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The Structure of an N-Carbamoyl Derivative of 2-Amino-Δ^2-thiazoline. Mass Spectrometry of ^{15}N Derivatives of 2-Amino-Δ^2-thiazoline

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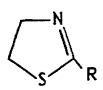
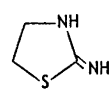
The reaction of 2-amino-Δ^2-thiazoline (Ia) with cyanate ion gives a carbamoyl derivative which may be formulated as 2-ureido-Δ^2-thiazoline (IIIa) or 2-imino-3-carbamoylthiazolidine (IIIb). Desulfurization of this derivative with Raney nickel gives urea. When 2-(^{15}N)-amino-Δ^2-thiazoline (Ib) was treated with cyanate and the product thus obtained was desulfurized, the urea which was formed contained the ^{15}N label, as determined by mass spectrometry. Structure IIIa, therefore, is the correct one. Analysis of the mass spectrum of 2-(^{15}N)-amino-Δ^2-thiazoline (Ib) confirms the correctness of the fragmentation pathway previously postulated for 2-amino-Δ^2-thiazoline (Ia). The mass spectra of 2-ureido-Δ^2-thiazoline (IIIa), 2-(1-^{15}N)-ureido-Δ^2-thiazoline (XIII), urea, and 1-(^{15}N)-urea are discussed.

The reactions of 2-amino-Δ^2-thiazoline (Ia) indicate that it is capable of existing in the tautomeric 2-iminothiazolidine form (II) and that the ring and exocyclic amino groups have different nucleophilicities. In most reactions of Ia involving the nitrogen atoms, the ring nitrogen reacts pref-



Ia; R = $^{14}NH_2$
Ib; R = $^{15}NH_2$



II

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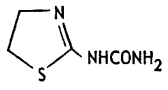
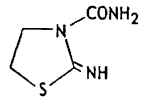
erentially. In the reaction of Ia with excess methyl iodide, for example, 2-imino-3-methylthiazolidine hydroiodide is formed exclusively.[1] The use of other alkylating agents also gives only the 3-substituted derivatives.[2] In alkaline aqueous media, Ia reacts with aromatic sulfonyl chlorides to give the corresponding 3-sulfonamides.[3] One equivalent of phenyl isothiocyanate reacts with Ia to give the 3-phenylthiocarbamoyl derivative.[4] In contrast to these observations, treatment of Ia with nitrous acid is reported to give 2-nitrosoiminothiazolidine.[5]

Schöberl and Kawohl [6] heated the hydrobromide salt of Ia with potassium cyanate in aqueous solution to obtain a urea derivative (III), for which two possible structures may be written, depending upon the site of attack of the cyanate ion. The authors preferred structure IIIa but failed to present any evidence which would have discriminated against structure IIIb.



IIIa

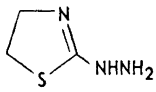


IIIb

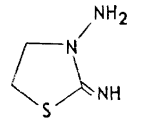
An attempt was made to synthesize the compound IIIb from potassium 2-ureidoethanethiosulfate [7] and potassium cyanide by the method developed in our laboratory.[8] No cyclization to the thiazolidine took place, presumably due to the low nucleophilicity of the secondary amido group in the urea moiety. No alternative method could be devised to give either IIIa or IIIb unequivocally.

$$H_2N-CO-NH-CH_2CH_2SSO_3^- + CN^- \longrightarrow SO_3^{2-} + [H_2N-CO-NH-CH_2CH_2SCN] \not\rightarrow \text{IIIb}$$

Since the Hofmann reaction is known [9] to convert aryl ureas to aryl hydrazines, compound III was treated with aqueous alkaline hypobromite under conditions established by Allen and Wolf [10] with a view to preparing either the known 2-hydrazine-Δ^2-thiazoline (IV) [11] or 2-imino-3-aminothiazolidine (V). Neither product was isolated from the reaction mixture from which only small amounts of starting material were recovered.



IV

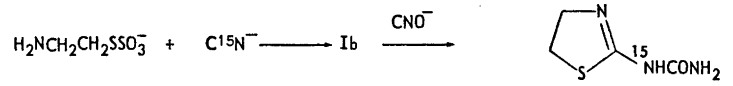


V

The Raney nickel desulfurization of 2-aminothiazoline-4-carboxylic acid is reported [12] to give alanine. It was therefore anticipated that upon treatment with Raney nickel, IIIb should give rise to N-ethylurea which we found to

be stable under those conditions. However, the product obtained from the Raney nickel desulfurization of III was urea, which was identified by its melting point, its infrared spectrum and by elemental analysis. Thus, compound IIIa appeared to be the more likely precursor of urea and was tentatively thought to be the structure of the carbamoyl compound.

In order to confirm this, 2-(^{15}N)-amino-Δ^2-thiazoline (Ib) was prepared by a slight modification of the method [8] mentioned earlier using ^{15}N labelled potassium cyanide and sodium 2-aminoethanethiosulfate. Compound Ib was converted to the N-carbamoyl derivative by treatment with potassium



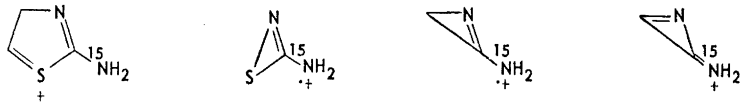
cyanate.[6] Raney nickel desulfurization led to the formation of urea as before, but this urea was found by mass spectrometry (*vide infra*) to contain the ^{15}N label. Structure IIIb becomes untenable therefore and it is concluded that IIIa is the structure of the N-carbamoyl derivative. Thus, the addition of cyanate to Ia does not follow the general pattern observed when the amino groups are involved.

MASS SPECTROMETRY

The mass spectrum of 2-(^{15}N)-amino-Δ^2-thiazoline (Ib), prepared from potassium cyanide containing 99.7 % ^{15}N, is shown in Fig. 1. The identity of the material is confirmed by the molecular ion at *m/e* 103 and the overall similarity of the spectrum to that of the unlabelled 2-amino-Δ^2-thiazoline (Ia). Of considerable interest is that the introduction of the isotope allows a check of the routes by which this system has previously been considered [8] to fragment. Thus the ions at *m/e* 59 and 60 appear unchanged in the spectrum of Ib and therefore do not contain ^{15}N as is consistent with their formulation as VI and VII, respectively.

VI VII

In contrast to this, the other major fragment ions in the spectrum of Ib all must contain ^{15}N as evidenced by their appearance one mass unit above the corresponding ions in the spectrum of Ia. Consequently, the ions in the spectrum of Ib at *m/e* 102, 75, 57, and 56 are correctly formulated as VIII—XI, respectively.



VIII (m/e 102) IX (m/e 75) X (m/e 57) XI (m/e 56)

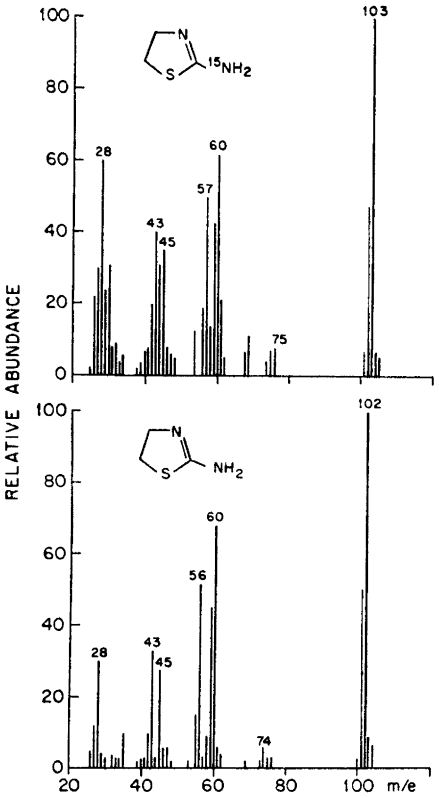


Fig. 1. The mass spectra of labelled and unlabelled 2-amino-Δ^2-thiazoline, respectively.

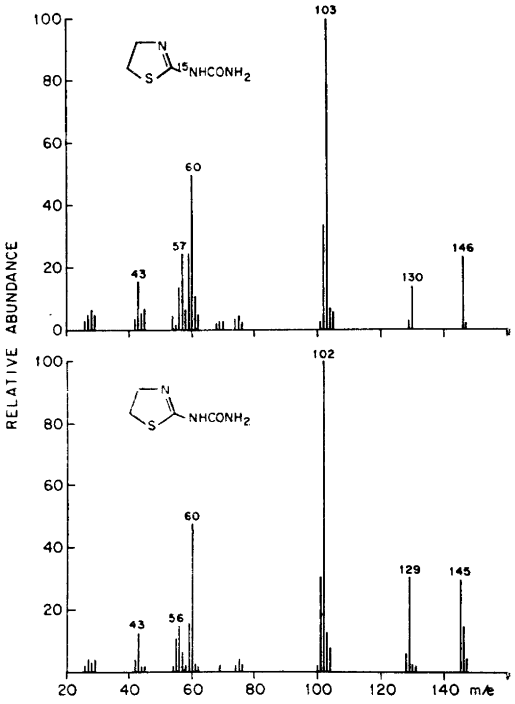


Fig. 2. The mass spectra of labelled and unlabelled 2-ureido-Δ^2-thiazoline, respectively.

No decision can be made between structures IIIa and IIIb for the N-carbamoyl derivative of 2-amino-Δ^2-thiazoline on the basis of its mass spectrum, shown in Fig. 2. The molecular ion of the unlabelled compound, at *m/e* 145, loses NH_2 by a simple cleavage to give the ion at *m/e* 129, but of considerably greater importance is the fragmentation yielding the ion with *m/e* 102. This is considered to involve a McLafferty-type rearrangement, resulting in the loss

XII (m/e 102)

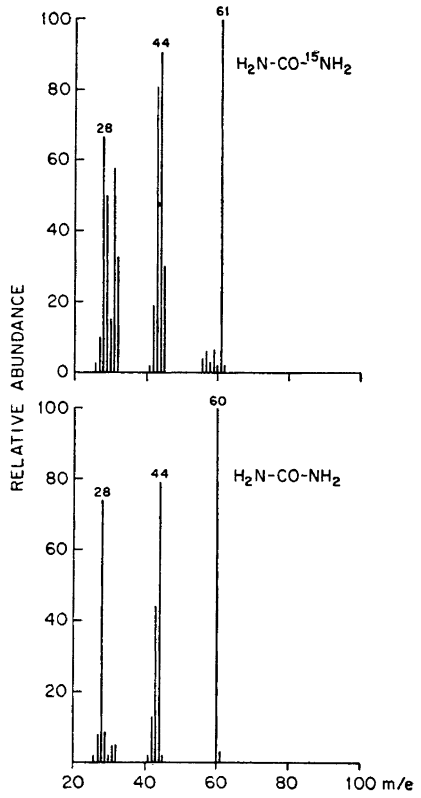


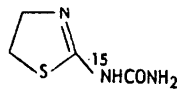
Fig. 3. The mass spectra of labelled and unlabelled urea, respectively.

of neutral HNCO. Unfortunately the molecular ion from IIIb is capable of an identical type of fragmentation, to give the tautomer of XII. Below *m/e* 102

m/e 102

the spectrum of IIIa is essentially that of 2-amino-Δ^2-thiazoline, and evidence derived from metastable ions indicates that all ions of $m/e < 102$ are, in fact, formed by fragmentation of the ion at *m/e* 102. The mass spectrum of 2-(1-^{15}N)-ureido-Δ^2-thiazoline (XIII) serves to confirm this breakdown pattern, and additional evidence is obtained from the high resolution mass measurement of IIIa which is given in Table 1.

The urea derived from the Raney nickel desulfurization of XIII contains ^{15}N as shown by its mass spectrum in Fig. 3. The three major fragment ions



XIII

in the spectrum of unlabelled urea, at *m/e* 60, 44, and 28 result from the molecular ion, *m/e* 60.0322 ($CH_4N_2O^+$ requires *m/e* 60.0324), which loses first one amino group and then the other, presumably in both cases by a simple cleavage.

The mass spectrum of the ^{15}N labelled urea formed from XIII can be explained in the same terms, the complexity of the spectrum arising from the non-isobaric nature of the two amino groups. The accurate mass to charge ratio of the molecular ion, 61.0293, compares well with the value of 61.0294 calculated for $CH_4{}^{14}N{}^{15}NO$ and confirms the presence of ^{15}N in the molecule.

Table 1. High resolution spectrum of 2-(1-^{15}N)-ureido-Δ^2-thiazoline.

Ion	*m/e* (found)	*m/e* (calculated)
$C_2H_4S^+$	60.0056	60.0034
$^{12}C_2{}^{13}CH_6N_2S^+$	103.028	103.028
$C_3H_6N_2S^+$	102.025	102.025
$C_3H_5N_2S^+$	101.017	101.017
$C_4H_5N_2OS^+$	129.014	129.012
$C_4H_6N_3OS^+$	144.027	144.023
$C_4H_7N_3OS^+$	145.032	145.031

EXPERIMENTAL

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were determined on a Beckman IR-5 spectrophotometer. Mass spectra were measured on an Associated Electrical Industries (U.K.) MS-9 double-focusing spectrometer at 70 eV. Accurate measurement of mass to charge ratio was carried out by comparison with a perfluorotributylamine standard.

2-(^{15}N)-Amino-Δ^2-thiazoline (Ib). 2-Aminoethanethiosulfuric acid (2.436 g, 15.5 mmoles) was dissolved in a solution of 0.620 g (15.5 mmoles) of sodium hydroxide in 20 ml of water. To the above was added 1.411 g (17.1 mmoles) of ^{15}N labelled potassium cyanide (isotopic purity, 99.7 %; assay 81 %-remainder KOH) and the resultant solution was periodically agitated for 2 h. The filtered solution was evaporated to dryness at reduced pressure on a rotary evaporator at 60° and the white residue was extracted with four 15 ml portions of chloroform. The combined chloroform extracts, on evaporation, left the product which crystallized upon scratching. Yield, 1.275 g (79.7 %), m.p. 80—81°; λ_{max}^{KBr} 6.12 μ (C=N).

2-(1-^{15}N)-Ureido-Δ^2-thiazoline. To a solution of 0.516 g (5 mmoles) of 2-(^{15}N)-amino-Δ^2-thiazoline in 5 ml of 1 N hydrochloric acid and 2.5 ml of water was added 0.405 g (5 mmoles) of potassium cyanate. The solution was heated on a steam bath for 1 h, filtered, and cooled overnight. The product which separated from the solution as colorless crystals, 0.0781 g (10.7 %), was collected by filtration, m.p. 167—168° (lit.[6] m.p. 167—168°).

Desulfurization procedure. A solution of 0.0681 g (0.466 mmole) of 2-(1-^{15}N)-ureido-Δ^2-thiazoline in 25 ml of water was refluxed for 2 h with approximately ten times its weight of freshly prepared Raney nickel. The nickel was filtered off and washed with water. The combined filtrate and washings were evaporated to dryness under reduced pressure leaving an oily residue which crystallized on trituration with tetrahydrofuran. The urea was recrystallized from tetrahydrofuran and weighed 0.0052 g (18.3 %), m.p. 131–132°.

In a previous run with unlabelled material, the urea obtained was identified by its melting point (132–135°), by its infrared spectrum which was superimposable with the spectrum of the authentic material, and by elemental analysis.

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