PYPROLOPHENOTHIAZINES. 2.* SOME ELECTROPHILIC REACTIONS OF 3H-PYRROLO[2,3-c]PHENOTHIAZINE 11,11-DIOXIDE

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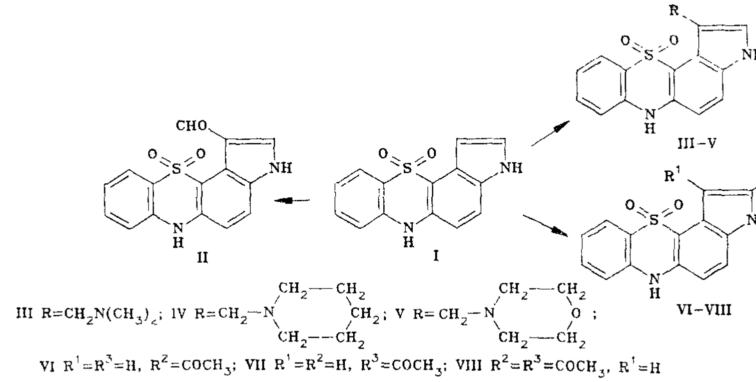
The reactivity of 3H-pyrrolo[2,3-c]phenothiazine 11,11-dioxide has been studied in the following electrophilic substitution reactions, which are typical of the indole series: the Mannich reaction, the Vilsmeier reaction, and acetylation. The physicochemical characteristics of the compounds synthesized have been considered.

Despite the large number of investigations devoted to the synthesis of phenothiazine derivatives, the properties of 3H-pyrrolo-[2,3-d]phenothiazine 11,11-dioxide (I) have not been described in the literature.

As a continuation of our investigations in a series of tetracyclic pyrrole-containing condensed systems, it seemed to be of interest to study the behavior of the heterocyclic just cited in the following electrophilic substitution reactions, which are typical of the indole series: the Mannich reaction, the Vilsmeier reaction, acetylation, and nitrogen coupling.



1-Formyl-3H-pyrrolo[2,3-c]phenothiazine 11,11-dioxide (II) was obtained by the formylation of compound I by N,N-dimethylformamide in the presence of phosphorus oxychloride. The absence of a signal for the 1-H proton in the PMR spectrum of compound II and the significant downfield shift of the signals of the 2-H and 3-H protons (Table 1) in comparison to the unsubstituted ring in I (7.44 and 10.6 ppm, respectively) [1] are indications of the replacement of the hydrogen atom in the pyrrole ring in the β position by an aldehydic group. At the same time, disappearance of the long-range spin–spin coupling constant of the transoid type $^5J_{1,4} \geq 0.5$ Hz characteristic of the unsubstituted analog I is also observed. In the mass spectrum of II there is an intense peak for the molecular ion $[M^+]$ at 298, and the nature of the further fragmentation does not contradict the proposed structure.†

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*For report 1 see [1]

†The values of m/z are given, and the relative intensities of the peaks of the ions as percentages of the maximum intensity are given in parentheses.

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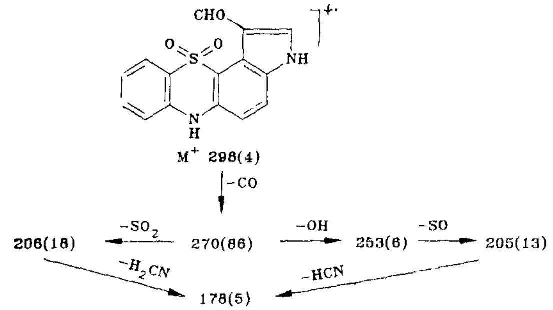

Compound I is easily aminomethylated by dimethylamine, piperdine, and morpholine under the conditions described for indole in [2]. In this case, too, the substitution unequivocally takes place in the β position of the pyrrole ring, as is indicated by the absence of a signal for the 1-H protons in the PMR spectra of compounds III-V, the vanishing of the small spin—spin coupling constant $^5J_{14}$, and the upfield shift of the signal of the 2-H protons under the effect of donor substituents (with the exception of compound III, which was obtained in the form of the hydrochloride).

The study of the behavior of I in a Friedel—Crafts reaction revealed that, unlike indole, which resinifies in the presence of Lewis acids, 3H-pyrrolo[2,3-c]phenothiazine 11,11-dioxide (I), as well as phenothiazine [3], readily undergo this reaction. This reaction was carried out under the conditions described for the formally similar compound (with respect to the presence of two NH groups) 3H-pyrrolo-[2,3-c]carbazole in [4]. However, in the case of the carbazole, the acetyl group enters the unsubstituted benzene ring, whereas in compound I the position of the pyrrole ring undergoes acetylation.

The behavior of compound I in an acetylation reaction under the conditions described for indole was also interesting. The reaction takes place more readily; however, here, too, the substitution takes place in the position α position of the pyrrole ring. For example, when 3H-pyrrolo[2,3-c]phenothiazine 11,11-dioxide is reacted with acetic anhydride in acetic acid, the 2,3-diacetyl derivative VIII forms along with the 3-acetyl derivative VII. Compound I apparently reacts only with acetic anhydride, and in this case, monosubstitution product VII unequivocally forms with a quantitative yield. Under similar conditions indole gives a mixture of mono- and diacyl derivatives [5]. Vilsmeier acetylation by the complex of N,N-dimethylacetamide and phosphorus oxychloride could not be carried out. This was clearly due to the low electrophilicity of the attacking complex. Acetylation products VI-VIII, unlike compounds II-V, either show a small spin—spin coupling constant $^5J_{14}$ in their PMR spectra or display broadening of the corresponding interacting signals, indicating that position 1 is unoccupied. The electron-acceptor and anisotropic properties of the substituent cause the corresponding downfield shifts of the signals of the nearby groups. The chemical shift of the 1-H proton in the 2,3-disubstituted compound VIII corresponds to the sum of the additive contributions from each of the substituents (6.86 ppm for compound I in DMSO). In order to obtain more convincing proof of the presence of one of the acetyl groups in compound VIII specifically in the α position of the pyrrole ring, a back synthesis was carried out. Saponification of VIII was carried out, and a substance identical with respect to all parameters to the monoacetyl derivative VI obtained in a Friedel—Crafts reaction, in which the position of the substituent is not questioned, was isolated.

Such behavior of 3H-pyrrolo[2,3-c]phenothiazine 11,11-dioxide (I) upon the introduction of aldehydic or acetyl groups is apparently attributable only to steric factors, since the absolute value of the chemical shift of the 1-H proton in the unsubstituted ring attests to the sufficiently large and predominant electron density in the β position of the pyrrole ring. The replacement of the formyl group by an acetyl group clearly causes great steric stresses and a strong dipole—dipole interaction between the carbonyl group and the SO_2 group.

Our attempt to study the influence of highly selective electrophiles on the course of the substitution reaction in dioxide I was unsuccessful. This heterocycle does not react at all with phenyldiazonium chloride or 4-chloro- and 4-nitrophenyldiazonium chloride. Such behavior is apparently attributable to the increased sensitivity of the nitrogen-coupling reaction to relatively small differences in electron density. The electron density of the α position in the pyrrole ring of compound I in the case of this reaction is insufficient for its attack by a selective electrophile. The presence of an SO_2 group prevents attack in the β position.

TABLE 1. Chemical Shifts and Spin–Spin Coupling Constants of Compounds II-VIII[a]

Compound	δ, ppm												J, Hz
	1-H	2-H	3-H	4-H	5-H	6-H	7-H	8-H, 9-H	10-H	CHO	CH_3	CH_2	
II	—	8,12	11,3	7,78	7,16	9,8	7,2	7,6	7,99	10,80	—	—	$J_{2\,CHO}=0{,}6$; $J_{23}=3{,}2$; $J_{45}==8{,}6$
III[b]	—	7,49	12,2	7,76	7,30	11,3	7,0	7,8	7,90	—	2,81	4,75	$J_{23}\approx 2{,}0$; $J_{45}=8{,}9$
IV	—	7,10	10,7	7,61	7,03	9,9	7,0	7,8	7,94	—	—	4,09[c]	$J_{23}\approx 2{,}3$; $J_{45}=8{,}9$
V	—	7,10	10,7	7,58	6,99	9,8	7,0	7,8	7,93	—	—	4,04[c]	$J_{23}\approx 2{,}0$; $J_{45}=8{,}9$; $J_{CH_2CH_2}=4{,}5$ (morpholine)
VI[d]	7,95	—	11,9	7,79	7,27	10,4	7,2	7,6	7,87	—	2,51	—	$J_{13}=1{,}7$; $J_{45}=8{,}8$
VII	7,07	7,96	—	8,50	7,29	10,7	7,2	7,6	7,88	—	2,67	—	$J_{12}=3{,}4$; $J_{14}=0{,}5$; $J_{45}=9{,}0$
VIII[d]	8,21	—	—	8,59	7,37	10,7	7,2	7,9	7,83	—	2,58 2,69	—	$J_{45}=9{,}2$

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[a] The spectra of compounds II, IV, and V were recorded in acetone-d_6, and the spectra of compounds III and VI-VIII were recorded in DMSO-d_6 at 80°C. [b] This compound was characterized in the form of the hydrochloride. [c] The remaining protons of the piperdine fragment are located in the 1.4-2.6-ppm region, and those of the morpholine fragment are at 2.59 and 3.65 ppm. [d] The signals of the 1-H and 4-H protons are broadened.

Analyzing the results of the experimental investigation of the reactivity of dioxide I, we arrive at the conclusion that the reason for the anomalous behavior of compound I, which is manifested by the formation of products of electrophilic substitution in the α position of the pyrrole ring and the significant decrease in the reactivity of this compound in nitrogen-coupling reactions, is the great steric stresses and the strong dipole–dipole interaction caused by the presence of the SO_2 grouping.

EXPERIMENTAL

The course of the reaction and the purity of the compounds were monitored on Silufol-254 plates. The UV spectra were recorded on a Specord spectrophotometer in ethanol, and the IR spectra were recorded on a UR-20 spectrometer with NaCl and LiF prisms (in liquid petrolatum), the rate of scanning being 160 and the spectral slit width being 4 cm^{-1}. The mass spectrum was recorded on an MKh-1303 spectrometer with direct introduction of the sample into the ion source. The emission current was 1.5 A, and the ionizing voltage was 50 V. The PMR spectra were recorded on a Varian CFE-20 spectrometer (80 MHz) with TMS as an internal reference. The accuracy was equal to 0.01 ppm, and the spin–spin coupling constants had an accuracry of 0.1 Hz.

1-Formyl-3H-pyrrolo[2,3-c]phenothiazine 11,11-Dioxide (II). A 0.35-ml portion (4 mmole) of phosphorus oxychloride is slowly added to 1.15 ml (4 mmole) of freshly distilled DMFA at 0°C. The reaction mixture is held at room temperature for 1 h, and 0.2 g (0.7 mmole) of I dissolved in 2 ml of DMFA is added. The mixture is heated to 35°C over the course of 3 h. The mixture is cooled, given an addition of 10 g of crushed ice, and alkalinized with 0.1 N NaOH. The precipitate is filtered out, washed with water, and dried. Then it is purified in a column with silica gel 100/250 μ (the eluents are ethyl acetate and then 1:1 ethyl acetate–acetone). The yield is 0.15 g (59%), and the mp 342-343°C. IR spectrum: 3465, 3270 (NH), 1650 cm^{-1} (C=O). UV spectrum, λ_{max} (log ε): 212 (4.80), 266 (4.78), 299 (4.44), 399 nm (4.41). Found: C, 59.9; H, 3.0; N. 9.2; S, 10.8. Calculated for $C_{15}H_{10}N_2O_3S$: C, 60.4; H, 3.3; N, 9.3; S, 10.7%.

3-(N,N-Dimethylaminomethyl)-3H-pyrrolo[2,3-c]phenothiazine 11,11-Dioxide (III). A 0.95-ml portion (1 mmole) of a 33% aqueous solution of dimethylamine is slowly given an addition with cooling of 0.95 ml of glacial acetic acid and then 0.5 ml of 40% formalin and 0.44 g (1.6 mmole) of compound I. The mixture is held for 3 h at 30-35°C, poured into water, and alkalinized by a 10% aqueous solution of NaOH. The precipitate formed is filtered out, washed with water, and dried in a vacuum desiccator over KOH. The yield is 0.45 g (84%), and the mp 314-315°C. UV spectrum, λ_{max} (log ε): 211 (4.78), 267.4 (4.66), 342 (4.25), 357 nm (4.09). Found: C, 62.2; H, 4.8; N, 12.9; S, 10.1%. Calculated for $C_{17}H_{17}N_3O_2S$: C, 62.3;

H, 5.1; N, 12.8; S, 9.7%.

1-(N-Piperidinomethyl)-3H-pyrrolo[2,3-c]phenothiazine 11,11-Dioxide (IV) is obtained in a similar manner from I with piperidine. The yield is 0.25 g (93%) , and the mp 199-200°C. UV spectrum, λ_{max} (log ε): 211 (4.46), 266.8 (4.33), 298.5 (3.78), 326 (3.98), 342 (3.94), 357 nm (3.83). Found: C, 65.3; H, 5.4; N, 11.2; S, 8.4%. Calculated for $C_{20}H_{21}N_3O_2S$: C, 65.3; H, 5.7; N, 11.4; S, 8.7%.

1-(N-Morpholinomethyl)-3H-pyrrolo[2,3-c]phenothiazine 11,11-Dioxide (V) is obtained in an analogous manner from I with morpholine. The yield is 0.2 g (74%), and the mp 210-211°C. UV spectrum, λ_{max} (log ε): 211 (4.49), 271.5 (4.37), 311.5 (3.96), 328 (3.94), 345 (3.97), 343 (3.89), 358 nm (3.81). Found: C, 61.7; H, 5.1; N, 11.1; S, 8.8%. Calculated for $C_{19}H_{19}N_3O_3S$: C, 61.7; H, 5.1; N, 11.3; S, 8.6%.

2-Acetyl-2H-pyrrolo[2,3-c]phenothiazine 11,11-Dioxide (VI). A solution of 0.4 g (3 mmole) of $AlCl_3$ in 5 ml of methylene chloride is given a dropwise addition of 0.25 ml (3 mmole) of acetyl chloride at 0°C. The complex is stirred for 30 min, 0.14 g (5 mmole) of compound I in 15 ml of methylene chloride is added 0°C, and the stirring is continued at room temperature for 3 h and then with heating for 1 h. The reaction mixture is cooled, decomposed by water, and given an addition of 0.1 ml of HCl. The crude substance is chromatographed in a column (silica gel 100/250 μ with acetone as the eluent). The yield is 0.03 g (19%), and the mp 274-276°C. IR spectrum: 3330 (NH), 1725 cm^{-1} (C=O). UV spectrum, λ_{max} (log ε): 213 (4.29), 270 (4.27), 339 (3.83), 353 nm (3.72). Found: C, 61.3; H, 3.8; N, 8.8; S, 10.1%. Calculated for $C_{16}H_{12}N_2O_3S$: C, 61.5; H, 3.8; N, 8.9; S, 10.2%.

Compound VI is also obtained by the saponification of 0.15 g (0.4 mmole) of diacetyl derivative VIII in an ethanolic solution of KOH at -5 to 0°C over the course of 2 h. The reaction mass is poured over ice and left to stand in a refrigerator overnight. The crystals precipitated are filtered out, washed with water and dried. The yield is 0.08 g (60%).

3-Acetyl- (VII) and 2,3-Diacetyl-3H-pyrrolo[2,3-c]phenothiazine 11,11-Dioxide (VIII). A mixture of 0.4 g (1.4 mmole) of compound I, 6 ml (5 mmole) of freshly distilled acetic anhydride, and 3.2 ml (5 mmole) of glacial acetic acid is boiled for 30 h. The precipitate formed is filtered out. The filtrate is poured into water and extracted with ethyl acetate, and the extract is thoroughly washed with a solution of $NaHCO_3$ and water and dried over Na_2SO_4. The product is purified in a compound with silica gel 100/250 μ in ether. The yield of VII is 0.18 g (39%), and the mp 280-281°C. IR spectrum: 3320 (NH), 1695 cm^{-1} (C=O). UV spectrum, λ_{max} (log ε): 208 (4.23), 222 (4.21), 261 (4.22), 285 (4.23), 319 nm (3.75). Found: C, 61.4; H, 3.5; N, 8.7; S, 10.3%. Calculated for $C_{16}H_{12}N_2O_3S$: C, 61.5; H, 3.8; N, 8.9; S, 10.2%. The crystals precipitated during the reaction are recrystallized from isopropanol with an addition of several drops of DMFA. The yield of VIII is 0.15 g (28%), and the mp 315-316°C. IR spectrum: 3310 (NH), 1700, 1740 cm^{-1} (C=O). UV spectrum, λ_{max} (log ε): 212 (4.47), 246 (4.09), 286 (4.63), 318 (3.95), 347 nm (3.97). Found: C, 61.1; N, 3.6; N, 7.7; S, 9.3%. Calculated for $C_{18}H_{14}N_2O_4S$: C, 61.0; H, 3.3; N, 7.9; S, 9.0%.

Compound VII was also obtained by boiling 0.1 g (0.3 mmole) of I in 10 ml of acetic anhydride for 5 h. The precipitate formed is filtered out, washed with water, and dried. The yield is 0.6 g (54%). An additional 0.04 g of VI is recovered by treating the filtrate with water. The total yield is 90%.

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