[CONTRIBUTION NO. 1262 FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

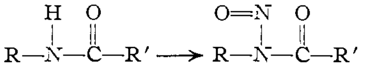
The Chemistry of the N-Alkyl-N-nitrosoamides. I. Methods of Preparation

BY EMIL H. WHITE

RECEIVED DECEMBER 23, 1954

Two new methods for the nitrosation of N-alkylamides have been developed: one using nitrogen tetroxide and the other, a sodium nitrite–acetic anhydride mixture. The limitations of the usual nitrosation methods were determined and a number of N-nitroso derivatives of amides, urethans and sulfonamides were prepared.

During the course of preparation of a number of N-alkyl-N-nitrosoamides required for a study of their thermal decomposition,[1] the limitations of the usual nitrosation procedures were determined and two new methods were developed. In one of the new methods, a sodium nitrite–acid anhydride mixture is used and in the other the reagent nitrogen tetroxide; the latter method proved to be the most satisfactory for the nitrosation of amides. The methods (A-E) will be discussed in order of their increasing generality.



$$R-\overset{H}{N}-\overset{O}{\overset{\|}{C}}-R' \longrightarrow R-\overset{O=N}{N}-\overset{O}{\overset{\|}{C}}-R'$$

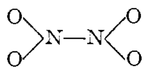
Method A. Aqueous Systems.—This method[2] usually involves the acidification of an aqueous solution of sodium nitrite and the amide. The reaction is slow (Table I, 40 hr. required at 0° for II). It is restricted to amides of primary carbinamines (RCH_2NH_2),[3] and yields products that are impure compared to those from methods D and E; it is convenient, however, for large-scale nitrosations of water-soluble amides.[4] A large excess of sodium nitrite is required, since considerable amounts of nitric oxide and nitrogen dioxide are evolved.

Method B. Sodium Nitrite–Acetic Anhydride.—This new method utilizes a mixture of sodium nitrite, acetic anhydride, acetic acid and the amide. It is applicable to amides of primary carbinamines and of cyclohexylamines, but fails with amides of acylic secondary carbinamines. Nitrosation by this method is more rapid than by method A (15 hr. required at 0° for II). The acetic anhydride–acetic acid mixture is an excellent solvent for amides. Moreover, the process of acetylation of an amine and the subsequent nitrosation may be carried out without isolation of the intermediate amide. The modified system in which phosphoric acid replaces the acetic acid is considerably more stable, *i.e.*, the quantity of nitrogen oxides evolved is less; however, in certain cases acetylation is observed rather than nitrosation.[5]

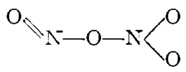
Method C. Nitrogen Trioxide.—In this method, the gases obtained either from the acidification of an aqueous solution of sodium nitrite[6] or from the reduction of nitric acid[7] are used to nitrosate the amide. A large excess of the "nitrous fumes" must be used because large amounts of nitric oxide and nitrogen dioxide are lost (nitrogen trioxide is instable at 0°). Since in practice an impure N-nitroso-N-(*sec*-butyl)-benzamide was obtained, this method was not investigated further.

Method D. Nitrosyl Chloride.—This reagent was first used for the nitrosation of N-arylamides by Hey.[8] Nitrosyl chloride, unlike the reagents of methods A and B, was found to be powerful enough to nitrosate N-(*sec*-butyl) amides. However, the method was not extensively used during the course of this work, since nitrogen tetroxide (method E) was readily available and in addition yielded purer products. Nitrosyl bromide was found to be ineffective, due largely to the extensive dissociation of the reagent into nitric oxide and bromine.[9]

Method E. Nitrogen Tetroxide.[10]—The reaction of nitrogen tetroxide with amides proved to be a general method for the preparation of nitrosoamides.[11] The reaction is rapid, 10 min. at 0° being sufficient for the preparation of any of the compounds listed in Table I. Since high yields of pure nitrosoamides were obtained, this would appear to be the method of choice.



IX



X

The nitrogen tetroxide is used with an excess of anhydrous sodium acetate, since in the absence of a base the reverse reaction of denitrosation by the nitric acid[12] occurs. The equilibrium yield of V

---

[1] E. H. White, THIS JOURNAL, **77**, 6011 (1955).

[2] M. F. Chancel, *Bull. soc. chim. France*, [3] **13**, 125 (1895); G. F. D'Alelio and E. E. Reid, THIS JOURNAL, **59**, 110 (1937).

[3] All attempts to prepare N-(*s*-butyl)-N-nitrosoacetamide by this procedure failed; the unreacted amide was recovered.

[4] For amides insoluble in water, acetic acid–water mixtures can be used; however, a strong acid must also be present (no nitrosation of the amide occurred in a mixture of N-(*n*-butyl)-acetamide, sodium nitrite, acetic acid, and water at 5° for 15 hr.).

[5] For example, N-(*n*-butyl)-*p*-toluenesulfonamide yielded N-acetyl-N-(*n*-butyl)-*p*-toluenesulfonamide.

[6] J. W. Haworth and D. H. Hey, *J. Chem. Soc.*, 365 (1940).

[7] H. J. Backer, *ibid.*, **101**, 593 (1912); H. v. Pechmann, *Ber.*, **28**, 856 (1895).

[8] H. France, I. M. Heilbron and D. H. Hey, *J. Chem. Soc.*, 369 (1940). See also A. T. Blomquist, J. R. Johnson and H. J. Sykes, THIS JOURNAL, **65**, 2446 (1943).

[9] With nitrosyl bromide, N-(*t*-butyl)-acetamide yielded stable, red crystals containing active bromine. These were also obtained from the amide hydrobromide and bromine, and proved to be the complex, $[\text{N-(}t\text{-butyl)-acetamide}]_2 \cdot HBr \cdot Br_2$. Details will be reported later.

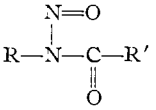
[10] Standard solutions were conveniently prepared by passing nitrogen dioxide (Matheson, Coleman and Bell, East Rutherford, N. J.) into the appropriate solvent at 0° and determining the titer iodimetrically (under N_2). Carbon tetrachloride and acetic acid proved satisfactory, whereas solutions in commercial pentane decomposed, yielding a nitrogen-containing oil.

[11] A number of other reactions are known in which nitrogen tetroxide acts as a nitrosating agent (J. L. Riebsomer, *Chem. Revs.*, **36**, 160 (1945)). These reactions have been explained by several authors on the basis that nitrogen tetroxide (IX) is in equilibrium with a small amount of X or with $ON^+ONO_2^-$ (F. Seel, *Z. anorg. Chem.*, **261**, 75 (1950); C. C. Addison and R. Thompson, *J. Chem. Soc.*, S211 (1949)). The symmetrical structure IX was assigned to crystalline nitrogen tetroxide by J. S. Broadley and J. M. Robertson, *Nature*, **164**, 915 (1949).

[12] This reaction occurs with all strong acids. Acetic acid is capable of denitrosation, but the rate is quite low (footnote 1, Table II, runs 4 and 15. See also R. Huisgen, *Ann.*, **574**, 185 (1951)).

TABLE I

N-ALKYL-N-NITROSOAMIDES,



$$R-\overset{\overset{\textstyle N=O}{|}}{N}-\underset{\underset{\textstyle O}{\|}}{C}-R'$$

Cmpd.	R	R′	Yield, %	Method	M.p. or b.p. °C. (mm.)	I.R., μ[a] C=O	I.R., μ[a] N=O
I[b]	*n*-Butyl	Methyl	80	A	35–37 (0.1)	5.75	6.60
II	Isobutyl	Methyl	73	A	30–32 (0.1)	5.81	6.52
III[d]	*n*-Butyl	3,5-Dinitrophenyl	96	B	63–63.5 dec.[c]	5.75	6.59
IV	Isobutyl	3,5-Dinitrophenyl	91	B	66.5–67 dec.[c]	5.81	[e]
			95	E	67–67.5 dec.[c]		
V	*sec*-Butyl	Phenyl	87[f]	E		5.84	6.59
VI	*sec*-Butyl	3,5-Dinitrophenyl	85[f]	D		5.81	[e]
VII	Cyclohexyl	Methyl	88[f]	E		5.73	6.58
VIII	Cyclohexyl	Ethoxyl	79[f]	B		5.70	6.55
IX	α-Phenylethyl	Methyl	88[f]	E		5.77	6.60

[a] In carbon tetrachloride. [b] n^{25}_D 1.4425. [c] Recrystallized from an ether–pentane mixture, m.p.'s uncorrected. [d] n^{25}_D 1.4400. [e] Present as an unresolved shoulder to the band of the nitro groups at 6.44μ. [f] The nitrosoamides, for which R = *sec*-alkyl, decompose at room temperature (stable for several hr. at 0°) and were not isolated, but rearranged immediately; in each case, the nitrosoamide was shown to be pure from the infrared spectrum. The yields given are the yields of products from the nitrogen elimination (footnote 1), a reaction for which the nitrosoamide must be the precursor; therefore, they represent *minimum* yields.

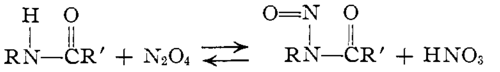
TABLE II

ANALYSES[a] (N-ALKYL-N-NITROSOAMIDES)

Cmpd.	Molecular formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
I	$C_6H_{12}N_2O_2$	49.98	50.30	8.39	8.40	19.44	19.26
II	$C_6H_{12}N_2O_2$	49.98	50.20	8.39	8.15	19.44	19.18
III	$C_{11}H_{12}N_4O_6$	44.60	44.88	4.08	3.95	18.91	18.88
IV	$C_{11}H_{12}N_4O_6$	44.60	44.77	4.08	4.13	18.91	18.70

[a] Schwartzkopf Microanalytical Laboratory, Woodside 77, Long Island, N. Y.

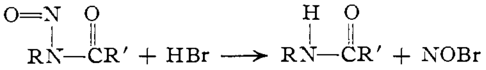
in a typical run was 60%, whereas in the presence of sodium acetate[13] essentially quantitative yields



$$R\overset{H}{\overset{|}{N}}-\overset{O}{\overset{\|}{C}}R' + N_2O_4 \rightleftharpoons R\overset{O=N}{\overset{|}{N}}-\overset{O}{\overset{\|}{C}}R' + HNO_3$$

$$HNO_3 + NaOAc \longrightarrow HOAc + NaNO_3$$

were obtained. Based on this reversal by strong acids and the instability of nitrosyl bromide, a rapid quantitative method of denitrosation was developed using a system of hydrogen bromide and sodium thiosulfate.[14] The nitrosation step is prob-

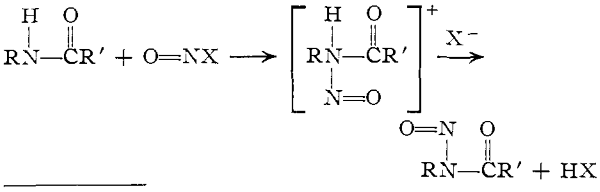


$$R\overset{O=N}{\overset{|}{N}}-\overset{O}{\overset{\|}{C}}R' + HBr \longrightarrow R\overset{H}{\overset{|}{N}}-\overset{O}{\overset{\|}{C}}R' + NOBr$$

$$2NOBr \rightleftharpoons 2NO\uparrow + Br_2$$

$$Br_2 + 2Na_2S_2O_5 \longrightarrow 2NaBr + Na_2S_4O_6$$

ably very similar for the five methods used. By analogy to the nitrosation of amines,[15] this reaction can be represented by



$$R\overset{H}{\overset{|}{N}}-\overset{O}{\overset{\|}{C}}R' + O=NX \longrightarrow \left[R\overset{H}{\overset{|}{\underset{\underset{\textstyle N=O}{|}}{N}}}-\overset{O}{\overset{\|}{C}}R'\right]^+ \xrightarrow{X^-} R\overset{O=N}{\overset{|}{N}}-\overset{O}{\overset{\|}{C}}R' + HX$$

where X = NO_3^- for method E, Cl^- for D, NO_2^- for C, OAc^- for B, and possibly NO_2^- or H_2O for method A. The physical constants of the amides used in this work (some of which have not been previously reported) are listed in Table III.

In general, nitrosoamides of primary carbinamines (I–IV) are stable compounds; *ca.* 10–15 hr. at 75° is required for their rearrangement.[1] Corresponding derivatives of α-phenylethylamine are less stable, decomposing at 50°, whereas those of secondary aliphatic carbinamines (V–VIII) decompose at 25° (the latter can be isolated at 0°). Nitrosomides of *t*-carbinamines are very unstable, eliminating nitrogen at −10°.

Experimental

Preparation of the Amides.—The acetamides were prepared by a general method described elsewhere,[1] and the urethans by previously reported procedures.[16] The 3,5-dinitrobenzamides were prepared from the amines and 3,5-dinitrobenzoyl chloride in an excess of pyridine. Since these amides are rather insoluble in common organic solvents, the reaction mixture was poured into an excess of water and the precipitated amides filtered and dried. The N-(*n*-butyl)- and the N-(isobutyl)-3,5-dinitrobenzamides were recrystallized from dioxane and the *sec*-butyl isomer from a mixture of dioxane and methyl acetate. The *n*-butyl amide forms a crystalline complex with dioxane. The dioxane can be removed, however, at 100° and 0.01 mm. The benzamides were prepared by the Schotten–Baumann procedure. The physical properties of the amides are given in Table III.

Nitrosation with an Acetic Anhydride–Sodium Nitrite Mixture (Method B).—A solution of the amide (0.010 mole) in a mixture of acetic acid (10 ml.) and acetic anhydride (50 ml.) was cooled to 0° and 15 g. of granular sodium nitrite (0.22 mole) was added during *ca.* 5 hr. After 10 hr. at 0°, the temperature was allowed to rise to 10–15° (during *ca.* 30 min.) and the mixture poured into a mixture of ice and water. The nitrosoamide was extracted with ether, and the upper phase was washed with water, with an aqueous solution of sodium carbonate (5%), with water, and then dried with anhydrous sodium sulfate. The solvent was removed (under vacuum), and depending on the properties of the nitrosoamide, the product was either distilled under vacuum (temp. <40°), or recrystallized from ether–pentane mixtures (see Table I for yields).

---

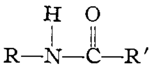
[13] No other base was used with nitrogen tetroxide, but in method D, pyridine proved to be as effective as sodium acetate.

[14] The sodium thiosulfate may be omitted if nitrogen is passed through the system to remove the nitric oxide. V. Braun (*Ber.*, **70B**, 979 (1937) has used HCl and $NaHSO_3$ to effect denitrosation and Angier, *et al.* (THIS JOURNAL, **74**, 408 (1952)) have used HCl and phenol.

[15] J. H. Dusenbury and R. E. Powell, THIS JOURNAL, **73**, 3269 (1951).

[16] W. W. Hartman and M. R. Brethen, "Organic Syntheses," Coll. Vol. II, second edition, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 278.

TABLE III

N-ALKYLAMIDES, 
$R-\overset{H}{\overset{|}{N}}-\overset{O}{\overset{\|}{C}}-R'$

R	R′	M.p.[a] (solvent) or b.p. °C. (mm.)	n^{25}D	I.R, μ C=O	Ref.
n-Butyl	Methyl	125(13)	1.4385	6.04(CCl_4)	[g]
Isobutyl	Methyl	125(20)	1.4360	6.02(CCl_4)	[h]
sec-Butyl	Methyl	119(18)	1.4358	6.06(CCl_4) 6.01($CHCl_3$)	[i]
t-Butyl	Methyl	99–100(ether)		6.01($CHCl_3$)	[j]
n-Butyl	3,5-Dinitrophenyl	109–110($CHCl_3$)		5.96($CHCl_3$)	
Isobutyl	3,5-Dinitrophenyl	161–162[b]		5.97($CHCl_3$)	[k]
sec-Butyl	3,5-Dinitrophenyl	173–174[b,c]		5.93($CHCl_3$)	
sec-Butyl	Phenyl	95–96[d](ether)		6.10[e](CCl_4)	[l]
Cyclohexyl	Methyl	106–107(ether)		5.92(CCl_4)	[m]
Cyclohexyl	Ethoxyl	57–58(pentane)			[m]
α-Phenylethyl	Methyl	78–91[f]		6.06(CCl_4)	[n]

[a] Uncorrected. [b] Recrystallized from ethyl acetate–ether mixtures. [c] *Anal.* Calcd. for $C_{11}H_{13}N_3O_5$: C, 49.44; H, 4.90; N, 15.75. Found: C, 49.53; H, 4.63; N, 15.49. The optically pure (+)-enantiomorph melted at 175.5–176° (from $CHCl_3$). [d] Melting point for the optically pure (+)-enantiomorph. [e] A broad band with a poorly defined maximum. [f] 46.3% optically pure. [g] R. H. Wiley, O. H. Borum and L. L. Bennett, THIS JOURNAL, **71**, 2899 (1949), report n^{25}D 1.4388. [h] A. W. Titherley, *J. Chem. Soc.*, **79**, 402 (1901), reports b.p. 225–227° (745 mm). [i] W. C. G. Baldwin, *Proc. Roy. Soc.* (*London*), **A162,** 215 (1937). No constants reported. [j] J. J. Ritter and P. P. Minieri, THIS JOURNAL, **70,** 4045 (1948), report 97–98°. [k] T. Reichstein, *Helv. Chim. Acta*, **9,** 803 (1926), reports 162° (benzene). [l] N. J. Leonard and E. W. Nommensen, THIS JOURNAL, **71,** 2808 (1949), report 92–92.5° for the pure (+)-enantiomorph. [m] S. Olsen and E. Enkemeyer, *Ber.*, **81,** 359 (1948), report 107–107.5° and 58–59°, respectively. [n] J. Götze, *ibid.*, **71B,** 2289 (1938), reports 79° for the racemic amide and 101–102° for the optically pure form.

Nitrosation with Nitrogen Tetroxide (Method E).—Anhydrous sodium acetate (0.03 mole) was added to a solution of nitrogen tetroxide (0.015 mole) in the appropriate solvent[10] at −60°. The mixture was warmed to 0° and the amide (0.01 mole) added with stirring. After 10–20 min., the mixture was poured into a slurry of ice and water. The subsequent work-up was identical to that given above for method B. In the case of unstable nitrosoamides (such as V, VI, VII and VIII), the operations were carried out at 0°. If the nitrosoamides were required in solvents other than carbon tetrachloride, either the latter solvent was removed at 0°, or the nitrosation was effected with a solution of nitrogen tetroxide in acetic acid, and after pouring the nitrosation mixture into ice-water, the extraction was performed with the solvent of choice.

Denitrosation with Hydrogen Bromide.—(+)N-(*sec*-Butyl)-benzamide (0.26 g., m.p. 90–91°, 64.6% optically pure) was nitrosated with nitrogen tetroxide in carbon tetrachloride as described above[17] (method E). After thorough washing, the solution in carbon tetrachloride was mixed with an aqueous solution of sodium thiosulfate (10 ml., 0.5 *N*), at 2°, and hydrogen bromide passed into the system for 10–15 min. The lower phase was separated, washed with water, and the solution dried with anhydrous sodium sulfate. Evaporation of the solvent yielded 0.208 g. of (+)N-(*sec*-butyl)-benzamide (m.p. 89–91°, 64.0% optically pure, 80% yield for the two-step reaction). The infrared spectrum of the product was superimposable on that of the starting material. Similar results were obtained from the denitrosation of compound I.

Nitrosation and Acylation of N-(*n*-Butyl)-*p*-toluenesulfonamide.[18]—(i) Nitrosation by method B yielded N-(*n*-butyl)-N-nitroso-*p*-toluenesulfonamide,[17] a yellow oil (94%). I.R.: N=O, 6.63 μ; S—O, 7.23 μ. (ii) Both acetylation and nitrosation occurred when the acetic acid in method B was replaced with phosphoric acid. From a run in which the sodium nitrite was omitted, only N-acetyl-N-(*n*-butyl)-*p*-toluenesulfonamide, m.p. 54.5–55°, was obtained (91% yield). *Anal.* Calcd. for $C_{13}H_{19}NO_3S$: C, 57.97; H, 7.11; N, 5.20. Found: C, 58.25; H, 7.10; N, 5.37. I.R.: C=O, 5.87 μ; S—O, 7.34 μ.

NEW HAVEN, CONNECTICUT

---

(17) The nitrosation was complete as indicated by the infrared spectrum.

(18) Eastman Kodak Co.