REACTION OF 5-HYDROXYINDOLE DERIVATIVES WITH o-NITROBENZENESULFENYL CHLORIDE

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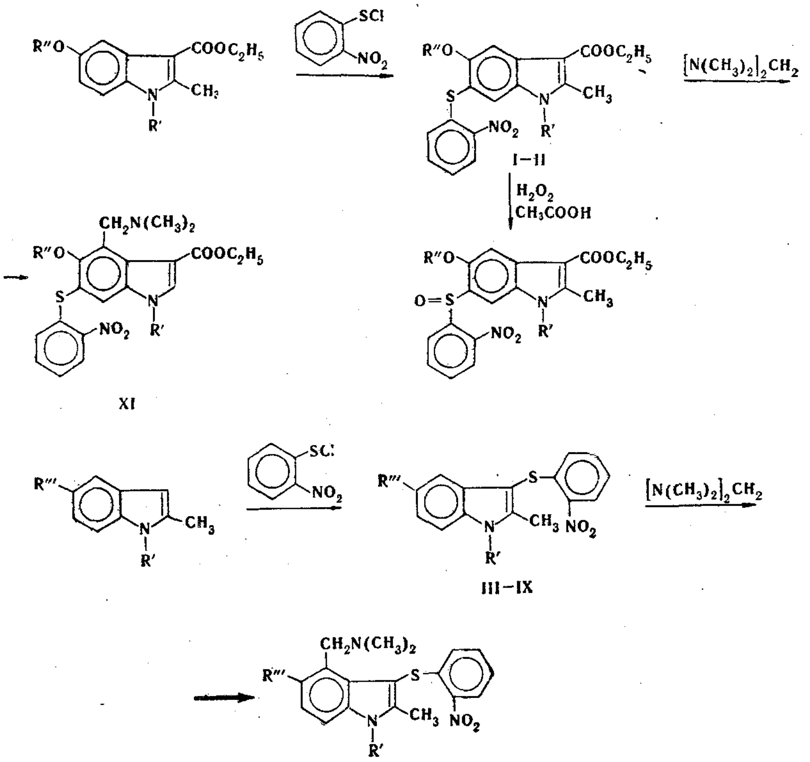
In the reaction of o-nitrobenzenesulfenyl chloride with 5-hydroxyindole derivatives, electrophilic substitution occurs in the 3 position. When there is a carbethoxy group in the 3 position, the o-nitrobenzenesulfenyl residue enters the 6 position. The corresponding 5-hydroxy derivatives, the aminomethylation of which leads to 4-dimethylaminomethyl derivatives, were obtained by hydrolysis of the 5-acetoxy derivatives of o-nitrophenyl 3-indolyl sulfides.

5-Hydroxyindole derivatives undergo electrophilic substitution with o-nitrobenzenesulfenyl chloride to give o-nitrophenyl 6-indolyl and o-nitrophenyl 3-indolyl sulfides.

Compounds I and II were obtained by heating equimolecular amounts of o-nitrobenzenesulfenyl chloride and 1,2-dimethyl-3-carbethoxy-5-methoxy- or 1,2-dimethyl-3-carbethoxy-5-hydroxyindole in dioxane.



I $R'=CH_3$, $R''=CH_3$; II $R'=CH_3$, $R''=H$; III $R'=CH_3$, $R'''=OCH_3$; IV $R'=CH_3$, $R'''=OCOCH_3$; V $R'=CH_3$, $R'''=OH$; VI $R'=C_6H_5$, $R'''=OCOCH_3$; VII $R'=C_6H_5$, $R'''=OH$; VIII $R'=CH_2C_6H_5$, $R'''=OCOCH_3$; IX $R'=CH_2C_6H_5$, $R'''=OH$; X $R'=CH_3$, $R''=CH_3$; XI $R'=CH_3$, $R''=H$; XII $R'=CH_3$, $R'''=OH$; XIII $R'=C_6H_5$, $R'''=OH$; XIV $R'=CH_2C_6H_5$, $R'''=OH$

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TABLE 1. o-Nitrophenyl Indolyl Sulfide Derivatives

Compound	Mp, °C	Empirical formula	Found, %				Calc., %				Yield, %
			C	H	N	S	C	H	N	S	
I	222,4—223,1	$C_{20}H_{20}N_2O_5S$	59,7	5,2	7,2	8,3	60,0	5,0	7,0	8,0	30
II	269—270	$C_{19}H_{18}N_2O_5S$	59,2	4,8	7,2	8,0	59,1	4,7	7,2	8,3	34
III	157,8—158,8	$C_{17}H_{16}N_2O_3S$	61,9	4,9	8,6	9,9	62,2	4,9	8,5	9,8	34
IV	157,7—158,2	$C_{18}H_{16}N_2O_4S$	60,5	4,9	7,7	8,6	60,7	4,5	7,9	9,0	60
V	183,4—184,0	$C_{16}H_{14}N_2O_3S$	60,9	4,4	—	10,0	61,1	4,5	—	10,2	75
VI	143,5—144,5	$C_{23}H_{18}N_2O_4S$	—	—	6,8	7,5	—	—	6,7	7,7	42
VII	165—168 dec.	$C_{21}H_{16}N_2O_3S$	—	—	7,6	7,7	—	—	7,4	8,5	95
VIII	172,1—173,1	$C_{24}H_{20}N_2O_4S$	—	—	6,5	7,4	—	—	6,5	7,4	26
IX	130,8—131,3†	$C_{22}H_{18}N_2O_3S$	—	—	—	—	—	—	—	—	74
X	216,6—217,3	$C_{20}H_{20}N_2O_6S$	57,4	4,7	—	7,6	57,7	4,8	—	7,7	53

*Compounds I and III were crystallized from alcohol, II was crystallized from dimethylformamide–benzene, and IV-X were crystallized from acetone.

† This compound was used in the transformations without additional purification.

TABLE 2. 4-Dimethylamino Derivatives of o-Nitrophenyl Indolyl Sulfides

Compound	Mp, °C	Empirical formula	Found, %					Calc., %					Yield, %
			C	H	Cl	N	S	C	H	Cl	N	S	
XI	189,2—189,8	$C_{22}H_{24}N_3O_5S$	59,6	5,6	—	9,5	7,5	59,7	5,5	—	9,5	7,3	66
XII	195,5—196,5	$C_{19}H_{21}N_3O_3S$	61,3	5,7	—	11,2	—	61,4	5,7	—	11,3	—	72
XIII	190,0—191,0	$C_{24}H_{23}N_3O_3S$	—	—	—	10,1	7,1	—	—	—	9,7	7,4	98
XIV	187,4—188,4	$C_{25}H_{25}N_3O_3S$	—	—	—	9,3	7,0	—	—	—	9,4	7,2	87
XV	225,6—226,6	$C_{19}H_{21}N_3O_3S \cdot HCl$	—	—	8,4	10,1	7,5	—	—	8,7	10,3	7,9	
XVI	170,0—171,0	$C_{24}H_{23}N_3O_3S \cdot HCl$	—	—	7,3	8,9	6,4	—	—	7,5	8,9	6,8	
XVII	229,5—230,5	$C_{25}H_{25}N_3O_3S \cdot HCl$	—	—	7,3	8,8	6,5	—	—	7,3	8,7	6,6	

*Compounds XI, XII, and XIV-XVII were crystallized from alcohol.

The reaction of 1,2-dimethyl-5-methoxyindole and various 2-methyl-5-acetoxyindoles with o-nitrobenzenesulfenyl chloride in dioxane leads to III-IX. Sulfides of 5-hydroxyindoles V, VII, and IX are formed in high yields in the hydrolysis of IV, VI, and VIII with alcoholic alkali. Transition from acetoxy derivatives IV, VI, and VIII to 5-hydroxy derivatives V, VII, and IX is accompanied by the disappearance of the band of carbonyl absorption of the acetoxy group at 1750-1755 cm^{-1} and the appearance of the band of a phenolic hydroxyl group at 3400-3700 cm^{-1}. 4-Dimethylaminomethyl derivatives (XI-XIV) and their hydrochlorides (XV-XVII) were obtained by aminomethylation of 5-hydroxyindole derivatives II, V, VII, and IX. o-Nitrophenyl 1,2-dimethyl-3-carbethoxy-5-methoxy-6-indolyl sulfide forms sulfoxide X on heating with 30% hydrogen peroxide in acetic acid.

Two singlets corresponding to the para protons (4-H and 7-H) of the benzene portion of the indole ring are observed in the PMR spectrum of II in $(CD_3)_2SO$. This indicates that the o-nitrobenzenesulfenyl group enters the 6 position. In addition to the signals of the phenyl ring, doublets of the 7-H ($J_{7,6}$ = 8.5 Hz) and 4-H ($J_{4,6}$ = 2.5 Hz) protons and a quartet of the 6-H proton ($J_{6,7}$ = 8.5 Hz, $J_{6,4}$ = 2.5 Hz) are observed in the aromatic portion of the PMR spectrum of IV in $(CD_3)_2CO$. The structures of these signals and the absence of the singlet of the 3-H proton unambiguously prove that the o-nitrophenylmercapto group occupies the 3 position in IV. A doublet of the 7-H proton at δ 7.20 ppm ($J_{7,6}$ = 8.5 Hz), a doublet of the 4-H proton at δ 7.11 ppm ($J_{4,7}$ = 2.5 Hz), a quartet of a 6-H proton at 6.74 ppm ($J_{6,7}$ = 8.5 Hz, $J_{6,4}$ = 2.5 Hz), and a singlet of the 3-H proton at 6.15 ppm are observed in the PMR spectrum in $(CD_3)_2CO$ of 1,2-dimethyl-5-acetoxyindole, used as the starting compound in the synthesis of IV.

EXPERIMENTAL*

The PMR spectra of the compounds were recorded with a JEOL CO JNM-4H-100 spectrometer with tetramethylsilane as the internal standard. The IR spectra were recorded with a Perkin–Elmer 457 spectrometer. The physical constants and yields of the compounds are presented in Tables 1 and 2.

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* The experimental portion of this research was accomplished with the participation of R. A. Zinov'eva.

o-Nitrophenyl 1,2-Dimethyl-3-carbethoxy-5-methoxy-6-indolyl Sulfide (I). A mixture of 2.6 g (10.5 mmole) of 1,2-dimethyl-3-carbethoxy-5-methoxyindole [1], 2.0 g (10.5 mmole) of o-nitrobenzenesulfenyl chloride [2], and 5 ml of dioxane was heated at 100° for 2 h, after which it was cooled to room temperature and filtered to remove the precipitated I. The product was washed on the filter with cold acetone and dried in a vacuum desiccator over calcium chloride.

o-Nitrophenyl 1,2-Dimethyl-3-carbethoxy-5-hydroxy-6-indolyl Sulfide (II). A mixture of 6.7 g (28.7 mmole) of 1,2-dimethyl-3-carbethoxy-5-hydroxyindole [3], 5.4 g (28.7 mmole) of o-nitrobenzenesulfenyl chloride, and 11 ml of dioxane was heated at 100° for 1 h, after which it was cooled to room temperature and filtered to remove the precipitated II. The product was washed on the filter with acetone and dried in a vacuum desiccator over calcium chloride. PMR spectrum, δ, ppm: s* 9.63 (5-OH), 7.74 (7-H), 7.65 (4-H), 3.71 (1-CH_3), 2.73 (2-CH_3), t 1.4 (CH_3), q 4.31 ($3\text{-COO}\underline{\text{CH}_2}\text{CH}_3$), m 6.79, 7.39, 8.24 (6-o-$NO_2C_6H_4S$).

o-Nitrophenyl 1,2-Dimethyl-5-methoxy-3-indolyl Sulfide (III). This compound was obtained by the method used to prepare I.

o-Nitrophenyl 1,2-Dimethyl-5-acetoxy-3-indolyl Sulfide (IV). A mixture of 1.7 g (8.23 mmole) of 1,2-dimethyl-5-acetoxyindole [4], 1.6 g (8.23 mmole) of o-nitrobenzenesulfenyl chloride, and 5 ml of dioxane was heated at 100° for 15 min, and the mixture was then cooled to room temperature. The precipitated IV was removed by filtration, washed with a small amount of cold acetone, and dried in a vacuum desiccator over calcium chloride. PMR spectrum, δ, ppm: s 3.83 (1-CH_3), 2.50 (2-CH_3), 2.18 ($5\text{-OCO}\underline{\text{CH}_3}$), d 7.07 (4-H), 7.47 (7-H), q 6.91 (6-H), m 6.80, 7.30, 8.20 (6 o-$NO_2C_6H_4S$). IR spectrum (in mineral oil): 1755 cm^{-1} (C=O).

Compounds VI and VIII were obtained by the method used to prepare IV.

o-Nitrophenyl 1,2-Dimethyl-5-hydroxy-3-indolyl Sulfide (V). A mixture of 6.8 g (19.1 mmole) of IV and 133 ml of 10% potassium hydroxide solution in methanol was refluxed at 70° for 1 h. The solution was then poured into a threefold volume of water, and the mixture was filtered to remove a small amount of a suspension. The filtrate was acidified with acetic acid until it was weakly acidic (pH $\sim$ 6), and the V was removed by filtration, washed on the filter with distilled water until it was neutral, and dried in a vacuum desiccator over P_2O_5 at 90° for 24 h. IR spectrum (in mineral oil): 3300 cm^{-1} (OH).

Compounds VII and IX were obtained by the method used to prepare V (Table 1).

o-Nitrophenyl 1,2-Dimethyl-3-carbethoxy-5-methoxy-6-indolyl Sulfoxide (X). A 3 g (7.49 mmole) sample of I was dissolved at 115° with stirring in 68 ml of glacial acetic acid, and 2 ml of 30% aqueous hydrogen peroxide with d_4^{20} 1.1122 (19.62 mmole) was added dropwise, after which the mixture was stirred for 1 h and poured into 90 ml of water. A 6.5 ml sample of 25% ammonium hydroxide was added to the mixture, and the precipitated X was removed by filtration.

o-Nitrophenyl 1,2-Dimethyl-4-carbethoxy-4-dimethylaminomethyl-5-hydroxy-6-indolyl Sulfide (XI). A mixture of 0.5 g (1.29 mmole) of II, 0.4 g (3.91 mmole) of bisdimethylaminomethane, and 5 ml of dimethylformamide (DMF) was stirred at 105° for 4 h, after which it was vacuum evaporated to dryness at 70°. The residue was treated with absolute ether, and the crystalline precipitate of XI was removed by filtration.

o-Nitrophenyl 1,2-Dimethyl-4-dimethylaminomethyl-5-hydroxy-3-indolyl Sulfide (XII). A mixture of 2.0 g (6.36 mmole) of V, 0.9 g (9.19 mmole) of bisdimethylaminomethane, 5 ml of dioxane, and 2 ml of DMF was heated at 100° for 2.5 h, after which it was vacuum evaporated to dryness at 70°. Water was added to the residue, and the precipitated XII was removed by filtration and washed with water.

Compounds XIII and XIV were obtained from VII and IX by the method used to prepare XII (Table 2).

Hydrochloride of XII (XV). Base XII was dissolved in the minimum amount of acetone, and a solution of hydrogen chloride in absolute ether was added. The mixture was then treated with absolute ether until the precipitation of hydrochloride XV was complete. The precipitate was removed by filtration, washed on the filter with absolute ether, and dried over P_2O_5 at 10 mm (mercury standard) and 90° for 6 h.

The hydrochlorides of bases XIII, XIV (XVI and XVII) were similarly obtained (Table 2).

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

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