

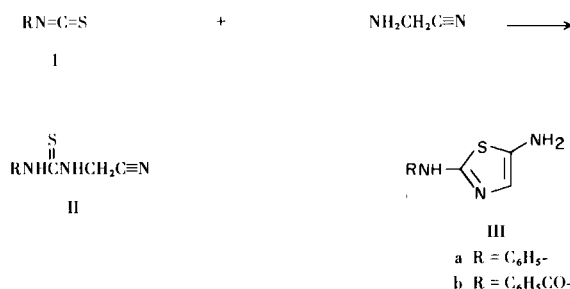
A Re-investigation of the Reaction between Isothiocyanates and Aminoacetonitrile

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It has been reported (2) that the reaction of phenyl isothiocyanate (Ia) with aminoacetonitrile leads directly to the formation of 5-amino-2-anilinothiazole (IIIa) while benzoyl isothiocyanate (Ib) and aminoacetonitrile react to produce 5-amino-2-benzamidothiazole (IIIb); the corresponding thioureas (IIa and IIb respectively) are reported to "enjoy at most a transitory existence". The

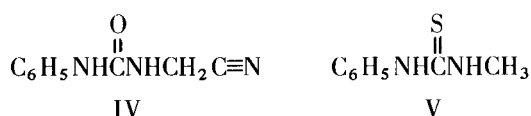


proof of structures IIIa and IIIb was based on chemical reactions of the products to form derivatives such as amine salts and Schiff's bases. We have found that the compounds previously identified as thiazoles IIIa and IIIb actually are thioureas IIa and IIb and that cyclization of structure II to structure III occurs during the formation of derivatives.

Using analytical techniques not available to the previous authors, we have assigned structure IIa to the product previously identified as IIIa on the basis of ir (potassium bromide pellet: nitrile at 2260 cm^{-1} and thiourea absorptions (3) at $1240, 1313,$ and $1560\text{-}1570\text{ cm}^{-1}$) and proton nmr spectra (d_6 -DMSO: δ 4.5 (d, 2, $J = 5\text{ Hz}$, NHCH_2), 7.1-7.5 (m, 5, C_6H_5), 8.0 (t, 1, $J = 5\text{ Hz}$, NHCH_2), and 10.0 ppm (s, 1, $\text{C}_6\text{H}_5\text{NH}$); a deuterium oxide exchange experiment removed the NHCH_2 coupling interactions.

These spectra compare favorably with the spectra of the corresponding cyanomethyl urea IV (ir (potassium bromide pellet) $1640\text{ (C=O)}, 2258\text{ (C}\equiv\text{N)},$ and 1570 and 3320 cm^{-1} (N-H): proton nmr (d_6 -DMSO) δ 4.15 (d, 2,

$J = 5\text{ Hz}$, NHCH_2), 6.6-7.6 (m, 6, C_6H_5 and NHCH_2), and 9.05 ppm (s, 1, $\text{C}_6\text{H}_5\text{NH}$). The proton nmr spectrum of IIa is also in agreement with that of *N*-methyl-*N'*-phenylthiourea (V) (d_6 -DMSO) δ 3.1 (d, 3, $J = 5\text{ Hz}$, CH_3), 6.4 (q, 1, $J = 5\text{ Hz}$, NHCH_3), 7.0-7.6 (m, 5, C_6H_5), and 8.9 ppm (s, 1, $\text{C}_6\text{H}_5\text{NH}$) (4).



In a similar manner, the compound previously assigned structure IIIb is reassigned structure IIb.

We have shown that thiourea IIb is cyclized to the thiazole IIIb by reaction with hydrogen chloride to give the amine salt, followed by treatment with base to give authentic 5-amino-2-benzamidothiazole (IIIb) whose spectra are clearly distinct from those of IIb.

It has been reported that the reaction of IIb and benzaldehyde resulted in the formation of the Schiff's base of IIIb (2). We observed that this reaction did not occur in absolute ethanol, but proceeded as described in 95 percent ethanol indicating the requirement for a more active proton source to catalyze the rearrangement of IIb to IIIb prior to the condensation.

EXPERIMENTAL (5)

N-Phenyl-*N'*-cyanomethylthiourea (IIa).

Compound IIa was obtained as white crystals, m.p. $145\text{-}146^\circ$ (lit. $146\text{-}147^\circ$ for the compound previously identified as IIIa) from the reaction of phenyl isothiocyanate and aminoacetonitrile performed as described in the literature.

N-Phenyl-*N'*-cyanomethylurea (IV).

A solution of 11.9 g. (0.1 mole) of phenyl isocyanate in 20 ml. of anhydrous ether was added over 10 minutes to a cooled stirred solution of 5.6 g. (0.1 mole) of aminoacetonitrile in 10 ml. of anhydrous ether under nitrogen. The solid which formed was filtered and dried at 1 mm. pressure to give 14.2 g. (81% yield) of white crystals, m.p. $142\text{-}144^\circ$, identified as IV in the text. An analytical sample, m.p. $154\text{-}155^\circ$ (dec.) was obtained by repeated recrystallization from ether.

Anal. Calcd. for $C_9H_9N_3O$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.91; H, 5.44; N, 23.91.

N-Benzoyl-*N'*-cyanomethylthiourea (IIb).

Compound IIb was obtained as white crystals, m.p. 156-157° (lit. 157° for the compound previously identified as IIIb) from the reaction of benzoyl isothiocyanate and aminoacetonitrile performed as described in the literature: ir (potassium bromide pellet) 1658 (C=O), 2250 (C≡N), and 3190 and 3360 cm^{-1} (N-H); proton nmr (d_6 -DMSO) δ 4.65 (d, 2, $J = 5$ Hz, $NHCH_2$), 7.3-8.1 (m, 5, C_6H_5), and 11.05 ppm (m, 2, NH).

5-Amino-2-benzamidothiazole (IIIb).

The amine hydrochloride of IIIb, m.p. 204-205° (lit. 201°) was obtained from IIb as described in the literature. To 11 g. of sodium bicarbonate in 400 ml. of water was added 6.3 g. (0.025 mole) of the amine hydrochloride of IIIb. The solution was rapidly stirred at room temperature for 10 minutes, extracted with four 250 ml. portions of methylene chloride and the organic phases combined, concentrated to 200 ml., diluted with 50 ml. of hexane, and refrigerated.

Filtration of the resultant precipitate afforded 1.7 g. (31% yield) of olive-tan powder, m.p. 167-168°. Three recrystallizations from 5% ethanol in methylene chloride afforded an analytical sample identified as IIIb, orange-tan, m.p. 172°: ir (potassium bromide pellet) 1550, 1660, 3160 (amide), 3325, and 3375 cm^{-1} (N-H) with no C≡N observed; proton nmr (deuteriochloroform) δ 4.5-5.5 (broad labile, 2, NH_2), 6.53 (s, 1, thiazole CH), 7.4-8.3 (m, 5, C_6H_5), and 11.45 ppm (s, 1, CONH).

Anal. Calcd. for $C_{10}H_9N_3OS$: C, 54.80; H, 4.13; N, 19.16; S, 14.62. Found: C, 54.78; H, 4.28; N, 18.94; S, 14.50.

2-Benzamido-5-benzylideneaminothiazole (Schiff's base of IIIb).

A solution of 1 g. of IIb and 1 g. of benzaldehyde in 40 ml. of 95% ethanol was reacted as described in the literature (for the compound previously identified as IIIb) to give 1.2 g. of yellow needles, m.p. 234-235° (lit. 233°). The reaction did not take

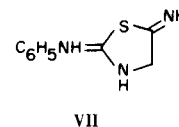
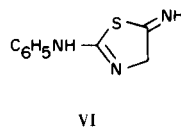
place in absolute ethanol. The identity of the product as the Schiff's base of IIIb was confirmed by spectral analysis: ir (potassium bromide pellet) 1680 (C=O), 1548 and 3175 cm^{-1} (N-H); proton nmr (d_6 -DMSO) δ 7.1-8.2 (m, 11, C_6H_5 and thiazole CH), 8.46 (s, 1, N=CH), and 12.5 ppm (s, 1, CONH).

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REFERENCES

- (1) To whom correspondence concerning this article should be addressed.
- (2) A. H. Cook, J. D. Downer, and I. Heilbron, *J. Chem. Soc.*, 1262 (1948).
- (3) R. Mecke, Jr. and R. Mecke, *Chem. Ber.*, **89**, 343 (1956).
- (4) These spectral correlations serve to eliminate possible tautomeric structures such as VI and VII.



- (5) Proton nmr spectra were recorded on a Varian A56/60 spectrometer and chemical shifts are reported in parts per million downfield from TMS. Infrared spectra were recorded on a Perkin-Elmer 21 spectrophotometer. Spectra and elemental analyses were obtained from the Analytical Department of the Corporate Chemical Research Laboratory, Allied Chemical Corporation. All references to the literature in this section are to reference 2.