REACTION OF PYRROLES WITH CARBON DISULFIDE IN KOH/DMSO SYSTEM

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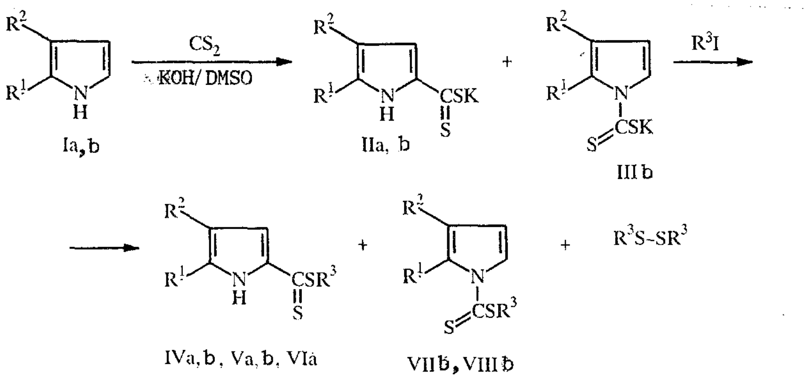
By the interaction of pyrroles with carbon disulfide and haloalkanes in a KOH/DMSO system, esters of 1- and 2-pyrrolyldithiocarboxylic acids have been synthesized. The influence of substituents on the direction of the reaction has been established.

The interaction of pyrroles with carbon disulfide and bases in aprotic solvents usually leads to pyrrole-N-dithiocarbamates [1]. Previously, in the example of 4,5,6,7-tetrahydroindole (Ia), we had shown that in the KOH/DMSO system, this reaction proceeds differently: A salt of 4,5,6,7-tetrahydro-2-indolyldithiocarboxylic acid IIa is formed; after this salt is treated with ethyl iodide, it gives the corresponding ester IVa [2].

We were interested in studying this reaction further, establishing the limits of its applicability and selectivity, and investigating the possibility of synthesis of new, functionally substituted dithio acids that may be biologically active [3]. With these goals in view, we studied the interaction of the pyrroles Ia, b with carbon disulfide and various alkyl halides in the presence of a base.



I—VIIIa R^1, R^2=(CH$_2$)$_4$; b R^1=Ph, R^2=H; VIa, VIb, VIIb R^3=Et; Va, Vb, VIIIb R^3=Bu; VIa R^3=Allyl

The reaction (~20°C, 4-6 h), depending on the structure of the original pyrrole, may proceed in different directions. From the pyrrole Ia, for example, as already mentioned [2], the salt IIa is formed, which, when treated with alkyl halides R^{3}I (R^3 = Et, Bu, allyl), gives the corresponding esters IVa-VIa with yields up to 71%.

From the pyrrole Ib (R^1 = Ph) and carbon disulfide, under standard conditions (reaction time of first stage 4 h), subsequent treatment with alkyl halides gives not only the corresponding esters of 2-pyrrolyldithiocarboxylic acid IVb and Vb (yields 52% and 58.7%), but also their structural isomers – esters of 1-pyrrolyldithiocarbamic acid VIIb and VIIIb, with

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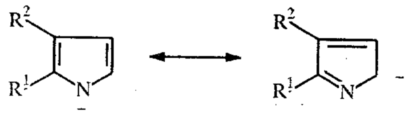
TABLE 1. Yields and Constants of Esters of Pyrrolydithiocarboxylic Acids

Pyrrole	Empirical formula	mp, °C	d_4^{20}	Yield, %
IVa	$C_{11}H_{15}NS_2$	69...69,5		71 (56)
V	$C_{13}H_{19}NS_2$	46...47		54
VIa	$C_{12}H_{15}NS_2$	37...38		44
IVb	$C_{13}H_{13}NS_2$	67...68		59
Vb	$C_{15}H_{17}NS_2$	48...48,5		52
VIIb	$C_{13}H_{13}NS_2$		1,1902	24
VIIIb	$C_{15}H_{17}NS_2$		1,0677	29

TABLE 2. Spectral Characteristics of Esters of Pyrrolyldithiocarboxylic Acids

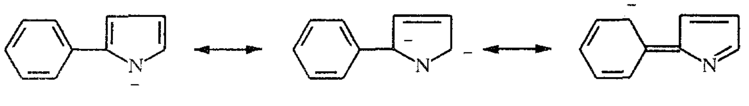
Pyrrole	IR spectrum cm^{-1} (KBr)	PMR spectrum, δ, ppm (DMSO-d_6)			
		R^1	R^2	R^3	3-H
IVa	500, 620, 680, 700, 810, 820, 830, 920, 950, 990, 1025, 1050, 1128, 1170, 1202, 1250, 1300, 1305, 1360, 1430, 1500, 1550, 2830, 2910, 3300	1,75	2,57	1,34 (Me), 3,34 (CH_2S)	6,84
Va	615, 692, 800, 820, 840, 910, 990, 1020, 1120, 1165, 1190, 1250, 1310, 1370, 1440, 1498, 1550, 2830, 2915, 3300, 3390	1,75	2,57	0,92 (Me), 1,56 (CH_2CH_2), 3,32 (CH_2S)	6,86
VIa	580, 697, 830, 915, 985, 1030, 1134, 1150, 1201, 1252, 1305, 1360, 1440, 1500, 1550, 1630, 2830, 2915, 3380	1,78	2,55	4,05 (CH_2S), 5,17 ($=CH_2$), 5,92 ($CH=$)	6,90
IVb	490, 577, 687, 750, 785, 820, 838, 925, 995, 1002, 1025, 1051, 1085, 1150, 1180, 1210, 1252, 1380, 1445, 1495, 1545, 1595, 2860, 2920, 2960, 3050, 3100, 3130, 3390	7,45; 7,97	6,84	1,35 (Me), 3,38 (CH_2S)	7,24
Vb	575, 680, 751, 812, 987, 1026, 1046, 1075, 1210, 1250, 1380, 1445, 1460, 1495, 1540, 1595, 2850, 2910, 2950, 3050, 3100, 3130, 3390	7,44; 7,94	6,82	0,94 (Me), 1,58 (CH_2CH_2), 3,33 (CH_2S)	7,24
VIIb*	690, 710, 750, 815, 830, 975, 1020, 1080, 1105, 1175, 1270, 1380, 1460, 1490, 1600, 2860, 2910, 2960, 3050, 3100, 3130	7,34	6,53	1,29 (Me), 3,29 (CH_2S)	6,39
VIIIb**	560, 625, 650, 708, 750, 815, 905, 975, 1040, 1082, 1100, 1180, 1270, 1380, 1460, 1495, 1600, 2860, 2930, 2960, 3050, 3100	7,25	6,34	0,88 (Me), 1,48 (CH_2CH_2), 3,25 (CH_2S)	6,23

* 2-H 7,52 ppm.
** 2-H 7,39 ppm.



respective yields of 24% and 29%. The total yields for the esters IVb, Vb, VIIb, and VIIIb are higher than for the corresponding esters IVa and Va.

The different directions of the reactions of the pyrroles Ia and Ib with carbon disulfide can apparently be explained by the influence of the substitutents on the properties of the ambidentate anion.



etc.

It is evident that donor substituents (tetrahydroindole Ia) should shift charge into position 2 and favor the formation of C-adducts (IIa, IVa), whereas acceptor substituents (phenyl, Ib), in contrast, should redistribute the charge in the direction of the substituent.

TABLE 3. UV Spectra of Esters of Pyrrolyldithiocarboxylic Acids (in acetonitrile)

Pyrrole	λ_{max}, nm	log ε
IVб	274, 417	4,13; 4,68
Vб	274, 417	4,04; 4,66
VIIб	261, 300, 435	4,08; 4,18; 1,40
VIIIб	261, 300, 435	3,90; 4,08; 1,20

Since the anionic center in position 5 of the pyrrole ring is sterically inaccessible in this particular case, carbon disulfide attacks primarily the nitrogen atom. Therefore, the probability of formation of the N-dithiocarbamates VIIb and VIIIb is increased.

It was suggested in [4] that N-pyrrolyldithiocarbamates may be rearranged to form 2-pyrrolyldithiocarboxylates; under our conditions, however, this hypothesis was not supported. When the pyrrole VIIb was stirred under our reaction conditions (KOH/DMSO, ~20°C, 2 h), the original pyrrole Ib was recovered with a 95% yield. Under these same conditions, the pyrrole IV b is stable, and was recovered quantitatively.

Still another source of instability of N-dithiocarbamates in the KOH/DMSO system is the formation of 2-dithiocarbonates. The alkanethiol that is formed as a result of hydrolysis of the N-dithiocarbamate grouping is converted, under the action of DMSO, [5], to a dialkyl disulfide (the corresponding disulfides were not isolated or characterized).

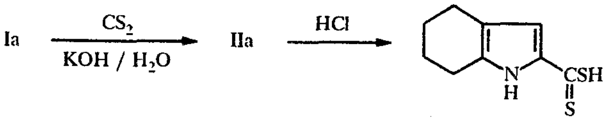
The esters of 2-pyrrolyldithiocarboxylic acids IVa, Va, IVb, and Vb are brightly colored yellow or orange crystals with low melting points. The esters of 1-pyrrolyldithiocarbamic acids VIIb and VIIIb are colored liquids (we were unable to determine their refractive indexes, because of the color. The yields and constants of the syntehsized esters are listed in Table 1.

In the PMR spectra (Table 2) of the adducts IVa-VIa, IVb, and Vb, there are no signals from protons in the α-position of the pyrrole ring (these signals do appear in compounds VIIb and VIIIb). The character and integral intensities of the signals are fully consistent with the structures assigned to the pyrroles IVa-VIa, IVb, Vb, VIIb, and VIIIb.

The absorption bands in the IR spectra (Table 2) corresponding to stretching vibrations of the C=S group occur over a broad interval for the different classes of compounds – from 1050 to 1300 cm^{-1} [6]. A comparison of the spectra of the compounds IVb and VIb with those of VIIb and VIIIb shows that the spectra of the latter two compounds contain intense bands at 1270 and 1300 cm^{-1}. We have assigned the first of these bands to a stretching vibration of the C=S group, the second (which is absent in the spectra of compounds IVb and VIb) to a C–N vibration [4]. Conjugation of the C=S band with the pyrrole ring in compounds IVa, b and Va, b leads to a lowering of its frequency to 1200 cm^{-1} (a similar lowering of ν C–O to 1700 cm^{-1} is observed in 2-carbomethoxypyrrole in comparison with its N-substituted analog, where this vibration appears at 1753 cm^{-1} [7]).

The UV spectra (Table 3) of the synthesized compounds provide a more reliable identification of the structures of compounds IVb, Vb, VIIb, and VIIIb. The spectra were compared with that of 2-phenylpyrrole, which contains two bands corresponding to $\pi-\pi^*$ transitions at 232 nm (log ε = 3.90) and 287 nm (log ε = 4.30) [8]. A thione grouping introduced into position 2 of the pyrrole ring, extending the conjugation chain, shifts the maximum of the long-wave absorption band into the visible region (417 nm) and increases its extinction by a factor of more than 2. The second band (274 nm) is also shifted bathochromically relative to phenylpyrrole, by 42 nm. In contrast to the spectra of compounds IVb and Vb, the spectra of VIIb and VIIIb contain two medium-intensity bands at 261 and 300 nm and a weak band with a maximum at 435 nm. The presence of the latter two bands, which are characteristic for the thione grouping (λ = 306 nm, log ε = 4.08, $\pi-\pi^*$ transition; and 460 nm, log ε = 1.26, $n-\pi^*$ transition in ethyl dithioacetate) [9], provides evidence of a slight interaction of the thione grouping with the p orbital of the nitrogen atom included in the π system of the pyrrole ring. The hypsochromic shift of the 274-nm band by 13 nm upon N-substitution, the same as in the case of 1-vinyl-2-phenylpyrroles [8], is due to disruption of the coplanarity of the pyrrole and benzene rings. Replacement of an ethyl group (compound VIIb) by the bulky butyl group (compound VIIIb) reduces the extinction of the 261-nm band, probably because of an increase of the dihedral angle between the rings [10].

In an attempt to reproduce the synthesis of 2-pyrrolyldithiocarboxylic acid in accordance with [11], from the pyrrole Ia and carbon disulfide in an aqueous medium, instead of the expected substance we recovered the original pyrrole (95%) from the reaction mixture. The acid IXa was formed with a yield of only 2%.



IXa

All of the pyrrole Ia was also recovered from the reaction with carbon disulfide in the presence of KOH in such solvents as ether, THF, and isopropyl alcohol. In ether or THF, carbon disulfide is consumed in reactions with KOH, apparently forming a mixture of potassium trithiocarbonates, carbonates, and sulfide; in isopropyl alcohol, the carbon disulfide is consumed in the formation of potassium isopropylxanthate.

EXPERIMENTAL

The IR spectra of the pyrroles were taken in a Specord IR-75 spectrophotometer in a microlayer (compounds VIIb and VIIIb) or in tablets with KBr (compounds IVa-b, IVb, V, IXa). The UV spectra were taken in a Specord UV-Vis spectrophotometer in acetonitrile. The PMR spectra were registered in a Tesla BS 567 A spectrometer (100 MHz) in DMSO-d_6.

The course of the reaction and the purity of the compounds that were obtained were monitored by means of TLC on Silufol UV-254 plates in a 1:1 hexane–ether system.

Elemental analyses for C, H, N, and S matched the calculated values.

Ethyl Ester of 4,5,6,7-Tetrahydro-2-indolyldithiocarboxylic Acid (IVa). A. A mixture of 1.2 g (0.01 mmole) of the pyrrole Ia and 1.12 g (0.02 mmole) of KOH in 20 ml of DMSO was stirred for 30 min, and 1.52 g (0.02 mmole) of carbon disulfide was added. The reaction mixture was held at room temperature for 2 h, after which 1.56 g (0.01 mmole) of ethyl iodide was added and the mixture was stirred for 2 h. The reaction mixture was diluted with water (40 ml) and extracted with ether. The residue after removal of the ether was recrystallized from hexane, obtaining 1.6 g (71%) of the ester IVa (yellow crystals).

B. The reaction was carried out under the conditions described in example A; the reaction mixture was diluted with water (40 ml) and extracted with ether. The residue after removal of the ether was passed through a column packed with aluminum oxide (eluent 1:1 hexane–ether). Recovered 0.6 g of diethyl disulfide, n_D^{20} 1.5063), PMR spectrum (DMSO-d_6): 1.32 ppm (6H, t, CH_3); 3.42 ppm (10H, q, CH_2). Yield 1.25 g (56%) of ester IVa.

Butyl Ester of 4,5,6,7-Tetrahydro-2-indolyldithiocarboxylic Acid (Va). Analogously, by method B, from the pyrrole Ia, carbon disulfide, and butyl iodide (1.84 g, 0.01 mmole), obtained 0.85 g of dibutyl disulfide and 1.35 g (53%) of the ester Va.

Allyl Ester of 4,5,6,7-Tetrahydro-2-indolylthicarboxylic Acid (VIa). Analogously, by method B, from the pyrrole Ia, carbon disulfide, and allyl iodide (1.68 g, 0.01 mmole), obtained 0.5 g of diallyl disulfide and 1.05 g (44%) of the ester VIa.

Interaction of 5-Phenylpyrrole (Ib) with Carbon Disulfide and Alkyl Halides. A mixture of 1.43 g (0.01 mmole) of the pyrrole Ib and 1.12 g (0.02 mmole) of KOH in 20 ml of DMSO was stirred for 30 min, and 1.52 g (0.02 mmole) of carbon disulfide was added. The reaction mixture was held at room temperature for 4 h, after which 1.56 g (0.01 mmole) of ethyl iodide was added and the mixture was stirred for 2 h. The reaction mixture was then diluted with water (40 ml) and extracted with ether. The residue after removal of the ether was passed through a column with aluminum oxide. Recovered 0.2 g of diethyl disulfide, 0.7 g (24%) of the ethyl ester of 5-phenyl-1-pyrrolyldithiocarbamic acid (VIIb), and 1.5 g (59%) of the ethyl ester of 5-phenyl-2-pyrrolyldithiocarboxylic acid (IVb).

Analogously, from the pyrrole Ib, carbon disulfide, and butyl iodide (1.84 g, 0.01 mmole), obtained 0.15 g of dibutyl disulfide, 0.8 g (29%) of the butyl ester of 5-phenyl-1-pyrrolyldithiocarbamic acid (VIIIb), and 1.43 g (52%) of the butyl ester of 5-phenyl-2-pyrrolyldithiocarboxylic acid (Vb).

Conversion of Ethyl Ester of 5-Phenyl-1-pyrrolyldithiocarbamic Acid (VIIb) in KOH/DMSO System. A mixture of 0.25 g (0.001) mmole of the pyrrole VIIb and 0.12 g (0.002 mmole) of KOH in 10 ml of DMSO was stirred for 2 h, after which it was diluted with water (20 ml) and extracted with ether. After removal of the ether, 0.13 g (95%) of the pyrrole Ib remained; the melting point and IR spectra of this substance were in complete agreement with literature data [12].

Conversion of Ethyl Ester of 5-Phenyl-2-pyrrolyldithiocarboxylic Acid (IVb) in KOH/DMSO System. A mixture of 0.25 g (0.001 mmole) of the pyrrole IVb and 0.12 g (0.002 mmole) of KOH in 10 ml of DMSO was stirred for 2 h, after which is was diluted with water (20 ml) and extracted with ether. After removal of the ether, 0.23 g of the pyrrole IVb remained.

Interaction of 4,5,6,7-Tetrahydroindole (Ia) with Carbon Disulfide and KOH. A. A mixture of 1.2 g (0.01 mmole) of the pyrrole Ia, 1.12 g (0.02 mmole) of KOH, 10.8 ml of water, and 1.52 g (0.02 mmole) of carbon disulfide was prepared and allowed to stand for one week, while shaking occasionally. The reaction mixture was extracted with ether; after removal of the ether, 1.15 g of the pyrrole Ia remained. The aqueous layer was acidified with 2 N HCl to an acidic reaction, and the crystals were filtered off, obtaining 0.04 g (2%) of the acid IXa ($C_9H_{11}NS_2$), mp 92-95°C; IR spectrum (KBr), cm^{-1}L 2450 (SH), 1190-1200 (C = S), 3330 (NH).

B. A mixture of 1.2 g (0.01 mmole) of the pyrrole Ia and 1.12 g (0.02 mmole) of KOH in 20 ml of ethyl ether was stirred for 30 min, after which 1.52 g (0.02 mmole) of carbon disulfide was added, and stirring was continued for 2 h. The precipitate was filtered off and washed with ether. Obtained 1.94 g of a solid substance that did not melt up to 350°C. IR spectrum (KBr), cm^{-1}: 650, 805, 820, 990, 1020, 1080, 1120, 1380, 1430, 1450, 2035, 2850, 2900, 2940, 300-3600 with a maximum at 3300. From the ether layer, recovered 1.1 g of the pyrrole Ia.

C. Analogously, from 1.2 g (0.01 mmole) of the pyrrole Ia, 1.12 g (0.02 mmole) of KOH, and 1.52 g (0.02 mmole) of carbon disulfide in 20 ml of tetrahydrofuran, obtained 1.13 g of the pyrrole Ia and 1.7 g of a powdered substance that did not melt up to 350°C. IR spectrum (KBr) cm^{-1}: 520, 610, 655, 1000, 1100, 1350, 1450, 1560, 1620, 2830, 2900, 3000-3600 with a maximum at 3300.

D. Analogously, from 1.2 g (0.01 mmole) of the pyrrole Ia, 1.12 g (0.02 mmole) of KOH, and 1.52 g (0.02 mmole) of carbon disulfide in 20 ml of isopropyl alcohol, recovered 1.15 g of the pyrrole Ia and 1.2 g of potassium isopropylxanthate, mp 205-210°C; IR spectrum (KBr), cm^{-1}: 1030, 1060, 1110, 1160, 1360, 1450, 2840, 2900, 2940.

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