9f, 21372-31-6; **9**, 21372-61-2; **10a**, 21372-32-7; **10b**, 21372-33-8; **10c**, 21372-34-9; **10e**, 21372-35-0; **10f**, 21372-36-1; **15**, 21363-71-3; **16a**, 21372-37-2; **16b**, 21389-72-0; **17** (*cis*), 21372-38-3; **17** (*trans*), 21372-62-3; **18** (*cis*), 21372-39-4; **18** (*trans*), 21372-63-4; **19** (*cis*), 21372-40-7; **19** (*trans*), 21372-64-5.

The Nitro Enol, 3-Hydroxy-4-nitro-5-phenyl-3-pyrrolin-2-one, and Its Reactive Methyl Ether[1]

PHILIP L. SOUTHWICK, JAMES A. FITZGERALD, R. MADHAV, AND DAVID A. WELSH

Department of Chemistry, Carnegie-Mellon University, Pittsburgh, Pennsylvania 15213

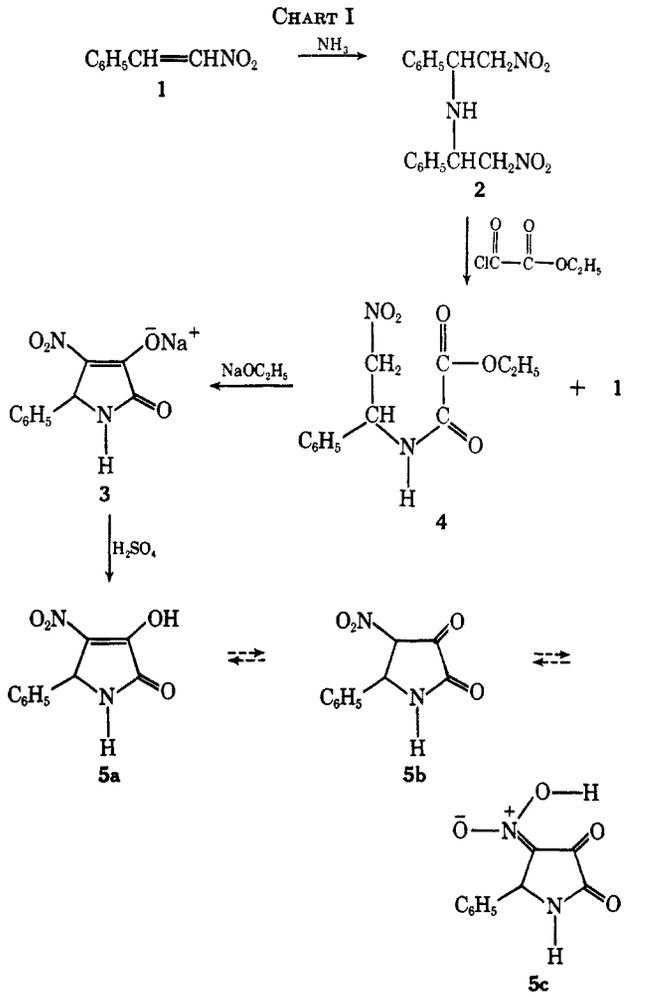
Received April 7, 1969

A completely enolized cyclic α-nitro ketone, 3-hydroxy-4-nitro-5-phenyl-3-pyrrolin-2-one (**5a**), was prepared by means of the base-catalyzed cyclization of ethyl N-(1-phenyl-2-nitroethyl)oxamate (**4**). The nitro enol, a very strong acid, was the only tautomer which could be detected. The enol underwent facile ring cleavage as a result of nucleophilic attack by water or amines at the 3 position. Methylation of the nitro enol with diazomethane yielded the methyl enol ether, 3-methoxy-4-nitro-5-phenyl-3-pyrrolin-2-one (**8**). The product was shown to be the enol ether rather than the isomeric keto nitronic ester by sodium borohydride reduction to 3-methoxy-4-nitro-5-phenylpyrrolidin-2-one (**10**) followed by stannous chloride reduction to 4-amino-3-methoxy-5-phenylpyrrolidin-2-one (**13**). The nitro enol ether (**8**) reacted rapidly with ammonia and with primary or secondary amines to yield 3-amino-4-nitro-5-phenyl-3-pyrrolin-2-ones (**9**, **11**, or **12**).

As has been shown in previous work,[2] 2,3-dioxopyrrolidines having a substituent in the 4 position are acidic, fully enolized compounds, and those having an electron-withdrawing carbethoxy or carbomethoxy group at the 4 position are similar in acid strength to carboxylic acids. It became of interest, therefore, to prepare and examine the properties of a 4-nitro-2,3-dioxopyrrolidine, wherein the strong electron-withdrawing effect of the nitro group might be expected to produce a still greater increase in the acidity of the enolic tautomer. Other α-nitro ketones give rise to rather acidic tautomers,[3] but all previously studied compounds of this type appear to have existed at least in part in the keto form, whereas it could be anticipated that 4-nitro-2,3-dioxopyrrolidines would be entirely enolic, *i.e.*, that they would in fact exist entirely as 4-nitro-3-hydroxy-3-pyrrolin-2-ones, and provide an opportunity to examine the chemistry of compounds having a vinylogous relationship to nitric acid. It was also felt that the chemistry of such derivatives of these nitro compounds as O-alkylation products (vinylogs of alkyl nitrates) would be of interest, and that these compounds might serve as useful intermediates in the synthesis of other pyrrolidines.

The synthesis of 4-nitro-5-phenyl-2,3-dioxopyrrolidine (**5**) was achieved by use of the sequence of reactions shown in Chart I. Addition of ammonia to β-nitrostyrene (**1**) in dry benzene yielded a bis adduct (**2**) incorporating two molecules of β-nitrostyrene and one of ammonia.[4] (No useful procedure was found for ob-

CHART I



(1) Supported by a research grant (GM-04371) from the National Institutes of Health, U. S. Public Health Service. This paper is based principally on theses submitted by J. A. Fitzgerald (1966) and D. A. Welsh (1968) for the degree of Doctor of Philosophy at Carnegie-Mellon University.

(2) (a) P. L. Southwick, E. P. Previc, J. Casanova, Jr., and E. Herbert Carlson, *J. Org. Chem.*, **21**, 1087 (1956); (b) W. L. Meyer and W. R. Vaughan, *ibid.*, **22**, 98, 1554, 1560 (1957); (c) W. R. Vaughan and I. S. Covey, *J. Amer. Chem. Soc.*, **80**, 2197 (1958); (d) P. L. Southwick and E. F. Barnas, *J. Org. Chem.*, **27**, 98 (1962); (e) P. L. Southwick and J. A. Vida, *ibid.*, **27**, 3075 (1962).

(3) See, for example, (a) R. E. Schaub, W. Fulmor, and M. J. Weiss, *Tetrahedron*, **20**, 373 (1964); (b) H. Feuer and P. M. Pivawer, *J. Org. Chem.*, **31**, 3152 (1966); (c) T. Simmons, R. F. Love, and K. L. Freuz, *ibid.*, **31**, 2400 (1966); (d) A. A. Griswald and P. S. Starcher, *ibid.*, **30**, 1687 (1965); (e) K. H. Meyer and P. Wertheimer, *Ber.*, **47**, 2374 (1914); (f) G. Vanags and J. Bungs, *ibid.*, **75B**, 987 (1942); (g) O. Neilands, J. Stradins, and G. Vanags, *Dokl. Akad. Nauk. SSSR*, **131**, 1084 (1960); *Chem. Abstr.*, **54**, 20911 (1960). In ref 3f and 3g and references cited therein, Vanags and his associates have described spectroscopic and chemical evidence of tautomerism in a number of 2-nitro-1,3 diketones. Some of these 1,3-diketone derivatives are probably completely enolic under appropriate conditions. 2-Nitrodimedone, for example, was regarded as highly enolized in the solid state, but in aqueous solution showed only relatively weak acidity (comparable with formic acid). 2-Nitro-1,3-indandione was found to be a very strong acid, but was considered to exist either as the nitro diketone or the nitronic acid tautomer, not as the nitro enol.

(4) This compound was first described by D. E. Worrall, *J. Amer. Chem. Soc.*, **49**, 1598 (1927). Difficulty was experienced with Worrall's preparative procedure, however, particularly in purification of the product.

taining a mole for mole adduct.) Treatment of the adduct **2** with ethoxalyl chloride resulted in acylation accompanied by an elimination reaction which produced β-nitrostyrene (**1**) and ethyl N-(2-nitro-1-phenylethyl)oxamate (**4**).

Although base-catalyzed α acylation of a nitroparaffin by an ester is apparently unprecedented,[5] treatment of compound **4** with sodium ethoxide in ethanol produced a cyclized sodium salt (**3**) in yields as high as 82%. Since the corresponding acid is considered to be a nitro enol (**5a**), the sodium salt (**3**) will be referred to hereafter as the "sodium enolate." This enolate was a crystalline substance which could be purified by recrystallization from absolute ethanol. When treated with hydrochloric acid in aqueous solution it afforded only poor yields of the free enol **5a** because of the exceptional acidity and appreciable water solubility of the latter compound, and because of its susceptibility to hydrolytic ring opening, which will be discussed below. However, treatment of the sodium enolate with 95% sulfuric acid in an absolute ethanol suspension did afford good yields (80%) of the free enol, 3-hydroxy-4-nitro-5-phenyl-3-pyrrolin-2-one (**5a**).

Compound **5a** displayed an infrared spectrum entirely consistent with an enolic structure. A very broad absorption at 3.5–4.0 μ resembling the hydrogen-bonded hydroxyl band of carboxylic acids could be attributed to the enolic hydroxyl. The ketonic carbonyl at 5.65 μ which is characteristic of unenolized 2,3-dioxopyrrolidines[2] was absent. Strong absorption at 5.82 and 6.01 μ could be assigned to the lactam carbonyl and the olefinic bond of the enolic structure, respectively. A strong band at 6.75 μ which evidently arose from the nitro group occurred at a considerably longer wavelength than that characteristic of the asymmetric stretching of the nitro group of simple nitroparaffins (6.39–6.47 μ) or of previously examined enols of nitro ketones (absorption at *ca.* 6.60 μ).[3] It is noteworthy that the infrared spectrum of the sodium enolate **3** was quite similar to that of the enol **5a**, with strong absorption from the nitro group at 6.75 μ.

The nuclear magnetic resonance (nmr) spectrum of the compound in dimethyl sulfoxide-d_6 could not be reconciled with the ketonic tautomer **5b**, but was consistent with either the enolic tautomer **5a** or the *aci*-nitro tautomer **5c**. Aside from the unsplit signal from the five protons of the benzene ring at τ 2.63 and a broad signal (acidic hydroxyl) with a chemical shift which varied with concentration and with the water or deuterium oxide content of the solution, only a one-proton doublet at τ 4.45 (J = 1.0 Hz) and a broad one-proton signal at τ 0.4 were evident. The doublet arose from the proton at position 5 and the broad signal at τ 0.4 from the lactam N–H proton at position 1; a similar doublet was seen in the spectrum of the derived 3-methoxy-4-nitro-5-phenyl-3-pyrrolin-3-one (**8**), and by means of deuterium exchange it was possible to remove the broad signal and collapse the doublet to a singlet in the case of the more soluble derivative **8** in which exchange with deuterium oxide was easily carried out using deuteriochloroform solutions. It was concluded that the compound did not correspond to the ketonic structure **5b**, since the nmr spectrum showed no evidence of a proton at position 4. The nmr spectrum in a deuteriochloroform–trifluoroacetic acid solution also failed to show any ketonic tautomer.

As had been anticipated, the nitro derivative **5a** was strongly acidic. Efforts to evaluate this acidity quantitatively were not completely successful, principally because of the susceptibility of the compound to hydrolytic cleavage when dissolved in water. It did not dissolve rapidly in cold water, and when aqueous solutions were obtained by heating or long periods of stirring much of the compound could be shown to have undergone cleavage to the oxamic acid derivative **6** while the solutions were being prepared. Extraction of these solutions with chloroform and concentration of the chloroform extracts yielded samples of compound **6**, identical with the product obtained by saponification of the ester **4**. Hydrolytic cleavage in this manner is a commonly observed reaction of α-nitro ketones,[3b,6] and unfortunately the absence of detectable amounts of a ketonic tautomer (**5b**) in equilibrium with the enol **5a** did not ensure the stability of the structure in water.

Compound **5a** was not readily subject to cleavage by reaction with methanol or ethanol, and potentiometric titration of the compound was attempted with sodium hydroxide in methanol. However, shortly after the titration was started precipitation of the sodium salt **3** began in the titration mixture, thereby preventing the determination of a good pK_a value even in methanol. The estimated pK_a in methanol, based upon three points of a titration determined before precipitation began, was 2.7. Considerably weaker acidity was evident in titrations in methanol of analogous enols of 2,3-dioxopyrrolidines having a carbethoxy group or a cyano group in place of the nitro group at the 4-position. For the enol of 4-cyano-1-cyclohexyl-2,3-dioxopyrrolidine the apparent pK_a value in methanol was 5.35; for the enol of 4-carbethoxy-1-cyclohexyl-2,3-dioxopyrrolidine it was 6.89. The expectation that all of these pK_a values would be markedly lower in aqueous solution[7] is born out by comparison of the 6.89 pK_a value of the latter 4-carbethoxy derivative in methanol with the value of 4.25 obtained previously[2] in 33% aqueous ethanol for the closely similar enol of 4-carbethoxy-1-benzyl-2,3-dioxopyrrolidine. It seems clear, therefore, that **5a** is a very strongly acidic substance which would display a pK_a considerably lower than 2.7 in aqueous solutions.

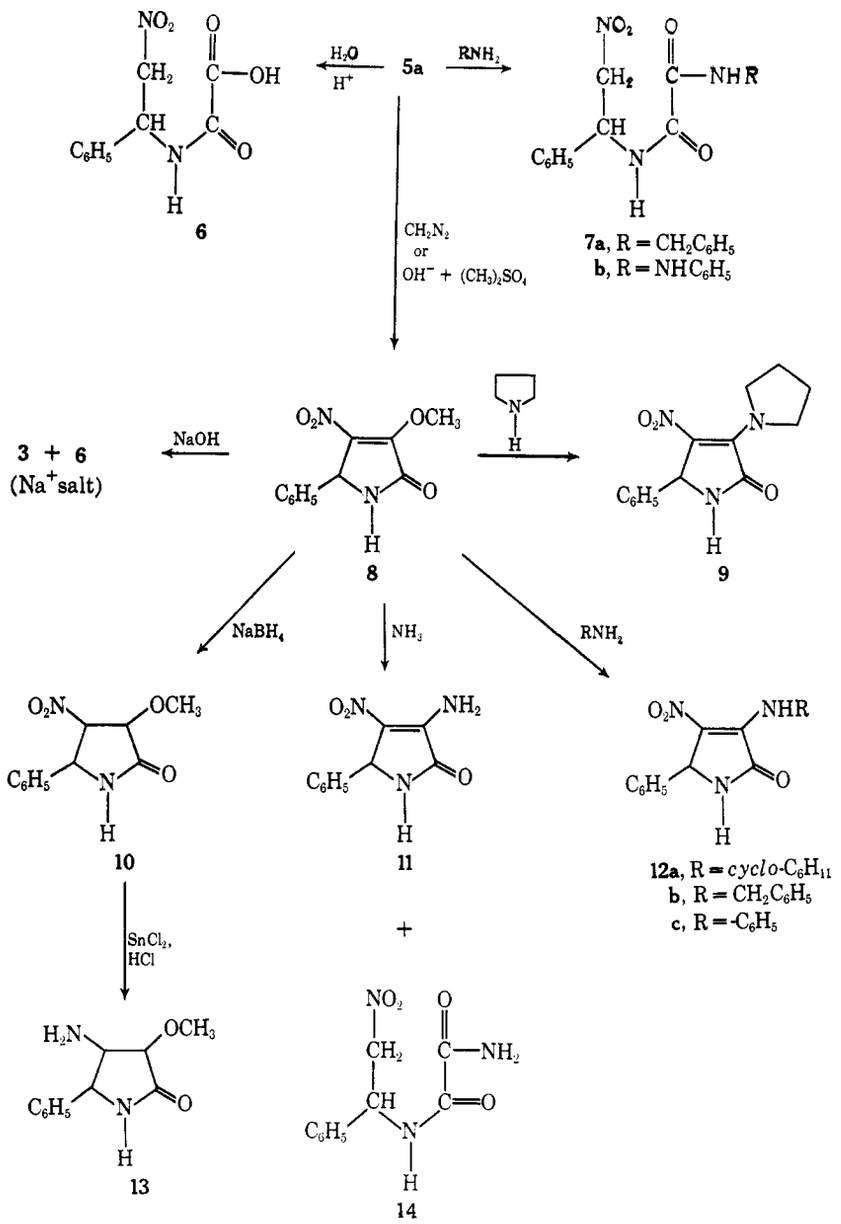
Other observations pointing to the strong acidity of **5a** included the nearly exact correspondence of the ultraviolet spectrum of **5a** with that of the sodium enolate (**3**) when both spectra were measured in 95% ethanol; in dilute solution (*ca.* 10^{-4} M) in ethanol **5a** must closely approach complete ionization. [The spectrum of compound **8**, the methyl ether of enol **5a**, which might be expected to approximate that of un-ionized **5a** differed from the spectra of **5a** and **3** in having its principal maximum at 257 mμ (ε 7,100) and in lacking strong absorption at 358 mμ, where **3** and **5a** display their principal maxima (ε 11,200)].

(5) Acylation of nitroparaffins by use of acyl cyanides has been employed successfully in the past. See G. B. Bachman and T. Hokama, *J. Org. Chem.*, **25**, 178 (1960).

(6) (a) F. Straus and W. Ekhard, *Justus Liebigs Ann. Chem.*, **444**, 146 (1925); (b) R. G. Pearson, D. H. Anderson, and L. L. Alt, *J. Amer. Chem. Soc.*, **77**, 527 (1955); (c) H. Feuer and R. S. Anderson, *ibid.*, **83**, 2960 (1961); (d) A. S. Matlack and D. S. Breslow, *J. Org. Chem.*, **32**, 1995 (1967).

(7) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, Inc., New York, N. Y., 1959, pp 107–110.

CHART II



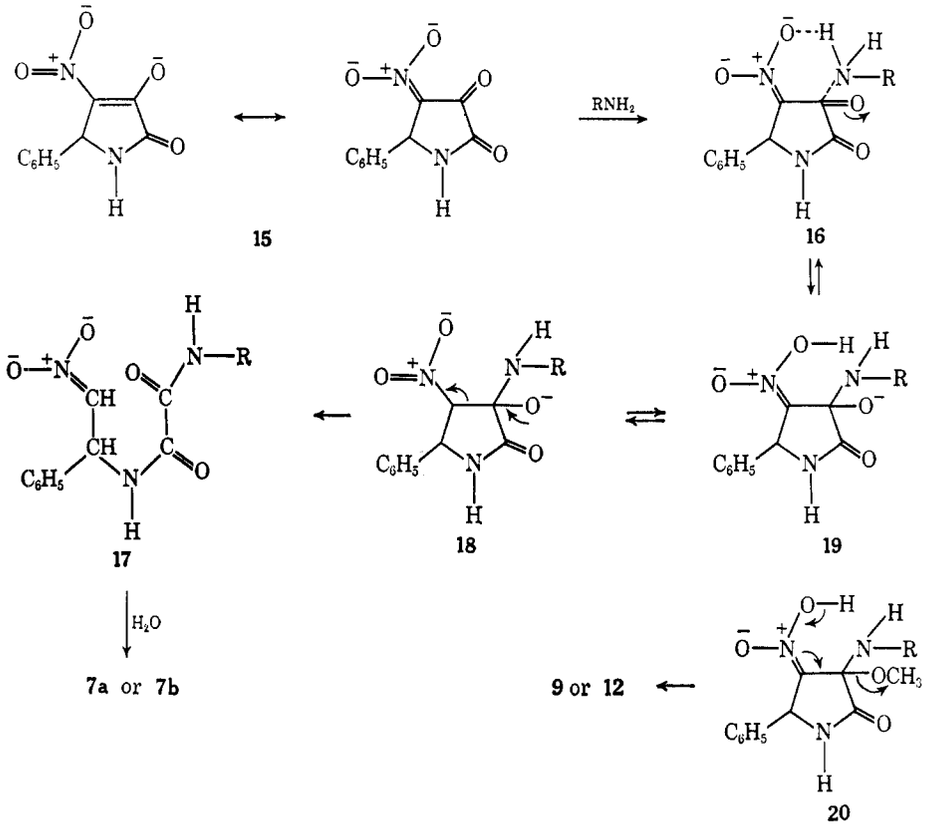
As is true of the hydroxylic acidic tautomers of other α-nitro ketones, two alternative structures must be considered, and are represented in this case by formula **5a**, the nitro enol, and **5c**, the keto nitronic acid. A possible means for securing evidence leading to a choice between these structures lay in methylation of the compound in question with diazomethane. According to Arndt and Rose, diazomethane converted the hydroxylic form of ω-nitro-*p*-bromoacetophenone mainly into a crystalline nitronic ester.[8] A second poorly characterized oily product was formed, and was presumed by these authors to be an enol ether. The nitronic ester structure was assigned to the major product on the basis of its vigorous thermal decomposition into formaldehyde and the aldoxime of *p*-bromophenylglyoxal. However, the major product (79% yield) which we obtained from the action of diazomethane on the compound believed to have structure **5a** was a crystalline substance, mp 164°, which was conclusively demonstrated to be the enol ether **8** on the basis of evidence to be recounted below.

Since the methyl derivative obtained with diazomethane could be reduced with sodium borohydride to the stable methoxynitropyrrolidinone **10** and the latter compound could in turn be reduced with stannous chloride to the stable methoxyaminopyrrolidinone **13** (Chart II) with retention of the methoxyl group in both reductions, a nitronic ester structure for the methyl derivative could be eliminated as a possibility. Infrared and nmr spectra were entirely consistent with structures **10** and **13** for the methoxynitropyrrolidinone and the methoxyaminopyrrolidinone, respectively. In compound **10** the nitro group displayed the infrared band at 6.46 μ expected for a nitroalkane. The nmr spectra of both compounds revealed the presence of the expected three coupled protons on the carbon atoms of ring positions 3, 4, and 5.

The methoxynitropyrrolidinone **10** was characterized in only one configuration; if other diastereomers were

(8) (a) F. Arndt and J. D. Rose, *J. Chem. Soc.*, 1 (1935). (b) For a recent account of the preparation and properties of nitronic esters see N. Kornblum and R. A. Brown, *J. Amer. Chem. Soc.*, **86**, 2681 (1964).

CHART III



formed in the sodium borohydride reduction of **8** it was only to a minor extent. Since stannous chloride in acid solution is known to reduce nitroalkanes with retention of configuration at the α carbon[9] the configuration of the methoxyaminopyrrolidinone **13** is assumed to be the same as that of **10**. In the case of **13** the chemical shifts for the protons at positions 3, 4, and 5 were sufficiently different to separate the two doublets arising from the protons at positions 3 and 5 as well as the doublet of doublets arising from the proton at position 4. The coupling constants were 8.0 and 8.5 Hz for the pairs of vicinal protons. Unfortunately, these values do not reveal the configuration of the structure, since coupling constants of *ca.* 8 Hz would be consistent with either a *cis* or *trans* relationship of vicinal protons on a five-membered ring.[10] The stereoselectivity evident in the sodium borohydride reduction of **8** would probably be a consequence of a preferential initial attack by borohydride ion on carbon 3 from the side of the ring opposite the phenyl group. It is likely, therefore, that the phenyl at position 5 is *cis* to the methoxyl at position 3 in both **10** and **13**, but concerning the configuration at position 4, presumably set by subsequent protonation on carbon of an intermediate nitronic acid or nitronate ion, there is little basis for surmise.

The fact that methylation of our acidic compound yielded the enol ether **8** rather than a nitronic ester did not in itself establish that this compound had the nitro enol structure **5a** rather than the keto nitronic acid structure **5c**. However, comparison of infrared data for the acidic compound and the enol ether **8** revealed such a close correspondence in the wavelengths and intensities of the principal bands[11] as to leave very little doubt that **5a**, the structure analogous to the enol ether **8**, represents the correct choice.

Reactions of the Nitro Enol (5a) and the Nitro Enol Ether (8) with Nucleophilic Reagents.—The hydrolytic cleavage of compound **5a** already mentioned is illustrative of the ease of attack on this type of structure by nucleophilic reagents. Benzylamine or phenylhydrazine in ethanol solution cleave compound **5a** at room temperature to yield the benzylamide **7a** and the phenylhydrazide **7b**, respectively. Since **5a** is such a strong acid, it seems probable that attack by these uncharged bases is occurring on the anion **15** and that amine adducts such as **18** and **19** intervene in the cleavage process. (Formula **16** represents a conception of one possible transition state for the initial attack of the amine.) It was postulated that if, as suggested by formulas **18** and **19**, the ring cleavage requires an intermediate with a negatively charged oxygen at ring position 3, then nucleophilic attack by amines on the methyl ether **8** should follow a different course not leading to ring cleavage. Such proved to be the case; compound **8** reacted readily at room temperature in ethanol solution with primary or secondary amines (cyclohexylamine, benzylamine, aniline, pyrrolidine) to produce 3-amino-4-nitro-3-pyrrolin-2-ones (**9** or **12**) in good yield, without the formation of significant amounts of cleavage products. The intermediates analogous to

(9) P. L. Southwick and J. E. Anderson, *J. Amer. Chem. Soc.*, **79**, 6222 (1957). Other observations recorded in doctoral theses by J. R. Stemniski (1959) and G. E. Milliman (1964), Carnegie Institute of Technology, confirm preservation of the configuration at the α carbon in stannous chloride reductions of nitro compounds under acid conditions.

(10) See, for example, W. O. Emrich, doctoral thesis, Carnegie–Mellon University, 1967, p 65. In the case of some related 2-pyrrolidinone derivatives, Emrich found values of *ca.* 7.0 and 8.0 Hz, respectively, for vicinal coupling constants of *cis* and *trans* protons at the 3 and 4 positions.

(11) Apparent correspondence of ten bands was seen, including the very significant enol olefinic absorption (6.01 for **5a**, 6.09 μ for **8**), nitro absorption (6.75 for **5a**, 6.69 μ for **8**), and lactam absorption (5.82 for **5a**, 5.81 μ for **8**).

18 or **19** in these reactions would have structures such as **20**, and the reactions could be completed by elimination of methanol or methoxide ion to form **9** or **12**. See Chart III.

That the products of these amine reactions were pyrroline derivatives was indicated by the results of elemental analysis and by nmr and infrared data. These compounds displayed only the expected two nmr signals for protons on the pyrroline ring, a somewhat broadened one-proton singlet located within the range τ 4.53–4.76 from the single hydrogen at position 5 and a broad one-proton singlet located in the range τ 2.00–3.15 from the lactam hydrogen at position 1. The infrared spectra of all of these compounds were very similar, with a lactam carbonyl band at 5.82–5.87, an olefinic band at 6.04–6.20, and a band from the conjugated nitro group at 6.72–6.79 μ.

The reaction of ammonia with the enol ether **8** differed from the reactions of amines in that in ethanol solution the type of ring-cleavage reaction occurred which was seen in the reaction of amines with the enol **5a**; the principal product formed was the open-chain amide **14**. On the other hand, when the reaction of ammonia with **8** was conducted in dry benzene, the aminopyrroline **11** was formed in 72% yield. The results in ethanol probably must be attributed to the presence of water, although absolute ethanol (commerical grade) was used with commercial anhydrous ammonia. The aminopyrroline derivative **11**, once formed, is not readily subject to hydrolytic ring cleavage, and it seems evident, therefore, that cleavage occurs as a result of the action of water on either compound **8** or on an intermediate produced in its reaction with ammonia. The enol ether **8** was found to undergo hydrolysis with aqueous sodium hydroxide to the sodium enolate **3** and the hydrolytic cleavage product **6** of the latter compound. It therefore seems possible that the formation of the amide **14** from **8** in the presence of water proceeds *via* an ammonium salt analogous to the sodium enolate **3**, the initial attack upon compound **8** having been made by hydroxide ion rather than by ammonia, with a succeeding attack by ammonia on the enolate.

Both the nitro enol **5a** and the enol ether **8** promise to hold further interest because of their high reactivity toward nucleophiles and their utility in the synthesis of new pyrrolidine derivatives.

Experimental Section[12]

Preparation of Bis(2-nitro-1-phenylethyl)amine (2).—The procedure was a modification of that of Worrall.[4] Anhydrous ammonia gas was bubbled for 2.5 hr at approximately 25° into a solution of 200 g (1.34 mol) of β-nitrostyrene (**1**) in 500 ml of benzene (sodium dried). The solution was filtered to remove polymeric material, and the solution was concentrated under reduced pressure on a rotary evaporator over a steam cone until approximately 25% of the original volume remained. The evaporation was then continued at room temperature until the oily residue solidified. The solid was recrystallized twice from carbon tetrachloride to give 141 g (67%) of the product **2** as fine white needles: mp 125–126° (lit.[4] mp 122–123°); ir 2.96 (N–H), 6.50 μ (asymmetric NO_2); nmr ($CDCl_3$) τ 2.76 (m, 10, aromatic H), 5.67 (m, 6, CH_2NO_2 and CHNH), 7.37 (s, 1, NH).

Preparation of N-Ethoxalyl-2-nitro-1-phenylethylamine (4).—A solution of 100 g (0.317 mol) of compound **2** and 48 g (0.350 mol) of ethoxalyl chloride in 200 ml benzene (dried over sodium) was refluxed for 4 hr. The solvent was evaporated on a rotary evaporator over a steam cone. The residual oil was allowed to cool and solidify. Ether was added to the yellow solid and the suspension was filtered. The solid was washed well with ether, leaving a white solid on the filter and giving a yellow filtrate. The solid was recrystallized twice from 95% ethanol to give 84.5 g (79%) of **4** as fine white needles: mp 129–130°; ir 2.98 (N–H), 5.73 (ester C=O), 5.91 (oxamide C=O), 6.44 μ (asymmetric NO_2); nmr ($CDCl_3$) τ 1.58 (s, 1, N–H), 2.28 (s, 5, C_6H_5), 3.97 (m, 1, CHNH), 4.84 (m, 2, CH_2NO_2), 5.45 (quartet, 2, J = 7.5 Hz, OCH_2CH_3), 8.58 (t, 3, J = 7.5 Hz, OCH_2CH_3).

Anal. Calcd for $C_{12}H_{14}N_2O_5$: C, 54.13; H, 5.30; N, 10.52. Found: C, 54.31; H, 5.45; N, 10.25.

When the yellow filtrate and ether washings from above were combined and the ether evaporated, a red oil remained which solidified (mp 51–53°) when seeded with a crystal of β-nitrostyrene, and showed the infrared spectrum of β-nitrostyrene.

Preparation of 3-Hydroxy-4-nitro-5-phenyl-3-pyrrolin-2-one (5a).—A solution of 5.6 g (0.244 g-atom) of sodium in 300 ml absolute ethanol was added to a suspension of 40 g (0.182 mol) of compound **4** in 600 ml of absolute ethanol. The resulting solution was stirred at room temperature for 4 hr. After about 1.5 hr, a yellow solid began to precipitate and continued to precipitate throughout the reaction period. The suspension was cooled to 5° in the refrigerator overnight, and filtered. The collected solid was dried and was then suspended in 250 ml of absolute ethanol and concentrated sulfuric acid was added dropwise until the suspension was strongly acid. The suspension was heated to boiling and filtered to remove sodium sulfate. The filtrate was cooled overnight in the refrigerator and filtered. The white solid obtained by filtration was recrystallized twice from absolute ethanol giving 26.0 g (78%) of fine white crystals of **5a**: mp 210° dec; ir 2.90 (oxamide N–H), 3.31 (OH), 5.82 (lactam C=O), 6.01 (C=C), 6.74 μ (conjugated NO_2); nmr (DMSO-d_6) τ 0.4 (s, 1, N–H), 2.63 (s, 5, C_6H_5), 4.45 (d, 1, J = 1.0 Hz, C-5 H); uv (95% EtOH) 358 mμ (ϵ 11,200).

Anal. Calcd for $C_{10}H_8N_2O_4$: C, 54.55; H, 3.66; N, 12.72. Found: C, 54.44; H, 3.72; N, 12.53.

The compound gives a positive ferric chloride test (red-brown), and dissolves in aqueous sodium bicarbonate solutions with the evolution of carbon dioxide.

Hydroxylic Cleavage of 3-Hydroxy-4-nitro-5-phenyl-3-pyrrolin-2-one (5a) into N-(2-Nitro-1-phenylethyl)oxamic Acid (6).—A suspension of 0.500 g (2.27 mmol) of compound **5a** in 5 ml of distilled water was heated to boiling to dissolve the solid. The solution was cooled to 0°. A clear colorless oil separated from the solution. The mixture was extracted with chloroform, the extract dried ($MgSO_4$) and the solvent evaporated to dryness, leaving a white solid residue. A fine white crystalline solid precipitated from the aqueous layer after it was allowed to stand at room temperature overnight. The two solid products, which were identical, amounted to a total of 0.510 g (94%) of **6**: mp 126–127°; ir 2.94 (NH), 5.64 (acid C=O), 5.90 (oxamide C=O), 6.44 μ (asymmetric NO_2); nmr (acetone) τ 0.85 (s, 2, NH and OH), 2.46 (m, 5, C_6H_5), 4.00 (m, 1, CHNH), 4.75 (m, 2, CH_2NO_2).

Anal. Calcd for $C_{10}H_{10}N_2O_5$: C, 50.42; H, 4.23; N, 11.76. Found: C, 50.45; H, 4.36; N, 11.51.

A solution of 5 g (0.019 mol) of compound **4** and 2.3 g (0.1 mol) of sodium hydroxide in 50 ml distilled water was allowed to stand at room temperature overnight. The solution was acidified with 20% hydrochloric acid and extracted with chloroform. The extract was dried ($MgSO_4$), filtered, and evaporated to give 3.5 g (78%) of **6** with melting point and spectral characteristics identical with those of the compound described above.

Cleavage of Compound 5a with Phenylhydrazine. Formation of N-Anilino-N'-(2-nitro-1-phenylethyl)oxamide (7b).—To a solution of 0.500 g (2.27 mmol) of compound **5a** in 10 ml of hot absolute ethanol was added 0.40 g (3.7 mmol) of phenylhydrazine. A yellow precipitate formed immediately. After allowing the suspension to cool to room temperature, it was filtered and the solid dried on the filter. Cooling the filtrate to −10° in the freezer caused precipitation of more yellow solid which was filtered, dried, and added to the first crop. The combined solid was recrystallized from absolute methanol to give 0.622 g (84%) of **7b** as yellow needles: mp 149.5–150.5° dec; ir 2.90 (oxamide

(12) All melting points are corrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn., and M. H. W. Laboratories, Garden City, Mich. All infrared spectra were obtained from potassium bromide pellets on Perkin-Elmer Infracord and Model 21 spectrophotometers. All nmr spectra were determined on a Varian A-60 spectrometer in deuteriochloroform with tetramethylsilane as an internal standard unless otherwise specified. Ultraviolet spectra were determined on a Cary Model 11 spectrophotometer.

NH), 3.03 (hydrazide NH), 5.89 (oxamide C=O), 6.00 (hydrazide C=O), 6.43 μ (asymmetric NO_2).

Anal. Calcd for $C_{16}H_{16}N_4O_4$: C, 58.53; H, 4.91; N, 17.07. Found: C, 58.19; H, 4.93; N, 16.88.

Cleavage of Compound 5a with Benzylamine. Formation of N-Benzyl-N'-(2-nitro-1-phenylethyl)oxamide (7a).—A solution of 0.500 g (2.27 mmol) of compound **5a** in 10 ml of benzylamine was stirred at room temperature for 24 hr. Petroleum ether (bp 60–110°) was added to the solution to precipitate the product, which was filtered from the mixture, air dried, and recrystallized twice from absolute ethanol to yield 0.510 g (66%) of **7a**: mp 174–175°; ir 2.96 (oxamide NH), 5.90 and 6.01 (oxamide C=O), 6.43 μ (asymmetric NO_2); nmr ($CDCl_3$) τ 2.17 and 2.24 (each s, 5, C_6H_5), 4.25 (m, 1, CHNH), 5.21 (m, 2, CH_2NO_2), 5.54 (m, 2, $CH_2C_6H_5$).

Anal. Calcd for $C_{17}H_{17}N_3O_4$: C, 62.37; H, 5.24; N, 12.84. Found: C, 62.25; H, 5.26; N, 12.63.

The same cleavage occurred at room temperature in ethanol. A solution of 0.25 g (1.14 mmol) of compound **5a** and 0.24 g (2.27 mmol) of benzylamine in 5 ml absolute ethanol was stirred at room temperature overnight. The solution was then cooled to −10° in the freezer. A white solid precipitated. This was filtered, air dried, and recrystallized once from 95% ethanol to give 0.18 g (46%) of **7a** with properties identical with those recorded above.

Preparation of 3-Methoxy-4-nitro-5-phenyl-3-pyrrolin-2-one (8).—A solution of diazomethane in 200 ml of methylene chloride was prepared from 7.0 g of N-methylnitrosourea according to the procedure of Arndt.[13] This solution was added dropwise to a stirred suspension of 7.0 g (0.023 mol) of compound **5a** in 600 ml of methylene chloride until evolution of nitrogen was no longer evident. A small quantity (0.65 g) of undissolved starting material was recovered by filtration. The excess diazomethane was destroyed by dropwise addition of glacial acetic acid. The solution was washed with saturated sodium bicarbonate solution, dried ($MgSO_4$), and concentrated to a small volume under reduced pressure at room temperature. The yellow solid residue was recrystallized from absolute ethanol to give 5.9 g (79% conversion, 87% yield) of **8** as pale yellow needles: mp 162–164° dec (melting point quite sharp if heating began at 155°); ir 2.85 (lactam NH), 5.81 (lactam C=O), 6.09 (C=C), 6.69 μ (conjugated NO_2); nmr τ 2.65 (s, 5, C_6H_5), 2.81 (s, 1, NH), 4.49 (d, 1, J = 1.5 Hz, C-5 H), 5.56 (s, 3, OCH_3);[14] uv (95% EtOH) 257 mμ (ϵ 7100).

Anal. Calcd for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.12; H, 4.30; N, 11.92.

Preparation of 3-Benzylamino-4-nitro-5-phenyl-3-pyrrolin-2-one (12b).—A solution of 0.25 g (1.07 mmol) of compound **8** in 25 ml benzylamine was stirred at room temperature for 2.5 hr. Petroleum ether (bp 60–110°) was added to precipitate the product **12b**. Recrystallization from ethanol afforded 0.291 g (88%) of **12b** as pale yellow needles: mp 174.5–175.5°; ir 3.00 (lactam NH), 3.10 (enamine NH), 5.82 (lactam C=O), 6.04 (C=C), 6.72 μ (conjugated NO_2); nmr (CS_2 and acetone) τ 2.00 (s, 1, lactam NH), 2.67 and 2.75 (each s, 5, C_6H_5), 4.65 (s, 2, $CH_2C_6H_5$), 4.76 (s, 1, C-5 H), 7.41 (s, 1, $NHCH_2C_6H_5$).

Anal. Calcd for $C_{17}H_{15}N_3O_3$: C, 66.01; H, 4.89; N, 13.59. Found: C, 66.24; H, 4.78; N, 13.72.

Preparation of 3-Anilino-4-nitro-5-phenyl-3-pyrrolin-2-one (12c).—A solution of 0.46 g (2 mmol) of compound **8**, 20 ml of absolute ethanol, and 0.36 g (3.9 mmol) of aniline was stirred at room temperature for 4.5 hr. After 0.5 hr a solid began to precipitate. The suspension was cooled to −10° in the freezer and filtered. The yellow solid was recrystallized once from absolute ethanol giving 0.365 g (62%) of **12c** as deep yellow needles: mp 178–179°; ir 2.90 (lactam NH), 3.00 (anilino NH), 5.86 (C=O), 6.13 (C=C), 6.29 (aromatic C=C), 6.79 μ (conjugated NO_2); nmr ($CDCl_3$) τ 0.30 (s, 1, NHC_6H_5), 2.60–2.73 (m, 10, C_6H_5), 3.15 (s, 1, lactam NH), 4.53 (s, 1, C-5 H); uv max (95% EtOH) 234 mμ (ϵ 9300), 385 mμ (ϵ 9300).

Anal. Calcd for $C_{16}H_{13}N_3O_3$: C, 65.08; H, 4.44; N, 14.23. Found: C, 64.87; H, 4.45; N, 14.47.

Preparation of 3-Cyclohexylamino-4-nitro-5-phenyl-3-pyrrolin-2-one (12a).—The procedure followed was identical with that used to prepare compound **12c**. The amounts used were 0.46 g (2.0 mmol) of compound **8**, 20 ml of absolute ethanol, and 0.40 g (4.0 mmol) of cyclohexylamine. The amount of purified **12a** obtained was 0.437 g (72%) as pale yellow needles: mp 171–172°; ir 2.91 (lactam NH), 3.10 (cyclohexylamino NH), 5.87 (C=O), 6.12 (C=C), 6.79 μ (conjugated NO_2); nmr τ 1.55 (s, 1, NHC_6H_{11}), 2.67 (s, 5, C_6H_5), 3.00 (s, 1, lactam NH), 4.60 (s, 1, C-5 H), 5.15 (m, 1, NH–CH), 7.90–8.88 (m, 10, cyclohexyl); uv max (95% EtOH) 372 mμ (ϵ 16,200).

Anal. Calcd for $C_{16}H_{19}N_3O_3$: C, 63.77; H, 6.36; N, 13.95. Found: C, 63.65; H, 6.59; N, 13.76.

Reaction of Compound 8 with Ammonia in Ethanol. Preparation of N-(2-Nitro-1-phenylethyl)oxamide (14).—Ammonia gas was bubbled into a solution of 0.46 (2.0 mmol) of compound **8** in 35 ml of absolute ethanol for 10 min. The solution was cooled to −10° in the freezer, causing the precipitation of a white crystalline solid which was filtered from the suspension, and recrystallized from absolute ethanol to give 0.371 g (78%) of **14** as white needles: mp 203.5–204°; ir 2.81 and 2.92 (oxamide NH), 6.01 (C=O), 6.29 (aromatic C=C), 6.53 μ (asymmetric NO_2); nmr (trifluoroacetic acid) τ 0.75, 1.88, and 2.50 (each s, 1, NH), 2.52 (s, 5, C_6H_5), 4.09 (m, 1, CHNH), 4.98 (m, 2, CH_2NO_2).

Anal. Calcd for $C_{10}H_{11}N_3O_4$: C, 50.63; H, 4.67; N, 17.72. Found: C, 50.69; H, 4.68; N, 17.79.

Reaction of Compound 8 with Ammonia in Benzene. Preparation of 3-Amino-4-nitro-5-phenyl-3-pyrrolin-2-one (11).—Anhydrous ammonia gas was bubbled into a solution of 2.0 g (8.5 mmol) of compound **8** in 80 ml of benzene (dried over sodium) for 20 min. A light brown solid precipitated from the solution throughout the reaction period. This solid was filtered from the suspension, and recrystallized twice from absolute ethanol to give 1.83 g (97%) of **11** as light tan cubes: mp 218–219°; ir 3.00 (NH), 5.80 (lactam C=O), 6.01 (C=C), 6.75 μ (conjugated NO_2); nmr (trifluoroacetic acid) τ 1.84 (s, 1, lactam NH), 2.68 (s, 5, C_6H_5), 4.39 (s, 1, C-5 H).

Anal. Calcd for $C_{10}H_9N_3O_3$: C, 54.79; H, 4.14; N, 19.17. Found: C, 55.05; H, 4.12; N, 19.20.

Preparation of 3-Pyrrolidino-4-nitro-5-phenyl-3-pyrrolin-2-one (9).—A solution of 1.00 g (4.3 mmol) of compound **8** and 2.0 g (0.028 mol) of pyrrolidine in 30 ml of benzene (dried over sodium) was stirred at room temperature for 24 hr. The solvent was evaporated in an air stream until an orange solid precipitated. The suspension was cooled to 5° in the refrigerator and filtered. The orange solid was recrystallized twice from absolute methanol to give 0.86 g (73%) of bright yellow needles: mp 136–137° dec; ir 3.08 (lactam NH), 5.86 (C=O), 6.20 (C=C), 6.75 μ (conjugated NO_2); nmr ($CDCl_3$) τ 2.72 (s, 6, C_6H_5 and NH), 4.61 (s, 1, C-5 H), 6.02–6.42 (m, 4, $-CH_2-NH-CH_2-$), 7.95–8.23 (m, 4, $-CH_2CH_2-$); uv max (95% EtOH) 242 mμ (ϵ 10,000), 402 mμ (ϵ 15,400).

Anal. Calcd for $C_{14}H_{15}N_3O_3$: C, 61.53; H, 5.53; N, 15.38. Found: C, 61.76; H, 5.83; N, 15.18.

Preparation of 3-Methoxy-4-nitro-5-phenyl-2-pyrrolidinone (10) by Sodium Borohydride Reduction of Compound 8.[15]—A solution of 1.00 g (4.3 mmol) of compound **8** and 0.325 g (9.6 mmol) of sodium borohydride in 60 ml of absolute ethanol was stirred at 0° for 1.5 hr. The solution was then acidified with 20% hydrochloric acid and diluted to 150 ml with water. The solution was extracted repeatedly with chloroform, the extract dried ($MgSO_4$), filtered, and the chloroform evaporated to yield a residual oil which soon crystallized to a white solid. This solid was recrystallized once from absolute methanol to give 0.93 g (92%) of **10** as fine white clumps of needles: mp 132–133°; ir 3.01 (lactam NH), 5.76 (C=O), 6.46 μ (asymmetric NO_2); nmr ($CDCl_3$) τ 2.25 (s, 1, NH), 4.87–5.40 (m, 3, C-3, C-4, and C-5 H's), 6.42 (s, 3, OCH_3).

Anal. Calcd for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.12; N, 11.86. Found: C, 55.96; H, 4.90; N, 11.62.

Preparation of 4-Amino-3-methoxy-5-phenyl-2-pyrrolidinone (13).—To a stirred solution of 5.3 g (0.024 mol) of stannous chlo-

(13) F. Arndt "Organic Syntheses," Coll. Vol. II, A. H. Blatt, Ed., John Wiley & Sons, Inc., New York, N. Y., 1943, p 165.

(14) The methyl proton signal of methyl nitronic esters has been observed at somewhat higher field (τ 6.00–6.3) compared with the value of 5.56 for methyl in this nitro enol ether. *Cf.* ref 8b; L. A. Cohen and W. M. Jones, *J. Amer. Chem. Soc.*, **85**, 3397 (1963); J. S. Meek, J. S. Fowler, P. A. Monroe, and T. J. Clark, *J. Org. Chem.*, **33**, 223 (1968).

(15) Reduction of 1-nitroalkenes to nitroalkanes by sodium borohydride has been described by several investigators. See (a) H. Shechter, D. E. Ley, and E. B. Roberson, Jr., *J. Amer. Chem. Soc.*, **78**, 4984 (1956); (b) A. Hassner and C. Heathcock, *J. Org. Chem.*, **29**, 1350 (1964); (c) A. I. Meyers and J. C. Sircar, *ibid.*, **32**, 4134 (1967).

ride dihydrate in 10 ml of concentrated hydrochloric acid at 60° was slowly added 1.219 g (5.17 mmol) of compound **10**. The resulting solution was stirred at 60° for 1.5 hr. The solid which precipitated during this time was dissolved by the addition of 5 ml of distilled water, and the solution was made basic with 50% potassium hydroxide while maintaining the temperature of the solution at 20–25° by immersing the flask in cold water. The solid which precipitated during neutralization redissolved in the presence of the excess base. The basic solution was diluted to 50 ml with water and extracted with eight 50-ml portions of chloroform. The extract was dried ($MgSO_4$), filtered, and concentrated on a rotary evaporator until the total volume of the solution was less than 50 ml, then concentrated further by evaporation in an air stream. The residual oil soon solidified, and was washed with *ca.* 1.0 ml of a 50:50 mixture of benzene and petroleum ether (bp 60–110°) to give 0.534 g (50%) of crude **13**, mp 107–109°. Recrystallization, performed by dropwise addition of petroleum ether (bp 60–110°) to a benzene solution afforded 0.402 g (38%) of pure **13**: mp 110.5–111.5°; ir 2.90, 3.07, and 3.20 (N–H), 5.90 μ (lactam C=O); nmr ($CDCl_3$) τ 2.69 (s, 5, C_6H_5), 3.51 (s, 1, lactam N–H), 5.92 (d, 1, J = 8.0 Hz, C-5 **H**), 6.25 (d, 1, J = 8.5 Hz, C-3 **H**), 6.36 (s, 3, OCH_3), 6.76 (quartet, 1, $J_{3,4}$ = 8.5 Hz, $J_{4,5}$ = 8.0 Hz, C-4 **H**), 8.41 (s, 2, NH_2).

Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 64.38; H, 6.93; N, 13.63.

An additional amount of product could be obtained by further extraction of the basified reaction mixture with benzene. The aqueous layer remaining after the chloroform extractions described above was diluted to *ca.* 200 ml with water and treated with 250 ml of benzene for 12 hr in an apparatus for continuous liquid–liquid extraction. The benzene extract was filtered and concentrated to a small volume under reduced pressure. Upon addition of petroleum ether (bp 60–110°) 0.21 g of white needles separated, mp 109–110°. The total yield of **13** was thereby increased to 0.75 g (71%).

Registry No.—**4**, 21690-64-2; **5a**, 21690-65-3; **6**, 21690-66-4; **7a**, 21690-67-5; **7b**, 21690-68-6; **8**, 21690-69-7; **9**, 21690-70-0; **10**, 21690-71-1; **11**, 21690-72-2; **12a**, 21690-73-3; **12b**, 21690-74-4; **12c**, 21690-75-5; **13**, 21690-76-6; **14**, 21690-77-7

A Novel Thiazole Synthesis.[1] 4,5,6,7-Tetrahydrothiazolo[4,5-*d*]pyrimidine-5,7-diones

I. M. GOLDMAN

Medical Research Laboratories, Chas. Pfizer & Co., Inc., Groton, Connecticut 06340

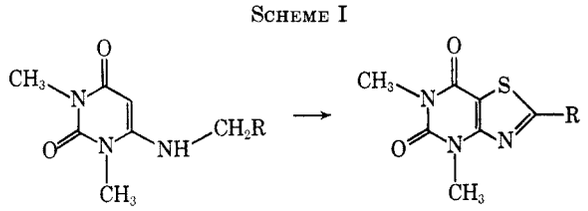
Received May 2, 1969

6-Amino-1,3-dimethyluracils (**1**, R = H, COOH, $COOC_2H_5$, C_6H_5, and CF_3) have been found to undergo facile conversion to the corresponding thiazolopyrimidines (**2**) upon treatment with thionyl chloride–pyridine, except for **1**, R = CF_3, where thionyl chloride is more effective in the absence of pyridine. Thiazolopyrimidines (**2**, R = H, COOH, and $COOC_2H_5$) have been reported previously by Schroeder.[2] The reaction is presumed to proceed *via* dehydration of the intermediate thiazoline S-oxides (**6**). A different reaction is observed when an inferior grade of thionyl chloride is used in the absence of pyridine, resulting in the formation of sulfides (**8**) and products derived therefrom. Speculation is offered on the mechanism of thiazole formation from suitably substituted 6-aminouracils.

Treatment of 6-carboxymethylamino-1,3-dimethyluracil (**1b**) with thionyl chloride–pyridine, in order to form the corresponding acid chloride, led to the formation of a highly fluorescent substance which was subsequently shown to be the known[2] thiazolopyrimidine **2c**. The present work is an outgrowth of this chance observation.

6-Amino-1,3-dimethyluracils (**1**, Scheme I) were prepared from 6-amino-1,3-dimethyluracil or 6-chloro-1,3-dimethyluracil and the corresponding amines, as described in Table I. Treatment of **1c** with an excess of thionyl chloride–pyridine at room temperature for 16 hr afforded the thiazolopyrimidine **2c**, a known compound,[2] in 90% yield. In a similar manner, compounds **1a**, **1b**, **1d**, and **1e** were converted to the corresponding thiazoles, as summarized in Table II. This reaction of 6-amino-1,3-dimethyluracils with thionyl chloride to form thiazolo[4,5-*d*]pyrimidines, a class of compounds previously prepared by Schroeder and Dodson from appropriately substituted pyrimido[5,4-*b*][1,4]-thiazines, represents a new synthesis of thiazoles.[3]

SCHEME I



1a, b, c, d, e → **2a, c, d, e**

a, R = H
b, R = COOH
c, R = COOEt
d, R = C_6H_5
e, R = CF_3

This reaction is envisioned as proceeding *via* dehydration of the presumed intermediate thiazoline S-oxides, as depicted in the hypothetical sequence proposed in Scheme II. Thionyl chloride is a bifunctional electrophile. Electrophilic attack at the electron-rich 5 position of **1** affords the intermediate 5-sulfinyl chloride **3**.[4] Dehydrohalogenation affords the sulfine **4**[5] which can cyclize, *via* anion **5**, to form the thiazoline S-oxide anion **6**. Dehydration of **6** *via* Pummerer reac-

(1) Paper I in the series: Reactions of 6-Amino-1,3-dimethyluracils with Thionyl Chloride.

(2) E. F. Schroeder, U. S. Patent 3,155,665 (1964); *Chem. Abstr.*, **62**, 4036 (1965). See also E. F. Schroeder and R. M. Dodson, *J. Amer. Chem. Soc.*, **84**, 1904 (1962).

(3) For examples of other thiazole syntheses, see J. M. Sprague and A. H. Land in "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., John Wiley & Sons, Inc., New York, N. Y., 1957, pp 484–722; "Chemistry of Carbon Compounds," Vol. IV, E. H. Rodd, Ed., Elsevier Publishing Co., New York, N. Y., 1957, Part A, p 385.

(4) J. Szmuszkovicz, *J. Org. Chem.*, **29**, 178 (1964), has reported an analogous reaction of thionyl chloride with indoles to form various isolable indole-3-sulfinyl chlorides or products derived therefrom.

(5) This is analogous to the formation of sulfene intermediates in reactions of some sulfonyl halides. Sulfines, unlike sulfenes, have been isolated. See, for examples, W. A. Sheppard and J. Diekmann, *J. Amer. Chem. Soc.*, **86**, 1891 (1964); J. Strating, L. Thijs, and B. Zwanenburg, *Rec. Trav. Chim.*, **86**, 641 (1967), and references cited therein; G. Optiz, *Angew. Chem. Intern. Ed. Engl.*, **6**, 107 (1967).