The reaction in the presence of sodium borofluoride gave similar results.

NaCl. A mixture of toluidine hydrochloride (3.602 g, 25.07 mmol), sodium chloride (0.571 g, 9.76 mmol), ethyl cyanoformate (2.50 g, 25.2 mmmol), and hydrogen chloride (0.0722 g, 1.98 mmol) in acetic acid (22.93 g) was heated at 90 °C for 2 h with occasional stirring. After filtration 6 N hydrochloride acid (20 mL) was added to the filtrate and the resulting solution was heated at 90 °C for 2 h. Then the reaction mixture was evaporated to near dryness under reduced pressure. The mixture of the solid, water (20 mL), and ethyl acetate (15 mL) was made basic by the addition of sodium carbonate. The white solid formed was separated by filtration, washed with water (200 mL) and with acetone (30 mL), and dried at 80 °C under vacuum. The solid (0.286 g) was free amidinoformic acid and *N*-(*p*-tolyl)amidinoformic acid was not obtained in any significant amount. A control experiment in the absence of sodium chloride gave *N*-(*p*-tolyl)amidinoformic acid (1.495 g, 33% yield based on ethyl cyanoformate).

Registry No.—**6,** 898-22-6; **7,** 29113-33-5; 2,4-xylidinium thiooxamate, 67662-69-5; 2-chloro-*o*-tolylammonium thiooxamate, 67662-70-8; 2,3-xylidinium thiooxamate, 67662-71-9; 3,4-xylidinium thiooxamate, 67662-72-0; 4-chloro-*o*-tolylammonium thiooxamate, 67662-73-1; 2,5-xylidinium thiooxamate, 67662-74-2; *m*-chloroanilinium thiooxamate, 67662-75-3; ethyl 1-carbethoxyformimidate, 816-27-3; 2,5-xylidine, 95-78-3; 2,6-diethylaniline, 579-66-8; *p*-toluidine, 106-49-0; 2,6-xylidine, 87-62-7; ethyl cyanoformate, 623-49-4; *p*-toluidine hydrochloride, 540-23-8; ethyl *o*-aminobenzoate, 87-25-2; *N,N'*-bis(2,5-xylyl)oxamide, 21022-14-0; *N,N'*-bis(2,4-xylyl)oxamide, 21022-26-4; *N,N'*-bis(4-chloro-*o*-tolyl)oxamide, 67662-76-4.

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Ring-Opening Reactions of 1*H*-Pyrrolo[3,2-*c*]pyridine-4,6(5*H*,7*H*)-dione (3,7-Dideazaxanthine) and Two of Its Derivatives

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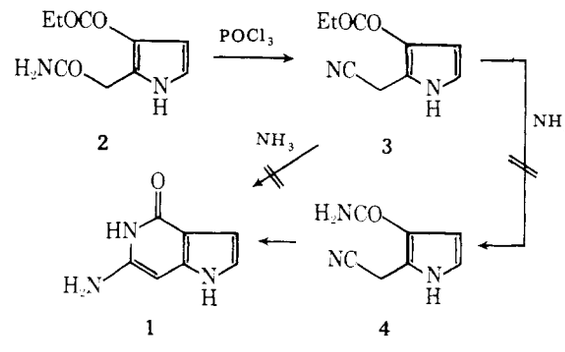
Failure to prepare 6-amino-1*H*-pyrrolo[3,2-*c*]pyridin-4(5*H*)-one (i.e., 3,7-dideazaguanine, **1**) by an anticipated route led to reconsideration of the mechanism of a reaction in which ethyl 3-(ethoxycarbonyl)pyrrole-2-acetate (**5**) was reacted with aqueous methylamine. This subsequently revealed that 1*H*-pyrrolo[3,2-*c*]pyridine-4,6(5*H*,7*H*)-dione (i.e., 3,7-dideazaxanthine, **12**) and its 5-methyl (**8**) and 5-oxa (**13**) analogues undergo nucleophilic ring opening at their C-6 carbonyl leading to a number of 2,3-disubstituted pyrrole derivatives not readily obtainable otherwise. On the other hand, reaction of the 5-oxa analogue (**13**) with diazomethane proceeded via formation of a spirooxirane at its C-4 carbonyl which was also susceptible to ring opening in water and methanol to provide additional 2,3-disubstituted pyrroles.

An approach to 6-amino-1*H*-pyrrolo[3,2-*c*]pyridin-4(5*H*)-one (3,7-dideazaguanine) (**1**) under recent scrutiny in this laboratory commenced with 3-(ethoxycarbonyl)pyrrole-2-acetamide (**2**)[1] as shown in Scheme I. The anticipated dehydration of **2** to 3-(ethoxycarbonyl)pyrrole-2-acetonitrile (**3**) occurred with no problems; however, attempts to convert **3** into **4**,[2] or directly into **1**,[2] with anhydrous ammonia consistently led to recovery of unreacted **3.**

The inability to transform **3** into **4** led to reconsideration of a reaction in which ethyl 3-(ethoxycarbonyl)pyrrole-2-acetate (**5**)[1,3] was treated with aqueous methylamine to produce **6** and **7** (Scheme II). Based on the results above with ammonia (see Scheme I) which indicated the 3-ethoxycarbonyl group of **3** to be unreactive toward nucleophilic substitution, simple amidation and amidation/partial hydrolysis of **5** by aqueous methylamine would not account for the formation of **6** and **7.** However, the formation of **6** and **7** can be rationalized if 5-methyl-1*H*-pyrrolo[3,2-*c*]pyridine-4,6(5*H*,7*H*)-dione (1-methyl-3,7-dideazaxanthine) (**8**)[1] arises from **5** and undergoes attack by methylamine and water at its C-6 carbonyl with ring opening to **6** and **7.** This pathway is confirmed by the short-term (5 min rather than 5 h) reaction

Scheme I



of **5** with aqueous methylamine to form **8** and the amide **9** (the precursor to **8**)[1] and the subsequent reaction of **8** with aqueous methylamine to give **6** and **7.**

The alternative attack of methylamine/water at the C-4 carbonyl of **8** to form **6** and **10** was ruled out by the decarboxylation of **7** to 3-(*N*-methyl)carboxamido-2-methylpyrrole (**11**).

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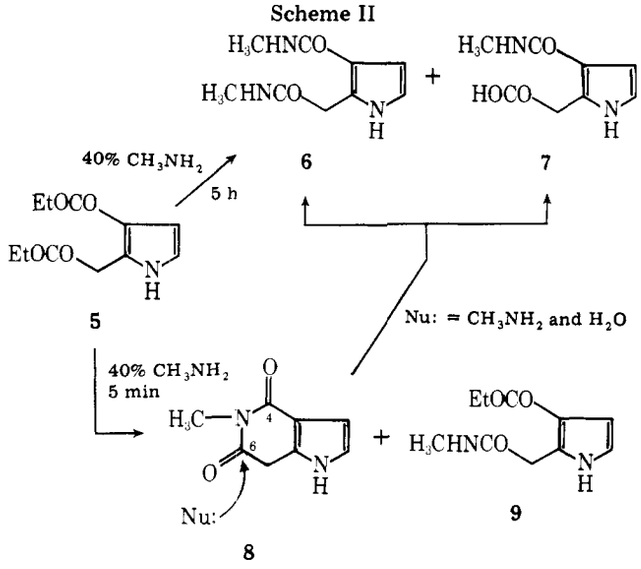
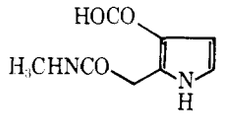
Scheme II



The ring opening observation of **8** suggested that similar reactions would also occur with 1*H*-pyrrolo[3,2-*c*]pyridine-



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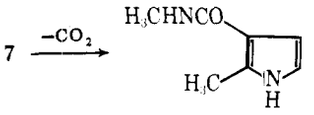
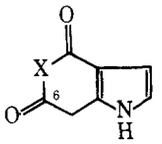


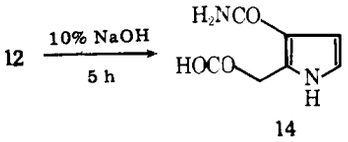
11

4,6(5*H*,7*H*)-dione (3,7-dideazaxanthine) (**12**)[1] and its 5-oxa analogue (**13**)[1] and lead to a number of 2,3-disubstituted

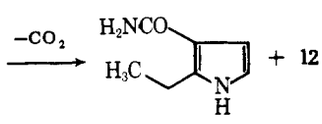


12, X = NH
13, X = O

pyrroles not readily accessible by other means. Thus, reaction of **12** with 10% sodium hydroxide solution for 5 h produced the acid–amide **14**.[4] Subjecting **2** to 10% sodium hydroxide solution for 10 h (vs. 5 h with **12**) also provided **14** in a process

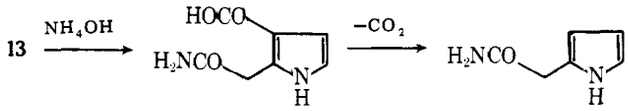


14



16

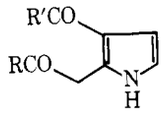
certainly involving **12** since basic conditions are necessary to convert **2** into **12**.[1] The above result is similar to the **5** to **6** and **7** transformation which went through **8**. Substantiation for assigning **14** (rather than **15**) as the structure of the product from basic treatment of **12** originated from two lines of evidence: (i) the decarboxylation of **14** to **16** (along with ring closure to **12**) rather than **17**, which would have resulted from decarboxylation of **15**, and (ii) the preparation of the isomeric

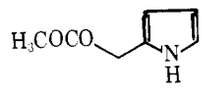


15 **17**

15 upon reacting **13** with ammonium hydroxide. Thus, **14** must have arisen from attack of hydroxide ion at C-6 of **12** and **15** from attack of ammonia (in the concentrated ammonium hydroxide) at C-6 of **13**.

Treatment of **12** with ammonia in a sealed vessel for 10 h did not form the diamide **18** but led to recovery of **12** in



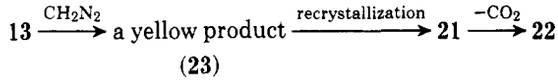


22

18, R = R′ = NH_2
19, R = NH_2; R′ = $NHCH_3$
20, R = OEt; R′ = OH
21, R = OCH_3; R′ = OH
24, R = R′ = OCH_3

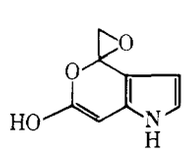
quantitative amounts, probably because removal of the proton on the imidic nitrogen by ammonia deactivates the C-6 carbonyl toward nucleophiles. The *N*-methyl derivative (**8**) did undergo ring opening to **19** upon reaction with ammonia. Compound **10** was obtained on treatment of **13** with aqueous methylamine while **20** and **21** were isolated from reaction of **13** with ethanol and methanol, respectively.

When **13** was treated with diazomethane, a yellow product was obtained which was characterized after recrystallization from benzene–petroleum ether as methyl 3-carboxypyrrole-2-acetate (**21**), the same product obtained from **13** and methanol. Structural proof for **21** was achieved by its decarboxylation to **22**. Upon closer examination of the **13** to **21**

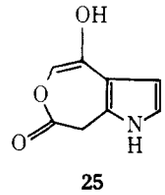


(23)

transformation, it was found that the spectral data used to identify **21** was different than that for the initially obtained yellow product before recrystallization. Principal to this discrepancy was the appearance of a two-proton singlet at δ 3.88, a vinyl singlet at δ 5.82, and a hydroxyl absorption (exchangeable with D_2O) at δ 3.6 in the ^1H NMR spectrum of the yellow species. These data, along with the microanalytical results, a subsequent reaction with water (vide infra), and the prevalency of oxirane formation in the reactions of diazomethane with carbonyl compounds,[5] led to assigning **23** as the structure of the yellow species.



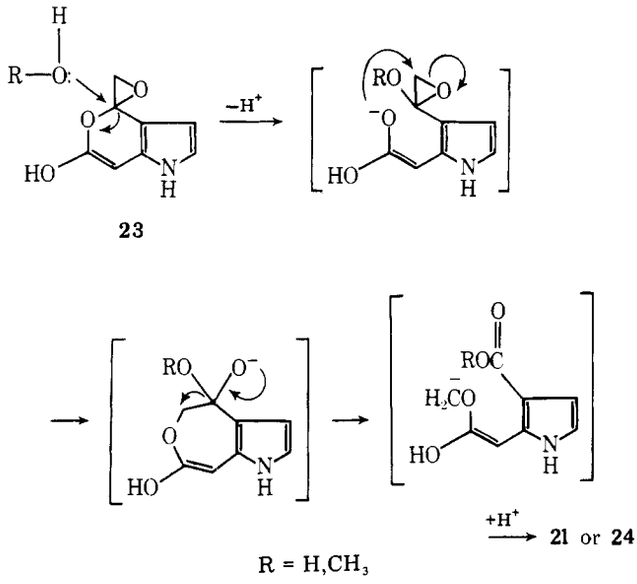
23



25

Transformation of **23** into **21** upon recrystallization from benzene–petroleum ether was found to be due to the trace amounts of water present in the benzene which opened the strained spirooxirane ring. Thus, recrystallization of **23** from dry benzene caused no appearance of **21** and resulted in isolation of purified **23** while brief reaction of **23** with warm water led to **21**. Similarly, reaction of **23** with methanol furnished

Scheme III



23

R = H,CH_3

the diester **24**. A proposed reaction pathway for the formation of **21** and **24** from **23** is outlined in Scheme III.

It should be noted that the ring expanded product **25** would also explain the data obtained above which led to designating **23** as the correct product for the reaction of diazomethane with **13**. However, the appearance of only one carbonyl band (1700 cm^{-1}) and the absence of a hydroxyl absorption in the infrared spectrum of the yellow species would not account for any tautomeric situation for **25** and, thus, eliminate it from structural consideration. These data, on the other hand, suggest that the keto tautomer prevails for **23** in the solid state.

Experimental Section

General. All melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman AccuLab 3 spectrophotometer and the proton NMR spectra were obtained on a Varian EM-360 spectrometer and are reported in parts per million downfield from tetramethylsilane as an internal standard. The spin multiplicities are indicated by the symbols s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Elemental analyses were performed by Het-Chem-Co., Harrisonville, Mo., and Galbraith Laboratories, Knoxville, Tenn.

3-(Ethoxycarbonyl)pyrrole-2-acetonitrile (3). 3-(Ethoxycarbonyl)pyrrole-2-acetamide (**2**)[1] (2.0 g, 10.0 mmol) was refluxed with 5 mL of phosphorus oxychloride (8.38 g, 55.0 mmol) for 20–25 min during which time it became a red solution. The solution was cooled following the reflux period and ice slowly added followed by concentrated NH_4OH which was added at such a rate to maintain the solution temperature below 10 °C and until the pH of the solution rose to ca. 6[6] (pH paper). To this solution was added 25 mL of AcOEt and the organic layer separated by means of a separatory funnel. A reddish oil resulted upon evaporation of the AcOEt on a rotary evaporator and this oil distilled (84–90 °C (5 mmHg)) to a colorless liquid which solidified and was recrystallized from petroleum ether to yield white needles of **3** (1.1 g, 6.2 mmol, 62%): mp 87–88 °C; ^1H NMR (Me_2SO-d_6) δ 1.28 (t, J = 7 Hz, 3 H, CH_3), 4.13 (q, J = 7.0 Hz, 2 H, CH_2 of ester), 4.13 (s, 2 H, CH_2 of acetonitrile), 6.43 (t, J = 3.0 and 2.7 Hz, 1 H, C_4H or C_5H), 6.74 (t, J = 3.0 and 2.7 Hz, 1 H, C_4H or C_5H), 11.65 (broad, 1 H, pyrrole NH); IR (KBr) 3230 (NH), 2250 (C≡N), 1660 (C=O) cm^{-1}.

Anal. Calcd for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.66; N, 15.73. Found: C, 60.32; H, 5.72; N, 16.07.

3-(*N*-Methyl)carboxamidopyrrole-2-(*N*-methyl)acetamide (6) and 3-(*N*-Methyl)carboxamidopyrrole-2-acetic Acid (7) from Ethyl 3-(Ethoxycarbonyl)pyrrole-2-acetate (5). The diester **5**[1,3] (2 g, 8.8 mmol) was added in small portions to 40 mL of boiling aqueous (40%) CH_3NH_2 solution. After the addition was complete, the solution was refluxed for an additional 5 h in an oil bath and was then filtered and the filtrate cooled and acidified (litmus) with 3 N H_2SO_4. The resulting solution was extracted with a mixture of Et_2O–AcOEt (1:4) (3 × 50 mL) and the combined extracts were dried over anhydrous Na_2SO_4. Removal of the solvent on a rotary evaporator left a white solid which recrystallized from AcOEt as white crystals of **7** (0.5 g, 2.8 mmol, 32%): mp 188–189 °C (dec); ^1H NMR (Me_2SO-d_6) δ 2.88 (d, J = 5.0 Hz, 3 H, NCH_3), 4.06 (s, 2 H, CH_2), 6.83 (t, J = 3.0 and 2.7 Hz, 1 H, C_4H or C_5H), 7.25 (t, J = 3.0 and 2.7 Hz, 1 H, C_4H or C_5H), 8.27 (broad, 1 H, amide NH), 11.66 (broad, 1 H, pyrrole NH), 13.88 (broad, 1 H, carboxylic acid OH); IR (KBr) 3280 (NH), 1730 (C=O) cm^{-1}.

Anal. Calcd for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.18. Found: C, 52.95; H, 5.74; N, 14.86.

The aqueous layer remaining after the above Et_2O–AcOEt extraction was basified (litmus) with concentrated NH_4OH and extracted again with Et_2O–AcOEt (1:4) (3 × 5 mL). Following the drying and solvent evaporation procedures carried out as above a brownish solid remained which was recrystallized from AcOEt as pale yellow crystals of **6** (1 g, 5.13 mmol, 58.3%): mp 178 °C; ^1H NMR (Me_2SO-d_6) δ 2.77 (d, J = 5.0 Hz, 3 H, NCH_3), 2.93 (d, J = 5.0 Hz, 3 H, NCH_3), 3.98 (s, 2 H, CH_2), 6.9 (t, J = 3.0 and 2.7 Hz, 1 H, C_4H or C_5H), 7.08 (t, J = 3.0 and 2.7 Hz, 1 H, C_4H or C_5H), 8.33 (broad, 1 H, amide NH), 8.67 (broad, 1 H, amide NH), 11.77 (broad, 1 H, pyrrole NH); IR (KBr) 3350 and 3220 (NH), 1660 (C=O) cm^{-1}.

Anal. Calcd for $C_9H_{13}N_3O_2$: C, 55.38; H, 6.67; N, 21.54. Found: C, 55.11; H, 7.04; N, 21.35.

3-(*N*-Methyl)carboxamidopyrrole-2-(*N*-methyl)acetamide (6) and 3-(*N*-Methyl)carboxamidopyrrole-2-acetic Acid (7) from 5-Methyl-1*H*-pyrrolo[3,2-*c*]pyridine-4,6(5*H*,7*H*)-dione (8). Compound **8**[1] (0.3 g, 1.83 mmol) was added in small portions to boiling aqueous (40%) CH_3NH_2 (12 mL) contained in a small three-necked flask fitted with a reflux condenser and a magnetic stirrer. After the addition was complete, the mixture was refluxed for another 5 h, filtered, cooled, and acidified with 20% aqueous H_2SO_4 to ca. pH 3. The aqueous solution was extracted with AcOEt (2 × 20 mL), the combined extracts were dried over anhydrous Na_2SO_4, and the solvent was evaporated to dryness on a rotary evaporator to produce a white solid which was recrystallized from AcOEt as white crystals of **7** (0.12 g, 0.66 mmol, 36%): mp 183–184 °C (dec). The IR spectrum of this compound was superimposable with that of compound **7** obtained from the reaction of **5** and aqueous (40%) CH_3NH_2.

The aqueous layer remaining after the AcOEt extraction was adjusted to a pH between 9 and 10 with concentrated NH_4OH and the mixture again extracted with AcOEt (2 × 15 mL). The combined extracts were dried over anhydrous Na_2SO_4 and the solvent was evaporated to dryness on a rotary evaporator to leave a white solid which was recrystallized from AcOEt as colorless crystals of **6** (0.04 g, 0.2 mmol, 11%): mp 176–177 °C. The IR spectrum of this compound was identical with that of **6** obtained from the reaction of **5** with aqueous (40%) CH_3NH_2.

5-Methyl-1*H*-pyrrolo[3,2-*c*]pyridine-4,6(5*H*,7*H*)-dione (8) and 3-(Ethoxycarbonyl)pyrrole-2-(*N*-methyl)acetamide (9). To 20 mL of boiling aqueous (40%) CH_3NH_2 solution compound **5**[1,3] (1 g, 4.4 mmol) was added in small portions with the solution becoming reddish brown. The mixture was refluxed for an additional 5 min, filtered, and the filtrate cooled and acidified (litmus) with 3 N H_2SO_4 to a bluish green solution from which needles began precipitating. After keeping the mixture at room temperature for 1 h, the bluish solid was isolated by filtration and air dried. This product was dissolved in 35 mL of C_6H_6, the C_6H_6 solution boiled with charcoal, filtered, and the filtrate concentrated to half of its original volume and cooled. After about 0.5 h, tiny green crystals identified as **8** (0.1 g, 0.61 mmol, 13.9%), mp >300 °C, separated. The IR and ^1H NMR spectra of this sample were identical with that of the authentic sample of **8** prepared by the reported procedure.[1]

While **8** was being obtained by filtration, white needles began forming in the filtrate. After 1 h, the resulting solid was isolated by filtration, air dried, and recrystallized from C_6H_6 into colorless needles of **9** (0.7 g, 3.3 mmol, 75.8%), mp 151 °C, whose IR and ^1H NMR spectra were identical with an authentic sample.[1]

Decarboxylation of 3-(*N*-Methyl)carboxamidopyrrole-2-acetic Acid (7). Compound **7** (0.5 g, 2.75 mmol) was mixed with 15 mL of absolute EtOH and 0.4 mL of Et_3N and this mixture refluxed in an oil bath for 6 h. The solution was evaporated to dryness on a rotary evaporator to furnish a semisolid which was distilled in a Kügelrohr distillation apparatus (110 °C (5 mmHg)) to obtain an orange jelly which was dissolved in 20 mL of AcOEt, boiled with animal charcoal, and filtered. The filtrate was concentrated to 8 mL and cooled. The light green crystals which separated were isolated by filtration and air dried. The IR spectrum of this solid, mp >300 °C, was superimposable with that of an authentic sample of **8**[1] (0.25 g, 1.5 mmol, 55%).

The filtrate obtained after removing **8** as described above was evaporated to dryness on a rotary evaporator to obtain a semisolid which was distilled in a Kügelrohr distillation apparatus (90 °C (5 mmHg)) to produce 3-(*N*-methyl)carboxamido-2-methylpyrrole (**11**) as a yellow liquid (0.15 g, 1.09 mmol, 40%): ^{1}H NMR (Me_2SO-d_6) δ 2.4 (s, 3 H, $2CH_3$), 2.68 (d, J = 5.0 Hz, 3 H, NCH_3), 6.45 (m, 2 H, C_4H and C_5H), 7.5 (broad, 1 H, amide NH), 10.85 (broad, 1 H, pyrrole NH); IR (KBr) 3260 (NH), 1725 (C=O) cm^{-1}.

Anal. Calcd for $C_7H_{10}N_2O$: C, 60.85; H, 7.30; N, 20.28. Found: C, 60.76; H, 7.24; N, 19.95.

3-Carboxamidopyrrole-2-acetic Acid (14). Method A. A mixture of **12**[2] (0.5 g, 3.3 mmol) and 20 mL of 10% aqueous NaOH was refluxed in an oil bath for 5 h. The mixture was cooled and acidified (litmus) with 2 N HCl, filtered, and the filtrate extracted with AcOEt (3 × 25 mL). The combined extracts were evaporated using a rotary evaporator to obtain a solid which was recrystallized from CH_3OH into pale yellow needles of **14** (0.4 g, 2.4 mmol, 72%): mp 195–200 °C (shrinks[7]); ^{1}H NMR (Me_2SO-d_6) δ 3.87 (s, 2 H, CH_2), 6.6 (m, 2 H, C_4H and C_5H), 7.15 (broad, 1 H, amide NH), 7.60 (broad, 1 H, amide NH), 11.7 (broad, 1 H, pyrrole NH), 13.2 (broad, 1 H, acid OH); IR (KBr) 3400 (NH), 1680 (C=O) cm^{-1}.

Anal. Calcd for $C_7H_8N_2O_3$: C, 49.99; H, 4.79; N, 16.66. Found: C, 49.95; H, 4.66; N, 16.71.

Method B. 3-(Ethoxycarbonyl)pyrrole-2-acetamide (**2**)[1] (3.0 g, 15.3 mmol) was mixed with 15 mL of 95% EtOH and the mixture was heated to 80 °C in an oil bath. Then, 20 mL of 10% aqueous NaOH was added. The solution became pink within a few minutes and was refluxed for an additional 10 h, cooled, and acidified with 2 N HCl followed by cooling in an ice bath. The pale yellow needles which separated were filtered in vacuo and recrystallized from CH_3OH into pale yellow needles of **14** (2.3 g, 13.7 mmol, 89%): mp 195–200 °C (shrinks[7]). The IR and ^{1}H NMR spectra of this sample were identical with the sample obtained by method A as described above.

Decarboxylation of 3-Carboxamidopyrrole-2-acetic Acid (14). In a manner similar to the decarboxylation of **7**, **14** (0.5 g, 2.97 mmol) was mixed with 15 mL of absolute EtOH and 0.4 mL of Et_3N and this mixture refluxed in an oil bath for 6 h. The mixture was then evaporated to dryness on a rotary evaporator to obtain a residue which was triturated with a few milliliters of $CHCl_3$ and filtered in vacuo. The crystalline triethylammonium salt thus obtained was placed in a 25-mL round-bottom flask and heated in a Kügelrohr distillation apparatus at 100 °C (5 mmHg) to produce an orange distillate which solidified on standing. The solid was recrystallized from AcOEt–ligroin into white needles of 3-carboxamido-2-methylpyrrole (**16**) (0.2 g, 1.6 mmol, 54%): mp 95 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.35 (s, 3 H, CH_3), 6.48 (m, 2 H, C_4H and C_5H), 6.8 (broad, 2 H, NH_2), 10.85 (broad, 1 H, pyrrole NH); IR (KBr) 3450 (NH), 1680 (C=O) cm^{-1}.

Anal. Calcd for $C_6H_8N_2O$: C, 58.05; H, 6.50; N, 22.57. Found: C, 57.98; H, 6.58; N, 22.42.

After the above distillation was complete, the solid remaining in the 25-mL flask was found to be **12** (0.15 g, 0.99 mmol, 34%), mp >300 °C, by comparison of its IR spectrum with that of an authentic sample of **12**.[1]

3-Carboxypyrrole-2-acetamide (15). A mixture of **13**[1] (0.25 g, 1.65 mmol) and 4 mL of concentrated NH_4OH in 7 mL of 95% EtOH was refluxed for 4 h. The mixture was cooled to room temperature and evaporated to dryness on a rotary evaporator. The resulting white solid was recrystallized from 95% EtOH as colorless crystals of **15** (0.22 g, 1.31 mmol, 79.4%): mp 209 °C (dec); ^{1}H NMR (Me_2SO-d_6) δ 3.75 (s, 2 H, CH_2), 6.3 (t, J = 3.0 and 2.7 Hz, 1 H, C_4H or C_5H), 6.6 (t, J = 3.0 and 2.7 Hz, 1 H, C_4H or C_5H), 6.85 (broad, 1 H, amide NH), 7.17 (broad, 1 H, amide NH), 11.16 (broad, 1 H, pyrrole NH); IR (KBr) 3400, 3350, and 3250 (NH), 1700–1650 (C=O) cm^{-1}.

Anal. Calcd for $C_7H_8N_2O_3$: C, 50.00; H, 4.76; N, 16.76. Found: C, 49.65; H, 4.99; N, 16.69.

3-(*N*-Methyl)carboxamidopyrrole-2-acetamide (19). A solution of **8**[1] (0.5 g, 3.0 mmol) in 25 mL of liquid NH_3 was heated in a steel bomb at 80 °C for 10 h. After cooling, the NH_3 was allowed to evaporate in the fume hood and the residual viscous mass extracted with AcOEt (3 × 25 mL). The combined extracts were boiled with charcoal, filtered, and the purple filtrate was evaporated with the aid of a rotary evaporator. The resulting solid was placed in 50 mL of $CHCl_3$, boiled for 5 min, and the insoluble solid collected with the aid of an aspirator and recrystallized from AcOEt–CH_3OH as white stars of **19** (0.3 g, 1.66 mmol, 55%): mp 193–194 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.7 (d, J = 5.0 Hz, 3 H, CH_3), 3.68 (s, 2 H, CH_2), 6.48 (m, 1 H, C_4H or C_5H), 6.6 (m, 1 H, C_4H or C_5H), 6.8 (broad, 1 H, methylamide NH), 7.72 (broad, 2 H, amide NH), 11.08 (broad, 1 H, pyrrole NH); IR (KBr) 3380 and 3165 (NH), 1640 (C=O) cm^{-1}.

Anal. Calcd for $C_8H_{11}N_3O_2$: C, 53.03; H, 6.12; N, 23.19. Found: C, 52.94; H, 6.13; N, 22.96.

3-Carboxypyrrole-2-(*N*-methyl)acetamide (10). Compound **13**[1] (0.5 g, 3.3 mmol) was mixed with 8 mL of aqueous (40%) CH_3NH_2 and the resulting mixture refluxed for 6 h. The solvent was then evaporated on a rotary evaporator to leave an oil which when placed under reduced pressure (vacuum pump) became a white crystalline residue. Recrystallization of the residue from 95% EtOH produced **10** as white needles (0.45 g, 2.5 mmol, 74.9%): mp 191–192 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.6 (d, J = 4.7 Hz, 3 H, CH_3), 3.8 (s, 2 H, CH_2), 6.3 (t, J = 3.0 and 2.7 Hz, 1 H, C_4H or C_5H), 6.6 (t, J = 3.0 and 2.7 Hz, 1 H, C_4H or C_5H), 7.65 (broad, 1 H, amide NH), 11.1 (broad, 1 H, pyrrole NH), 11.3–11.9 (broad, 1 H, carboxylic acid OH); IR (KBr) 3400 and 3350 (N–H), 1675–1625 (broad C=O) cm^{-1}.

Anal. Calcd for $C_8H_{10}N_2O_3$: C, 52.75; H, 5.49; N, 15.38. Found: C, 52.81; H, 5.62; N, 15.22.

Ethyl 3-Carboxypyrrole-2-acetate (20). Compound **13**[1] (0.25 g, 1.65 mmol) was dissolved in 35 mL of hot 95% EtOH and the resulting solution boiled on a hot plate until the volume was reduced to 10 mL. Evaporation of the remaining solution to dryness on a rotary evaporator left a white solid which was recrystallized from C_6H_6 as tiny colorless needles of **20** (0.19 g, 0.96 mmol, 58.5%): mp 114 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.15 (t, J = 7.0 Hz, 3 H, CH_3), 3.83 (s, 2 H, CH_2 of acetate), 4.05 (q, J = 7.0 Hz, 2 H, CH_2 of ester), 6.26 (t, J = 3.0 and 2.7 Hz, 1 H, C_4H or C_5H), 6.6 (t, J = 3.0 and 2.7 Hz, 1 H, C_4H or C_5H), 11.2 (broad, 1 H, pyrrole NH), 11.72 (broad, 1 H, carboxylic acid OH); IR (KBr) 3400 (NH), 1725 and 1675 (C=O) cm^{-1}.

Anal. Calcd for $C_9H_{11}NO_4$: C, 54.82; H, 5.58; N, 7.11. Found: C, 55.09; H, 5.72; N, 7.37.

Methyl 3-Carboxypyrrole-2-acetate (21). Compound **13**[1] (300 mg, 1.98 mmol) was mixed with 15 mL of CH_3OH and 2 mL of glacial AcOH and this mixture refluxed in an oil bath for 1 h. The mixture was then cooled and the solvent evaporated to dryness on a rotary evaporator to leave a solid which was recrystallized from AcOEt–ligroin as white needles of **21** (0.285 g, 1.56 mmol, 78%): mp 181–182 °C; ^{1}H NMR (Me_2SO-d_6) δ 3.62 (s, 3 H, CH_3), 3.97 (s, 2 H, CH_3), 6.38 (t, J = 3.0 and 2.7 Hz, 1 H, C_4H or C_5H), 6.70 (t, J = 3.0 and 2.7 Hz, 1 H, C_4H or C_5H), 11.18 (broad, 1 H, pyrrole NH); IR (KBr) 3380 (NH), 1725 and 1670 (C=O) cm^{-1}.

Anal. Calcd for $C_8H_9NO_4$: C, 52.46; H, 4.95; N, 7.65. Found: C, 52.65; H, 5.03; N, 7.70.

Methyl Pyrrole-2-acetate (22). Finely powdered **21** (340 mg, 1.86 mmol) was placed in a small round-bottom flask and heated in an oil bath at 220 °C for 13 min, cooled to room temperature, and extracted with AcOEt (2 × 20 mL). The combined AcOEt extracts were dried over anhydrous Na_2SO_4 and then evaporated to an oil with the aid of a rotary evaporator. This oil was distilled (59–60 °C (1.2 mmHg)) using a Kügelrohr distillation apparatus to give **22** as a colorless liquid (135 mg, 0.97 mmol, 52%): ^{1}H NMR (Me_2SO-d_6) δ 3.6 (s, 3 H, CH_3), 5.85 (m, 2 H, C_3H and C_5H), 6.58 (m, 1 H, C_4H), 10.58 (broad, 1 H, pyrrole NH); IR (KBr) 3380 (NH), 1730 (C=O) cm^{-1}.

Anal. Calcd for $C_7H_9NO_2$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.26; H, 6.52; N, 9.97.

Reaction of 13 with Diazomethane. To a suspension of **13**[1] (0.5 g, 3.3 mmol) in 30 mL of dry dioxane was slowly added a cold ethereal solution (25 mL) of dry diazomethane (6.6 mmol) at room temperature. After stirring at room temperature for 4 h, the excess diazomethane was decomposed with a few drops of glacial AcOH and the solvent evaporated using a rotary evaporator to produce an intensely yellow product which was recrystallized for microanalysis from either dry C_6H_6 or dry xylene as yellow crystals of **23** (0.5 g, 3.0 mmol, 91%): mp 149–150 °C; ^{1}H NMR (Me_2SO-d_6) δ 3.6 (s, 1 H, hydroxyl OH). 3.88 (s, 2 H, CH_2), 5.82 (s, 1 H, vinyl CH), 6.53 (m, 1 H, C_3H), 7.03 (t, J = 3.0 Hz, 1 H, C_2H), 11.68 (broad, 1 H, pyrrole NH); IR (KBr) 3200 (NH), 1700 (C=O), cm^{-1}.

Anal. Calcd for $C_8H_7NO_3$: C, 58.18; H, 4.27; N, 8.48. Found: C, 58.41; H, 4.42; N, 8.58.

Reaction of 23 with Water. Compound **23** (15.0 mg, 0.09 mmol) was placed in a 15-mL beaker and 5 mL of H_2O was added. The mixture was boiled for 2 min on a hot plate, cooled, and then extracted with AcOEt (2 × 10 mL). The combined extracts were dried over anhydrous Na_2SO_4 and the solvent was evaporated to dryness using a rotary evaporator to leave a solid (13.0 mg, 0.071 mmol, 79%), mp 181–182 °C, whose IR spectrum was superimposable with **21** prepared from **13** as detailed above.

Reaction of 23 with Methanol. In a manner similar to that for the reaction of **23** with water, **23** (15.0 mg, 0.091 mmol) was placed in a 15-mL beaker, 5 mL of CH_3OH was added and the resultant mixture boiled on a hot plate until the volume was reduced to ca. 0.5 mL. The procedure was repeated using 5 mL of CH_3OH except that the boiling was continued until the last traces of the solvent had evaporated. The

white solid which remained was extracted with ligroin (2 × 5 mL), and the combined extracts were concentrated to 3 mL and then cooled in a refrigerator overnight. After this period, the white needles of **24** which separated were isolated by filtration (5 mg, 0.025 mmol, 28%), mp 70–71 °C, and found to have IR and ^{1}H NMR spectra which were superimposable with those of an authentic sample of **24**.[1]

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References and Notes

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(2) This approach is analogous to that used in the synthesis of 6-amino-1*H*-imidazo[4,5-*c*]pyridin-4(5*H*)-one (3-deazaguanine) (P. D. Cook, R. J. Rousseau, A. M. Mian, P. Dea, R. B. Meyer, Jr., and R. K. Robins, *J. Am. Chem. Soc.*, **98**, 1492 (1976)) and 6-amino-1*H*-pyrazolo[4,3-*c*]pyridin-4(5*H*)-one (K. W. Ehler, R. K. Robins, and R. B. Meyer, Jr., *J. Med. Chem.*, **20**, 317 (1977)).
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(4) Although not conclusively proven, a similar reaction was believed (R. K. Robins, J. K. Horner, C. V. Greco, C. W. Noell, and C. G. Beames, Jr., *J. Org. Chem.*, **28**, 3041 (1963)) to have occurred when 4,6-dihydroxy-1*H*-imidazo[4,5-*c*]pyridine (3-deazaxanthine) was subjected to basic treatment.
(5) Although no reports of oxirane formation in the reaction of diazomethane with anhydrides could be found in the literature, oxiranes can result from the reaction of diazomethane with the carbonyl functionality of aldehydes and ketones (see C. D. Gutsche, *Org. React.*, **8**, 364 (1954)).
(6) If pH 6 is considerably exceeded, the product desired (i.e., **3**) is not obtained.
(7) Several attempts to note the exact melting point of **14** were unsuccessful because of a black fog accumulation inside the capillary tube near the sample as the temperature approached 200 °C.

Mass Spectral Studies of Unsymmetrical Dialkyl Disulfides. Intramolecular 1,2-, 1,3-, and 1,4-Hydrogen Migration Processes

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The mass spectra of several unsymmetrical dialkyl disulfides have been evaluated in terms of 1,2- and 1,3-hydrogen transfer mechanisms, using deuterium labeling and high-resolution analysis. Unprecedented 1,4-hydrogen shift in disulfides and novel electron impact induced skeletal rearrangements of alkyl and alkenyl hydrodisulfides are reported.

The literature abounds in reports on the chemistry and applications of symmetrical organic disulfides.[1] This family of compounds represents the most generally active class of chemicals for protection against lethal ionizing radiation,[2] and extensive studies about the physiological responses to these compounds have also been made. By contrast, unsymmetrical disulfides have been much less exploited as synthetic intermediates and industrial chemicals,[3,4] in spite of their ubiquitous presence in nature as organoleptic substances and constituents of essential oils, natural pesticides,[5,6a] and insect pheromones.[6b]

Since GC–mass spectrometry has become an expeditious technique for the study of mixtures of natural origin, the elucidation of fragmentation processes of individual components is of crucial importance. Previous investigations[7–13] have revealed two main decomposition pathways of organic disulfides upon electron impact besides simple bond disconnection: skeletal rearrangement and intramolecular hydrogen transfer. The former is evidenced by the appearance of $M^+ - S$, $M^+ - SH$, and $M^+ - 2S$ ions,[9,11] which become particularly noticeable in the mass spectra of dibenzyl, diphenyl,[9] dimethyl, and diallyl disulfides[11] to give alkyl hydrodisulfides[14] which decompose further to yield H_2S_2. That the mechanism involved is a 1,2- and 1,3-hydrogen transfer from vicinal and homovicinal carbons, respectively, has been supported by data put forth recently by Block et al.[13] for deuterium-labeled diethyl disulfide. These investigations, however, have limited their scope to symmetrical disulfides. We have now studied the fragmentation of a series of unsymmetrical disulfides which can provide two sets of hydrogen transfer derived fragment ions. This strategy allows for a more detailed analysis of competing processes taking place in each side of the unsymmetrical system to be put forward.

Results and Discussion

In spite of the considerable number of investigations bearing on the subject,[6a,c,15] a generalized and satisfactory synthetic procedure to obtain some of the hindered disulfides required in the present study is not yet available,[15c] the reason being probably that these methods utilize a sterically sensitive bimolecular attack of a nucleophilic form of sulfur onto a sulfur atom bearing a suitable leaving group.[6c] Forcing conditions lead usually to disproportionation[16,20] and polysulfide formation.[17a,b] The construction of the desired model compounds, however, was conveniently achieved in satisfactory yields and purity by modification[18] of the Bunte salt approach.[17b] In essence this change consisted of the addition of an organic cosolvent to the aqueous alkyl halide–sodium thiosulfate reaction mixture in order to prevent the formation of a two phase system; thus, smoother reaction conditions were required. The results are portrayed in Table I.

Compounds **1–15** were so constructed as to display an increasing α-substitution pattern on the R group in order to correlate its contribution to hydrogen transfer processes with changes on R′, whereas a set of four groups with various degrees of hydrogen availability were chosen for R′.

Examination of the mass spectra of compounds **1–15** (see supplementary material) suggests a consistent fragmentation pattern in which hydrogen transfer and bond breakage are predominant.[19] In Table II are collected the fragments cor-

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