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

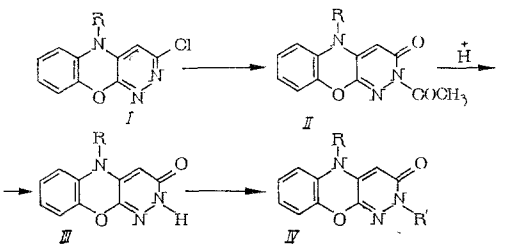
V. SYNTHESIS OF 2-OXO-10-ALKYL- AND 2-OXO-10-DIALKYLAMINOALKYL-2,3-DIHYDRO-3,4-DIAZAPHENOXAZINES AND THEIR 3-SUBSTITUTED DERIVATIVES

T. V. Gortinskaya, V. G. Nyrkova,
N. V. Savitskaya, M. N. Shchukina,
A. I. Polezhaeva, and M. D. Mashkovskii

UDC 615.21:547.867.6].012.1

We previously synthesized 2-substituted 10-alkyl- or 10-dialkylaminoalkyl-3,4-diazaphenoxazines [1, 2]. One of these compounds under the name "azaphene" [2-(4-methylpiperazinyl-1)-10-methyl-3,4-diazaphenoxazine] has been approved for medical practice as a psychotropic (antidepressive) agent [3-5].

In the further search for substances possessing pharmacological activity, we synthesized derivatives of 3,4-diazaphenoxazine with the general formula IV. It was established that 2-chloro-10-alkyl- or 2-chloro-10-dialkylaminoalkyl-3,4-diazaphenoxazine (I) is converted into the corresponding 2-oxo-3-acetyl-10-alkyl- or 10-dialkylaminoalkyl derivatives of 2,3-dihydro-3,4-diazaphenoxazine (II) when they are boiled with acetic anhydride; depending on the conditions of treating the reaction mixture, either II or III can be isolated [6, 7].



R		R	R'
Ia, IIa, IIIa, CH_3 Ib, IIb, IIIb, C_2H_5 Ic, IIc, IIIc, C_4H_9 Id, IId, IIId, $(CH_2)_3N(CH_3)_2$	IVa IVb IVc IVd	CH_3 CH_3 CH_3 $(CH_2)_3N(CH_3)_2$	CH_3 $(CH_2)_2N(C_2H_5)_2$ $(CH_2)_3N(CH_3)_2$ C_4H_9

The structure of these compounds was confirmed by IR and UV spectral data. An absorption band $\nu_{CO} = 1650\text{-}1680\ cm^{-1}$ is distinctly observed in the IR spectra of compounds III. An additional absorption band $\nu_{CO} = 1730\ cm^{-1}$ is observed in the IR spectrum of compound II which has a $COCH_3$ group in position 3. The UV spectra of II and III almost coincide but differ from the UV spectrum of the original I (see Fig. 1).

A similar conversion of the chloro derivatives to the corresponding oxo derivatives is known for the pyridine N-oxide and substituted pyridazine series [8-10]. The conversions of the 2-chloro derivatives of

S. Ordzhonikidze All-Union Chemical and Pharmaceutical Scientific-Research Institute, Moscow.
Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 6, No. 5, pp. 8-10, May, 1972. Original article submitted September 30, 1970.

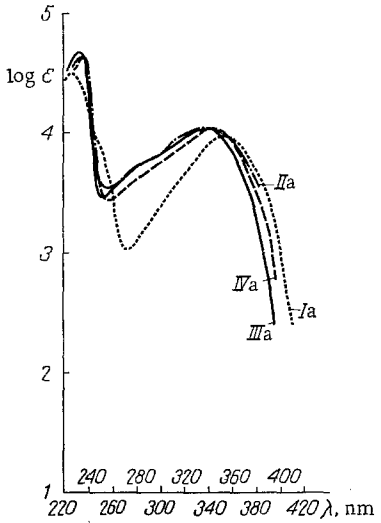
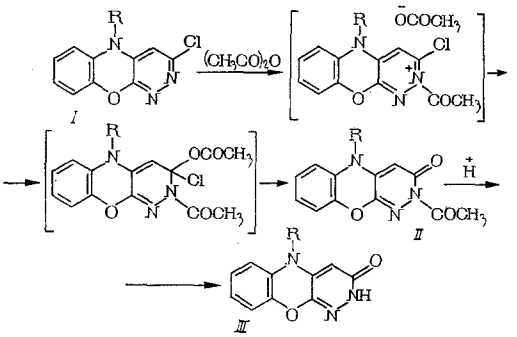


Fig. 1. UV Spectra of 3,4-diazaphenoxazine derivatives (in alcohol).

3,4-diazaphenoxazine (I) into the corresponding 2-oxo-2,3-dihydro-3,4-diazaphenoxazines (III) evidently proceed by a mechanism which is similar to that proposed for the chloro derivatives of the pyridine N-oxides [8]:



The corresponding 3-N-alkyl- or 3-N-dialkylaminoalkyl derivatives of 2-oxo-2,3-dihydro-3,4-diazaphenoxazine (IV) are formed during the alkylation of III with alkyl halides or dialkylaminoalkyl chlorides in an alcoholic solution of a sodium alkoxide or in alcoholic solutions of alkali hydroxides.

Of the compounds we synthesized, 3-diethylaminoethyl-2-oxo-2,3-dihydro-10-methyl-3,4-diazaphenoxazine (IVb) was investigated with respect to a number of pharmacological indicators. It was established that the compound possesses properties characteristic for tricyclic antidepressants. When the preparation is administered to white rats subcutaneously in a dose of 10 mg/kg, the duration of the phenamine stereotypy is increased from 53 (44-62) to 92 (80-104) min; the "group toxicity of phenamine" was increased during the subcutaneous administration of the preparation in doses of 25-50 mg/kg in experiments on white mice. The preparation attenuated the depressive effects (adynamia, ptosis, and hypothermia) caused by reserpine. The preparation had no expressed effect on the sympathetic nervous system. The LD_{50} for white mice amounts to 99 mg/kg for intravenous administration and 470 mg/kg for subcutaneous administration. This compound in less active than the known antidepressant imipramine and also azaphene, which is related to this same group of diazaphenoxazine derivatives.

EXPERIMENTAL

2-Oxo-2,3-dihydro-3-acetyl-10-methyl-3,4-diazaphenoxazine (IIa). A mixture of 5 g of Ia and 25 ml of acetic anhydride was boiled for 3 h, the acetic anhydride was evaporated off in vacuo, and the remainder was recrystallized from dimethylformamide. A total of 4.9 g (89.4%) of IIa was obtained, a colorless substance, mp 252-254°C. IR spectrum (Nujol mull): ν_{CO} 1680, 1730 cm^{-1}. UV spectrum in ethanol, λ max, nm (lg ε): 234 (4.69), 340 (4.01). Found %: C 61.03; H 4.40; N 16.17. $C_{13}H_{11}N_3O_3$. Calculated %: C 60.69; H 4.31; N 16.33.

2-Oxo-2,3-dihydro-3-acetyl-10-ethyl-3,4-diazaphenoxazine (II b). The reaction was carried out with 3 g of Ib and 30 ml of acetic anhydride as it was for compound IIa. A total of 2 g (66.4%) of IIb was obtained, a colorless substance, mp 229-230°C (from dimethylformamide). Found %: C 62.21; H 5.01; N 15.46. $[C_{14}H_{13}N_3O_3$. Calculated %: C 61.98; H 4.83; N 15.49.

2-Oxo-2,3-dihydro-10-methyl-3,4-diazaphenoxazine (IIIa). A mixture of 4.9 g of IIa and 25 ml of dilute hydrochloric acid (1:3) was boiled for 30 min. A total of 4.0 g (95.5%) of IIIa was obtained, a colorless substance, mp 325-327°C (decomp.). IR spectrum, Nujol mull: ν_{CO} 1685 cm^{-1}. UV spectrum in ethanol, λ_{max}, nm (lg ε): 235 (4.60); 340 (4.01). Found %: C 61.39; H 4.32; N 19.13. $C_{11}H_9N_3O_2$. Calculated %: C 61.34; H 4.32; N 19.53.

2-Oxo-2,3-dihydro-10-ethyl-3,4-diazaphenoxazine (IIIb). The reaction was carried out as for compound IIIa. A mixture of 2 g of IIb and 20 ml of dilute hydrochloric acid (1:3) was boiled for 3 h. A total of 1.4 g (77.8%) of IIIb was obtained, a colorless substance, mp 272-274°C (from dimethylformamide). Found %: N 18.19. $C_{12}H_{11}N_3O_2$. Calculated %: 18.34.

2-Oxo-2,3-dihydro-10-butyl-3,4-diazaphenoxazine (IIIc). A mixture of 2 g of Ic and 20 ml of acetic anhydride was boiled for $2\frac{1}{2}$ h, the acetic anhydride was removed by vacuum distillation, water was added, and the mixture was vacuum distilled once more. A total of 1.8 g (96.3%) of IIIc was obtained, a colorless substance, mp 223-225°C (from dimethylformamide). Found %: C 65.73; H 5.81; N 15.92. $C_{14}H_{15}N_3O_2$. Calculated %: C 65.38; H 5.88; N 16.33.

2-Oxo-2,3-dihydro-10-(3-dimethylaminopropyl)-3,4-diazaphenoxazine dihydrochloride (IIId). A mixture of 4g of Id and 70 ml of acetic anhydride was boiled for 7 h, and left to recrystallize for 12 h. The precipitate IIId (2.05 g) was filtered off. The filtrate was evaporated in vacuo, the residue was triturated with water, and an additional 0.6 g of IIId was obtained (the overall yield was 70%). After recrystallization from water, a colorless, crystalline powder was obtained, mp 200-201°C. Found %: C 62.92; H 6.59; N 19.56. $C_{15}H_{18}N_3O_2$. Calculated %: C 62.92; H 6.34; N 19.57.

2-Oxo-2,3-dihydro-3,10-dimethyl-3,4-diazaphenoxazine (IVa). To a hot suspension of 0.7 g of IIIa in 7 ml of 96% alcohol was added 0.4 g of 85% potassium hydroxide, it was heated until complete dissolution was obtained, 0.5 ml of methyl iodide was added, the mixture was boiled for 2 h, and left for 24 h. The precipitate was filtered off, washed with water, and dried. A total of 0.4 g (53%) of IVa was obtained, a colorless substance, mp 254-255°C (from dimethylformamide). IR spectrum, Nujol mull: ν_{CO} 1655 cm^{-1}. UV spectrum in ethanol, λmax, nm (lg ε): 235 (4.60); 340 (4.01). Found %: C 62.87; H 4.83; N 18.33. $C_{12}H_{11}N_3O_2$. Calculated %: C 62.68; H 4.84; N 18.24.

2-Oxo-2,3-dihydro-3-(2-diethylaminoethyl)-10-methyl-3,4-diazaphenoxazine (IVb). An alcoholic potassium hydroxide solution (from 42 g of 80% potassium hydroxide and 84 ml of ethyl alcohol), 6.35 g of IIIa, and 5.5 g of diethylaminoethyl chloride hydrochloride was boiled for 2 h and filtered. The filtrate was treated with activated carbon, evaporated to dryness, the residue was boiled with 200 ml of ethyl acetate, filtered, and again evaporated to dryness. The residue (3 g) was crystallized from ethyl acetate. A total of 2.5 g (32.3%) of IVb was obtained, a colorless substance, mp 129.5-130.5°C. Found %: C 65.41; H 7.16; N 17.31. $C_{17}H_{22}N_4O_2$. Calculated %: C 64.94; H 7.05; N 17.82.

IVb Dihydrochloride. Compound IVb, 2.5 g, was dissolved in 28 ml of acetone, concentrated hydrochloric acid was added to pH 2.0, and the IVb dihydrochloride precipitate was filtered off. A total of 2.8 g (87.4%) of the substance was obtained, mp 237-238°C. Found %: C 50.40; H 6.57; N 14.30; Cl 17.74. $C_{17}H_{22}N_4O_2 \cdot 2$ HCl. Calculated %: C 50.4; H 6.38; N 13.82; Cl 17.52.

2-Oxo-2,3-dihydro-3-(3-dimethylaminopropyl)-10-methyl-3,4-diazaphenoxazine (IVc). An alcoholic solution of sodium ethylate (from 1.15 g of sodium and 50 ml of ethanol) was boiled with 4.35 g of IIIa, 4 g of 3-dimethylaminopropyl chloride hydrochloride was added, the mixture was boiled 3 h, and filtered. The filtrate was evaporated to dryness, the remainder was recrystallized twice from ethyl acetate. A total of 1 g (16.7%) of IVc was obtained, a colorless substance, mp 141.5-142.5°C. Found %: C 63.73; H 6.72; N 18.56. $C_{16}H_{20}N_4O_2$. Calculated %: C 63.98; H 6.71; N 18.66.

2-Oxo-2,3-dihydro-3-butyl-10-(3-dimethylaminopropyl)-3,4-diazaphenoxazine (IVd). An alcoholic solution of potassium hydroxide (from 0.1 g of potassium hydroxide and 3 ml of ethanol), 0.35 g of IIId, and 0.2 g of n-butyl bromide was boiled for 4 h, the solvent was distilled off, the residue triturated with water, and filtered. A total of 0.2 g (47.95%) of IVd was obtained, a colorless substance, mp 107-109°C (from hexane). Found %: C 66.63; H 7.79. $C_{19}H_{26}N_4O_2$. Calculated %: C 66.68; H 7.65.

LITERATURE CITED

1. V. G. Nyrkova, T. V. Gortinskaya, and M. N. Shchukina, Zh. Obshch. Khim., 34, 3132 (1964).
2. V. G. Nyrkova, T. V. Gortinskaya, and M. N. Shchukina, Ibid., 35, 1688 (1965).
3. M. D. Mashkovskii and A. I. Polezhaeva, Farmakol. i Toksikol., No. 6, 656 (1969).
4. A. I. Polezhaeva, O. P. Vertogradova, and M. R. Bagreeva, Khim.-Farmats. Zh., No. 2, 59 (1970).
5. M. D. Mashkovskii, A. I. Polezhaeva, G. Ya. Avrutskii, et al., Zh. Nevropatol. i Psikhiatr., 8, 1234 (1969).
6. T. V. Gortinskaya, N. V. Savtiskaya, M. N. Shchukina, et al., Letter of Invention. No. 239343, Izobreteniya, No. 11 (1969).
7. T. V. Gortinskaya, V. G. Nyrkova, N. V. Savitskaya, et al., Letter of Invention No. 243619, Izobreteniya, No. 17 (1969).

8. H. Hamana and M. Jamazoki, Yakugaku Zasshi, 81, 574 (1961).
9. F. Voneda and V. Nitta, Chem. Pharm. Bull. (Tokyo), 11, No. 2, 269, 271 (1963).
10. T. Kuraichi, Ibid., 6, 331, 641 (1958).