The Reaction of Imidazolidine-2-thione with Carbon Disulphide

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The reaction of imidazolidine-2-thione (ethylenethiourea) with carbon disulphide in the presence of strong bases was investigated. The use of sodium hydride as base afforded 1,2-bis-[(2-thioxoimidazolidin-1-yl)thiocarboxamido]ethane (6) and 2,3,6,7-tetrahydrodi-imidazo[2,1-*b*:1,2-*e*][1,3,5]thiadiazine-5-thione (8). On the other hand, reaction using n-butyl-lithium, followed by methylation, gave a dimethylated compound, methyl 2-methylthio-4,5-dihydroimidazole-1-carbodithioate (11).

In our studies on the chemistry of carbon disulphide, we found that cyclopentanone reacted with carbon disulphide in the presence of ammonia to produce 2-iminocyclopentane-1-carbodithioic acid.[1,2] Similarly, five-membered lactams such as 2-pyrrolidone, imidazolidin-2-one, and imidazolidine-2,4-dione were converted into the corresponding free *N*-carbodithioic acids.[3]

These results suggest that sulphur-substituted five-membered heterocycles can also react with carbon disulphide to give interesting and synthetically useful compounds. Imidazolidine-2-thione (ethylenethiourea), a five-membered cyclic thiourea, is well known as a versatile starting material for the syntheses of heterocycles having physiological activity.[4] The compound has two active hydrogens and may be readily metallated to generate the highly reactive mono- or di-anions. We have now examined the reaction of ethylenethiourea with carbon disulphide in the presence of strong bases.

RESULTS AND DISCUSSION

Reaction in the Presence of Sodium Hydride.—Our initial experiments were conducted with carbon disulphide in various solvents, using sodium hydride as the base. When the reaction was carried out in a mixed solvent of tetrahydrofuran (THF), hexamethylphosphoramide (HMPA), and diethyl carbonate, two interesting compounds were isolated. The bis(thioamide) (6), which involved one ring-opened ethylenethiourea and two ethylenethiourea nuclei, was obtained as the major product in 66% yield. Alternatively, treatment of the mother-solution with methyl iodide gave the methylated derivative (7) in 26% yield.

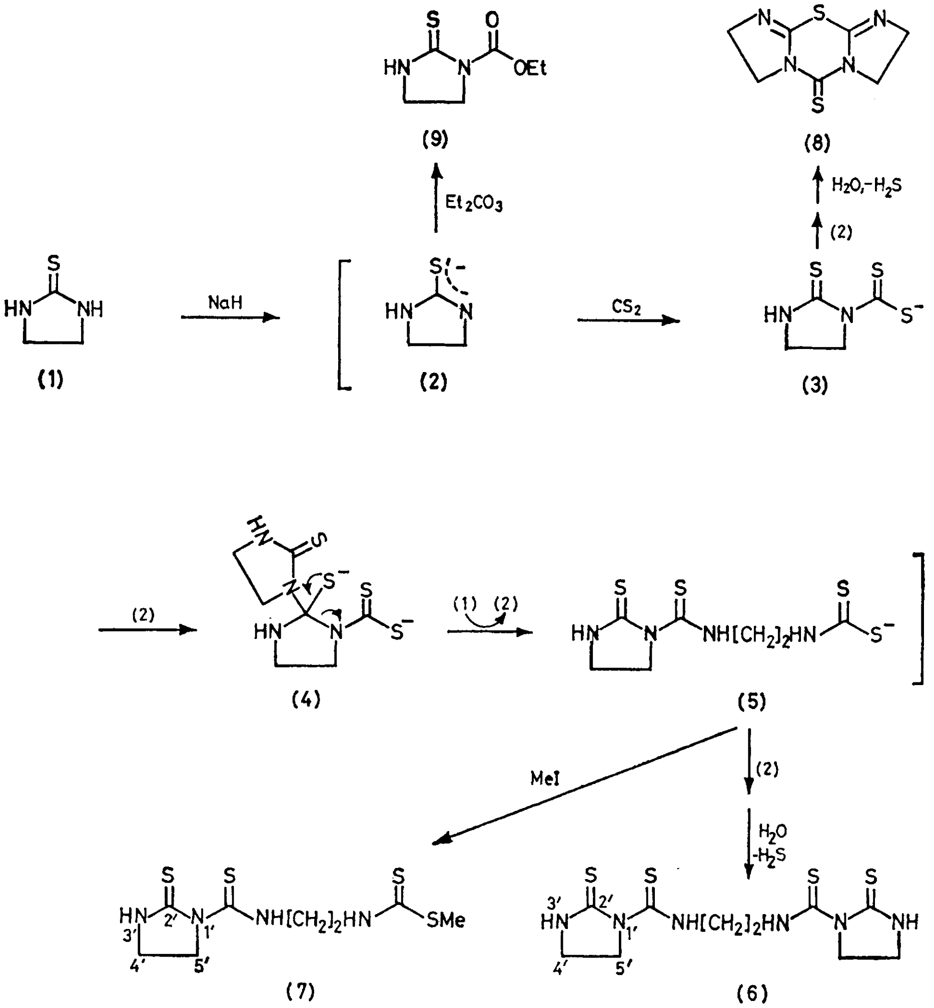
Diethyl carbonate was necessary for the reaction: in the absence of this compound the yields of (6) and (7) decreased remarkably. HMPA was also important; the reaction in THF–diethyl carbonate at reflux afforded only ethyl 2-thioxoimidazolidine-1-carboxylate (9). The use of dimethyl sulphoxide (DMSO) instead of diethyl carbonate accompanied a different reaction, producing the tetrahydrodi-imidazothiadiazinethione (8) (16% yield) together with (6) (64%).

These reactions may be explained by assuming several intermediates (see Scheme 1). Ethylenethiourea (1) is initially metallated with NaH to generate the anion (2), which immediately attacks carbon disulphide to produce another active species (3). The anion (3), upon coupling with (2), forms a dianion species (4). This intermediate (4) readily undergoes a ring-opening reaction followed by protonation to afford the anion (5), which reacts further with (2) followed by hydrolysis to yield a stable compound (6) with elimination of hydrogen sulphide. The existence of (5) was confirmed by trapping with methyl iodide to give (7). In DMSO, (3) couples with (2), in a different pattern from the case using ethyl carbonate, to produce (8). This side-reaction may be due to the strong nucleophilicity of (2) in dipolar aprotic solvents.

An important factor for these reactions seem to be the controlled slow generation of (2) in the co-existence of (1) and carbon disulphide. In fact, neither (6) nor (7) were isolated when (1) was completely converted into its anion (2) followed by addition of carbon disulphide to the resulting mixture. The effect of diethyl carbonate on this reaction has not yet been elucidated. On the other hand, it was expected that (2) would react with diethyl carbonate to give (9); this reaction did not proceed under the conditions employed above, but did under more drastic conditions (at reflux temperature).

The structures of the compounds obtained were determined on the basis of their spectroscopic data and elemental analyses. In our preliminary communication,[5] we tentatively proposed somewhat different isomeric structures [compounds (7), (11), and (10) of ref. 5] instead of (6), (7), and (8) respectively. However, further detailed examination and analyses of the spectroscopic data, especially the mass fragmentation patterns and ^{13}C n.m.r. spectra, support the structures (6), (7), and (8).

The i.r. spectrum of (7) showed a very strong absorption (3240 cm^{-1}) due to NH groups and a strong absorption ($\nu_{max.}$ 2 900 cm^{-1}) for aliphatic CH. The ^{1}H n.m.r. spectrum of (7) (in [$^{2}H_{6}$]DMSO) showed three singlets at δ 12.16 (for NH of the imidazolidine ring), 9.86 (for N*H*CSSMe), and 9.82 (for a remaining NH, disappearing on deuterium exchange), and a triplet (5'-CH_2, *J* 8 Hz), a multiplet (NHCH_2CH_2NH), a triplet (4'-CH_2, *J* 8 Hz), and a singlet (SCH$_3$) at δ 4.47, 3.84, 3.50, and 2.52, respectively. The presence of a peak appearing near 200 p.p.m. in the ^{13}C n.m.r. spectrum of (7) rules out the



SCHEME 1

alternative structure 1-[(4,5-dihydroimidazol-1-ylthio)-thiocarboxamido]-2-[(methylthio)thiocarboxamido]-ethane. In the mass spectra of (6) and (7), the fragment ions from *m/e* 246 downwards were very similar except for the parent ions. Our interpretations for the fragmentation patterns are summarized in Scheme 2.

The structure of (8) was determined on the basis of the ^{1}H and ^{13}C n.m.r. spectra. The ^{1}H spectrum shows only a typical A_2B_2 pattern [δ 4.15 (t, *J* 8 Hz) and 3.95 (t, *J* 8 Hz) in [$^2H_6$]DMSO) and four signals are observed in the ^{13}C spectrum, supporting a symmetrical structure for (8).

Reaction in the Presence of n-Butyl-lithium.—When ethylenethiourea (1) was treated with 2 mol equiv. of n-butyl-lithium in THF and then allowed to react with carbon disulphide followed by succesive treatments with methyl iodide and acetic acid, the hydroiodide (10) was isolated as yellow needles in 36% yield. The structure (10) was assigned on the basis of the spectroscopic data and elemental analyses, and was supported by the following evidence.

An aqueous solution of (10) reacted with silver nitrate to yield a light yellow precipitate of silver iodide. When (10) was treated with pyridine, the dithio-ester (11) was isolated along with pyridinium iodide.* Compound (10) was regenerated quantitatively by treatment of (11) with 57% hydrogen iodide solution. On treatment with lithium aluminium hydride, (11) was converted into *N*-methylimidazolidine-2-thione (13) † in 25% yield. Methyl 2-oxoimidazolidine-1-carbodithioate (12) ‡ was also obtained by refluxing (11) with acetic acid.

Compound (11) was also prepared in a one-pot reaction by successive treatment of the above reaction mixture with water and methyl iodide. The inter-relation between products from the reaction of (1) with n-butyl-lithium are summarized in Scheme 3.

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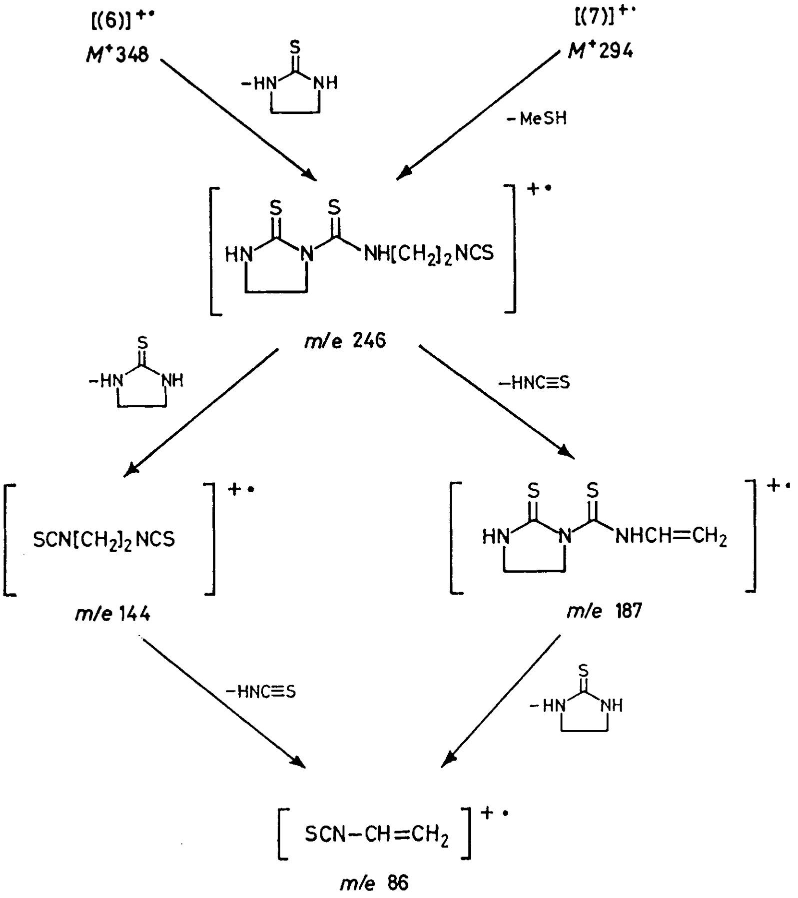
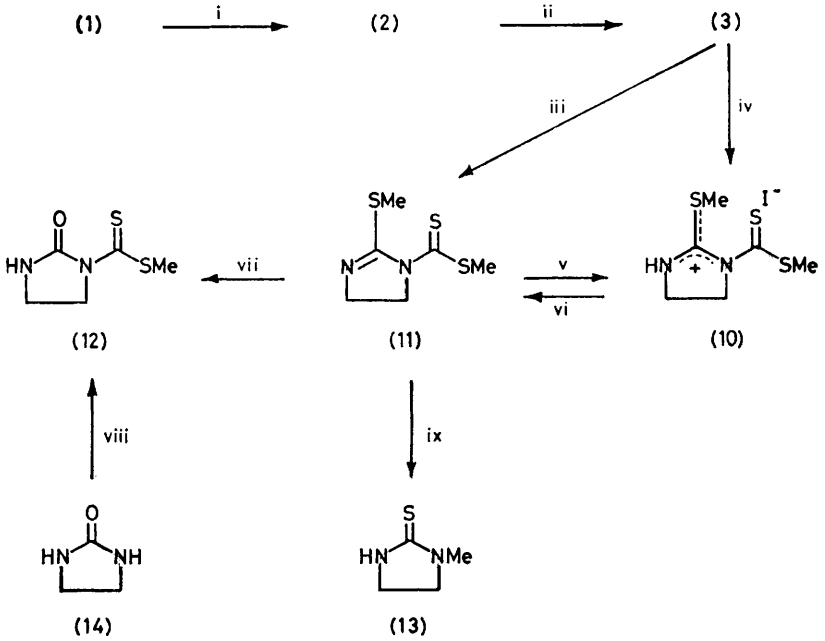
* The i.r. spectrum coincided with that of an authentic sample prepared from pyridine and 57% HI.

† An authentic sample was prepared by Mckay's method (ref. 6).

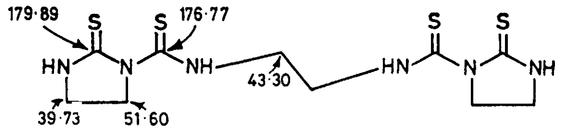
‡ The i.r. spectrum of this compound was superimposable with that of an authentic specimen prepared by our method (ref. 3).



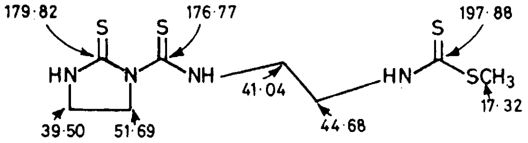
Scheme 2



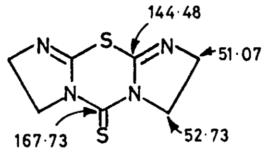
Scheme 3 *Reagents:* i, Bu^{n}Li; ii, CS_2; iii, MeI; iv, MeI, H^+; v, HI; vi, pyridine; vii, H_3O^+, heat; viii, NaH, CS_2, MeI; ix, $LiAlH_4$



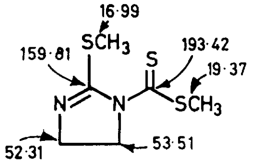
(6)



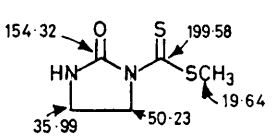
(7)



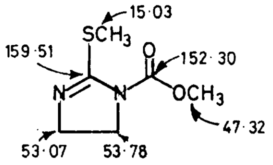
(8)



(11)



(12)



(15)

^{13}C N.m.r. spectral assignments for compounds (6), (7), (8), (11), (12), and (15). Spectra were recorded for solutions in [$^2H_6$]-DMSO except for that of compound (15) which was recorded in $CDCl_3$. Chemical shifts are expressed in p.p.m. downfield from internal tetramethylsilane

EXPERIMENTAL

Microanalyses were performed at the Analytical Center of Chiba University. I.r., u.v., mass, and ^{1}H and ^{13}C n.m.r. spectra were measured by Japan Spectroscopic Co. DS-403G, Hitachi EPS-3T, RMU-6MC, Japan Electron Optics Lab. Co. C-60HL, and FX-100 instruments, respectively.

1,2-*Bis*-[(2-*thioxoimidazolidin*-1-*yl*)*thiocarboxamido*]-*ethane* (6).—A mixture of imidazolidine-2-thione (ethylenethiourea) (1) (1 g, 9.8 mmol), sodium hydride (50% dispersion in oil; 1.5 g, 31 mmol), dry tetrahydrofuran (THF) (10 ml, distilled over $LiAlH_4$), and diethyl carbonate (20 ml, dried over Zeolite A-3) was stirred for 0.5 h at 50—60 °C under nitrogen. To the reaction mixture was added dropwise a mixture of carbon disulphide (3 ml, 64 mmol) and hexamethylphosphoramide (HMPA) (5 ml, distilled over CaH_2). The resulting mixture was stirred for 1 h at room temperature and then poured into ice–water (100 ml) to afford some light yellow material. Recrystallization from pyridine gave white *prisms* (0.75 g, 66%), m.p. 224—225 °C; $\nu_{max.}$ (KBr) 3 290, 3 220, 3 120 (NH), and 2 925 cm^{-1} (CH); $\lambda_{max.}$ (99% EtOH) 262 (ε 27 000), and 280 nm (31 500); δ ([$^2H_6$]DMSO) 12.24 (2 H, s, NH of imidazolidine ring), 9.76 (2 H, s, NH), 4.38 (4 H, t, *J* 8 Hz, 5′-CH_3), 3.84 (4 H, t, CH_2, *J* 8 Hz), 3.46 (4 H, t, *J* 8 Hz, 4′-CH_2) (Found: C, 34.7; H, 4.65; N, 24.0; S, 36.6. $C_{10}H_{16}N_6S_4$ requires C, 34.46; H, 4.63; N, 24.11, S, 36.80%).

1-[(*Methylthio*)*thiocarboxamido*]-2-[(2-*thioxoimidazolidin*-1-*yl*)*thiocarboxamido*]*ethane* (7).—The filtrate separated from (6) above was washed with benzene and then treated with a mixture of methyl iodide (2 ml) and ethanol (10 ml). The mixture was allowed to stand in a refrigerator overnight when some light yellow material was obtained. Recrystallization from THF–water gave light yellow plates (0.38 g, 26%), m.p. 195—196 °C; $\lambda_{max.}$ (99% EtOH) 264 (sh) (ε 30 500) and 272 nm (30 800) (Found: C, 32.8; H, 4.9; N, 19.0; S, 43.8. $C_8H_{14}N_4S_4$ requires C, 32.63; H, 4.79; N, 19.02; S, 43.56%).

2,3,7,8-*Tetrahydrodi-imidazo*[2,1-b:1,2-e][1,3,5]*thiadiazine*-5-*thione* (8).—The reaction described for the preparation of (6) from ethylene thiourea (1 g) was repeated but using DMSO (10 ml) in place of diethyl carbonate. The crude white products (0.75 g) [consisting of (6) (yield 64%) and (8) (16%) in the ratio 4 : 1 (^{1}H n.m.r.)] were collected and separated by preparative t.l.c. on silica gel (AcOEt–benzene 1 : 1 v/v). Compound (8) was recrystallized from EtOH to afford white *plates*, m.p. 189—190 °C; $\nu_{max.}$ (KBr) 2 970, 2 950, 2 920, 2 865 (CH), and 1 595 cm^{-1} (C=N); $\lambda_{max.}$ (99% EtOH) 245 (ε 20 000) and 285 nm (28 000); *m/e* 212 (M^+, 100%), 179 (23), 140 (46), and 111 (36) (Found: C, 39.8; H, 3.8; N, 26.2; S, 30.2. $C_7H_8N_4S_2$ requires C, 39.61; H, 3.80; N, 26.38; S, 30.21).

Ethyl 2-*Thioxoimidazolidine*-1-*carboxylate* (9).—A mixture of (1) (1 g, 9.8 mmol), sodium hydride (50% dispersion in oil; 1.5 g, 31 mmol), dry THF (10 ml), and diethyl carbonate (20 ml) was refluxed for 0.5 h under nitrogen. The mixture was then poured into ice–water (100 ml) and extracted with chloroform. The extract was evaporated *in vacuo* and recrystallized from ethanol–water to afford *needles* (1.5 g, 98%), m.p. 162—163 °C; $\nu_{max.}$ (KBr) 3 300, 3 250 (NH), 2 960, 2 890 (CH), and 1 730 cm^{-1} (CO); $\lambda_{max.}$ (99% EtOH) 227 (ε 10 000) and 264 nm (10 870); *m/e* 174 (M^+, 29%), 142 (7), 128 (44), and 102 (100); δ($CDCl_3$) 7.57br (1 H, NH, disappeared on deuterium exchange), 4.34 (2 H, q, *J* 7 Hz CH_2CH_3), 4.16 (2 H, t, *J* 8 Hz, 5-CH_2), 3.60 (2 H, t, *J* 8 Hz, 4-CH_2), and 1.34 (3 H, t, *J* 7 Hz, CH_2CH_3) (Found: C, 41.15; H, 5.85; N, 15.95; S, 18.4. $C_6H_{10}N_2O_2S$ requires C, 41.37; H, 5.79; N, 16.07; S, 18.40%).

Methyl 2-*Methylthio*-4,5-*dihydroimidazole*-1-*carbodithioate* (11).—n-Butyl-lithium (15% solution in hexane, 30 ml, 47.8 mmol) was added to a mixture of (1) (2 g, 19.6 mmol) and dry THF (40 ml) with stirring below 0 °C under nitrogen. After stirring had been continued for 0.5 h, a mixture of carbon disulphide (6 ml) and THF (40 ml) was added in drops. The resulting mixture was stirred for an additional 1 h, and then water (20 ml) and methyl iodide (8 ml) were added.

The red mixture was shaken for 0.5 h at room temperature and allowed to stand in a refrigerator overnight. The organic layer of the mixture was separated and evaporated to give a red oil, which gave light yellow crystals on trituration with ethanol. Recrystallization from methanol gave light yellow *prisms* (2.8 g, 79%) m.p. 90—91 °C; $\nu_{max.}$ (KBr) 2 900, 2 850 (CH), and 1 570 cm^{-1} (C=N); $\lambda_{max.}$ (99% EtOH) 312 nm (ε 9 700); δ($CDCl_3$) 4.27 (2 H, t, *J* 8 Hz, 5-CH_2), 4.03 (2 H, t, *J* 8 Hz, 4-CH_2), 2.63 (3 H, s, $CSSCH_3$), and 2.47 (3 H, s, SCH_3) (Found: C, 34.9; H, 4.95; N, 13.7; S, 46.45. $C_6H_{10}N_2S_3$ requires C, 34.93; H, 4.89; N, 13.57 S, 46.62%).

2-*Methylthio*-1-[(*methylthio*)*thiocarbonyl*]-4,5-*dihydroimidazolium Iodide* (10).—The reaction described in the preparation of (11) was run without water (20 ml). The corresponding red oil was treated with acetic acid to give yellow crystals (6 g). Recrystallization from methanol gave yellow *needles* (2.2 g, 36%), m.p. 176—177 °C (decomp.); $\nu_{max.}$ (KBr) 3 120 (NH), 2 960 (CH), and 1 575 cm^{-1} (C=N); $\lambda_{max.}$ (99% EtOH) 281 (ε 11 230) and 308 nm (10 000); δ ([$^2H_6$]-DMSO) 7.00 (signal of NH overlapping with that of H_2O in solvent), 4.65 (2 H, t, *J* 8 Hz, 5-CH_2), 4.05 (2 H, t, *J* 8 Hz, 4-CH_2), 2.70 (3 H, s, SCH_3), and 2.65 (3 H, s, $CSSCH_3$) (Found: C, 21.75; H, 3.35; N, 8.55; S, 29.0. $C_6H_{11}IN_2S_3$ requires C, 21.56; H, 3.32; N, 8.38; S, 28.78%).

N-*Methylimidazolidine*-2-*thione* (13).—To dry ether (45 ml) containing the dithio-ester (11) (0.7 g) was added a suspension of lithium aluminium hydride (0.5 g) in dry ether (45 ml). The mixture was stirred at room temperature for 1 h and then poured into water (150 ml). The resulting solution was extracted with chloroform, and the extract was dried (Na_2SO_4) and evaporated to afford the crude product (0.1 g). Recrystallization from hexane–ethanol gave needles, m.p. 129—130 °C (lit.,[6] 131—132 °C).

Methyl 2-*Oxoimidazolidine*-1-*carbodithioate* (12).—A mixture of (11) (0.6 g, 2.9 mmol), 10% sulphuric acid (3 ml), and ethanol (3 ml) was refluxed for 0.5 h. Addition of water (10 ml) to the mixture gave a pink precipitate which was recrystallized from ethanol to give *needles* (0.1 g, 20%), m.p. 211—212 °C; $\nu_{max.}$ (KBr) 3 160, 3 100 (NH), 2 950, 2 880 (CH), and 1 730 cm^{-1} (CO); $\lambda_{max.}$ (99% EtOH) 299 nm (ε 3 550); *m*/*e* 176 (M^+, 34%), 128 (100), and 86 (36); δ ([$^2H_5$]pyridine) 9.10br (1 H, NH), 4.27 (2 H, t, *J* 8 Hz, 5-CH_2), 3.33 (2 H, t, *J* 8 Hz, 4-CH_2), and 2.65 (3 H, s, CH_3) (Found: C, 34.15; H, 4.6; N, 15.85; S, 36.45. $C_5H_8N_2OS_2$ requires C, 34.07; H, 4.57; N, 15.89; S, 36.38%).

Methyl 2-*Methylthio*-4,5-*dihydroimidazole*-1-*carboxylate* (15).—Methyl 2-thioxoimidazolidine-1-carboxylate, synthesized from ethylenethiourea and dimethyl carbonate in 54% yield by the method described for the preparation of the ethyl analogue (8), was methylated with methyl iodide in methanol under reflux, followed by treatment with triethylamine to give the methyl ester (15) as white prisms, m.p. 101—102 °C (from EtOH) (quantitative).

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REFERENCES

[1] T. Takeshima, M. Yokoyama, T. Imamoto, M. Akano, and H. Asaba, *J. Org. Chem.*, 1969, **34**, 730.

[2] M. Muraoka, M. Yokoyama, K. Yamamoto, and T. Takeshima, *Bull. Chem. Soc. Jpn.*, 1970, **43**, 2134.

[3] T. Takeshima, M. Ikeda, M. Yokoyama, and N. Fukada, *J. Chem. Soc., Perkin Trans. 1*, 1979, 692.

[4] E. E. Reid, 'Organic Chemistry of Bivalent Sulfur,' Chemical Publishing Co., 1963, vol. 5, p. 53.

[5] M. Yokoyama, S. Ohtuki, M. Muraoka, and T. Takeshima, *Tetrahedron Lett.*, 1978, 3823.

[6] A. F. Mckay and M. E. Kreling, *J. Org. Chem.*, 1957, **22**, 1581.