SYNTHESIS OF 5H-PYRIDAZO[3,4-b]-1,4-BENZOXAZINES (3,4-DIAZAPHENOXAZINES)

VI. SYNTHESIS AND PHARMACOLOGICAL STUDY OF 3,4-DIAZAPHENOXAZINE-7-SULFONIC ACID DERIVATIVES

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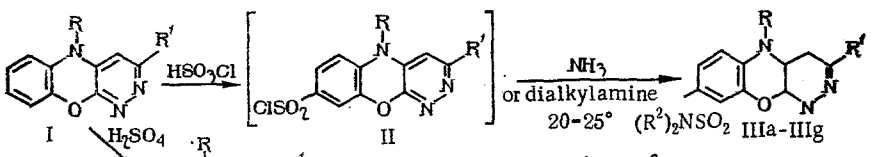
In continuation of our work on the preparation of 3,4-diazaphenoxazine derivatives to further the search for substances with psychotropic activity, we have synthesized 2,10-disubstituted 3,4-diazaphenoxazine-7-sulfonic acids and a number of derivatives thereof according to the scheme:



IIIa: R=$(CH_2)_2N(CH_3)_2$; R′=Cl, R^2=H
IIIb: R=$(CH_2)_2N(CH_3)_2$; R′=Cl, $R^2=C_2H_5$
IIIc: R=CH_3, R′=Cl, R^2=H
IIId: R=CH_3, R′=Cl, $R^2=C_4H_9$
IIIe: R=CH_3, R′=$OCH_2CH_2N(C_2H_5)_2$, R^2=H
IIIf: R=CH_3, R′=N⟨⟩NCH_3, R^2=H
IIIg: R=CH_3, R′=N⟨⟩NCH_3, $R^2=C_4H_9$
IVa: R=CH_3, R′=N⟨⟩NCH_3
IVb: R=CH_3, R′=Cl

Chlorosulfonation of 2,10-disubstituted 3,4-diazaphenoxazines (I), which were synthesized by a method which we developed in [1], gave the 7-sulfonyl chlorides of I (II), which were treated, without being isolated, with ammonia or dialkylamines to give the 7-sulfonamides or 7-N,N-dialkylsulfonamides of the 2,10-disubstituted 3,4-diazaphenoxazines (IIIa-IIIg; see Table 1). To demonstrate the position of the substituent in the benzene ring, we performed the following back syntheses:

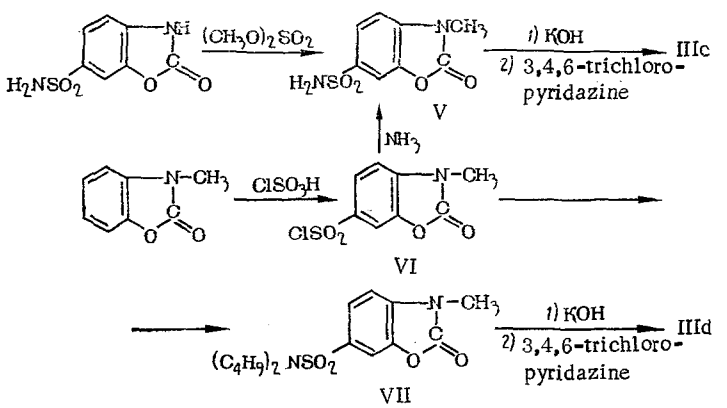


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TABLE 1. 3,4-Diazaphenoxazine-7-sulfonic Acid Derivatives

Compound	Yield (%)	Melting point (deg)	Found (%)					Empirical formula	Calculated (%)				
			C	H	Cl	N	S		C	H	Cl	N	S
IIIa	47,5	226–227,5*	47,00	4,54	8,99	18,06	8,18	$C_{15}H_{18}ClN_5O_3S$	46,93	4,73	9,24	18,25	8,36
IIIa dihydrochloride	—	295 (decomp.)	—	—	23,16	—	7,18	$C_{15}H_{18}ClN_5O_3S \cdot 2HCl$	—	—	23,29	—	7,02
IIIb	53,5	169,5–70,5†	51,65	5,82	7,80	15,53	7,34	$C_{19}H_{26}ClN_5O_3S$	51,87	5,98	8,06	15,94	7,29
IIIb dihydrochloride	—	216 (decomp.)	—	—	—	13,43	5,90	$C_{19}H_{26}ClN_5O_3S \cdot 2HCl$	—	—	—	13,66	6,25
IIIc	37	Infusible up to 320*	42,01	3,03	11,13	—	10,06	$C_{11}H_9ClN_4O_3S$	—	—	11,34	—	10,26
IIId	36	256–7 ‡	53,63	6,13	8,31	13,31	7,39	$C_{19}H_{25}ClN_4O_3S$	53,70	5,93	8,34	13,19	7,54
IIIe	44	318 (decomp.)*	52,13	6,13	—	18,00	8,35	$C_{17}H_{23}N_5O_4S$	51,89	5,89	—	17,80	8,15
IIIe dihydrochloride	—	Infusible up to 320	—	—	15,11	14,69	—	$C_{17}H_{23}N_5O_4S \cdot 2HCl$	—	—	15,20	15,02	—
IIIf	46	298–9*	51,08	5,39	—	22,50	8,66	$C_{16}H_{20}N_6O_3S$	51,05	5,36	—	22,33	8,52
IIIf dihydrochloride	—	308 (decomp.)	—	—	15,51	—	7,03	$C_{16}H_{20}N_6O_3S \cdot 2HCl$	—	—	15,77	—	7,14
IIIg	62	228–230 **	59,45	7,29	—	17,23	6,61	$C_{24}H_{36}N_6O_3S$	59,00	7,43	—	17,20	6,56
IVa	70,8	Infusible up to 350 ††	51,22	5,38	—	—	8,64	$C_{16}H_{19}N_5O_4S$	50,91	6,07	—	—	8,50
IVa sulfate	—	—	—	—	—	15,96	11,08	$C_{16}H_{19}N_5O_4 \cdot 1/2H_2SO_4$	—	—	—	16,12	11,28
IVb	—	—	36,94	2,10	9,95	11,91	8,45	$C_{11}H_8ClN_3O_4S$	37,55	2,00	10,07	11,95	9,10

*From DMF.
†From ethyl acetate.
‡From acetic acid.
**From ethanol.
††From water.

Two methods were used to prepare 3-methyl-6-sulfonamidobenzoxazolone (V), viz., methylation of 6-sulfonamidobenzoxazolone [2] and chlorosulfonation of 3-methylbenzoxazolone followed by treatment of the resulting 3-methyl-6-chlorosulfonylbenzoxazolone (VI) with ammonia; 3-methyl-6-dibutylsulfonamidobenzoxazolone (VII) was prepared by reacting VI with dibutylamine.

The N-methylamino-2-hydroxy-4-sulfonamido- and 4-N,N-dibutylsulfonamidobenzenes obtained by alkaline hydrolysis of V and VIII were converted, without being isolated, into IIIc and IIId by condensation with 3,4,6-trichloropyridazine. In view of the high melting points of IIIc and IIId, they were converted into IIIf and IIIg, respectively, to facilitate identification; the IR and UV spectra of the latter were identical to those of IIIf and IIIg obtained according to the first scheme.

Compounds IIIa, IIIc, IIIe, and IIIf, all of which contain a sulfonamido group in the 7 position, are distinguished by a characteristic absorption band in the 3230-3320 cm^{-1} region.

When I is heated with sulfuric acid, the corresponding sulfonic acids are obtained (IVa and IVb; see Table 1). Since there is no reason to suppose that the sulfonic acid group would be attached in a different position from that of the chlorosulfonyl group, we considered it possible to assign them a 2,10-disubstituted 3,4-diazaphenoxazine-7-sulfonic acid structure.

Of the newly synthesized compounds, IIIf and IVa are analogs of azaphene [3]; they both contain an N-methylpiperazine residue in the 2 position (R'), but differ in their additional substituent in the 7 position (SO_2NH_2 or SO_3H).

Compound IIIb contains a dimethylaminopropyl chain as the substituent attached to the nitrogen atom in the 10 position; this substituent is characteristic of a number of tricyclic psychotropic agents such as the neuroleptic aminazine and the antidepressant imizine (imipramine).

In view of what has been said, a number of the compounds obtained (IIIa, IIIb, IIIe, IIIf, and IVa) were tested pharmacologically for properties characteristic of neuroleptic and antidepressant agents. The tests were carried out on white mice and rats. In the case of the mice, we studied the effect of the compounds on their general condition, determined the LD_{50} (subcutaneous), and investigated their effect on hypothermia and blepharoptosis induced by reserpine (2 mg/kg, i.p.), on the hyperthermic action of amphetamine (10 mg/kg, s.c.), and on the "group toxicity" of amphetamine. In the case of the rats, we studied the effect of the compounds on catalepsy induced by tryptazine (6 mg/kg, i.p.).

It was found that none of the compounds investigated gave effects characteristic of neuroleptic agents when administered subcutaneously at a dose of 25 to 100 mg/kg; no hypothermia, blepharoptosis, decrease in locomotion, or catalepsy was observed in the mice.

Some of the compounds did, however, give effects characteristic of antidepressant action.

When administered subcutaneously in doses of 25 and 50 mg/kg, compounds IIIe, IIIf, and IVa prolonged the hyperthermic action of amphetamine. In a control group of mice, amphetamine (10 mg/kg, s.c.) produced a maximum increase in body temperature of 1.5 ± 0.3°, and the original temperature was restored in 90-120 min. After administration of the above compounds, the temperature of the mice receiving amphetamine also increased by up to 2°, but the original temperature was restored in 2-3 h.

In analogous experiments, amphetamine produced a temperature increase of 2-3° in mice receiving azaphene (25 mg/kg, s.c.), and the original temperature was restored in 3-4 h.

At a dose of 100 mg/kg (s.c.), compounds IIIe and IIIf potentiated the group toxicity of amphetamine. Thus, amphetamine at a dose of 10 mg/kg (s.c.) caused the death of 30% of the mice, while simultaneous administration of amphetamine and compounds IIIe and IIIf led to the death of 80-90% of the animals. Compound IVa was less active in these experiments. Administration of the compounds at a dose of 100 mg/kg caused the death of 60% of the animals. Compounds IIIe and IIIf also diminished the depressant effect of reserpine. Blepharoptosis in mice was reduced by 30-35% under the influence of these compounds (25-50 mg/kg, s.c.). Compound IVa was of low activity. Compounds IIIe, IIIf, and IVa had no appreciable effect on the hypothermic action of reserpine or tryptazine-induced catalepsy. Compounds IIIa and IIIb had no pronounced pharmacological properties characteristic of antidepressants.

The subcutaneous LD_{50} was 720 mg/kg for IIIa, 600 mg/kg for IIIb, 420 mg/kg for IIIe, 775 mg/kg for IIIf, and 730 mg/kg for IVa.

The subcutaneous LD_{50} of azaphene is 390 mg/kg.

Thus, all the compounds studied are of low activity according to their neuroleptic characteristics. Compound IIIb, which is the closest to aminazine in the elements of its chemical structure (tricyclic nucleus, dialkylaminopropyl chain, and a Cl atom in the 2 position), has none of the elements of neurotropic activity. This compound is also inactive according to its antidepressant characteristics. The elements of pharmacological activity characteristic of antidepressants are displayed by compounds IIIe and IIIf, and to a lesser extent by IVa, but IIIe and IIIf are considerably less active than azaphene. It should be pointed out that according to our data, the compound analogous to IIIe but not containing an SO_2NH_2 group in the 7 position possesses pronounced antidepressant activity.

Consequently, the introduction of a sulfonamide group into the molecule of diazaphenoxazine derivatives weakens their antidepressant activity, and the introduction of a sulfonic acid group leads to the loss of this activity.

EXPERIMENTAL

The IR spectra were recorded with a UR-10 spectrophotometer in mineral oil, and the UV spectra were recorded with a Hitachi instrument.

2-(4-Methyl-1-piperazinyl)-7-sulfonamido-10-methyl-3,4-diazaphenoxazine (IIIf). A. A 3-g (10 mmole) portion of 2-(4-methyl-1-piperazinyl)-10-methyl-3,4-diazaphenoxazine was added gradually to 12.2 g (100 mmole) of 95.5% chlorosulfonic acid while stirring at 8-10°. The mixture was stirred at 20-25° for 30 min and at 60° for 2 h, and then poured into a cooled (−8°) 24% aqueous ammonia solution (about 50 ml). After a few hours, the precipitate was filtered off, washed with water, and dried to give 1.74 g of IIIf. IR spectrum, cm^{-1}: 3280.

Compounds IIIa-IIIe and IIIg were prepared analogously (see Table 1).

IIIf Dihydrochloride. A solution of 0.8 g of IIIf in 6 ml of concentrated hydrochloric acid was poured into 30 ml of absolute ethanol. After a few hours, the precipitate was filtered off and washed with absolute ethanol and ethyl acetate, to give 0.8 g of IIIf•2HCl. UV spectrum (water), λ_{max}, nm (log ε): 355 (4.13), 257 (4.56).

The dihydrochlorides of IIIa and IIIe were prepared analogously (see Table 1).

IIIb Dihydrochloride. This was prepared by treating a solution of IIIb in ethyl acetate with a solution of hydrogen chloride in absolute ethanol.

B. A mixture of 2.38 g (7.6 mmole) of IIIc and 1.52 g (15.2 mmole) of N-methylpiperazine in 20 ml of dimethylformamide was boiled for 18 h, cooled, and the crystallized material filtered off, washed with ether, and triturated with an aqueous sodium bicarbonate solution. The precipitate was filtered off, washed with water, and dried, to give 1.74 g (60.5%) of IIIf, mp 301-302° (decomp.).

2-Chloro-10-methyl-7-sulfonamido-3,4-diazaphenoxazine (IIIc). A mixture of 6 g (26.3 mmole) of V and a solution of 7 g (105 mmole) of 85% potassium hydroxide in 8 ml water was boiled for 3 h, treated with 70 ml alcohol, stirred for 15 min while boiling, and gradually treated with a solution of 6.65 g (36.3 mmole) of 3,4,6-trichloropyridazine in 15 ml alcohol. The mixture was boiled for 5 h, cooled, and the precipitate filtered off, washed with alcohol and water, and dried to give 5.88 g (71.5%) of IIIc. This compound was infusible up to 320°. IR spectrum, cm^{-1}: 3250, 3330.

2-(4-Methyl-1-piperazinyl)-7-(N,N-dibutylsulfonamido)-3,4-diazaphenoxazine (IIIg). A mixture of 1.92 g (4.53 mmole) of IIId, 2 ml of N-methylpiperazine, and 8 ml of dimethylformamide was boiled for 14 h, cooled, and the precipitate filtered off, washed with ether, and triturated with a 4% aqueous solution of sodium hydroxide. The precipitate was filtered off, washed with water, and dried to give 1.32 g (62%) of IIIg, mp 228-228° (from alcohol). The mixed melting point with IIIg obtained according to the first scheme showed no depression. UV spectrum (alcohol), λ_{max}, nm (log ε): 336 (4.08), 265 (4.49).

2-Chloro-7-(N,N-dibutylsulfonamido)-10-methyl-3,4-diazaphenoxazine (IIId). A mixture of 6.8 g (20 mmole) of VII and a solution of 4 g of 85% potassium hydroxide in 8 ml water was boiled for 6 h, cooled, treated with 50 ml alcohol, heated to boiling, and gradually treated

with a solution of 5.5 g (30 mmole) of 3,4,6-trichloropyridazine in 10 ml alcohol. The mixture was boiled for 7 h, cooled, and the precipitate filtered off, washed with water, and dried to give 6 g (70.7%) of IIId, mp 257-258° (from glacial CH_3COOH). The mixed melting point with IIId obtained according to the first scheme showed no depression.

3-Methyl-6-sulfonamidobenzoxazolone (V). A. A solution of 0.84 g (20 mmole) of 95% sodium hydroxide, 11 ml of water and 1.8 g (8.4 mmole) of 6-sulfonamidobenzoxazolone was treated dropwise at 25° with 1.26 g (10 mmole) of dimethyl sulfate. The reaction mixture was stirred for 1 h at room temperature, and the precipitate filtered off, washed with water, and recrystallized from water to give 1 g (52%) of V, mp 194-195°. IR spectrum, cm^{-1}: $\nu_{SO_2NH_2}$ 3270, 3360, ν_{CO} 1775. UV spectrum (water), λ_{max}, nm (log ε): 278 (3.88), 249 (4.16). Found, %: C 42.00; H 3.65; N 12.27; S 14.27. $C_8H_8N_2O_4S$. Calculated, %: C 42.01; H 3.54; N 12.28; S 14.05.

B. A solution of 15 g (60 mmole) of VI in 45 ml of 15% alcoholic ammonia solution was boiled for 2.5 h, cooled, and the precipitate filtered off and washed with water to give 12 g (86.7%) of V, mp 193-195°. This did not give mixed melting point depression with V obtained by method A.

3-Methyl-6-chlorosulfonylbenzoxazolone (VI). A 22.35 g (150 mmole) portion of 3-methylbenzoxazolone was gradually added at 10-15° to 52 ml of chlorosulfonic acid. The mixture was stirred at room temperature for 1 h, heated at 60-70° for 2 h, poured onto ice, and the precipitate filtered off and dissolved in chloroform. Removal of the solvent gave 25 g (67.5%), of VI, mp 138-139° (from chloroform). UV spectrum (alcohol), λ_{max}, nm (log ε): 286 (4.02), 254 (3.91). Found, %: C 39.16; H 2.68; N 5.57; Cl 14.60; S 13.06. $C_8H_6ClNO_4S$. Calculated, %: C 38.80; H 2.45; N 5.66; Cl 14.32; S 12.95.

3-Methyl-6-(N,N-dibutylsulfonamido)benzoxazolone (VII). A suspension of 8 g (32 mmole) of VI in 50 ml benzene was gradually treated with 10 g (77 mmole) of dibutylamine. The mixture was boiled for 3.5 h, cooled, and the precipitate filtered off, washed with benzene, and the combined benzene solutions evaporated. The residue was triturated with petroleum ether, filtered off, washed with cold alcohol and water, and dried to give 10 g (91%) of VII, mp 107-108° (from alcohol). IR spectrum, cm^{-1}: 1785. Found, %: C 56.54; H 7.05; N 8.38; S 9.57. $C_{16}H_{24}N_2O_4S$. Calculated, %: C 56.45; H 7.11; N 8.23; S 9.42.

2-(4-Methyl-1-piperazinyl)-10-methyl-3,4-diazaphenoxazine-7-sulfonic Acid (IVa). A mixture of 10 g of 2-(4-methyl-1-piperazinyl)-10-methyl-3,4-diazaphenoxazine and 100 ml of concentrated sulfuric acid was heated on a water bath for 4 days, and then cooled and poured onto ice. After 5 h, the precipitate was filtered off, washed with a small amount of ice water, and dried to give 9 g of IVa. UV spectrum (water), λ_{max}, nm (log ε): 342 (3.95), 251 (4.13). The sulfate of IVa was isolated by treating the filtrate with acetone.

Compound IVb (see Table 1) was prepared analogously but was isolated in the form of its potassium salt, which was purified by recrystallization from 50% aqueous ethanol.

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