PYRROLOPHENOTHIAZINES.

1. SYNTHESIS OF ISOMERIC PYRROLOPHENOTHIAZINE DIOXIDES

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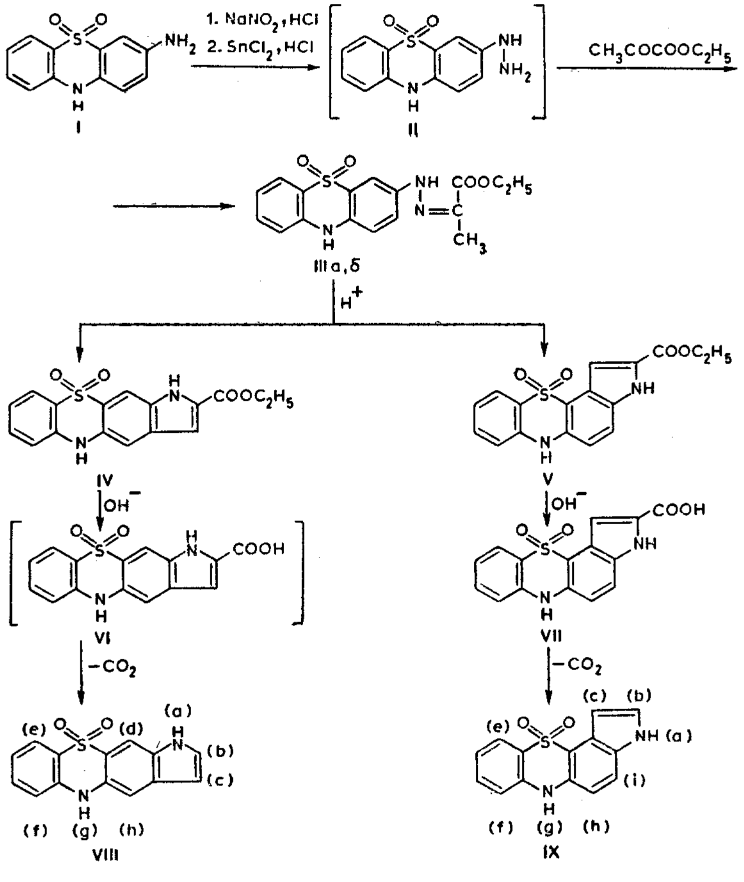
The synthesis of 1H-pyrrolo[3,2-b]phenothiazine 10,10-dioxide and 3H-pyrrolo[2,3-c]phenothiazine 11,11-dioxide was realized on the basis of 3-aminophenothiazine 5,5-dioxide by means of the Fischer reaction. The structures of the synthesized compounds were proved by data from the IR, UV, PMR, and mass spectra.

Continuing our research on four-ring pyrrolo-containing condensed systems we accomplished the synthesis of previously undescribed 1H-pyrrolo[3,2-b]phenothiazine 10,10-dioxide and 3H-pyrrolo[2,3-c]phenothiazine 11,11-dioxide by means of the Fischer reaction via the scheme*:



We selected 3-aminophenothiazine 5,5-dioxide as the starting compound. 3-Nitrophenothiazine 5-oxide is formed in the nitration of phenothiazine. Oxidation of this product with hydrogen peroxide gives 3-nitrophenothiazine 5,5-dioxide, the subsequent reduction of which leads to 3-aminophenothiazine 5,5-dioxide (I) [1].

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*The positions of the protons are indicated by letters in parentheses for convenience in the interpretation of the PMR spectra.

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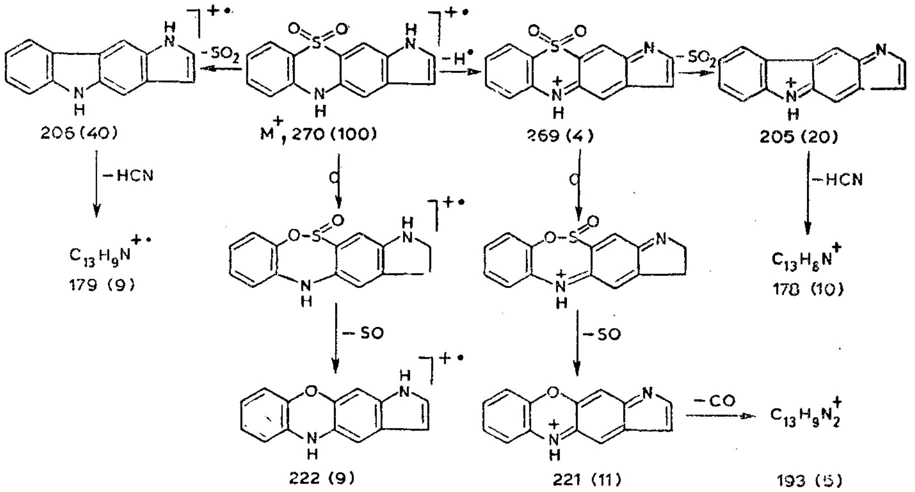
The diazotization of I and the subsequent reduction of the diazo compound to give a hydrazine were accomplished by the usual methods [2, 3]. The reaction of the resulting hydrochloride of 3-phenothiazinylhydrazine 5,5-dioxide (II) with ethyl pyruvate leads to the formation of hydrazone III in the form of a mixture of geometrical isomers. We were able to separate the latter by means of column chromatography to give the syn and anti forms (IIIa, b).

A shift to weak field of the signal of the proton of the exocyclic NH group of isomer IIIa (12.0 ppm) as compared with the corresponding signal of the proton of isomer IIIb (9.3 ppm) due to an intramolecular hydrogen bond, the formation of which is also indicated by the changes in the IR and UV spectra, is observed when one compares the PMR spectra of solutions of the stereoisomeric forms of the hydrazone in $CDCl_3$.

From the mixture of products formed in the cyclization of hydrazone III under the influence of ethyl polyphosphate we were able to isolate ethyl 1H-pyrrolo[3,2-b]phenothiazine-2-carboxylate 10,10-dioxide and 3H-pyrrolo[2,3-c]phenothiazine-2-carboxylate 11,11-dioxide (IV and V) in 3 and 35% yields, respectively, and were able to characterize them.

By saponification of esters IV and V we obtained the corresponding carboxylic acids VI and VII, the thermal decarboxylation of which leads to the formation of 1H-pyrrolo[3,2-b]-phenothiazine 10,10-dioxide (VIII) in 25% yield and 3H-pyrrolo[2,3-c]phenothiazine 11,11-dioxide (IX) in 35% yield.

Data from PMR, IR, UV, and mass spectrometry confirm the structures of the synthesized compounds. An intense molecular-ion peak (M^+) with m/z 270 is observed in the mass spectra of the isomeric pyrrolophenothiazine dioxides, and the character of the subsequent fragmentation does not contradict the proposed structures [4, 5]. As a consequence of the monotypic character of the scheme of the fragmentation for the mass spectra of the isomeric heterocycles, we will present the fragmentation scheme only for 1H-pyrrolo[3,2-b]phenothiazine 10,10-dioxide*:



The linear and angular isomers (Table 1) were identified on the basis of the observed (for the latter) AB spectrum, which is characteristic for the signals of the ortho protons ($J_{ortho} \sim 9$ Hz) of the ring adjacent to the pyrrole ring. The assignment of the signals of the protons of this ring was made for both isomers with allowance for the existence of a long-range spin–spin coupling constant of the transoid type (${}^5J$) with the β proton of the pyrrole ring. (Similar coupling with the proton of the NH group is not observed because of rapid deuterium exchange with the solvent.) In addition, as expected, in the case of the derivatives of the angular isomer the β proton of the pyrrole ring (c) experiences a strong anisotropic effect of the closely located SO_2 group (0.5–0.6 ppm). For this reason (the electron-acceptor properties of the SO_2 group), the (e) proton of the other benzene ring is more deshielded than the (f) proton, while the signal of the (d) proton of the linear isomer is found at weakest field.

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*The m/z values are presented; the relative intensities of the ion peaks in percent of the maximum peak are given in parentheses.

TABLE 1. Chemical Shifts and Spin–Spin Coupling Constants in the PMR Spectra of IV, V, and VII-IX in d_6-Acetone

Compound	δ, ppm									J, Hz
	(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)	(i)	
IV	11,0	4,39; 1,38 (Et)	7,12	8,18	7,90	7,47	9,4	7,56	—	$J_{CH_2CH_3}=7,1$; $J_{a,c}=2,2$; $^5J_{c,d}=1,0$
V	11,3	4,38; 1,39 (Et)	7,65	—	7,98	7,52	9,8	7,25	7,76	$J_{CH_2CH_3}=7,1$; $J_{a,c}=2,1$; $^5J_{c,i}=0,7$; $J_{h,i}=9,0$
VII*	12,1	—	7,34	—	—	—	10,6	—	—	$J_{a,c}=2,2$; $^5J_{c,i}=0,9$
VIII	10,5	7,44	6,46	8,07	7,90	~7,5	9,5	~7,5	—	$J_{a,b}=2,5$; $J_{a,c}=2,1$; $^5J_{c,d}=1,0$
IX	10,6	7,44	7,02	—	7,96	—	9,7	7,04	7,66	$J_{a,b}=2,5$; $^5J_{c,i}=0,9$; $J_{a,c}=2,0$; $J_{b,c}=3,1$; $J_{h,i}=8,7$

*The spectrum of VII in d_6-DMSO was recorded at 60°C; COOH $\rightleftarrows$ H_2O (solvent exchange is observed, and the spectrum of the aromatic protons is not a first-order spectrum.

EXPERIMENTAL

The course of the reactions and the purity of the compounds were monitored on plates with a fixed layer of Silufol 254 silica gel. The UV spectra of solutions of the compounds in ethanol were recorded with a Specord spectrophotometer. The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer with NaCl and LiF prisms; the scanning rate was 160 at a spectral slit width of 4 cm^{-1}. The mass spectrum was recorded with an MKh-1303 spectrometer with direct introduction of the sample into the ion source at a cathode emission current of 1.5 μA and an ionizing voltage of 50 V. The PMR spectra were recorded with a Varian CFT-20 high-resolution spectrometer (80 MHz); the chemical shifts were measured relative to tetramethylsilane as the internal standard with an accuracy of 0.01 ppm, while the spin–spin coupling constants (SSCC) were measured with an accuracy of 0.1 Hz.

Ethyl Pyruvate 3-Phenothiazinylhydrazone 5,5-Dioxide (III). A solution of 2.76 g (0.04 mole) of $NaNO_2$ in 11 ml of water was added at room temperature to a suspension of 10 g (0.04 mole) of I in 100 ml of HCl and 800 ml of H_2O, and the diazo compound was reduced with a solution of 45 g of $SnCl_2 \cdot 2H_2O$ in 100 ml of HCl. After the addition of the reducing agent, the reaction mixture was maintained at 20°C for 2 h. The undissolved mass was removed by filtration, a saturated solution of sodium acetate was added to the filtrate, thereby bringing the pH of the medium up to three, and the resulting precipitate was again removed by filtration. A solution of 4.64 ml (0.04 mole) of ethyl pyruvate in 8 ml of ethanol was added to the filtrate, and the mixture was stirred for 30 min. The resulting yellow precipitate was removed by filtration, washed with water, and dried to give 10 g (60%) of the hydrazone. The mixture of stereoisomers of hydrazone III was separated with a column filled with 100/250 μ silica gel [elution with chloroform–ether (2:1)]; the ratio of the syn and anti forms was 1:3. Isomer IIIa had mp 228-229°C and R_f 0.60 (Silufol, ether). IR spectrum: 3470, 3280 (NH); 1670 cm^{-1} (C=O). UV spectrum (in alcohol), λ_{max} (log ε): 219 (4.57), 276 (4.30), 351 (4.46), 355 (4.47), and 388 nm (4.33). Found: C 56.8; H 4.7; N 11.7; S 8.7%. $C_{17}H_{17}N_3O_4S$. Calculated: C 56.8; H 4.7; N 11.7; S 8.9%. Isomer IIIb had mp 243-244°C and R_f 0.30 (Silufol, ether). IR spectrum: 3315, 3295 (NH); 1690 cm^{-1} (C=O). UV spectrum (in alcohol), λ_{max} (log ε): 220 (4.54), 270 (4.16), 308 (4.25), and 343 nm (4.53). Found: C 56.8; H 4.8; N 11.4; S 8.7%. $C_{17}H_{17}N_3O_4S$. Calculated: C 56.8; H 4.7; N 11.7; S 8.9%.

Ethyl 1H-Pyrrolo[3,2-b]phenothiazine-2-carboxylate 10,10-Dioxide and 3H-Pyrrolo[2,3-c]-phenothiazine-2-carboxylate 11,11-Dioxide (IV, V). A 5-g sample of III was added to 50 g of polyphosphoric acid ester, and the mixture was heated to 80°C with constant stirring for 30 min. It was then cooled and poured into water, and the resulting precipitate was removed by filtration, washed with water, and dried. The mixture of IV and V was separated with a column filled with 100/250 silica gel. The eluent for IV was chloroform–ether (1:1), while the eluent for V was ether. The yield of ester IV, with mp 321-322°C and R_f 0.57 (ether), was 0.12 g (3%). IR spectrum: 3340, 3300 (NH); 1725 cm^{-1} (C=O). UV spectrum (in alcohol), λ_{max} (log ε): 206 (4.30), 238 (4.38), 280 (4.64), 303 (4.26), 315 (4.25), and 420 nm (4.14). Found: C 59.6; H 4.1; N 8.1; S 9.3%. $C_{17}H_{14}N_2O_4S$. Calculated: C 59.6; H 4.0; N 8.1; S 9.3%. The yield of ester V, with mp 329-331°C and R_f 0.20 (ether), was 1.4 g (35%). IR spectrum: 3460, 3240 (NH); 1680 cm^{-1} (C=O). UV spectrum (in alcohol), λ_{max} (log ε): 207 (4.50), 215 (4.55), 256.5 (4.46), 277 (4.43), 303 (4.41), and 361 nm (4.14). Found: C 59.4; H 4.2; N 8.1; S 9.5%. $C_{17}H_{14}N_2O_4S$. Calculated: C 59.6; H 4.0; N 8.1; S 9.3%.

3H-Pyrrolo[2,3-c]phenothiazine-2-carboxylic Acid 11,11-Dioxide (VII). A mixture of 0.47 g (1 mmole) of ester V, 23 ml of H_2O, and 1.41 g (25 mmole) of KOH was refluxed with stirring for 3 h, and the resulting solution was cooled and filtered. The filtrate was adjusted to pH 7-8 with dilute HCl solution and filtered, and the filtrate was acidified to pH 1. Compound VII was washed with water and dried over P_2O_5 to give 0.38 g (88%) of a product with mp 368-369°C and R_f 0.25 (ethyl acetate). IR spectrum: 3220, 3140 (NH); 1690 cm^{-1} (C=O). UV spectrum (in alcohol), λ_{max} (log ε): 215 (4.56), 255 (4.40), 276 (4.58), 304 (4.33), and 374 nm (4.17). Found: C 57.1; H 3.4; N 8.8; S 10.2%. $C_{15}H_{10}N_2O_4S$. Calculated: C 57.3; H 3.1; N 8.9; S 10.1%.

1H-Pyrrolo[3,2-b]phenothiazine 10,10-Dioxide (VIII). A mixture of 0.16 g (0.5 mmole) of ester IV, 8 ml of H_2O, and 0.48 g (8 mmole) of KOH was refluxed with stirring for 3 h, and the resulting solution was cooled and filtered. The filtrate was adjusted to pH 7-8 with a dilute solution of HCl and filtered, and the filtrate was acidified to pH 1. Compound VI was washed with water and dried over P_2O_5. It was obtained in quantitative yield. A 0.14-g sample of crude acid VI was decarboxylated at 325-330°C in the course of 30 min. The material was cooled and purified with a column filled with 100/250 silica gel (elution with ether) to give 0.03 g (25%) of a product with mp 309-311°C and R_f 0.77 [ethyl acetate–ether (1:1)]. IR spectrum: 3380, 3330 cm^{-1} (NH). UV spectrum (in alcohol), λ_{max} (log ε): 226 (4.434), 242 (4.474), 276 (4.612), and 364 nm (3.750). Mass spectrum, m/z (intensities of the ion peaks in percent of the maximum peak): 270 (100), 269 (5.5), 253 (10.5) 238 (13.0), 225 (25.0), 222 (9.5), 221 (11.5), 206 (40.0), 205 (20.0), 193 (6.5), 179 (9.0), 178 (10.5), 177 (8.0). Found: C 62.3; H 3.8; N 10.0; S 11.7%. $C_{14}H_{10}N_2O_2S$. Calculated: C 62.2; H 3.7; N 10.3; S 11.8%.

3H-Pyrrolo[2,3-c]phenothiazine 11,11-Dioxide (IX). A 0.56-g sample of acid VII was decarboxylated at 375-380°C in the course of 30 min. The material was cooled and purified with a column filled with 100/250 silica gel (elution with ether) to give 0.15 g (35.7%) of a product with mp 314-316°C and R_f 0.44 [ethyl acetate–ether (1:1)]. IR spectrum: 3420, 3310 cm^{-1} (NH). UV spectrum (in alcohol), λ_{max} (log ε): 213 (4.31), 270 (4.25), 304 (3.87), and 340 nm (3.82). Found: C 62.1; H 3.8; N 10.7; S 11.9%. $C_{14}H_{10}N_2O_2S$. Calculated: C 62.2; H 3.7; N 10.3; S 11.8%.

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