

AN ANOMALOUS REACTION BETWEEN 2-AMINO-4-METHYLOXAZOLE AND
ISOTHIOCYANATES

G. Crank

Department of Applied Organic Chemistry, The University of New South Wales,
P.O. Box 1, Kensington, N.S.W. 2033, Australia

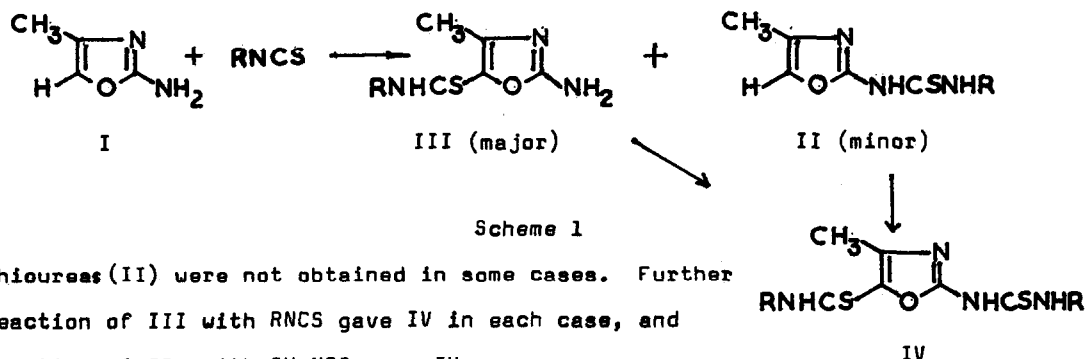
(Received in UK 1 November 1974; accepted for publication 13 November 1974)

Reactions of ring substituted 2-amino-oxazoles and isothiocyanates are generally straightforward and give the expected thioureas.¹

However when 2-amino-4-methyloxazole (I) was heated with an equimolar portion of methyl isothiocyanate in toluene the thiourea (IIa) (a colourless crystalline solid m.p. 191-192^o) was a minor product ($\sim 15\%$), whilst the major product was a yellow crystalline solid (m.p. 196-197^o) (IIIa), formed in 65% yield.

Elemental analysis and the mass spectrum (M.W. 171) confirmed that this product had a molecular composition $C_6H_9N_3OS$ and was an isomer of IIa. It was then identified as 2-amino-4-methyl-5-(N-methylthiocarbamyl)-oxazole by spectral interpretation. The n.m.r. spectrum (d-D.M.S.O.) had peaks at $\delta = 2.50$ (singlet, 3H, CH_3 at position 4), 3.15 (doublet, 3H, $\underline{CH_3}$ -NH, $J = 5.0$ Hz, singlet after D_2O exchange), 6.6 (broad, 2H, $-NH_2$, lost after D_2O exchange), 8.5 (broad, 1H, CH_3NH- , lost after D_2O exchange). Differences between this spectrum and the n.m.r. spectra of I and IIa are clearly shown. In I and IIa the CH_3 at position 4 appears as a doublet at $\delta = 1.95$ and $\delta = 2.15$ respectively ($J = 1.4$ Hz in each case), and the proton at C-5 shows as a quartet at $\delta = 6.75$ and $\delta = 7.05$ respectively ($J = 1.4$ Hz). The absence of this proton in IIIa and the appearance of the $\underline{CH_3}$ as a singlet indicate substitution at C-5. The presence of the $-NH_2$ group was indicated additionally by the i.r. spectrum (3350, 3400 cm^{-1}) and chemically by the conversion of IIIa into a hydrochloride salt, an acetyl derivative and by reaction with another molar amount of CH_3NCS , a thiourea (IVa). The i.r. and u.v. spectra of I, IIa, IIIa and IVa had similarities indicating the retention of the oxazole ring throughout.

The generality of the reaction is shown in Scheme I and Table 1.

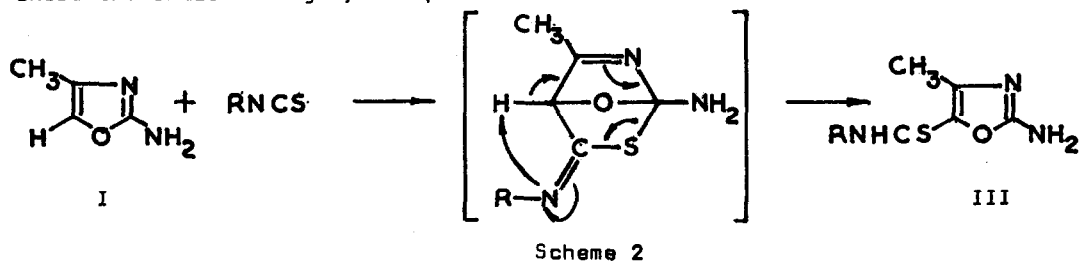


Thioureas (II) were not obtained in some cases. Further reaction of III with RNCS gave IV in each case, and reaction of IIa with CH_3NCS gave IVa.

TABLE I

Isothiocyanate	Product	m.p.	Yield(%)
CH_3NCS	IIIa (R = CH_3 -)	196-197	65
$\text{CH}_3\text{CH}_2\text{NCS}$	IIIb (R = CH_3CH_2 -)	217-218	60
$\text{CH}_2=\text{CHCH}_2\text{NCS}$	IIIc (R = $\text{CH}_2=\text{CH}\cdot\text{CH}_2$ -)	154-155	55
$\text{C}_6\text{H}_5\text{NCS}$	IIId (R = C_6H_5 -)	218-220	90
CH_3NCS (2 moles)	IVa (R = CH_3 -)	221-223	58

The mechanism of this reaction is not at present clear, but it possibly involves a Diels-Alder type of addition (Scheme 2), examples of which have previously been reported for oxazoles.² In these examples however, thermal or acid treatment of the intermediates produce different heterocyclic systems, contrasting to the present case, where the oxazole ring system persists.



The reaction does not occur with isocyanates, which give only ureas.

REFERENCES

1. Crank, G., Neville, M. and Ryden, R., *J. Med. Chem.*, 16, 1402 (1973).
2. (a) Firestone, R.A., Harris, E.E. and Reuter, W., *Tetrahedron*, 23, 943 (1967).
 (b) Murakami, M. *et al.*, *Bull. Chem. Soc. Japan*, 41, 628 (1968).
 (c) Grigg, R. and Jackson, J.L., *J. Chem. Soc. (C)*, 552 (1970), and earlier references cited therein.