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SYNTHESIS AND PROPERTIES OF AZOLES AND THEIR DERIVATIVES.

34.* SYNTHESIS OF 4-SUBSTITUTED 2-(3-INDOLYL)THIAZOLES

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4-Substituted 2-(3-indoly1)thiazoles were synthesized by condensation of indole-3thiocarboxamide with halomethyl ketones. Reactions involving the nucleophilic substitution of the chlorine atom in 4-chloromethy1-2-(3-indoly1)thiazole were examined.

There has recently been increased interest in noncondensed bisheterocyclic systems that contain indole and thiazole fragments simultaneously. The special interest in heterocycles of this type is due to the fact that substances with a broad spectrum of biological activity have been found among them [2-4]. It has also been noted that some indolyl-containing thiazoles display radioprotective properties [5].

In order to search for new potential biologically active substances we synthesized some previously undescribed indolylthiazoles and studied their properties. In the present research for the synthesis of heterocycles of the indicated type we used the reaction of the accessible indole-3-thiocarboxamide (I) with α -halo-substituted carbonyl compounds. There has thus far been only one report of the synthesis of indolylthiazoles from thiocarboxamides of the indole series [6].

The condensation of thiocarboxamide I with α -halomethyl ketones was carried out by refluxing mixtures of equimolar amounts of the reagents in alcohol for several hours. The resulting 4-substituted 2-(3-indoly1)thiazole hydrohalides were converted to free bases II-VI by treatment with ammonium hydroxide.



X=Cl, Br; II R=CH₃, III R=C₆H₅, IV R=4-CH₃OC₆H₄, V R=2- thieny1, VI R=CH₂C1

*See [1] for communication 33.

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The IR spectra of indoly1thiazoles II-VI contain a broad absorption band at 3215-3250 cm⁻¹, which indicates the presence of an indole NH group with strong hydrogen bonds [7]. However, this band vanishes in the IR spectrum of the hydrobromide of 4-pheny1-2-(3-indoly1)thiazole (III), and an intense band at 3435 cm^{-1} , which constitutes evidence for the presence of a free indole N-H bond, appears. A number of bands of variable intensity that are characteristic for the stretching vibrations of a 3-substituted indole ring (1600-1610, 1565-1575, and 1490-1500 cm⁻¹) [7, 8], as well as a 2,4-disubstituted thiazole ring (1620-1630, 1520-1550, and 1412-1430 cm⁻¹) [8, 9], are observed in the spectra of indoly1thiazoles II-VI at 1400-1640 cm⁻¹. The intense absorption maxima at 960-980 and 875-890 cm⁻¹ (thiazole ring CH) and at 765-805 and 750-755 cm⁻¹ (indole ring CH) correspond to the out-of-plane deformation vibrations of the C-H bond. The absorption frequencies of medium intensity at 1145-1160 cm⁻¹ are due to the in-plane deformation vibrations of the C-H bond in 2,4-disubstituted thiazoles [8].

Signals of five aromatic protons of the indole ring (7.05-7.86 ppm), as well as a singlet at 6.64-6.72 ppm, which we assigned to the resonance of the proton in the 5 position of the thiazole ring [8], were observed in the PMR spectra of indolylthiazoles II-VI. The signals of the 2-H proton of the pyrrole ring show up in the form of a doublet at 7.56-7.68 ppm with spin-spin coupling constants (SSCC) 2.2-4.0 Hz and are shifted to weak field as compared with unsubstituted indole and 3-phenylindole (6.68 and 7.03 ppm, respectively [7]).

The molecular masses of II-VI determined by mass spectrometry correspond to the calculated values, and the character of the subsequent fragmentation of the molecular ions (M⁺), which was confirmed by metastable transitions, is in agreement with the proposed structures. The M⁺ peak in the mass spectra of the indolylthiazoles is the maximum peak and has rather high stability with respect to electron impact ($W_M = 24-35\%$); this is characteristic for most bisheteroaromatic compounds [10, 11]. The fragmentation of M⁺ proceeds via the scheme that is typical for 2,4-disubstituted thiazoles [12]. Intense peaks of fragment ions with m/z 116, 115, 90, 89, and 63, which are characteristic for indole [7], are observed in the mass spectra of indolylthiazoles II-VI. An appreciable [M - C1]⁺ ion peak is also present in the spectrum of chloro derivative VI.

It is known [13] that 4-halomethylthiazoles are strongly reactive compounds and are similar in this respect to benzyl halides. In this connection it seemed of interest to us to examine some exchange reactions of the chlorine atom in 4-(chloromethyl)-2-(3-indolyl)thiazole (VI) in order to synthesize indolylthiazole derivatives with various functional groups in the side chain. We studied the reaction of thiazole VI with secondary cyclic amines, viz., morpholine and piperidine, as well as with potassium thiocyanate.



The reactions involving nucleophilic substitution of the chlorine in VI were carried out by brief heating of an equimolar mixture of the reagents in absolute alcohol in the presence of potassium carbonate.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of solutions in deuteromethanol were obtained with a Tesla BS-487C spectrometer (80 MHz) with hexamethyldisiloxane as the internal standard. The mass spectra were obtained with an LKB-2091 mass spectrometer with a system for direct introduction of the samples into the ion source at an electron-ionization energy of 70 eV, an emission current of $25 \ \mu$ A, and a sample-vaporization temperature of 110-120°C. The course of the reaction and the purity of the compounds obtained were monitored by means of thin-layer chromatography (TLC) on activity II aluminum oxide in benzene-methanol (10:1 or 20:1) with development by iodine vapors.

The starting indole-3-thiocarboxamide (I) was synthesized by the method in [14] and had mp 147-148.5°C (from toluene).

- pu	mp, ^a °C	_{R_f} b	PMR spectrum, ppm	Found, %			Empirical	: Calc., %			d, %
Con				С	н	N	tormula	с	н	N	Yiel
IIc	153—154	0,54	2,40 (3H, s. CH ₃); 6,61 (1H, s, thiazole 5-H); 7,05-7,84 (5H, :: m, in- dole); 7,60 (1H d. in- dole 2-H); 8.22 (1H, s,	67,4	4,7	13,0	C ₁₂ H ₁₀ N ₂ S	67,3	4,7	13,1	67
Шq	166—167	0,68	NH) 6,65 (1H, s, thiazole 5-H) 6,84-7,76 (10H, m, aro- matic protons);	73,8	4,3	10,2	C ₁₇ H ₁₂ N ₂ S	73,9	4,4	10,1	76
IV	136—137	0,75	7,64 (1H, d, indole 2-H);, 8,31 (1H, br, NH) 3,54 (3H, s, CH ₃ O); 6,54 (1H, s, thiāzole 5-H); 7,127,82 (9H, m, aro- matic protons); 7,70	70,7	4,5	9,3	C ₁₈ H ₁₄ N ₂ OS	70,6	4,6	9,1	74
v	147—148	0,83	(1H, d, indole 2-H); 8.12 (1H,s, NH) 6,63 (1H, s, thiazole 5-H) 6,74-7,76 (8H, m, aro- matic protons); 7.60	63,7	3,5	10,1	$C_{15}H_{10}N_2S_2$	63,8	3,5	9,9	85
VI ^e	103—104	0,64	(1H, d, indole 2-H); 8.28 (1H,br, NH) 4,46 (2H, s, CH ₂); 6,67 (1H, s, thiazole 5-H); 7,10-7,68 (5H,m, in- dole); 7,58 (1H, d, in- dole 2-H); 8.16 (1H, s, ,				C₁₂H₃CIN₂S ^f			-	67

TABLE 1. 4-Substituted 2-(3-Indoly1)thiazoles

^aThe compounds were recrystallized: II and III from 50% alcohol, IV and V from 30% methanol, and VI from absolute alcohol-hexane (1:2). ^bIn a benzene-methanol system (10:1 for II, III, and VI and 20:1 for IV and V). ^cThe hydrochloride of II had mp 209-210°C (dec., from absolute alcohol). ^dThe hydrobromide of III had mp 200-201°C (from absolute alcohol). ^eThe picrate of VI had mp 126-127°C (dec., from acqueous alcohol). Found: C 45.0; H 2.6; N 14.4%. $C_{12}H_9CIN_2S \cdot C_6H_3N_3O_7$. Calculated: C 45.2; H 2.5; N 14.6%. ^fFound: C1 14.4%. Calculated: C1 14.4%.

4-Substituted 2-(3-Indoly1)thiazoles (II-VI). A solution of 20 mmole of the corresponding bromomethyl ketone (1,3-dichloroacetone in the preparation of indoly1thiazole VI) in 20 ml of absolute alcohol was added dropwise to a stirred solution of 3,32 g (20 mmole) of thiocarboxamide I in 40 ml of absolute alcohol, and the mixture was refluxed with stirring for 1.5 h and allowed to stand overnight. It was then poured into water, and the aqueous mixture was neutralized with 10% ammonium hydroxide. The precipitate was collected and dried,

In the preparation of indolylthiazole III the hydrobromide precipitated from the reaction mixture after it was maintained at 0°C for 12 h. The hydrochlorides of II-VI were obtained by passing dry hydrogen chloride into solutions of the corresponding thiazoles in absolute alcohol—absolute ether (1:3) at 0°C.

 $\frac{4-(4-Morpholinomethyl)-2-(3-indolyl)thiazole (VII)}{4}$ A solution of 3.0 g (12 mmole) of VI in 20 ml of absolute alcohol was added with stirring to a mixture of 1.0 g (12 mmole) of morpholine and 0.84 g (6 mmole) of K₂CO₃ in 20 ml of absolute alcohol, and the mixture was stirred at 40°C for 1 h. The precipitate was removed by filtration, the filtrate was evaporated at reduced pressure, and the residue was extracted with acetone (two 10-ml portions). The extract was chromatographed with a column (3.5 by 50 cm) packed with Al₂O₃ by elution with benzene-methanol (10:1). Removal of the solvents gave 3.28 g (91%) of VII in the form of a viscous colored oil with R_f 0.81 [benzene-methanol (20:1)]. IR spectrum (mineral oil): 3245 (NH); 2960 (CH₂); 1635 (C=N); 1605, 1570, 1505 (indole ring); 1540, 1425 (thiazole ring); 1230, 1060 (C-O-C); 960, 880, 805, 750 cm⁻¹ (CH). The hydrochloride of VII had mp 216-217°C [from absolute alcohol-ether (1:2)]. Found: Cl 10.3; N 12.7%. C₁₆H₁₈N₃OS•HC1. Calculated: Cl 10.6; N 12.5%.

4-(N-Piperidinomethy1)-2-(3-indoly1)thiazole (VIII). This compound was similarly obtained in 86% yield and had R_f 0.65 [benzene-methanol (20:1)]. The hydrochloride of VIII

had mp 187-189°C [dec., from absolute alcohol-ether (1:3)]. Found: Cl 10.9; N 12.5%. $C_{17}H_{19}-N_3S$ •HCl. Calculated: Cl 10.7; N 12.7%.

<u>4-(Cyanomercaptomethyl)-2-(3-indolyl)thiazole (IX)</u>. A mixture of 1.74 g (7 mmole) of VI and 0.7 g (7.2 mmole) of potassium thiocyanate in 15 ml of absolute alcohol was stirred at 40-45°C for 5 h, after which it was cooled to 0°C and poured into 50 ml of ice water. The resulting precipitate was removed by filtration and crystallized from methanol-water (1:3) to give 1.63 g (86%) of IX with mp 75-76°C. IR spectrum: 3250 (NH), 2972 (CH₂), 2220 (C \equiv N), 1635 (C=N), 1610, 1572, 1505 (indole ring); 1550, 1430 (thiazole ring); 970, 890, 810, 750 cm⁻¹ (CH). PMR spectrum: 2.84 (2H, s, CH₂), 6.70 (1H, s, thiazole 5-H), 7.16-7.80 (5H, m, indole), 7.65 (1H, d, indole 2-H), and 8.15 ppm (1H, s, NH). Found: C 57.7; H 3.4; N 15.3%.

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