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A Cyclization of 1,2-Bisureido Compounds with Sodium Nitrite[1]

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Nitrosation of bisureido compounds with sodium nitrite in the presence of acid was examined.

The treatment of 1,2-bisureidoethane with sodium nitrite in 6% sulfuric acid, afforded 1-carbamoyl-3-nitroso-2-imidazolidinone in 86% yield. Similarly, the same nitrosation of 1,2-bisureidopropane gave an isomeric mixture of cyclized N-nitroso compounds in 87% yield. On the other hand, nitrosation of *o*-phenylenebisurea with sodium nitrite and 25% sulfuric acid, gave only cyclized 1-carbamoyl-2-benzimidazolidinone in 58% yield, and nitroso compound was not obtained.

This nitrosative cyclization occurs only in 1,2-bisureido compounds which have no substituent in the ureido nitrogens. The mechanism of this cyclization was also discussed.

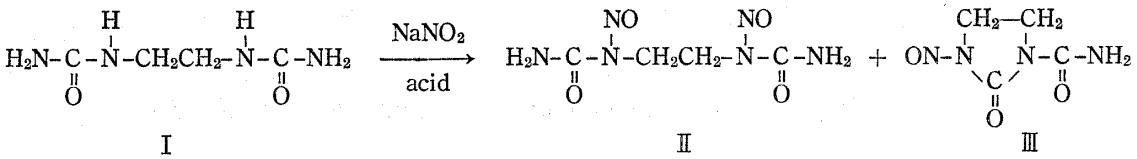
Keywords——nitrosation; nitrosative cyclization; 1,2-bisureido compounds; 2-imidazoridinones; N-nitrosoureas

In the course of our studies for preparing new N-nitroso derivatives having antitumor effects, 1,1′-ethylenebis(1-nitrosourea) (II) was designed as a bis-adduct of 1-methyl-1-nitrosourea which had some activity against L-1210.[3] Generally, N-nitrosoureas were prepared by the nitrosation of the corresponding ureas with sodium nitrite under the acidic conditions.[4]

However, the same trial on 1,1′-ethylenebisurea (I) gave 1-carbamoyl-3-nitroso-2-imidazolidinone (III) unexpectedly. On the other hand, 2-imidazolidinones were generally synthesized by following methods; acylation of 1,2-diamine with urea[5] or ethyl carbonate,[6] reaction of 1,2-diamine with phosgene.[7] There has been no report on the formation of 2-imidazolidinone by the cyclization of 1,2-bisureido compounds under the nitrosative conditions. This paper describes a cyclization of 1,2-bisureido compounds with sodium nitrite under the acidic conditions.

Samour *et al.*[8] reported that II was obtained from the reaction of I with sodiun nitrite and 6 N sulfuric acid. However, our re-examination of this reaction gave III together with II. The yield of III was much higher than that of II and varied by concentrations of acid. The correlation between the concentrations of acid and yields of II and III, were shown in Chart 1. On the other hand, II was obtained as the sole product by the reaction of I with sodium nitrite and 85% formic acid. The yield of II was higher than that in the former condi-

1) This work was presented at the 96 and 97th Annual Meeting of the Pharmaceutical Society of Japan (1976, Nagoya and 1977, Tokyo).
2) Location: *Kamiyoga 1-18-1, Setagaya, Tokyo.*
3) *a*) T.P. Johnston, G.S. McCaleb, and J.A. Montgomery, *J. Med. Chem.*, **6**, 669 (1963); *b*) F.M. Schabel, Jr., T.P. Johnston, G.S. McCaleb, J.A. Montgomery, W.R. Laster, and H.E. Skipper, *Cancer Res.*, **23**, 725 (1963).
4) E.H. White, *J. Am. Chem. Soc.*, **77**, 6008 (1955).
5) S. Petersen und H.F. Piepenbrink, "Methoden der Organischen Chemie" (Houben-Weyl), Band VIII, Sauerstoffverbindungen III, ed. by E. Müller, Georg Thieme Verlag, Stuttgart, 1952, p. 140.
6) E. Fischer and H. Koch, *Ann.*, **232**, 222 (1886).
7) S. Frankel and M. Cornelius, *Chem. Ber.* **51**, 1654 (1918).
8) C.M. Samour and J.P. Mason, *J. Am. Chem. Soc.*, **76**, 441 (1954).



Acid	Yield (%) II	Yield (%) III
85% HCOOH	43	—
50% H_2SO_4	0	3
25% H_2SO_4	2	48
12% H_2SO_4	3	58
6% H_2SO_4	8	86

Chart 1

tions. Those combinations generate nitrous acid or formyl nitrite,[9,10] and the activity of the true nitrosating agents effected the yields.

In regard to the structure of III, two possible structures, five-membered ring compound III and seven-membered ring compound IV, were considered from its elemental analysis and spectral data. Some chemical reactions were carried out to determine its structure. As shown in Chart 2, its treatment with acetic anhydride gave the denitroso compound VI in 32% yield, and nitrosation of VI with sodium nitrite and 25% sulfuric acid, afforded the same N-nitroso compound III.

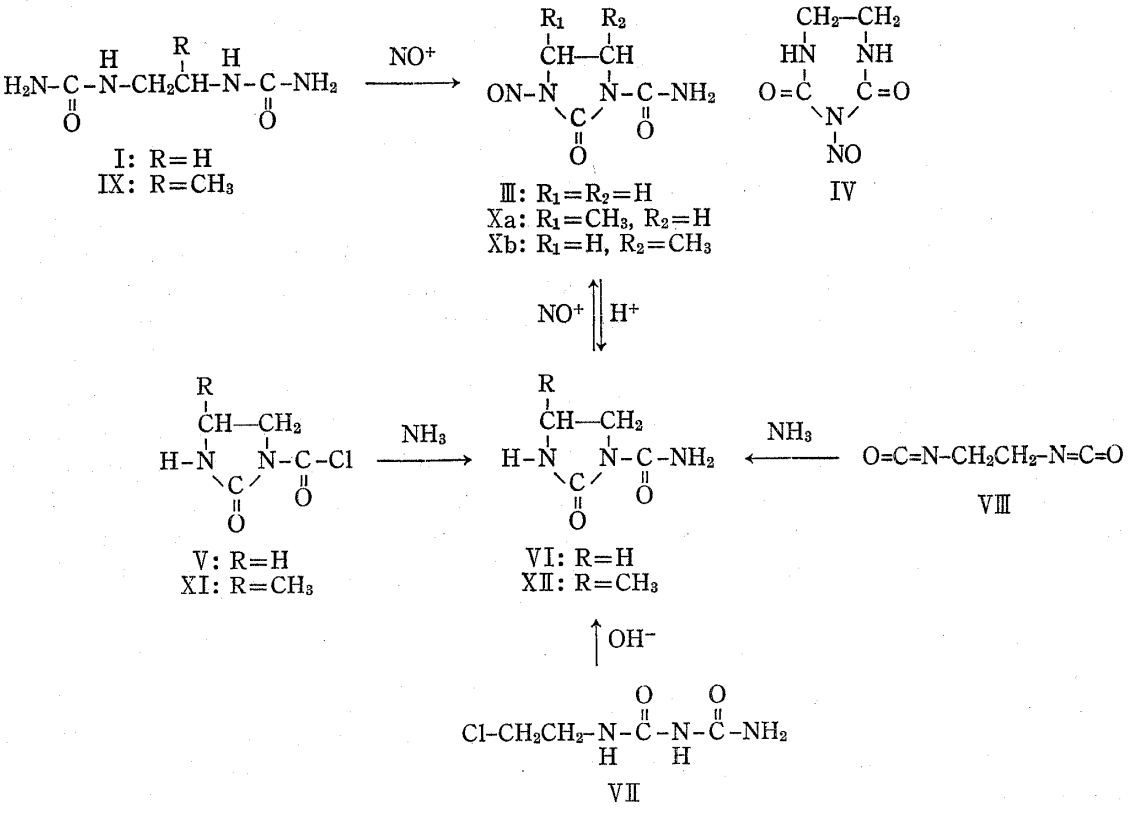


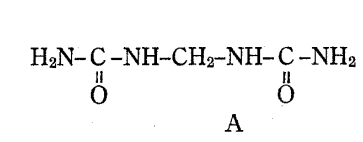
Chart 2

9) J.A. Montgomery, *Cancer Treatment Rep.*, **60**, 651 (1976).
10) B.C. Challis and A.R. Butler, "The Chemistry of the Amino Group," ed. by S. Patai, Interscience Publishers, Inc., London, 1968, p. 305.

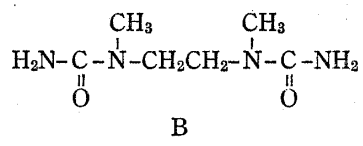
Each compound which had the structure of III and VI, was already reported by Johnston *et al.*[11] According to their procedures, 1-(2-chloroethyl)biuret (VII) was treated in alkaline solution. The resulting product was identical with that obtained from I. However, the physical data of this compound were different from the literature values. Therefore, the structure of III was comfirmed by the synthesis through the different routes indicated in Chart 2. The treatment of 2-imidazolidinone N-carbonyl chloride (V),[12] which had five-membered ring system, with ammonia gas, afforded VI in 62% yield. Also, the reaction of ethylene-diisocyanate (VIII)[13] with ammonia gas, gave a mixture of VI and I (1: 1) in 47% total yield. The compound VI resulted from these two reactions was identical with the product obtained from I. Thus, the structure of III obtained by nitrosation of I, was 1-carbamoyl-3-nitroso-2-imidazolidinone.

As mentioned above, since there has been no report on the formation of imidazolidinones by ring closures of 1,2-bisureido compounds, nitrosation of some other bisureido derivatives were examined.

Nitrosation of bisureidomethane (A)[14] and 1,1′-ethylenebis(1-methylurea) (B) with sodium nitrite and 25% sulfuric acid, did not give any nitroso compounds. They may decompose, for the color of the reaction mixture changed to blue when the sodium nitrite solution was added to it.



A



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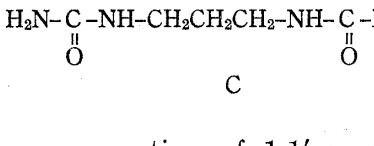
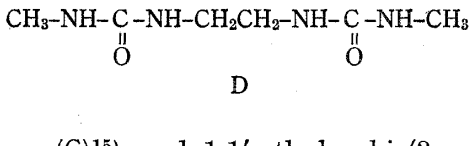


C



D

The same reaction of 1,1′-propylenebisurea (C)[15] and 1,1′-ethylenebis(3-methylurea) (D)[3a] gave 1,1′-propylenebis(1-nitrosourea)[15] and 1,1′-ethylenebis(3-methyl-3-nitrosourea),[3a] respectively, as open-chain bis-nitroso compounds.

Thus, only 1,2-bisureido compounds seemed to cyclize to produce imidazolidinones with sodium nitrite and acid. Then, we examined the unsymmetrical 1,2-bisureidoethane derivative and aryl *o*-bisureido derivatives.

The nitrosation of 1,2-bisureidopropane (IX) with sodium nitrite and 25% sulfuric acid, afforded an isomeric mixture (1: 1) of imidazolidinone derivatives, Xa and Xb. The ratio of Xa and Xb was determined from nuclear magnetic resonance (NMR) integral ratio of methyl groups. Several attempts to separate them, were unsuccessful. The structure of Xa was also comfirmed by the synthesis through another route. The reaction of 4-methyl-2-imidazolidinone N-carbonyl chloride (XI)[12] with ammonia gas in benzene, gave XII in 65% yield. The nitrosation of XII with sodium nitrite and formic acid, afforded Xa. In order to specify the structure of Xb, the spectral data of Xa+Xb were compared with those of III, Xa and related 2-imidazolidinones. The infrared (IR) spectrum of III showed two intense bands at 1705 cm^{-1} and 1775 cm^{-1}, due to the ring carbonyl and ureido carbonyl groups. In the ultraviolet (UV) spectra, III and Xa+Xb showed the characteristic, weak bands (n-π^*) at 386, 401, 419 and 392, 407, 425 nm, respectively. Those spectra were the shapes typical for N-nitroso compounds. IR and UV spectral data are tabulated in Table I.

11) T.P. Johnston and P.S. Opliger, *J. Med. Chem.*, **10**, 657 (1965).
12) H. Ulrich, J.N. Telley, and A.A.R. Sayigh, *J. Org. Chem.*, **29**, 2402 (1964).
13) T. Curtius, *J. Pract. Chem.*, **105**, 289 (1923).
14) H. Kadowaki, *Bull. Chem. Soc. Jpn.* **11**, 249 (1936).
15) Th. Lieser and G. Beck, *Chem. Ber.* **83**, 137 (1950).

Table I. IR and UV Spectral Data of Cyclic Compounds

Compound	IR ν_{max}^{Nujol} cm^{-1}					UV λ_{max}^{EtOH} (ε)
	NH	C=O	N=O	N–NO	ring vibr.	
III	3400	1775	1345	1165	1220	252 (11600)
	3220	1705				386 (89)
	1595					401 (136)
						419 (133)
Xa+b	3390	1765	1320	1135	1205	252 (6200)
	3220	1700		1120		392 (37)
	1595					407 (550)
						424 (51)
XIV	3380	1760			1200	235 (5030)
	3100	1706				277 (3370)
	1585					285 (3110)

The NMR spectrum of III had only two peaks at 7.50 (NH) and 3.57 (-CH_2CH_2-) ppm. on the other hand, the spectra of VI and Xa showed the corresponding signals of methylene groups as the shapes typical for AA'BB' and AMX system, respectively. However, the spectrum of Xa+Xb can be understood as that the two AMX systems were overlapped in the chart. The NMR spectra and assignment of their signals of Xa and the mixture (Xa+b), were shown in Fig. 1. J and V values were calculated from the peaks. In order to comfirm the Xb structure, mass spectroscopy was also perched on III, Xa and Xa+b, and the fragmentations are illustrated in Chart 3. Those spectra exhibited the common base peaks at M−43, which reveals from M^+ ion by the loss of isocyanic acid through McLafferty rearrangement. After the ring-opening the fragments *via* oxydiazo-isocyanate intermediate ions underwent α-fission. Since the resulting fragment ions will differ between Xa and Xb, the spectrum of Xa exhibited 2 peaks at 73 and 56, and on the other hand, the spectrum of Xa+b showed 3 peaks at 73, 56 (from Xa), and 70 (from Xb). Thus the structure of Xb could be assigned as 1-carbamoyl-3-nitroso-5-methyl-2-imidazolidinone.

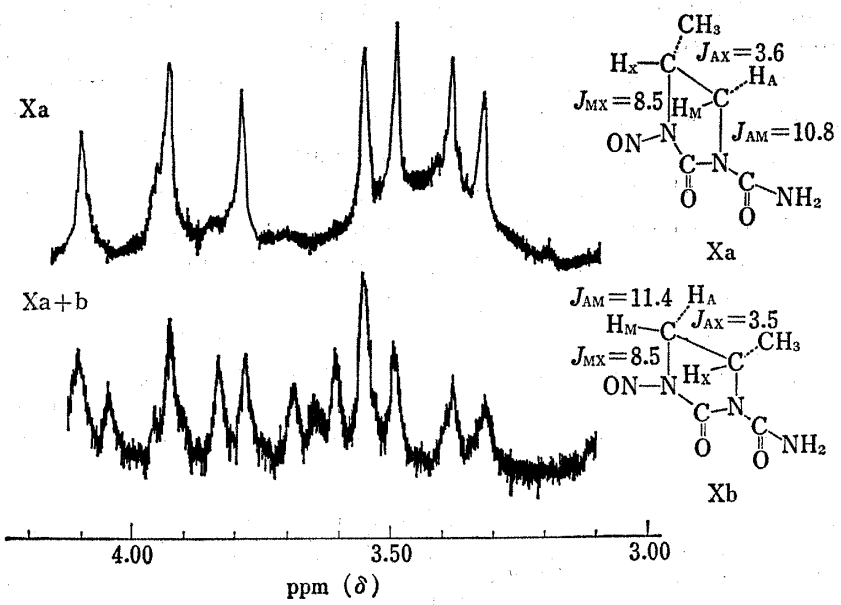


Fig. 1. NMR Spectra of Xa and Mixture of Xa and Xb

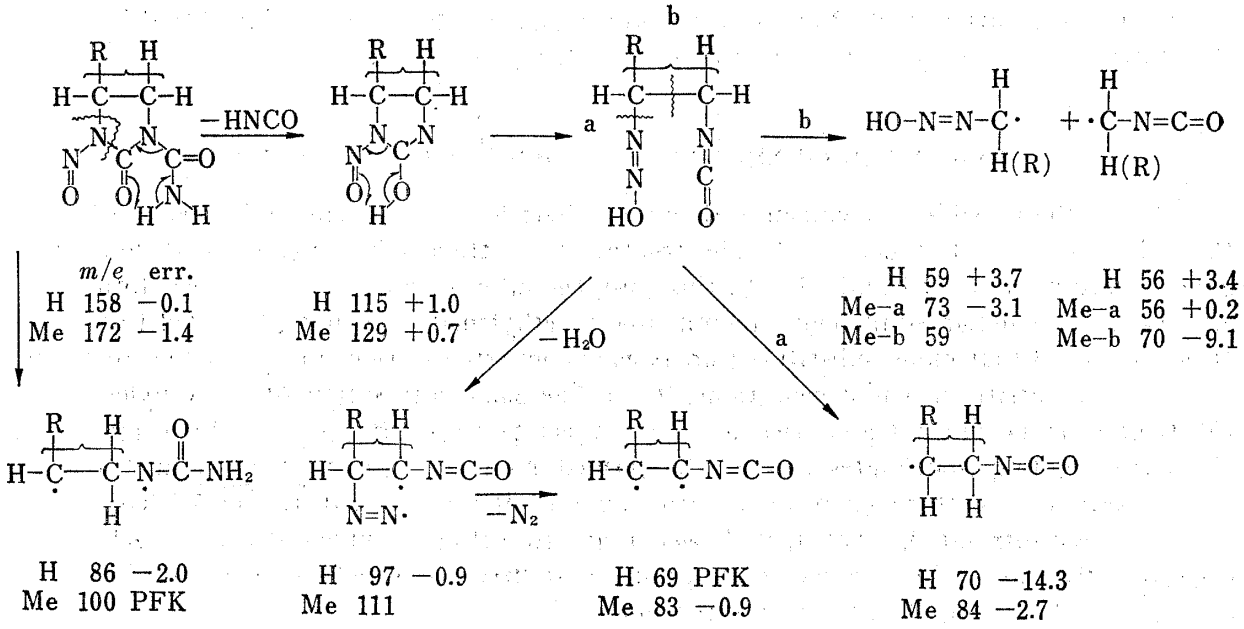


Chart 3

Similarly, the nitrosation of *o*-phenylenebisurea[16] gave 1-carbamoyl-2-benzimidazolidinone (XIV) in 58% yield. In this case, although cyclization occurred, the 3-position nitrogen was not nitrosated in this conditions because of the low basicity of the imino group in the cyclized compound XIV. No characteristic absorption bands due to N-nitroso group, appeared in UV and IR spectra. The assignment of signals of the NMR spectrum of XIV is illustrated in Chart 4. The signals of proton e and f were disappeared slowly when deuterium oxide was added. The anisotropic effect of the carbonyl group affected the proton a and the signal appeared in low field.

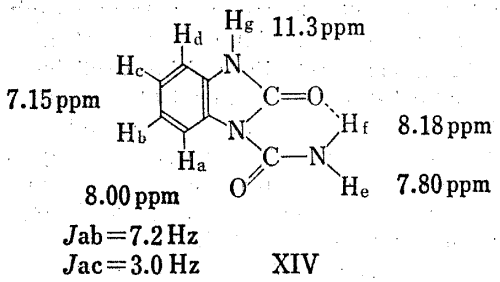


Chart 4

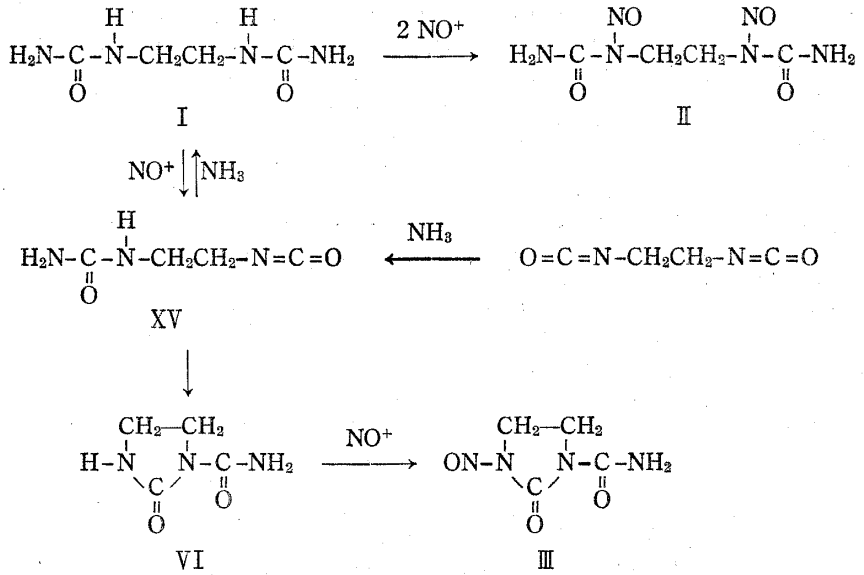
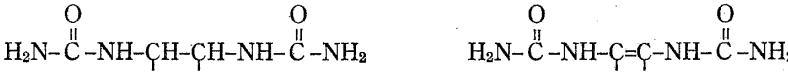


Chart 5

16) Eug. Lellmann, *Chem. Ber.* **16**, 592 (1883).

On the nitrosative cyclization of bisureido compounds, it can be concluded that following structures are necessary in the molecules of starting materials.



One of the possible mechanism is shown in Chart 5. This scheme will be supported by the following lines of evidence. 1) The treatment of ethylenediisocyanate with ammonia, gave a mixture (1: 1) of I and VI. In this case, the intermediate XV, which was formed by addition of one molar equivalent of ammonia to ethylenediisocyanate, cyclized to VI. 2) It was reported that mono-substituted ureas were converted to isocyanates by the treatment with sodium nitrite in acidic conditions.[17] 3) The same nitrosation of 1,1′-ethylenebis(1-substituted ureas) did not give rise any cyclic compounds. Because of their structure, the corresponding isocyanates can not be formed by the treatment with sodium nitrite. 4) Nitrosation of *o*-phenylenebisurea with sodium nitrite afforded the cyclic compound which was not nitrosated. This fact showed that nitrosation occurred after the cyclization. Consequently, one of the primary amido group is at first converted to isocyanate XV, then cyclized to VI, and finally VI is nitrosated to give III.

Experimental

The following instruments were used for physical data. IR spectra: a JASCO model IR-S spectrophotometer; UV spectra: Shimadzu double beam spectrophotometer UV 210; NMR spectra: Varian 360-A and JEOL 60C spectrometer (tetramethylsilane as an internal standard); Mass spectra: JEOL LMS-01 SG-2 spectrometer. All melting points are uncorrected.

1-Carbamoyl-3-nitroso-2-imidazolidinone (III)——An aqueous solution (5 ml) of sodium nitrite (2.1 g) was added dropwise to a cold (0—5°), stirred solution of 1,1′-ethylenebisurea (1.5 g) in 6% H_2SO_4 (30 ml). Stirring was continued at 0—5° for 1.5 hr. The yellow crystals separated were collected, and III was extracted with acetone. The extract was evaporated to dryness under reduced pressure. Recrystallization of the residue from small portion of acetone gave orange-yellow crystals, mp 184°. Yield 86%. *Anal.* Calcd. for $C_4H_6N_4O_3$: C, 30.38; H, 3.82; N, 35.44. Found: C, 30.43; H, 3.79; N, 35.71. High MS: molecular ion at *m/e* 158.0420. Calcd. 158.0439.

1,1′-Ethylenebis(1-nitrosourea) (II)——A solution of 1,1′-ethylenebisurea (1.5 g) in 85% formic acid (10 ml) was chilled (0—5°) in an ice–bath. An aqueous solution (5 ml) of sodium nitrite (2.1 g) was added dropwise with stirring under cooling. Stirring was continued for 1 hr, and the pale yellow crystals formed were filtered and washed with cold water, and then dried over P_2O_5. Pale yellow crystalline powder, mp 132° (dec.). Yield 43%. *Anal.* Calcd. for $C_4H_8N_6O_4$: C, 23.53; H, 3.95; N, 41.17. Found: C, 23.81; H, 4.01; N, 40.49. IR ν_{max}^{Nujol} cm^{-1}: 3420, 3260, 1710, 1412, 1208, 1010, 855. NMR (DMSO-d_6) δ (ppm): 3.72 (s, $2CH_3$), 7.74 (s, $2NH_2$). High MS: $M^+/2$ at 102.0284. Calcd. 102.0303.

Denitrosation of III——III was dissolved in a mixture of acetic anhydride (25 ml) and acetic acid (25 ml). The solution was warmed at 80° for 2 hr until the yellow color disappeared. The solvent was evaporated under reduced pressure. The residue was recrystallized from water to give VI, mp 193°, yield 32%. *Anal.* Calcd. for $C_4H_7N_3O_2$: C, 37.21; H, 5.46; N, 32.55. Found: C, 36.96; H, 5.25; N, 32.68. IR ν_{max}^{Nujol} cm^{-1}: 3370, 3200, 1740, 1680, 1580, 1270, 1080. NMR (DMSO-d_6) δ (ppm): 3.30—4.10 (AA′BB′, 4H, $-CH_2CH_2-$), 6.85 (s, 2NH), 7.40 (s, $2NH_2$). High MS: molecular ion at *m/e* 129.0418. Calcd. 129.0538.

Nitrosation of 1-Carbamoyl-2-imidazolidinone (VI)——According to the method of Johnston *et al.*,[6] VI was nitrosated. The nitroso compound III resulted was identical with a sample obtained from I in the mixed melting point determination and spectral data.

Nitrosation of 1,2-Diureidopropane——A solution of 1,2-diureidopropane (1.7 g) in 6% H_2SO_4 (50 ml) was chilled (below 0°) in an ice-bath. An aqueous solution (5 ml) of sodium nitrite (2.1 g) was added dropwise with stirring. Stirring was continued for 1 hr with cooling, orange-yellow crystals separated were collected, and washed with cold water. Recrystallization from ethanol gave a mixture of Xa and Xb. This mixture sublimated about 160—170°. Total yield 87%. *Anal.* Calcd. for $C_5H_8N_4O_3$: C, 34.88; H, 4.68; N, 32.55. Found: C, 35.00; H, 4.72; N, 32.38. High MS: molecular ion *m/e* at 172.0595. Calcd. 172.0596.

Nitrosation of Phenylenebisurea——An aqueous solution (5 ml) of sodium nitrite (2.1 g) was added dropwise to a cold, stirred suspension of *o*-phenylenebisurea (1.9 g) in 25% H_2SO_4 (50 ml), and stirring was

17) S. Ross, A. Riva, and B. Piantanida, *Chim. Ind.* (Miran.), **42**, 1243 (1960); *Chem. Abstr.*, **55**, 25850 (1961).

continued at 0—5° for 2 hr. The pale yellow crystals formed were collected and washed with cold water. Recrystallization from ethanol gave 1-carbamoyl-2-benzimidazolidinone (XIV). This compound sublimated about 240—250°. Yield 58%. *Anal.* Calcd. for $C_8H_7N_3O_2$: C, 54.23; H, 3.98; N, 23.72. Found: C, 53.81; H, 3.90; N, 23.78. High MS: molecular ion *m/e* at 177.0736. Calcd. 177.0538.

Synthesis of VI from V——NH_3 was bubbled into stirred suspension of 2-imidazolidinone N-carbonyl chloride (V) in benzene (20 ml) at moderate rate for 30 min. The stirring was continued for 15 min. The white precipitates were collected and recrystallized from water. Yield 73%.

Reaction of Ethylenediisocyanate with Ammonia——Ammonia gas was bubbled into a cold (0—5°), stirred suspension of ethylenediisocyanate (1.12 g) in benzene (20 ml) at moderate rate until white precipitates were formed. The stirring was continued at room temperature for 20 min, and the white crystals separated were collected. The separation of VI and I was not attempted. This products consisted of I and VI (1: 1), from NMR integral ratio of the ethylene groups. Total yield 47%.

1,1′-Propylenebis(1-nitrosourea)——This compound was prepared according to the method of Lieser *et al.*[15] mp 108° (dec.), (reported,[15] 123°). *Anal.* Calcd. for $C_5H_{10}N_6O_4$: C, 27.52; H, 4.62; N, 38.52. Found: C, 27.59; H, 4.61; N, 38.12. IR ν_{max}^{Nujol} cm^{-1}: 3400, 3190, 1740, 1608, 1275, 1185, 1070. NMR (DMSO-d_6) δ (ppm): 1.35 (q, $-C-CH_2-C-$), 3.62 (t, $2N-CH_2-$), 7.75 (s, $2NH_2$).

1,1′-Ethylenebis(3-methyl-3-nitrosourea)——This compound was prepared according to the method of Johnston *et al.*[3a] mp 130°. IR ν_{max}^{Nujol} cm^{-1}: 3380, 1705, 1235, 1165, 1040. NMR (DMSO-d_6) δ (ppm): 3.07 (s, CH_3), 3.45—3.55 (m, $-CH_2CH_2-$), 8.85 (s, 2NH).

1,1′-Ethylenebis(1-methylurea)——N,N′-Dimethylethylenediamine hydrochloride (1.2 g) and potassium cyanate (0.8 g) were dissolved in water (50 ml). The solution was heated at 80° for 1.5 hr. The crystals formed were filtered, and recrystallized from water. mp 145—155° (sub.). High MS: molecular ion *m/e* at 174.1153. Calcd. 174.1190 for $C_6H_{14}N_4O_2$. IR ν_{max}^{Nujol} cm^{-1}: 3350, 3150, 1660, 1600, 1500, 1300, 1100, 1035. NMR (DMSO-d_6) δ (ppm): 2.80 (s, CH_3), 3.24 (s, $-CH_2CH_2-$), 5.77 (s, NH_2).