SYNTHESIS IN THE PHENOTHIAZINE SERIES

XXXIV.* 3,7-DIAMINO-10-ACETYLPHENOTHIAZINE 5-OXIDE

G. A. Khutornenko, N. S. Panshina,
and S. V. Zhuravlev

UDC 547.869.2

A method was developed for the preparation of 3,7-diamino-10-acetylphenothiazine 5-oxide by the reduction of 3,7-dinitro-10-acetylphenothiazine 5-oxide with hydrazine hydrate in the presence of a nickel catalyst.

3,7-Diaminophenothiazine, obtained by repeated reduction of 3,7-dinitrophenothiazine or its sulfoxide, was oxidized (without isolation) to a thionine dye (Lauth's violet) [2-4]. The preparation of a thionine leuco base by the reduction of thionine with ammonium sulfate [2] or tin in hydrochloric acid [5] is mentioned in the literature, but the compound has not been characterized. This is apparently associated with the difficulties involved in its isolation, since 3,7-diaminophenothiazine is extremely readily oxidized to form blue-colored quinoid compounds. The introduction of an acyl substituent into the 10 position and oxidation to the sulfoxide confer considerable resistance to oxidation and prevent the formation of quinoid compounds, which we confirmed by the synthesis of 3,7-diamino-10-acetylphenothiazine 5-oxide.

3,7-Dinitrophenothiazine (I), obtained by a known method [4], was acetylated with acetic anhydride in the presence of pyridine to 10-acetyl-3,7-dinitrophenothiazine (II), which was oxidized with nitric acid to 10-acetyl-3,7-dinitrophenothiazine 5-oxide (III). The latter has the same melting point as 10-acetyl-3,7-dinitrophenothiazine and does not depress its melting point. However, the results of elementary analysis for these compounds and the IR and UV spectra are different. The IR spectrum of KBr pellets of III contain an absorption band at 1044 cm^{-1}, which can be assigned to the stretching vibration of the SO group [6], but this band is absent in the IR spectrum of II. The UV spectrum of II has λ_{max} at 266 nm (log ε 4.50), while λ_{max} in the spectrum of III is at 287 nm (log ε 4.02). Only the nitro groups were selectively reduced by the reduction of III with hydrazine hydrate on Raney nickel [7], and the 10-acetyl-3,7-diaminophenothiazine 5-oxide (IV) was isolated as the hydrochloride. Base IV is oxidized very rapidly in light on contact with air. Our experiments demonstrated that it is best to isolate it as the oxalate, maleate, or (optimally) as the hydrochloride.

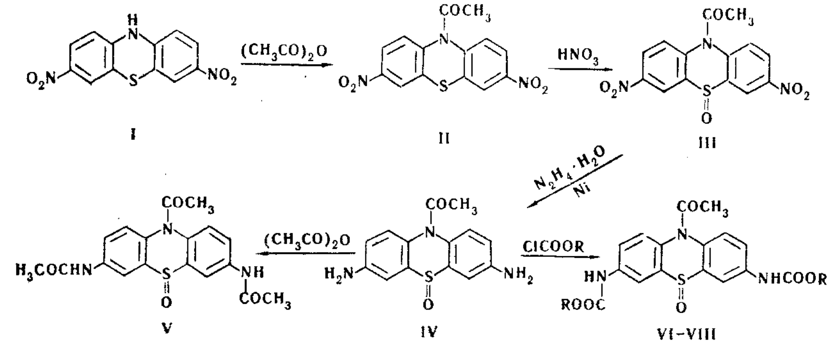
We have studied several reactions of 10-acetyl-3,7-diaminophenothiazine 5-oxide (see the scheme below) and have obtained several new substances. Some of them may serve as starting compounds for subsequent synthesis of pharmacologically active preparations.

To confirm the presence of the S=O group in the urethanes obtained, the IR spectra of mineral-oil suspensions of them were recorded. We will assign the absorption bands at 1077, 1078, and 1070 cm^{-1} of VI, VII, and VIII, respectively, to the stretching vibrations of the S=O group.

---

[*] See [1] for communication XXXIII.

Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 325-327, March, 1972. Original article submitted March 22, 1971.



VI $R = CH_3$; VII $R = C_2H_5$; VIII $R = C_4H_9$

EXPERIMENTAL

10-Acetyl-3,7-dinitrophenothiazine (II). A mixture of 15 g of 3,7-dinitrophenothiazine (I) [4], 75 ml of acetic anhydride, and 60 ml of pyridine was refluxed for 10 h. The warm solution was poured carefully into ice water with stirring, and the resulting precipitate was filtered to give 15 g (88%) of a substance that melted at 221-223° after two recrystallizations from acetone. The sand-colored crystals were quite soluble in alcohol, dichloroethane, chloroform, and toluene. Found: C 50.9, 50.8; H 2.5, 2.6; N 12.5, 12.4; S 9.6, 9.8%. $C_{14}H_9N_3O_5S$. Calculated: C 50.8; H 2.7; N 12.7; S 9.7%.

10-Acetyl-3,7-dinitrophenothiazine 5-Oxide (III). A 10-g sample of II was dissolved by heating in 100 ml of dioxane, the solution was cooled to room temperature, and 50 ml of concentrated nitric acid was added with cooling in such a way as to keep the temperature from rising. Ten minutes after the addition of the nitric acid, the reaction solution was poured into cold water, and the resulting precipitate was separated, dried, and crystallized from toluene to give 9 g (85%) of a lemon-yellow substance with mp 220-223°. The product did not depress the melting point of II and was soluble (with greater difficulty) in the same solvents as II. Found: C 48.2, 48.2; H 2.6, 2.7; N 12.0, 11.8; S 9.6, 9.8%. $C_{14}H_9N_3O_6S$. Calculated: C 48.4; H 2.6; N 12.1; S 9.3%.

3,7-Diamino-10-acetylphenothiazine 5-Oxide Dihydrochloride (IV). A 9-g (0.18 mole) sample of hydrazine hydrate was added dropwise in the course of 30 min with vigorous stirring under nitrogen to 10.4 g (0.03 mole) of III and 12 g of moist nickel catalyst in 300 ml of alcohol while maintaining the temperature at no higher than 50°. After the addition, the reaction mass was stirred under the same conditions for another 1.5 h until the starting material dissolved. The colorless solution was filtered rapidly away from the catalyst into a flask containing alcohol or ether saturated with the calculated amount of hydrogen chloride necessary for the formation of the dihydrochloride. The reaction solution took on a blue color on contact with air and in light. The alcohol solution of the dihydrochloride was cooled, and the resulting precipitate was separated and washed with ether to give 9.5 g (98%) of a light-blue substance. The substance darkened on heating above 250°, was quite soluble in water, and slightly soluble in alcohol. Found: N 11.2, 11.1; Cl 19.3, 1.91%. $C_{14}H_{13}N_3O_2S \cdot 2HCl$. Calculated: N 11.3; Cl 19.1%.

3,7-Diacetamido-10-acetylphenothiazine 5-Oxide (V). Pyridine (6 ml) and 4 ml of acetic anhydride were added to 1.08 g (0.03 mole) of IV at room temperature. After 2 h, the reaction mass was poured into 50 ml of cold water, and the resulting precipitate was separated to give 0.9 g (82%) of a substance, which was crystallized from 50% isopropyl alcohol. The greyish crystals, which became rose-colored on storage, had mp 313-316° and were quite soluble in aqueous methanol, ethanol, and isopropyl alcohol. Found: N 11.1, 11.2; S 8.6, 8.8%. $C_{18}H_{17}N_3O_4S$. Calculated: N 11.3; S 8.6%.

Dimethyl 10-Acetylphenothiazine-3,7-dicarbamate 5-Oxide (VI). A solution of 0.4 g (0.01 mole) of sodium hydroxide in 1.5 ml of water was added to 1.8 g (0.005 mole) of IV in 60 ml of absolute alcohol, the mixture was cooled rapidly to 5-7°, and 0.66 g (0.0053 mole) of methyl chlorocarbonate was added from a dropping funnel in the course of 15 min while maintaining the temperature at no higher than 10°. A 0.7-g (0.0057 mole) sample of methyl chlorocarbonate and 0.93 g of sodium carbonate in 3 ml of water were then added simultaneously at the same temperature in 20 min. The reaction mass was stirred for another 1 h, 200 ml of water was added, and the resulting precipitate was separated to give 1.74 g (87%) of a gray-blue substance. Three recrystallizations from dichloroethane–dioxane gave a white substance with mp 230-231° that was soluble in alcohol, chloroform, and acetone and less soluble in toluene. Found: N 10.5, 10.4; S 7.8, 8.1%. $C_{18}H_{17}N_3O_6S$. Calculated: N 10.2; S 7.9%.

Diethyl 10-Acetylphenothiazine-3,7-dicarbamate 5-Oxide (VII). Under similar conditions, 1.44 g (0.004 mole) of IV, 0.32 g (0.008 mole) of sodium hydroxide, 0.95 g (0.0088 mole) of ethyl chlorocarbonate, and 0.8 g of sodium carbonate gave 1.5 g (88%) of a white substance with mp 190-191° (after three recrystallizations from toluene). The product was soluble in acetone, alcohol, chloroform, and dichloroethane. Found: N 9.9, 9.9; S 7.11, 7.2%. $C_{20}H_{21}N_3O_6S$. Calculated: N 9.7; S 7.4%.

Diisobutyl 10-Acetylphenothiazine-3,7-dicarbamate 5-Oxide (VIII). This compound was similarly obtained in 91% yield as colorless crystals with mp 140-143° (after three recrystallizations from toluene) and was quite soluble in alcohol, dichloroethane, and chloroform. Found: N 8.6, 8.9; S 6.5, 6.5%. $C_{24}H_{29}N_3O_6S$. Calculated: N 8.6; S 6.6%.

LITERATURE CITED

1. V. V. Shavyrina and S. V. Zhuravlev, Khim. Geterotsikl. Soedin., 38 (1972).
2. A. Bernthesen, Ann., 230, 100 (1885).
3. F. Kehrmann and O. Nossenko, Ber., 46, 2809 (1913).
4. C. Bodea and M. Răileanu, Studii si Cercetări de Chimie Acad. RPR Fil. Cluj, 8, 303 (1957).
5. F. Kehrmann, Ber., 39, 914 (1906).
6. C. Bodea and I. Silberg, Advances in Heterocyclic Chemistry, 9, 322 (1968).
7. V. A. Skorodumov, N. K. Shagako, and S. V. Zhuravlev, Zh. Obshch. Khim., 34, 621 (1964).