SYNTHESIS OF SUBSTITUTED 5H-PYRADAZINO[3,4-b]-1,4-BENZOXAZINE (3,4-DIAZAPHENOXAZINE)

III.* SYNTHESIS OF 2-CHLORO-10-ALKYL- AND 2-CHLORO-10-DIALKYLAMINOALKYL-3,4-DIAZAPHENOXAZINES

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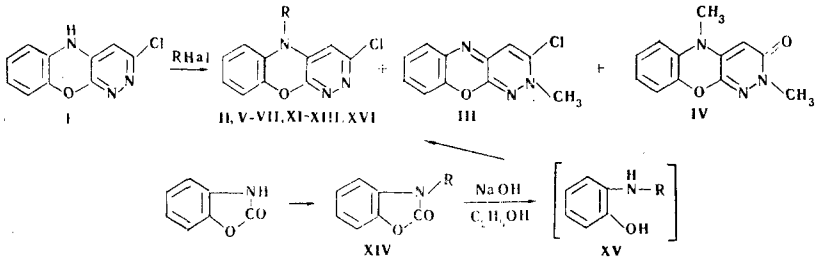
UDC 547.867.6'861.07

10-Methyl-2-chloro- and 2-chloro-3-methyl-3,4-diazaphenoxazines as well as 2-oxo-3,10-dimethyl-2,3-dihydro-3,4-diazaphenoxazine were obtained by methylation of 2-chloro-3,4-diazaphenoxazines. Depending on the conditions, alkylation of 2-chloro-3,4-diazaphenoxazine with β-diethylaminoethyl chloride gave 1-ethylimidazolino[1',2':1,2]pyridazo[3,4-b]-1,4-benzoxazine or 2-ethoxy-10-(β-diethylaminoethyl)-3,4-diazaphenoxazine. A number of 10-alkyl- and 10-dialkylaminoalkyl-2-chloro-3,4-diazaphenoxazines were obtained by condensation of 3,4,6-trichloropyridazine with substituted o-aminophenols.

In a continuation of our research on the synthesis of 3,4-diazaphenoxazine derivatives we have obtained 2-chloro-10-alkyl- and 2-chloro-10-dialkylaminoalkyl-3,4-diazaphenoxazines (II, V-VII, and XI-XIII), which are intermediates for the synthesis of substances with potential pharmacological activity. Compounds II, V-VII, XI-XIII, and XVI were synthesized from o-aminophenol via two schemes:



Three substances (II-IV) were isolated by the condensation of o-aminophenol with 3,4,6-trichloropyridazine [3] and subsequent methylation of the resulting 2-chloro-3,4-diazaphenoxazine (I) with methyl iodide in the presence of sodium alkoxide. According to their elementary composition, II and III corresponded to monomethyl derivatives of I; according to spectroscopic data and elementary analysis, IV corresponded to 2-oxo-2,3-dihydro-3,10-dimethyl-3,4-diazaphenoxazine; IV was also obtained by alternative synthesis from 2-oxo-2,3-dihydro-10-methyl-3,4-diazaphenoxazine [4-6].

One of the monomethyl derivatives of I (II) was an almost colorless compound with mp 206-207°C, the UV spectrum of which coincided with the UV spectrum of I (Fig. 1). Compound II was also obtained by the condensation of 2-methylaminophenol with 3,4,6-trichloropyridazine. On the basis of these results, we assumed that II is 2-chloro-10-methyl-3,4-diazaphenoxazine.

*See [1] for communication II.

S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical Chemistry Institute, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 750-754, June, 1971. Original article submitted April 20, 1970.

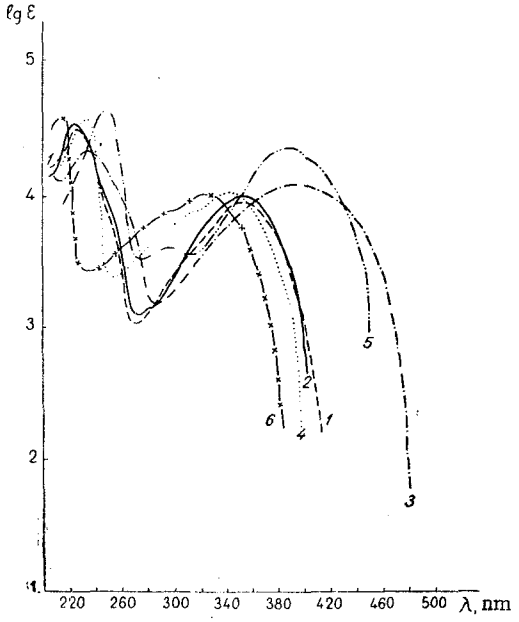
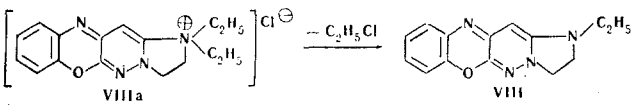


Fig. 1. UV spectra (in alcohol): 1) 2-chloro-3,4-diazaphenoxazine (I); 2) 2-chloro-10-methyl-3,4-diazaphenoxazine (II); 3) 2-chloro-3-methyl-3,4-diazaphenoxazine (III); 4) 2-oxo-2,3-dihydro-10-methyl-3,4-diazaphenoxazine (IV); 5) 1-ethylimidazolino[1',2':1,2]pyridazo-[3,4-b]-1,4-benzoxazine (VIII); 6) 2-oxo-2,3-dihydro-10-β-diethyl-aminoethyl-3,4-diazaphenoxazine (X).

The second monomethyl derivative of (III) with mp 183-184° was bright-yellow. A bathochromic shift of the long-wave absorption band by 42 nm as compared with the UV spectra of I and II was observed in the UV spectrum of III. For this compound we proposed the second of two possible structures, viz., the 2-chloro-3-methyl-3,4-diazaphenoxazine structure.

The methylation of I with methyl iodide proceeded at the 10-position in rather high yield (66%). The yields of 10-alkyl derivatives decrease with increasing length of the alkyl radical on alkylation with other alkyl halides. The yields of V-VII did not exceed 14.7-30%, respectively.

Treatment of I with diethylaminoethyl chloride in the presence of 1 mole of sodium ethoxide gave 20% of a bright-yellow substance of the composition $C_{14}H_{14}N_4O$, which, from the UV and PMR spectral data, was an imidazolinopyridazobenzoxazine derivative (VIII). It is possible that the formation of VIII proceeds through a quaternary salt (VIIIa) [7].



Alkylation of I with diethylaminoethyl chloride in the presence of 2 moles of sodium ethoxide gave (as the dipicrate) a compound of the composition $C_{18}H_{24}N_4O_2 \cdot 2C_6H_3N_3O_7$ (IX). Successive treatment of IX with concentrated HCl and K_2CO_3 gave 2-oxo-2,3-dihydro-10-β-diethylaminoethyl-3,4-diazaphenoxazine (X) [4]. The UV spectrum of X coincided almost completely with the UV spectrum of IV. An absorption band at 1650 cm^{-1} was observed in the IR spectrum of this compound. It is possible that X is formed via the following scheme:

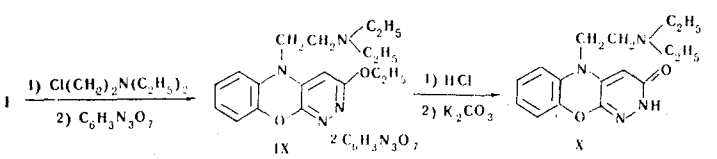
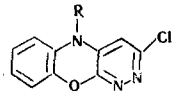


TABLE 1.



Comp.	R	mp (crystallization solvent) °C	Empirical formula
II	CH_3	206—207 (DMF)	$C_{11}H_8ClN_3O$
V	C_2H_5	196,5—197,5 (DMF)	$C_{12}H_{10}ClN_3O$
VI	C_3H_7	160—162 (ethyl acetate)	$C_{13}H_{12}ClN_3O$
VII	C_4H_9	154—155 (ethyl acetate)	$C_{14}H_{14}ClN_3O$
XI	$(CH_2)_3N(CH_3)_2$	173—174 (isopropyl alco)	$C_{15}H_{17}ClN_4O$
XI · 2HCl	$(CH_2)_3N(CH_3)_2$	251—252 (decomp.)	$C_{15}H_{17}ClN_4O \cdot 2HCl \cdot H_2O$
XII	$(CH_2)_2N(CH_3)_2$	167—168 (ethanol)	$C_{14}H_{15}ClN_4O$
XII · 2HCl	$(CH_2)_2N(CH_3)_2$	263 (dec.)	$C_{14}H_{15}ClN_4O \cdot 2HCl \cdot H_2O$
XIII · HCl	$(CH_2)_2N(C_2H_5)_2$	271—272 (dec., aqueous ethanol)	$C_{16}H_{19}ClN_4O \cdot HCl$
XVI	$CH_2C_6H_5$	229,5—230,5 (ethanol)	$C_{17}H_{12}ClN_3O$

Compound	Found %				Calc. %				Yield, %
	C	H	Cl	N	C	H	Cl	N	
II	56,6	3,6	15,2	17,9	56,6	3,4	15,2	18,0	61,5 (34,5)
V	58,7	4,3	—	17,0	58,2	4,1	—	17,0	45,5 (15,9)
VI	59,7	4,6	13,6	16,1	59,7	4,6	13,7	16,1	21,6 (10,5)
VII	60,4	5,2	12,8	15,2	61,0	5,1	12,9	15,2	20,5 (7,7)
XI	59,2	5,6	11,5	—	59,1	5,6	11,6	—	44 (9,7)
XI · 2HCl	—	H_2O—4	26,8	14,6	—	H_2O—4,5	26,9	14,2	43,8
XII	58,0	5,4	12,8	19,4	57,8	5,2	12,2	19,3	—
XII · 2HCl	—	—	27,5	14,7	—	—	27,9	14,7	31
XIII · HCl	54,0	5,8	19,8	15,7	54,0	5,6	20,0	15,8	36
XVI	65,5	3,8	11,6	13,3	65,9	3,9	11,4	13,6	5,8

*The yield indicated is based on o-aminophenol for synthesis through benzoxazoline, while the yield given in parentheses is based on o-aminophenol for synthesis through alkylation of I.

Pronounced resinification of the reaction mass was observed during the alkylation of I with γ-dimethylaminopropyl chloride in dimethylformamide in the presence of sodium amide, and 2-chloro-10-γ-dimethylaminopropyl-3,4-diazaphenoxazine (XI) was isolated in only 18.6% yield.

In connection with the fact that the alkylation of I gave V-VII and XI in low yields, while 2-chloro-10-β-dimethylaminoethyl-3,4-diazaphenoxazine (XII) and 2-chloro-10-β-diethylaminoethyl-3,4-diazaphenoxazine could not be obtained, we attempted to synthesize these compounds from the corresponding alkyl- or dialkylaminoalkyl derivatives of o-aminophenol (XV) and 3,4,6-trichloropyridazine in the presence of alkaline agents. The starting substances for the preparation of XV were N-alkyl- or N-dialkylaminoalkylbenzoazolones (XIV). The latter were subjected to alkaline hydrolysis, and the XV formed, without isolation from the reaction mass, were condensed with 3,4,6-trichloropyridazine. This method was used to obtain high yields of II, V-VII, XI-XIII, and XVI (Table 1). The UV spectra of V-VII and XI-XIII coincided completely with the UV spectra of I and II.

EXPERIMENTAL

Benzoxazolone. This was obtained in 90% yield by the method in [8].

3-Methylbenzoxazolone (XIV, R = CH_3). Dimethyl sulfate [82 g (0.65 mole)] was added with stirring at 20-25° to a solution of 80 g (0.593 mole) of benzoxazolone in 400 ml of 6% aqueous sodium hydroxide, the mixture was allowed to stand for 1 h, and the precipitate was filtered, washed with water, and dried to give 75.5 g (85.5%) of XIV with mp 85-86°. Found %: C 64.7; H 4.8; N 9.4. $C_8H_7NO_2$. Calculated %: C 64.4; H 4.7; N 9.4.

2-Chloro-10-methyl-3,4-diazaphenoxazine (II) [2]. A. A mixture of 29.8 g (0.2 mole) of XIV (R = CH_3) and 40 g (0.6 mole) of 85% potassium hydroxide in 240 ml of ethanol was refluxed for 1 h, after which 36.7 g

(0.2 mole) of 3,4,6-trichloropyridazine in 100 ml of ethanol was added dropwise, and the mixture was refluxed for another 5 h. The precipitate that formed on cooling was filtered, washed with water and ethanol, and dried to give 37.4 g (80%) of II with mp 206-207° (from DMF). UV spectrum,* λ_{max}, nm (log ε): 226 (4.54); 358 (3.98). Found %: C 56.6; H 3.6; Cl 15.2; N 17.9. $C_{11}H_8ClN_3O$. Calculated %: C 56.6; H 3.5; Cl 15.2; N 17.6.

B. A mixture of 3.6 g (29 mmole) of XV (R = CH_3), 5.3 g (29 mmole) of 3,4,6-trichloropyridazine, and 9.3 ml (67 mmole) of triethylamine in 25 ml of ethanol was refluxed for 6 h and cooled, and the resulting precipitate was filtered, washed with water and ethanol, and dried to give 5.34 g (79%) of II.

2-Chloro-10-ethyl-3,4-diazaphenoxazine (V). A mixture of 27 g (0.2 mole) of benzoxazolone in 30 ml of ethanol, 31.2 g (0.2 mole) of ethyl iodide, and 13.2 g (0.2 mole) of 85% potassium hydroxide in 70 ml of ethanol and 8 ml of water was refluxed for 3 h, cooled, a hot solution of 40 g (0.6 mole) of 85% potassium hydroxide in 100 ml of ethanol was added, and the mixture was refluxed for 1 h. A hot solution of 36 g (0.195 mole) of 3,4,6-trichloropyridazine in 60 ml of ethanol was then added gradually at 60-70°, and the mixture was refluxed for another 6 h. The reaction mass was cooled, the precipitate was filtered, washed with ethanol and water, and dried to give 25 g (50.5%) of V, which was soluble on heating in ethanol and ethyl acetate.

Products VI, VII, and XVI were similarly obtained in 24, 22.8, and 6.5% yields, respectively (based on benzoxazolone).

2-Chloro-10-γ-dimethylaminopropyl-3,4-diazaphenoxazine (XI). A solution of 67.5 g (0.5 mole) of benzoxazolone in 100 ml of absolute ethanol was added at 80° to a solution of sodium ethoxide prepared from 23 g (1 g-atom) of Na in 320 ml of absolute ethanol, the mixture was stirred for 5 min, and 83.5 g (0.5 mole) of 94.9% γ-dimethylaminopropyl chloride hydrochloride was added. The mixture was refluxed for 2 h, cooled to 40-50°, a solution of 100 g (1.5 mole) of 85% potassium hydroxide in 43 ml of water, was added, and the mixture was refluxed for 2 h. A solution of 91.7 g (0.5 mole) of 3,4,6-trichloropyridazine in 145 ml of alcohol was added gradually to the reaction mass (cooled to 60-70°), and the mixture was refluxed for 5 h, cooled to 20-25°, and allowed to stand for 12 h for crystallization. The precipitate was filtered, washed with 500 ml of 5% aqueous sodium hydroxide and water, and dried to give 74 g (48.7%) of XI, which was soluble on heating in alcohol, ethyl acetate, and acetone.

Products XII and XIII were similarly obtained in 34.6 and 40% yields, respectively (based on benzoxazolone).

Methylation of 2-Chloro-3,4-diazaphenoxazine (I). A total of 2 ml (33 mmole) of methyl iodide was added slowly at room temperature with stirring to 6.6 g (30 mmole) of I in a sodium ethoxide solution prepared from 0.76 g (0.033 g-atom) of Na and 80 ml of absolute ethanol. After 40 min, the precipitate was filtered, washed with a small amount of cooled alcohol and water, and dried to give 5.1 g of product. This was refluxed with 30 ml of ethyl acetate, and the precipitate (4.2 g) was filtered and refluxed in 135 ml of ethanol. The insoluble residue was filtered to give 0.3 g (4.6%) of 2-oxo-2,3-dihydro-3,10-dimethyl-3,4-diazaphenoxazine (IV) as a colorless, crystalline substance with mp 254-255° (from DMF). UV spectrum, λ_{max}, nm (log ε): 235 (4.60), 340 (4.01). IR spectrum:† ν_{CO} 1655 cm^{-1}. Found %: C 62.9; H 5.0; N 18.3. $C_{12}H_{11}N_3O_2$. Calculated %: C 62.9; H 4.8; N 18.3. Cooling of the alcoholic mother liquor yielded 2.45 g (34.9%) of II, which was identical to that described above.

The ethyl acetate mother liquor was evaporated, and the residue was washed with alcoholic sodium ethoxide and crystallized from isopropyl alcohol to give 0.3 g of a substance with mp 162-168°, whose alcohol solution was chromatographed on a plate with activity II Al_2O_3 (in benzene). The bright-yellow layer with R_f 0.4 was separated, and the substance was leached out with alcohol. The alcohol was removed by distillation to give 0.1 g (1.4%) of 2-chloro-3-methyl-3,4-diazaphenoxazine (III) as bright-yellow crystals with mp 183-184° (from ethyl acetate). UV spectrum, λ_{max}, nm (log ε): 234 (4.32), 400 (4.06). Found %: C 56.6; H 3.6; Cl 15.4; N 18.2. $C_{11}H_8ClN_3O$. Calculated %: C 56.6; H 3.5; Cl 15.7; N 18.0. Compound II was obtained in 66% yield by refluxing I with ethyl iodide for 5 h.

Compounds V-VII were similarly obtained in 30.3, 20, and 14.7% yields, respectively.

*The UV spectra were obtained from ethanol solutions.

†The IR spectra were obtained from mineral oil suspensions.

1-Ethylimidazolino[1',2':1,2]pyridazo[3,4-b]-1,4-benzoxazine (VIII). Freshly distilled β-diethylaminoethyl chloride [5.4 g (44 mmole)] was added dropwise with stirring to 4 g (1.8 mmole) of I in a solution of sodium ethoxide [from 0.42 g (0.18 g-atom) of Na and 20 ml of absolute ethanol], the mixture was cooled, the precipitate was filtered, and the filtrate was vacuum evaporated. The residue was extracted with benzene, and the oily residue obtained on evaporation of the benzene was triturated with ether to give 0.97 g (20.9%) of bright-yellow crystals of VIII with mp 177-177.5° (from alcohol) that were soluble in alcohol and benzene and insoluble in water. UV spectrum, λ_{max}, nm (log ε): 250 (4.62); 275 (3.51); 296 (3.60); 315 (3.54); 390 (4.35). PMR spectrum (in acetic acid), *ppm: triplet 1.33 (CH_3); quartet 3.40 (CH_2); triplets 3.82 and 4.60 (CH_2-CH_2); singlet 6.05 (H). Found %: C 66.1; H 5.8; N 22. $C_{14}H_{14}N_4O$. Calculated %: C 66.1; H 5.6; N 22.0. The hydrochloride of VIII was obtained as a bright-yellow substance with mp 298-299° (decomp.). Found %: Cl 11.4; N 18.6. $C_{14}H_{14}N_4O \cdot HCl \cdot H_2O$. Calculated %: Cl 11.5; N 18.1.

2-Ethoxy-10-(β-diethylaminoethyl)-3,4-diazaphenoxazine Dipicrate (IX). Freshly distilled β-diethylaminoethyl chloride [10.8 g (80 mmole)] was added with stirring to a mixture of 12 g (55 mmole) of I in a solution of sodium ethoxide prepared from 2.5 g (108 g-atom) of Na in 40 ml of absolute ethanol, and the mixture was refluxed for 3 h and cooled. The precipitate was filtered, and the filtrate was evaporated in vacuo. The oily residue was treated with water, the unchanged I (4.01 g) was filtered, and the filtrate was vacuum evaporated. The oily substance remaining was extracted with benzene. The residue (4.8 g) after removal of the solvent was treated with alcoholic picric acid, and the precipitate was filtered and washed with hot alcohol and acetone to give 4.01 g (24.8%) of IX with mp 167° (decomp., from acetic acid). Found %: C 46.4; H 3.9; N 17.6. $C_{18}H_{24}N_4O_2 \cdot 2C_6H_3N_3O_7$. Calculated %: C 45.8; H 3.8; N 17.8.

2-Oxo-2,3-dihydro-10-β-diethylaminoethyl-3,4-diazaphenoxazine (X). A mixture of 2.6 g (3.3 mmole) of IX in 70 ml of concentrated HCl was allowed to stand at 20° for 18 h. The picric acid was removed by filtration, and the filtrate was evaporated to dryness and treated with a solution of K_2CO_3. The oily residue was triturated with water, filtered, and dried to give 0.9 g (91.0%) of colorless, crystalline X with mp 206-207° (from acetone). UV spectrum, λ_{max}, nm (log ε): 235 (4.60), 354 (4.01). IR spectrum: ν_{CO} 1650 cm^{-1}. Found %: C 63.7; H 6.7; N 18.4. $C_{16}H_{20}N_4O_2$. Calculated %: C 64.0; H 6.7; N 18.7.

2-Chloro-10-γ-dimethylaminopropyl-3,4-diazaphenoxazine Hydrochloride (XI). A mixture of 3 g (14 mmole) of I, 1 g (26 mmole) of sodium amide, and 60 ml of dimethylformamide was heated with stirring at 140° for 40 min, 7.4 g (61 mmole) of freshly distilled γ-dimethylaminopropyl chloride in 15 ml of dimethylformamide was added, and the mixture was heated for 1.5 h. The dimethylformamide was removed by vacuum distillation, and the residue was extracted with benzene. The benzene was removed by vacuum distillation, and the residue of oily crystals was treated with alcoholic HCl to give 0.95 g (18.6%) of light-yellow crystals of XI that were soluble in water. UV spectrum, λ_{max}, nm (log ε): 226 (4.44); 354 (3.94).

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*The spectrum was recorded with a JNM-4H-100 spectrometer with an operating frequency of 100 MHz.