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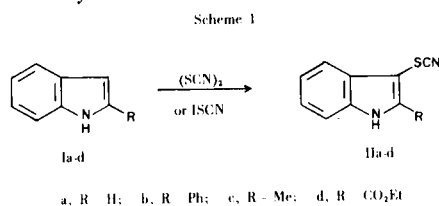
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Treatment of indole, 2-phenylindole, 2-methylindole, and ethyl indole-2-carboxylate with thiocyanogen in acetic acid at 0° afforded the corresponding 3-thiocyanatoindoles in quantitative yields, whereas similar treatment of 3-methyl-2-phenylindoles and 2,3-diphenylindoles gave the corresponding 6-thiocyanatoindoles in high yields.

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Thiocyanation of indole (Ia) using thiocyanogen [(SCN)₂] at -70° in methanol has been reported to occur at the 3-position to give 3-thiocyanatoindole (IIa) in 89% yield (1). In comparison, very little is known about the effect of substituents on the reactivity of the indole ring towards thiocyanating agents. In connection with our interest in the reaction of pseudohalogens with heterocycles (2), we have now investigated the thiocyanation of indoles and found that thiocyanation takes place at the 3 or 6 position, depending upon the nature and position of substituents.

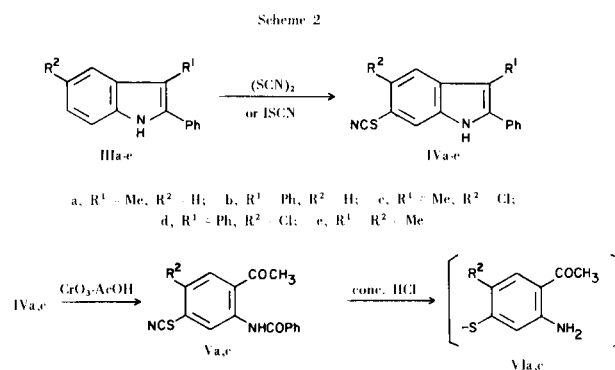
Treatment of indole (Ia) with thiocyanogen (generated from lead thiocyanate and bromine in methylene chloride) (3) in acetic acid at 0° (Method A) gave 3-thiocyanatoindole (IIa) in quantitative yield. Similarly, 2-phenylindole (Ib), 2-methylindole (Ic), and ethyl indole-2-carboxylate (Id) gave the corresponding 3-thiocyanatoindoles (IIb-d) in quantitative yields (Table I). That thiocyanation took place at the 3-position was confirmed by the presence of a weak band at 2130-2140 cm⁻¹ in their ir spectra and disappearance of the H³ signal in their nmr spectra. Reaction of Ia or Ib with iodine thiocyanate (ISCN) generated *in situ* from iodine monochloride and potassium thiocyanate in methylene chloride (4) (Method B) also gave the corresponding 3-thiocyanatoindoles IIa and IIb, but in much lower yields.



In contrast, the reaction of 3-methyl-2-phenylindole (IIIa) with thiocyanogen in acetic acid (Method A) or with iodine thiocyanate in dry methylene chloride (Method B) gave 3-methyl-2-phenyl-6-thiocyanatoindole (IVa) in yields listed in Table II. The structure of IVa was assigned on the basis of the spectral and chemical evidence; its ir spectrum shows an indole NH band at 3330 cm⁻¹ and a weak band at 2140 cm⁻¹ due to SCN and its nmr spectrum reveals the presence of a methyl singlet at δ 2.40. Oxidation of IVa with chromium trioxide in acetic acid followed by hydrolysis of the resulting 4-thiocyanato-2-benzamidoacetophenone (Va) with concentrated hydrochloric acid gave di-3-amino-4-acetylphenyl disulfide (VIa). The mole-

cular ion in the mass spectrum of VIa appears at m/e 332 and the nmr spectrum consists of a singlet at δ 2.40 (3H, COCH₃), a doublet of doublets at δ 6.60 (1H, J = 2 and 9 Hz, H⁶), a doublet at δ 6.84 (1H, J = 2 Hz, H²), and a doublet at δ 7.61 (1H, J = 9 Hz, H⁵).

Similar conversion of several 3-substituted 2-phenylindoles (IIIb-e) to the corresponding 6-thiocyanatoindoles (IVb-e) was accomplished in yields listed in Table II. The structure of IVc was also confirmed by its conversion to VIc.



Reaction of 2,3-dimethylindole or 1,2,3,4-tetrahydrocarbazole with either thiocyanogen or iodine thiocyanate, however, gave resinous products.

These results parallel the behaviour of indoles towards bromine (5). The formation of II and IV would involve electrophilic substitution of SCN⁺ or its equivalent to I and III. In the case of iodine thiocyanate, however, entirely different pathway can be considered which would involve initial formation of 3-iodoindoleninium intermediates followed by nucleophilic substitution by thiocyanate ion at the 3 or 6 position. In a separate communication, we will show that this is a less likely alternative, particularly for the formation of IV (6).

EXPERIMENTAL

All melting points are uncorrected. Ir spectra were recorded on an Hitachi EPI-G2 spectrophotometer, nmr spectra on an Hitachi R-20A spectrometer (tetramethylsilane as internal standard). Merck silica gel 60 and Merck silica gel GF₂₅₄ were used for column chromatography and preparative tlc, respectively.

General Procedure for thiocyanation.

(Method A) By Thiocyanogen.

To a solution of thiocyanogen [prepared *in situ* from lead

Table I

Preparation of 3-Thiocyanatoindoles

Compound	M.p. (°C)	Recrystallized from	Yield (%)		Formula	Calcd.			Analysis			Ir ν max (Potassium chloride) cm^{-1}
			(A) (a)	(B) (a)		(c)	(A) (a)	(B) (a)	(c)	Found	Calcd.	
IIa	75-76.5 (b)	Ethanol-Water	quant.	(c)	$\text{C}_{15}\text{H}_{10}\text{N}_2\text{S}$	71.99	4.03	11.20	71.86	3.79	11.18	3330 2140
IIb	166-168	Ethanol-Water	quant.	28	$\text{C}_{10}\text{H}_8\text{N}_2\text{S}$	63.80	4.28	14.88	63.84	4.34	14.91	3330 2130
IIc	102-103	Ligroin	quant.	----	$\text{C}_{12}\text{H}_{10}\text{N}_2\text{O}_2\text{S}$	58.52	4.09	11.38	58.54	4.09	11.41	3320 2140
IId	133-134	Ligroin	quant.	----								3290 2140

(a) See Experimental. (b) Lit. (I), m.p. 76.5-78°. (c) An intractable mixture was obtained. The presence of IIa was detected on tlc.

Table II

Preparation of 6-Thiocyanatoindoles

Compound	M.p. (°C)	Recrystallized from	Yield (%)		Formula	Calcd.			Analyses			Ir ν max (Potassium chloride) cm^{-1}
			(A) (a)	(B) (a)		(b)	(A) (a)	(B) (a)	(b)	Found	Calcd.	
IVa	141-142	Ligroin	54 (b)	32 (b)	$\text{C}_{16}\text{H}_{12}\text{N}_2\text{S}$	72.68	4.57	10.60	72.38	4.36	10.58	3330 2140
IVb	159-160	Methanol	quant.	58 (b)	$\text{C}_{21}\text{H}_{14}\text{N}_2\text{S}$	77.28	4.32	8.58	77.45	4.39	8.33	3320 2140
IVc	186-187	Benzene	----	30 (b)	$\text{C}_{16}\text{H}_{11}\text{N}_2\text{ClS}$	64.43	3.71	9.38	64.45	3.73	9.41	3340 2145
IVd	187	Methanol	quant.	51 (b)	$\text{C}_{21}\text{H}_{13}\text{N}_2\text{ClS}$	69.92	3.63	7.77	69.79	3.65	7.77	3280 2140
IVe	147-148	Ligroin	----	35 (b)	$\text{C}_{17}\text{H}_{14}\text{N}_2\text{S}$	73.37	5.07	10.07	73.18	5.07	10.12	3340 2130

(a) See Experimental. (b) The rest of the product was resinous material.

thiocyanate (6 mmoles) and bromine (2 mmoles) in dry methylene chloride (10 ml.) at 0° (3)] was added dropwise a solution of an indole (1 mmole) in acetic acid (10 ml.) at 0°. After stirring at the same temperature for 30 minutes, water was added into the reaction mixture. The organic layer was washed with water, 10% sodium carbonate solution, and water, dried over magnesium sulfate, and concentrated to give a crude product, which was purified by recrystallization.

(Method B) By Iodine Thiocyanate.

A solution of an indole (9.7 mmoles) in dry methylene chloride (10 ml.) was added dropwise to a solution of iodine thiocyanate [prepared *in situ* from iodine monochloride (3.15 g., 19.4 mmoles) and potassium thiocyanate (2.82 g., 29.1 mmoles) in dry methylene chloride (30 ml.) at 0° (4)]. After stirring at the same temperature for 1 hour and then at room temperature overnight, the mixture was washed with 10% aqueous sodium thiosulfate solution and water, dried over magnesium sulfate, and concentrated to give a crude mixture, which was purified by column chromatography on silica gel and benzene as solvent and then by recrystallization.

The results are summarized in Tables I and II.

4-Thiocyanato-2-benzamidoacetophenone (Va).

To a solution of IVa (800 mg.) in acetic acid (30 ml.) was added dropwise a solution of chromium trioxide (840 mg.) in water (3 ml.) at room temperature. Stirring was continued overnight. The reaction mixture was poured into water. The precipitated white solid was collected by filtration, washed with water, dried, and recrystallized from ethanol to give colorless crystals of Va, m.p. 174°, yield, 778 mg. (87%); ir (potassium chloride): cm^{-1} 3150 (NH), 2140 (SCN), 1665 (CO), and 1640 (CO).

Anal. Calcd. for $\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_2\text{S}$: C, 64.85; H, 4.08; N, 9.45. Found: C, 64.74; H, 4.13; N, 9.40.

Di-3-amino-4-acetylphenyl Disulfide (VIa).

A solution of Va (180 mg.) in acetic acid (8 ml.) and concentrated hydrochloric acid (7 ml.) was heated under reflux for 5 hours. The mixture was diluted with water, neutralized with 10% sodium hydroxide solution, and extracted with methylene chloride. The extract was dried over magnesium sulfate and concentrated. The residue was submitted to preparative tlc on silica gel using methylene chloride as solvent to give pale yellow crystals (65 mg.) of VIa, m.p. 180-182° (from ethanol-water); ir (potas-

sium chloride): cm^{-1} 3420 and 3310 (NH_2), and 1635 (CO); nmr (dimethylsulfoxide- d_6): δ 7.61 (1H, d, $J_{5,6} = 9$ Hz, H^5), 6.84 (1H, d, $J_{2,6} = 2$ Hz, H^2), 6.60 (1H, dd, $J_{5,6} = 9$ Hz, $J_{2,6} = 2$ Hz, H^6), and 2.40 (3H, s, COCH_3).

Anal. Calcd. for $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_2\text{S}_2$: C, 57.80; H, 4.85; N, 8.43. Found: C, 57.74; H, 4.86; N, 8.13.

5-Chloro-4-thiocyanato-2-benzamidoacetophenone (Vc).

By the procedure as described above for the preparation of Va, compound Vc (800 mg., 72%) was obtained from IVc (1.0 g.) as colorless crystals, m.p. 199-200° (from ethanol); ir (potassium chloride): cm^{-1} 3170 (NH), 2150 (SCN), 1670 (CO), and 1655 (CO).

Anal. Calcd. for $\text{C}_{16}\text{H}_{11}\text{ClN}_2\text{O}_2\text{S}$: C, 58.09; H, 3.35; N, 8.47. Found: C, 58.13; H, 3.41; N, 8.56.

Di-3-amino-4-acetyl-6-chlorophenyl Disulfide (VIc).

By the procedure as described above for the preparation of VIa, compound VIc (155 mg.) was obtained from Vc (400 mg.) as pale yellow crystals, m.p. 200-202° (from ethanol-water); ir (potassium chloride): cm^{-1} 3440 and 3340 (NH_2), and 1635 (CO); nmr (dimethylsulfoxide- d_6): δ 7.71 (1H, s, H^5), 6.91 (1H, s, H^2) and 2.49 (3H, s, COCH_3).

Anal. Calcd. for $\text{C}_{16}\text{H}_{14}\text{Cl}_2\text{N}_2\text{O}_2\text{S}_2$: C, 47.88; H, 3.52; N, 6.98. Found: C, 48.14; H, 3.94; N, 6.99.

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