Contribution to the Cyclization of Hydrazones of α,β-Unsaturated Carbonyl Compounds. The Biscarbamyl- and Bisthiocarbamylhydrazones of Malondialdehyde

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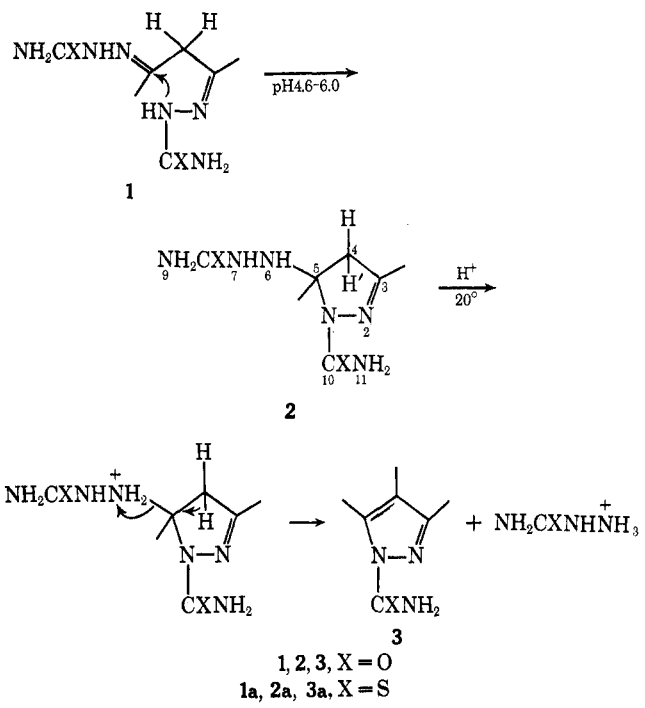
The symmetrical bissemicarbazone of malonaldehyde **1** readily cyclized during its preparation to form the isomeric semicarbazido-substituted carbamylpyrazoline **2**. The cyclization proceeded by nucleophilic addition of the acidic hydrazine nitrogen in one semicarbazone group to the polarized azomethine (imine) double bond ($-N^{-\delta}=^{+\delta}C<$) in the adjacent group. The thiosemicarbazone of malonaldehyde **1a** reacted similarly to form a thiosemicarbazido-substituted thiocarbamylpyrazoline **2a**. In a suspension of water at 20°, increasing hydrogen ion concentrations catalyzed elimination of the semicarbazido or thiosemicarbazido substituents with the formation of pyrazole-1-carboxamide (**3**) or pyrazole-1-thiocarboxamide (**3a**).

In the course of our studies concerning reactions of malondialdehyde with various nitrogenous bases, we reexamined the structures of a number of known products of this compound. Reaction of phenyl-[1] or dinitrophenylhydrazine,[2] hydrazine, semicarbazide,[3] or thiosemicarbazide[4] with tetraalkoxypropanes gave the corresponding 1-substituted pyrazoles as reported. Although the semicarbazones and phenylhydrazones of α,β-unsaturated aldehydes and ketones have provided a convenient route to the substituted 2-pyrazolines[5,6] and the cyclization of monohydrazones of 1,3 diketones leading to the formation of pyrazoline and pyrazole has recently been described,[7] the formation of substituted pyrazolines from bishydrazones of 1,3-dialdehydes have not been reported previously. Neither has the formation of the known 1-substituted pyrazoles[1-4] been considered to proceed *via* the respective pyrazoline intermediates. Earlier attempts to obtain the semicarbazones of 1:1 condensation products of malonaldehyde and various amino acids gave a single, difficultly soluble product on each occasion, which best analyzed for the bissemicarbazone of malonaldehyde,[8] previously described by L. Claisen's laboratory in 1904.[9]

SCHEME I



Results and Discussion

Reaction of the semicarbazide HCl with malondialdehyde in aqueous acetate buffer, pH 4.6, gave a white crystalline product which analyzed ($C_5H_{10}O_2N_6$) for the expected bissemicarbazone of malondialdehyde **1** (Scheme I). Under more acidic conditions the principal product isolated was pyrazole-1-carboxamide **3**. Further, heating of the so-called bissemicarbazone to 135° gave a sublimate consisting predominantly of pyrazole and traces of **3** which were readily identified from their nmr and mass spectra. However, initial nmr data did not provide the expected evidence for the chemically equivalent methylene protons of the open-chain bissemicarbazone structure **1** nor any evidence for the conjugated form of **1**.

Direct evidence in support of the pyrazoline structure **2** for the bissemicarbazone of malondialdehyde was obtained from the 100-MHz nmr spectrum in D_2O given in Figure 1, where chemical shifts are expressed in parts per million from *tert*-butyl alcohol, δ 1.28 from TMS. The azomethine proton H_3 appeared as a closely spaced quartet at 5.8 ppm and H_5, centered at 4.0 ppm, was also a quartet. The geminal protons, H_4 and $H_{4'}$, constitute the AB part of an ABMX pattern and appeared as two octets to high field with calculated chemical shifts of 1.57 and 1.96 ppm, respectively. The geminal coupling constant of −19.5 Hz was close to that reported for a number of substituted pyrazolines.[10] The geminal coupling constant $J_{4,4'}$ was assumed to be negative since this seems to be in keeping with experimental values for sp^3-hybridized groups and since the magnitude of geminal coupling in five-membered ring systems becomes more negative, in the range of −(16–17 Hz), if the nonequivalent methylene protons are adjacent to a π system.[11] $H_{4'}$ was assigned the high-

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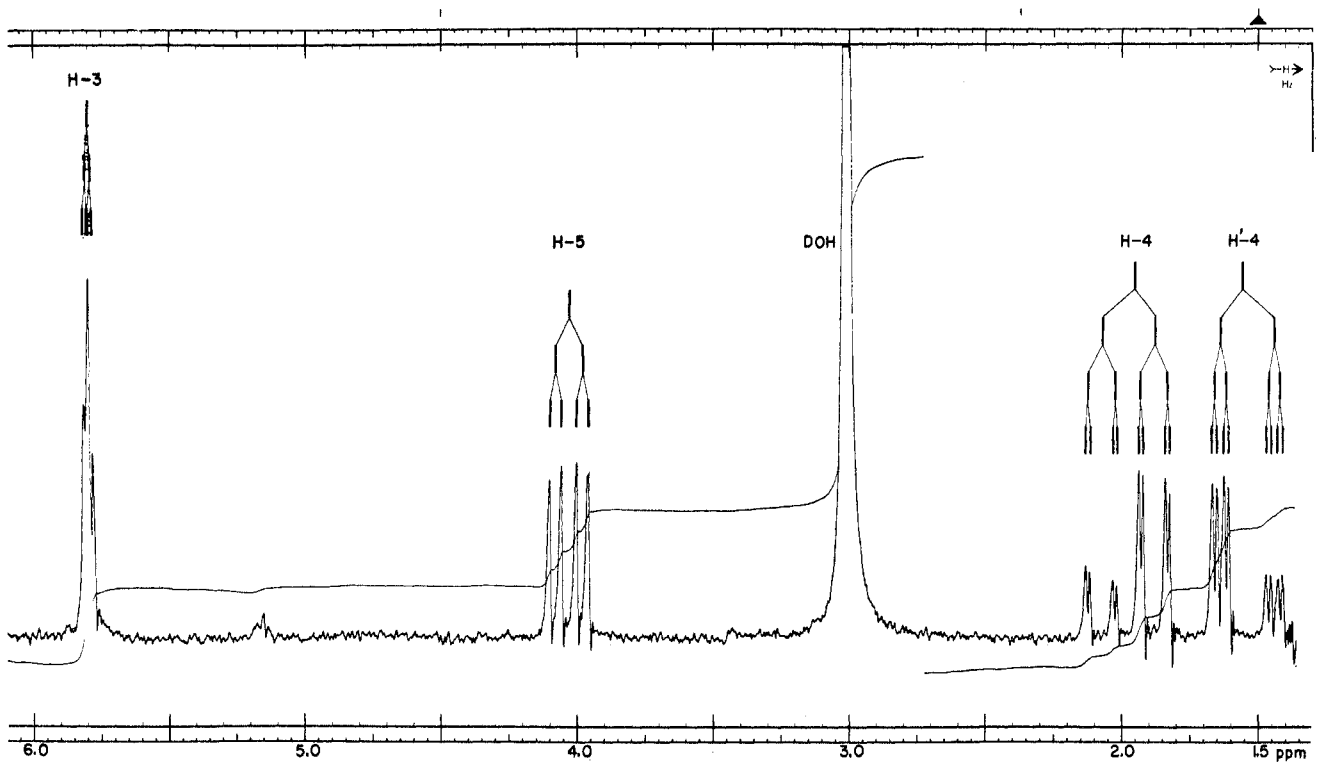

Figure 1.—Nmr spectrum of **2** in D_2O at 60°, 100 MHz, chemical shift from *tert*-butyl alcohol, δ 1.28 from TMS.

field multiplet due to shielding by H_5 with which it has a smaller coupling constant, $J_{4',5} = 4.0$ Hz, by comparison to H_4 which by virtue of its transdiaxial disposition to H_5 had a $J_{4,5}$ of 10.0 Hz. The 100-MHz nmr spectrum of **2** in dimethyl sulfoxide-d_6 (DMSO-d_6) gave, on the addition of a drop of pyridine-d_5, H_5 and H_6 as a multiplet, at δ 5.4 ppm composed of H_5, a sextet, which was partly obscured by the doublet of H_6. Coupling between H_5 and H_6 was ~5 Hz. On the addition of D_2O, H_6 exchanged out rapidly and H_5 collapsed to a quartet. HCNH coupling is observed only in those cases where proton exchange is sufficiently slow.[12] Presumably, in the absence of a trace of pyridine there was sufficient acid present to promote rapid exchange of the NH protons since H_6 appeared as a singlet and H_5 as a poorly resolved quartet in pure DMSO-d_6. H_7 was assigned to the sharp singlet at δ 7.5 ppm while H_9,$H_{9'}$ and H_{11},$H_{11'}$ were assigned to singlets at δ 6.7 and 6.3 ppm, respectively. H_3 was represented by a singlet at δ 7.1 and the geminal protons H_4 and $H_{4'}$ appeared very similarly to the 16-line pattern described in Figure 1.

The 100-MHz nmr spectrum of **2a** in DMSO-d_6 corroborated evidence provided from the mass spectrum in support of its structural assignment. H_3 appeared as a poorly resolved triplet, δ 7.6 ppm, while H_4 and $H_{4'}$ had a geminal coupling constant of −18.0 Hz. H_4 was partially obscured by the DOH signal. H_5 appeared as a six-line multiplet and was composed of 4-Hz coupling each to H_6 and $H_{4'}$ and 10-Hz coupling to H_4. H_7 appeared as a sharp singlet, δ 9.0 ppm, and H_9 and $H_{9'}$ as nonequivalent broadened peaks at δ 8.4 and ~8.2 ppm, respectively. On the addition of D_2O, H_6 exchanged out and H_5 collapsed to the expected quartet.

Due to a greater contribution of the dipolar resonance form $^-S—C{=}N^+<$ to their ground states, thioamides display significantly greater barriers to rotation about the C–N bond than do their corresponding amides.[13] As a consequence, *N*-alkyl substituents show magnetic nonequivalence[14] and, for those cases reported, the substituents syn to sulfur were assigned to higher field signals. Assignment of $H_{9'}$ to the high field of H_9 was tentative and made by analogy to the assignments for alkyl substituents.

H_{11} and $H_{11'}$ showed chemical shift equivalence and formed a broad singlet centered at δ 8.0 ppm and supported the suggestion that the ring π electrons contributed more effectively to the dipolar character of the 1-thione substituent than did the nitrogen carrying H_{11} and $H_{11'}$. Although restricted rotation about the thione–N bond in substituted thioureas has been reported,[15] no account of restricted rotation about the C–N bond in unsubstituted thioamides has appeared previously.

Fragmentation of **2** in the mass spectrometer went according to Schemes II and III and is supported where indicated by the corresponding metastable peaks (m*). The mass spectrum was devoid of the parent ion *m/e* 186, and the expected ion for the fragmentation of aliphatic semicarbazones, $NH_2CONH^+N{\equiv}CH$, *m/e* 86,[16] was conspicuous for its low (2%) abundance. Instead the mass spectrum bore a striking resemblance to that for pyrazole carboxamide **3**. The highest mass fragments and base peaks occurred at 112 and 69 for the so-called bissemicarbazone and 111 and 68 for the pyrazole carboxamide.

Initial uncertainty as to the mode of fragmentation

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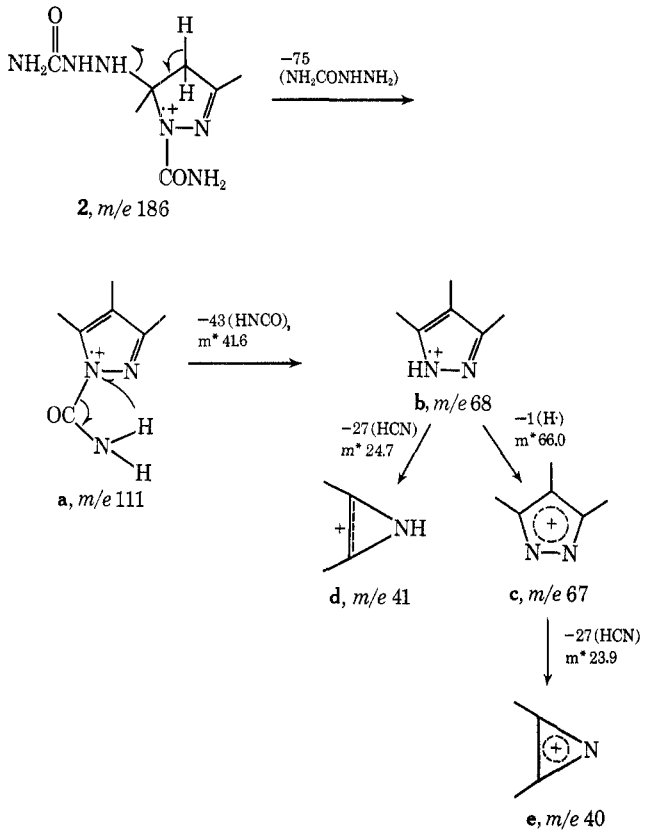
SCHEME II



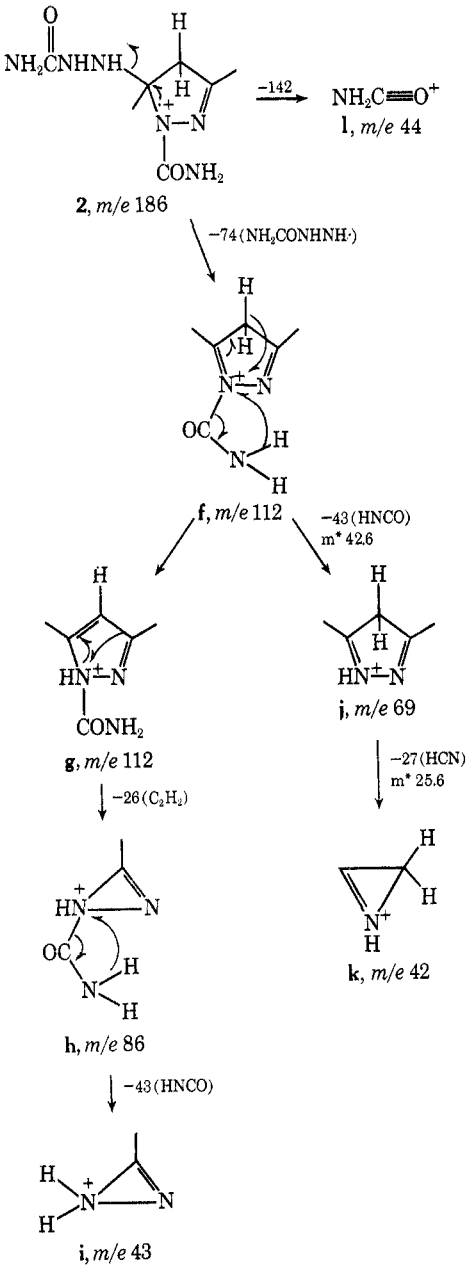
existed also due to the fact that **2** could give rise to *m/e* 111 (**a**) by thermal degradation or the molecular ion of **2** could lose semicarbazide *m/e* 75 as a neutral fragment on electron impact ($M\cdot^+ - 75 = 111$). The latter process was favored as the ratios *m/e* 112/111 and *m/e* 69/68 were not significantly altered by source temperatures between 130 and 320°.

Fragmentation arising from charge localization on the heterocyclic ring generated ions by two paths. The first (Scheme II), by loss of a neutral semicarbazide fragment, produced *m/e* 111 (**a**) and by subsequent loss of HNCO gave *m/e* 68 (**b**) which by either the loss of HCN or hydrogen gave **d** or **c**, respectively. The latter ion *m/e* 67 subsequently lost 27 mass units (HCN) to give **e**.

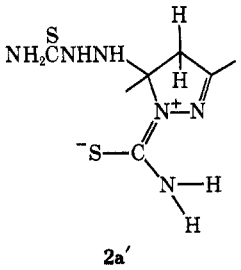
The structure of the highest mass fragment *m/e* 112 (**f**) (Scheme III) in the spectrum was inferred by its transformation to the base peak *m/e* 69 (**j**) by way of the loss of a neutral HNCO fragment and the most intense metastable ion (m* 42.6) in the spectrum confirmed this transition. Although the loss of the $NH_2CONHNH\cdot$ radical was not observed in the mass spectra of the semicarbazones previously examined,[16] it along with ion **f** would be expected to make up the major fragmentation product of **2**. No metastable ions were observed in support of the transitions **f** → **g** → **h** → **i**. The structures **h** and **i** were proposed for *m/e* 86 and 43 rather than $NH_2CONHN^+{\equiv}CH$ and $NH_2N^+{\equiv}CH$ to be more consistent with the proposed pyrazoline structure **2** rather than the open chain bissemicarbazone **1**. The ion **l** of mass 44 was also present in the spectra of semicarbazones of aliphatic aldehydes and ketones as a result of amide cleavage.[16]

The mass spectrum of **2a** differed in several significant respects from that of **2**. The molecular ion *m/e*

SCHEME III



218 for **2a** was observed and the pyrazolium (*m/e* 68) rather than the pyrazolinium (*m/e* 69) ion constituted the base peak. Although thermal degradation could account for the *m/e* 127 ($M\cdot^+ - 91$) and *m/e* 91 ($NH_2CSNHNH_2$) ions, only about half of the pyrazole (*m/e* 68) ion could arise from this source in the extreme, as the ratio *m/e* 127/68 in pyrazole-1-thiocarboxamide (**3a**) was 0.5. These differences might be rationalized on the basis of the possible contribution of the dipolar resonance form **2a′** to the ground state of **2a**, thus di-



2a′

minishing the tendency for charge localization on the heterocyclic ring of the molecular ion. Consequently, charge localization on either ring substituent is favored and fragmentation proceeds by the loss of thiosemicarbazide as both a neutral fragment giving *m/e* 127 and a radical ion (*m/e* 91).

Experimental Section

Melting points were determined microscopically on a hot stage. Nmr spectra were recorded with a Varian HA-100 instrument, and, for mass spectral analysis, a Nuclide 12-90-G mass spectrometer with a direct insertion probe, source temperature 240°, 70 eV, and 100-μA trap current was used.

5-Semicarbazido-1-carbamyl-2-pyrazoline (2).—A solution containing 4.95 g of sodium acetate and 3.34 g (0.03 mol) of semicarbazide HCl in 18 ml of water was made up. Malonaldehyde (β-hydroxyacrolein) was then prepared by hydrolyzing 3.1 g (0.014 mol) of 1,1,3,3-tetraethoxypropane with 1.5 ml of 1 *N* HCl at 45–50°, for about 20 min, until the solution was miscible and clear. The malonaldehyde and the buffered semicarbazide solutions were mixed (pH 4.6) and heated monentarily in a boiling water bath, and the reaction mixture was then left overnight at room temperature. The white crystals (1.6 g) which formed had a two-stage melting point, *i.e.*, a rearrangement (see Pyrazole, B), melting, and resolidification took place quite sharply and reproducibly at 208–210° and, upon further heating, the compound melted at 248–250°. Recrystallization was carried out from saturated hot water solutions: yield 61.5%; uv max (H_2O) 234 nm (ϵ 8150) at pH 6.0; ^{1}H nmr (D_2O, 60°), lock signal *tert*-butyl alcohol (δ 1.28 from TMS), δ 7.08 (t, 1 H, $J_{3,4'} = 1.6$, $J_{3,4} = 1.2$ Hz, H-3), 5.28 (qt, 1 H, $J_{5,4} = 10.0$, $J_{5,4'} = 4.0$ Hz, H-5), 3.26 midpoint, 3.24 calcd (8-line pattern, 1 H, gem $J_{4,4'} = -19.5$, $J_{4,5} = 10.0$, $J_{4,3} = 1.2$ Hz, H-4), 2.82 midpoint, 2.85 calcd (8-line pattern, 1 H, gem $J_{4',4} = -19.5$, $J_{4',5} = 4.0$, $J_{4',3} = 1.6$ Hz, H′-4) (relative intensities of inner and outer lines of overall 16-line pattern calcd[11] 1:2.6); ^{1}H nmr (DMSO-d_6, 10% pyridine-d_5, 31.5°) δ 7.46 (s, 1, NH of hydrazine, H-7), 7.08 (s, unresolved triplet, 1, CH, H-3), 6.72 (s, 2, NH of amide, H-9 and H′-9), 6.32 (s, 2, NH of amide, H-11 and H′-11), 5.50 (d, 1, NH of hydrazine, H-6), 5.33 (m, 1 H, H-5), 3.28 (center of 8-line pattern, 1 H, $J_{4,4'} = -18$ Hz, H-4), 2.95 (center of 8-line pattern, 1 H, $J_{4',4} = -18$ Hz, H′-4) (relative intensities of inner and outer lines of overall 16-line pattern 1:2.6); mass spectrum (70 eV) *m/e* (rel intensity) 112 (18), 111 (2), 86 (3), 76 (2), 75 (10), 70 (7), 69 (100), 68 (45), 67 (4), 60 (2), 59 (2), 58 (3), 55 (3), 54 (4), 52 (3), 44 (25), 43 (43), 42 (43), 41 (14), 40 (7), 39 (7), 38 (2).

Anal. Calcd for $C_5H_{10}N_6O_2$: C, 32.23; H, 5.41; N, 45.14. Found: C, 32.25; H, 5.35; N, 45.17.

During the crystallization of the pyrazoline, a further 0.2 g of an unidentified yellow product cocrystallized, mp 257°.

Pyrazole-1-carboxamide (3).—Acid-catalyzed conversion of the pyrazoline derivative to pyrazolecarboxamide was achieved by suspending **2** in a small amount of water and by titrating it with 1 *N* HCl. On addition of a few drops of acid with stirring, **2** dissolved and after a few minutes rod-like crystals precipitated. The newly formed compound **3**, mp 142–145°, sublimed at 70–80° to an air-cooled cold finger or could be recrystallized from hot water: mp 141° (corr); yield 70%; uv max (H_2O) 234 nm (ϵ 9180) at pH 6.0; ^{1}H nmr (DMSO-d_6–$CDCl_3$, 3:1), from TMS, δ 8.26 (qt, 1 H, $J_{5,4} = 2.6$, $J_{5,3} = 0.8$ Hz, H-5), 7.70 (qt, 1 H, $J_{3,4} = 1.5$, $J_{3,5} = 0.8$ Hz, H-3), 6.47 (qt, 1 H, $J_{4,5} = 2.6$, $J_{4,3} = 1.5$ Hz, H-4), amide protons exchanged with D_2O; mass spectrum *m/e* (rel intensity) 111 M^+ (7), 69 (6), 68 (100), 67 (14), 44 (12), 43 (35), 42 (10), 41 (50), 40 (21), 39 (13), 38 (9).

Pyrazole. A.—When the pyrazoline **2** was heated to 135° in a sublimation apparatus at 1 atm, long, flat needles, mp 64–66°, were deposited on the air-cooled condenser and a brown residue remained. Recrystallizations of the sublimate from *n*-heptane yielded a product, mp 68–69°. For comparative purposes, pyrazole was also prepared from hydrazine HCl and malonaldehyde: mp 69–70°;[3] uv max (H_2O) 210 nm (ϵ 3520) at pH 6.0; ^{1}H nmr ($CDCl_3$), from TMS, δ 6.28 (t, 1 H, $J_{4,3} = 2.0$, $J_{4,5} = 2.0$ Hz, H-4), 7.55 (d, 2 H, $J_{5,4}$ and $J_{3,4} = 2.0$ Hz, H-3 and H-5), 11.92 (s, 1 H, HN); mass spectrum *m/e* (rel intensity) 68 M^+ (100), 69 (8), 67 (15), 42 (9), 41 (50), 40 (29), 39 (19), 38 (12), 37 (5).

B.—When the pyrazoline **2** was heated at 205° for 0.5 hr in a sealed, evacuated tube about 5% of pyrazole was formed. The remaining white solid, mp 262°, was only sparingly soluble in hot water and other solvents; however, 20% solutions could be prepared in 70% perchloric acid; this product was therefore not further analyzed. Pyrazole-1-carboxamide by itself will, however, sublime quite readily, at atmospheric pressure or under vacuum and no decomposition was evident.

5-Thiosemicarbazido-1-thiocarbamyl-2-pyrazoline (2a).—A suspension consisting of 2.73 g (0.03 mol) of thiosemicarbazide and 10 ml of water was prepared. In a separate flask was hydrolyzed 3.1 g (0.014 mol) of 1,1,3,3-tetraethoxypropane with 1.5 ml of 1 *N* HCl at 50°, for about 20 min, until the solution was miscible and a clear yellow. To the hydrolyzed acetal was added 1.0 ml of 2.0 *N* NaOH, and the solution was adjusted to pH 4.5–4.6 and added to the thiosemicarbazide suspension. A tan-colored flocculent precipitate formed with slow dissolution of the remaining thiosemicarbazide. After standing overnight at room temperature, the suspension was cooled in ice and filtered. The dried material (40–50%) was recrystallized two times from a boiling water solution. On cooling, feather-like, light brown-yellow crystals formed: mp 159–161°; uv max (H_2O) 237 nm (ϵ 1.9×10^4), 264 (1.7×10^4) at pH 6.0; ^{1}H nmr (DMSO-d_6, 31.5°) δ 8.96 (s, 1, NH of hydrazine, H-7), 8.43 (s, 1, NH of amide, H-9), 8.00 (s, 3, NH of amides, H′-9, H-11, and H′-11), 7.60 (s, unresolved triplet, 1 H, H-3), 6.19 (d, 1, NH of hydrazine, H-6), 5.83 (m, 1 H, H-5), 3.58 (center of 8-line pattern, 1 H, $J_{4,4'} = -18$ Hz, H-4), 3.13 (center of 8-line pattern, 1 H, $J_{4',4} = -18$ Hz, H′-4) (relative intensities of inner and outer lines of overall 16-line pattern 1:2.2); mass spectrum *m/e* (rel intensity) 218 M^+ (6), 128 (10), 127 (21), 102 (12), 91 (57), 75 (6), 69 (29), 68 (100), 67 (13), 61 (8), 60 (32), 59 (54), 58 (7), 57 (5), 43 (14), 42 (39), 41 (38), 40 (19).

Anal. Calcd for $C_5H_{10}N_6S_2$: C, 27.28; H, 4.81; N, 38.45; S, 29.23. Found: C, 27.50; H, 4.62; N, 38.50; S, 29.37.

Pyrazole-1-thiocarboxamide (3a).—Treatment of **2a** in 2 *N* HCl on a steam bath (10 min) gave pyrazole-1-thiocarboxamide: mp 140°; uv max (H_2O) 256 nm (ϵ 6400), 285 (1.0×10^4); uv max (EtOH) 252 nm (ϵ 7900), 291 (1.1×10^4); ^{1}H nmr (DMSO-d_6–$CDCl_3$, 1:1), from TMS, δ 8.65 (qt, 1 H, $J_{5,4} = 2.7$, $J_{5,3} = 0.7$ Hz, H-5), 7.68 (qt, 1 H, $J_{3,4} = 1.4$, $J_{3,5} = 0.6$ Hz, H-3), 6.40 (qt, 1 H, $J_{4,5} = 2.7$, $J_{4,3} = 1.4$ Hz, H-4), 10.00 and 8.80 (broad singlet peaks, amide protons, NH); mass spectrum *m/e* (rel intensity) 127 M^+ (45), 69 (22), 68 (100), 67 (16), 60 (23), 59 (16), 57 (8), 56 (5), 55 (7), 45 (5), 44 (4), 43 (5), 42 (12), 41 (80), 40 (17), 39 (16), 38 (8).

Registry No.—**2**, 31819-63-3; **2a**, 31819-64-4; **3**, 931-08-8; **3a**, 1794-34-9.