cm^{-1}). Distillation gave 5 g (19%) of a thick yellow oil, bp 132–138° (0.25 mm). The ir spectrum displayed significant peaks at 3050 (shoulder), 3000, 2940, 1700, 1650, 1610, 1370, and 1240 cm^{-1}. The nmr spectrum indicated the presence of the imino ester and some impurity (*ca.* 15%) that could not be removed by repeated distillation. The good chemical analysis indicates that the impurity is an isomer of the imino ester (but it is not the ketenimine). The nmr displayed peaks ($\delta^{TMS}_{CCl_4}$) at 7.0 (broad multiplet, 5 H) for the phenyl protons, 6.72 (singlet, 1 H) for the vinyl proton which was superimposed on the phenyl protons, and three singlets at 3.90, 3.70, and 3.64, each representing three protons for the three methoxy groups. *Anal.* Calcd for $C_{14}H_{15}NO_5$: C, 60.60; H, 5.40; N, 5.05. Found: C, 60.12; H, 6.02; N, 5.36.

D. *o*-Tolyl Isocyanide.—After removal of the methanol, the thick oil, which showed no ir absorption in the ketenimine region, was distilled, giving a 60% yield of the imino ester **8**, bp 126–127° (0.25 mm). The ir spectrum displayed significant peaks at 3050 (shoulder), 3000, 2950, 1700, 1650, 1610, 1575, and 1250 cm^{-1}. The nmr spectrum displayed peaks ($\delta^{TMS}_{CCl_4}$) at 6.9 (broad multiplet, 4 H) for the phenyl protons, 6.80 (singlet, 1 H) for the vinyl proton superimposed on the phenyl protons, 3.95, 3.37, and 3.55, all singlets, each representing three protons for the three methoxy groups, and 2.12, a singlet (3 H) for the *o*-methyl group. *Anal.* Calcd for $C_{15}H_{17}NO_5$: C, 61.25; H, 5.50; N, 5.15. Found: C, 61.05; H, 5.75; N, 5.22.

E. *p*-Nitrophenyl Isocyanide. Ortho Ester Formation (13).—To 4.7 g (0.032 mol) of *p*-nitrophenyl isocyanide in 200 ml of methanol was added 4.5 g (0.032 mol) of dimethyl acetylenedicarboxylate. The solution was let stand for 2 weeks and the methanol was removed using a rotary evaporator. The viscous oil was dissolved in 50 ml of benzene and the benzene solution was allowed to evaporate at room temperature. After 2 days crystals had formed; they were collected and recrystallized from benzene, yield 2.2 g (20%), mp 155–159°. The ir spectrum (KBr) displayed significant peaks at 3340, 1725, 1650, 1550, and 1500 cm^{-1}. The nmr spectrum, in deuterioacetone, displayed a quartet at δ 8.10 (4 H, *p*-nitrophenyl protons), a singlet at 6.70 (1 H, vinyl proton), a singlet at 3.80 (3 H, carbomethoxy protons), and a singlet at 3.25 (9 H, methyl ortho ester protons). In addition, a very broad, ill-defined absorption centered at 9.66 integrating for one proton was also present (hydrogen bonded NH). *Anal.* Calcd for $C_{15}H_{18}N_2O_8$: C, 50.84; H, 5.08: N, 7.91; mol wt, 354. Found: C, 50.95; H, 5.10; N, 7.87; mol wt, 343.

F. *p*-Nitrophenyl Isocyanide. Imino Ester Formation (8).—If the above reaction mixture was let stand for only 1 week and the same work-up procedure was used, a small amount (*ca.* 1–2%) of the imino ester **8** could be isolated, mp 94–97°. The ir displayed significant peaks at 2950, 1700, 1670, and 1250 cm^{-1}. The nmr spectrum ($\delta^{TMS}_{CCl_4}$) displayed two doublets (4 H) for the *p*-nitrophenyl protons at 8.10 and 6.84, a singlet (1 H) at 6.75 for the vinyl proton, and three singlets, each representing three protons, at 3.91, 3.80, and 3.75 for the three methoxy groups. *Anal.* Calcd for $C_{14}H_{14}N_2O_7$: C, 52.20; H, 4.35; N, 8.70. Found: C, 52.19; H, 4.47; N, 8.70.

Reaction of Isocyanides with Phenylpropiolic Acid.—Phenylpropiolic acid (1 g) was dissolved in 35 ml of dry benzene and an equimolar amount of an isocyanide (cyclohexyl, *tert*-butyl, benzyl, or *p*-methoxyphenyl) was added. The solution was allowed to stand overnight. (If the benzene was moist, a small amount of the amine salt of phenylpropiolic acid would form owing to hydrolysis of the isocyanide.) Removal of the benzene using a rotary evaporator gave 0.4–0.6 g of pale yellow crystals, mp 255–257°. The ir spectrum displayed two strong peaks at 1820 and 1760 cm^{-1}, the former being weaker than the latter (a cyclic anhydride). A mixture melting point with an authentic sample[21] of 1-phenyl-2,3-naphthoic anhydride gave no depression. The ir spectrum of the product was identical with that of an authentic sample of 1-phenyl-2,3-naphthoic anhydride obtained by refluxing phenylpropiolic acid with acetic anhydride.

Registry No.—**6** (R = cyclohexyl), 38355-41-8; **7** (R = cyclohexyl), 31849-65-7; **8** (R = cyclohexyl), 38308-75-7; **8** (R = phenyl), 38308-76-8; **8** (R = *o*-tolyl), 38308-77-9; **8** (R = *p*-$NO_2C_6H_4$), 38308-78-0; **9** (R = cyclohexyl), 38308-79-1; **9** (R = *t*-Bu), 38308-80-4; **13** (R = *p*-$NO_2C_6H_4$), 38308-81-5; methyl propiolate, 922-67-8; cyclohexyl isocyanide, 931-53-3; dimethyl acetylenedicarboxylate, 762-42-5; *tert*-butyl isocyanide, 7188-38-7; *o*-tolyl isocyanide, 10468-64-1; phenylpropiolic acid, 637-44-5; 1-phenyl-2,3-naphthoic anhydride, 1985-37-1.

(21) F. G. Badder, *J. Chem. Soc.*, 1267 (1948).

Methyl- and Ethylnitrosocyanamide. Some Properties and Reactions[1]

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Methylnitrosocyanamide (**3**) and ethylnitrosocyanamide (**4**) were synthesized by aqueous nitrosation of the cyanamides. The ir spectra showed C≡N and N=O bands. The uv spectra indicated resonance structures similar to those of nitrosoureas and nitrosamines. The pmr of **3** and **4** (like those of dialkylnitrosamines) showed N-alkyl nonequivalence attributed to restricted rotation about the N–NO bond. In contrast, the pmr of alkylnitrosoureas showed NH_2 nonequivalence. The mass spectra of **3** and **4** had prominent peaks due to NO^+ and loss of N_2. Compound **4** was more stable to alkali and less stable to acid than ethylnitrosourea. In acid, **3** and **4** gave HNO_2 and the corresponding nitrosoureas (30–61%), perhaps because they are denitrosated to alkylcyanamides, hydrolyzed to alkylureas, and renitrosated. In alkali, **4** gave diazoethane (25%) and cyanate (79%). Nitrosation of methylguanidine proceeded slowly to give **3** (2%), methylnitrosourea (up to 35%), and a third unidentified uv-absorbing product.

Most *N*-nitroso compounds are powerful carcinogens in experimental animals and hence could be involved in the etiology of certain types of human cancer, if they were present in food or were synthesized by acid-catalyzed nitrosation in the stomach.[2] In support of the latter possibility, kinetic studies[3] showed that the acid-catalyzed N-nitrosation of some secondary amines, *N*-alkylureas, and *N*-alkylcarbamates proceeds very readily.

We reported[3d] that nitrosation of methylguanidine (**1**) gave methylnitrosourea (**2**), the new compound methylnitrosocyanamide (**3**), and an unidentified

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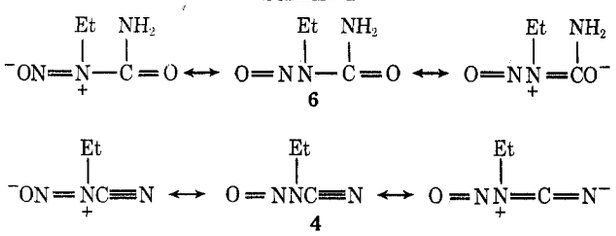
(2) (a) H. Druckrey, R. Preussmann, S. Ivankovic, and D. Schmähl, *Z. Krebsforsch.*, **69**, 103 (1967); (b) P. N. Magee and J. M. Barnes, *Advan. Cancer Res.*, **10**, 163 (1967); (c) J. Sander, *Arch. Hyg. Bakteriol.*, **151**, 22 (1967).

(3) (a) J. Sander, F. Schweinsberg, and H. P. Menz, *Z. Physiol. Chem.*, **349**, 1691 (1968); (b) J. Sander, G. Bürkle, L. Flohe, and B. Aeikens, *Arzneim.-Forsch.*, **21**, 411 (1971); (c) S. S. Mirvish, *J. Nat. Cancer Inst.*, **44**, 633 (1970); (d) S. S. Mirvish, *ibid.*, **46**, 1183 (1971); (e) S. S. Mirvish in "Analysis and Formation of Nitrosamines," International Agency for Research in Cancer, Lyon, France, in press.

third product, but the synthesis of **3** from **1** was given in summary only and its identification was not discussed. Since **1** occurs naturally in meat and fish, and nitrosation of arginine appears to yield analogous products, these reactions present a potential human hazard, though the reaction rates are very much slower than those for the nitrosation of alkylureas.[3d] In this paper we describe the synthesis of **3** and ethylnitrosocyanamide (**4**) from the cyanamides, some properties of **3** and **4**, and the synthesis of **3** from **1**.

Synthesis and Physical Properties of Methyl- and Ethylnitrosocyanamides (3 and 4).—Ethylcyanamide (**5**) was synthesized by treating ethylamine with cyanogen bromide. Nitrosation of **5** gave nitrosocyanamide **4** as shown by elemental analysis, molecular ion of the mass spectrum at *m/e* 99, and ir, uv, and pmr spectra. Strong ir bands at 2230 (C≡N) and 1540 cm^{-1} (N=O) were indicative of the structure. The three weak uv maxima of **4** at 377–406 nm were similar to those shown by ethylnitrosourea (**6**), but were shifted 6 nm hypsochromically. The uv absorption of nitrosourea **6** and nitrosocyanamide **4** is attributed to the resonance structures shown in Scheme I, similar

SCHEME I



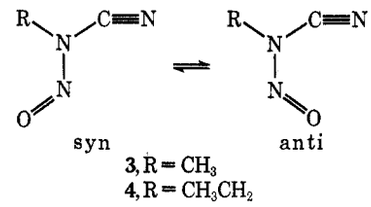
to the explanation of the uv absorption of nitrosamines.[4]

Crude methylcyanamide (**7**) was synthesized from methylamine and cyanogen bromide, and then nitrosated to give **3**. Nitrosocyanamide **3** could not be prepared analytically pure, but was identified by the uv, ir, and pmr spectra, the molecular ion of the high-resolution mass spectrum, and analogy with **4**.

The pmr of nitrosocyanamide **4** at 37° in methylene chloride gave a broad singlet at δ 4.17 attributed to the methylene protons and a poorly resolved triplet centered at 1.41 attributed to the methyl group. At and below 0°, the singlet was split into two quartets centered at δ 4.66 and 3.77 and the triplet was split into two triplets centered at 1.58 and 1.28 (ratio 1:0.84, respectively). At 60°, the pmr showed a single quartet at δ 4.14 and a triplet at 1.42. We attribute this temperature dependence to mobile syn and anti isomers (Scheme II), by analogy with nitrosamines.[5]

The pmr of nitrosocyanamide **3** in methylene chloride showed similar effects. The methyl resonance appeared as a singlet (δ 3.51) at 60°, a broad singlet at 37°, and two singlets at −40° (δ 4.18 and 3.23, ratio 1:2.85, *cf.* 1:0.84 in **4**). In both **3** and **4** we attribute the upfield resonance to the syn isomer (alkyl syn to nitroso), in agreement with the assignments in nitrosamines.[5a] Hence, changing the alkyl group from

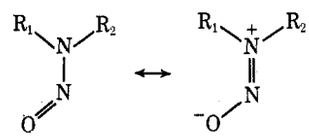
SCHEME II



methyl to ethyl decreases the relative population of syn isomer. This is attributed to steric hindrance by the ethyl group, as in nitrosamines.[5a]

The two conformers of nitrosamines are apparent in the pmr at 36°. Their presence is attributed to restricted rotation about the N–N bond (Scheme III,

SCHEME III

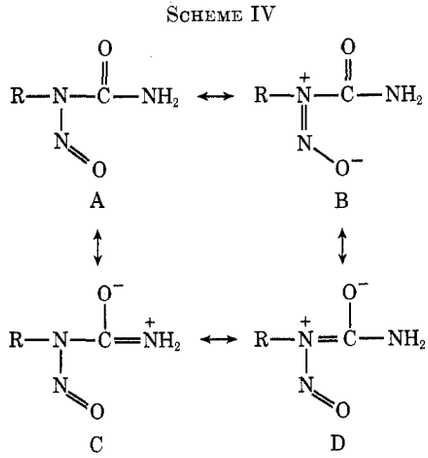


R_1 and R_2 = alkyl).[5a] The inductive effect of the N-alkyl groups would tend to stabilize the dipolar resonance form In nitrosocyanamides **3** and **4** (Scheme III, R_1 = alkyl, R_2 = CN) the electron-withdrawing cyano group would tend to destabilize the dipolar resonance form and hence lower the coalescence temperature.

In contrast, the pmr of nitrosourea **2** in acetone-d_6 showed a sharp methyl peak and that of nitrosourea **6** in acetone-d_6 showed a sharp methylene peak, both of which remained unchanged from 60 to −40°. However, at −40° the protons bound to nitrogen were split into two singlets in both **2** (δ 7.52 and 8.02) and **6** (7.50 and 7.98). This is probably not a solvent effect, since the pmr of **4** showed a similar temperature dependence in acetone-d_6 as in methylene chloride.

In nitrosoureas **2** and **6**, which can be represented by four resonance forms (Scheme IV), the absence of

SCHEME IV



N-alkyl nonequivalence is attributed to the destabilizing of resonance form B (Scheme IV) by the electron-withdrawing amide group, which would lower the barrier to rotation about the N–N bond. The presence of N–H nonequivalence is attributed to restricted

(4) J. T. D'Agostino and H. H. Jaffe, *J. Amer. Chem. Soc.*, **92**, 5160 (1970).

(5) (a) G. J. Karabatsos and R. A. Taller, *ibid.*, **86**, 4373 (1964); (b) W. Lijinsky, L. Keefer, and J. Loo, *Tetrahedron*, **26**, 5137 (1970); (c) J. T. D'Agostino and H. H. Jaffe, *J. Org. Chem.*, **36**, 992 (1971).

rotation about the C–NH_2 bond, owing to the contribution of form C.

The accurate mass measurements for the mass spectral fragmentations of **3** and **4** are given in Table I. Both compounds gave a large *m/e* 30 (NO^+) peak.

TABLE I
ACCURATE MASS MEASUREMENTS

Nominal mass	Determined mass	Ion assignment	Calculated mass
	Methylnitrosocyanamide (**3**, $C_2H_3N_3O$)		
85	85.0277	$C_2H_3N_3O$	85.0276
57	57.0211	C_2H_3NO	57.0214
55	55.0288	$C_2H_3N_2$	55.0296
43	43.0061[a]	CHNO	43.0058
43	43.0182[a]	C_2H_3O	43.0183
41	43.0263	C_2H_3N	41.0265
30	29.9978	NO	29.9980
29	29.0026[b]	CHO	29.0027
29	29.0264[b]	CH_3N	29.0265
	Ethylnitrosocyanamide (**4**, $C_3H_5N_3O$)		
71	71.0361	C_3H_5NO	71.0361
70	69.9998	CN_3O	70.0041
68	68.0360	$C_3H_4N_2$	68.0352
56	56.0134	C_2H_2NO	56.0136
55	55.0290	$C_2H_3N_2$	55.0296
53	53.0133	C_2HN_2	53.0140
41	41.0140	CHN_2	41.0139
40	40.0187	C_2H_2N	40.0177

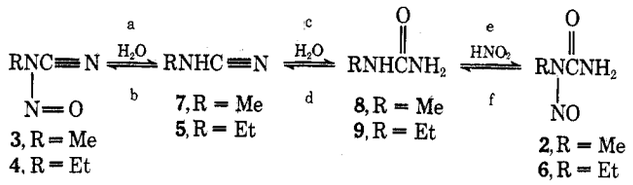
[a] $CHNO/C_2H_3O$ is 1/9. [b] CHO/CH_3N is 1/6.

This fragmentation is common in nitrosamines but is generally of lower intensity.[6] An M − NO peak was observed in **3** but not **4**. A common fragmentation of dialkylnitrosamines is cleavage of one alkyl radical.[6a,f] Loss of an ethyl radical (*m/e* 70) was observed in **4**, but there was no analogous fragmentation in **3**. Interestingly, the mass spectra of **3** and **4** showed prominent peaks resulting from loss of N_2 (*m/e* 57 and 71, respectively). This has been reported in the thermolysis[7] but not the mass spectra of nitrosamines. Most other fragments from **3** and **4** cannot readily be explained by simple cleavages or rearrangements. Loss of 17 (OH)[6] or 31 (NHO),[6f] which are other characteristic fragmentations of nitrosamines, does not occur.

Chemical Properties of Methyl- and Ethylnitrosocyanamides (3 and 4).—Compounds **3** and **4** were unstable, but less so than parent cyanamides **5** and **7**, and were readily extracted by methylene chloride from aqueous solution. Alkaline solutions of **3** and **4** decomposed with a few seconds, as shown by the loss of uv absorption at 370–410 nm. Acidic solutions of **3** and **4** partly decomposed within 10 min at 0° to give HNO_2. The half-lives at 25° of nitrosourea **6** and nitrosocyanamide **4** in various buffers are compared in Table II. Base-induced decomposition of **6** began to occur rapidly at pH 8 (in agreement with previous studies[8]), but **4** remained fairly stable up to pH 10. Acid-induced decomposition of **6** began to proceed rapidly only in 1.0 *N* HCl, but that of **4** occurred rapidly at pH 2.

When **3** was left overnight in cold 3 *N* sulfuric acid, nitrosourea **2** was obtained in 61% yield. Similar treatment of **4** gave nitrosourea **6** in 30% yield. These reactions could occur by direct hydration of the nitrosocyanamides. However, the instability of nitrosocyanamides (Table II) and the formation of HNO_2 in acid suggest that **3** and **4** first lose HNO_2 to give alkylcyanamidees **7** and **5**, which are hydrolyzed to methylurea (**8**) and ethylurea (**9**),[9] and then renitrosated by the HNO_2 liberated in reaction a (Scheme V).

SCHEME V



All these reactions should be reversible; *e.g.*, reactions b and e are those used to synthesize the nitroso derivatives and reaction c is reversible.[9]

This acid-induced decomposition of **3** and **4** to give HNO_2 and (presumably) cyanamides **5** and **7** (reaction a) resembles the acidic decomposition of nitrosoureas (reaction f), which can give quantitative yields of nitrite.[10] In explanation of the greater sensitivity to acid of **4** compared with nitrosourea **6**, the alkyl-substituted nitrogen of **4** should be more basic than that of **6** (*cf.* cyanamide, pK_a 10.3, and urea, pK_a 0.1[11]). This would make **4** more susceptible to protonation of this nitrogen,which presumably initiates the hydrolysis.

Under the highly acidic conditions used, decomposition of **4** (reaction a) would be favored over its formation (reaction b). In contrast, the reverse reaction occurred in our synthesis of **4**, where excess nitrite was used and the pH was 2. The question arises as to why Scheme V proceeds from right to left, *i.e.*, why nitrosation of ureas **8** and **9** is favored over that of cyanamides **5** and **7**. This is not due to a more rapid formation of the nitrosoureas, since cyanamides are nitrosated at least as fast as ureas, as shown in preliminary studies indicating that the kinetic equation for the nitrosation of **4** is similar to that for nitrosation of ureas **8** and **9**.[3d] Instead, the direction of Scheme V is attributed to the more rapid denitrosation of nitrosocyanamides (reaction a) in strong acid as compared with the denitrosation of nitrosoureas (reaction f) (*cf.* Table II). The higher yield of nitrosourea from methyl compound **3** as compared to ethyl compound **4** might be due to the 3.5-fold higher rate constant for the nitrosation of urea **8** compared with urea **9**.[3d]

Alkaline decomposition of **4** in a methanol–ether mixture gave diazoethane in 25% yield, as measured

(6) (a) J. Collin, *Bull. Soc. Roy. Sci. Liege*, **23**, 201 (1954); (b) S. S. Dubov and A. M. Khokhlova, *Zh. Obshch. Khim.*, **34**, 1961 (1964); (c) G. Schroll, R. G. Cooks, P. Klemmensen, and S. O. Lawesson, *Ark. Kemi*, **28**, 413 (1967); (d) S. Billets, H. H. Jaffe, and F. Kaplan, *J. Amer. Chem. Soc.*, **92**, 6964 (1970); (e) J. W. ApSimon and J. D. Cooney, *Can. J. Chem.*, **49**, 1367 (1971); (f) M. J. Saxby, *J. Ass. Offic. Anal. Chem.*, **55**, 9 (1972).

(7) W. Rickatson and T. S. Stevens, *J. Chem. Soc. D*, 3960 (1963).

(8) E. R. Garrett, S. Goto, and J. F. Stubbins, *J. Pharm. Sci.*, **54**, 119 (1965).

(9) (a) M. J. Sullivan and M. L. Kilpatrick, *J. Amer. Chem. Soc.*, **67**, 1815 (1945); (b) T. Mukaiyama, S. Ohishi, and H. Takamura, *Bull. Chem. Soc. Jap.*, **27**, 416 (1954).

(10) (a) A. Forist, *Anal. Chem.*, **36**, 1338 (1964); (b) R. Preussmann in "Analysis and Formation of Nitrosamines," International Agency for Research in Cancer, Lyon, France, in press.

(11) D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution," Butterworths, London, 1965.

TABLE II

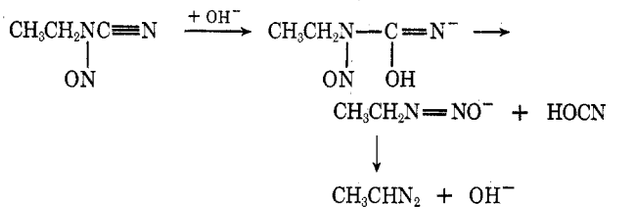
HALF-LIVES AT 25° OF ETHYLNITROSOUREA (6) AND ETHYLNITROSOCYANAMIDE (4), GIVEN IN HOURS

Buffer	1.0 *N* HCl	0.1 *N* HCl	pH 2	pH 3	pH 4	pH 5	pH 6	pH 7	pH 8	pH 9	pH 10	0.1 *N* NaOH
Compound 6	1.7	>50	>50	>50	>50	>50	22	2.6	0.45	0.022	0.008	0.002
Compound 4	<0.002	0.07	0.28	1.6	7.8	20	46	37	25	12	1.2	0.004

by distillation of the diazoethane into a benzoic acid solution and estimation of ethyl benzoate. Alkaline decomposition of **4** in aqueous solution gave a 79% yield of cyanate. Under similar conditions, nitrosourea **6** gave a 45% yield of diazoethane and a 66% yield of cyanate (*cf.* ref 12).

To explain the greater stability toward base of nitrosocyanamides as compared with nitrosoureas, we note that the first step in the base-induced decomposition of nitrosoureas may be abstraction of H^+ from the amide NH_2.[12] In the base-induced decomposition of nitrosocyanamides, such a step is impossible and a less facile mechanism must be operating. One possibility is attack of OH^- on the carbon atom of the cyanide group, analogous to mechanisms proposed for the acid-catalyzed hydrolysis of cyanamides[9] and (perhaps wrongly[12]) for the alkaline decomposition of nitrosoureas[8] (Scheme VI).

SCHEME VI

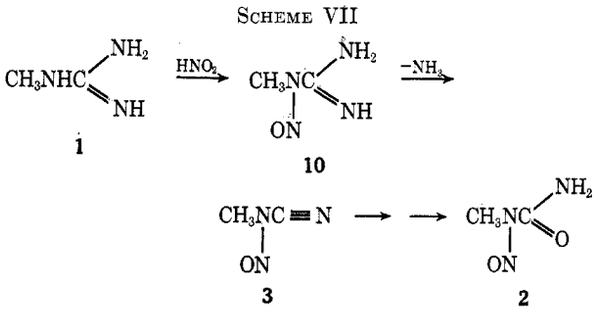


Formation of Methylnitrosocyanamide (3) from Methylguanidine (1).—When 0.05 *M* guanidine **1** was treated with 0.2 *M* nitrite at pH 1 and 25°, methylene chloride extracts of the reaction mixture contained both nitrosocyanamide **3** and nitrosourea **2**. Under these conditions, the yield of **3** rose to 2% of **1** at 3 hr and then declined, and the yield of **2** continued rising to 7% of **1** at 10 hr.[3d] Under highly acidic conditions, the yield of **2** was 35% and **3** was not detected.[3d] The identity of **3** prepared from **1** with **3** prepared from cyanamide **7** was demonstrated by the similar uv, ir, and pmr spectra and similar reaction in acid to give HNO_2 and nitrosourea **2**.

The aqueous solution after nitrosation of guanidine **1** contained a third product which was not extractable by methylene chloride and showed uv max (acetone) 382, 397, and 415 nm. The uv spectrum changed reversibly on adding triethylamine to an acetone solution, or in aqueous solutions above pH 8, to give a substance with uv max (acetone) 370 (inflection), 381, and 397 nm. The product, which has not been purified, was unstable in strong acid (when it yielded HNO_2) and alkali. It could be the unknown *N*-methyl-*N*-nitrosoguanidine (**10**).

We speculate (Scheme VII) that acid-catalyzed nitrosation of **1** first gives nitrosoguanidine **10**. Then **10** could lose ammonia to give **3**, which would be slowly converted to **2** as in Scheme V. Related reactions have been reported for nitrosoguanidine,[13,14] *N*-alkyl-*N'*-nitrosoguanidines,[14] *N*-alkyl-*N'*-nitroguanidines,[15] and *N*-alkyl-*N*-nitroso-*N'*-nitroguanidines.[16] Nitrosation of creatine and creatinine gave nitrososarcosine and a C-nitroso derivative, respectively.[17]

SCHEME VII



In Vivo **Effects.**—Nitrosocyanamide **4** was highly toxic to rats, with an acute LD_{50} of 15 mg/kg body weight when injected intraperitoneally in tricaprolein solution.[18] We are now testing the effect of long-term feeding of **4** to rats.

Experimental Section

N-Nitroso compounds were kept at or below 0° where possible, never heated above 25°, and treated with care because of their actual or potential carcinogenic activity.[2] Solutions in methylene chloride were dried over sodium sulfate and evaporated at 25 mm. Infrared (ir) spectra were determined on a Beckman IR-18 spectrophotometer. Proton magnetic resonance (pmr) spectra were determined on a Varian HA-100 spectrometer equipped with a Model V-4343 variable temperature accessory. Mass spectra were determined on an AEI Model MS-9 mass spectrometer. Exact mass measurements were determined at a resolving power of 14,000. Melting points are corrected. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill.

Ethylcyanamide (5) (Modified from Literature[9b]).—A solution of 40 g (445 mmol) of ethylamine in 150 ml of CH_2Cl_2 was cooled to −10 to −20° in a flask fitted with a separating funnel and drying tube. A solution of 30.4 g (286 mmol) of cyanogen bromide in 180 ml of CH_2Cl_2 was added over 1 hr, and the mixture was stirred at −10 to −20° for another hour and filtered. To retard polymerization, the filtrate was just acidified (as shown by adding drops to wet indicator paper) with 97% formic acid, when two phases formed. The bottom phase was evaporated to give 16.15 g (81%) of crude **5** as a colorless, viscous oil. The product was stored overnight under N_2 at −15° and then nitrosated.

A small sample of **5** was distilled at 54–56° (0.3 mm) [lit.[9b] bp 94–95° (4 mm)]. The distillate was less stable than the crude product and solidified after 2–3 days at −15°. Freshly distilled **5** showed little uv absorption; ir (CCl_4) 3220 (NH), 2980 (CH), and 2230 cm^{-1} (C≡N) [undistilled material also showed ir peaks at 1720 (C=N of ? dimer) and 1610 cm^{-1} (NH of ? dimer)];

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pmr at 0° ($CDCl_3$) δ 1.17 (t, 3, J = 7 Hz, CH_3), 3.03 (q, 2, J = 7 Hz, CH_2), 5.4–5.9 (broad, 1, NH); mass spectrum (70 eV, gallium inlet system) m/e (rel intensity) 70 (42), 55 (100), 53 (20), 43 (26), 42 (36), 41 (25), 40 (18), 30 (26), 29 (57), 28 (69), 27 (74), 26 (24).

Ethylnitrosocyanamide (4).—Crude cyanamide **5** (16.1 g, 231 mmol) was dissolved in 500 ml of $HClO_4$–0.05 M sodium citrate buffer at pH 2. To this was added a freshly prepared solution of 34.5 g (500 mmol) of $NaNO_2$ in 250 ml of water acidified to pH 2 with $HClO_4$. After 1 hr at 25° without stirring, another similar solution of HNO_2 was added. After another hour the mixture was extracted with 4 × 150 ml of CH_2Cl_2. The extract was dried and evaporated to give 11.3 g of greenish-brown oil. This was distilled at 22° (0.4 mm) and the distillate was collected in a tube cooled with Dry Ice–ethanol. The first fraction (2.4 g) contained solvent, but the second fraction, 7.6 g of brownish-yellow lachrymatory oil, was pure **4** (33%). This was always handled in a hood, and was stable when stored at −15° under N_2: d^{25}_4 1.0444; uv max (CH_2Cl_2) 256 nm (ε 3410), 362 (inflection, 72), 377 (116), 390 (156), and 406 (135); uv max (water) 257 nm (ε 3640), 376 (104), 388 (126), and 402 (100); ir (CCl_4) 2980 and 2940 (CH), 2230 (C≡N), 1540 (N=O), and 925 cm^{-1} (NNO); pmr ($CDCl_3$) δ 1.41 (m, 3, CH_3) and 4.17 (very broad, 2, CH_2); mass spectrum (70 eV, direct inlet system) m/e (rel intensity) 99 (6), 70 (47), 68 (31), 67 (19), 56 (10), 55 (82), 53 (52), 43 (30), 42 (34), 41 (34), 40 (24), 30 (100), 29 (53), 28 (100), 27 (78), 26 (25).

Anal. Calcd for $C_3H_5N_3O$: C, 36.4; H, 5.1; N, 42.4. Found: C, 36.5; H, 5.2; N, 42.1.

Ethylnitrosourea (6).[3d]—This showed uv max (CH_2Cl_2) 237 nm (ε 7100), 382 (79), 396 (121), and 414 (111) (*cf.* ref 3d); pmr ($CDCl_3$) δ 1.00 (t, 3, J = 7.5 Hz, CH_3) and 3.83 (q, 2, J = 7.5 Hz, CH_2).

Methylnitrosocyanamide (3) from Methylcyanamide (7).—Methylamine and cyanogen bromide were allowed to react as for the synthesis of **5**, to give **7** as an impure oil:[9b] ir (CH_2Cl_2) 3400 (NH), 3000 (CH), 2250 and 2230 (C≡N of monomer and ? dimer), 1740 (C=N of ? dimer), and 1670 cm^{-1} (NH of ? dimer). Compound **7** could not be distilled owing to its ready polymerization[9b] and was nitrosated directly by the method used to synthesize **4**. The resulting solution of **3** in CH_2Cl_2 was distilled at 20° (0.4 mm) to give a volatile, lachrymatory oil, which was redistilled. The middle fraction of the final distillate was nearly pure **3**: uv max (CH_2Cl_2) 253 nm (ε 3240), 373 (121), 385 (164), 401 (145); ir (CCl_4) 3080 and 2960 (CH), 2250 (C≡N), 1540 (N=O), and 910 cm^{-1} (NNO); pmr ($CDCl_3$) δ 3.39 (s, CH_3); mass spectrum (70 eV, direct inlet system) m/e (rel intensity) 85 (100), 57 (20), 56 (8), 55 (6), 47 (7), 43 (9), 41 (8), 30 (60), 29 (12). The accurate mass of the molecular ion, obtained by introducing the sample through an unheated gas manifold, was 85.0277 (calcd for $C_2H_3N_3O$, 85.0276); by this method of introduction CH_2Cl_2 (m/e 88, 86, and 84) was also detected. The elemental analysis of a sample subjected to 1-mm vacuum to remove CH_2Cl_2 was within 0.2% of the theoretical value for C and H, but was 1% low for N. The CH_2Cl_2–pH 5 buffer partition coefficient was 17:1 at 25°, as determined at 385 nm (ε in pH 5 buffer 135).

Methylnitrosourea (3).[3d]—This showed pmr ($CDCl_3$) δ 3.14 (s, CH_3).

Acidic Decomposition of Methyl- and Ethylnitrosocyanamide (3 and 4).—A solution of 135 mg of **3** in 80 ml of ice-cold 3 N H_2SO_4 was left for 10 min at 0° and then extracted with CH_2Cl_2. The extract had uv maxima at 358, 372, and 386 nm indicative of HNO_2.[3d] Similar acidic solutions of 199 mg of **3** were left overnight at 4° and then extracted with 6 × 50 ml of CH_2Cl_2. Evaporation of the extract gave 147 mg of impure **2** (61%, mp 111–113°), which was recrystallized twice from CH_2Cl_2–hexane (1:1)[3d] to give crystals, mp 125°, not depressed on admixture with pure **2** (lit.[3d] mp 126°), uv (CH_2Cl_2), and pmr ($CDCl_3$) spectra as for pure **2**. Compound **4** (192 mg) was treated similarly to give 67 mg (30%) of **6**, mp 99°, not depressed on admixture with pure **6** (mp 99–100°[3d]), uv (CH_2Cl_2) and pmr ($CDCl_3$) as for pure **6**.

Alkaline Decomposition of Ethylnitrosocyanamide (4) (Based on Literature[19]).—A mixture of 209 mg (2.11 mmol) of **4** in 10 ml of ether and 10 ml of 10% KOH in methanol was stirred at 0° in a hood until A at 390 nm reached a minimum of *ca.* 0.300 (*ca.* 1 hr). The ether was then distilled into 15 ml of ice-cold ether containing benzoic acid (1.0 mmol) to give 31 ml of solution A. In 5 ml of solution A, unreacted benzoic acid was back-titrated with 0.1 N NaOH after adding 5 ml of water, 2.5 ml of ethanol, and phenolphthalein. The results showed that 0.52 mmol of benzoic acid (25% from **4**) had reacted with the diazoethane formed from **4**. After the titration, the ether solution contained ethyl benzoate corresponding to 23% from **4**, as estimated by A at 272 nm.

The remainder of ether solution A was extracted with 6 × 25 ml of saturated Na_2CO_3 solution and 3 × 25 ml of water, and dried over Na_2SO_4 to give solution B. An aliquot of solution B was evaporated to dryness, dissolved in absolute ethanol, and subjected to glc on 15% Chromosorb W at 125°. A single peak was observed, with correct retention time for ethyl benzoate and peak height corresponding to 19% yield from **4**. Another aliquot of solution B showed (after evaporation) ir (CCl_4) identical with that of pure ethyl benzoate. A similar experiment with nitrosourea **6** gave a 45% yield of ethyl benzoate, as estimated by back-titration of unreacted benzoic acid.

To demonstrate the formation of cyanate, a solution of 100 mg of **4** in 20 ml of 0.04 N NaOH was left for 10 min at 25° (solution C.) This was analyzed for cyanate using the blue copper nitrate–pyridine complex,[20] which showed the correct absorption spectrum (max 680 nm). An aliquot of solution C was evaporated to dryness (0.1 mm, 25°). The residue showed ir (Nujol mull) 2220 (s), 1290 (w), and 1200 (w), as given by authentic NaCNO.[21] Cyanate was also estimated after similar decomposition of 100 mg of nitrosourea **6**.

Methylnitrosocyanamide (3) from Methylguanidine (1).—A solution of 3.65 g of methylguanidine sulfate [recrystallized from ethanol–H_2O (6:1), mp 243–244°, 30 mmol of **1**], 13.8 (200 mmol) of $NaNO_2$, and 8.8 g (50 mmol) of trisodium citrate·$2H_2O$ in 1 l. of water was acidified with $HClO_4$ to pH 1 (pH meter), allowed to react at 25° for 2 hr, and extracted with 5 × 200 ml of CH_2Cl_2. The dried extract was evaporated to give 1.2 g of crude **3**, which was distilled twice as before, to give 150 mg of distillate. The uv (CH_2Cl_2), ir (CCl_4), and pmr ($CDCl_3$) spectra were identical with those of **3** synthesized from **7**. The uv absorption disappeared rapidly in alkali. A once-distilled sample (202 mg, 2.48 mmol) of **3** synthesized from **1** was dissolved in 120 ml of ice-cold 3.0 N H_2SO_3 and its decomposition was examined as before. The products were HNO_2 (shown by the uv spectrum) and 148 mg of impure nitrosourea **2** (58%, 1.43 mmol), mp 108–110°. This was recrystallized from CH_2Cl_2–hexane (1:1) to give 48 mg of **2**, mp 118°, not depressed when mixed with pure **2** (lit.[3d] mp 126°), uv (CH_2Cl_2) and pmr ($CDCl_3$) the same as for pure **2**.

Registry No.—**1**, 471-29-4; **3**, 33808-17-6; **4**, 38434-77-4; **5**, 38434-78-5; **6**, 759-73-9; **7**, 4674-68-4.

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