table 1).

b). A suspension of VII (5.75 g: 0.03 mole) in an 85% solution of potassium hydroxide (6 g: 0.09 mole) in water (7 ml) was boiled for 1.5 h, alcohol (50 ml) was added, and the mixture boiled for 15 min. Then 3,4,6-trichloropyridazine (5.5 g: 0.03 mole) in alcohol (20 ml) was added gradually and the mixture was boiled for 5 h. After cooling, the solid was filtered off, washed with alcohol, with water, and dried. Compound IIa (3.3 g: 39.8%) was obtained which did not melt up to 320°. IR spectra of samples of IIa obtained by methods a and b were identical.

Found, %: C 56.49; H 3.68; Cl 12.53; N 15.03. $C_{13}H_{10}ClN_3O_2$. Calculated, %: C 56.64; H 3.66; Cl 12.86; N 15.24.

2-(4-Methylpiperazin-1-yl)-7-acetyl-10-methyl-3,4-diazaphenoxazine (IIc). a). Compound IIc (2.72 g) was synthesized under conditions analogous to those described for the preparation of IIa from Ic (4 g: 0.017 mole), anhydrous aluminum chloride (17.9 g: 0.134 mole), and acetyl chloride (15 g: 0.17 mole).

Compounds IIb and IId were obtained similarly (see Table 1).

The hydrochlorides of IIb-d were obtained by treatment of solutions of the appropriate bases in absolute alcohol with a saturated solution of hydrogen chloride in absolute alcohol (see Table 1).

b). A mixture of IIa (1.2 g), N-methylpiperazine (1.3 ml), and cyclohexanol (6 ml) was boiled for 55 h, water was added, the cyclohexanol was distilled off with the water, the residue was made alkaline, and extracted with chloroform. The residue, after distilling off the chloroform, was recrystallized from alcohol. Compound IIc (0.25 g) was obtained having mp 236-237° and gave no depression of melting point in a mixing test with a specimen of IIc obtained by method a.

Found, %: N 20.58, $C_{18}H_{21}N_5O_2$. Calculated, %: N 20.64.

3-Methyl-6-acetylbenzoxazolone (VII). Acetyl chloride (31 ml) was added gradually with stirring and cooling to a mixture of VI (14.9 g: 0.1 mole) and anhydrous aluminum chloride (53.5 g: 0.4 mole) and the mobile dark brown reaction mass was heated at 50-55° for 2 h. Ice (100 g) and 10% hydrochloric acid (40 ml) were added gradually with stirring to the cooled reaction mass which was then kept at room temperature for 1 h. The precipitate was filtered off, washed with water, dried, and recrystallized from ethyl acetate. Compound VII (7.8 g: 37.8%) was obtained having mp 162-164°, after a second recrystallization from ethyl acetate it had mp 166-168°. IR spectrum, cm^{-1}: ν_{CO} 1685, 1765. PMR spectrum (CD_3OD), δ, ppm: singlet 2.61 (CH_3CO), 3.44 (NCH_3); doublet 7.24 (4H), 7.86 (7H), quartet 7.98 (5H).

Found, %: C 62.45; H 4.76; N 7.40. $C_{10}H_9NO_3$. Calculated, %: C 62.83; H 4.75; N 7.38.

2-Chloro-7-acetyl-10-methyl-3,4-diazaphenoxazine Oxime (VIII). A mixture of IIa (3 g: 0.01 mole), hydroxylamine hydrochloride (3 g: 0.043 mole), absolute alcohol (30 ml), and dry pyridine (30 ml) was boiled for 3 h, cooled, the solid was filtered off, washed with alcohol, with water, and dried.

Compound VIII (1.5 g) was obtained. Compound IX was obtained similarly (see Table 1).

2-Butoxy-7-acetyl-10-methyl-3,4-diazaphenoxazine (X). A solution of IIa (2 g: 0.007 mole) in dimethylformamide (30 ml) was added to a hot solution of sodium butylate, obtained from metallic sodium (0.17 g: 0.007 g-atom) and absolute butanol (9 ml), and the mixture was boiled for 5 h. The solvent was distilled off, the residue was triturated with water, filtered off, washed with water, and dried. Compound X (1.74 g) was obtained.

2-Chloro-7-methoxy-10-methyl-3,4-diazaphenoxazine (IVa). A suspension of IIIa (4.35 g: 0.024 mole) in a solution of 85% potassium hydroxide (4.8 g: 0.072 mole) in water (4 ml) was boiled for 1 h, alcohol (16 ml) was added, and the mixture boiled 10 min further. 3,4,6-Trichloropyridazine (4.4 g: 0.024 mole) in alcohol (25 ml) was added gradually to the hot solution, the mixture was boiled for 5 h, and cooled. The solid was filtered off, washed with alcohol, with water, and dried. Compound IVa (3.9 g) was obtained. UV spectrum, λ_{max}, nm (log ε): 360 (3.99); 232 (4.56).

Compounds IVb, IVd-e were obtained similarly (see Table 2).

2-Chloro-7-ethoxy-10-γ-dimethylaminopropyl-3,4-diazaphenoxazine (IVc). 3-Dimethylamino-1-chloropropane hydrochloride (3.74 g: 0.025 mole) was added to a mixture of an alcoholic solution of sodium alcoholate [obtained from metallic sodium (1.15 g: 0.05 g-atom) and absolute alcohol (15 ml)] and 6-ethoxybenzoxazolone

TABLE 1. 7-Acetyl-2,10-Substituted 3,4-Diazaphenoxazines and Their Derivatives

Compound	Yield, %	Melting point, deg*	Found, % C	Found, % H	Found, % Cl	Found, % N	Empirical formula	Calculated, % C	Calculated, % H	Calculated, % Cl	Calculated, % N	IR-spectrum ν_{CO}, cm^{-1}
IIa	78	>320	56,66	3,64	12,47	15,13	$C_{13}H_{10}ClN_3O_2$	56,84	3,66	12,86	15,24	1680
IIb	66	210—13	58,65	5,55	10,17	16,17	$C_{17}H_{19}ClN_4O_2$	58,87	5,52	10,22	16,15	1690
	—	200 (dec.)	—	—	20,53	13,37	$C_{17}H_{19}ClN_4O_2 \cdot 1,5HCl \cdot H_2O$†	—	—	21,13	4,29	
IIc	47,8	235—7	63,85	6,12	—	20,86	$C_{18}H_{21}N_5O_2$	63,70	6,24	—	20,64	1680
	—	>300	—	—	16,10	15,88	$C_{18}H_{21}N_5O_2 \cdot 2HCl \cdot 1,5H_2O$‡	—	—	16,15	15,94	
IId	35,8	185—7	63,74	6,68	—	15,74	$C_{19}H_{24}N_4O_3$	64,02	6,79	—	15,72	1685
	—	>300	—	—	8,53	14,77	$C_{19}H_{24}N_4O_3 \cdot 2HCl$	—	—	9,02	14,26	
VIII	47,2	>300	53,40	3,93	12,03	19,10	$C_{13}H_{11}ClN_4O_2$	53,71	3,81	12,19	19,28	—
IX	46	230—1	56,05	5,56	9,68	19,11	$C_{17}H_{20}ClN_5O_2$	56,43	5,57	9,80	19,35	—
X	77	217—8	64,96	6,19	—	13,60	$C_{17}H_{19}N_3O_3$	65,20	6,12	—	13,43	1675

*Compounds (IIa, VIII, IX) were crystallized from diemthylformamide; (IIb, IIc) from ethanol; (IId) from ethyl acetate; (X) from benzene.

†Found, %: H_2O 4.51. Calculated, %: H_2O 4.29.

‡Found, %: H_2O 6.06. Calculated, %: H_2O 6.15.

TABLE 2. 2,7,10- and 2,8,10-Substituted 3,4-Diazaphenoxazines

Compound	Yield, %	Melting point, deg*	Found, % C	Found, % H	Found, % Cl	Found, % N	Empirical formula	Calculated, % C	Calculated, % H	Calculated, % Cl	Calculated, % N
IVa	61	203—4	—	—	13,02	15,59	$C_{12}H_{10}ClN_3O_2$	—	—	13,45	15,94
IVb	61,5	179—80	56,08	4,55	11,89	15,18	$C_{13}H_{12}ClN_3O_2$	56,22	4,36	12,40	15,13
IVc	32,2	166—7	57,96	5,92	9,94	15,97	$C_{17}H_{21}ClN_4O_2$	58,53	6,07	10,15	16,06
		238—40 (decomp.)	—	—	22,75	13,06	$C_{17}H_{21}ClN_4O_2 \cdot 1,75HCl \cdot H_2O$†	—	—	22,64	13,01
IVd	28	>320	47,24	2,22	27,58	16,39	$C_{10}H_5Cl_2N_3O$	47,25	1,98	27,92	16,55
IVe	59	239—40	48,88	2,61	26,16	15,64	$C_{11}H_7Cl_2N_3O$	49,28	2,63	26,45	15,68
IVf	45,6	213—14	52,96	4,91	20,78	16,52	$C_{15}H_{16}Cl_2N_4O$	53,11	4,75	20,91	16,52
		251—252 (decomp.)	—	—	34,44	13,73	$C_{15}H_{16}Cl_2N_4O \cdot 2HCl$	—	—	34,41	13,60
IVg	57,3	178—9	52,67	5,21	20,82	16,47	$C_{15}H_{16}Cl_2N_4O$	53,11	4,75	20,91	16,52
		223—4	43,78	3,35	12,25	16,88	$C_{15}H_{16}Cl_2N_4O \cdot C_6H_3N_3O_7$	44,38	3,37	12,48	17,25
		258—9 (decomp.)	—	—	34,11	13,62	$C_{15}H_{16}Cl_2N_4O \cdot 2HCl$	—	—	34,41	13,60
Va	84,5	195,5—6	62,38	6,56	—	21,04	$C_{17}H_{21}N_5O_2$	62,36	6,46	—	21,39
Vb	67,5	177—8	63,65	6,92	—	20,18	$C_{18}H_{23}N_5O_2$	63,32	6,79	—	20,51
		278—9 (decomp.)	—	—	16,13	15,87	$C_{18}H_{23}N_5O_2 \cdot 2HCl \cdot 1,5H_2O$‡	—	—	16,06	15,88
Vc	51,5	225—6	58,06	5,90	—	21,14	$C_{16}H_{18}ClN_5O$	57,91	5,47	—	21,11
		>300	—	—	25,17	16,07	$C_{16}H_{18}ClN_5O \cdot 2HCl \cdot 1,5H_2O$**	—	—	24,64	16,23
Vd	58	165—4,5	58,50	5,86	10,28	16,35	$C_{17}H_{21}ClN_4O_2$	58,53	6,07	10,16	16,06
		>320	44,18	5,55	31,25	12,14	$C_{17}H_{21}ClN_4O_2 \cdot 3HCl$	44,56	5,28	30,95	12,23
Ve	30	173—5	59,38	6,40	8,73	—	$C_{20}H_{27}ClN_6O$	59,62	6,75	8,80	—
		260 (decomp.)	—	—	28,91	15,72	$C_{20}H_{27}ClN_6O \cdot 3,25HCl$	—	—	28,85	16,12
Vf	76	167—8	59,76	6,96	8,69	16,63	$C_{21}H_{30}ClN_5O$	60,06	7,20	16,68	8,23
		240 (decomp.)	—	—	26,98	13,12	$C_{21}H_{30}ClN_5O \cdot 3HCl$	—	—	26,79	13,23

*Compounds IVa, IVb, Vc · 2HCl · $5H_2O$ were crystallized from methanol; IVc, IVg, IVg · $C_6H_3N_3O_7$, Vb, Vf from ethanol; IVd, IVf from dimethylformamide; IVe from chlorobenzene; Va, Bd from ethyl acetate; Ve from acetone.

†Found, %: H_2O 4.58. Calculated, %: H_2O 4.18.

‡Found, %: H_2O 5.77. Calculated, %: H_2O 6.12.

**Found, %: H_2O 5.97. Calculated, %: H_2O 6.26.

(4 g: 0.02 mole) in absolute alcohol (18 ml). The reaction mass was boiled for 4 h. After cooling, a solution of 85% potassium hydroxide (4 g: 0.06 mole) in water (3 ml) was added and the mixture boiled for 2 h. A solution of 3,4,6-trichloropyridazine (4.1 g: 0.022 mole) in alcohol (7 ml) was then gradually poured in and the mixture boiled a further 5 h. After cooling, the solid was filtered off, washed with alcohol, with water, and dried. Compound IVc (2.5 g) was obtained. UV spectrum, λ_{max}, nm (log ε): 365 (3.96); 232 (4.52). Compound IVf was obtained similarly.

The hydrochlorides of IVc, IVf were obtained under conditions analogous to those described for the preparation of IIb-d hydrochlorides.

3-Dimethylaminopropyl-5-chlorobenzoxazolone (IIIg). 3-Dimethylaminopropyl chloride hydrochloride (94%, 24.7 g: 0.156 mole) was added to a mixture of an alcoholic solution of sodium alcoholate [obtained from metallic sodium (6.7 g: 0.29 g-atom) and absolute alcohol (100 ml)] and 5-chlorobenzoxazolone (24.7 g: 0.147 mole) in absolute alcohol (130 ml). The mixture was boiled for 10 h. After distilling off the alcohol in vacuum water was added to the residue and the mixture was extracted with chloroform. The hydrochloric acid solution obtained after treatment of the chloroform solution with 10% hydrochloric acid was made alkaline and the oily substance which separated was extracted with chloroform. The chloroform solution was washed with water and dried with magnesium sulfate. After removal of chloroform the residue was recrystallized from hexane. Compound IIIg (18 g: 48.3%) was obtained. Repeated recrystallization gave IIIg of mp 50-51°. IR spectrum, cm^{-1}: ν_{CO} 1785.

Found, %: C 56.84; H 5.96; Cl 14.14; N 11.14. $C_{12}H_{15}ClN_2O_2$. Calculated, %: C 56.58; H 5.93; Cl 13.92; N 11.01.

The maleate of IIIg was obtained by mixing ethyl acetate solutions of IIIg base and maleic acid and had mp 160-161° (from ethyl acetate). Found, %: C 52.02; H 5.23; Cl 9.29; N 7.35. $C_{12}H_{15}ClN_2O \cdot C_4H_4O_4$. Calculated, %: C 51.80; H 5.18; Cl 9.56; N 7.57.

2,8-Dichloro-10-γ-dimethylaminopropyl-3,4-diazaphenoxazine (IVg). The alkylation of 5-chlorobenzoxazolone with 3-dimethylaminopropyl chloride was carried out under analogous conditions to those described for the preparation of IIIg and all components were used in the same amounts. After distilling off the alcohol in vacuum a solution of 85% potassium hydroxide (25 g: 0.445 mole) in water (26 ml) was added to the residue and the mixture was boiled for 50 min. Further reaction was conducted as described in the preparation of IVc. Compound IVg (28.6 g) was obtained. UV spectrum, λ_{max}, nm (log ε): 356 (4.00), 233 (4.50).

The hydrochloride of IVg was obtained by treatment of a suspension of (IVg) in boiling alcohol with concentrated hydrochloric acid (see Table 2).

2-(4-Methylpiperazin-1-yl)-7-methoxy-10-methyl-3,4-diazaphenoxazine (Va). A mixture of IVa (1.32 g: 0.005 mole) and N-methylpiperazine (2 g: 0.02 mole) in cyclohexanol (15 ml) was boiled for 5 h, cooled, the precipitate was filtered off, and cyclohexanol was distilled off from the solid with water. The residue was treated with an aqueous solution of sodium carbonate, filtered off, washed with water, and dried. Compound Va (1.4 g) was obtained. UV spectrum, λ_{max}, nm (log ε): 352 (3.98); 313 (3.93); 254 (4.53).

Compounds Vb, c, e were obtained analogously (see Table 2).

The hydrochloride of Vb was obtained under conditions analogous to those described for the preparation of (IVc) hydrochloride (see Table 2).

2-Diethylaminoethoxy-7-chloro-10-methyl-3,4-diazaphenoxazine (Vd). A mixture of metallic sodium (0.23 g: 0.01 g-atom) and diethylaminoethanol (2.1 g: 0.018 mole) in xylene (16 ml) was boiled until complete solution of sodium. The solution was cooled to 60-70°, IVe (2.7 g: 0.01 mole) was added, and the mixture boiled for 4 h. The solvent and excess diethylaminoethanol were distilled off, the residue was triturated with water, filtered off, washed with water, and dried. Compound Vd (2.03 g) was obtained.

Compound Vf was obtained similarly (see Table 2).

The hydrochlorides of Vd, f were obtained by treatment of chloroform solutions of Vd or Vf with a saturated solution of hydrogen chloride in absolute alcohol (see Table 2).

1,2,7-Trichloro-10-methyl-3,4-diazaphenoxazine (XI). a). Chlorine was passed for 3 h at 18-20° into a suspension of Ia (2 g: 0.008 mole) in acetic acid (20 ml) in the presence of a few crystals of iodine. About 11 g chlorine was absorbed. The undissolved solid was filtered off and the solution stored overnight. The precipitate was filtered off, washed with water, and dried. Compound XI (0.86 g: 33%) was obtained having mp 220-221° (from alcohol). PMR spectrum (in trifluoroacetic acid), δ, ppm: singlet 3.84 (NCH); 7.03 (9H), 7.08 (6H); quartet 7.25 (7H).

Found, %: C 43.37; H 2.12; Cl 34.94; N 13.83. $C_{11}H_6Cl_3N_3O$. Calculated, %: C 43.67; H 1.99; Cl 35.16; N 13.96.

b). Sulfuryl chloride (5 ml) was added to a suspension of IVe (5 g) in dimethylformamide (40 ml) at 25°. At the end of the addition of sulfuryl chloride heating of the reaction mass to 50° was observed, the green solid dissolved, and a yellow solid precipitated. The reaction mass was stirred at room temperature for 3 days and cooled. The precipitate was filtered off, washed with water, and dried. Compound XI (4.25 g: 76%) was obtained having mp 220-221° (from alcohol); a mixing test of this sample with a sample obtained by method *a* gave no depression of melting point.

2-Methyl-10-γ-dimethylaminopropyl-3,4-diazaphoxazine (XII). A mixture of 3-γ-dimethylaminopropylbenzoxazolone (8.9 g: 0.04 mole) and a solution of 85% potassium hydroxide (8 g: 0.12 mole) in water (5 ml) was boiled for 2 h, alcohol (20 ml) was added, the mixture boiled for 5 min, then a solution of 3,4-dichloro-6-methylpyridazine (6.5 g: 0.04 mole) in alcohol (28 ml) was gradually poured in, and the reaction mass was heated to boiling for a further 4.5 h. After cooling, the solid was filtered off and washed with alcohol. The combined alcoholic filtrate was evaporated, the residue triturated with ether, filtered off, dried, and recrystallized from a mixture of heptane and benzene. Compound XII (5.24 g: 46.5%) was obtained having mp 153-154°.

UV spectrum, λ_{max}, nm (log ε): 350 (4.16); 226 (4.47).

Found, %: C 67.43; H 7.28; N 19.69. $C_{16}H_{20}N_4O$. Calculated, %: C 67.57; H 7.12; N 19.70.

The maleate of XII was obtained in the same way as IIIg maleate and had mp 165° (decomposition).

Found, %: C 57.40; H 5.78; N 12.44. $C_{16}H_{20}N_4O \cdot C_4H_4O_4$. Calculated, %: C 57.63; H 5.70; N 12.22.

Pharmacology

Of the compounds synthesized IIb-d, IVb, IVf, IVg, Vd-f were studied pharmacologically. We have established previously [8, 9] that compounds close in structure (azafen, etc.) possess pharmacological properties characteristic of antidepressant preparations.

The synthesized compounds were studied from the same point of view.

The influence on the effects of amphetamine was investigated: a) on the hyperthermic action, b) on group toxicity, c) on stereotypy; the influence on the effects of reserpine: blepharoptosis and hypothermia; on catalepsy caused by triftazin; influence on the overall state of animals; the LD_{50} was determined (on subcutaneous administration).

The investigations carried out showed that IIb-d, IVb, i.e., compounds containing an acetyl or ethoxy group in position 7 of the diazaphenoxazine ring, possess some properties characteristic of antidepressants.

The most active compounds were IVf, IVg, Vc-f containing chlorine in position 7 or 8; however, the various compounds differed in activity.

Influence on the Effect of Amphetamine. a). In experiments on white mice, compounds IIb-d, IVb (25-50 mg/kg subcutaneously) intensified somewhat and extended the hyperthermic effect of amphetamine (10 mg/kg subcutaneously). Compounds IVf, IVg, Vc-f were more active in this respect.

Compounds IVf, Vd-f were close in action to azafen.

On subcutaneous administration at a dose of 25-50 mg/kg together with amphetamine the temperature of mice was 1.5-2° higher than on administration of amphetamine alone. These compounds act however in a less prolonged manner than azafen.

Compounds IVg, Vc were less active than IVf, Vd-f.

b). In the influence on the group toxicity of amphetamine (experiments on white mice) among compounds containing an acetyl or ethoxy group the most active were IIb and IVb. On simultaneous administration of these compounds (50 mg/kg subcutaneously) with amphetamine (7.5 mg/kg subcutaneously) death of animals was 50-70% against 40% on injection of amphetamine alone.

Compounds containing an atom of chlorine in place of an acetyl or ethoxy group strongly influenced the group toxicity of amphetamine. The most active in this respect were IVf, Vd-f also. Administered at a dose of 25 mg/kg subcutaneously together with amphetamine (at 7.5 mg/kg) they caused death of animals in 70-90% cases and were close to azafen in action. Compounds IVg, Vc were less active.

TABLE 3. Influence on Stereotypy Caused by Amphetamine*

Compounds	Duration of stereotypy, min
Amphetamine + 0.9% sodium chloride solution	51 (41÷61)
The same + IVf	105 (81÷129)
The same + IVg	128 (116÷140)
The same + Vc	89 (56÷122)
The same + Vd	106 (84÷128)
The same + Ve	90 (68÷112)
The same + Vf	104 (83÷125)
The same + azafen	117 (95÷139)

*Dose of investigated compounds was 25 mg/kg.

TABLE 4. Influence on Blepharoptosis Caused by Reserpine

Compounds	Degree of blepharoptosis, score
Reserpine + 0.9% sodium chloride solution	3,7±0,2
The same + IVf	3,2±0,3
The same + IVg	2,8±0,7
The same + IVc	2,4±0,5
The same + IVd	3,2±0.2
The same + IVe	2,8±0.4
The same + IVf	3,0±0,2
The same + azafen	2,3±0,3

c). Compounds IVf, IVg, Vc-f intensified stereotypy caused by amphetamine (4 mg/kg intraperitoneally) in rats (Table 3).

Influence on Reserpine Effects. Compounds IIb-d, IVg (25-50 mg/kg subcutaneously) did not show a significant influence on blepharoptosis and hypothermia in mice caused by reserpine (2 mg/kg intraperitoneally). Analogs containing a chlorine atom in position 7 or 8 (compounds IVf, IVg, Vc-f) were more active. Injected subcutaneously at a dose of 50 mg/kg they reduced blepharoptosis [10] (Table 4).

All compounds injected at a dose of 25 mg/kg failed to show a constant action on hypothermia caused by reserpine but with an increase of dose to 50-100 mg/kg an intensification of the hypothermic effect and blepharoptosis took place in a majority of experiments.

Influence on Catalepsy. Of the studied compounds containing an acetyl or ethoxy group in position 7 and a chlorine atom, only Vc (25 mg/kg subcutaneously) reduced the cataleptic effect of triftazin (6-8 mg/kg intraperitoneally) in rats by 25%. Azafen in these experiments was twice as active.

Overall Action and Toxicity. All compounds, starting with a dose of 100-200 mg/kg subcutaneously, caused a small locomotor stimulation and slowing down of respiration in mice. With an increase in dose (250-400 mg/kg) clonic-tonic spasm developed which usually began 10-15 min after administration. The LD_{50} (mg/kg) on subcutaneous administration to white mice was IIb 390, IIc 610, IId 720, IVb 300, IVf 360, IVg 320, Vc 720, Vd 340, Ve 655, and Vf 800.

Thus, the investigations carried out showed that the studied compounds possessed the elements of antidepressant activity. The most active among the investigated compounds proved to be IVf, IVg, and Vc-f containing chlorine in position 7 or 8. In their ability to strengthen the central effects of amphetamine the majority of these compounds were close to azafen. However, the hypothermic and autonomic actions of reserpine were reduced to a lesser extent by them than by azafen.

They possessed no anticataleptic properties.

All the compounds were superseded by azafen in the investigated aspects of antidepressant action.

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FURTHER STUDY OF THE TRANQUILLIZING ACTIVITY OF OXYLIDINE

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Oxylidine (3-benzoyloxyquinuclidine hydrochloride) has a tranquillizing action on the central nervous system [1-4] and has found use in medical practice [5, 6] in the treatment of patients with neurotic states and other diseases accompanied by excitement and tension.

In the last few years, the method of a conflict situation, which is considered one of the most specific for evaluating tranquillizing activity, has come into use. In view of this, we have investigated the action of oxylidine by this method. The study was performed in comparison with diazepam, which is one of the most active modern tranquillizers, and also with nitrazepam.

The investigation was performed on randomly-bred albino male rats weighing 150-200 g in an apparatus with the automatic recording of the behavior of the animals [7].

In order to create a state of high excitability of the drink center in the rats, the animals were previously maintained for 48 h on dry fodder and then at the same time of day for 3 days they were placed in a chamber where they could obtain water from a drinking trough for 5 min. On the day of the experiment, 5 sec after the beginning of drinking the apparatus was changed to automatic working conditions in which the taking of water by a rat caused the closure of an electric circuit (with a voltage of 80 V). The apparatus automatically recorded the following indices: 1) the number of times water was taken; 2) the reaction of the approach to the drinking bowl and departure; and 3) the magnitude of the total motor activity.

Observations on the behavior of the animals were performed for 20 min. In the investigatigations we used the following drugs: oxylidine, diazepam, and nitrazepam administered intraperitoneally in doses of 5, 25, 50, and 75; 5 and 10; and 10 mg/kg, respectively, and orally in doses of 20, 40, 80, and 160; 20; and 20 mg/kg, respectively, in the form of a starch suspension 1 h before the beginning of the experiment; the rats of a control group were given starch suspension by the same routes before the experiment.

Under the conditions of the conflict situation the administration of the oxylidine to the rats led to an increase in the number of times water was taken and in the number of approaches to the bowl, in spite of the fact that they then received painful electric discharges (see Table 1). The observed changes taken as a whole can

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