INDOLE DERIVATIVES. CVI.* SYNTHESIS OF MERCAPTO DERIVATIVES OF TRYPTAMINE

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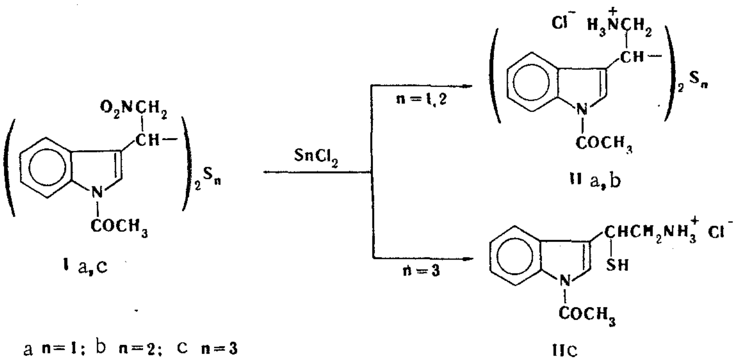
The nature of the products of reduction of nitro compounds of the indole series containing a polysulfide chain depends on the length of the latter. In mono- and disulfides only the nitro groups are reduced, and diamino monosulfides and diamino disulfides are formed. In the reduction of the dinitro trisulfide the chain is cleaved and an amino thiol is formed. The reduction of acetylthionitro compounds is accompanied by migration of the S—N bond, as a result of which an acetamido thiol is formed.

The reduction of the nitro group in the products of addition of sulfur-containing reagents to nitrovinylindole [1-3] opens up a pathway to tryptamine derivatives with the corresponding substituents in the aliphatic chain, the biological properties of which are of interest [4]. The selection of a reducing agent and the reduction conditions is complicated by the presence of a labile grouping with sulfur in unoxidized form. The use of reducing agents that have basic properties, including lithium aluminum hydride, leads to cleavage of the sulfur-containing residues. Catalytic reduction methods are also inapplicable. The reduction can be accomplished by metals in acidic media at low temperatures. In this case, stannous chloride reduces the nitro group to an amino group, whereas zinc reduces the nitro group to a hydroxylamino group [5].

The ability of the polysulfide chain to undergo reduction depends on its length. The sulfide and disulfide groups are not reduced either by stannous chloride or by zinc. Amino sulfides (IIa, b) are therefore obtained in the reduction of nitro sulfides Ia and Ib. Only the trisulfide gives an amino thiol (IIc) on reduction.



I a,c

II a,b

IIc

a n=1; b n=2; c n=3

Diamino sulfide IIa can be separated by crystallization into two isomers (IIa' and IIa") which are apparently the d,*l* and meso forms, which owe their existence to the two asymmetric carbon atoms.

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*See [1] for communication CV.

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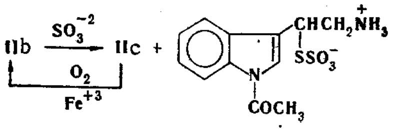
The reduction of nitroethyl sulfides with a weaker nonacetylated indole ring is accompanied by cleavage of sulfur. Thus treatment of 1-acetylmercapto-1-(3-indolyl)-2-nitroethane, bis[1-(3-indolyl)-2-nitroethyl]sulfide, and bis[1-(3-indolyl)-2-nitroethyl]-disulfide in acidic media with stannous chloride or zinc at low temperatures gives resinous red masses, from which a small amount of tryptamine can be isolated. Thin-layer chromatography (TLC) showed that the reaction mixtures did not contain sulfur-containing indole compounds.

Rapid migration of the S—N bond of the acetyl group occurs in the reduction of 1-acetylthio-1-(1-acetyl-3-indolyl)-2-nitroethane (III), and the reaction product is 1-(1-acetyl-3-indolyl)-2-acetamidoethanethiol (IV).

Amino thiol IIc, amino disulfide IIb, or a mixture of them are converted to 2-amino-1-(1-acetyl-3-indolyl)ethanethiosulfonic acid (V) by a method similar to that described in [6] by reaction with ammonium sulfite and oxygen in the presence of a catalytic amount of ferric ions.



V

EXPERIMENTAL METHOD

The PMR spectra were recorded with a JNM 4H-100 spectrometer with tetramethylsilane as the internal standard. The IR spectra of mineral oil suspensions of the compounds were recorded with a Perkin—Elmer spectrometer. Thin-layer chromatography (TLC) was carried out on Silufol with elution by the upper layer of a butanol—acetic acid—water mixture (4:1:5) and detection of the spots with ninhydrin.

1-(1-Acetyl-3-indolyl)-2-aminoethanethio Hydrochloride (IIc). A 1.5-g (2.7 mmole) sample of trisulfide Ic was added with ice cooling to 55 ml of a mixture of 48 ml of glacial acetic acid, 6.5 g (0.10 mole) of hydrogen chloride, and 11 g (5.5 mmole) of anhydrous stannous chloride, after which the suspension was maintained at 5° for 7 days. The precipitated double salt of the imine hydrochloride and stannic chloride was removed by filtration, washed with glacial acetic acid and an hydrous ether, and air dried. It was then dissolved in 300 ml of water, the tin was precipitated with hydrogen sulfide, and the precipitated sulfides were removed by filtration. The filtrate was vacuum evaporated to dryness, and the residue was crystallized from absolute alcohol to give 0.5 g (60% based on converted trisulfide) of colorless crystals of IIc with mp 218° and R_f 0.32. Found: C 53.3; H 5.5; Cl 12.9; N 10.0; S 11.6%. $C_{12}H_{15}ClN_2OS$. Calculated: C 53.2; H 5.6; Cl 13.1; N 10.3; S 11.8%. IR spectrum: 3050-3250, 2400-2850 (NH_3^+); 1723 (C=O); 772, 767 cm^{-1} (aromatic CH). PMR spectrum (D_2O): 2.55 (s,* $COCH_3$), 3.55 (m, CH_2), 4.60 (q, CH), 7.24-8.04 (m, aromatic protons), and 7.60 ppm (s, 2-H). The precipitated tin sulfides were washed with chloroform, and the chloroform washings were evaporated to give 0.6 g of unchanged trisulfide Ic.

Bis[1-(1-acetyl-3-indolyl)-2-aminoethyl] Disulfides Dihydrochloride (IIb). A suspension of 1.8 g (3.3 mmole) of disulfide Ib in 27 ml of the reducing solution was maintained at 5° for 10 days, after which it was worked up as described above to give 0.4 g (62% based on converted disulfide) of colorless crystals of IIb with mp 210° and R_f 0.20. Found: C 53.4; H 5.0; Cl 12.9; N 10.4; S 11.9%. $C_{24}H_{28}Cl_2N_4OS_2$. Calculated: C 53.5; H 5.2; Cl 13.2; N 10.2; S 11.9%. IR spectrum: 3100-3350, 2750-2500 (NH_3^+); 1700 (C=O); 767, 754 cm^{-1} (aromatic CH). PMR spectrum (D_2O): 2.18 (s, $COCH_3$), 3.44 (m, CH_2), 4.42 (t, CH), 7.0-7.94 (m, indole ring protons), and 7.04 ppm (s, 2-H). The precipitated sulfide was washed with acetone to give 1.1 g of the starting disulfide.

Bis[1-(1-acetyl-3-indolyl)-2-aminoethyl] Sulfide Dihydrochloride (IIa). A 2.5-g (5.1 mmole) sample of sulfide Ia was reduced as described above to give 1.43 g (59%) of colorless crystals of a mixture of IIa' and IIa" with R_f 0.21. Fractional crystallization from alcohol gave 0.62 g of isomer IIa'. Found: C 54.5; H 5.8; Cl 13.1; N 10.5; S 6.0%. $C_{24}H_{28}Cl_2N_4O_2S \cdot H_2O$. Calculated: C 54.6; H 5.7; Cl 13.4; N 10.5; S 6.0%. IR spectrum: 3400 (OH); 3050-3200, 2500-2800 (NH_3^+); 1710 (C=O); 1600 (aromatic C=C); 754 cm^{-1} (aromatic CH). PMR spectrum (D_2O):

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*Here and subsequently, s is singlet, d is doublet, q is quartet, t is triplet, and m is multiplet.

1.96 (s, $COCH_3$), 3.48 (m, CH_2), 4.44 (m, CH), 6.89-7.74 ppm (m, indole ring protons). Work-up of the mother liquor gave 0.37 g of isomer IIa". Found: C 56.6; H 5.6; Cl 13.7; N 10.7; S 6.2%. $C_{24}H_{28}Cl_2N_4O_2S$. Calculated: C 56.8; H 5.5; Cl 14.0; N 10.8; S 6.3%. IR spectrum: 2700-3200 (NH_3^+), 1730 (C=O), 1585 (aromatic C=C), and 760 cm^{-1} (aromatic CH). PMR spectrum (D_2O): 2.03 (s, $COCH_3$), 3.48 (m, CH_2), 4.44 (m, CH), and 6.90-7.74 ppm (m, indole ring protons).

1-(1-Acetyl-3-indolyl)-2-acetamidoethanethiol (IV). A 5-g (16 mmole) sample of acetylthio compound III was reduced as described above, and crystallization of the product from 20% alcohol gave 1.2 g of colorless crystals of IV with mp 163-164°. Found: C 61.0; H 5.9; N 10.0; S 11.5%. $C_{14}H_{16}N_2O_2S$. Calculated: C 60.8; H 6.8; N 10.1; S 11.5%. IR spectrum: 3293 (NH); 1698, 1650, 1555 (C=O); 750 cm^{-1} (aromatic CH). PMR spectrum ($CDCl_3$): 1.93 (s, $NHCOCH_3$), 2.54 (s, $NCOCH_3$), 3.30-4.60 (m, $CH-CH_2$), 7.10-8.50 (m, indole ring protons), 7.67 (s, 2-H), and 5.98 ppm (broad s, NH and SH; vanishes when CD_3OD is added).

2-Amino-1-(1-acetyl-3-indolyl)ethanethiosulfonic Acid (V). Disulfide Ib or a mixture of Ib with trisulfide Ic (3 g) was reduced with stannous chloride as described above. The resulting amino disulfide IIb or a mixture of IIb with amino thiol IIc was dissolved in 60 ml of water, 5 ml of a 12.5% solution of ammonium sulfite (pH 6) and 50 mg of ferric chloride were added, and air was bubbled through the mixture for 30 min. The addition of the sulfite and bubbling of air were repeated four to five times until the spots of amines IIb and IIc vanished on the thin-layer chromatograms. The resulting precipitate was recrystallized from 80% alcohol to give 2.93 g of colorless crystals of thiosulfonic acid V with R_f 0.50. Found: C 46.0; H 4.6; N 9.0; S 20.2%. $C_{12}H_{14}N_2O_4S_2$. Calculated: C 45.8; H 4.6; N 8.9; S 20.4%. IR spectrum: 3050-3300, 2500-2800 (NH_3^+); 1722 (C=O); 1100-1250 (S_2O_3); 750 cm^{-1} (aromatic CH). PMR spectrum in $(CD_3)_2NCDO$: 2.67 (s, $COCH_3$), 4.00 (d, CH_2), 7.20-8.40 (m, indole ring protons), 7.98 ppm (s, 2H); the CH signal is covered by the signal of the water impurity in the solvent.

LITERATURE CITED

1. O. D. Shalygina, O. S. Anisimova, L. Kh. Vinograd, and N. N. Suvorov, Khim. Geterotsikl. Soedin., 792 (1975).
2. O. D. Shalygina, L. Kh. Vinograd, and N. N. Suvorov, Khim. Geterotsikl. Soedin., 792 (1975).
3. O. D. Shalygina, L. Kh. Vinograd, and N. N. Suvorov, USSR Author's Certificate No. 367095 (1973); Byul. Izobr., No. 8, 61 (1973).
4. M. V. Vasin, F. V. Antipov, N. N. Suvorov, L. M. Orlova, L. Kh. Vinograd, and O. D. Shalygina, Radiobiologiya, 14, 610 (1974).
5. L. Kh. Vinograd, O. D. Shalygina, N. N. Bulatova, N. P. Kostyuchenko, T. N. Zykova, A. L. Mikerina, G. S. Arytyunyan, and N. N. Suvorov, Khim.-Farmats. Zh., No. 12, 15 (1971).
6. N. N. Suvorov, L. Kh. Vinograd, M. V. Vasin, and V. S. Minaeva, Khim. Geterotsikl. Soedin., 1505 (1973).