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PREPARATION OF N-SUBSTITUTED 3H-PYRROLO[2,3-*c*]PHENO-THIAZINE 11,11-DIOXIDE

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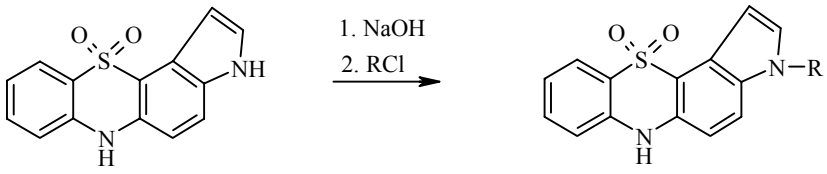
A method has been developed for N-alkylating 3H-pyrrolo[2,3-c]phenothiazine 11,11-dioxide with alkyl chlorides in absolute dimethylformamide in the presence of sodium hydroxide.

Keywords: aminazine, diprazin, indole, pyrrolophenothiazine, phenothiazine, etapyrazine.

As is known N-alkylindoles are used for obtaining analogs of indomethacin possessing anti-inflammatory activity and also for carrying out various syntheses in a series of indole. The high pharmacological activity of phenothiazine derivatives is also known and the N-alkyl derivatives of phenothiazine are of the greatest interest in this respect [1-4]. Highly active compounds such as aminazine, diprazin, etapyrazine, etc. have been discovered among them [5].

The alkylation of indole is effected through its metallated derivatives and the nature of the metal and solvent shows the greatest effect on the direction of alkylation. An increase in the ionic character of the nitrogen–metal bond when using the alkali metals (Na, K) [6] and aprotic polar solvents [7,8] favor N-alkylation.

Our problem of the N-alkylation of 3H-pyrrolo[2,3-*c*]phenothiazine-11,11-dioxide is complicated by the presence of two NH groups, in the thiazine and in the pyrrole rings of its molecule. It turned out that the pyrrole ring NH group possesses the greater reactivity.



1 **2–6**

2 R = $CH_2CH_2N(CH_3)_2$; **3** R = $CH_2CH_2N(C_2H_5)_2$; **4** R = $CH_2CH_2CH_2N(CH_3)_2$;
5 R = $CH_2CH_2CH_2N(C_2H_5)_2$; **6** R = $CH_2C(CH_3)_2CH_2N(CH_3)_2$

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Attempts to introduce a substituent into the NH group of the thiazine ring were not successful. At 80-100°C substitution proceeds only at the NH group of the pyrrole ring, but on increasing the temperature to 150-170°C, according to data of TLC and ^{1}H NMR spectroscopy, a second product, the disubstituted derivative appeared. However at this temperature the reaction mixture was strongly resinified and the product of disubstitution was formed in negligible small quantities. The alkylation of compound **1** was carried out under the conditions described for phenothiazine and its derivatives in [9,10].

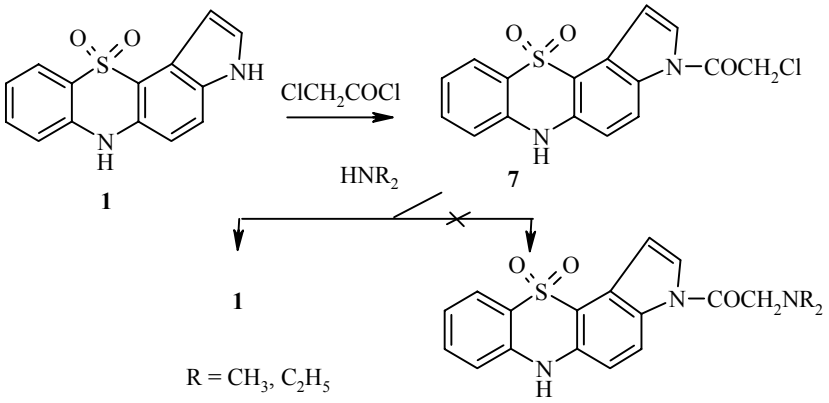
The (dialkylamino)alkyl derivatives **2-6** obtained do not contain contamination by the initial dioxide **1**, which was always present in the reaction mixture in other methods of synthesis irrespective of the reaction duration, the excess of (dialkyl-amino)alkyl chloride taken, and the temperature of the reaction mixture. In our method, in contrast to known procedures, reagents such as sodium amide or sodium hydride and also large quantities of aprotic solvent were not used. The simplicity of carrying out the reaction enables it to be recommended for obtaining N-alkyl derivatives (at the pyrrole ring) in the dioxide **1** series.

To study their biological activity we also obtained compounds **2-6** as the water soluble hydrochlorides. The structure of these compounds was established by ^{1}H NMR spectroscopy.

The signal for the 3-H proton at the nitrogen atom of the pyrrole ring was not observed in the spectra of compounds **2-6**, but there were signals for CH_2 and CH_3 groups at 4.10-4.26, 1.80-2.50, and 0.90-2.15 ppm, respectively, proving the replacement of the hydrogen atom of the pyrrole ring by a (dialkylamino)alkyl group in dioxide **1** (Table 1).

The data of elemental analysis and IR spectra of the compounds synthesized were in agreement with the structure proposed. The IR spectra of compounds **2-6** show an absorption band characteristic for an NH group at 3330, 3320, 3350, 3340, and 3310 cm^{-1}, respectively. Unfortunately, due to the poor solubility of the alkylation products **2-6** in ethanol, it was not possible to register their UV spectra.

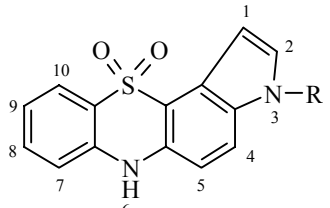
On interacting dioxide **1** with chloroacetyl chloride we isolated and characterized the N-substitution product **7**. This was confirmed by the absence of a signal for the 3-H proton and the presence of a high-field signal at 5.11 ppm characteristic of a CH_2 group in ^{1}H NMR spectrum.



Attempts to introduce an amino group into the side chain of compound **7** proved to be unsuccessful. On treating compound **7** with an aqueous solution of dimethylamine in a slightly basic medium fission of the chloroacetyl group occurred with the formation of the initial dioxide **1**.

A similar result was also obtained by the action of a benzene solution of diethylamine. Only the initial dioxide **1** was isolated in quantitative yield from the reaction mixture.

TABLE 1. Chemical Shifts (δ, ppm) and Coupling Constants (*J*, Hz) of Compounds **2-7** in DMSO-d_6



2–7

Com-pound	R	δ, ppm										*J*, Hz
		R	1-H	2-H	4-H	5-H	6-H	7-H	8-H	9-H	10-H	
2	–CH_2–CH_2–$N(CH_3)_2$ α β β'	α CH_2 = 4.15; β CH_2 = ~2.20; β' CH_3 = 2.15	6.86	7.45	7.28	7.55	10.50	7.61	7.45	7.47	7.80	J_{12} = 2.8 J_{45} = 9.0
3	–CH_2–CH_2–$N(CH_2$–$CH_3)_2$ α β α' β'	α CH_2 = 4.26; β CH_2 = ~2.50; α' CH_2 = 4.35; β' CH_3 = 0.89	6.85	7.48	7.31	7.74	10.42	*	7.40	7.45	*	J_{12} = 2.9 J_{45} = 9.1
4	–CH_2–CH_2–CH_2–$N(CH_3)_2$ α β γ β'	α CH_2 = 4.22; β CH_2 = γ CH_2 = 2.10-1.80; β' CH_3 = 2.12	6.83	7.42	7.06	7.86	10.41	7.80	7.40	7.48	7.80	J_{12} = 2.7 J_{45} = 8.8
5	–CH_2–CH_2–CH_2–$N(CH_2$–$CH_3)_2$ α β γ α' β'	α CH_2 = 4.25; β CH_2 = γ CH_2 = 2.21-1.90; α' CH_2 = 4.30; β' CH_3 = 0.90	6.80	7.47	7.21	7.77	10.40	7.72	7.38	7.55	7.80	J_{12} = 2.7 J_{45} = 8.9
6	–CH_2–$C(CH_3)_2$–CH_2–$N(CH_3)_2$ α β γ β'	α CH_2 = 4.10; β CH_3 = 0.89; γ CH_2 = 2.30; β' CH_3 = 2.30	6.89	7.41	7.31	7.37	10.50	7.11	7.42	7.60	7.89	J_{12} = 3.3 J_{45} = 8.8 J_{14} = 0.7
7	–CO–CH_2–Cl β	β CH_2 = 5.07	7.14	7.98	8.49	7.28	10.80	7.54	7.39	7.60	7.89	J_{12} = 3.9 J_{45} = 9.1

*Complex overlap of signals of the aromatic protons.

EXPERIMENTAL

A check on the progress of reaction and the purity of compounds was carried out on Silufol 254 plates (benzene–acetone, 10:1). The UV spectrum was taken on a Specord UV-vis spectrophotometer (in ethanol). The IR spectra (in nujol) were taken on a UR 20 instrument with NaCl and LiF prisms, the scanning rate was 160 at a spectral slit width of 4 cm. The ^{1}H NMR spectra were recorded on a Varian CFT 20 spectrometer with an operating frequency of 80 MHz and on a WP 200 SY spectrometer (200 MHz), internal standard was TMS.

3-[(Dimethylamino)ethyl]-3H-pyrrolo[2,3-*c*]phenothiazine 11,11-Dioxide (2). A mixture of abs. DMF (10 ml) and powdered NaOH (0.14 g, 3.5 mmol) was stirred for 15 min, then compound **1** (0.2 g, 0.7 mmol) was added and the mixture stirred for further 45 min. 2-(Dimethylamino)ethyl chloride hydrochloride (0.2 g, 1.4 mmol) was introduced in portions into the reaction mixture, then was heated at 80-100°C for 20 h.

The crystals of NaCl and the excess of NaOH which precipitated on cooling were filtered off, dissolved in dilute HCl solution, and the solution was filtered once again. A 10% solution of NaOH was added dropwise to the filtrate. The precipitated solid was filtered off, washed thoroughly with water, and dried in a vacuum desiccator over P_2O_5. Compound **2** (0.15 g, 60%) was obtained; mp 295-297°C (decomp.). IR spectrum: 3330 cm^{-1} (NH). Found, %: C 63.6; H 5.8; N 12.5; S 9.9. $C_{18}H_{19}N_3O_2S$. Calculated, %: C 63.3; H 5.6; N 12.3; S 9.4. The data of the ^{1}H NMR spectrum are given in Table 1.

3-[(2-Dimethylamino)ethyl]-3H-pyrrolo[2,3-*c*]phenothiazine 11,11-Dioxide Hydrochloride (2a). The dioxide **2** (0.3 g, 1 mmol) was suspended in abs. ethanol (100 ml), 20% alcoholic HCl solution (several drops) was added, and the mixture was stirred for 1 h. The solid formed after adding abs. ether was filtered off, washed with abs. ether, and dried in a desiccator over P_2O_5. Compound **2a** (0.28 g, 85%) was obtained; mp 281°C (decomp.). Found, %: C 57.4; H 5.7; N 11.5; S 8.9; Cl 9.9. $C_{18}H_{20}ClN_3O_2S$. Calculated, %: C 57.2; H 5.3; N 11.1; S 8.5; Cl 9.4.

3-[(2-Diethylamino)ethyl]-3H-pyrrolo[2,3-*c*]phenothiazine 11,11-Dioxide (3) was obtained analogously to compound **2** from dioxide **1** (0.2 g, 0.7 mmol) and 2-(diethylamino)ethyl chloride hydrochloride. Yield of compound **3** 63%; mp 207-208°C. IR spectrum: 3320 cm^{-1} (NH). Found, %: C 64.8; H 6.0; N 11.5; S 8.9. $C_{20}H_{23}N_3O_2S$. Calculated, %: C 65.0; H 6.2; N 11.4; S 8.7. The data of the ^{1}H NMR spectrum are given in Table 1.

3-[(2-Diethylamino)ethyl]-3H-pyrrolo[2,3-*c*]phenothiazine 11,11-Dioxide Hydrochloride (3a) was obtained analogously to compound **2a** from dioxide **3** (0.3 g, 1 mmol). Yield of compound **3a** 0.25 g (75%); mp 187-188°C. Found, %: C 59.2; H 6.1; N 10.2; S 8.0; Cl 9.2. $C_{20}H_{24}ClN_3O_2S$. Calculated, %: C 59.2; H 5.9; N 10.4; S 7.9; Cl 8.8.

3-[(3-Dimethylamino)propyl]-3H-pyrrolo[2,3-*c*]phenothiazine 11,11-Dioxide (4) was obtained analogously to compound **2** from dioxide **1** (0.2 g, 0.7 mmol) and 3-(dimethylamino)propyl chloride. Yield of compound **4** 0.17 g (65%); mp 227-228°C. IR spectrum: 3350 cm^{-1} (NH). Found, %: C 64.4; H 5.7; N 11.5; S 8.8. $C_{19}H_{21}N_3O_2S$. Calculated, %: C 64.2; H 5.9; N 11.8; S 9.0. The data of the ^{1}H NMR spectrum are given in Table 1.

3-[(3-Dimethylamino)propyl]-3H-pyrrolo[2,3-*c*]phenothiazine 11,11-Dioxide Hydrochloride (4a) was obtained analogously to compound **2a** from dioxide **4** (0.3 g, 1 mmol). Yield of compound **4a** 0.25 g (76%); mp 197-198°C (decomp.). Found, %: C 58.0; H 5.5; N 10.5; S 8.4; Cl 19.2. $C_{19}H_{22}ClN_3O_2S$. Calculated, %: C 58.2; H 5.6; N 10.7; S 8.2; Cl 9.1.

3-[3-(Diethylamino)propyl]-3H-pyrrolo[2,3-*c*]phenothiazine 11,11-Dioxide (5) was obtained analogously to compound **2** from dioxide **1** (0.2 g, 0.7 mmol) and 3-(diethylamino)propyl chloride hydrochloride. Yield of dioxide **5** 0.15 g (54%); mp 218-220°C. IR spectrum 3340 cm^{-1} (NH). Found, %: C 65.9; H 6.6; N 10.9; S 8.6. $C_{21}H_{25}N_3O_2S$. Calculated, %: C 65.8; H 6.5; N 11.0; S 8.4. The data of the ^{1}H NMR spectrum are given in Table 1.

3-[(3-Diethylamino)propyl]-3H-pyrrolo[2,3-*c*]phenothiazine 11,11-Dioxide Hydrochloride (5a) was obtained analogously to compound **2a** from dioxide **5** (0.3 g, 1 mmol). Yield of compound **5a** 0.26 g (82%); mp 189-191°C (decomp.). Found, %: C 59.9; H 6.0; N 10.1; S 7.8; Cl 8.8. $C_{21}H_{26}ClN_3O_2S$. Calculated, %: C 60.0; H 6.2; N 10.0; S 7.6; Cl 8.5.

3-[(3-Dimethylamino)-2,2-dimethylpropyl]-3H-pyrrolo[2,3-*c*]phenothiazine 11,11-Dioxide (6) was obtained analogously to compound **2** from dioxide **1** (0.2 g, 0.7 mmol) and 3-(dimethylamino)-2,2-dimethylpropyl chloride hydrochloride. The yield of dioxide **6** 0.25 g (89%); mp 268-270°C (decomp.). IR spectrum: 3310 cm^{-1} (NH). Found, %: C 66.0; H 6.7; N 11.1; S 8.8. $C_{21}H_{25}N_3O_2S$. Calculated, %: C 65.8; H 6.5; N 11.0; S 8.4. The data of the ^1H NMR spectrum are given in Table 1.

3-[(3-Dimethylamino)-2,2-dimethylpropyl]-3H-pyrrolo[2,3-*c*]phenothiazine 11,11-Dioxide Hydrochloride (6a) was obtained analogously to compound **2a** from dioxide **6** (0.3 g, 1 mmol). Yield of compound **6a** 0.3 g (91%); mp 249-250°C (decomp.). Found, %: C 60.2; H 6.5; N 9.9; S 7.7; Cl 8.7. $C_{21}H_{26}ClN_3O_2S$. Calculated, %: C 60.0; H 6.2; N 10.0; S 7.6; Cl 8.5.

3-Chloroacetyl-3H-pyrrolo[2,3-*c*]phenothiazine 11,11-Dioxide (7). A mixture of compound **1** (0.2 g, 0.7 mmol) in chloroacetyl chloride (10 ml) was refluxed for 5 h. The precipitated solid was filtered off, washed with acetone, and dried. Yield of dioxide **7** 0.2 g (77%); mp 294-295°C. IR spectrum, ν, cm^{-1}: 3360 (NH), 1735 (C=O). UV spectrum, λ_{max} (log ε), nm: 207 (4.23), 241 (3.95), 285 (4.30), 339 (4.71). Found, %: C 55.2; H 3.0; N 8.1; S 9.0; Cl 10.5. $C_{16}H_{11}ClN_2O_3S$. Calculated, %: C 55.4; H 3.2; N 8.1; S 9.2; Cl 10.2. The data of the ^1H NMR spectrum are given in Table 1.

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