INDOLE DERIVATIVES.

136.* 4-, 5-, 6-, AND 7-NITRO-3-INDOLESULFONIC CHLORIDES AND SULFONAMIDES

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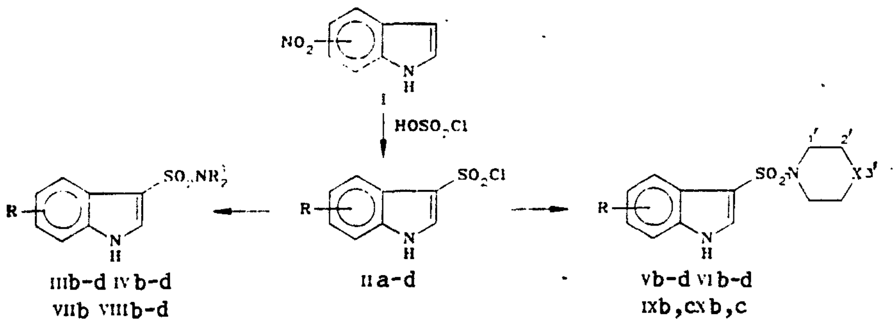
The reaction of nitroindoles with chlorosulfonic acid in the presence of sodium sulfate was used to synthesize 4-, 5-, 6-, and 7-nitroindole-3-sulfonyl chlorides. Under the influence of ammonia and several amines these compounds were converted to nitroindole-3-sulfonamides which were reduced with hydrazine hydrate in the presence of Raney nickel to the corresponding amines.

Until the present research, virtually no sulfonyl chlorides of the indole series had been obtained. The synthesis of 2-oxo-3,5-dichloroindole-5-sulfonyl chloride and 2-oxo-3,5-dichlorindole-7-sulfonyl chlorides from isatin with chlorosulfonic acid was described only in [2].

The aim of the present research was to develop a preparative method for the synthesis of 4-, 5-, 6-, and 7-nitroindole-3-indolesulfonyl chlorides II, to investigate the physicochemical properties of these compounds, and to obtain from them nitro- and aminosulfonamidoindoles – analogs of known sulfanilamide preparations [3].

Nitroindole-3-sulfonyl chlorides II were obtained by the addition of nitroindoles I [4-7] in dry chloroform to a mixture of freshly distilled chlorosulfonic acid and sodium sulfate in chloroform at room temperature; the yields of sulfonylchlorides II were 85%. The absence of sodium sulfate in the reaction medium decreases the yields of the final products to 20-30%, while the addition of the reagents in the reverse order, i.e., the addition of chlorosulfonic acid to the nitroindoles, leads to the formation of II in only 8% yield. However, the principal products of the reaction under these conditions (68-70%) are nitro-3-(nitro-2-indolinyl)indoles – dimers and, to a greater extent, trimers [8] of the starting nitroindoles, the PMR spectra of which are characterized by a weak-field shift of these signals, including the aliphatic protons due to the effect of the nitro group.



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*See [1] for Communication 135.

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Nitroindole-3-sulfonamides III and IV were obtained by the reaction of nitroindole-3-sulfonyl chlorides II with ammonia and dimethylamine. Nitro-3-indolylsulfonylpiperidines V and nitro-3-indolylsulfonylmorpholines VI were synthesized by the reaction of nitroindole-3-sulfonyl chlorides II with ammonia and dimethylamine.

The corresponding aminoindole-3-sulfonamides VII-X were obtained in 45-90% yields by reduction of sulfonamides III-VI with hydrazine hydrate in the presence of Raney nickel.

An absorption band of stretching vibrations at 3200-3470 cm^{-1}, which is characteristic for the NH group of the indole ring, appears clearly in the IR spectra of II-X in mineral oil. The nitro group has absorption bands at 1520-1545 and 1320-1350 cm^{-1}, while characteristic absorption bands of a chlorosulfonyl group are observed at 1330-1373 and 1160 cm^{-1}. In the IR spectra of VII-X stretching vibrations of NH_2 groups are observed at 3350-3600 cm^{-1}, while several absorption bands of $SO_2NR_2{}^1$ groups appear at 1320-1380 and 1120-1190 cm^{-1}.

The PMR spectra of II do not contain signals of 3-H protons (Table 1), but a weak-field shift of the 2-H signal is observed, which constitutes evidence for the presence of an electron-acceptor substituent in the 3 position. The absence of signals of 4-H, 5-H, 6-H, and 7-H protons for 4-, 5-, 6-, and 7-nitroindole-3-sulfonyl chlorides, respectively, weak-field shift of the signals of the remaining protons, and the character of the spin-spin coupling (SSC) confirm the presence of nitro groups in the indicated positions of the indole rings. One's attention is drawn to the presence of a strong intramolecular hydrogen bond (IMHB) in the case of 7-nitroindoles: for example, for IId and IVd in an inert medium ($CDCl_3$) one observes much greater weak-field shifts of the protons of the NH group than for 5- and 6-nitro isomers IIb and IIId. Acetone, being a weak base, partially disrupts the IMHB; two forms are observed in the spectrum of IId, while dimethyl sulfoxide ties up the imino group in an intermolecular hydrogen bond (intermolecular HB) completely.

Of interest is the fact that, in contrast to known indoles [9], which display a weak-field shift of the signal of the 2-H proton with an increase in the basicity of the medium, in the given series one observes a reverse tendency (see Table 1), i.e., it is equivalent to the fact that the introduction of a strong acceptor group such as an SO_2Cl group, despite what one expects, virtually does not change the shift of the 2-H proton as compared with the 3-unsubstituted nitro analog. Thus, for 5-nitroindole in $CDCl_3$ the signal of the 2-H proton lies at 7.38 ppm, while it is found at 8.14 ppm for its 3-SO_2Cl derivative IIb in $CDCl_3$, as compared with only 7.65 ppm in DMSO. The shifts of the remaining aromatic protons in DMSO are also shifted to strong field. This may be a consequence of the different relative orientations of the molecules in the case of solvation of the labile proton of the imino group of indole by a basic solvent and by the absence of such an effect in $CDCl_3$. An acid–base type of interaction of the proton of the NH group with the sulfo groups evidently predominates for inert media. The introduction of bulkyl NR_2 substituents (III-VI) into the sulfo group in place of chlorine probably hinders interaction of the π systems, and the shifts of all of the protons in DMSO are found at weaker field.

EXPERIMENTAL

The IR spectra of suspensions of the compounds in mineral oil were recorded with a UR-20 spectrometer with NaCl and LiF prisms. The PMR spectra of solutions in $CDCl_3$ and $(CD_3)_2CO$ were obtained with a Bruker WP-200-SY spectrometer with tetramethylsilane (TMS) as the internal standard. The course of the reaction and the purity of the compounds were monitored by TLC on Silufol UV-254.

The results of elementary analysis for C, H, and N corresponded to the calculated values, just as did the molecular masses of II-X, which were determined by mass spectrometry.

5-Nitroindole-3-sulfonyl Chloride (IIb). A 0.8 g (4.9 mmoles) sample of 5-nitroindole in 20 ml of dry chloroform was added with stirring at room temperature in the course of 1 h to a solution of 3 ml (2.5 mmoles) of freshly distilled chlorosulfonic acid in 30 ml of dry chloroform and 0.7 g (4 mmoles) of sodium sulfate, after which the reaction mixture was stirred for another 30 min. The solution was separated by decantation from the liberated oil, 20 ml of water was added to the oily precipitate, and the mixture was stirred for 5 min. The resulting crystalline precipitate was removed by filtration, washed with water until the wash water was neutral, and dried to give 1.1 g (85%) of a product with mp 189-190°C (from dioxane).

Sulfonyl Chlorides IIa, c, d. These compounds were similarly obtained.

3-Sulfonamido-4-nitroindole (IIIb). A solution of 0.2 g (0.7 mmole) of IIb in 15 ml of dioxane was added gradually with stirring at room temperature to 5 ml of concentrated NH_4OH, after which the reaction mass was evaporated in vacuo to one-third of its initial volume, and the concentrate was cooled to room temperature and diluted with 50 ml of water. The resulting precipitate was removed by filtration, washed with water until the wash water was neutral, and dried to give 0.1 g (55%) of a product with mp 215-216°C.

Compounds IIIc, d. These compounds were similarly obtained.

TABLE 1. Characteristics of II-X

Compound	Empirical formula	R	R'	X	T_{mp}, °C*1	PMP spectra, δ ppm (in $(CD_3)_2SO$)										SSCC J, Hz	Yield, %
						1-H	2-H	4-H	5-H	6-H	7-H	1'-CH_2	2'-CH_2	3'-CH_2	SO_2NR_2'		
IIa	$C_8H_5ClN_2O_4S$	4-NO_2	H	—	210...212	11,64*2, *3	7,79	—	8,18	7,52	8,04	—	—	—	—	$J_{12}=2,2$; $J_{56}=J_{67}=8,0$; $J_{57}=1,1$	84
IIb	$C_8H_5ClN_2O_4S$	5-NO_2	H	—	189...190	9,09*4	8,14	8,98	—	8,35	7,60	—	—	—	—	$J_{12}=3,4$; $J_{46}=2,4$; $J_{67}=9,5$	85
						11,86	7,65	8,70	—	8,08	7,55	—	—	—	—	$J_{12}=2,1$; $J_{46}=2,6$; $J_{67}=9,0$	
IIc	$C_8H_5ClN_2O_4S$	6-NO_2	H	—	165...166	9,55*4	8,25	8,17	8,33	—	8,53	—	—	—	—	$J_{12}=3,3$; $J_{45}=8,8$; $J_{57}=1,9$	80
						11,77	7,77	7,92	7,92	—	8,31	—	—	—	—	$J_{12}=3,3$;	
IId	$C_8H_5ClN_2O_4S$	7-NO_2	H	—	172...173	10,60*4, *5 (VMVS)*7	8,20	8,44	7,58	8,37	—	—	—	—	—	$J_{14}=J_{46}=0,7$; $J_{45}=J_{56}=8,0$	82
						12,62*3 (VMVS)*7	8,58	8,43	7,71	8,41	—	—	—	—	—	—	
						11,78*3 (MMVS)*7	8,06	8,35	7,49	8,29	—	—	—	—	—	—	
						11,78	7,43	8,24	7,27	8,11	—	—	—	—		$J_{12}=2,6$; $J_{45}=7,7$; $J_{55}=8,0$	
IIIb	$C_8H_7N_3O_4S$	5-NO_2	H	—	215...216	12,60	8,08	8,82	—	8,14	7,70	—	—	—	7,45	$J_{46}=2,2$; $J_{67}=9,2$	55
IIIc	$C_8H_7N_3O_4S$	6-NO_2	H	—	210...212	12,43	8,21	8,03	8,10	—	8,43	—	—	—	7,38	$J_{45}=9,1$; $J_{57}=1,8$	55
IIId	$C_8H_7N_3O_4S$	7-NO_2	H	—	225...226	12,47	7,91	8,35	7,46	8,26	—	—	—	—	7,46	$J_{45}=8,4$; $J_{56}=8,8$	55
IVb	$C_{10}H_{11}N_3O_4S$	5-NO_2	CH_3	—	226...227	12,75	8,31	8,67	—	8,15	7,74	—	—	—	2,63	$J_{46}=2,2$; $J_{67}=9,2$	94
IVc	$C_{10}H_{11}N_3O_4S$	6-NO_2	CH_3	—	215...216	12,60	8,00	7,99	8,07	—	8,45	—	—	—	2,62 2,63	$J_{45}=8,8$; $J_{57}=1,8$	94
IVd	$C_{10}H_{11}N_3O_4S$	7-NO_2	CH_3	—	198...199	11,24*4	7,94	8,37	7,39	8,27	—	—	—	—	2,76	$J_{45}=7,6$; $J_{56}=7,9$	94
Vb	$C_{13}H_{15}N_3O_4S$	5-NO_2	—	CH_2	207...208	10,36	8,21	8,63	—	8,04	7,69	2,93	1,53	1,35	—	$J_{46}=1,8$; $J_{67}=8,9$; $J_{CH_2CH_2}=5,3$	86
Vc	$C_{13}H_{15}N_3O_4S$	6-NO_2	—	CH_2	190...191	11,52	8,25	7,95	8,06	—	8,44	2,95	1,54	1,35	—	$J_{45}=8,8$; $J_{57}=2,2$; $J_{CH_2CH_2}=5,5$	86
Vd	$C_{13}H_{15}N_3O_4S$	7-NO_2	—	CH_2	194...195	12,00	8,03	8,31	7,47	8,27	—	2,93	1,57	1,32	—	$J_{45}=J_{56}=7,3$	86
VIb	$C_{12}H_{13}N_3O_5S$	5-NO_2	—	O	255...256	12,80	8,30	8,65	—	8,15	7,75	2,89	3,64	—	—	$J_{46}=2,2$; $J_{67}=9,1$; $J_{CH_2CH_2}=4,4$	87

VIc	$C_{12}H_{13}N_3O_5S$	6-NO_2	—	O	203...204	12,84	8,37	7,97	8,09	—	8,45	2,91	3,63	—	—	$J_{45}=8,8; J_{57}=2,2;$ $J_{CH_2CH_2}=5,1$	87
VId	$C_{12}H_{13}N_3O_5S$	7-NO_2	—	O	199...200	12,18	8,02	8,26	7,46	8,26	—	2,95	3,63	—	—	$J_{45}=J_{56}=8,0;$ $J_{CH_2CH_2}=4,8$	87
VIIb	$C_8H_9N_3O_2S$	5-NH_2	H	—	192...193	11,33*6	7,56	6,94	—	6,61	7,16	—	—	—	6,96	$J_{12}=2,9; J_{46}=1,4;$ $J_{67}=9,1$	69
VIIIb	$C_{10}H_{13}N_3O_2S$	5-NH_2	CH_3	—	198...199	10,83*3, *6	7,69	7,17	—	6,72	7,27	—	—	—	2,64	$J_{46}=2,2; J_{47}=0,7;$ $J_{67}=8,8$	90
VIIIc	$C_{10}H_{13}N_3O_2S$	6-NH_2	CH_3	—	185...186	11,55	7,58	7,42	6,55	—	6,61	—	—	—	2,55	$J_{12}=2,9; J_{45}=8,4;$ $J_{57}=1,5$	67
VIIId	$C_{10}H_{13}N_3O_2S$	7-NH_2	CH_3	—	180...181	11,70	7,88	7,04	6,90	6,45	—	—	—	—	2,57	$J_{12}=3,3; J_{45}=8,0;$ $J_{56}=7,3$	59
IXb	$C_{13}H_{17}N_3O_2S$	5-NH_2	—	CH_2	162...163	11,70*6	7,65	6,97	—	6,61	7,18	2,88	1,53	1,31	—	$J_{12}=2,2; J_{46}=1,8;$ $J_{67}=8,4;$ $J_{CH_2CH_2}=5,1$	45
IXc	$C_{13}H_{17}N_3O_2S$	6-NH_2	—	CH_2	155...156	11,52	7,54	7,40	6,55	—	6,61	2,85	1,52	1,29	—	$J_{12}=2,6; J_{45}=8,4;$ $J_{57}=1,7$	56
Xb	$C_{12}H_{15}N_3O_3S$	5-NH_2	—	O	165...167	11,70*6	6,68	6,95	—	6,65	7,20	2,89	3,63	—	—	$J_{12}=2,2; J_{46}=1,5;$ $J_{67}=8,8$	45
Xc	$C_{12}H_{15}N_3O_3S$	6-NH_2	—	O	140...142	11,61	7,59	7,40	6,56	—	6,62	2,83	3,61	—	—	$J_{12}=2,6; J_{45}=8,4;$ $J_{57}=1,5;$ $J_{CH_2CH_2}=4,6$	56

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*1The compounds were recrystallized: IIa, b, d from dioxane, IIc from ethyl acetate, IIIb-d, IVb-d, Vb-d, and VIb-d from alcohol, and VIIb, VIIIb-d, IXb, c, and Xb, c from benzene.

*2Retarded rotation of the bulky 3-SO_2Cl and 4-NO_2 groups is observed; the signals of the 2-H and 5-H protons are split into doublets.

*3In $(CD_3)_2CO$.

*4In $CDCl_3$.

*5Broad signal – exchange with acid traces

*6For VII-X (R = NH_2) the chemical shift of the NH_2 group at 4.5-5.3 ppm.

*7VMVS: Intramolecular hydrogen bond, MMVS: Intermolecular hydrogen bond.

3-N,N-Dimethylsulfonamido-5-nitroindole (IVb). A 5-ml sample of a 33% aqueous solution of dimethylamine was added gradually with stirring at room temperature to a solution of 0.2 g (0.7 mmole) of IIb in 15 ml of dioxane, and the mixture was heated at 80°C in the course of 10 min, after which the reaction mass was evaporated in vacuo to one-third of the initial volume. It was then diluted with 50 ml of water with vigorous stirring, and the resulting precipitate was removed by filtration, washed with water until the wash water was neutral, and dried to give 0.2 g (94%) of a product with mp 226-227°C (from alcohol).

Compounds IVc, d, Vb-d,* and VIb-d.* These compounds were similarly obtained.

3-Sulfonamido-5-aminoindole (VIIb). A 0.2 g sample of Raney nickel was added in portions to a mixture of 0.5 g (0.2 mmole) of IVb in 20 ml of 2-propanol and 3-5 ml of hydrazine hydrate, after which the mixture was heated to 50°C, and 25 ml of hydrazine hydrate was added in the course of 1.5 h. The mixture was then refluxed until the solution became completely colorless (2.5-3 h). The hot solution was filtered and cooled, and the resulting precipitate was removed by filtration and dried to give 0.3 g (69%) of a product with mp 192-193°C (from benzene).

Compounds VIIc, d, VIIIb-d, IXb, c, and Xb, c. These compounds were similarly obtained.

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*In the synthesis of Vb-d and VIb-d piperidine and morpholine were used in the same molar ratios.