INDOLE DERIVATIVES

XXIX. Indolylakylthioureas

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In order to study their biological activity, N- and S-substituted thioureas have been synthesized. The reaction of 5-methoxytryptamine with silicon tetraisothiocyanate has given N-β-(5-methoxy-3-indolyl)ethylthiourea, and that of its hydrochloride with ammonium thiocyanate has given N, N'-di[β-(5-methoxy-3-indolyl)ethyl]thiourea. Unsymmetrical disubstituted thioureas have been obtained by the reaction of tryptamines with aryl isothiocyanates. S-3-indolylalkylisothiouronium salts have been synthesized by the reaction of thiourea with (3-indolyl)alkyl bromides.

In recent years, thiourea derivatives have been attracting increasing interest from chemists, pharmacologists, and radiobiologists. Thus, for example, it is known that thiocarbanilide derivatives include compounds possessing high antitubercular activity [1], and a large number of the S-substituted thiourea derivatives studied have the properties of effective prophylactic agents against radiation sickness [2, 3]. It appeared to us to be of interest to obtain a number of indolylalkylthioureas in order to study their biological activity.

In the synthesis of N-substituted thioureas we started from the tryptamines (I) obtained previously [4, 5]. N-β-(5-Methoxy-3-indolyl)ethylthiourea (**III**, R = OCH_3) was obtained by the reaction of 5-methoxytryptamine (**I**, R = OCH_3) with silicon tetraisothiocyanate [6]. N, N-Di[β-(5-methoxy-3-indolyl)ethyl]thiourea (**IV**, R = = OCH_3) was obtained by heating 2 moles of the hydrochloride of 5-methoxytryptamine (**I**) with 1 mole of ammonium thiocyanate at 160–165° C.

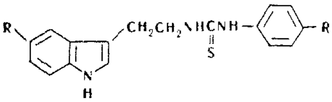
The reaction of these substances in equimolecular ratios at 100° C leads to 5-methoxytryptamine thiocyanate (**II**, R = OCH_3), and further heating of this to 160° C gives a mixture of **II**, **III**, and **IV**).

When the tryptamines (I) were heated with various aryl isothiocyanates in benzene, a number of unsymmetrical disubstituted N-indolylethyl-N'-phenylthioureas (V) were obtained. By the action of methyl iodide in acetone, the indolylethylthioureas III–V) were converted into the corresponding S-methylisothiouronium hydriodides (VI).

The starting materials in the synthesis of S-substituted thioureas were esters of 3-indolylalkanoic acids (VII) [4, 7–9], which were converted via the corresponding alcohols and bromides in accordance with the scheme given below into S-indolylalkylisothiouronium salts (**X–XII**) [10].

Since the isothiouronium bromides (**X**) could not be obtained in the crystalline state, they were converted into the crystalline sulfates or hydriodides.

Table 1



R	R′	Mp, °C	Empirical formula	Found, %	Calculated, %	Yield, %
OCH_3	H	108–110 (benzene)	$C_{18}H_{19}N_3OS$	C 66.69 H 6.06 N 12.74 S 9.84	C 66.46 H 5.85 N 12.92 S 9.84	83.4
OCH_3	OC_4H_9	166–167 (ethanol)	$C_{22}H_{27}N_3O_2S$	C 66.81 H 6.76 N 10.75 S 7.84	C 66.50 H 6.81 N 10.58 S 8.06	92.0
$OCH_2C_6H_5$	OC_2H_5	123–125 (benzene)	$C_{26}H_{27}N_3O_2S$	C 70.62 H 5.92 N 9.45 S 7.21	C 70.11 H 6.07 N 9.44 S 7.19	85
H	OC_2H_5	138.5–140.5 (aqueous ethanol)	$C_{19}H_{21}N_3OS$	C 67.98 H 6.40 N 12.32 S 9.46	C 67.24 H 6.20 N 12.39 S 9.44	94.4

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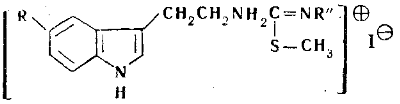
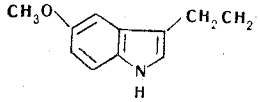
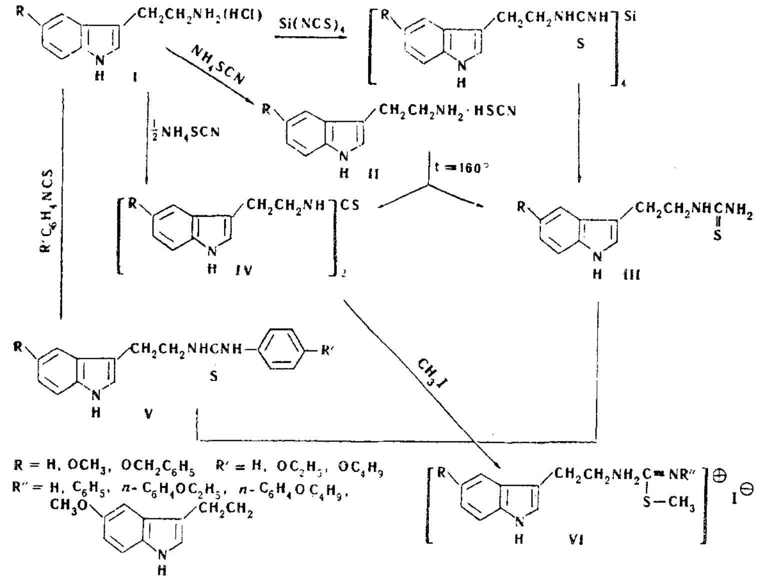
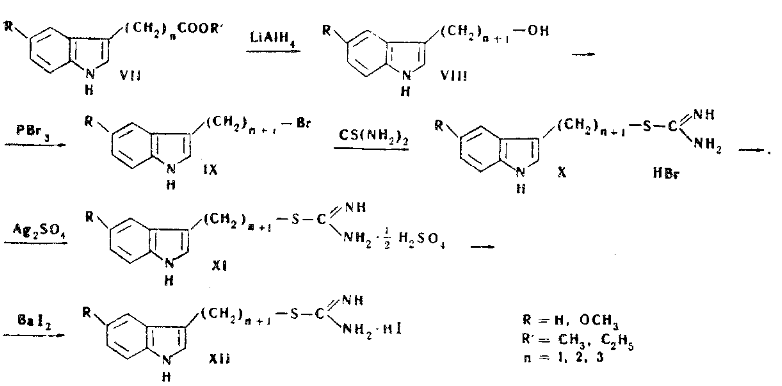
*For communication XXVIII, see [11].

Table 2



R″	R	Mp, °C	Empirical formula	Found, %	Calculated, %	Yield, %
C_6H_5	OCH_3	153—154.5 (ethanol–ethyl acetate)	$C_{19}H_{22}IN_3OS$	C 49.11 H 4.80 N 8.80 S 6.65 I 27.15	C 48.82 H 4.71 N 8.99 S 6.85 I 27.19	84.5
n-$C_6H_4OC_2H_5$	OCH_3	101—105 (decomp, ethanol–ethyl acetate)	$C_{21}H_{26}IN_3O_2S$	N 8.11 S 6.34 I 24.85	N 8.22 S 6.26 I 24.85	86.5
n-$C_6H_4OC_4H_9$	OCH_3	94—98 (ethanol–ethyl acetate)	$C_{23}H_{30}IN_3O_2S$	C 51.71 H 5.56 N 8.09 I 23.99	C 51.20 H 5.56 N 7.79 I 23.56	91.0
	OCH_3	197—199 (decomp, methanol–ether)	$C_{24}H_{29}IN_4O_2S$	C 51.49 H 5.34 N 9.71 S 5.74 I 22.80	C 51.06 H 5.14 N 9.93 S 5.67 I 22.52	72.0
n-$C_6H_4OC_2H_5$	H	124—126 (ethanol–ethyl acetate)	$C_{20}H_{24}IN_3OS$	C 49.55 H 5.05 N 8.34 S 6.90 I 26.71	C 49.90 H 4.99 N 8.73 S 6.65 I 26.40	92.0
n-$C_6H_4OC_2H_5$	$OCH_2C_6H_5$	180—182.5 (methanol–ether)	$C_{27}H_{30}IN_3O_2S$	C 55.22 H 5.24 N 7.36 I 22.10	C 55.20 H 5.11 N 7.15 I 21.64	93.0





EXPERIMENTAL

N-β-(5-Methoxy-3-indolyl)ethylthiourea (III). With stirring, a suspension of 5.2 g of silicon tetraisothiocyanate in 100 ml of benzene was rapidly added to a suspension of 15.2 g of 5-methoxytryptamine (I, R = OCH_3) in 300 ml of dry benzene, and the mixture was boiled for 4 1/2 hr and after the solvent had been distilled off and the residue was boiled for 30 min in a mixture with 90 ml of isopropanol and 10 ml of water. The hot solution was filtered and the gelatinous precipitate on the filter was washed with acetone. The combined filtrates were evaporated, washed with cold water until the wash waters gave no reaction for the thiocyanate ion, and compound III was extracted with boiling water. Yield 5.65 g (28.2%). Mp 159–161.5° C. Found, %: C 57.61; H 5.97; N 16.60; S 12.65. Calculated for $C_{12}H_{15}N_3OS$, %: C 57.84; H 6.02; N 16.87; S 12.85. IR spectrum, cm^{-1}: 3420; 3290, 3250, 3200 (NH), 1625 (NH_2), 1550 (C=S), 1490 (C=C), 1218 (OCH_3).

N, N-Di[β-(5-methoxy-3-indolyl)ethyl]thiourea (IV). A mixture of 5 g of 5-methoxytryptamine hydrochloride (I, R = OCH_3), 0.84 g of ammonium thiocyanate, and 22 ml of paraffin oil was heated with stirring at 160–165° C for 2 1/2 hr. After the elimination of the paraffin oil, the residue was washed with benzene and petroleum ether by decanting and was crystallized twice from ethanol. Yield 2.2 g (47.4%). Mp 147° C and 173° C. Found, %: C 65.72; H 6.36; N 13.14; S 7.65. Calculated for $C_{23}H_{26}N_4O_2S$, %: C 65.40; H 6.16; N 13.27; S 7.60. IR spectrum, cm^{-1}: 3430, 3350, 3260 (NH), 1625, 1570, 1525, 1490 (C=C, C=S), 1220 (OCH_3).

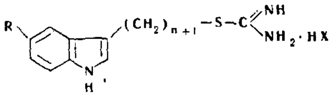
N-β-(5-Methoxy-3-indolyl)ethyl-N′-p-ethoxyphenylthiourea (V, R = OCH_3; R′ = OC_2H_5). With stirring, a solution of 1 g of p-ethoxyphenyl isothiocyanate in 8 ml of benzene was added to a boiling solution of 1.06 g of 5-methoxytryptamine (I, R = OCH_3) in 8 ml of dry benzene. The reaction mixture was boiled for 30 min. After cooling, the precipitate was filtered off and crystallized from ethanol. Yield 1.83 g (89%). Mp 183–183.5° C. Found, %: C 65.43; H 6.19; N 11.53; S 8.69. Calculated for $C_{20}H_{23}N_3O_2S$, %: C 65.04; H 6.23; N 11.38; S 8.67. IR spectrum, cm^{-1}: 3260 (NH), 1580, 1550, 1520 (C=C, C=S). The compounds given in Table 1 were obtained similarly.

N-β-(5-Methoxy-3-indolyl)ethyl-S-methylisothiouronium iodide (VI, R = OCH_3, R″ = H). A solution of 4 g of N-(5-methoxy-3-indolyl)-ethylthiourea (III, R = OCH_3) in 50 ml of dry acetone was treated with 4 ml of dry methyl iodide, and the solution was left at room temperature in the dark for 20 hr. After the elimination of the solvent, the residue was purified by precipitation with absolute ether from ethanolic solution. Yield 5.83 g (93%). Mp 134–135.5° C. Found, %: C 39.81; H 4.64; N 10.79; S 8.21; I 32.63. Calculated for $C_{13}H_{18}IN_3OS$, %: C 39.89; H 4.61; N 10.74; S 8.18; I 32.48. IR spectrum, cm^{-1}: 3280, 3150, 2280 (NH), 1640, 1610 (C=N, NH_2^+), 1520, 1490 (C=C).

Picrate—mp 197–199° C (decomp). Found, %: C 46.40; H 4.18; N 17.08; S 6.53. Calculated for $C_{13}H_{17}OS \cdot C_6H_3N_3O_7$, %: C 46.33; H 4.06; N 17.08; S 6.50. The compounds given in Table 2 were obtained similarly.

5-Methoxytryptophol (VIII, R = OCH_3, n = 1). A solution of 4.17 g of ethyl 5-methoxy-3-indolylacetate (VII, R = OCH_3, R_1 = C_2H_5, n = 1) in 180 ml of absolute ether was added to 2 g of lithium aluminum hydride in 100 ml of absolute ether, and the reaction mixture was stirred at room temperature for 4 hr. The excess of lithium aluminum hydride was decomposed by the addition of 2 ml of water, 2 ml of 15% sodium hydroxide, and 6 ml of water. The precipitate was filtered off and washed with ether. The combined filtrate was dried with $MgSO_4$, evaporated to a volume of 15 ml, and passed through a column of alumina,

Table 3



R	X	*n*	Mp, °C	Empirical formula	Found, %	Calculated, %	Yield, %
H	$\frac{1}{2}SO_4$	1	183 —184 (ethanol)	$C_{22}H_{28}N_6O_4S_3$	C 49.44 H 5.29 N 15.56 S 17.60	C 49.25 H 5.22 N 15.67 S 17.91	76
H	$C_6H_2O(NO_2)_3$	1	176 —177 (ethanol)	$C_{17}H_{16}N_6O_7S$	C 45.70 H 3.71 N 18.65 S 7.13	C 45.54 H 3.57 N 18.75 S 7.14	—
H	$\frac{1}{2}SO_4$	2	208 —209 (water)	$C_{24}H_{32}N_6O_4S_3$	C 51.00 H 5.80 N 14.78 S 16.86	C 51.18 H 5.68 N 14.88 S 17.00	67.5
H	I	2	111.5—112.5 (water)	$C_{12}H_{16}IN_3S$	C 39.87 H 4.43 N 11.45	C 39.88 H 4.43 N 11.63	88.1
H	$C_6H_2O(NO_2)_3$	3	182 (ethanol)	$C_{19}H_{20}N_6O_7S$	C 47.86 H 4.28 N 17.59 S 6.65	C 48.00 H 4.21 N 17.65 S 6.74	—

using ether as solvent. Yield 3 g (87.5%): n_D^{18} 1.594. Found, %: C 69.28; H 7.01; N 7.16. Calculated for $C_{11}H_{13}NO_2$, %: C 69.11; H 6.88; N 7.33.

β-(5-Methoxy-3-indolyl)ethyl bromide (IX, R = OCH_3, n = 1). With stirring and ice-cooling, 1.37 g of phosphorus tribromide in 70 ml of absolute ether was added to 2.89 g of 5-methoxytryptophol (VIII, R = = OCH_3, n = 1) in 230 ml of absolute ether. The solution was kept at room temperature for a day, washed with water, sodium bicarbonate solution, and water again, dried with magnesium sulfate, and evaporated to dryness. Yield 1.86 g (48.30%). Mp 48.5–49.5° C (benzene–petroleum ether). Found, %: C 51.83; H 4.81; N 5.69; Br 31.34. Calculated for $C_{11}H_{12}BrNO$, %: C 51.97; H 4.72; N 5.51; Br 31.60.

S-β-[(5-Methoxy-3-indolyl)ethyl]isothiouronium sulfate (XI, R = = OCH_3, n = 1). A solution of 1.25 g of the bromide (IX, R = OCH_3, n = 1) in 30 ml of ethanol was added to a boiling solution of 0.4 g of thiourea in 50 ml of ethanol and the mixture was boiled for 6 hr. After the ethanol had been distilled off, the residue was dissolved in 120 ml of hot water. A saturated solution of silver sulfate was added, the precipitate of silver bromide filtered off, the filtrate evaporated to dryness, and the residue crystallized from ethanol. Yield 1.05 g (72%). Mp 178–179° C. Found, %: C 48.27; H 5.47; N 14.35; S 16.16. Calculated for $C_{24}H_{32}N_6O_6S_3$, %: C 48.32; H 5.37; N 14.10; S 16.10. The compounds given in Table 3 were obtained similarly.

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