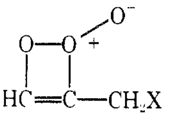
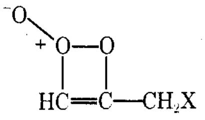
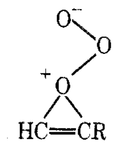


VIIa



VIIb



VIII

where the positive oxygen was three atoms away from the CH_2X group, the relative insensitivity of the reaction to varying inductive effects and the good linear correlation would not be unreasonable. However, it is unreasonable to expect that VIIb could possibly be the exclusive intermediate over the range of substituents used in this study and in light of the strongly supported intermediacy of the two possible acylcarbonyl oxides in Bailey's study.[3] The two acylcarbonyl oxides, II and III, could only arise from two four-membered ring precursors which differ in addition orientation, as in VIIa and VIIb. If varying proportions of VIIa and VIIb were formed, depending on the substituent, it would be highly unlikely that a linear correlation would exist; instead, as one went to more electron-donating substituents, VIIa would be favored, resulting in marked curvature up as one went to decreasing σ^* values, something that is not observed.

The initial rate-determining formation of a symmetrical π complex, or of a symmetrical three-membered ring of the type VIII, cannot be ruled out. However, the relative insensitivity of the rate of reaction to changing substituents and changing solvent polarity does tend to make it less likely that charge is developed in the transition state.

The above supports the intermediacy of a symmetrical intermediate of the type V whose cleavage could then be affected by the substitution pattern but whose formation would be only slightly affected by inductive and solvent effects, since no charge is developed.

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Registry No.—Ozone, 10028-15-6.

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Reaction of Diaminomaleonitrile with Acetaldehyde

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The reaction of diaminomaleonitrile with acetaldehyde in an aqueous buffer at pH 6.8 proceeds rapidly at 5° and leads to the formation of a product which results from the condensation of three molecules of acetaldehyde and one molecule of diaminomaleonitrile with the elimination of one molecule of water. The properties of the compound are consistent with a heterotricyclic ring system.

Diaminomaleonitrile,[1] a tetramer of hydrogen cyanide, has been implicated as an intermediate in the prebiotic synthesis of purines.[2] It has also been shown to be a very useful intermediate in the preparation of a variety of heterocyclic compounds containing from five to seven members in the rings.[3]

Except for the investigations concerned with chemical evolution, the synthetic procedures utilizing diaminomaleonitrile have largely employed nonaqueous solvents. This report deals with the reaction of diaminomaleonitrile with acetaldehyde in an aqueous buffer. The reaction proceeds rapidly under very mild conditions (pH 6.8, 5°) leading to an unexpected and unusual product. This is identified as a heterotricyclic system (structure **3**) resulting from the condensation of three molecules of acetaldehyde with one molecule of diaminomaleonitrile.

Results and Discussion

The crystalline product obtained from the reaction of diaminomaleonitrile with acetaldehyde was initially assumed to be a dihydroimidazole derivative (structure **1**, Scheme I). However, the proton magnetic resonance spectrum (Figure 1) revealed that three molecules of acetaldehyde had been incorporated into the product and that all three of the incorporated CH_3CH groups were in different chemical environments. That the three CH_3CH groups were each incorporated intact was shown by a spin-decoupling experiment in which the upfield methyl signals (integrating for nine protons) were irradiated, causing a collapse of the quartets in the δ 4–6 region of the spectrum. (The quartets integrated for three protons in a ratio of 1:1:1.) Addition of a small amount of D_2O to the $Me_2SO\text{-}d_6$ solution resulted in a disappearance of the two exchangeable NH signals at δ 7.96 and 8.22, each integrating for one proton. All of the incorporated acetaldehyde molecules were covalently bound because heating overnight at 100° under constant oil pump vacuum caused no significant loss of weight or change in the ir spectrum.

The low-resolution electron impact mass spectrum of the product is found in Figure 2. It can be seen that the spectrum is complex. In view of the fact that the product analyzed satisfactorily for $C_{10}H_{14}N_4O_2$ (mol wt 222) it is evident that the molecular ion is not sufficiently stable to appear in the low-resolution mass spectrum. However, a high-

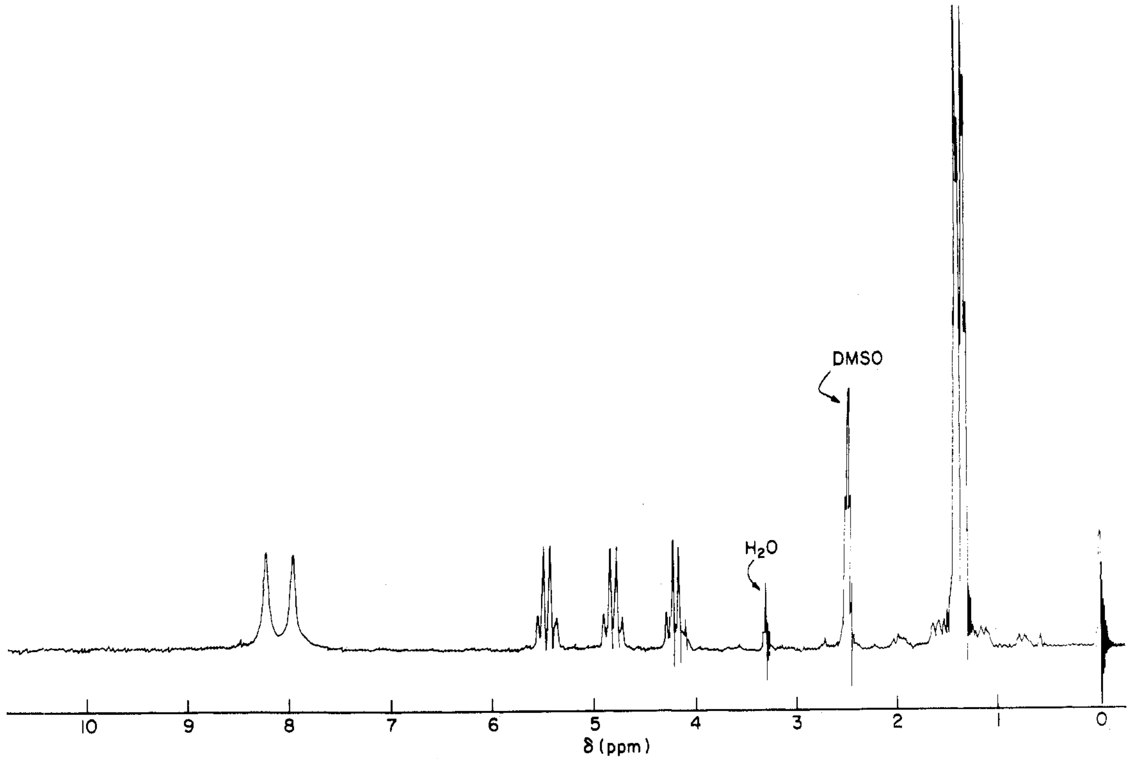
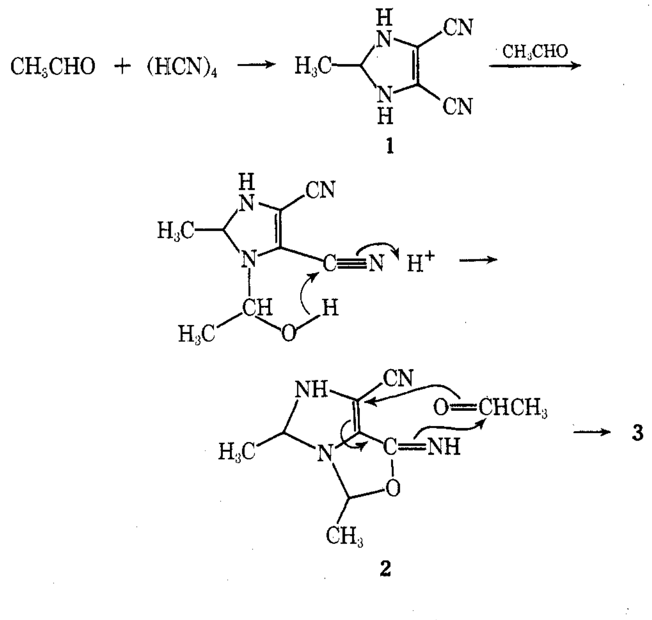
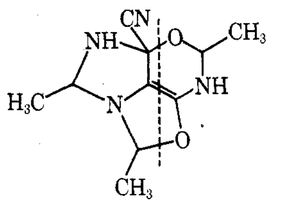


Figure 1. Proton magnetic resonance spectrum of the product of the reaction of acetaldehyde and diaminomaleonitrile. Solvent in Me$_2$SO-d_6; reference is Me$_4$Si; frequency, 100 MHz.

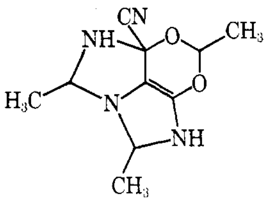
Scheme I



resolution mass spectrum of the compound also was obtained and it showed an ion at mass 222 providing that a very strong exposure was employed. A bar-graph spectrum constructed from the high-resolution data is identical, except for intensity differences, to the low-resolution spectrum provided in Figure 2. However, two other significant peaks are found in the high-resolution spectrum, namely peaks at 221 (M − H$^+$) and 196 (M − CN). The high-resolution data indicate that the signals at 180, 178, and 163 mass units can be explained by loss of methyl plus HCN, acetaldehyde, and acetaldehyde plus methyl, respectively. Of particular interest are the signals at 162 and 161 mass units. The high-resolution data can be accommodated only by the loss of $CH_3CH(NH)O$ plus one and two protons, respectively, and not by the loss of $CH_3CH(O)O$ plus zero and one proton. This particular fragmentation can reasonably be explained only from structure **3** and not from the alternative structure **4**. Loss of one and two protons is frequently found throughout the high-resolution spectrum, probably owing to formation of imidazole derivatives and/or loss of hydrogen from the six-membered ring. High-resolution analysis reveals that 25% of the signal at 135 can be accounted for by loss of $C_3H_5O_2N$. This is most readily explained by the fragmentation shown in **3**. A number of other signals in the low-resolution spectrum can be tentatively identified in combination with the high-resolution data. The base peak at 44 in the high-resolution mass spectrum consists almost entirely of signals for C_2H_4O, CH_2NO, and C_2H_6N. The electron impact mass spectrum is complemented by the chemical ionization mass spectrum. The (M + 1)$^+$ signal at 223 is very prominent in the chemical ionization mass spectrum, confirming the molecular weight of 222.



3



4

Ultraviolet spectroscopy of the product of the reaction of diaminomaleonitrile and acetaldehyde shows that the absorption maximum of the starting material at around 300 nm in ethanol has disappeared. Hence the double bond conjugated to the nitrile groups is no longer present. The infrared spectrum has in it a very weak CN absorption band at 2250 cm^{-1} which is consistent with the loss of the double bond.

At ambient temperatures, and under conditions where acetaldehyde is 0.15 *M*, diaminomaleonitrile is 6 × 10^{-5} *M*, and the buffer is 0.25 *M* each in NaH_2PO_4 and Na_2HPO_4,

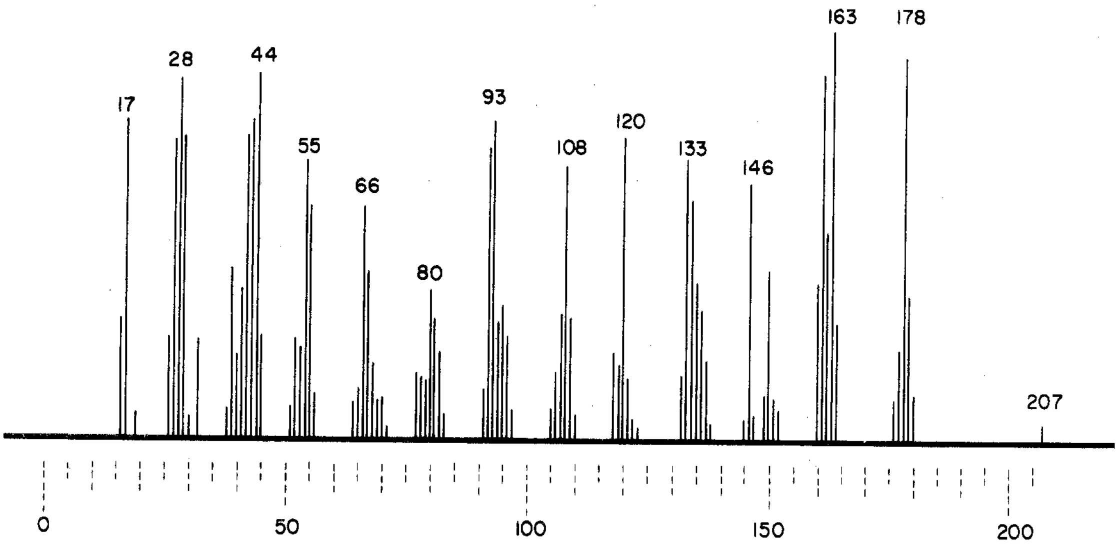


Figure 2. Low-resolution electron impact mass spectrum of **3**.

the pseudo-first-order rate constant for the disappearance of the double bond, determined spectrophotometrically, is 3.98×10^{-2} min^{-1}, corresponding to a half-life of 17.4 min. Under otherwise identical conditions, the absorbancy of diaminomaleonitrile at 295 nm does not decrease in the absence of acetaldehyde.

Synthesis of the above information leads to **3** as the structure of the product. A reasonable route for the formation of **3** is proposed in Scheme I.

The first step involves formation of a dihydroimidazole, followed by addition of acetaldehyde to one of the secondary amino groups. The resulting carbinolamine then converts the nitrile to the imide **2**. (A number of examples for the participation of neighboring OH in nitrile hydrolysis are available, e.g., ref 4–6.) The final step, leading to the heterotricyclic product **3**, is analogous to a Diels–Alder reaction in which a heterodienophile, acetaldehyde, reacts with a heterodiene.[7]

The facility of the formation of the compound isolated is perhaps surprising. The driving force may be its precipitation. Inspection of structure **3** shows that there are four potentially asymmetric carbon atoms in the product. However, the proton magnetic resonance spectrum shown in Figure 1 is a very clean spectrum and suggests that only one of the possible D, L stereoisomeric pairs has crystallized out of the aqueous solvent. An analogous reaction is not observed between diaminomaleonitrile and either formaldehyde or acetone under similar conditions.

Reaction of diaminomaleonitrile with a variety of aldehydes in methanol has been investigated by Begland et al.[3] No reaction analogous to the one reported herein was found. Furthermore, Robertson and Vaughan[8] have reported that there is no reaction between diaminomaleonitrile and acetaldehyde in hot alcohol. Hence the chemistry of diaminomaleonitrile in aqueous solvents can be substantially different from that in organic solvents and, in view of its utility as a synthetic intermediate, merits further attention.

Experimental Section

Reaction of Diaminomaleonitrile with Acetaldehyde. Diaminomaleonitrile (4.4 g, 0.04 mol) was suspended with stirring in 750 ml of ice-cold pH 6.8 phosphate buffer (0.25 *M*). To this was added 35 ml of ice-cold acetaldehyde. Within 5 min, a clear solution was obtained. After approximately 20 min, a granular precipitate was evident. The reaction mixture was kept overnight in a refrigerator. The precipitate (4.84 g, 53% of theory) was filtered, washed with water, dried, dissolved in hot acetonitrile, and decolorized with Darco G-60 and Norit A. Recrystallization from acetonitrile yielded white crystals, mp 163–164° dec.

Anal. Calcd for $C_{10}H_{14}N_4O_2$: C, 54.04; H, 6.35; N, 25.21. Found: C, 54.08; H, 6.43; N, 25.49.

The ir spectrum (Nujol) was obtained on a Perkin-Elmer 237B spectrometer: 3430, 3310, 3230, 2250, 1705, 1650, 1620, 1200–1080, 910, 830 cm^{-1}. The uv spectrum (2×10^{-4} *M* in spectroquality acetonitrile) was taken manually on a Zeiss PMQII spectrophotometer and showed only a plateau around 225 nm ($\epsilon \sim 2500$) and trailing absorption.

The high-resolution electron impact mass spectrum was obtained with an instrument tolerance set at an upper limit of 2.2×10^{-3} amu. Calcd for $C_{10}H_{13}N_4O_2$, $C_9H_{11}N_4O_2$, $C_9H_{14}N_3O_2$, $C_8H_{10}N_4O$, $C_7H_7N_4O$, $C_8H_8N_3O$, $C_8H_7N_3O$, $C_7H_9N_3O$, and $C_7H_4N_3O$: *m/e* 221.10385, 207.08820, 196.10860, 178.08546, 163.06198, 162.06673, 161.05891, 151.07456, and 146.03543. Found: *m/e* 221.10487, 207.08712, 196.11015, 178.08676, 163.06196, 162.06596, 161.05891, 151.07495, and 146.03623. The chemical ionization mass spectrum had in it signals at 223 $(M + 1)^+$, 196 (base peak), 179, 152, and 135.

The low-resolution mass spectrum, NMR spectrum (solvent, $Me_2SO\text{-}d_6$), and chemical ionization mass spectrum were kindly provided by Drs. N. Ling, J. Rivier, and K. Kirk, respectively. The high-resolution mass spectral data were obtained from Drs. K. Biemann and C. Costello.

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Registry No.—**3**, 55759-62-1; diaminomaleonitrile, 1187-42-4; acetaldehyde, 75-07-0.

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