N-Nitroso- and N-Nitrotrialkylureas and Their Decomposition

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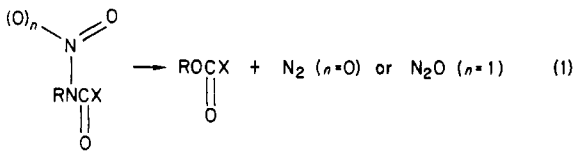
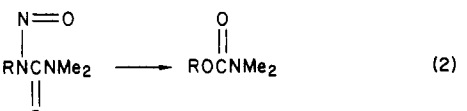
The synthesis and decomposition of *N*-(*n*-butyl)-*N'*,*N'*-dimethyl-*N*-nitrosourea (**2a**), *N*-(*n*-butyl)-*N'*,*N'*-dimethyl-*N*-nitrourea (**3a**), *N'*,*N'*-dimethyl-*N*-(1-norbornyl)-*N*-nitrosourea (**2b**), and *N'*,*N'*-dimethyl-*N*-(1-norbornyl)-*N*-nitrourea (**3b**) are described. Several of the compounds show complex NMR spectra ascribable to rotational isomerism. Decomposition of **2a** and **3a** gave *n*-butyl *N*,*N*-dimethylcarbamate and tetramethylurea, while decomposition of **2b** and **3b** in methylene chloride gave 1-norbornyl *N*,*N*-dimethylcarbamate and 1-norbornyl chloride. These products are formed via diazotic acid derivatives and carbonium ion pairs; the reaction mechanism is essentially the same as that established for the closely related *N*-nitrosoamides. In concentrated solutions, nitrosourea **2a** yielded a new product, amino acid **20**.

Introduction. We have previously reported the synthesis and decomposition of alkyl nitrosoamides[1,2] (eq 1, R = alkyl; n = 0; X = alkyl or aryl), nitroamides[3-6] (n = 1; X = alkyl or aryl), nitrosocarbamates[6] (n = 0; X = O-alkyl), and nitrocarbamates[3-7] (n = 1, X = O-alkyl). We have now extended the series to the nitroso and nitroureas (X = NR_2). (In following articles in this series, we also outline the deamination chemistry of the nitro- and nitrosohydroxylamines.)



(1)

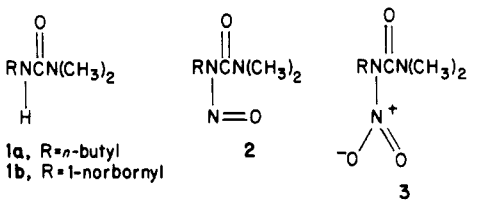
The decomposition of several nitrosoureas in aqueous media was studied many years ago.[8] A renewed interest[9] has been evinced in these compounds, presumably because a number of the *N*-alkyl-*N*-nitrosoureas have been reported to be chemical carcinogens.[10] Reactions of the nitrosoureas in organic media are less well-known. Jones et al.[11] reported that the thermal decomposition of *N'*,*N'*-dimethyl-*N*-(2,3-diphenylcyclopropenyl)-*N*-nitrosourea yielded 2,3-diphenylcyclopropenyl *N*,*N*-dimethylcarbamate (eq 2). Shortly after, we briefly described the decomposition of *N'*,*N'*-dimethyl-*N*-(1-norbornyl)-*N*-nitrosourea and the *N*-nitro analogue in halogenated solvents; major products were 1-norbornyl *N*,*N*-dimethylcarbamate and 1-norbornyl chloride.[12] More recently, Singer described the decomposition of several *N*,*N'*,*N'*-trialkyl-*N*-nitrosoureas as neat liquids, or in one instance as a solution in hexadecane.[13] In addition to the expected carbamates, novel amino acid products were formed (referred to at the end of the discussion section).



(2)

In this paper we report the results of our studies of the synthesis and decomposition of *N*-(*n*-butyl)-*N'*,*N'*-dimethyl-*N*-nitrosourea (**2a**), *N*-(*n*-butyl)-*N'*,*N'*-dimethyl-*N*-nitrourea (**3a**), *N'*,*N'*-dimethyl-*N*-(1-norbornyl)-*N*-nitrosourea (**2b**), and *N'*,*N'*-dimethyl-*N*-(1-norbornyl)-*N*-nitrourea (**3b**).

Syntheses. The reactions of *n*-butyl and 1-norbornyl isocyanates with dimethylamine produced the corresponding ureas, **1a** and **1b**, which on nitrosation with dinitrogen tetraoxide[1] yielded *N*-nitrosoureas **2a** and **2b**.



Nitration of the ureas proceeded with more difficulty. Fuming nitric acid in acetic anhydride[3] produced only the *N*-nitrosoureas. The use of nitronium tetrafluoroborate or nitronium hexafluorophosphate again led to nitrosation as the major process, accompanied by 3–5% yields of the desired *N*-nitroureas **3a** and **3b**. In addition, large amounts of dimethylnitroamine were formed. White and Grisley[3] have observed that systems that can be oxidized, or nitrating media that contain oxides of nitrogen, often lead to nitrosation. More recently, Gidaspov et al.,[14] in an examination of the nitration of secondary amines with nitronium tetrafluoroborate, found nitrosation to be a competing reaction. The nitrosation was attributed to the reduction of NO_2^+ by the amine to give NO_2, a nitrosating agent.[15] While the authors were able to lower the yields of nitrosoamine to 6% by operating at −40 °C (as compared to a 44% yield at 25 °C), the nitration of **1a** at −78 °C showed no change in the yield of nitrosourea compared to the reaction at 25 °C. The use of dinitrogen pentoxide at −30 °C (with **1a**) or a mixture of nitric and sulfuric acids at −15 °C (with **1b**) produced the desired compounds, but in low yields (11% for **3a** and 2% for **3b**).

(1) White, E. H. *J. Am. Chem. Soc.* **1955**, *77*, 6008, 6011, 6014.
(2) White, E. H.; Aufdermarsh, C. A. *J. Am. Chem. Soc.* **1961**, *83*, 1179.
(3) White, E. H.; Grisley, D. W. *J. Am. Chem. Soc.* **1961**, *83*, 1191.
(4) White, E. H.; Baumgarten, R. J. *J. Org. Chem.* **1964**, *29*, 3636.
(5) White, E. H.; Chen, M. C.; Dolak, L. A. *J. Org. Chem.* **1966**, *31*, 3038.
(6) White, E. H.; Dolak, L. A. *J. Am. Chem. Soc.* **1966**, *88*, 3790.
(7) White, E. H.; Field, K. W. *J. Am. Chem. Soc.* **1975**, *97*, 2148–2153.
(8) Werner, E. A. *J. Chem. Soc.* **1919**, *115*, 1093.
(9) (a) Singer, S. S.; Cole, B. B. *J. Org. Chem.* **1981**, *46*, 3461. (b) Snyder, J. S.; Stock, L. M. *J. Org. Chem.* **1980**, *45*, 1990. This article has a good summary of previous work in the field.
(10) Lijinsky, W.; Garcia, H.; Keejer, L.; Loo, J.; Ross, A. E. *Cancer Res.* **1972**, *32*, 893.
(11) Jones, W. M.; Stowe, M. E.; Wells, E. E., Jr.; Lester, E. W. *J. Am. Chem. Soc.* **1968**, *90*, 1849.
(12) White, E. H.; Ryan, T. J.; Field, K. W. *J. Am. Chem. Soc.* **1972**, *95*, 1360.
(13) Singer, S. S. *J. Org. Chem.* **1982**, *47*, 3839.
(14) Ilyushin, M. A.; Golod, E. L.; Gidaspov, B. V. *Zh. Org. Khim.* **1977**, *13*, 11.
(15) White, E. H.; Feldman, W. R. *J. Am. Chem. Soc.* **1957**, *79*, 5832.

0022-3263/84/1949-4860$01.50/0

Chart I

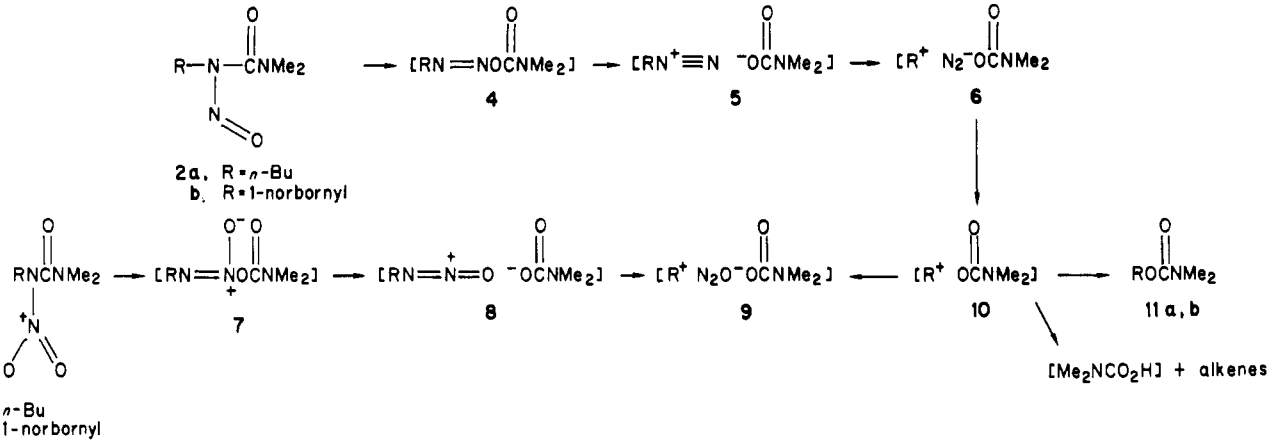
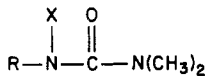


Table I. ^{1}H NMR Data of Substituted Ureas

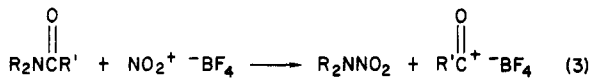


1-3

compd	temp, °C	δ $N(CH_3)_2$[a]
1a, R = *n*-Bu; X = H	25	2.86
1b, R = 1-norbornyl; X = H	25	2.88
	−59	2.91
2a, R = *n*-Bu; X = NO	25	3.13
	−63	3.10, 3.22
2b, R = 1-norbornyl; X = NO	25	2.75, 3.05
3a, R = *n*-Bu; X = NO_2	25	3.07
	−64	3.09, 3.14

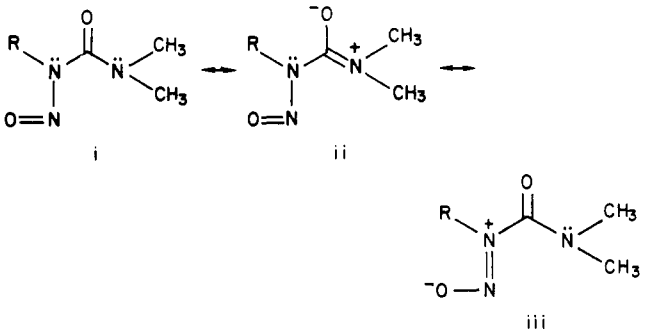
[a] In $CDCl_3$ (relative to Me_4Si), except for **1a** (in CCl_4).

The formation of dimethylnitramine in the nitrations undoubtedly stems from attack of the nitronium ion on the more basic *N,N*-dimethylamino grouping. In a related case, Andreev et al.,[16] have reported the cleavage of *N,N*-dialkylamides by nitronium tetrafluoroborate to give *N*-dialkyl-*N*-nitroamines (eq 3).

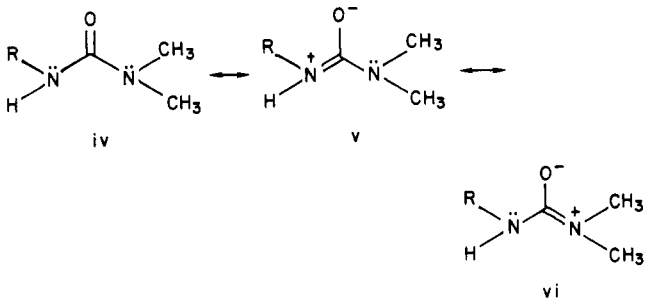


Where the products of decomposition of the nitroureas are of major interest, the low yields of nitroureas referred to above can be circumvented through use of the "salt" modification of the deamination reaction (see eq 4).

NMR Spectra. The spectra of the *n*-butylnitroso- and *n*-butylnitroureas are temperature dependent. At 25 °C, the hydrogens of the dimethylamino groups appear as singlets, while at ~−60 °C they appear for each compound as two equally intense peaks (Table I).[17] For norbornylnitrosourea (**2b**), the doubled signal is observed even at room temperature. This splitting of the dimethylamino absorption is similar to that observed for dimethylformamide,[18] and presumably the phenomena are related. In the present case, delocalization of the electron pair on the dimethylamino nitrogen (form ii) leads to partial C–N



double bond character and thus to restricted rotation about that bond. The methyl groups are in different environments (on the NMR time scale) and they have different chemical shifts. The second nitrogen in the *N*-nitroso- (and *N*-nitro) ureas is effectively "neutralized" in cross-conjugation with the carbonyl group, since its electron pair is partially delocalized over the nitroso group (form iii) (similarly involving the nitro group in the case of **3a** and **3b**). In the parent urea (iv), the nitrogens compete ef-



fectively equally in interactions with the carbonyl group (v, vi); less C–N double bond character per bond and a lower rotational barrier is the result.[19] Experimentally, the parent ureas show only singlets for the dimethylamino groups regardless of the temperature range over which they were examined. A similar effect of competing electronic delocalization has been observed with substituted phenyl esters of dimethylcarbamic acid.[20]

The persistence of doubling of the methyl signal for the norbornylnitrosourea (**2b**) at room temperature may be a result of the population of a new conformation (vii) resulting from mutual repulsion of the bulky norbornyl group and the nitroso group (the transoid NO–CO conformation shown in form i has been shown to be the most stable one

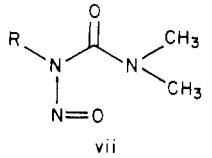
(16) (a) Andreev, S. A.; Novik, L. A.; Lebedev, B. A.; Tselinskii, I. V.; Gidaspov, B. V. *Zh. Org. Khim.* **1978**, *14*, 240. (b) Andreev, S. A.; Lebedev, B. A.; Tselinskii, I. V.; Shohbor, I. N. *Ibid.* **1980**, *16*, 1353. (c) Andreev, S. A.; Lebedev, B. A.; Tselinskii, I. V. *Ibid.* **1980**, *16*, 1360. (d) Andreev, S. A.; Lebedev, B. A.; Tselinskii, I. V. *Ibid.* **1980**, *16*, 1365.

(17) Similar observations have been made for several trialkylnitrosoureas: Synder, J. K.; Stock, L. M. *J. Org. Chem.* **1980**, *45*, 886–891.

(18) Phillips, W. D. In "Determination of Organic Structures By Physical Methods"; Academic Press: New York, 1962; Vol. II.

(19) The same analysis would pertain to hydrogen-bonded dimers of the urea.

(20) Valega, T. M. *J. Org. Chem.* **1966**, *31*, 1150.



vii

in the case of the *N*-nitrosoamides[21]). The resulting enhanced nonbonded interactions of the nitroso and dimethylamino groups in vii could well slow the rotation rate of the latter group. This effect of large substituents on conformer distribution has been noted in the case of the *N*-nitrosoamides.[5,21,22]

Decomposition. The nitroso and nitroureas were decomposed at elevated temperatures, the half-lives for the compounds being 36 h for **2a** (60 °C in CCl_4), 72 h for **3a** (110 °C in CCl_4), 1.3 h for **2b** (61 °C in CH_2Cl_2), and ca. 24 h for **3b** (105 °C in CH_2Cl_2). These decomposition rates are considerably lower than those of comparable carbamate derivatives, presumably because of deactivation of the carbonyl group ($>N^+=C-O^- > -O^+=C-O^-$, structure ii, e.g.). The decomposition of ethyl *N*-nitro-*N*-(1-norbornyl)carbamate, e.g., had a half-life of ~5 h at 105 °C in $CHCl_3$,[23] about a fifth the corresponding urea value. The rates for the urea derivatives showed the expected increase with the size of the alkyl substituent;[6,21] also, consistent with other series, the *N*-nitroureas are more stable than their *N*-nitroso analogues.[6]

The products from the thermal decomposition of these urea derivatives were determined by GLC and NMR (Table II). The products can be accounted for by the general reaction mechanism developed for the *N*-nitrosoamide decomposition;[1,24] the nitrosoureas rearrange in the rate-determining step to the corresponding diazotic carboxylic anhydride (**4**), which then decomposes by fast ionic steps to give products derived from the carbonium carboxylate ion pair (**10** in Chart I). In concentrated solutions, a new type of product, an amino acid, is formed (vide infra).

The *N*-nitroso- and nitroureas yield carbamate esters, as expected on the basis of the conversion of nitrosoamides into the corresponding carboxylate esters (eq 1). The nitrosourea decompositions are more complex, however, due to the higher temperatures required for reasonable reaction rates and the formation of amines as products ($HOCONMe_2 \rightarrow CO_2 + Me_2NH$). The amines react with the starting nitrosourea to give tetramethylurea. In

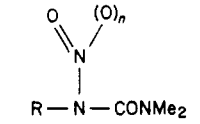
$$2 \text{ or } 3 + Me_2NH \rightarrow \underset{\mathbf{13}}{Me_2NCONMe_2} + RN_2O^- \text{ (or } RN_2O_2^-)$$

halogenated solvents, a small portion of the urea is also formed directly from the reaction of dimethylamine with the solvent (the role of water, oxygen, phosgene, etc. in these reactions is unknown). Polyhalogenated compounds

$$Me_2NH + CCl_4 \rightarrow \mathbf{13}$$

are known to react with amines,[25] but the corresponding urea has not been hitherto reported as a product.

Table II. Products from the Decomposition of the *N*-Nitroso- and *N*-Nitroureas

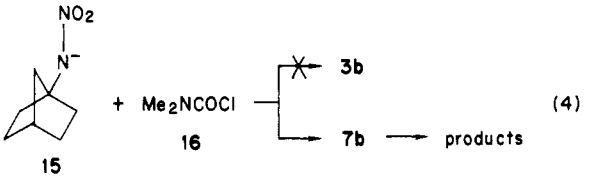


R = *n*-Bu	*n*	solvent	temp, °C	products, % 11a	13	20
2a	0	CCl_4	60	37	26	12
		neat	83	45	23	32
3a	1	CCl_4	110	7	19[a]	

R = 1-norbornyl	*n*	solvent	temp, °C	products, % 11b	14
2b	0	CH_2Cl_2	40	21–23[b]	62–68[b]
	0	CH_2Cl_2	105	24[c]	70[b]
	0	acetic acid	25	1[d]	
3b	1	CH_2Cl_2	105	5	62
	1	CH_2Cl_2[e]	105	6	66
15 + **16** → **7**	1	CH_2Cl_2	105	12	78

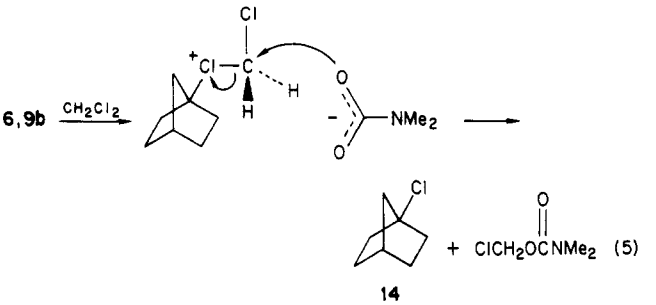
[a] 10% of urea **1a** was also found. [b] Triplicate runs. [c] Duplicate run. [d] Major product was 1-norbornyl acetate (68–74% yield). [e] With 1.8 equiv of solid K_2CO_3.

The difficulty in obtaining good yields of the *N*-nitroureas referred to above can be bypassed (if the decomposition products are desired) through use of the "salt approach",[3] as exemplified by eq 4. The required nitroamine can be readily prepared from the *N*-nitrocarbamates.[2,3] The product distribution observed in this approach is essentially the same as that in the decomposition of **3b** (Table II).



(4)

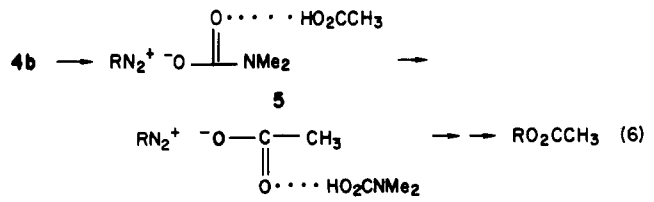
In the decomposition of the bridgehead norbornyl compounds **2b** and **3b**, a solvent derived product was formed in halogenated solvents, namely 1-chloronorbornane (**14**). The mechanism of this reaction involves an interesting solvent–cage interaction (eq 5).[26,27]



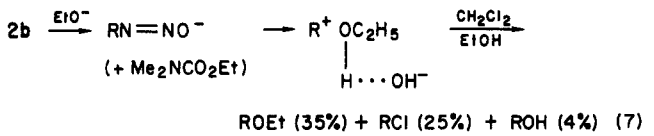
(5)

The norbornyl nitrosourea **2b** was decomposed under several different conditions to gain insight into the reaction. In acetic acid, almost exclusive "front-side exchange" occurred to give the acetate ester[28] (Table II); this reaction occurs to the extent that the external acid is stronger than the conjugate acid of the counterion in ion pair **5** (eq 6).

(21) Huisgen, R.; Reimlinger, H. *Liebigs Ann. Chem.* **1956**, *599*, 183.
(22) White, E. H.; Lewis, C. P.; Ribi, M. A.; Ryan, T. J. *J. Org. Chem.* **1981**, *46*, 552–558.
(23) White, E. H.; Tiwari, H. P.; Todd, M. J. *J. Am. Chem. Soc.* **1968**, *90*, 4734.
(24) Huisgen, R.; Rüchardt, C. *Liebigs Ann. Chem.* **1956**, *601*, 21.
(25) (a) Collins, R. F. *Chem. Ind. (London)* **1957**, 704. (b) Cromwell, N. H.; Foster, P. W.; Wheeler, M. M. *Chem. Ind. (London)* **1959**, 228. (c) Beichl, G. J.; Colwell, J. E.; Miller, J. G. *Chem. Ind. (London)* **1960**, 203. (d) Foster, R. *Chem. Ind. (London)* **1960**, 1355. (e) Stevenson, D. P.; Coppinger, G. M. *J. Am. Chem. Soc.* **1962**, *84*, 149. (f) Fenby, D. V. *Aust. J. Chem.* **1973**, *26*, 1143.
(26) White, E. H.; McGirk, R. H.; Aufdermarsh, C. A., Jr.; Tiwari, H. P.; Todd, M. J. *J. Am. Chem. Soc.* **1973**, *95*, 8107.
(27) Free radical reactions are unlikely since less than 0.5% norbornane was formed in the decomposition of nitrourea **3b** in methylene chloride.
(28) White, E. H.; Woodcock, D. J. In "The Chemistry of the Amino Group"; Patai, S., Ed.; J. Wiley and Sons: New York, 1968; Chapter 8.



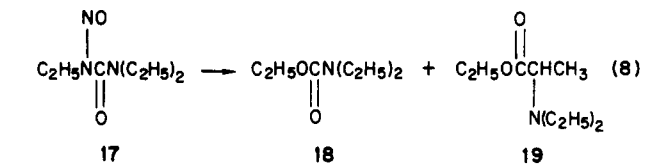
The effect of acetic acid on the decomposition of the nitrosocarboxamides is less,[1,28] as expected on the basis of the greater acidity of the carboxylic acids. In a related study, introduction of the "acetic acid" in the form of its conjugate base (as tetrabutylammonium acetate, 7/1 ratio to **2b**) in methylene chloride had little effect on the reaction; the major product was still 1-norbornyl chloride (41%), and only 14% of the acetate was formed. Finally, the reaction in methylene chloride/ethanol (mole ratio 1.8/1) via the diazotate (eq 7) produced the ether and



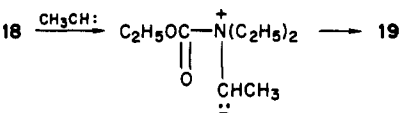
alcohol, as expected, but nevertheless a modest amount of the chloride. The ether is produced in excess of that expected on the basis of the solvent composition because ethanol becomes a part of the reactive complex through hydrogen bonding (eq 7).

In summary, the nitroso- and nitroureas decompose in a manner which is analogous to that of the corresponding amide and carbamate derivatives. The basicity of the counter anion ($R_2NCO_2^-$, $ROCO_2^-$, RCO_2^-) has no profound effect on the reaction; recently, we have shown that even when the very weakly basic tosylate counterion is used, no effect on the reaction course can be detected.[23] Further, the data show that the substitution of nitrous oxide for nitrogen gas as the inert molecule separating the carbonium and carboxylate ions has no detectible effect on the reaction course. Because of the complexity of these reactions, the yield data (Table II) support this conclusion in only its broadest sweep; a more rigorous comparison of the substitution of N_2O for N_2 with similar conclusions was reported elsewhere.[12]

Recently, the decomposition of several trialkylnitrosoureas (neat liquids and in hexadecane) was reported to yield, as the major product (up to 70%), an amino acid derivative [for *N*-nitrosotriethylurea, ethyl α-(diethylamino)propionate (**19**, eq 8)].[13] This novel and potentially

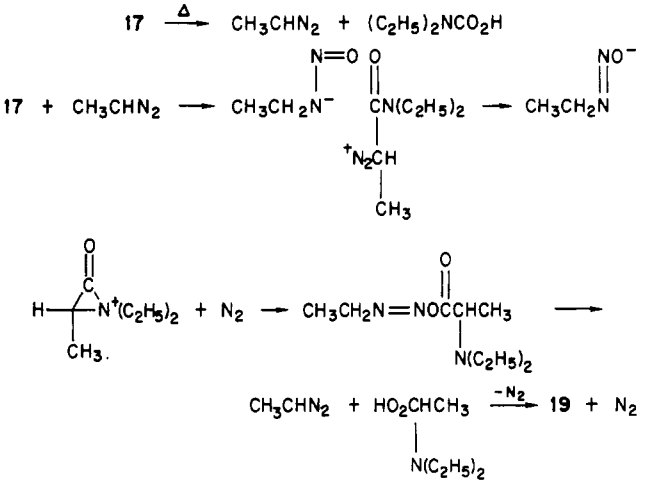


useful conversion was ascribed to the insertion of a carbene into an amide C–N bond. A slight revision of this possibility in terms of an ylide intermediate and a Steven's rearrangement[29] seems plausible, at face value (maximum yield of **19** = 50%). However, in view of the expectation

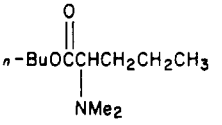


(29) Lepley, A. R. *J. Am. Chem. Soc.* **1969**, *91*, 1237.

Chart II



that methyl carbene would react in a less discriminate fashion and that it would yield ethylene in addition to insertion products,[30] we propose a variant utilizing diazoethane directly[31] (Chart II). The acylation of diazoethane utilized in the second step is analogous to the first step in the Arndt–Eistert reaction of acid chlorides with diazoalkanes.[32] We have decomposed neat *N*-(*n*-butyl)-*N'*,*N'*-dimethyl-*N*-nitrosourea and have observed (by NMR) the carbamate (**11a**), tetramethylurea (**13**), and the corresponding amino acid derivative, **20** (30% yield), as products. In the dilute solutions used for most of the runs



20

with the butyl nitroso compound **2a** in the present study (Table II), compound **20** was formed in yields of about 10%; amino acid **20** was not detected in the decomposition of the nitrourea analogue **3a**.

Experimental Section

General Methods. Spectra were measured on a Perkin-Elmer Model 457A IR spectrophotometer, Varian A-60, XL-400, and Jeol JNM-MH-100 NMR spectrometers (with tetramethylsilane as an internal standard), a Varian Techtron 635 UV-spectrophotometer, and a Hitachi-Perkin-Elmer RMU-6E mass spectrometer (70 eV). Gas-liquid chromatography was performed on a Varian Aerograph Model 1800 instrument. Melting points were obtained on a Thomas-Hoover apparatus and are reported uncorrected. Elemental analyses were determined by Galbraith Laboratories, Inc., of Knoxville, TN.

***N*-(*n*-Butyl)-*N'*,*N'*-dimethylurea (1a). Method A.** A solution of dimethylamine (8 mL, 5.43 g, 120 mmol) in methylene chloride (50 mL) was added with stirring to a solution of *n*-butyl isocyanate (9.85 g, 100 mmol) in methylene chloride (150 mL) at 0 °C. The reaction mixture was incubated at room temperature for 2 h. The solution was concentrated to one-half on a rotary evaporator and the remaining solution was washed with 10% HCl (2 × 50 mL) and with water (2 × 50 mL). After drying over anhydrous sodium sulfate and removing the solvent on a rotary evaporator, the residue was distilled (bp 82–92 °C (0.07 mm) (lit.[33]

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bp 100–110 °C (0.8 mm)) to yield 10.0 g (72 mmol, 72%) of a clear oil, which solidified on standing in the freezer: mp 32–33.5 °C; IR (thin film) 3300, 1630, 1355, 1235 cm^{-1}; NMR (CCl_4) δ 0.65–1.54 (m, 7 H), 2.87 (s, 6 H), 2.96–3.30 (m, br, 1.3 H), 5.95 (s, br, 0.6 H).

Method B. To a solution of *n*-butylamine (13.8 mL, 140 mmol) in 75 mL of CH_2Cl_2 was added 6.5 mL (70 mmol) of dimethylcarbamoyl chloride dropwise. The mixture was stirred for ca. 2 h and then it was washed by water (3 × 25 mL). The organic layer was dried over Na_2SO_4 and the solvent was removed by rotary evaporator. The resulting brown liquid was distilled (ca. 0.1 mm with a 100 °C oil bath) to give 7.4 g (73%) of urea **1a** as a clear, colorless, viscous liquid whose IR and NMR matched those of **1a** prepared by Method A.

***N',N'*-Dimethyl-*N*-(1-norbornyl)urea (1b).** A solution of 2.4 g (37 mmol) of sodium azide was added to a solution of 1.8 g (11.4 mmol) of the acid chloride of 1-carboxynorbornane[34] in 40 mL of CH_2Cl_2. The resulting mixture was stirred for 10 h at room temperature and 75 h at reflux. The reaction mixture was chilled in an ice bath and 10 mL (6.8 g, 150 mmol) of dimethylamine was added with stirring. After 8 h, the reaction mixture was washed with water (10 × 30 mL) and dried over sodium sulfate, and the solvent was evaporated with a water pump. The residue was recrystallized from methanol–petroleum ether to give 1.9 g (77%) of product: mp 181–182 °C; IR (CH_2Cl_2) 3440, 1650, 1520 cm^{-1}; NMR ($CDCl_3$) δ 1.50–1.93 (m, 10 H), 2.02–2.22 (br m, 1 H), 2.88 (s, 6 H).

***N*-(*n*-Butyl)-*N',N'*-dimethyl-*N*-nitrosourea (2a).** The nitrosation was carried out according to the procedure of White and Aufdermarsh.[2] Sodium acetate (2.5 g, 30 mmol) and N_2O_4 (2 mL, 65 mmol) were slurried in methylene chloride (20 mL) at −40 °C, and a solution of *N*-(*n*-butyl)-*N',N'*-dimethylurea (774 mg, 5.4 mmol) in CH_2Cl_2 (10 mL) was added. The solution was warmed to 0 °C, stirred for 35 min, and then poured onto crushed ice (ca. 25 g). The aqueous layer was extracted with methylene chloride (2 × 25 mL) and the organic layers were combined and washed with cold water (1 × 25 mL), cold 5% sodium bicarbonate (2 × 25 mL), and cold water (2 × 25 mL). After drying over sodium sulfate, the solvent was removed on a rotary evaporator to yield 943 mg of a yellow oil, which was distilled at 0.1 mm in a small bent tube (pot temperature 80 °C) to yield 156 mg of a pale yellow oil (0.9 mmol, 17%): IR (thin film) 1700, 1480 cm^{-1}; NMR ($CDCl_3$) δ 0.8–1.0 (m, 3 H), 1.0–1.5 (m, 4 H), 3.13 (s, 6 H), 3.77 (br t, J = Hz, 2 H); NMR at −33 °C ($CDCl_3$) δ 0.8–1.0 (m, 3 H), 1.0–1.5 (m, 4 H), 3.10, 3.22 (s, s in 1/1 ratio, 6 H), 3.79 (br t, J = 9, 2 H). Anal. Calcd for $C_7H_{15}N_3O_2$: C, 48.57; H, 8.67; N, 24.28. Found: C, 48.59; H, 8.48; N, 23.57.

***N*-(1-Norbornyl)-*N',N'*-dimethyl-*N*-nitrosourea (2b).** A mixture of 1.0 g (5.5 mmol) of *N',N'*-dimethyl-*N*-(1-norbornyl)urea, 3.0 g (37 mmol) of anhydrous sodium acetate, and 30 mL of CH_2Cl_2 was cooled in a dry ice/acetone bath. Then, 2.5 mL (3.75 g, 81.5 mmol) of dinitrogen tetraoxide was added with stirring. The solution was warmed to 0 °C and stirred. The mixture was poured into ice water, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with ice water, 5% cold sodium bicarbonate (2 × 20 mL), and with ice water. The solution was dried over sodium sulfate and the solvent was removed on a rotary evaporator to give 1.1 g of an orange-colored residue which slowly decomposed at room temperature. Recrystallization from methylene chloride/petroleum ether (1:6) gave pure material: mp 35.5–36.5 °C dec; IR (CH_2Cl_2) 1705, 1406 cm^{-1}; UV λ_{max} (ether) 390 nm (ϵ 97), 248 (5.23×10^{-3}); ^1H NMR ($CDCl_3$) δ 1.40–2.00 (m, 10 H), 2.10–2.20 (br, 1 H), 2.75 (s, 3 H), 3.05 (s, 3 H). Anal. Calcd for $C_{10}H_{17}N_3O_2$: C, 56.85; H, 8.11. Found: C, 57.17; H, 8.41.

***N*-(*n*-Butyl)-*N',N'*-dimethyl-*N*-nitrourea (3a). Method A.** A solution of *N*-(*n*-butyl)-*N',N'*-dimethylurea (501 mg, 3.5 mmol) in CH_2Cl_2 (15 mL) was slurried with anhydrous sodium acetate (700 mg, 8.5 mmol) and the mixture was cooled to −30 °C. A solution of dinitrogen pentaoxide[35] (1.0 g, 9.3 mmol) in CH_2Cl_2 (20 mL) was added in portions with stirring at −30 °C over a period of 2 h. Ammonia gas was then bubbled through the mixture at −30 °C to consume excess dinitrogen pentaoxide, and the mixture was warmed to 0 °C. The mixture was poured into an ice/water mixture, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (1 × 50 mL). The organic phases were combined and washed with 2% HCl (2 × 50 mL), 2% sodium bicarbonate (2 × 50 mL), and water (2 × 50 mL). After drying over anhydrous sodium sulfate, the solvent was removed on a rotary evaporator to give 430 mg of a pale yellow oil. The oil was dissolved in 25 mL of CCl_4 and the solution was refluxed for 48 h to decompose any *N*-(*n*-butyl)-*N',N'*-dimethyl-*N'*-nitrosourea present. The resulting mixture was purified by preparative TLC (silica gel, developed by benzene) to give 127 mg of a pale yellow oil (R_f 0.45) that was a mixture of dimethylnitramine and *N*-(*n*-butyl)-*N',N'*-dimethyl-*N*-nitrourea. The volatiles (30 mg) were removed with a sublimer at 25 °C (0.05 mm). The residue was dissolved in petroleum ether and cooled to −78 °C to yield a precipitate of dimethylnitramine: mp 54–55 °C; IR (CH_2Cl_2) 1520 and 1316 cm^{-1}; NMR (CCl_4) δ 3.38; UV (dioxane) δ_{max} 244 (ϵ 4600) [lit.[36] mp 57 °C; UV (dioxane) 240 (6300)]. The mother liquor was separated and the solvent removed on a rotary evaporator to give a yellow oil which was distilled in a short path still (ca. 5 mm, liquid N^2 cooled cold finger, 50 °C (0.06 mm)) to give **3a** as a pale yellow oil. The yield was 77 mg (0.4 mmol, 11%): IR (CCl_4) 2950, 1715, 1550, 1480 cm^{-1}; UV λ_{max} (*n*-hexane) 242 nm (ϵ 4.7×10^3); NMR ($CDCl_3$) δ 0.80–1.00 (m, 3 H), 1.0–1.5 (m, 4 H), 3.07 (s, 6 H), 3.83 (br t, J = 10 Hz, 2 H); NMR at −33 °C ($CDCl_3$) 0.8–1.0 (m, 3 H), 1.0–1.5 (m, 4 H), 3.09, 3.14 (25, ca. 1:1, 6 H), 3.7–4.0 (m, 2 H). The material was distilled twice more as above (40 °C (0.02 mm)) to give a sample for analysis. Anal. Calcd for $C_7H_{15}N_3O_3$: C, 44.43; H, 7.99; N, 22.21. Found: C, 44.29; H, 7.97; N, 21.47.

Method B. In a N_2-filled flask connected to an oil bubbler, 3.0 g (22 mmol) of urea **1a** (dissolved in 150 mL of dry CH_2Cl_2) was stirred with 9.0 g (47 mmol) of NO_2PF_6 and 23 g of solid Na_2CO_3 (220 mmol) for 3 h at room temperature. The reaction mixture was filtered and washed with 5% sodium bicarbonate and then water. The organic layer was dried over sodium sulfate and the solvent removed at room temperature on a rotary evaporator. The resulting oil was purified by TLC and distillation as described in Method A to give 125 mg (3%) of **3a**.

In an attempt to lower the amount of nitrosourea formed in the nitrations, the urea **1a** was stirred in dry CH_2Cl_2 (100 mL/mmol) at −78 °C under nitrogen with 2 equiv NO_2PF_6 and 10 equiv Na_2CO_3. After 1.5 h, an aliquot was withdrawn, filtered, washed with 5% $NaHCO_3$, and dried over sodium sulfate. Removal of the solvent and examination of the residual liquid by NMR showed that the reaction was ca. 10% complete and that the *N*-nitrosourea **2a** was still the major product. The amount of *N*-nitrourea **3a** had not been increased significantly. After 24 h at −78 °C, the reaction was ca. $^2/_3$ complete and the ratio of **2a**/**3a** had remained the same (ca. 2.5:1). Dimethylnitroamine was also present.

A third sample of **1a** was nitrated in acetonitrile (in which NO_2PF_6 is soluble) with a molar ratio of urea/NO_2PF_6/Na_2CO_3 of 1/5/10 at −20 °C. After 15 min, examination of the reaction mixture showed the nitrosourea **2a** to be the major product.

A fourth attempt at nitration of **1a** was made with the reaction between the anion of the urea **1a** (formed from the reaction of **1a** with 1 equiv of *n*-BuLi in hexane at −25 °C and NO_2PF_6 (1:1 equiv in hexane at −60 °C). The reaction mixture was warmed to room temperature over 45 min and after workup the NMR spectrum showed no **3a**. The mixture was nitrosourea **2a** and starting urea **1a**. No dimethylnitroamine was formed.

***N*-(1-Norbornyl)-*N',N'*-dimethyl-*N*-nitrourea (3b).** *N',N'*-Dimethyl-*N*-(1-norbornyl)urea (212 mg, 1.0 mmol) was added in portions to a mixture of nitric acid (0.6 mL, specific gravity 1.42) and sulfuric acid (3 mL, specific gravity 1.84) at −15 °C with stirring. The mixture was stirred for 10 min at −15 °C and then poured onto 50 mL of crushed ice. The ice was allowed to melt and the solution was extracted with ether (2 × 25 mL). The ether solution was washed with water (2 × 25 mL), 10% potassium

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carbonate solution (2 × 25 mL), and water (2 × 25 mL). After drying over anhydrous sodium sulfate, the solution was filtered, and the solvent was removed on a rotary evaporator to yield a white solid. This was recrystallized from petroleum ether/ether solution to yield 9 mg (0.038 mmol, 4%) of starting material. The mother liquor yielded 6 mg (0.022 mmol, 2%) of *N*-(1-norbornyl)-*N'*,*N'*-dimethyl-*N*-nitrourea: mp 74–74.5 °C; IR (CCl_4) 1715, 1545, 1480, 1455 cm^{-1}. Anal. Calcd for $C_{10}H_{17}N_3O_3$: C, 52.86; H, 7.40. Found: C, 52.61; H, 7.11.

n-Butyl *N*,*N*-Dimethylcarbamate (11a). In a 50-mL round-bottomed flask (connected to an oil bubbler), a mixture of 15 mL of ether and 1.37 g of 57% NaH (32 mmol) was stirred at 0 °C. Then 3 mL of *n*-BuOH (32 mmol) was added dropwise over ca. 5 min. The mixture was stirred at 0 °C until H_2 evolution had nearly ceased (ca. 15 min). Then 3 mL (32 mmol) of *N*,*N*-dimethylcarbamoyl chloride was added dropwise over ca. 10 min. More gas was evolved during the addition. After the addition was complete, the mixture was stirred until gas evolution was negligible (ca. 15 min). Then 15 mL of ether was added and the solution was filtered. The ether was removed on a rotovap at room temperature to give a liquid. The liquid was distilled at ca. 0.1 mm (50 °C water bath) to give 2.7 g (57%) of the carbamate as a clear colorless liquid: ^1H NMR (CCl_4) δ 0.73–1.16 (m, 3 H), 1.16–1.77 (m, 4 H), 2.86 (s, 6 H), 3.95 (t, J = 6 Hz, 2 H) [lit.[20] δ 2.86 (s, 6 H)].

1-Norbornyl *N*,*N*-Dimethylcarbamate (11b). 1-Norborneol (0.5 g, 4.2 mmol) was dissolved in 35 mL of dry ether and to this solution 0.27 g (7.0 g, atom) of potassium metal was added with stirring. The resulting mixture was stirred at room temperature for 1.5 h and then cooled to 0 °C. *N*,*N*-Dimethylcarbamoyl chloride (1.1 g, 10 mmol) was added dropwise, and the mixture was stirred for 1 h at 0 °C and then for 30 min at room temperature. Ethanol (2 mL) was added to decompose the excess potassium metal and then 30 mL of water was added cautiously. The aqueous layer was extracted with ether (2 × 30 mL) and the combined organic layers were washed with water (2 × 30 mL), 5% aqueous sodium carbonate (2 × 20 mL), and water (2 × 30 mL). The organic layer was dried over anhydrous sodium sulfate and the solvent was removed on a rotary evaporator. Chromatography of the resulting liquid over neutral alumina (elution with ether) gave **11b** in 30% yield (0.25 g): IR (neat) 1700 cm^{-1}. Analytically pure material was obtained by distillation (30 °C (0.015 mm)) in a small bent tube. Anal. Calcd for $C_{10}H_{12}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.92; H, 9.64; N, 7.33.

Decomposition of *N*-(*n*-Butyl)-*N'*,*N'*-dimethyl-*N*-nitrosourea (2a). A solution of 110 mg of **1a** was dissolved in 0.5 mL of CCl_4 (containing ca. 0.3% Me_4Si and 60 μL of CH_2Cl_2 as an internal standard) and was degassed by using 3 freeze–thaw cycles at ca. 0.1 mm. The tube, after sealing, was fully immersed in a 60 °C water bath. The rate of reaction was determined by following the disappearance in the NMR of the signal of the NMe_2 group for the starting nitrosourea. After 163 h at 60 °C, five signals were seen for the NMe_2 groups: δ 3.13 (nitrosourea **2a**, 6%), 2.86 (compound **11a**, 37%), 2.75 (tetramethylurea, 26%), 2.27 (amino acid **20**, 12%), and 2.15 (unknown, 18%, also formed in the reaction of CCl_4 and $HNMe_2$). By comparison with the neat decomposition, it was estimated that ca. 10% of the tetramethylurea formed came from the reaction between Me_2NH and CCl_4.

A second sample of **2a** was decomposed neat at 83 °C. The reaction was >95% complete after 40 h with a half-life of ca. 4 h. The NMR spectrum showed *n*-butyl *N*,*N*-dimethylcarbamate (45%), tetramethylurea (23%), and the α-amino acid derivative **20** (32%). TLC of the resulting mixture (silica gel, ethyl acetate, I_2) proved to be complex. The plate showed tetramethylurea (R_f 0.18), *n*-butyl *N*,*N*-dimethylcarbamate (R_f 0.61), and six additional spots. It was noted that at early stages of the reaction (10 min) the amino acid derivative (**20**) constituted 50% of the product while at the 40-h point the value was 30%. This result suggests, as shown in Chart II, that the starting nitrosourea is involved directly in the formation of compound **20**.

The decomposition mixture was dissolved in CH_2Cl_2 and washed with 5% HCl. The aqueous layer was then made basic with $NaHCO_3$ (pH 8–9) and extracted with CH_2Cl_2. The organic layer was dried over sodium sulfate and evaporated to give a yellow-brown liquid which was purified by preparative TLC (silica gel, ethyl acetate). Collection of the yellow band with R_f 0.54 gave *n*-butyl 2-(dimethylamino)pentanoate (**20**) as a yellow-brown liquid: IR (neat) 1745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.8–1.7 (m, 14 H), 2.33 (s, 6 H), 3.11 (t, J = 7 Hz, 1 H), 4.11 (t, J = 6 Hz, 2 H).

Decomposition of *N*-(*n*-Butyl)-*N'*,*N'*-dimethyl-*N*-nitrourea (3a). In an NMR tube, 37 mg (0.2 mmol) of **3a** was dissolved in 0.5 mL of CCl_4 containing ca. 0.3% Me_4Si; 60 μL of CH_2Cl_2 was added as an internal standard. The solution was degassed by three freeze–thaw cycles and sealed. The tube was fully immersed in a 110 ± 1 °C oil bath. The rate was followed in the NMR by the disappearance of the signal for the NMe_2 group at δ 3.07. Product yields were determined by comparison of the NMe_2 signals to the internal standard (Table II).

Decomposition of *N*-(1-Norbornyl)-*N'*,*N'*-dimethyl-*N*-nitrosourea (2b). *N*-(1-Norbornyl)-*N'*,*N'*-dimethyl-*N*-nitrosourea (42.7 mg, 0.202 mmol) dissolved in methylene chloride (2 mL) was placed in a glass tube, degassed by three freeze–thaw cycles and sealed under vacuum (10^{-2} torr). The tube was placed in an oil bath at 105 °C for 2 h. Analysis by GLC (10% SE-30/120 °C) gave peaks corresponding to 1-norbornyl chloride and 1-norbornyl *N*,*N*-dimethylcarbamate. *n*-Octyl acetate (36.4 mg) was added as the standard. A portion of this reaction solution including the standard was placed in a tube and sealed under high vacuum, after degassing by the three freeze–thaw cycles. The tube was placed in an oil bath at 105 °C for 4 days. Analysis by GLC (10% SE-30/120 °C) indicated that the products were stable under the reaction conditions since no change in peak area ratios had occurred (Table II).

A second sample (0.4 g) was heated in 40 mL of refluxing methylene chloride for 24 h. In addition to the carbonyl band at 1700 cm^{-1} for the carbamate ester (**11b**), a band at 1725 cm^{-1} in a ratio of 1/1.7 was observed. After solvent removal, the product was distilled at 25 °C and 10^{-2} torr resulting in an enrichment of the 1725 cm^{-1} compound in the more volatile phase. The distillation was repeated six times to give 30 mg of the 1725 cm^{-1} compound [NMR (in CCl_4) δ 2.97 and 5.75 in a ratio of 2/1] contaminated with norbornyl chloride. Mass spectroscopic analysis gave a parent ion at 137 m/e and the strongest cracking peak at 72 ($CONMe_2$). The identification of this compound as chloromethyl dimethylcarbamate from the physical data was confimed by its conversion into tetramethylurea with dimethylamine.

A third sample of **2b** (15.3 mg, 0.0725 mol) was stirred overnight in 1.0 mL of acetic acid. An IR spectrum (CH_2Cl_2) of the extracts (after neutralization of the acetic acid with bicarbonate) showed an absence of the NO stretching frequency for the starting material. GLC analysis (5% QF-1 at 95 and 180 °C) showed the presence of 1-norbornyl acetate, 1-norbornyl *N*,*N*-dimethylcarbamate, and three unknowns (Table II). The carbamate was shown to be stable under the reaction conditions by allowing a sample of it to stir with acetic acid overnight. No detectable amount of acetate could be found by GLC (<1%).

A fourth sample of **2b** (26.3 mg, 0.12 mmol) was dissolved in 2 mL of methylene chloride and 0.25 g (0.84 mmol) of tetra-*n*-butylammonium acetate (dried over phosphorous pentaoxide) was added. The resulting mixture was refluxed for 24 h. *n*-Octyl acetate was added as an internal standard and the reaction mixture was washed with water, dried over sodium sulfate, and then analyzed by GLC (5% QF-1 at 90 °C). The analysis showed 1-norbornyl chloride (42%), 1-norbornyl acetate (14%), 1-norbornyl *N*,*N*-dimethylcarbamate (9%), and several unknowns.

A fifth sample of **2b** (9.15 mg, 0.043 mmol) was dissolved in 2 mL methylene chloride and 1.0 mL of 5 × 10^{-2} M EtONa in ethanol was added dropwise with stirring over 15 min. No appreciable reaction was observed so the reaction mixture was allowed to stand overnight with stirring (a gray precipitate formed). Water was added and the organic layer was separated and washed with water. After drying over sodium sulfate, the solution was analyzed by GLC (5% QF-1 and 10% SE-30 at 100 °C). The products found were 1-norbornyl ethyl ether (35%), 1-norbornyl chloride (25%), 1-norbornyl alcohol (4%), and one unknown.

Decomposition of *N*-(1-Norbornyl)-*N'*,*N'*-dimethyl-*N*-nitrourea (3b). *N*-(1-Norbornyl)-*N'*,*N'*-dimethyl-*N*-nitrourea (3.124 mg, 0.0138 mmol) in methylene chloride (200 μL) was placed

in a glass tube and degassed by three freeze–thaw cycles. The tube was placed in an oil bath at 105 °C for 5 days. *n*-Octyl acetate (2.328 mg) was added as standard and the amount of each product was quantitated by GLC (10% SE-30/120 °C). The carbamate **11b** was present in 5% yield and 1-norbornyl chloride in 62%. A very small peak with a retention time the same as norbornane was observed on GLC (5% QF-1/25 °C). From a comparison of the height of this peak with that for 1-norbornyl chloride, it can be estimated that the amount of norbornane was under 0.5%.

In a small bulb blown in the end of an 8-mm glass tube, a second sample of **3b** (2.66 mg, 1.2×10^{-5} mol) was dissolved in 200 μL of CH_2Cl_2 and 29.52 mg (2.1×10^{-4} mol) of K_2CO_3 was added. A small magnetic stir bar was added, the system was degassed by three freeze–thaw cycles, and the tube was sealed under vacuum. The sample was decomposed at 105 °C with stirring for 8 days. Analysis by GLC (10% Se-30 at 120 °C, *n*-octyl acetate was an internal standard) showed 66% norbornyl chloride and 6% of the carbamate **11b**.

Reaction of the Sodium Salt of 1-Norbornylnitramine (15) with *N*,*N*-Dimethylcarbamoyl Chloride (16). The sodium salts of 1-norbornylnitramine[24] (17.2 mg, 0.096 mmol) and *N*,*N*-dimethylcarbamoyl chloride (36.5 mg, 0.34 mmol) were added to methylene chloride (2 mL) in a glass tube. The suspension was degassed by three freeze–thaw cycles and the sealed tube was placed in an oil bath at 105 °C for 6.5 days. The solution turned brown after a few days of heating. GLC (10% Se-30/125 °C) with *n*-octyl acetate (27.9 mg) as an internal standard gave peaks for 1-norbornyl chloride, 1-norbornyl *N*,*N*-dimethylcarbamate, and *N*,*N*-dimethylcarbamoyl chloride (Table II).

Reaction of Dimethylamine with Carbon Tetrachloride. A solution of dimethylamine in CCl_4 was examined periodically by NMR spectroscopy. After 2 days, the signal at δ 2.35 for dimethylamine had disappeared. Two new singlets appeared in at δ 2.78 (tetramethylurea gives a signal at δ 2.78) and 2.15 (unknown). An IR of the solution showed a strong band at 1650 cm^{-1} (the same position as the carbonyl of tetramethylurea). TLC (silica gel, ether) showed a spot that corresponded to tetramethyl urea (R_f 0.2).

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Nitrosation of the *N*-Alkyl-*O*-acylhydroxylamines. A New Deamination Method

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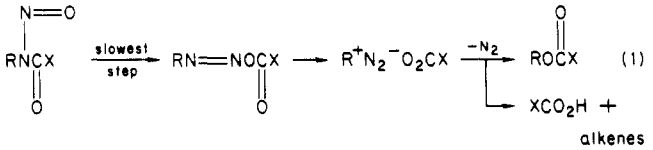
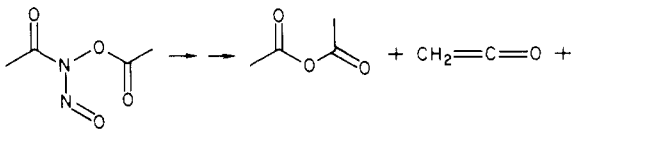
The nitrosation of *N*-alkyl-*O*-acylhydroxylamines leads to immediate decomposition at dry ice temperatures; the corresponding ester and nitrous oxide are formed. An ^{18}O study has shown that the nitroso-*O*-acylhydroxylamines fragment directly rather than undergo a rearrangement reaction (as observed with the nitrosoamides). The product yields are respectable, especially at low temperatures, and the method has promise for the generation of high energy carbonium ions.

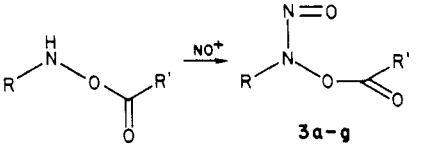
N-Nitrosoamides of various types decompose via a slow rearrangement step (eq 1, X = R, OR, NR_2);[1] *N*-nitrosoamides[2] and *N*-nitroso- and *N*-nitrosulfonamides follow a similar course.[3] We have also observed that *N*-nitrosodiacetylhydroxylamine (**1**) decomposes to yield a similar set of products (eq 2).[4] The present contribution describes our studies of deamination via the related *N*-alkyl-*N*-nitroso-*O*-acylhydroxylamines (**3**).





CH_3CO_2H (2)

Syntheses. The required *N*-alkyl-*O*-acylhydroxylamines (**2**) were prepared by the reaction of alkylamines with diacylperoxides.[5] The nitrosation step, leading to **3**, was carried out principally with dinitrogen tetraoxide[6] or nitrosyl chloride, although nitrosonium tetrafluoroborate was used in a few cases.



2a-g

a, R = isobutyl; R' = phenyl
b, R = *tert*-butyl; R' = phenyl
c, R = benzyl; R' = phenyl
d, R = 1-phenylethyl; R' = phenyl
e, R = 1-phenylethyl; R' = 2-naphthyl
f, R = 1-benzhydryl; R' = phenyl
g, R = 1-norbornyl; R' = phenyl

The Reaction. All of the *N*-alkyl-*N*-nitroso-*O*-acylhydroxylamines that we tested decomposed to the corresponding esters; for nonbridgehead alkyl groups with β-hydrogens, alkenes were also formed. The product set was

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(4) Footnote 12 in ref 2.
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