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Thiocyanation of Amino-2-methylbenzothiazoles

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Thiocyanation of the four amino-2-methylbenzothiazole isomers has been studied: in three of these the thiocyano group is oriented *ortho* to the amino group and consequently three new angular benzobisthiazoles have been obtained. The 7-thiocyano derivative was obtained from 4-amino-2-methylbenzothiazole. The structure of the benzobisheterocycles has been confirmed by NMR spectroscopy.

Much research has been done on benzothiazole for the purpose of establishing the naphthoid or benzenoid character of this benzoheterocycle. Generally this research has been concerned with electrophilic reactions conducted on substituted derivatives in the aromatic nucleus (1-6). These experiments indicate that the above benzoheterocycle is a typical link between the benzenoid and naphthoid series.

For some time our interest has been centered on various benzoheterocycles containing either a sulfur or a nitrogen heteroatom; the present work is concerned with the thiocyanation of the amino-2-methylbenzothiazole isomers.

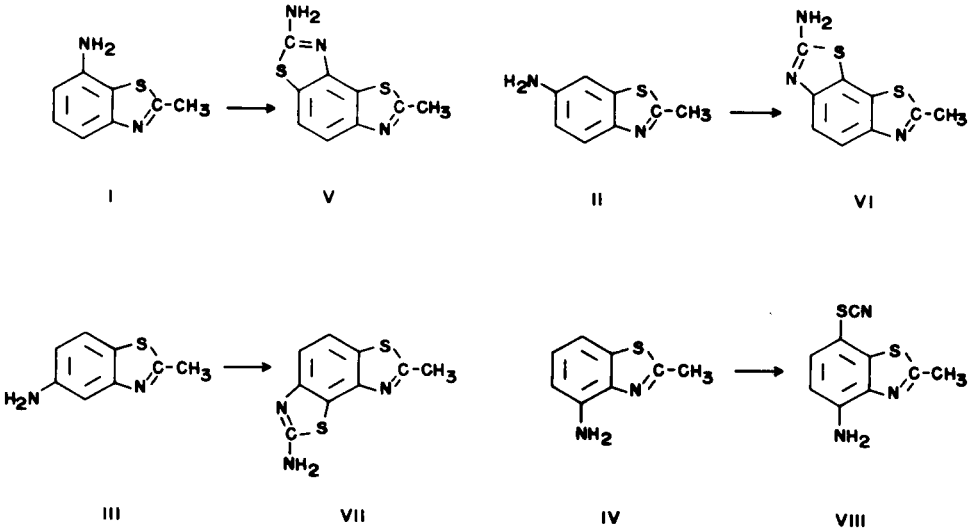
Our purpose was to study the thiocyanation of this heterocycle and to obtain a benzobisthiazole with potential pharmacological activity. These compounds could also be important intermediates in the synthesis of various dyes since they contain reactive methyl and amino groups.

The four isomers studied were: 7-amino- (I), 6-amino- (II), 5-amino- (III) and 4-amino-2-methylbenzothiazole (IV).

Compound IV was obtained by reduction of the corresponding nitro derivative (3); the other isomers were prepared by literature methods. The thiocyanation of I, II, III and IV was effected with excellent yields, in acetic acid solution, using dichlorourea and ammonium thiocyanate. This technique has already been used successfully by one of the authors (7).

It was not possible to isolate the aminothiocyano derivatives of isomers I, II and III, since spontaneous thiazole formation occurred during the reaction with the formation of the 2-methyl-7-aminobenzo[2,1-d:4,3-d']dithiazole (V), 2-methyl-7-aminobenzo[1,2-d:3,4-d']dithiazole (VI), and 2-methyl-5-aminobenzo[1,2-d:3,4-d']dithiazole (VII), respectively. This indicates that the thiocyano group is *ortho* to the amino group in I also.

Thiocyanation of the amino derivative (IV) on the other hand, produced 4-amino-7-thiocyano-2-methylbenzothiazole (VIII), in which the thiocyano group is *para* to the amino group. When compound VIII was heated with mineral acids it was recovered unchanged.



I V II VI

III VII IV VIII

TABLE I*

Nuclear Magnetic Resonance Spectra

Compound	H in benzo (a)	$\delta_A - \delta_B$	J_{AB}(c.p.s.)	CH_3	NH_2	$CO-CH_3$
V	8.18	----	---	3.37	8.98 (b)	----
Acetyl derivative of V	8.29 (q)	0.19	9.0	3.38	----	2.65
VI	8.10 (q)	0.20	9.0	3.32	8.80 (b)	----
Acetyl derivative of VI	8.36	----	---	3.35	----	2.62
VII	8.09 (q)	0.30	9.0	3.30	8.72 (b)	----
Acetyl derivative of VII	8.29 (q)	0.07	9.0	3.35	----	2.63
VIII	7.87 (q)	0.24	8.5	3.21	----	----
Acetyl derivative of VIII	8.04 (q)	0.28	8.5	3.38	----	2.56

* The values are expressed in δ units. All signals in the first and fifth columns correspond to two protons, and those in the fourth and sixth columns to three protons. (a) The values shown correspond to the center of the quartet. (b) Broad singlet. (q) Quartet; all the other non-marked signals are singlets.

TABLE II

Benzobisthiazoles and Derivatives

Compound	M.p. °C	Crystal form	Recrystallization Solvent	Yield %	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	S, % Calcd.	S, % Found
V	335	white prisms	Ethanol	68	48.87	48.90	3.17	3.38	-----	-----
Acetyl deriv. of V	300	white prisms	Acetic Acid	--	-----	-----	----	----	24.37	24.21
VI	315 decom.	ivory prisms	Dioxane	64	48.87	48.93	3.17	3.22	28.96	29.17
Acetyl deriv. of VI	319	white needles	Acetic Acid	--	-----	-----	----	----	24.37	24.41
VII	295 decom.	ivory prisms	Ethanol	70	48.87	48.71	3.17	3.29	-----	-----
Acetyl deriv. of VII	273	white plates	Ethanol	--	-----	-----	----	----	24.37	24.29
VIII	139	white prisms	Ethanol	75	48.87	48.78	3.17	3.23	-----	-----
Acetyl deriv. of VIII	176	white needles	Methanol	--	-----	-----	----	----	24.37	24.33

The structure of the benzobisthiazoles (V), (VI) and (VII), and the consequent orientation of the thiocyano group, was demonstrated by NMR spectroscopy. Table I shows the values of the chemical shifts of the benzobisthiazoles (V), (VI) and (VII), and the corresponding acetyl derivatives.

In the aromatic region the spectra indicate an AB quartet with J_{AB} = 9 c.p.s., characteristic of two protons *ortho* to each other. Two exceptions are the benzobisthiazole (V) and the acetyl derivative of VI whose spectra do not show an AB quartet, but rather a singlet (area = 2 protons), due to the fact that in these compounds the two protons have the same δ value and are equivalent. The spectra of the acetyl derivative of V and compound VI, however, exhibit the AB quartet. The values of the chemical shifts of the compounds shown in Table I are in agreement with references in the literature on the NMR of benzobisheterocycles (8).

The exact location, as indicated by NMR, of the position occupied by the thiocyano group in the amines studied, seems to confirm the naphthoid character of benzothiazole inasmuch as II and III behave, during thiocyanation, like β-naphthylamine (9), producing α-substituted derivatives. Moreover, position 6 in 2-methyl-7-aminobenzothiazole (I), in which the thiocyano group is oriented, is not in disagreement with the behavior of the α-naphthylamines. Furthermore, this position is favored, not only by the electron-donating character of the amino group, but also by the influence of the nitrogen atom in the thiazole nucleus, which, as is known (10), has an analogous influence as the nitro group, and therefore deactivates position 4, where substitution could have taken place. The thiocyanation of compound IV is also in agreement with these facts. The 7 position is preferred because of the influence exerted by the sulfur atom.

EXPERIMENTAL

The NMR spectra were determined in trifluoroacetic acid solution (since the compounds are insoluble in other common solvents) and with tetramethylsilane as the internal standard, on a Varian A-60 spectrometer. All melting points were taken on a Kofler apparatus and are uncorrected.

The spectral data, the yields, the physical constants and the analytical data are recorded in Tables I and II.

4-Amino-2-methylbenzothiazole (IV).

4-Nitro-2-methylbenzothiazole (3) (1 g.) was added slowly to a stirred solution of stannous chloride (4 g.) in concentrated hydrochloric acid (6 ml.). (The reaction was exothermic.) The solution was heated on a water bath for 30 minutes. The tin salt of the amine began to separate after 15 minutes. The solution was cooled with ice and the crystalline precipitate collected by filtration, dissolved in a small amount of water and any residual material removed by filtration. On addition of 30% sodium hydroxide solution to the filtrate the amine separated. It was removed by filtration and recrystallized from water as long white needles, m.p. 93°.

Anal. Calcd. for $C_8H_8N_2S$: C, 58.53; H, 4.87. Found: C, 58.57; H, 5.05.

The acetyl derivative was prepared by briefly heating IV with acetic anhydride. It crystallized from acetic acid as white needles, m.p. 113-114°.

2-Methyl-7-aminobenzo[2,1-d:4,3-d']dithiazole (V), 2-methyl-7-aminobenzo[2,1-d:3,4-d']dithiazole (VI), 2-methyl-5-aminobenzo[1,2-d:3,4-d']dithiazole (VII) and 4-amino-7-thiocyano-2-methylbenzothiazole (VIII).

The general procedure used for the thiocyanation of I, (11), II (11), III (12) and IV was the following: a solution of 1.64 g. (0.0125 mole) of dichlorourea in 10 ml. of acetic acid was added slowly to an ice-cooled stirred solution of 4.1 g. (0.025 mole) of amino-2-methylbenzothiazole and 1.9 g. (0.025 mole) of ammonium thiocyanate in 30 ml. of glacial acetic acid. The mixture was allowed to stand for 1-2 hours and then was poured into cold water. The precipitate was separated and recrystallized as shown in Table II. Compound VII was separated from the acidic solution by making it alkaline with sodium carbonate.

The acetyl derivatives of the benzobisthiazoles (V), (VI) and (VII) and of the aminothiocyano-2-methylbenzothiazole (VIII) were obtained by refluxing the amines in acetic anhydride. Only in the case of VIII was the acetyl derivative separated by cooling the solution; separation of the other aminoacetyl derivatives was obtained from the boiling solution. The characteristics of these derivatives are summarized in Table II.

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