INDOLE DERIVATIVES

LXXII.* REACTION OF NITROVINYLINDOLE WITH HYDROGEN SULFIDE

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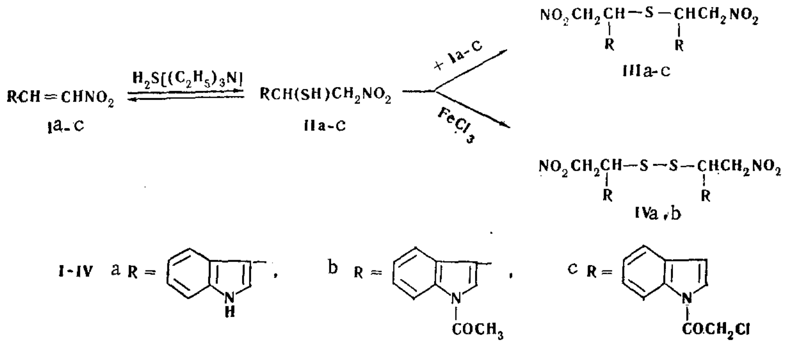
UDC 547.232.332.547.752

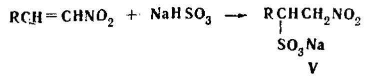
1-(3-Indolyl)-2-nitroethanethiol and bis[1-(3-indolyl)-2-nitroethyl] sulfide were obtained by the reaction of nitrovinylindole with hydrogen sulfide. The thiol was oxidized to the corresponding disulfide. Similar transformations were accomplished for 1-acetyl- and 1-(chloroacetyl)nitrovinylindoles.

The base-catalyzed addition of hydrogen sulfide to compounds with an activated double bond, particularly nitrovinyl compounds, is used for the introduction of sulfur into the β-position with respect to the activating group [2-4]. The thiol is capable of reacting with a second molecule of unsaturated compound to form a sulfide [5].

In a study of the reaction of hydrogen sulfide with nitrovinylindole (Ia) in the presence of catalytic amounts of triethylamine, we also observed the formation of thiol IIa and sulfide IIIa.



The reaction with concentrated solutions of the starting materials in dimethylformamide leads to sulfide IIIa containing only a small admixture of thiol IIa. The first step of the reaction is reversible, and the removal of hydrogen sulfide by bubbling argon through the mixture therefore leads to complete conversion of thiol IIa to Ia, which was converted to



$$RCH{=}CHNO_2 + NaHSO_3 \longrightarrow \underset{\displaystyle SO_3Na}{RCHCH_2NO_2}$$

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sulfonate V [6], which is quite soluble in water. Pure sulfide IIIa was synthesized via this route.

Thiol IIa could not be prepared by separation of a mixture of it with the sulfide. Raising the hydrogen sulfide concentration up to the point of using liquid hydrogen sulfide† did not make it possible to obtain the

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*See [1] for communication LXXI.

† We thank M. A. Korshunov and V. E. Mazaev for their assistance in the studies with liquid hydrogen sulfide.

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1062-1065, August, 1971. Original article submitted July 20, 1970.

TABLE 1. IR Spectra

Compound	Frequencies, cm^{-1} (in mineral oil)				
	NH	SH	CO	NO$_2$	CH (arom)
IIIa	3440	—	—	1566, 1346	755
IVa	3420	—	—	1560, 1344	756
IIb	—	2530	1690	1558, 1335	771, 762
IIIb	—	—	1697	1566, 1337	774, 760
IIIb*	—	—	1712	1565, 1335	—
IVb	—	—	1694	1560, 1334	773, 762
IVb*	—	—	1714	1565, 1335	—

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*In chloroform.

TABLE 2. PMR Spectra

Compound	Chemical shifts, ppm (No. of protons)[a]			
	COCH$_3$	CH—CH$_2$	Indole ring protons	NH
IIIa		4,40—4,90 m (6)	6,70—8,20 m	8,07 (2)
IIIb	2,40 s (6)	4,79 s (6)	7,00—8,40 m	—
IVa	—	4,50—4,77 m(6)[b]	6,75—8,10 m	8,06 (2)
IVb	2,55 s (6)	4,81 s (6)[c]	6,90—8,40 m	—

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[a] s is singlet, and m is multiplet.
[b] ABC system.
[c] ABM system.

thiol without sulfide contamination. However, when dilute solutions of nitrovinylindole in methanol were used, it was possible to control the course of the reaction and stop it by neutralization of the catalyst, thereby not permitting the formation of the sulfide. Thiol IIa obtained by this method was isolated as the disulfide (IVa).

Thiol IIa and sulfide IIIa are extremely unstable, and this interferes with their purification. Acetylated products IIb and IIIb are more stable. The introduction of an acetyl or, especially, a chloroacetyl group considerably facilitates the addition of hydrogen sulfide, but the conversion of thiols IIb,c to sulfides IIIb,c is also accelerated, so that, under comparable conditions, the chief products are sulfides. Electron-donor groups apparently cause an increase in the electrophilicity of the double bond in Ib,c and also facilitate the conversion of thiols IIb,c to anions. Nevertheless, thiol IIb can be obtained when sufficiently dilute solutions in methanol or ethanol are used.

The course of the transformations and the mixture compositions in all stages were monitored by means of thin-layer chromatography on a fixed layer of silufol UV$_{254}$ silical gel. A benzene–acetone mixture (9 : 1) was used for the elution. The substances were detected after spraying with 10% phosphomolybdic acid in alcohol with subsequent heating at 110 deg. The thiols gave a characteristic rose coloration with sodium nitroprusside, while the disulfides gave a violet coloration on successive treatment with potassium cyanide and sodium nitroprusside solutions. This method also made it possible to show the presence of thiol IIc (R_f 0.63) and sulfide IIIc (R_f 0.45) in the products of the conversion of Ic without isolating them.

The synthesized sulfides, disulfides, and thiols have superimposable UV spectra (in CHCl$_3$) λ_{max}, nm (ε): 274 (4.09-4.12) and 279 (4.08) for IIIa and IVa; 293 (4.15-4.17) and 301-302 (4.17-4.19) for IIb, IIIb, and IVb. The IR and PMR spectra are also very similar (Tables 1 and 2).

EXPERIMENTAL

The PMR spectra of 8-10% solutions in deuterochloroform were obtained with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard. The IR spectra were obtained with a UR-10 spectrometer, and the UV spectra were recorded with an EPS-3 spectrophotometer.

1-[1-(Chloroacetyl)-3-indolyl]-2-nitroethylene (Ic). A solution of 8.47 g (0.075 mole) of chloroacetyl chloride in 40 ml of acetone was added to a solution of 9.4 g (0.05 mole) of Ia and 9.1 g (0.09 mole) of triethylamine in 100 ml of acetone at 5 deg. After 30 min, the mixture was poured into a mixture of 200 ml of water and 200 g of ice. This mixture was stirred for 1 h and filtered. The solid residue was washed with ice water, dried in air, and recrystallized from 210 ml of acetone to give 9.96 g (75%) of yellow crystals with mp 191-191.6 deg and R_f 0.70. Found: C 54.6; H 3.4; Cl 13.2; N 10.5%. $C_{12}H_9ClN_2O_3$. Calculated: C 54.4; H 3.4; Cl 13.4; N 10.6%.

Bis[1-(3-indolyl)-2-nitroethyl] Sulfide (IIIa). Triethylamine (0.1 g) was added at 0 deg to a solution of 28.5 g (0.84 mole) of hydrogen sulfide in 300 ml of distilled dimethylformamide, and a solution of 16 g (0.085 mole) of Ia in 140 ml of dimethylformamide was then added dropwise in the course of 30 min. Cooling was discontinued after 15 min, and a stream of argon was passed through the reaction mixture until it no longer gave a positive reaction for hydrogen sulfide and thiol (R_f 0.42). The solution was poured into 3 liters of water containing ice, and the mixture was extracted with ethyl acetate or ether. The extract was dried with magnesium sulfate and evaporated in vacuo. The residue was dissolved in the minimum amount of methanol, and a saturated aqueous solution of 30 g of sodium metabisulfite was added dropwise to this solution. After 1-2 h, the mixture was poured into 1 liter of water, and air dried. Recrystallization from ether gave 13.3 g (76%) of a light-cream-colored powder with mp 91 deg (dec.) and R_f 0.21. Found: C 58.9; H 4.3; N 13.6; S 8.2%. $C_{20}H_{18}N_4O_4S$. Calculated: C 58.5; H 4.4; N 13.6; S 7.73%.

Bis[1-(3-indolyl)-2-nitroethyl] Disulfide (IVa). A) A solution of 1 g (0.0053 mole) of Ia in 300 ml of methanol was saturated at 0 deg with hydrogen sulfide, 0.1 g of triethylamine was added, and hydrogen sulfide passage through the mixture was continued. After 20-30 min, at the moment of maximum thiol content, the reaction was stopped, and the catalyst was neutralized with dilute hydrochloric acid (to pH 6.8-7.5). Argon was passed through the mixture until it no longer gave a positive reaction for hydrogen sulfide, and 4 g of ferric chloride was added. The mixture was poured into 2 liters of water, and the yellow precipitate was removed by filtration, washed with water, air dried, and worked up as described for IIIa to give 0.98 g (85%) of a light-cream-colored powder with mp 87 deg (dec.) and R_f 0.23. Found: C 54.0; H 4.3; N 12.8; S 14.2%. $C_{20}H_{18}N_4O_4S_2$. Calculated: C 54.3; H 4.1; N 12.7; S 14.5%.

B) A solution of 1 g (0.0053 mole) of Ia in 20 ml of tetrahydrofuran and 0.1 g of triethylamine was placed in a 100 ml stainless steel ampul. The ampul was cooled to -79 deg in liquid nitrogen, and 20 ml of liquid hydrogen sulfide was poured in. The sealed ampul was held at 0 deg for 1 h, cooled again, and the catalyst was neutralized with dilute hydrochloric acid. The excess hydrogen sulfide was removed in a stream of nitrogen, and the solvent was removed by vacuum distillation. The mixture was then worked up as described for IIIa to give 0.97 g (85%) of light-cream-colored powdered IVa containing IIIa.

Bis[1-(1-acetyl-3-indolyl)-2-nitroethyl] Sulfide (IIIb). A solution of 6 g (0.026 mole) of IIa in 380 ml of tetrahydrofuran was saturated with hydrogen sulfide at 0 deg, 0.1 g of triethylamine was added, and hydrogen sulfide was passed through the mixture until the conversion of IIa was complete (~1 h). The mixture was neutralized with dilute hydrochloric acid, and the precipitate of triethylamine hydrochloride was removed by filtration. The filtrate was vacuum evaporated, and the residue was extracted with hot methanol. The insoluble portion was recrystallized from 165 ml of chloroform and 105 ml of cyclohexane to give 2.76 g (64%) of colorless crystals with mp 183-184 deg and R_f 0.34. Found: C 58.1; H 4.4; N 11.6; S 6.6%. $C_{24}H_{22}N_4O_6S$. Calculated: C 58.3; H 4.5; N 11.3; S 6.5%.

1-(1-Acetyl-3-indolyl)-2-nitroethanethiol (IIb). The methanol extract from the preparation of IIIb was evaporated to dryness, the residue was extracted with methanol, and the extract was evaporated. The residue was recrystallized from methanol to give 1.2 g (17%) of colorless crystals with R_f 0.53. Found: C 54.3; H 4.7; N 10.7; S 11.7%. $C_{12}H_{12}N_2O_3S$. Calculated: C 54.5; H 4.6; N 10.6; S 12.1%.

Bis[1-(1-acetyl-3-indolyl)-2-nitroethyl] Disulfide (IVb). The methanol extract from the preparation of IIIb was concentrated, 3 g of ferric chloride was added, and the solution was heated to the boiling point. The resulting precipitate was filtered, washed with water and methanol, recrystallized from chloroform, and dried in vacuo over calcium chloride and paraffin to give 1.6 g (32%) of colorless crystals with mp 140 deg and R_f 0.41. Found: C 50.0; H 4.0; N 9.3; S 10.8; Cl 8.7%. $2C_{24}H_{22}N_4O_6S_2 \cdot CHCl_3$. Calculated: C 50.2; H 3.9; N 9.5; S 10.9; Cl 9.1%.

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