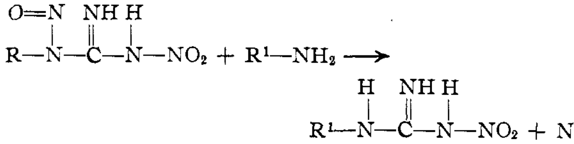
[Contribution from the Department of Chemistry, Queen's University]

The Preparation of N-Substituted-N^1-nitroguanidines by the Reaction of Primary Amines with N-Alkyl-N-nitroso-N^1-nitroguanidines[1]

By A. F. McKay

It has been reported[1a] that the reaction of primary aliphatic amines and aniline with N-methyl-N-nitroso-N^1-nitroguanidine gives N-alkyl- and N-phenyl-N^1-nitroguanidines. Since this was the first description of a method of producing N-aryl-N^1-nitroguanidines this reaction was investigated more fully. The compounds prepared along with their physical properties are listed in Table I. In general primary amines react with N-alkyl-N-nitroso-N^1-nitroguanidines to give N-substituted-N^1-nitroguanidines as follows



$$\mathrm{R{-}\overset{\overset{O=N}{|}}{N}{-}\overset{\overset{NH}{\|}}{C}{-}\overset{\overset{H}{|}}{N}{-}NO_2 + R^1{-}NH_2 \longrightarrow R^1{-}\overset{\overset{H}{|}}{N}{-}\overset{\overset{NH}{\|}}{C}{-}\overset{\overset{H}{|}}{N}{-}NO_2 + N_2}$$

R = methyl, ethyl or butyl

R^1 = alkyl, aralkyl or aryl groups

TABLE I

N-Substituted-N^1-Nitroguanidines

N-Substituent	Yield, % Method A	Yield, % Method B	M. p., °C.[c]	Formula	Analyses, % Calculated C	Calculated H	Calculated N	Calculated X[d]	Found C	Found H	Found N	Found X[d]
Allyl		64.4	107–108	$C_4H_8N_4O_2$	33.3	5.55	38.9		33.4	5.70	39.2	
γ-Diethylaminopropyl		72.0	135–136	$C_8H_{19}N_5O_2$	44.2	8.76	32.2		44.4	8.76	32.3	
Cyclohexyl		46.4	197–198	$C_7H_{14}N_4O_2$	45.1	7.54	30.1		45.2	7.56	30.4	
Benzyl[a]	94.8		182.5–183.5									
dl-α-Phenylethyl		84.7	117–118	$C_9H_{12}N_4O_2$	51.9	5.76	26.9		52.0	5.70	27.0	
β-Phenylethyl	93.0		162–163	$C_9H_{12}N_4O_2$	51.9	5.76	26.9		51.9	5.60	27.1	
Phenyl[b]	88.5	90.1	152–153									
p-Methylphenyl	97.0	88.8	165–166	$C_8H_{10}N_4O_2$	49.4	5.15	28.8		49.5	5.18	29.0	
m-Methylphenyl	69.6	80.8	125–126	$C_8H_{10}N_4O_2$	49.4	5.15	28.8		48.9	5.10	28.9	
o-Methylphenyl		91.0	202.5–203.5 (dec.)	$C_8H_{10}N_4O_2$	49.4	5.15	28.8		49.6	4.96	28.8	
p-Methoxyphenyl	92.5		153–154	$C_8H_{10}N_4O_3$	45.7	4.76	26.6		45.7	4.91	26.7	
m-Methoxyphenyl	92.5		154–155	$C_8H_{10}N_4O_3$	45.7	4.76	26.6		45.8	4.58	26.4	
o-Methoxyphenyl	89.2	74.4	136–137	$C_8H_{10}N_4O_3$	45.7	4.76	26.6		45.8	4.70	26.4	
p-Ethoxyphenyl	83.0		175–176	$C_9H_{12}N_4O_3$	48.2	5.35	25.0		47.8	5.44	25.2	
m-Ethoxyphenyl	89.0		135–136	$C_9H_{12}N_4O_3$	48.2	5.35	25.0		47.9	5.40	25.1	
o-Ethoxyphenyl	69.0		127–127.5	$C_9H_{12}N_4O_3$	48.2	5.35	25.0		47.9	5.14	24.8	
p-Chlorophenyl	77.8	76.0	167.5–168.5	$C_7H_7ClN_4O_2$	39.2	3.26	26.1	16.55	38.5	3.47	26.2	16 9
m-Chlorophenyl	61.5	76.8	162.5–163.5	$C_7H_7ClN_4O_2$	39.2	3.26	26.1	16.55	39.1	3.35	26.5	16.7
o-Chlorophenyl	0.0	31.5	187–188	$C_7H_7ClN_4O_2$	39.2	3.26	26.1	16.55	39.0	3.33	26.4	16.9
p-Bromophenyl	76.5		189.2–190.2	$C_7H_7BrN_4O_2$	32.4	2.70	21.6	30.8	32.1	2.66	21.7	31.2
m-Bromophenyl	63.7		182–183	$C_7H_7BrN_4O_2$	32.4	2.70	21.6	30.8	32.6	2.57	21.6	31.3
p-Dimethylaminophenyl		72.4	196–197	$C_9H_{13}N_5O_2$	48.4	5.84	31.3		48.8	5.63	31.0	
p-*t*-Amylphenyl		61.2	174–175	$C_{12}H_{18}N_4O_2$	57.5	7.20	22.4		57.6	7.32	22.4	
2,5-Dimethylphenyl	66.2	74.9	161–162.7	$C_9H_{12}N_4O_2$	51.9	5.77	26.9		51.7	5.73	27.1	
2-Methyl-5-isopropylphenyl		26.8	125–126	$C_{11}H_{16}N_4O_2$	55.9	6.79	23.7		55.8	6.66	23.5	
p-Acetamidophenyl		88.1	223 (dec.)	$C_9H_{11}N_5O_3$	45.6	4.64	29.5		45.6	4.58	29.0	

[a] Previously reported.[2] [b] Previously reported.[1] [c] All melting points uncorrected. [d] X = halogen.

It was observed generally that the more basic amines reacted at a faster rate with the N-alkyl-N-nitroso-N^1-nitroguanidines than the less basic ones. Whereas aniline reacts slowly with methylnitrosonitroguanidine in 50% aqueous ethanol over a period of one and a half hours benzylamine reacts immediately with this compound. In the latter case the rate of reaction has to be controlled by cooling the solution and adding the nitrosamine portionwise. The rate of reaction of amines with the alkylnitrosonitroguanidines is also dependent on the medium in which the reaction is conducted. With aniline in ether–water the reaction time is several days, whereas in 50% aqueous ethanol the reaction is complete in one and a half hours.

As previously reported[1] the only secondary amine to react with N-methyl-N-nitroso-N^1-nitroguanidine to give a N-disubstituted-N^1-nitroguanidine was dimethylamine. Other secondary amines, *e. g.*, diethylamine or di-*n*-propylamine cause decomposition of methylnitrosonitroguanidine with gassing but no nitroguanidine derivatives can be isolated from the reaction mixture. When methylnitrosonitroguanidine is heated in 85% aqueous ethanol with either N-methylaniline or N-ethylaniline denitrosation occurs and methylnitroguanidine is recovered in good yield.

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[1] This paper was presented in part before the Chemical Institute of Canada Meeting, Montreal, June, 1948.

[1a] A. F. McKay and G. F. Wright, This Journal, **69**, 3028 (1947).

[2] T. L. Davis and S. B. Luce, *ibid.*, **49**, 2303 (1927).

Experimental

N-Methyl-N-nitroso-N^1-nitroguanidine.—The procedure for the preparation of N-methyl-N-nitroso-N^1-nitroguanidine by McKay and Wright[1a] has been modified slightly. In a typical run, 100 g. (0.848 mole) of methylnitroguanidine was dissolved in 300 cc. of nitric acid (sp. gr. 1.42) and this solution was diluted with 1000 cc. of water. The clear solution was cooled to 10° and maintained at this temperature while 124.0 g. (1.80 moles) of sodium nitrite in 200 cc. of water was added. During the addition of the sodium nitrite solution, which required fifteen minutes, and for a further period of seventeen minutes, the reaction was mechanically stirred. The yellow crystals of methylnitrosonitroguanidine were removed by filtration and washed thoroughly with cold water. It is important to remove all acid from the nitrosamine or partial denitrosation will occur during subsequent purification. A crude yield (m. p. 112–113° with decomposition) of 85% was obtained. One crystallization from the minimum quantity of boiling methanol (3.3 cc./g.) gave pure material melting at 118° with decomposition. On concentration of the filtrate to *ca.* 80 cc. a second crop of pure product was recovered. The total yield of pure methylnitrosonitroguanidine was 82% by theory. Some thirty runs were completed using this procedure and the purified yields varied from 72–82%. It is important that all yields of alkylnitrosoguanidines be air-dried and not dried in an oven.

N-Ethyl-N^1-nitroguanidine.—The preparation of ethylnitroguanidine by the method of Davis and Abrams[3] gave a product contaminated with nitroguanidine. Since the purification of this product by crystallization from ethanol resulted in large losses, the reaction was reinvestigated. In a series of thiry-one runs the effects of varying reaction temperature, reaction time and molar quantities were studied. Two methods were found to give fairly consistent results.

Procedure I.—One mole (104 g.) of nitroguanidine was added to a solution of 78.4 g. (1.4 moles) of potassium hydroxide in 250 cc. of water. To this mixture 94 g. (1.15 moles) of ethylamine hydrochloride was added with stirring and the temperature of the mixture was raised to 68° over a period of fifteen minutes. This temperature was maintained for twenty-five minutes. After fifteen minutes at 68° a second portion of 20 g. (0.245 mole) of ethylamine hydrochloride was added. At the end of the heating period the reaction mixture was cooled to 7° and the white solid removed by filtration. The crude product melted at 125–128°, yield 102.5 g. or 77.8%. Purification of the product was effected by solution in 50 cc. of warm 70% nitric acid and pouring into 10 vol. of water. The resulting mixture was allowed to stand overnight at room temperature after which the crystals were filtered off and washed with water. The purified ethylnitroguanidine melted at 146–147°, yield 69.2 g. (52.4%).

Procedure II.—Fifty-two grams (0.5 mole) of nitroguanidine and 70 cc. of 70% aqueous ethylamine (0.85 mole) were added to 107 cc. of water. The temperature of the stirred mixture was increased to 60° over a period of thirteen minutes and maintained at 59 ± 1° for an additional twenty-five minutes. After cooling to 7°, the white solid was filtered off and washed with water (30 cc.). The crude product melted at 146–147° with preliminary softening at 130°. One crystallization from 140 cc. of 95% ethanol gave a product melting at 147–148°, yield 34.0 g. or 51.6%.

N-Ethyl-N-nitroso-N^1-nitroguanidine.—One mole (132.1 g.) of ethylnitroguanidine was dissolved in 356 cc. of nitric acid (sp. gr. 1.42) and diluted with 1100 cc. of water. The nitrosation was carried out in the same manner described for the preparation of methylnitrosonitroguanidine. A yellow crystalline solid (m. p. 110° with decomposition) separated which was filtered off, washed thoroughly with water and air-dried, yield 132.3 g. (82.8%). Pure crystals were obtained on crystallizing from 400 cc. of absolute methanol. A second crop was obtained by concentrating the methanolic filtrate to 80 cc. The combined yield of pure ethylnitrosonitroguanidine was 124 g. or 77%. The final melting point was 114.5° with decomposition.

Anal. Calcd. for $C_3H_7N_5O_3$: C, 22.3; H, 4.34; N, 43.4. Found: C, 22.6; H, 4.21; N, 43.0.

N-*n*-Butyl-N^1-nitroguanidine.—Butylnitroguanidine was prepared using the method outlined in procedure II for the preparation of ethylnitroguanidine. On cooling the reaction mixture the excess butylamine caused the product to separate as an oil. The mixture was made acid to litmus paper with hydrochloric acid (1:1) after which the butylnitroguanidine was obtained as a white crystalline product. One crystallization from 95% ethanol raised the melting point from 80–82° to 83–84.5°, yield 52.7%.

N-*n*-Butyl-N-nitroso-N^1-nitroguanidine.—Butylnitroguanidine (92.5 g., 0.58 mole) was dissolved in 202 cc. of 70% nitric acid solution and diluted with 202 cc. of water. Nitrosation of this solution was effected as outlined in the preparation of methylnitrosonitroguanidine. An efficient means of stirring must be used because of the tendency of the crystalline butylnitrosonitroguanidine to occlude evolved gases. The crude yield of product (m. p. 112–113° with decomposition) varied from 72–77%. One crystallization from methanol (0.44 g./cc.) and filtration after cooling to −26° gave 67–73% of pure N-*n*-butyl-N-nitroso-N^1-nitroguanidine melting at 121° with decomposition.

Anal. Calcd. for $C_5H_{11}N_5O_3$: C, 31.7; H, 5.82; N, 37.0. Found: C, 31.61; H, 5.80; N, 36.6.

N-Substituted-N^1-nitroguanidines from N-Methyl-N-nitroso-N^1-nitroguanidine. Method A.—The amine (0.09 mole) was dissolved in 50 cc. of ether to which 20 cc. of water was added. To this mixture 5 g. (0.034 mole) of methylnitrosonitroguanidine was added and the temperature maintained at 22°. After the evolution of gas had ceased, the crystalline product was filtered off and washed with fresh ether. The reaction time varied from several hours to several days depending on the amine used. The more basic amines reacted at a faster rate. Purification was effected by crystallizing from 95% ethanol. The products and yields obtained are recorded in Table I.

Method B.—Methylnitrosonitroguanidine (0.034 mole) was treated with a primary amine in aqueous ethanol as a solvent. The reaction conditions and yields are recorded in Table II. The product was recovered by pouring the reaction mixture into 200 cc. of water and filtering off the precipitate, which was washed with ether (20–30 cc.). It was then crystallized from 95% ethanol.

Both methods A and B had to be modified slightly when the aliphatic amines, aralkyl amines and *p*-dimethylaminoaniline were used. These amines are more basic than the arylamines and react rapidly with N-alkyl-N-nitroso-N^1-nitroguanidines. Therefore these amines were dissolved in the aqueous ethanol or ether–water mixture and then the alkylnitrosonitroguanidines were added portionwise. The rate of addition was regulated to maintain the temperature at 20–25° with water–ice cooling. After the evolution of gas had ceased, the product was recovered by direct filtration or by dilution with water and then filtration.

N-Substituted-N^1-nitroguanidines from N-Ethyl-N-nitroso-N^1-nitroguanidines.—Cyclohexyl- and benzylnitroguanidines were prepared in 49.3 and 92.5% yield, respectively, by adding 0.034 mole of ethylnitrosonitroguanidine portionwise to 0.09 mole of the appropriate amine dissolved in 35 cc. of 50% aqueous ethanol.

Phenyl-, *p*-methylphenyl- and *p*-methoxyphenylnitroguanidines were prepared in 85.9, 95.0 and 91.5% yield, respectively. In these runs the ethylnitrosonitroguanidine was added in one portion and the reaction allowed to proceed until gas evolution ceased. The substituted nitroguanidines were identified by mixed melting point determinations.

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(3) T. L. Davis and A. J. J. Abrams, *Proc. Am. Acad. Sci.*, **61**, 437 (1926).

Table II

N-Substituted-N^1-nitroguanidines Prepared by Method B

Amine[a]	Reaction medium aqueous ethanol % Ethanol	Vol., cc.	Reaction time, hr.	N–R–N^1-Nitroguanidine R	Yield, %
Aniline[b] *R*	50	35	0.4	Phenyl	85.0
Aniline[c] *R*	50	35	0.6	Phenyl	78.4
Aniline *R*	95	35	2.5	Phenyl	65.4
Aniline *R*	95	35	6.5	Phenyl	62.2
Aniline	75	35	1.05	Phenyl	73.5
Aniline	50	35	1.05	Phenyl	83.4
Aniline	50	35	2.0	Phenyl	83.4
o-Anisidine	51	36	3.0	*o*-Methoxyphenyl	74.4
p-Toluidine	55	50	1.5	*p*-Methylphenyl	88.8
m-Toluidine	50	35	1.5	*m*-Methylphenyl	80.0
p-Aminoacetanilide	50	35	3.5	*p*-Acetamidophenyl	88.1
2-Amino-*p*-cymene	68	55	72.0	2-Methyl-5-isopropylphenyl	26.8
2-Amino-1,4-dimethylbenzene	54	38	42.5	2,5-Dimethylphenyl	74.9
p-Chloroaniline	65	50	12.0	*p*-Chlorophenyl	76.0
m-Chloroaniline	56	40	12.0	*m*-Chlorphenyl	76.8
o-Chloroaniline *R*	52	37	4.5	*o*-Chlorophenyl	31.5
o-Chloroaniline *R*	85	38	21.5	*o*-Chlorophenyl	11.6
o-Chloroaniline *R*	85	38	48.0	*o*-Chlorophenyl	20.6

[a] Ratio of amine to methylnitrosonitroguanidine 2.65:1. [b] Ratio of amine to methylnitrosonitroguanidine 1.76:1. [c] Ratio of amine to methylnitrosonitroguanidine 1.17:1. [R] Reactions carried out at reflux temperature. All other runs recorded were carried out at a temperature of 22°.

N-Substituted-N^1-nitroguanidines from N-*n*-Butyl-N-nitroso-N^1-nitroguanidine.—Phenyl-, *p*-acetamidophenyl- and *p*-ethoxyphenylnitroguanidines were obtained in 83.4, 98.2 and 89.4% yield, respectively. Butylnitrosonitroguanidine (0.034 mole) was added in one portion to 0.09 mole of the appropriate amine dissolved in 50% aqueous ethanol. The reaction was allowed to proceed to completion at 22° when the product was recovered and identified by mixed melting point determinations.

Denitrosation of N-Methyl-N-nitroso-N^1-nitroguanidine.—To a solution of 10.89 g. (0.09 mole) of N-ethylaniline in 50 cc. of 75% ethanol was added 5 g. (0.034 mole) of methylnitrosonitroguanidine. The reaction mixture was heated for one and a half hours at 83°. Then it was cooled to *ca.* 7° and the crystals removed by filtration. After washing with ether, the crystals melted at 157°; yield 3.4 g. (84.7%). One crystallization from methanol raised the melting point to 159–161°. Admixture with an authentic sample of N-methyl-N^1-nitroguanidine did not depress the melting point.

A similar experiment using N-methylaniline in place of N-ethylaniline gave a 72% yield of methylnitroguanidine (m. p. 159–161°).

Summary

A series of N-substituted-N^1-nitroguanidines have been prepared by the reaction of primary amines with N-alkyl-N-nitroso-N^1-nitroguanidines. Denitrosation of N-methyl-N-nitroso-N^1-nitroguanidine is effected by heating with an aqueous alcoholic solution of N-methyl or N-ethylaniline.

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[Contribution from the Department of Chemistry, Queen's University]

The Nitration Products of Some Substituted 2-Nitramino-1,3-diazacylcoalkenes-2

By A. F. McKay and D. F. Manchester

In a previous paper on the nitration products of 2-nitramino-1,3-diazacycloalkenes-2[1] it was stated that the five-membered ring compound 2-nitramino-1,3-diazacylcopentene-2 was the only one that gave a 1-nitro derivative. However 2-nitramino-1,3-diazacyclohexene-2 and 2-nitramino-1,3-diazacycloheptene-2 could be easily converted to the corresponding 1,3-dinitro-1,3-diazacycloalkanone-2. This investigation has been extended to the nitration of formerly described[2] 2-nitramino-4(or 5)-methyl-1,3-diazacyclopentene-2 I (n = 0), 2-nitramino-4(or 6)-methyl-1,3-diazacyclohexene-2 I (n = 1) and 5-hydroxy-2-nitramino-1,3-diazacyclohexene-2 V to ascertain the effect of substituents on the course of nitration.

The 2-nitramino-4(or 5)-methyl-1,3-diazacyclopentene-2 I (n = 0) on treatment with 2 mole equivalents of nitric acid in acetic anhydride gave 1-nitro-2-nitramino-4(or 5)-methyl-1,3-diazacyclopentene-2 IIa or IIb (n = 0). On the other hand the two substituted 2-nitramino-1,3-diazacyclohexenes-2 I (n = 1) and V failed to give a 1-nitro derivative when treated with nitric acid–acetic anhydride mixture or mixed acid. This substantiates the previous observations[1] on the unsubsti-

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[1] A. F. McKay and G. F. Wright, This Journal, **70**, 3990 (1948).

[2] A. F. McKay and G. F. Wright, *ibid.*, **70**, 430 (1948).