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

VII. SYNTHESIS OF DERIVATIVES OF 7-NITRO- AND 7-AMINO-3,4-DIAZAPHENOXAZINES

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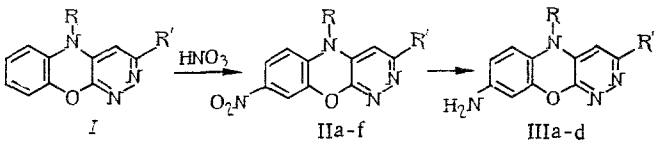
In order to elucidate the effect of a nitro and an amino group on the psychotropic activity of 3,4-diazaphenoxazine derivatives the synthesis of 2,10-disubstituted 7-nitro- and 7-amino-3,4-diazaphenoxazines has been effected by the scheme



I IIa-f IIIa-d

where a) $R = CH_3$, $R' = N\langle\rangle NCH_3$;
b) $R = (CH_3)_2N(CH_2)_3$; $R' = Cl$
c) $R = (CH_3)_2N(CH_2)_3$; $R' = H$
d) $R = CH_3$, $R' = OCH_2CH_2N(C_2H_5)_2$
e) $R = H$, $R' = Cl$
f) $R = CH_3$, $R' = Cl$

7-Nitro-2,10-disubstituted 3,4-diazaphenoxazines (IIa-f; see Table 1) were obtained by the nitration of 2,10-disubstituted 3,4-diazaphenoxazines (I) synthesized previously [1, 2].

The position of the nitro group was demonstrated in the following way.

6-Nitro- (IVa) and 3-methyl-6-nitrobenzoxazolones (IVb) were obtained from benzoxazolone by a known method [3, 4], (IVb) was converted by alkaline hydrolysis into the corresponding 4-nitro-o-aminophenol, which without isolation was condensed directly in alcoholic solution with 3,4,6-trichloropyridazine. The diazaphenoxazines (IIe) and (IIf) were obtained in that way. These compounds however have a high melting point which hampers comparison of them with (IIe) and (IIf) obtained by the direct nitration of (Ie) and (If). Consequently methylation of (IIe) was carried out and the (IIf) obtained was converted by condensation with N-methylpiperazine into (IIa) identical with the compound isolated on nitration of (Ia).

By the interaction of (IVa) with 3-dimethylaminopropyl chloride, 3-dimethylaminopropyl-6-nitrobenzoxazolone (V) was obtained which without isolation was converted into (IIb) by direct alkaline hydrolysis and subsequent condensation with 3,4,6-trichloropyridazine. On interaction of (IIb) with sodium alcoholate, (II)[$R = (CH_3)_2N(CH_2)_3$, $R^1 = C_2H_5O$], i.e., (VI), was obtained.

Attempts to reduce the nitro group in (IIa-f) with tin or stannous chloride in hydrochloric acid or in a mixture of hydrochloric acid and alcohol, with iron filings in acetic acid, and also by catalytic hydrogenation in the presence of Raney nickel catalyst proved to be unsuccessful. Amines (IIIa-d) were obtained by the reduction of (IIa-d) with hydra-

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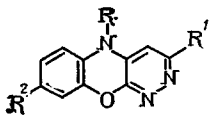
zine hydrate in the presence of Raney nickel catalyst. However reduction of (IIf) by this method led to a mixture of substances difficult to separate from which it was not possible to isolate any individual compound. The IR spectra of compounds (IIIa-d), containing an amino group in position 7, had an absorption band in the 3220-3400 cm^{-1} region characteristic of an NH group.

Methylation of amine (IIIb) was effected and the obtained 7-dimethylamino derivative was best isolated as the methiodide (VII).



VII: $R=(CH_3)_2N(CH_2)_3$, $R^1=Cl$, $R^2=N(CH_3)_2$

VIII: $R=CH_3$, $R^1=N\langle\rangle NCH_3$, $R^2=NHC(S)NHC_6H_5$

IX: $R=(CH_3)_2N(CH_2)_3$, $R^1=Cl$, $R^2=N=CH-\langle\rangle-OCH_3$

X: $R=(CH_3)_2N(CH_2)_3$, $R^1=R^2=H$

azaphene: $R=CH_3$, $R^1=N\langle\rangle NCH_3$, $R^2=H$

By the interaction of (IIIa) with phenyl isocyanate and (IIb) with anisaldehyde, compounds (VIII) and (IX) respectively were obtained.

PHARMACOLOGICAL INVESTIGATIONS

It has been established previously that a series of derivatives of 3,4-diazaphenoxazine proved to have antidepressant action. The greatest activity was detected in the dihydrochloride of 2-(4-methylpeperazinyl-1)-10-methyl-3,4-diazaphenoxazine (azaphene). Of the compounds synthesized for the first time (IIa-d), (IIIa, b), (VII), and (X) were studied pharmacologically. In connection with the fact that (IIa-d), (IIIa), and (IIIb) are analogs of azaphene and of other compounds studied previously having amino and nitro groups in position 7 the study was conducted in relation to properties characteristic of substances possessing neurotropic and antidepressant action. The activity of compounds was compared to the activity of azaphene in a series of experiments. Azaphene has been confirmed for use in medicinal practice as an antidepressive agent [5, 6].

In experiments on white mice and rats the influence of preparations was studied on general condition, the LD_{50} was determined (by subcutaneous injection), the effect of preparations was investigated on hyperthermia caused by amphetamine, stereotype and its group toxicity, on hypothermic action, on blepharoptosis caused by reserpine (2 mg/kg intraperitoneally), and on catalepsy caused by tetrabenazine and triftazine.

The effect of preparations was studied on arterial pressure and respiration and on the peripheral adreno- and cholino-reactive systems in experiments on cats under urethane anesthesia. It was established in rats and mice that not one of the compounds caused hypothermia, blepharoptosis, reduction of locomotion, or catalepsy, i.e., the phenomena characteristic for the action of neuroleptic substances.

However all the compounds studied except (VII) gave effects characteristic of substances possessing antidepressant activity. The most active of the compounds mentioned was (IIb) (conditionally named nitroxazine).

In experiments on mice a strengthening took place of the stimulating effect of amphetamine. On injecting (IIc) (25 mg/kg subcutaneously) together with amphetamine (10 mg/kg subcutaneously) the body temperature of mice was raised by 1.5-2° more than by an injection of amphetamine alone. Restoration of the initial temperature took place more slowly (over 1-2 h) than on injection of amphetamine. Compound (IIb) significantly enhanced the group toxicity of amphetamine. Thus amphetamine at a dose of 5 mg/kg injected subcutaneously caused the death of 10% mice, and 65% at a dose of 10 mg/kg. On simultaneous injection of amphetamine with (IIb) (25 mg/kg subcutaneously) death was caused in 85 and 95% cases. Under the same experimental conditions azaphene proved to have approximately the same action on injection of 50 mg/kg subcutaneously.

In experiments on rats, (IIb) injected subcutaneously at a dose of 10 mg/kg increased the duration of stereotypy caused by amphetamine (4 mg/kg subcutaneously) by 48%, azaphene by 41%.

Preparation (IIb) also reduced the hypothermic action of reserpine. Blepharoptosis in mice after injection of reserpine (2 mg/kg intraperitoneally) amounted to 3.2 ± 0.1 points after 2 h; on injection of reserpine after (IIb) (25 mg/kg subcutaneously) the size of the ptosis after 2 h was 2.4 ± 0.28 points. The preparation was more active than azaphene in

TABLE 1. Derivatives of 7-Nitro- and 7-Amino-3,4-diazaphenoxazines

№	Yield, %	Melting point, °C	Found, %				Empirical formula	Calculated, %			
			C	H	Cl	N		C	H	Cl	N
IIa	80,5	236—7*	55,91	5,22	—	24,20	$C_{16}H_{18}N_6O_3$	56,13	5,30	—	24,55
IIa·2HCl		>300	45,79	5,23	16,68	—	$C_{16}H_{18}N_6O_3 \cdot 2HCl$	46,27	4,85	17,07	—
IIb	86,0	199—200	51,33	4,56	10,04	19,89	$C_{15}H_{16}ClN_5O_3$	51,50	4,61	10,14	20,03
IIb·2HCl		275 (decomp.)	42,30	4,46	24,88	16,60	$C_{15}H_{16}ClN_5O_3 \cdot 2HCl$	42,62	4,29	25,16	16,57
IIc	88,3	173—4 ‡	57,30	5,54	—	21,90	$C_{15}H_{17}N_5O_3$	57,13	5,43	—	22,21
IIc·2HCl		258,5—60 (dec.)	—	—	17,84	17,12	$C_{10}H_{17}N_5O_3 \cdot 2HCl \cdot H_2O$	—	—	17,45	17,24
IId	96,5	169—70 †	57,12	5,89	—	19,22	$C_{17}H_{21}N_6O_4$	56,81	5,89	—	19,49
IId·2HCl		>300	47,31	5,29	15,75	16,16	$C_{17}H_{21}N_5O_4 \cdot 2HCl$	47,28	5,36	16,40	16,20
IIe	57,4	>300 *	45,20	2,00	13,19	21,20	$C_{10}H_5ClN_4O_3$	45,47	1,90	13,40	21,17
IIf	91,7	303* (decomp.)	47,44	2,43	12,97	19,83	$C_{11}H_7ClN_4O_3$	47,41	2,53	12,73	20,11
VI	37,2	225—6 **	56,55	6,09	—	19,89	$C_{17}H_{21}N_5O_4$	56,81	5,89	—	19,49
IIIa	80,3	244—6 **	61,40	6,18	—	26,63	$C_{16}H_{20}N_6O$	61,52	6,45	—	26,90
IIIa·HCl		330—2 (dec.)	—	—	22,37	—	$C_{16}H_{20}N_6O \cdot 2^1/_2HCl$	—	—	21,97	—
IIIb	76,5	200—1,5 ††	56,19	5,87	10,82	21,86	$C_{15}H_{18}ClN_5O$	56,33	5,67	11,08	21,90
IIIb·3HCl		>300	41,25	5,08	31,85	15,72	$C_{15}H_{18}ClN_5O \cdot 3HCl \cdot {}^1/_2H_2O$	41,11	5,06	32,36	15,99
IIIc	89,5	220—2**	63,25	6,75	—	24,48	$C_{15}H_{19}N_5O$	63,14	6,71	—	24,55
IIId	79,0	178—9‡	61,85	7,10	—	21,33	$C_{17}H_{23}N_5O_2$	61,98	7,04	—	21,26
VII		>300‡‡	43,96	5,27	—	14,16	$C_{18}H_{25}ClIN_5O$***	44,14	5,13	—	14,30
VIII		259—60*	62,13	5,31	—	21,87	$C_{23}H_{25}N_7OS$†††	61,86	5,64	—	21,96
IX		210—1*	62,99	5,72	—	16,08	$C_{23}H_{24}ClN_5O_2$	63,08	5,52	—	15,99
X	71,4	153—3 ‡	67,11	6,58	—	20,87	$C_{15}H_{18}N_4O$	66,64	5,68	—	20,72
Azaphene											

*From dimethylformamide (DMFA).
†From benzene.
‡From ethyl acetate.
**From ethanol.
††From butanol.
‡‡From DMFA + acetone.
***Found: I 25.99%. Calculated: I 25.91%.
†††Found: S 7.53%. Calculated: S 7.18%.

these experiments. In experiments on rats, (IIb) injected at a dose of 25 mg/kg subcutaneously reduced catalepsy caused by tetrabenazine and triftazine (5-6 mg/kg intraperitoneally) by 50-60%. Azaphene was also less active in these experiments.

Similarly to azaphene, compound (IIb) (5 mg/kg intravenously) increased hypothermia in rabbits caused by the injection of 5-hydroxytryptophan (40 mg/kg intraveneously) to the same extent. Somewhat lower activity in all the properties being studied was possessed by compound (IIIb) containing an amino group in place of an NO_2 group. Nitro and amino analogs of azaphene [compounds (IIa) and (IIIa)] and also compound (IId) were less active than compound (IIIb).

Compounds (IIc) and (X) exerted no marked action in the pharmalogical properties characteristic of antidepressants. All the compounds had no significant activity in peripheral adreno- and cholino-reactive systems and also did not display antihistamine action.

Compound (VII), a quaternary salt of a substituted 3,4-diazaphenoxazine, possessed curate-like activity.

In experiments on cats under urethane anesthesia recording contractions of the gastrocnemius muscle caused by stimulating the peripherally severed sciatic nerve with electrical impulses of square wave form, compound (VII) injected intravenously at 0.15 mg/kg reduced the amplitude of contractions by approximately 50%. In this type of activity compound (VII) was significantly inferior to d-tubocurarine. The effect of compound (VII) was enhanced by d-tubocurarine and was reduced by neostigmine, i.e., the preparation belongs to the group of substances with an antidepolarizing type of action. LD_{50} on subcutaneous injection were: (IIb) 340 mg/kg; (IIa) 460 mg/kg; (IId) 320 mg/kg; (IIc) 502 mg/kg; (IIIa) 465 mg/kg; (IIIb) 320 mg/kg; (VII) 1.85 mg/kg; (X) 500 mg/kg.

Thus in the characteristics of neuroleptic activity all the compounds studied were weakly active. The greatest antidepressant activity was possessed by compound (IIb), the dihydrochloride of 2-chloro-7-nitro-10-(3-dimethylaminopropyl)-3,4-diazaphenoxazine. In the majority of properties compound (IIb) surpassed azaphene. Compound (IIIc) containing an amino group in place of a nitro group at position 7 was somewhat less active. The introduction of amino and nitro groups into the azaphene molecule (compounds IIa and IIIa) led to a reduction of activity compared to compound (IIb) and azaphene. Compound (IId) was close in activity to (IIa) and (IIIa). Still lower activity in properties characteristic of antidepressant action was possessed by (IIc) which contained no chlorine atom in the 2 position (R^1 = H). Compound (VII) being a quaternary salt of a substituted 3,4-diazaphenoxazine possessed curare-like activity.

EXPERIMENTAL

IR spectra were taken on a UR-10 spectrophotometer in paraffin oil, and UV spectra on a Hitachi (Japan) instrument in alcohol.

Method A

2-Chloro-7-nitro-3,4-diazaphenoxazine (IIe). To a suspension of 2-chloro-3,4-diazaphenoxazine (13.2 g: 0.06 mole) in acetic acid (60 ml) was added dropwise with cooling over 15 min nitric acid (sp. gr. = 1.4) (5.6 ml: 0.084 mole) in acetic acid (60 ml) at a temperature not exceeding 30°. The mixture was left for 6 h at the same temperature. The reaction mixture was poured into ice water (260 ml), filtered, the solid was washed with water, dried, and recrystallized from dimethylformamide (DMFA). Compound (IIe) (9.1 g) was obtained. Compound (IIf) was prepared similarly (see Table 1).

2-Chloro-7-nitro-10-(3-dimethylaminopropyl)-3,4-diazaphenoxazine (IIb). a) Compound (I) [R = $(CH_2)_3N(CH_3)_2$, R^1 = Cl] (19.28 g: 0.06 mole) was dissolved at 60° in acetic acid (40 ml), the solution was cooled to room temperature, and a solution of nitric acid (sp. gr. = 1.4) (20 ml: 0.29 mole) in acetic acid (64 ml) was added dropwise. The mixture was left overnight at the same temperature. The reaction mass was poured into ice water (400 ml), the solid which separated was filtered off, washed with 10% alkali solution, and then with water. Compound (IIb) (18.75 g) was obtained as a yellow fine crystalline powder. UV spectrum: λ_{max}, nm (log ε): 401 (4.161); 264 (4.25).

b) Nitric acid (sp. gr. = 1.4) (154 ml: 2.23 mole) was added over 30 min at a temperature below 30° to (I) [R = $(CH_2)_3N(CH_3)_2$, R^1 = Cl] (170 g: 0.229 mole) and the mixture was kept for

2 h at room temperature. The solution was gradually poured into water (400 ml) at 0-5°, the nitrate salt which separated at this temperature was treated with 10% aqueous sodium hydroxide solution to pH 9.0-9.5. The reaction mixture was kept at 5-10° for 1 h, the solid was filtered off, and washed with water. Compound (IIb) (77 g: 96.5%) of mp 198-200° (from DMFA) was obtained. A mixing test with a sample of the same substance obtained by method a) gave no depression of melting point. Compounds (IIa), (IIc), and (IId) were prepared similarly (see Table 1).

Dihydrochloride of (IIb). Compound (IIb) (2.3 g) was dissolved in concentrated hydrochloric acid (10 ml) and the solution poured into absolute ethanol (40 ml). After 3-4 h the solid was filtered off, washed with alcohol, and dried over phosphorus pentoxide. Compound (IIb) (2.2 g) was obtained. The dihydrochloride of (IIa) was obtained similarly (see Table 1).

Dihydrochlorides of (IIc) and (IId) were obtained by treatment of solutions of the appropriate bases in absolute ethanol with a solution of hydrogen chloride in absolute ethanol (see Table 1).

Method B

2-Chloro-7-nitro-3,4-diazaphenoxazine (IIe). Compound (IVa) (5.8 g: 0.043 mole) was suspended in a solution of potassium hydroxide (6.3 g: 0.112 mole) in water (6.5 ml) and the mixture obtained was boiled for 5 h. Ethanol (49 ml) was added to the mixture, which was boiled for a further 30 min. A solution of 3,4,6-trichloropyridazine (6.2 g: 0.034 mole) in ethanol (16 ml) was gradually added to the hot solution, which was boiled for 5 h, cooled, the solid was filtered off, washed with ethanol, and with water. Compound (IIe) (4.11 g: 35.7%) was obtained which did not melt below 330°. Found, %: C 45.81; H 2.00; N 20.87; Cl 12.98. The IR spectra of (IId) obtained by methods A and B were identical.

2-Chloro-7-nitro-10-methyl-3,4-diazaphenoxazine (IIf). a) A suspension of (IVb) (5.85 g: 0.03 mole) in a solution of potassium hydroxide (5.1 g: 0.09 mole) in water (5 ml) was boiled for 30 min. Further treatment was carried out as described for (IIe). Compound (IIf) (6.37 g: 76%) was obtained having decomposition point 303° (from DMFA).

b) To a solution of (IIe) (2.7 g: 0.01 mole), ethanol (30 ml), water (1 ml), and potassium hydroxide (1 g: 0.015 mole) was added methyl iodide (2.4 g: 0.017 mole), and the solution was boiled for 4 h. The mixture was cooled, the solid was filtered off, washed with water, with alcohol, and dried. Compound (IIf) (1.4 g: 49.4%) was obtained having decomposition point 303°. Found, %: C 47.60; H 2.48; Cl 12.68; N 19.75.

2-Chloro-7-nitro-10-(3-dimethylaminopropyl)-3,4-diazaphenoxazine (IIb) [7]. To a mixture of an alcoholic solution of the alcoholate [obtained from metallic sodium (4.35 g: 0.1892 mole) and absolute ethanol (70 ml)] and (IVa) (13.44 g: 0.075 mole) in absolute ethanol (500 ml) was added 3-dimethylaminopropyl chloride hydrochloride (15 g: 0.095 mole), and the solution was boiled for $4^1/_2$ h. A solution of potassium hydroxide (14.42 g: 0.258 mole) in water (36 ml) was added and the solution was boiled for a further $2^1/_2$ h. A solution of 3,4,6-trichloropyridazine (17.35 g: 0.094 mole) in ethanol (30 ml) was carefully poured into the hot reaction mass, which was then boiled for 5 h. After cooling, the solid was filtered off, washed with alcohol, and with water giving (IIb) (6.61 g: 26.1%) of mp 198-199° (from ethanol); a sample of (IIb) mixed with (IIb) obtained by method A gave no depression of melting point.

2-(4-Methylpiperazinyl-1)-7-nitro-10-methyl-3,4-diazaphenoxazine (IIa). A mixture of (IIf) (5.57 g: 0.02 mole), N-methylpeperazine (4 g: 0.04 mole), and DMFA (35 ml) was boiled for 5 h. After cooling, the solid was filtered off, washed with DMFA, with ethanol, treated with a saturated solution of sodium bicarbonate, filtered, washed with water, and dried. Compound (IIa) (4.7 g: 68%) was obtained having mp 233-234° (from DMFA), a sample of (IIa) mixed with (IIa) obtained by method A gave no depression of melting point.

2-Ethoxy-7-nitro-10-(3-dimethylaminopropyl)-3,4-diazaphenoxazine (VI). A mixture of (IIb) (10.5 g: 0.03 mole) and an alcoholic solution of alcoholate [obtained from metallic sodium (0.71 g: 0.031 mole) and absolute ethanol (40 ml)] was heated at 150° for 10 h. After cooling, the solid was filtered off, washed with alcohol, with water, and dried. Compound (VI) (4 g) was obtained.

2-(4-Methylpiperazinyl-1)-7-amino-10-methyl-3,4-diazaphenoxazine (IIIa). To a boiling mixture of (IIa) (9.25 g: 0.027 mole) in methanol (230 ml) and Raney nickel catalyst paste (7 g) was added gradually hydrazine hydrate (9.25 ml) in methanol (9 ml). The mixture was boiled for 4 h, methanol was added to dissolve the precipitate which had separated from the reaction mixture, and the catalyst was filtered off. The methanolic solution was cooled, the crystals which separated were filtered off, washed with methanol, and dried. Compound (IIIa) (6.77 g) was obtained. Compounds (IIIb-d) were obtained similarly (see Table 1).

Hydrochlorides of (IIIa-b) were obtained by treating solutions of (IIIa) or (IIIb) in absolute ethanol with concentrated hydrochloric acid (see Table 1).

2-Chloro-7-dimethylamino-10-(3-dimethylaminopropyl)3,4-diazaphenoxazine Methiodide (VII). A mixture of (IIIb) (5 g), formic acid (50 ml), and formalin (50 ml) was heated on a boiling water bath for 25 h, the solvent was distilled off in vacuum, the oily residue was treated with ethanol, filtered, and the filtrate evaporated. The residue was dissolved in water and made alkaline with aqueous sodium carbonate solution, the viscous substance which separated was extracted with chloroform, and the solution dried with magnesium sulfate. The chloroform was distilled off, absolute ethanol (17 ml) and methyl iodide (5 ml) were added to the residue, and the mixture was boiled for 2 h. After cooling, the dark yellow colored solid was filtered off, washed with absolute ethanol, and dried. Compound (VII) (2 g) was obtained (see Table 1).

N-[2-(4-Methylpiperazinyl-1)-10-methyl-3,4-diazaphenoxazinyl-7]-N'-phenylthiourea (VIII). A mixture of (IIIa) (1 g) and phenyl isothiocyanate (5 ml) in benzene (10 ml) was boiled for 5 h, cooled, the solid was filtered off, washed with benzene, and dried. Compound (VIII) (1.36 g) was obtained (see Table 1).

2-Chloro-7-anisylidenamino-10-(3-dimethylaminopropyl)-3,4-diazaphenoxazine (IX). A solution of (IIIb) (0.2 g), anisaldehyde (0.3 g), and concentrated hydrochloric acid (1 drop) in ethanol (20 ml) was boiled for 4 h, cooled, the solid was filtered off, washed with alcohol, and was recrystallized from DMFA. Compound (IX) (0.2 g) was obtained (see Table 1).

10-(3-Dimethylaminopropyl)-3,4-diazaphenoxazine (X). A mixture of (I) [R = $(CH_3)_2N(CH_2)_3$, R^1 = Cl] (30.5 g: 0.1 mole), 5% palladium on charcoal (9.4 g), 98% potassium hydroxide (4.1 g), and ethanol (450 ml) was hydrogenated in an autoclave at 50° and 20 atm until absorption of hydrogen finished. The catalyst was filtered off, the filtrate was evaporated, the residue was rubbed with water, filtered, washed with water, and dried. Compound (X) (19.2 g) was obtained (see Table 1).

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