INDOLE DERIVATIVES

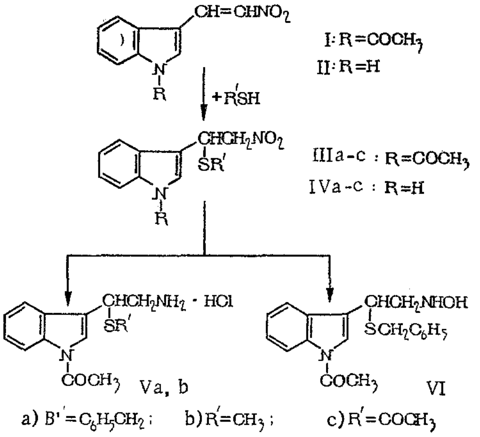
LXXII. ADDITION OF SULFUR-CONTAINING REAGENTS TO NITROVINYLINDOLE

L. Kh. Vinograd, O. D. Shalygina,
N. N. Bulatova, N. P. Kostyuchenko,
T. N. Zykova, A. L. Mikerina,
G. S. Arutyunyan, and N. N. Suvorov

UDC 547.752

The present work is a continuation of research on the addition of sulfur-containing nucleophilic reagents to unsaturated nitro compounds of the indole series [1]. We have established that 1-acetyl-3-nitrovinylindole (I) and 3-nitrovinylindole (II) readily add mercaptans in the presence of catalytic amounts of triethylamine. The stability of the alkyl- and acylmercapto derivatives of 1-indolyl-2-nitroethane so obtained (IIIa-c, IVa-c) varies from case to case. Compounds IIIa-c, which contain an N-acetylated indole nucleus, can be kept at a temperature around 0° for over a year without noticeable decomposition. The nitrosulfides IVa and IVb are unstable. They could not be isolated, and the judgment that they had been formed was made from chromatograms. The thioether IVc has intermediate stability. Samples of it always contain some nitrovinylindole and thioacetic acid.

In all cases, formation of only one nitrosulfide isomer is observed. The NMR spectra show that, as was to be expected, the addition to the double bond takes place in the β-position relative to the nitro group.



The nitrosulfides IIIa and IIIb were reduced with stannous chloride in acid medium to the corresponding aminosulfides (Va and Vb). In the action of zinc or of lithium aluminum hydride on IIIa, a hydroxylamine (VIa) is formed; in the latter case, the reduction is accompanied by a splitting out of benzyl mercaptan.

In chemotherapeutic tests in vitro, a weak germistatic activity (500-250 μg ml) of Va with respect to 17 forms of microorganisms was observed. The anti-tuberculosis activity (against strain H-37, R_V) was 30 μg/ml for Va of 4 μg/ml for VI (in the absence of serum). In the pharmacological tests of Va we studied its general action, the effect on smooth muscle, blood circulation and respiration, body temperature, its reaction with hexenal and pyrazid, and its antiserotonin, antihistamine, anticonvulsive, and anesthetic action. These studies showed that this preparation possesses weak pharmacological activity, and in particular

---

S. Ordzhonikize All-Union Pharmaceutical Chemistry Institute, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 5, No. 12, pp. 15-17, December, 1971. Original article submitted June 29, 1970.

TABLE 1. Chromatographic Characteristics of Compounds Synthesized

Compound	R_f	Eluent	Coloration		
			with phosphomolybdic acid	with p-dimethylaminobenzaldehyde	with ninhydrin
I	0.65	A	Red	Colorless	Colorless
II	0.35	A	Dark cherry	Orange	"
IIIa	0.70	A	Light brown	Colorless	"
IIIb	0.58	A	The same	"	"
IIIc	0.57	A	"	"	"
IVa	0.75*	C	Dark cherry	Orange	"
IVb	0.37	A	"	"	"
IVc	0.53	A	"	"	"
Va	0.53	B	Colorless	–	Violet
Vb	0.40	B	"	–	"
VIa	0.36*	C	Blue	–	–

Notation: A) mixture of benzene and acetone, 9 : 1; B) upper layer from a mixture of butanol, glacial acetic acid, and water, 4 : 1 : 5; C) mixture of benzene and alcohol, 9 : 1.

*On unbonded layer of aqueous silicic acid.

causes a mild spasmogenic effect and a slight increase in vessel permeability, and intensifies the soporific action of hexenal. The LD_{50} on intravenous injection into mice is 45 mg/kg.

EXPERIMENTAL

The NMR spectra were obtained in a JNM-4H-100 instrument for 8-10% solutions of the substances; $\delta_{TMS} = 0$. The IR spectra were taken in a UR-10 instrument (suspension in vaseline oil). Chromatography (see Table 1) was carried out on plates having a bonded layer of "Silufol UV 254" silica gel. The substances were detected by illumination under UV light, and also by spraying the plates with an alcoholic solution of phosphomolybdic acid, p-dimethylaminobenzaldehyde, or ninhydrin, with subsequent warming at 10-100°.

1-Benzylmercapto-1'-(1'-acetyl-3'-indolyl)-2-nitroethane (IIIa). To a suspension of 11.91 g of I and 6.4 g of benzylmercaptan in 150 ml of methanol was added, with stirring, 0.2 ml of triethylamine. After 10-15 min, a transparent solution was formed, from which crystals quickly began to separate. The flask was set in a refrigerator overnight. The precipitate which had settled out was filtered off, washed with methanol containing a little acetic acid, and was dried over sodium hydroxide. There was obtained 14.3 g (80.7%) of colorless crystals, mp 107-108° (from a mixture of chloroform and petroleum ether). Found, %: C 64, 67; H 5.16; N 7.86; S 8.85. $C_{19}H_{18}N_2O_3S$. Calculated, %: C 64.39; H 5.12; N 7.90; S 9.03. ν_{max}: 1723 (C = O), 1595 (C = C, aromatic), 1550, 1327 (NO_2), and 760 and 751 cm^{-1} (CH, aromatic). δ in deuterochloroform: 2.6 (singlet, CH_3), 3.75 (singlet, SCH_2), 4.66 (multiplet, $CHCH_2$), A_2B system, 7.2-8.6 ppm (multiplet, aromatic protons).

1-Methylmercapto-1-(1'-acetyl-3'-indolyl)-2-nitroethane (IIIb). Methyl mercaptan was passed through a suspension of 6.9 g of I in 120 ml of benzene containing 0.2 g of triethylamine until the precipitate dissolved (about 3 h). The flask was placed in a refrigerator overnight. The precipitate was filtered off, washed with benzene and with ether, and was dried under vacuum. There was obtained 7.12 g (85.3%) of slightly yellowish crystals, mp 153-154° (from acetone). Found, %: C 56.14; H 5.04; N 10.23; S 11.67. $C_{13}H_{14}N_2O_3S$. Calculated, %: C 56.10; H 5.07; N 10.06; S 11.49. ν_{max}: 1688 (C = O), 1595 (C = C, aromatic), 1560, 1340 (NO_2), 772, 760 cm^{-1} (CH, aromatic), δ (in deuterated acetone): 2.63 (singlet, $NCOCH_3$), 4.84-5.13 (multiplet, $CHCH_2$), 7.05-8.40 ppm (multiplet, protons of indole ring); the signals of the SCH_3 protons were overlapped by the solvent.

1-Acetylmercapto-1-(1'-acetyl-3'-indolyl)-2-nitroethane (IIIc). To a suspension of 11.51 g of I and 5.35 g of thioacetic acid in 70 ml of benzene was added, with stirring, 0.1 g of triethylamine. After 2-3 min, the precipitate dissolved. The flask was set in a refrigerator overnight. The crystals which spearated were filtered off, washed with benzene, and dried in air. There was obtained 12 g (78.5%) of a colorless powder, mp 121-122° (from a mixture of chloroform and hexane). Found, %: C 54.88; H 4.40; N 9.30; S 10.57%.

$C_{14}H_{14}N_2O_4S$. Calculated, %: C 54.89; H 4.60; N 9.14; S 10.44%. ν_{max}: 1730 (SC=O), 1686 (C=O), 1590 (C=C, aromatic), 1550, 1330 (NO_2), 757 cm^{-1} (CH, aromatic). δ (in deuterochloroform): 2.38 (singlet, $SCOCH_3$), 2.61 (singlet, $NCOCH_3$), 4.95-5.58 (multiplet, $CHCH_2$), 7.20-8.45 ppm (multiplet, indole ring protons).

1-Acetylmercapto-1-(3'-indolyl)-2-nitroethane (IVc). This compound was prepared analogously to IIIc, from 0.05 mole of II. The yield was 8.1 g (61.4%), mp 99-101° (from chloroform). Found, %: C 54.36; H 4.35; N 10.69; S 12.19. $C_{12}H_{12}N_2O_3S$. Calculated, %: C 54.54; H 4.57; N 10.60; S 12.11. ν_{max}: 3400 (NH), 1680 (C=O), 1600 (C=C, aromatic), 1546, 1326 (NO_2), 753 (CH, aromatic). δ (in deuterochloroform): 2.33 (singlet, CH_3), 4.95 (doublet, CH_2), 5.64 (triplet, CH), 7-8 ppm (multiplet, indole ring protons).

1-Benzylmercapto-1-(1'-acetyl-3'-indolyl)-2-aminoethane hydrochloride (Va). Into a cooled solution of 18.3 g of hydrogen chloride and 55 g of stannous chloride dihydrate in 90 ml of glacial acetic acid was introduced 7.08 g of IIIa, and the suspension was set in a refrigerator (at about 6°). After 3 days, the transparent solution which had been formed was poured into 400 g of an ice–water mixture. The double salt which precipitated in the form of a stick mass (about 12 g) was dissolved in 30 ml of alcohol, 100 ml of water was added, and the mixture was saturated with hydrogen sulfide. The precipitate of sulfides was washed with water and methanol, the filtrates obtained were evaporated under vacuum, and there was obtained 4.31 g of a light-brown oil. This oil was dissolved in 25 ml of warm absolute alcohol, 120 ml of dry ether was added, and the solution was set in a refrigerator overnight. The precipitate was filtered off, and washed with ether, and 3.65 g of colorless crystals was obtained (50.2%), mp 195-196°. Found, %: C 63.02; H 5.90; Cl 9.54; N 8.02; S 8.53%. $C_{19}H_{21}N_2OS \cdot HCl$. Calculated, %: C 63.23; H 5.86; Cl 9.83; N 7.76; S 8.86%. ν_{max}: 3200-2500, 1605 (NH_3^+), 1702 (C=O), 1598 (C=C, aromatic), 715, 750 cm^{-1} (CH, aromatic). δ (in deuterated methanol): 2.60 (singlet, CH_3), 3.74 (quartet, SCH_2), 3.49 (quartet, CH_2N), 4.40 (triplet, CH), 7.10-8.30 ppm (multiplet, aromatic protons).

1-Methylmercapto-1-(1'-acetyl-3'-indolyl)-2-aminoethane hydrochloride (Vb). This compound was prepared analogously to Va from 2 g of IIIb. The yield was 0.29 g (14.2%), mp 119-120°. Found, %: C 54.40; H 5.94; Cl 12.94; N 9.68; S 10.83, $C_{13}H_{16}N_2OS \cdot HCl$. Calculated, %: C 54.82; H 6.01; Cl 12.46; N 9.83; S11.23. ν_{max}: 3200-2480, 1610 (NH_3^+), 1703 (C=O), 1575 (C=C, aromatic), 752 cm^{-1} (CH, aromatic). The precipitate of sulfides was washed additionally once more with acetone, and after evaporation 0.71 g of starting IIIb was obtained.

1-Benzylmercapto-1-(1'-acetyl-3'-indolyl)-2-hydroxylaminoethane (VIa). To a solution of 4 g of IIIa in 250 ml of glacial acetic acid was added 20 ml of water, and during 20-25 min 5.6 g of zinc dust was added at 2-4°. The stirring was continued for another 40 min, 150 g of finely chopped ice was added, plus 150 ml of ether, and then 330 ml of a concentrated ammonia solution was added dropwise (temperature not over 28°). The organic layer was separated, the water layer was extracted 3 times with ether, the combined extracts were washed with water, dried with magnesium sulfate, and evaporated. The oil formed was washed with petroleum ether to remove benzyl mercaptan, the residue was triturated with dry ether, and there was obtained 1.9 g (38.4%) of a colorless powder, mp 105-106°. Found, %: C 67.19; H 5.62; N 7.79; S 9.36. $C_{19}H_{20}N_2O_2S$. Calculated, %: C 67.04; H 5.92; N 8.23; S 9.40. ν_{max}: 3280 (NHOH), 1710 (C=O), 1610, 1510 (C=C, aromatic), 773, 756 cm^{-1} (CH, aromatic). δ (in deuterochloroform): 2.53 (singlet, CH_3), 3.64 (singlet, SCH_2), 3.34-4.39 (multiplet, $CHCH_2$, A_2B system), 7.10-8.40 ppm (multiplet, aromatic protons).

LITERATURE CITED

1. O. D. Shalygina, N. P. Kostyuchenko, L. Kh. Vinograd, et al., Khim. Geterotsikl. Soed., No. 2, 205 (1971).