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

IV.* SYNTHESIS OF 2- AND 2,10-SUBSTITUTED 3,4-DIAZAPHENOXAZINES

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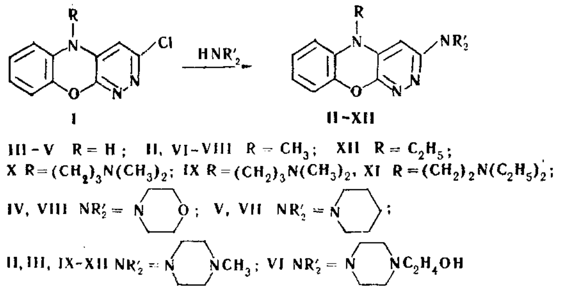
A number of 2,10-substituted 3,4-diazaphenoxazines were obtained by the condensation of 2-chloro-3,4-diazaphenoxazine and its 10-substituted derivatives with cyclic amines.

We have accomplished the synthesis of a number of 2-substituted 3,4-diazapheoxazines (III-V) and 2,10-disubstituted 3,4-diazaphenoxazines (II, VI-XII). One of the compounds obtained – 2-(4-methyl-1-piperazinyl)-10-methyl-3,4-diazaphenoxazine (II) dihydrochloride – has been authorized for wide application in medical practice as an antidepressant under the name "azafen." Compound II was obtained by the reaction of N-methylpiperazine with 2-chloro-10-methyl-3,4-diazaphenoxazine (I, R = CH_3), the synthesis of which is described in our previous paper [1].



The condensation of I (R = CH_3) with N-methylpiperazine was carried out by refluxing in both cyclohexanol and dimethylformamide. Substance XII was also obtained by the reaction of III with C_2H_5I. The UV spectra of III-V proved to be similar to the UV spectrum of II, but differed from the UV spectra of I.

Compounds III-XII are inferior to II in pharmacological activity.

EXPERIMENTAL

2-(4-Methyl-1-piperazinyl)-10-methyl-3,4-diazaphenoxazine (II). A) A mixture of 16.4 g (70 mmole) of I (R = CH_3) and 24.6 g (246 mmole) of N-methylpiperazine in 115 ml of cyclohexanol was refluxed for 6 h with stirring, water was added, and the cyclohexanol was removed by azeotropic distillation with the water. The residue was dissolved in 175 ml of water, and the solution was treated with charcoal and filtered. A total of 11.7 g (227 mmole) of 95% NaOH was added to the filtrate at no higher than 10 deg, and the mixture was allowed to stand at 0-5 deg for 12 h for crystallization. The precipitate was filtered, washed with water, and dried to give 19.4 g (93%) of II with mp 194-195 deg (from ethanol). UV spectrum (in alcohol), λ_{max}, nm (log ε): 252 (4.50). Found: C 64.7; H 6.3; N 23%. $C_{16}H_9N_5O$. Calculated: C 64.5; H 6.4; N 23.5%.

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*See [1] for communication III.

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TABLE 1. Azafen Analogs

Compound	mp (crystallization solvent)	Empirical formula	Found, %			Calc., %			Yield, %
			C	H	N	C	H	N	
IV	340 (dimethylformamide)	$C_{14}H_{14}N_4O_2$	62,7	5,3	20,9	62,2	5,2	20,7	91,5
V	321—323 (dec., dimethylformamide)	$C_{15}H_{16}N_4O$	67,5	6,0	20,7	67,1	6,0	20,9	96,4
V · HCl	350 (ethanol-water (3 : 2)	$C_{15}H_{16}N_4O \cdot HCl$	—	—	18,4	—	—	18,4	—
VI	215—216 (ethanol)	$C_{17}H_{21}N_5O_2$	62,1	6,5	21,5	62,4	6,5	21,4	72
VI · 2HCl	289—290 (dec., ethanol—water (3 : 2)	$C_{17}H_{21}N_5O_2 \cdot 2HCl$	50,9	5,8	—	51,0	5,8	—	—
VII	172—173,5 (ethyl acetate	$C_{16}H_{18}N_4O$	67,8	6,4	19,6	68,1	6,4	19,9	71,1
VII · 2HCl	300 (dec.)	$C_{16}H_{18}N_4O \cdot 2HCl$	—	—	17,7	—	—	17,6	—
VIII	238—239,5 (dec., dimethylformamide)	$C_{15}H_{16}N_4O$	63,0	5,6	19,7	63,4	5,7	19,7	84,2
IX	105—106 (acetone)	$C_{20}H_{28}N_6O$	65,3	7,8	22,3	65,2	7,7	22,8	42
IX · 3HCl	252 (dec.)	$C_{20}H_{28}N_6O \cdot 3HCl \cdot H_2O$	—	H_2O—3,8	16,4	—	H_2O—3,6	16,9	
X	161—162 (acetone)	$C_{19}H_{26}N_6O$	64,5	7,5	23,4	64,4	7,4	23,7	26
XI	86—89 (acetone)	$C_{21}H_{30}N_6O$	65,9	8,0	21,9	65,9	7,9	22,0	45
XII	177—178 (ethanol		—	—	22,4	—	—	22,5	—
XII · 2HCl	298—300 (dec.)	$C_{17}H_{21}N_5O \cdot 2HCl$	52,8	5,9	—	53,1	6,0	—	25,8

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* The composition of the hydrochlorides of V, VII, IX, and XII was also confirmed by determining the percentage of chlorine.

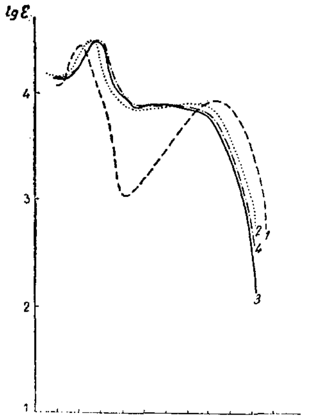

Fig. 1. UV spectra (in alcohol): 1) 2-chloro-10-methyl-3,4-diazaphenoxazine (I); 2) 2-(4-methyl-1-piperazinyl)-3,4-diazaphenoxazine (II); 3) 2-piperidino-3,4-diazaphenoxazine (V); 4) 2-piperidino-10-methyl-3,4-diazaphenoxazine (VII).

A total of 14.9 ml (158 mmole) of concentrated HCl was added with stirring at 70 deg to a solution of 23.7 g (79.5 mmole) of II in 165 ml of alcohol, and the mixture was allowed to stand at 10 deg for 12 h for crystallization. The precipitate was filtered, washed with alcohol, and dried at 70-80 deg to give 30 g (97%) of the dihydrochloride of II as a crystalline, lemon-yellow powder with mp 315 deg (dec.). Found: Cl 18.9; N 18.8%. $C_{16}H_{19}N_5O \cdot 2HCl$. Calculated: Cl 19.1; N 18.9%.

Compounds VII-XII were similarly obtained (Table 1).

B) A mixture of 163.8 g (0.7 mole) of I, 354 ml (1.4 mole) of a 48% aqueous solution of N-methylpiperazine dihydrochloride, and 1170 ml of cyclohexanol was refluxed with stirring until water separation ceased and then for another 5 h. The reaction mass was cooled to 70 deg, and the yellow, crystalline precipitate was filtered, washed with ethyl acetate, dried, and dissolved in 1700 ml of water. Activated charcoal (20 g) was added to the solution, and the mixture was heated to 70 deg, filtered, and cooled to 10 deg. The addition of 110 g (2.62 mole) of 95% NaOH yielded 194 g (93%) of II with mp 192-194 deg.

2-(4-Methyl-1-piperazinyl)-3,4-diazaphenoxazine (III). A mixture of 8.8 g (40 mmole) of 2-chloro-3,4-diazaphenoxazine (I, R = H) and 26 ml (235 mmole) of N-methylpiperazine in 40 ml of cyclohexanol was refluxed for 20 h. Water (250 ml) was added, and the cyclohexanol was removed by distillation with the water. The residue was filtered, washed with water, and dried to give 9.3 g (81.6%) of colorless crystals of III with mp 298-299 deg (dec., from dimethylformamide). Found: C 64.0; H 6.1; N 24.4%. $C_{15}H_{17}N_5O$. Calculated: C 63.6; H 6.0; N 24.7%. The dihydrochloride of III had mp 303-304 deg (dec.). Found: Cl 19.9. $C_{15}H_{17}N_5O \cdot 2HCl$. Calculated: Cl 19.9%.

Compounds IV and V were similarly obtained (Table 1).

2-(4-Methyl-1-piperazinyl)-10-ethyl-3,4-diazaphenoxazine (XII). Ethyl iodide [2.6 ml (32.5 mmole)] was added to 6.5 g (22.7 mmole) of III in a solution of sodium ethoxide [obtained from 0.6 g (26 mg-atom) of Na and 75 ml of ethanol], and the mixture was refluxed for 4 h. The precipitate was filtered and washed with 10 ml of absolute alcohol. The filtrate was evaporated in vacuo. The residue was washed with water, dried, and dissolved in absolute alcohol. Treatment of this solution with alcoholic HCl gave 2 g (25.8%) of yellow-green crystals of the dihydrochloride of XII.

LITERATURE CITED

1. T. V. Gortinskaya, V. G. Nyrokova, N. V. Savitskaya, and M. N. Shchukina, Khim. Geterotsikl. Soedin., 750 (1971).