A Structure Proof for the Cyclized Product from the Alkylation of a 1,1,3-Trisubstituted Thiourea

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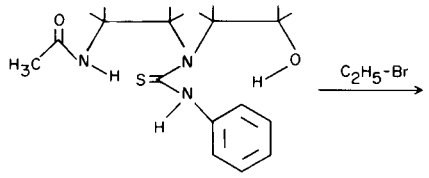
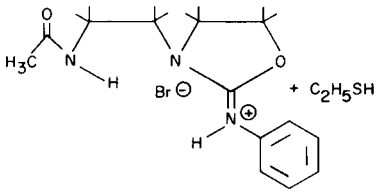
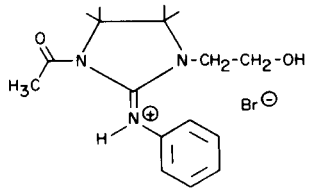
In connection with out studies of organosulfur compounds (1) it was necessary to study the alkylation of 1-(2-hydroxyethyl)-1-(2-acetamidoethyl)-3-phenylthiourea (I). The reaction of I and ethyl bromide could result in the formation of the *S*-ethyl isothiouronium salt (2). Furthermore, the ethyl bromide promoted cyclization of I would be expected to produce the 2,3-disubstituted oxazoline (II) (3). However, cyclization of I to the imidazole (III) is not precluded especially in recognition of the analogous cyclization of the *S*-methyl ether of phenylguanylthiourea (IV) to phenylguanazole (V). In this reaction the amide-like nitrogen of the substrate acts as a nucleophile to displace methyl thiol (4).



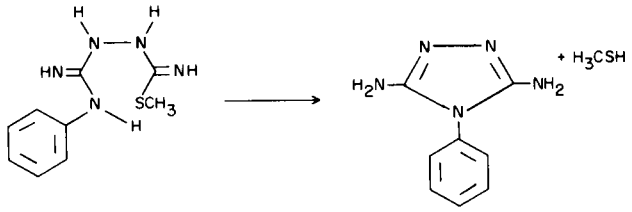
I



II



III



IV V

Elemental analysis of the reaction product eliminated the *S*-ethyl isothiouronium salt as the reaction product. However, a structure proof was required for the product of the ring closure reaction of I. In lieu of a synthesis of the oxazoline by an unambiguous alternative route, we turned to physical methods in the hope of finding a quick and straightforward solution to the problem.

The infrared spectrum of the product contained a medium intense moderately broad band at 3210 cm^{-1}. This absorption could be interpreted as due to the N-H stretching in the secondary amide II. However, it is well known (5) that overlapping occurs in the observed positions of N-H stretching frequencies of secondary amides and the O-H stretching frequencies in alcohols. Therefore, an unequivocal choice between structures II and III is not possible using only the infrared spectrum of the product.

The 100 MHz ^1H nmr spectrum of the ring closure product was consistant with structures II and III. Both structures are expected to give a spectrum with a methyl group hydrogen singlet about 2 ppm downfield from tetramethylsilane; several methylene group hydrogen multiplets between 2-5 ppm; and a phenyl hydrogen multiplet between 7-8 ppm. The two structures can be distinguished by nmr only if the signals from the hydroxyl and amide protons can be clearly recognized. The peak positions, relative intensities, and assignments in the 100 MHz nmr spectrum of the product are given in Table I.

TABLE I

Proton Magnetic Resonance Peak Positions, Relative Intensities, Assignments for the Product of the Ring Closure of I

Assignment	s ppm (a)	Relative Intensity	Multiplicity
H_3C	2.10	3	s
H_2C	3.61	2	s (b)
H_2C	3.61	2	s (b)
H_2C	3.82	2	t
H_2C	4.56	2	t
C_6H_5	7.29	5	m
OH or NH	8.24	1	s (b)

(a) Chemical shifts are downfield from external tetramethylsilane; (b) broad.

The nmr spectrum was observed in dimethylsulfoxide-d_6 since it is known (6) to hydrogen bond strongly to hydroxyl protons which frequently slows down proton exchange sufficiently to allow observation of nuclear spin-spin coupling between the hydroxyl proton and the proton (s) attached to adjacent carbon atoms. Therefore the presence of a triplet at 4-5.5 ppm downfield from TMS which disappears after addition of a few drops of deuterium oxide would be strong evidence for structure III.

However, the only absorption in the nmr spectrum of the product which vanished after addition of a few drops of deuterium oxide was the broad peak at 8.24 ppm. While the position of this absorption tends to favor the amidic proton, it is clear that it could be due to the hydroxyl protonof III whose exchange rate was increased sufficiently by the basic nitrogen to remove coupling with the methylene group hydrogens. Therefore the 100 MHz nmr spectrum of the product is consistent with both structures II and III and does not permit an unequivocal choice between the two.

The ring closure product was unequivocally assigned structure II after an analysis of its unit resolution mass spectrum (Table II).

Structure III is a 2-aminoethanol derivative whose mass spectrum should contain the characteristic 2-aminoethanol fragmentation which is cleavage of the carbon-carbon bond of the side chain (α-cleavage) with predominent charge retention at the nitrogen (7). Therefore a predominent ion in the mass spectrum of III will be an M^+-31 ion at m/e = 216. On the other hand II cannot lose 31 mass units but should give a series of ions corresponding to fragmentation

TABLE II

The Unit Resolution Mass Spectrum of the Product of Ring Closure of I

m/e	Relative Abundance	m/e	Relative Abundance
51	6	118	1
54	5	119	4
55	5	120	20
56	52	121	4
57	6	131	3
63	3	132	5
64	6	133	3
65	5	134	4
66	3	135	2
68	3	147	1
69	3	160	7
70	6	161	81
77	15	162	100
78	3	163	29
83	2	164	4
86	3	175	7
87	2	176	2
91	11	186	3
92	5	187	3
93	9	188	3
100	5	189	2
103	2	204	2
104	5	232	2
106	4	247	15
112	2	248	3
114	2		

of the side chain at M^+-15, M^+-43, M^+-58, M^+-72, and M^+-86 (*i.e.*, m/e = 232, 204, 189, 175, and 161). The presence of all these ions in the mass spectrum of the product as well as the base peak at m/e = 162, which corresponds to loss of the entire side chain with a single hydrogen rearrangement, is strong evidence for structure II.

EXPERIMENTAL

All melting points were taken with the Thomas Hoover capillary melting point apparatus. Microanalytical work was performed by Galbraith Laboratories, Knoxville, Tennessee. The nmr spectrum was determined with a Varian HA-100 spectrometer using deuterated dimethylsulfoxide as a solvent and tetramethylsilane as an external reference and lock signal. Mass spectra were obtained with a Varian-MAT CH-4B medium resolution mass spectrometer. The procedure for thin layer chromatography was essentially that of Peifer (8).

1-(2-Hydroxyethyl)-1-(2-acetamidoethyl)-3-phenylthiourea (I).

To a solution of *N*-[2-(2-hydroxyethylamino)ethyl]acetamide (9) (14.6 g., 0.2 mole) in 85 ml. of 80% ethanol was added 11.5 ml. (0.2 mole) of phenylisothiocyanate. The flask was shaken and the temperature rose to 42°. After standing for 1 hour, the solvent was removed *in vacuo*. The solid obtained in this way was recrystallized from ethanol and gave 23 g. (81%) of product, m.p., 141-143°, R_f = 0.51 (ethanol).

Anal. Calcd. for $C_{13}H_{19}N_3O_2S$: C, 55.49; H, 6.81; N, 14.93; S, 11.39. Found: C, 55.39; H, 6.81; N, 14.73; S, 11.57.

2-Phenylimino-3-(2-acetamidoethyl)oxazolidine-hydrobromide (II).

Ethyl bromide (4.8 ml., 0.066 mole) and (I) (18.5 g., 0.066 mole) was heated under reflux in 150 ml. of ethanol for 3 hours. The alcohol was concentrated *in vacuo* to a volume of 35 ml. when anhydrous ether was added to render the solution cloudy. On cooling, 6.2 g. (41%) of white crystalline product precipitated, m.p. 133-136°. Recrystallization from alcohol-ether gave m.p., 135-140°; R_f = 0.84 (chloroform:methanol, 2:1).

Anal. Calcd. for $C_{13}H_{18}BrN_3O_2$: C, 47.57; H, 5.53; Br, 24.35; N, 12.80. Found: C, 47.38; H, 5.70; Br, 24.26; N, 12.58.

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