Synthesis and Reactions of 1-Nitroso-1-alkyl-2-guanyl- and -2-carbamylhydrazines

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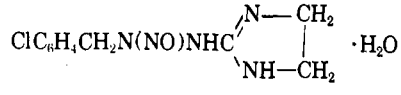
The 1-nitroso derivatives of representative 1-alkyl-2-guanyl- and -2-carbamylhydrazines have been synthesized and characterized. 1-Cyclohexyl-2-guanyl-1-nitrosohydrazine cyclizes to 3-cyclohexyl-5-imino-1,2,3,4-oxatriazoline hydrochloride in concentrated hydrochloric acid at ambient temperature, but decomposes to cyclohexyl chloride, ammonium chloride, and carbamyl azide in hot acid. 1-Benzyl-2-guanyl-1-nitrosohydrazine yields benzyl chloride, ammonium chloride, and carbamyl azide on treatment with concentrated hydrochloric acid at ambient temperature, whereas the analogous 2-carbamyl compound cyclizes to 3-benzyl-1,2,3,4-oxatriazolin-5-one. 1-Benzyl-2-carbamyl-1-nitrosohydrazine, on heating in neutral aqueous suspension, yields 1-benzylurea and nitrous oxide through a reaction involving a 1,2-shift of the benzyl group.

As part of a continuing program on the chemistry of polynitrogen compounds, the hydrolytic and thermal behavior of a number of substituted nitroso guanyl- and carbamylhydrazines, both new and previously described, was studied. The position of nitrosation of the guanylhydrazines was elucidated as part of the investigation.

The majority of the substituted guanylhydrazinium salts were made by the catalytic hydrogenation of the corresponding alkylidene guanylhydrazone hydrochlorides,[1] following a procedure described previously[2] or a modification of it. These derivatives, $RNHN(R')C(NR'')NHR''\cdot HCl$ (R = benzyl or cyclohexyl; R′ = hydrogen or methyl; and R″ = hydrogen, methyl, or bridge ethylene), were similar in that the hydrazino nitrogens β to the guanyl group bore a single proton; these derivatives nitrosated readily and the nitroso derivatives of the free bases were isolated and characterized. 1,1-Dimethyl-2-guanylhydrazinium sulfate, $(CH_3)_2NNHC(NH)NH_2\cdot 0.5H_2SO_4$, was conveniently synthesized by the solvent-free reaction of 2-methyl-2-thiopseudouronium sulfate with excess 1,1-dimethylhydrazine; this hydrazinolysis was much less successful when attempted in aqueous solution. The advantage of using excess 1,1-dimethylhydrazine as a solvent was also demonstrated in the synthesis of 1-(N-dimethylaminoguanyl)-1-methylhydrazine, $(CH_3)_2NNHC(NH)N(CH_3)NH_2$. Since 1,1-dimethyl-2-guanylhydrazinium sulfate did not nitrosate, it was concluded that nitrosation occurred on the hydrazino group β to the guanyl group, *i.e.*, $RN(NO)NR'C(NR'')NHR''$. An X-ray crystallographic study[3] of nitroso-1-(4-chlorobenzyl)-2-(4,5-dihydro-2-imidazolyl)-hydrazine hydrate confirmed that the nitroso group was on the nitrogen bearing the benzyl group.



The 1-alkyl-2-guanyl-1-nitrosohydrazinium salts are soluble and reasonably stable in cold dilute aqueous acids; the free bases are precipitated upon neutralization of the acidic solutions. The alkylguanylnitrosohydrazines can be recrystallized from water or aqueous base without decomposition. Recrystallization from ethanol or ethanol–ether solutions could be accomplished without decomposition if the cooled solutions were seeded and the crystalline product was removed promptly; if these solutions were allowed to stand without nucleation, however, a slow air oxidation of the nitroso derivative occurred and the corresponding alkylidene aminoguanidinium nitrate was recovered. Catalytic hydrogenolysis (Adams platinum oxide in ethanol solution) resulted in the formation of the starting 1-alkyl-2-guanylhydrazines. In contrast to many nitroso amines, the solid, recrystallized alkylguanylnitrosohydrazines are unusually stable; thus the melting point of 1-cyclohexyl-2-guanyl-1-nitrosohydrazine, $C_6H_{11}N(NO)NHC(NH)NH_2$ (I), remained unchanged after storage for 12 years at ambient temperature. Although this stability suggested that the free bases existed in a cyclic, resonance-stabilized form, the X-ray study reported above did not confirm this thought.

Several related hydrazinium chlorides, including 1-benzyl-2-carbamyl-,[4] 1-benzyl-2-methyl-2-carbamyl-, 1-benzyl-2-benzoyl-, and 1-benzyl-2-benzoyl-2-methyl-, were also nitrosated and the nitroso derivatives were isolated.[5] On the other hand, 1-(N-nitroguanyl)-2-phenylhydrazine, $C_6H_5NHNHC(NH)NHNO_2$, did not nitrosate but was slowly oxidized by nitrite ion to the azo derivative, $C_6H_5N{=}NC(NH)NHNO_2$.

The behavior of the nitrosoalkylguanylhydrazines in acidic and neutral media has been examined systematically. Nitroso derivatives of the type $C_6H_5CH_2N(NO)N(CH_3)C(NH)NHR$ (R = H or methyl) were stable in hot concentrated hydrochloric acid for at least 10 min.

Nitroso derivatives of the type $RN(NO)NHC(NR')NHR'$, where R = an alkyl or aralkyl group and R′ = hydrogen, methyl, or a bridge ethylene group, were unstable in acidic media. The mode of decomposition depended on the nature of the acid, on the structure of R, and on the temperature of the reaction. The nature of these decompositions was elucidated by a detailed study of the decompositions of 1-cyclohexyl-2-guanyl-1-nitrosohydrazine (I) and 1-benzyl-2-guanyl-1-nitrosohydrazine (II) in various acidic media. In systems containing anhydrous hydrogen chloride in an oxygen-free solvent such as acetonitrile, denitroxylation occurred to give the alkylidene aminoguanidinium

(1) W. G. Finnegan, R. A. Henry, and E. Lieber, *J. Org. Chem.*, **18**, 779 (1953).

(2) W. G. Finnegan, R. A. Henry, and G. B. L. Smith, *J. Am. Chem. Soc.*, **74**, 2981 (1952).

(3) G. J. Palenik, *Acta Cryst.*, in press.

(4) S. Kessler and H. Rupe, *Ber.*, **45**, 26 (1912).

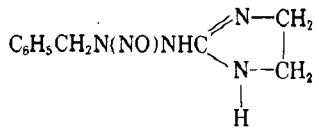
(5) J. Thiele [*Ann.*, **376**, 250 (1910)] prepared 1-benzyl-2-benzoyl-1-nitrosohydrazine by benzoylation of 1-benzyl-1-nitrosohydrazine. For an interesting and novel synthesis of 1-alkyl-2-benzoyl-1-nitrosohydrazines, see P. A. S. Smith and H. G. Pars, *J. Org. Chem.*, **24**, 1325 (1959).

chloride. The decomposition of 1-benzyl-2-guanyl-1-nitrosohydrazine (II) in concentrated hydrochloric acid at ambient temperature for 2-4 hr. or at steam-bath temperature for a few minutes (until the exothermic reaction subsided) led to the formation of benzyl chloride, ammonium chloride, and carbamyl azide in good yields. A similar decomposition, run in glacial acetic acid at 100° for 5 min., yielded benzyl acetate, a minor amount of benzyl azide, and ammonium acetate, but no isolable carbamyl azide. Moderate gas evolution occurred and hydrazoic acid could be detected. Oxides of nitrogen were noted in only small quantities, and a minor amount of benzalaminoguanidine could be isolated as its picrate salt.

Fusion of an intimate mixture of 1 equiv. of compound II with 2 equiv. of benzoic acid at 100° resulted in an exothermic reaction which raised the temperature of the melt to 120–125°. On work-up of the resulting mixture, moderate yields of benzyl benzoate and ammonium acid benzoate were obtained; no carbamyl azide could be isolated. A minor product, which was present in the neutral ester fraction and which showed azide absorption at 4.75 μ, was isolated as its triphenylphosphinimide. Hydrolysis of this derivative in ethanol yielded triphenylphosphine oxide, benzaldehyde, and benzoic acid, suggesting that this minor product was benzylidene benzoate azide, $C_6H_5CH(N_3)O_2CC_6H_5$. The n.m.r. spectrum of the triphenylphosphinimide of a similar by-product obtained in the fusion of II with benzilic acid was in agreement with the proposed structure. To further explore this novel alkylation reaction, the decomposition of II was attempted in 5-trifluoromethyltetrazole,[6] a strong liquid nitrogen acid. On treatment with the anhydrous acid, denitroxylation occurred to give benzalaminoguanidine, isolated in 76.5% yield as its picrate salt. In aqueous 5-trifluoromethyltetrazole, a smooth exothermic reaction ensued on heating to give a mixture of 1- and 2-benzyl-5-trifluoromethyltetrazoles. 2,4-Dinitrophenol and II reacted in aqueous suspension at steam-bath temperature to give 2,4-dinitrophenyl benzyl ether in 26% yield. Fusion of the reactants in the absence of water led to decomposition of the nitroso compound. Phenol, on the other hand, reacted with II in the absence of water to give phenyl benzyl ether in low yield (<20%).

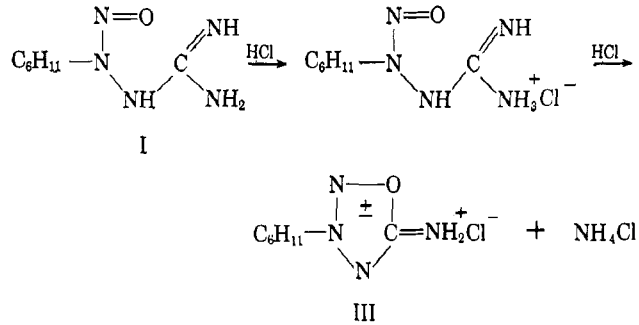
1-Cyclohexyl-2-guanyl-1-nitrosohydrazine (I) decomposed in concentrated hydrochloric acid at steam-bath temperatures to yield cyclohexyl chloride, ammonium chloride, and carbamyl azide in the same manner as was observed for the corresponding benzyl derivative. At ambient temperature in concentrated hydrochloric acid, cyclization occurred to give 3-cyclohexyl-5-imino-1,2,3,4-oxatriazoline hydrochloride (III). This product was also obtained in good yield by performing the reaction in dilute hydrochloric acid at 50° for 30 min. but decomposition to cyclohexyl chloride was an accompanying reaction; prolonged reaction times led to complete decomposition. The structure of this new *meso*-ionic compound was established by analysis, by its further decomposition to cyclohexyl chloride and carbamyl azide in hot aqueous acidic solution, and by analogy with the formation of the 3-alkyl-1,2,3,4-oxatriazolin-5-ones from 1-alkyl-2-carbamyl-1-nitrosohydrazines. On fusion with 3 equiv. of benzoic acid at 100° (exotherm to 144°), I yielded cyclohexene rather than cyclohexyl benzoate.

The reaction of 1-benzyl-2-(4,5-dihydro-2-imidazolyl)-1-nitrosohydrazine in hot concentrated hydrochloric



acid yielded benzyl chloride and N-(β-aminoethyl)-carbamyl azide hydrochloride, $N_3CONHCH_2CH_2NH_3^+Cl^-$. The isolation of the latter salt in this reaction, together with the fact that carbamyl azide was recovered in the decompositions of I and II in hot concentrated hydrochloric acid, showed that the alkylation reactions did not proceed through the formation and subsequent reaction of diazoalkanes. It is evident that the chain of three nitrogen atoms in the nitroso derivative remained intact during the alkylation reaction. Furthermore, since guanyl azide hydrochloride is stable in hot concentrated hydrochloric acid, the carbamyl azides were not formed by hydrolysis of an intermediate guanylazide.

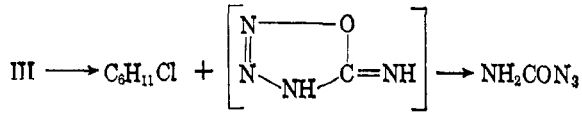
The behavior of I in hydrochloric acid can be described by the following possible reaction scheme.



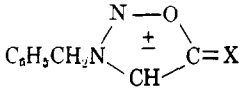
I

III

At elevated temperatures, the reaction proceeds further.



The acid decomposition of II probably follows a similar route although the existence of 3-benzyl-5-imino-1,2,3,4-oxatriazoline hydrochloride, analogous to III, was not demonstrated as an intermediate. Recent work on the synthesis of "sydnonimines" has shown that 3-benzyl-5-imino-1,2,3-oxadiazoline salts[7] (IVa) are also unstable in hot aqueous solution, whereas aryl and alkyl analogs are quite stable under similar conditions.



IVa, $X=NH_2^+Cl^-$
b, $X=NCOCH_3$

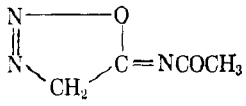
Catalytic hydrogenation of 3-benzyl-5-acetimino-1,2,3-oxadiazoline(IVb) in methanol solution, using palladium on carbon, yielded, in part, N-acetyldiazoacetamide,[8] $N_2CHCONHCOCH_3$. It was postulated

(6) W. P. Norris, *J. Org. Chem.*, **27**, 3248 (1962).

(7) H. W. Daeneker and J. Druey, *Helv. Chim. Acta*, **46**, 2426 (1963).

(8) H. W. Daeneker and J. Druey, *ibid.*, **46**, 805 (1963).

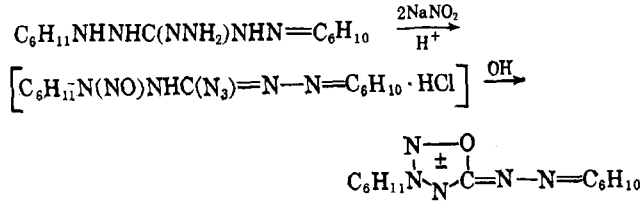
that this latter compound appeared by spontaneous ring opening of the intermediate 5-acetimino-1,2,3-oxadiazoline resulting from the debenzylation reaction.



The formation of carbamyl azide in the present instance from the spontaneous ring opening of the proposed 5-imino-1,2,3,4-oxatriazoline is quite analogous.

The failure of 1-benzyl-2-guanyl-2-methyl-1-nitrosohydrazine, $C_6H_5CH_2N(NO)N(CH_3)C(NH)NH_2$, to undergo a rapid decomposition to benzyl chloride in aqueous hydrochloric acid must be related to an inability to form a *meso*-ionic ring system; or conversely, those situations where reaction occurs appear to be those in which a *meso*-ionic intermediate is possible and in which the small additional resonance stabilization in this intermediate provides the driving force for the elimination of NH_4^+.

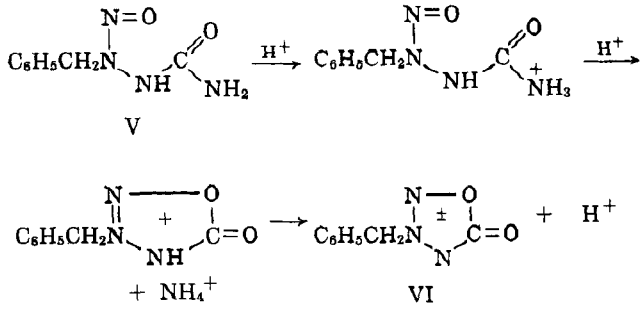
An interesting related cyclization reaction occurred, presumably *via* an azide ion elimination, when the dinitrosation of cyclohexylidene 1,2-diamino-3-cyclohexylaminoguanidinium chloride was attempted. On making the reaction solution basic to pH 8, cyclohexylidene 3-cyclohexyl-1,2,3,4-oxatriazolon-5-hydrazone was obtained. It is possible that cyclization occurred prior to making the reaction solution basic.



The bisnitroso derivative of 1,2-bis(benzylamino)-guanidinium chloride, $(C_6H_5NHNH)_2C{=}NH\cdot HCl$, could not be obtained. Vigorous gas evolution and separation of benzyl chloride occurred during the nitrosation (approximately 50% recovered in one experiment); uncharacterized azido-containing materials were also produced.

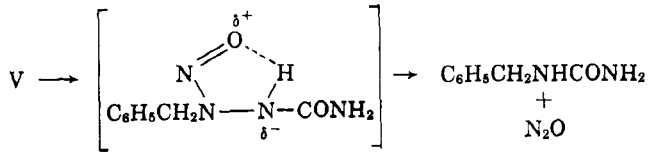
The solubility and stability of 1-benzyl-2-carbamyl-1-nitrosohydrazine, $C_6H_5CH_2N(NO)NHCONH_2$, (V), in strongly basic solutions at ambient temperature, as reported by Kessler and Rupe,[4] has been confirmed. The reaction of this hydrazine derivative in warm aqueous hydrochloric acid (both dilute and concentrated) and with benzoic acid at 100° yielded 3-benzyl-1,2,3,4-oxatriazolin-5-one[9] (VI).

This cyclization probably proceeds in a manner similar to that proposed for the cyclization of I. On the other hand, when an aqueous solution of V was refluxed for 1 hr., nitrous oxide was evolved and 1-benzylurea was formed in 64.5% yield. On refluxing in aqueous suspension, 1-benzyl-1-nitroso-2-(N-phenylcarbamyl)hydrazine, $C_6H_5CH_2N(NO)NHCONHC_6H_5$ (VII), which was prepared by nitrosation of 1-benzyl-2-(N-phenylcarbamyl)hydrazine,[10] decomposed to



1-benzyl-2-phenylurea. This result showed that the reaction involved a 1,2-shift of the benzyl group. 1-Benzyl-2-carbamyl-2-methyl-1-nitrosohydrazine, $C_6H_5CH_2N(NO)N(CH_3)CONH_2$, was reasonably stable under these conditions; slight evolution of NO occurred but the major part of the starting material could be recovered. The dry, thermal decomposition of VII at 140° for 1.5 hr. did not furnish 1-benzyl-3-phenylurea; since oxides of nitrogen were evolved copiously, the most likely product would be benzal 4-phenylsemicarbazone, which arises from a denitroxylation reaction.

The mechanism for the decomposition of the 1-benzyl-2-carbamyl-1-nitrosohydrazines to benzylureas and nitrous oxide is not readily apparent. One possible route, suggested by the stability of 1-benzyl-2-carbamyl-2-methyl-1-nitrosohydrazine in hot water, involves forming a five-membered hydrogen-bonded ring system which increases the electron density on the nitrogen adjacent to the carbamyl group. Simultaneous migration of the benzyl group and loss of nitrous oxide could then occur. The decomposition does not proceed *via* cyclization to the oxatriazolin-5-one (VI)



and its subsequent decomposition, since VI was stable in boiling water and could be recovered quantitatively. Furthermore, no 1-benzylurea was formed when VI was refluxed in aqueous ammonia; rather 1-benzyl-1-nitrosohydrazine[11] was obtained, which offered additional proof of the correctness of the structure assignment of this ring system. The analogous 5-imino-1,2,3-oxadiazolines ("sydnonimines") were also unstable in aqueous base and reverted to the N-substituted nitrosoacetonitriles.[7] 1-Benzyl-2-(N,N-dimethylcarbamyl)-1-nitrosohydrazine, $C_6H_5CH_2N(NO)NHCON(CH_3)_2$, on refluxing in aqueous suspension yielded 1-benzyl-1-nitrosohydrazine as the only isolable product rather than 1-benzyl-3,3-dimethylurea. Cyclization to VI and further decomposition of this in the basic solution must have been the predominant reaction sequence.

2-Benzoyl-1-benzyl-2-methyl-1-nitrosohydrazine, $C_6H_5CH_2N(NO)N(CH_3)COC_6H_5$, denitroxylated spontaneously on an attempted recrystallization. 2-Benzoyl-1-benzyl-1-nitrosohydrazine, $C_6H_5CH_2N(NO)NHCOC_6H_5$, is relatively stable and denitroxylation was not observed in acid solution. Heating this nitroso

(9) The syntheses of 3-alkyl-1,2,3,4-oxatriazolin-5-ones from 1-alkyl-2-carbamylhydrazines has been reported [J. H. Boyer and F. C. Carter, *J. Am. Chem. Soc.*, **77**, 1280 (1955)]. The intermediate nitroso compounds were not isolated, however.

(10) S. R. Bailey and A. T. McPherson, *ibid.*, **39**, 1322 (1917).

(11) T. Curtius, *Ber.*, **33**, 2561 (1900); A. Wohl and C. Oesterlin, *ibid.*, **33**, 2736 (1900).

derivative in concentrated hydrochloric acid for 10 min. yielded 22.4% of 1-benzyl-2-benzoylhydrazine hydrochloride and an unidentified azide-containing oil. No benzyl chloride could be identified.

Another type of cyclization of nitrosohydrazine derivatives is seen in the previously reported synthesis of 2-phenyl-5-cyanotetrazole[12] and 2-(2,4-dibromophenyl)-5-phenyltetrazole[13] by the nitrosations of "dicyanophenylhydrazine", $C_6H_5NHNHC(NH)CN$, and ω-aminobenzaldehyde 2,4-dibromophenylhydrazone, $C_6H_5C(NH_2)=NNHC_6H_3Br_2$, respectively. Since the formation of tetrazoles has not been observed in the present work, the possibility exists that the nitrosations of these latter hydrazine derivatives do not occur on the hydrazine moiety.

Experimental

Benzal 1-(N-methylguanyl)hydrazinium chloride was obtained by the following sequence of reactions: hydrazinolysis of 1,2-dimethyl-2-thiopseudouronium iodide, conversion to the hydrazone with benzaldehyde, and conversion of the iodide to the chloride *via* the acetate. After two recrystallizations from 2-propanol–diethyl ether followed by drying at 80° (25 mm.) for 72 hr., the compound melted 135–136°, resolidified, and remelted 148–149°.

Anal. Calcd. for $C_9H_{13}ClN_4$: C, 50.82; H, 6.16; N, 26.34. Found: C, 51.03; H, 6.29; N, 25.89.

Benzal 1-(N-methylguanyl)-1-methylhydrazinium iodide after recrystallization from water melted at 218–220°.

Anal. Calcd. for $C_{10}H_{15}IN_4$: C, 37.75; H, 4.75; N, 17.61. Found: C, 37.87; H, 5.11; N, 17.65.

Benzal 2-Hydrazino-4,5-dihydroimidazole.—The hydroiodide of the title compound[1] was converted to the free base and recrystallized from 50% aqueous ethanol, m.p. 158.5–159.5°.

Anal. Calcd. for $C_{10}H_{12}N_4$: C, 63.80; H, 6.43; N, 29.77. Found: C, 63.94; H, 6.47; N, 29.95.

1,1-Dimethyl-2-guanylhydrazinium Sulfate.—A slurry consisting of 13.9 g. (0.05 mole) of 2-methyl-2-thiopseudouronium sulfate and 30 ml. of 1,1-dimethylhydrazine was refluxed for 12 hr. Methanethiol was evolved slowly; the character of the solid changed. The cold slurry was stirred with 25 ml. of diethyl ether and filtered; the solid was then washed twice with 25-ml. portions of ether and once with a 50-ml. portion of 1:1 ether–ethanol. The dried product weighed 14.9 g. (98.2%). One recrystallization from 65 ml. of 95% ethanol gave white, felted needles, m.p. 191–192°.

Anal. Calcd. for $C_6H_{22}N_8O_4S$: C, 23.84; H, 7.34; N, 37.07. Found: C, 23.55; H, 7.27; N, 37.89.

The picrate after recrystallization from 95% ethanol was obtained as orange needles, m.p. 212–213° dec.

Anal. Calcd. for $C_9H_{13}N_7O_7$: C, 32.63; H, 3.95; N, 29.60. Found: C, 32.49; H, 3.53; N, 29.78, 29.24.

Some of the picrate was converted to the hydrochloride by solution in 3 *N* hydrochloric acid, repeated extraction with diethyl ether to remove the picric acid, evaporation, and recrystallization from ethanol–ether; it had m.p. 154.5–155.5°

Anal. Calcd. for $C_3H_{11}ClN_4$: Cl, 25.58; N, 40.42. Found: Cl, 25.25; N, 39.98.

The hydrazinolysis was much less successful when 0.1 mole of the thiopseudouronium salt and 0.2 mole of 1,1-dimethylhydrazine were refluxed in 125 ml. of water for 7.5 hr. The product was gummy and could not be induced to crystallize; the picrate prepared from this gum melted at 170–172° and required repeated recrystallizations to bring its melting point up to 209–210° dec. Small amounts of both guanidine picrate and 3,4,5-triamino-1,2,4-triazole picrate were isolated and characterized; the latter compound most likely arises from hydrazine which is present as an impurity in the dimethylhydrazine.

Attempted Synthesis of 1,1-Dimethyl-2-guanylhydrazinium Nitrate.—Guanidinium nitrate (12.2 g., 0.1 mole), 1,1-dimethylhydrazine (12.0 g., 0.2 mole), and 50 ml. of water was refluxed for 24 hr. Some ammonia was evolved. When the solution was cooled at 0° for several days, 6.65 g. of guanidinium nitrate, m.p. 213–215°, crystallized and was removed by filtration. An additional 2.7 g., m.p. 212–215°, was recovered by evaporating the aqueous mother liquors to dryness, dissolving the residue in 50 ml. of 95% ethanol, and chilling. The combined recovery of the nitrate salt amounted to 76.5%. When the alcoholic mother liquors were treated with picric acid, substantial quantities of guanidinium picrate were also isolated. Nothing corresponding to 1,1-dimethyl-2-guanylhydrazinium picrate was recovered by fractional crystallization of the picrate.

The same negative results were obtained when 3 moles of 1,1-dimethylhydrazine/mole of guanidinium ion were employed in an aqueous system. Only guanidinium chloride was recovered when 20 g. of this salt was refluxed for 24 hr. with 60 ml. of 1,1-dimethyl hydrazine (neat).

1,1-Dimethyl-2-(N-nitroguanyl)hydrazine.—1,1-Dimethylhydrazine (1.3 g.) in 5 ml. of cold water was added all at once to a slurry of 3.0 g. of 1-methyl-1-nitroso-2-nitroguanidine in 20 ml. of ice-cold 50% aqueous ethanol. Since there was essentially no gas evolution during 2 hr. at 0°, the slurry was allowed to stand 16 hr. at ambient temperature. The nitroso compound dissolved slowly but completely during this period. Rechilling to 5° for several days yielded 0.6 g. of white crystalline product, m.p. 135–155°. Several recrystallizations from ethyl acetate gave felted needles, dec. pt. 185–190°. The analyses suggest that this fraction is impure 1,1-dimethyl-2-nitroguanidine, reported[14] to melt at 193.5–195°

Anal. Calcd. for $C_3H_8N_4O_2$: C, 27.27; H, 6.10; N, 42.41. Found: C, 26.98; H, 6.28; N, 42.50.

Evaporation of the original ethanolic mother liquors gave another crop of material, which melted 138–140° after wasteful recrystallization from water.

Anal. Calcd. for $C_3H_9N_5O_2$: C, 24.49; H, 6.16; N, 47.60. Found: C, 24.28; H, 6.21; N, 47.76.

1-(N-Dimethylaminoguanyl)-1-methylhydrazine.—2,3-Dimethylisothiosemicarbazide sulfate[15] (13.8 g.) and 40 ml. of 1,1-dimethylhydrazine were mixed and allowed to stand at ambient temperature for 10 days. The evolution of methanethiol was slow; the system was never completely homogeneous. After the mixture had been refluxed for 4 hr., 75 ml. of absolute ethanol was added and the now homogeneous solution was chilled at 5° for 3 days. A small quantity (0.5 g.) of crystalline material separated, was removed by filtration, and was washed with ethanol–ether. Recrystallization from 35 ml. of 70% aqueous ethanol gave rosettes of small white needles melting above 300°. This water-soluble material which contained sulfate proved to be 1-guanyl-1-methylhydrazinium sulfate; its picrate, by itself and in admixture with authentic 1-guanyl-1-methylhydrazinium picrate, melted at 229–230°.

Anal. Calcd. for $C_4H_{18}N_8O_4S$: N, 40.85; S, 11.69. Found: N, 40.66; S, 11.48.

The alcoholic mother liquors were diluted with 25 ml. more of ethanol and treated with 20 g. of picric acid. A solid crystalline picrate was obtained which was recrystallized twice from 95% ethanol, 7 g., m.p. 138–139°. The analyses are consistent with those required for the picrate of the title compound.

Anal. Calcd. for $C_{10}H_{16}N_8O_7$: C, 33.33; H, 4.48; N, 31.10. Found: C, 33.23; H, 4.59; N, 30.64.

When the combined mother liquors from the preparation and recrystallization of the above picrate were shaken with excess benzaldehyde, 9.4 g. of crude **benzal hydrazone** was precipitated. Two recrystallizations from 95% ethanol yielded coarse yellow prisms which decomposed 215.5–216.5°. The sample for analysis was dried at 70° (25 mm.) for 96 hr.

Anal. Calcd. for $C_{17}H_{20}N_8O_7$: C, 45.53; H, 4.50; N, 24.99. Found: C, 45.23; H, 4.46; N, 25.10, 25.06.

Benzal 1-Benzoyl-1-methylhydrazine.—Benzal 1-benzoyl-1-methylhydrazine, white needles, m.p. 208–209°, after recrystallization from 2-propanol–benzene (1:1), was made by refluxing an ethanolic solution of methylhydrazine (3 moles) and ethyl benzoate (1 mole) for 16 hr., stripping solvent and excess hydrazine under reduced pressure, redissolving in hot ethanol, reacting with 1 mole of benzaldehyde, re-evaporating the solvent, and triturating with ether.

Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 75.60; H, 5.92; N, 11.76. Found: C, 75.49; H, 5.50; N, 12.63, 12.01.

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TABLE I

HYDRAZINIUM SALTS

$RNHN(R')C(X)R''\cdot HY$

R	R′	X	R″	Y	M.p., °C.	Recrystn. solvent	Formula	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	N, % Calcd.	N, % Found	Cl, % Calcd.	Cl, % Found
$C_6H_5CH_2$	CH_3	NH	NH_2	Cl	141.5–142.5	Ethanol	$C_9H_{15}N_4Cl$	50.34	50.06	7.04	7.18	26.10	25.71	16.52	16.31
$C_6H_5CH_2$	H	NH	$NHCH_3$	Picrate	136.5–137.5	Ethanol	$C_{15}H_{17}N_7O_7$	44.22	44.45	4.21	4.31	24.07	24.32		
$C_6H_5CH_2$	CH_3	NH	$NHCH_3$	Cl	145–146	2-Propanol–ether	$C_{10}H_{17}N_4Cl$	52.51	52.54	7.49	7.46	24.50	24.33	15.50	15.54
$C_6H_5CH_2$	H	NH	$NHNHCH_2C_6H_5$	Cl	165–166	Acetonitrile	$C_{15}H_{20}ClN_5$	58.91	58.38	6.59	6.54	22.91	22.68	11.60	11.62
$C_6H_5CH_2$	H	NH	$NHNHCH_2C_6H_5$	Picrate	151.5–152.5	Ethanol	$C_{21}H_{22}N_8O_8$	50.60	50.90	4.45	4.56	22.49	22.59		
$C_6H_5CH_2$	H	NH	$NHN{=}CHC_6H_5$	Cl	192–194	Acetonitrile or ethanol	$C_{15}H_{18}ClN_5$	59.30	59.21	5.97	5.45	23.06	23.14	11.67	11.66
CH_2CH_2	H	NH	NH_2	Cl	208–209	Methanol	$C_4H_{16}Cl_2N_8$	19.44	19.40	6.53	6.70	45.35	44.99	28.69	28.83
$C_6H_5CH_2$	H	O	C_6H_5	Cl	208–209 dec.	2-Propanol	$C_{14}H_{15}ClN_2O$	63.99	64.56	5.75	5.68	10.66	10.78		
$C_6H_5CH_2$	CH_3	O	C_6H_5	Cl	198–200 dec.	2-Propanol (trace aq. HCl)	$C_{15}H_{17}ClN_2O$	65.09	64.86	6.19	6.40	10.13	10.52		
$C_6H_5CH_2$	H	O	$N(CH_3)_2$	Cl	181–183	Ethanol	$C_{10}H_{16}ClN_3O$	52.28	52.15	7.02	7.11	18.30	18.10		
C_6H_{11}	H	NNH_2	$NHN{=}C_6H_{10}$	Cl	178–179 dec.	Ethanol	$C_{13}H_{27}ClN_6$[a]	51.55	51.63	8.99	9.00	27.75	27.72		
C_6H_{11}	H	NNH_2	$NHN{=}C_6H_{10}$	Picrate	128–130	Ethanol	$C_{19}H_{29}N_9O_7$					25.45	25.65		

[a] A proton n.m.r. spectrum (trifluoroacetic acid soln.) at 60 Mc. was consistent with the structure of $C_6H_{11}NHNHC(NNH_2)NHN{=}C_6H_{10}\cdot HCl$. Four broad peaks with approximate τ-values 6.9, 7.6, 8.5, and 8.9 were observed. Integral values based on a total of 21 nonexchanging protons were 0.9 (CH) and 20.1 (CH_2).

TABLE II

NITROSO DERIVATIVES

$RN(NO)N(R')C(X)R''$

R	R′	X	R″	Derivative	M.p., °C., dec.	Recrystn. solvent	Formula	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	N, % Calcd.	N, % Found	Halogen, % Calcd.	Halogen, % Found
$C_6H_5CH_2$	H	NH	NH_2	...	125–126	H_2O	$C_8H_{11}N_5O$	49.73	49.83	5.74	5.55	36.26	35.56		
$C_6H_5CH_2$	H	NH	NH_2	Picrate	231–232	Ethanol	$C_{14}H_{14}N_8O_8$	39.81	39.99	3.34	3.48	26.54	26.65		
$C_6H_5CH_2$	CH_3	NH	NH_2	...	104–105	Benzene	$C_9H_{13}N_5O$	52.16	51.94	6.32	6.29	33.80	33.60		
$C_6H_5CH_2$	CH_3	NH	NH_2	Picrate[a]	169–170	Ethanol	$C_{15}H_{16}N_8O_8$	41.28	41.48	3.70	4.11	25.69	25.92		
$C_6H_5CH_2$	H	NH	$NHCH_3$	...	109.5–110.5	2-Propanol	$C_9H_{13}N_5O$	52.16	52.56	6.32	6.33	33.80	33.73		
$C_6H_5CH_2$	H	NH	$NHCH_3$	Picrate	127	Ethanol	$C_{15}H_{16}N_8O_8$	41.28	41.95	3.70	3.81	25.69	25.82		
$C_6H_5CH_2$	CH_3	NH	$NHCH_3$	Picrate[b]	121–122	THF–ether	$C_{16}H_{18}N_8O_8$	42.67	42.73	4.03	4.01	24.89	25.11		
$C_6H_5CH_2$	H	NH	$NHN{=}C_7H_6$	...	140–142	2-Propanol	$C_{15}H_{16}N_6O$	...	...	..	..	28.36	28.42		
4-$ClC_6H_4CH_2$	H	NH	NH_2	...	147.5–148	H_2O	$C_8H_{10}ClN_5O$	42.20	42.28	4.43	4.55	30.77	30.70	15.58	15.45
4-$BrC_6H_4CH_2$	H	NH	NH_2	...	157–158	H_2O	$C_8H_{10}BrN_5O$	35.31	35.28	3.70	3.87	25.74	25.71	29.37	29.43
$C_6H_5CH_2$	H		$-NCH_2CH_2NH-$	...	121.5–122.5	2-Propanol	$C_{10}H_{13}N_5O$	54.78	55.50	5.97	6.31	31.95	30.81		
$C_6H_5CH_2$	H		$-NCH_2CH_2NH-$	$1.5H_2O$	119–120	H_2O	$C_{10}H_{16}N_5O_{2.5}$	48.78	50.24	6.55	6.53	28.45	28.13		
4-$ClC_6H_4CH_2$	H		$-NCH_2CH_2NH-$	...	130.5–131.5	2-Propanol	$C_{10}H_{12}ClN_5O$	47.34	47.36	4.77	4.90	27.61	27.41	13.98	13.87
4-$ClC_6H_4CH_2$	H		$-NCH_2CH_2NH-$	H_2O	65–67	H_2O	$C_{10}H_{14}ClN_5O_2$	44.20	44.16	5.19	5.32	25.78	25.76	13.05	12.97
C_6H_{11}	H	NH	NH_2	...	156–158	60% ethanol	$C_7H_{15}N_5O$	45.39	45.71	8.16	7.97	37.82	38.71		
$-CH_2CH_2-$	H	NH	NH_2	...	188	H_2O	$C_4H_{12}N_{10}O_2$	20.69	20.76	5.21	5.29	60.33	60.09		
$C_6H_5CH_2$	CH_3	O	NH_2	...	101–102	Benzene	$C_9H_{12}N_4O_2$	51.91	52.14	5.81	5.98	26.91	26.82		
$C_6H_5CH_2$	H	O	NHC_6H_5	...	135–136	Benzene	$C_{14}H_{14}N_4O_2$	62.21	62.31	5.22	5.28	20.73	20.71		
$C_6H_5CH_2$	H	O	$N(CH_3)_2$	...	111–112	Benzene	$C_{10}H_{14}N_4O_2$	54.04	54.34	6.36	6.53	25.21	24.53		

[a] The hydrazinium iodide was also prepared, as an uncrystallizable oil, by methylation of 1-benzyl-2-guanyl-1-nitrosohydrazine with methyl iodide in methanol solution at ambient temperature. The structure of this methylation product was established by conversion to its picrate, m.p. and m.m.p. 169–170°. [b] The free base was obtained as an uncrystallizable oil.

Di(cyclohexylidene)triaminoguanidinium Chloride.—Triaminoguanidinium chloride (14.1 g., 0.1 mole) and 30 g. of cyclohexanone in 200 ml. of 50% aqueous ethanol were heated for 2 hr. in the steam bath. The orange-colored solution was cooled at 5° for 4 days; the product was removed by filtration, washed twice with cold water, and dried, 12.0 g., m.p. 190–191° dec. Recrystallization from 120 ml. of 50% ethanol gave 7.6 g. of pale orange plates.

Anal. Calcd. for $C_{13}H_{25}ClN_6$: N, 27.94. Found N, 27.44.

1-Alkyl-2-guanylhydrazinium Salts.—A considerable improvement can be made in the procedure reported[2] for the catalytic hydrogenation of alkylidene aminoguanidinium salts by conducting the hydrogenation in ethanol instead of glacial acetic acid solution and by using palladium black as catalyst. Glacial acetic acid occasionally acylated the product, particularly if the hydrogenations were run at elevated temperatures. The Adams platinum catalyst used previously is readily poisoned by sulfur-containing products which are often present in trace quantities since hydrazinolysis of 2-methyl-2-thiopseudouronium salts is the most convenient route to the alkyl-substituted aminoguanidinium salts. At elevated temperatures, platinum black also catalyzed the hydrogenolysis of aminoguanidinium salts to guanidine derivatives. Palladium black does not appear to be so readily poisoned by traces of sulfur compounds nor does it appear to catalyze the hydrogenolysis reaction. New 1-alkyl-2-guanyl-, 2-carbamyl-, and 2-benzoylhydrazinium salts are reported in Table I.

1-Alkyl-2-guanyl-1-nitrosohydrazines.—The nitrosation of 1-benzyl-2-guanylhydrazinium chloride is given as an example. The nitroso derivatives prepared are reported in Table II.

1-Benzyl-2-guanylhydrazinium chloride (20.1 g., 0.10 mole) was dissolved in 50 ml. of distilled water. Concentrated hydrochloric acid (9 ml., 0.106 mole) was added and the solution was cooled to 0° in a salt–ice bath. A solution of 6.9 g. (0.1 mole) of sodium nitrite in 25 ml. of distilled water was then added slowly with stirring until a permanent starch–iodide end point was obtained. At this point, the solution was clear and yellow in color. The solution was then adjusted to pH 8 with 50% sodium hydroxide solution; a yellow oil separated during the addition. On continued stirring and cooling, or on seeding, the oil crystallized to a white or pale yellow solid. The pH of the solution was again adjusted to 8 if necessary. The product (14.9 g.) was separated by filtration and recrystallized from a minimum of hot water, yielding 9.92 g. (51.4%) of 1-benzyl-2-guanyl-1-nitrosohydrazine (II) as pale yellow needles, m.p. 125–126°.

An attempted recrystallization of the nitroso compound from 2-propanol resulted in the slow formation of benzalaminoguanidinium nitrate, m.p. 176–176.5° dec., by air oxidation.

Anal. Calcd. for $C_8H_{11}N_5O_3$: C, 42.66; H, 4.92; N, 31.10. Found: C, 43.03; H, 4.96; N, 33.57.

An X-ray powder pattern was identical with that of an authentic sample.

Attempted Nitrosation of 1-(N-Nitroguanyl)-2-phenylhydrazine.—A solution of sodium nitrite (0.025 mole) in 5 ml. of distilled water was added dropwise with stirring to a slurry of 4.88 g. (0.025 mole) of 1-(N-nitroguanyl)-2-phenylhydrazine in 25 ml. of distilled water and 5 ml. of concentrated hydrochloric acid. The slurry was cooled to 5° during the addition. Nitrite uptake was slow; a negative nitrite test was obtained in 5 hr.

After removal of the product by filtration, it was recrystallized from 2-propanol and then from benzene to give 2.94 g. (60.7%) of **1-(N-nitroguanyl)-2-phenyldiimide** as golden plates, m.p. 153–155° dec.

Anal. Calcd. for $C_7H_7N_5O_2$: C, 43.52; H, 3.65; N, 36.26. Found: C, 43.51; H, 3.85; N, 36.02.

Decomposition of 1-Benzyl-2-guanyl-1-nitrosohydrazine (II) in Acetonitrile–Hydrogen Chloride Solution.—The nitroso compound II (1.93 g., 0.01 mole) was dissolved in 25 ml. of dry acetonitrile and approximately 7 g. of gaseous hydrogen chloride was bubbled into the solution with ice-bath cooling. The resulting clear solution was slowly heated to 70°; hydrogen chloride was evolved copiously and a solid precipitated. After a few minutes, the solution was cooled to room temperature. The solid was removed by filtration: yield 1.70 g. (85.7%) of benzal aminoguanidinium chloride, m.p. and m.m.p. 139–140°.

Decomposition of II in Concentrated Hydrochloric Acid.—The nitroso compound II (1.93 g., 0.01 mole) was dissolved in 5 ml. of concentrated hydrochloric acid (forming a bright yellow solution) and heated to 100° on a steam bath in a 25-ml. round-bottom flask equipped with a condenser. An exothermic reaction ensued and subsided within 5 min. and the solution turned colorless. After cooling and dilution with 100 ml. of water, the insoluble oil was extracted from the solution with 25 ml. of pentane. Evaporation of the pentane on a steam bath left 1.05 g. (83%) of benzyl chloride contaminated with some carbamyl azide. The aqueous hydrochloric acid solution was evaporated to dryness at reduced pressure on the steam bath leaving 0.46 g. (86%) of ammonium chloride. In a separate experiment, the hydrochloric acid solution, after heating, was evaporated to dryness under reduced pressure at room temperature. The solid residue was extracted with diethyl ether. Evaporation of the ether left 0.16 g. (37%) of carbamyl azide, m.p. and m.m.p. 95.5–98.5°. An X-ray powder pattern was identical with that of an authentic sample prepared from semicarbazide hydrochloride. The fact that carbamyl azide sublimes readily at reduced pressures may account for the low yield.

Guanyl azide hydrochloride is stable to concentrated hydrochloric acid at comparable temperatures. After heating 2.43 g. (0.02 mole) of guanyl azide hydrochloride in 5 ml. of concentrated hydrochloric acid for 5 min., the solution was evaporated to dryness at room temperature. The residue was soluble in absolute ethanol. Evaporation of the ethanol left 2.37 g. (97.6%) of recovered guanylazide hydrochloride, m.p. and m.m.p. 154–155° dec.

Decomposition of II in Glacial Acetic Acid.—The nitroso compound II (5.79 g., 0.03 mole) was dissolved in 10 ml. of glacial acetic acid and the solution was heated to 100° on a steam bath. A vigorous exothermic reaction with moderate gas evolution ensued and subsided within a few minutes. The solution was cooled to room temperature and diluted with 50 ml. of ice water. After neutralization with 25% sodium hydroxide solution (phenolphthalein end point), the solution was extracted with two 25-ml. portions of hexane. After drying the solution with magnesium sulfate, the hexane was removed by distillation to yield 4.62 g. of oily residue. Infrared analysis showed the product to be predominantly benzyl acetate with a minor amount of an azide-containing impurity. Distillation of the sample at reduced pressure left a minor residue (0.1 g.) of benzalaminoguanidine, identified as its picrate, m.p. 248–250° dec. Analysis of the distillate by n.m.r. spectroscopy indicated it to be approximately 95% benzyl acetate and 5% benzyl azide.

Fusion of II with Benzoic Acid.—When 3.9 g. (0.02 mole) of II and 7.32 g. (0.06 mole) of benzoic acid were mixed in a large test tube and placed in an oil bath at 100°, an exothermic reaction occurred within 5 min. The tube was removed from the bath and the temperature rose to 127°, then dropped slowly. When it was down to 100°, the mix was replaced in the oil bath and heated for 20 min. more. Trace amounts of oxides of nitrogen were evolved. The cooled reaction mixture was stirred with 50 ml. of diethyl ether and filtered; the solid cake was washed once with 50 ml. of ether and twice with 25-ml. portions. The 2.2 g. of ether-insoluble material, m.p. 170–190°, was soluble in water and evolved ammonia when it was made alkaline with cold, aqueous sodium hydroxide. Two recrystallizations from absolute ethanol gave white plates which melted at 187–189°. This fraction was mainly ammonium acid benzoate admixed with some ammonium benzoate; the X-ray powder pattern shows new lines which are distinctly different from those for either ammonium benzoate or benzoic acid.

Anal. Calcd.: N, 5.36. Found: N, 5.94.

The combined ethereal extracts were diluted with 150 ml. of pentane and allowed to stand overnight at 5°. The ether–pentane layer was decanted from a brown gum. (The latter gave 0.69 g. of benzalaminoguanidinium picrate, m.p. 241–243°, when dissolved in 95% ethanol and treated with picric acid; the X-ray powder pattern was identical with that for an authentic sample.) The solution was washed several times with saturated aqueous sodium bicarbonate to remove excess benzoic acid, then with cold water, and finally dried over sodium sulfate. Evaporation of the filtered solution left 2.4 g. of a neutral oil whose infrared spectrum showed both ester carbonyl at 5.8 μ and azide function at 4.75 μ. The oil was dissolved in 15 ml. of cyclohexane and treated with small portions of triphenylphosphine until nitrogen was no longer evolved. Addition of 50 ml. of pentane and cooling at 5° precipitated 0.75 g. of a viscous oil (see below).

The cyclohexane–pentane solution was evaporated; the residual oil was slurried in absolute ethanol, chilled in a Dry Ice bath, and filtered from excess triphenylphosphine (m.p. 77–79°). The oil which remained after evaporation of the ethanol was next

slurried with a small volume of pentane; the latter solution was decanted from some insoluble material and evaporated to leave 1.4 g. (34%) of a fragrant liquid whose infrared spectrum was identical with that for authentic benzyl benzoate. A small additional amount of ester was recovered by reworking the alcohol- and pentane-insoluble fractions. The total yield probably approached 50% of theory. In another experiment on a smaller scale, the yield of ester was 37%. In a third experiment in which the ratio of benzoic acid to substituted hydrazine was 2:1, the yield of recovered ester was 30.3%. In a fourth experiment, the reactants were refluxed in dry tetrahydrofuran for 6.5 hr.; oxides of nitrogen were evolved and cubic ammonium nitrate (based on X-ray powder pattern) was deposited in the condenser; the other products appeared to be the same as in the first three runs.

All efforts to get the oily triphenylphosphinimide to crystallize were unsuccessful, and hydrolysis of this material in ethanol yielded impure triphenylphosphine oxide, (m.p. 147–149°), benzaldehyde (isolated and identified as its 2,4-dinitrophenylhydrazone), and benzoic acid.

When benzilic acid was used instead of benzoic acid, the yield of benzyl benzilate, once recrystallized from methanol and melting 72–74°, was 27%. In this case the ester was recovered directly from the crude product which remained after the base-extracted ether–pentane solution had been evaporated to dryness. The methanolic recrystallization liquors were evaporated to a viscous oil which was dissolved in dry cyclohexane, filtered from a small amount of insoluble material, and treated with triphenylphosphine until gas evolution ceased. An oily phosphinimide precipitated from the cyclohexane; the solvent was decanted and the oil was triturated with more dry cyclohexane, which was also decanted and discarded. The oil was vacuum dried (1.1 g. was recovered in an experiment involving 0.02 mole of nitroso compound); it could not be induced to crystallize. A proton n.m.r. spectrum (deuteriochloroform solution) was consistent with the structure $(C_6H_5)_3P{=}NCH(C_6H_5)OOCC(OH)(C_6H_5)_2$. A complex phenyl multiplet was centered at approximately τ 2.8. A single benzyl CH line was observed at τ 4.85 superimposed on a broad OH line. Integral values corresponded to 30 phenyl protons and 2 others. Benzilic acid was isolated and identified as one of the products from an acid hydrolysis.

Fusion of I with 3 molar equiv. of benzoic acid gave mainly volatile material (which, based on odor, is probably cyclohexene) and only traces of ester-containing liquid products.

Benzylation of 5-Trifluoromethyltetrazole.—The nitroso compound II (1.95 g., 0.01 mole) was dissolved in a solution of 2.76 g. (0.02 mole) of 5-trifluoromethyltetrazole in 3 ml. of water, the yellow solution was heated for 12 min. on a steam bath, and the solution turned colorless. After cooling and diluting of the reaction mixture with 10 ml. of water, it was neutralized to a phenolphthalein end point with 50% sodium hydroxide solution and extracted with two 15-ml. portions of hexane. The hexane solution was dried with magnesium sulfate and then evaporated to give 1.13 g. (49.5%) of liquid residue. Comparison of an infrared spectrum of the residue with that of an authentic mixture of 1- and 2-benzyl-5-trifluoromethyltetrazoles (see next paragraph) showed them to be identical except for an azide impurity absorption at 4.80 μ in the former and absorptions attributable to benzyl chloride in the authentic sample.

1- and 2-Benzyl-5-trifluoromethyltetrazoles.—A solution of 4.0 g. (0.025 mole) of the sodium salt of 5-trifluoromethyltetrazole and 3.15 g. (0.025 mole) of benzyl chloride in 50 ml. of dry acetonitrile was refluxed for 6 hr., filtered to remove sodium chloride, then concentrated to dryness at reduced pressure on a steam bath. The residue was extracted with 25 ml. of ether. The ether solution was evaporated, leaving 4.59 g. of an oily mixture of 1- and 2-benzyl-5-trifluoromethyltetrazoles with some benzyl chloride. N.m.r. spectroscopy of the mixture indicated it to be about 80% 2-benzyl-5-trifluoromethyltetrazole, 10% 1-benzyl-5-trifluoromethyltetrazole, and 10% benzyl chloride.

Distillation of the mixture gave 2.82 g. (49.6%) of 2-benzyl-5-trifluoromethyltetrazole, b.p. 107° (5.5 mm.).

Anal. Calcd. for $C_9H_7F_3N_4$: C, 47.37; H, 3.09; F, 24.98; N, 24.56. Found: C, 47.69; H, 3.09; F, 24.85; N, 24.47.

2,4-Dinitrophenyl Benzyl Ether.—The nitroso compound II (1.6 g.), 4.0 g. of 2,4-dinitrophenol, and 5 ml. of water were heated on the steam bath for 1 hr. An exothermic reaction was noted soon after the mixture reached bath temperature; complete solution was obtained. Toward the end of the heating, solid began to separate. The cooled mixture was diluted with water and extracted with ether. The ether solution was washed in turn with cold water, cold saturated aqueous sodium carbonate, and then with cold water. Evaporation of the dried ether solution left 0.6 g. (26%) of brown solid. After one recrystallization from ethanol the orange-yellow ether melted 149–150°, lit.[16] m.p. 149.5°.

Anal. Calcd. for $C_{13}H_{10}N_2O_5$: C, 56.93; H, 3.68; N, 10.22. Found: C, 57.28; H, 3.97; N, 10.15.

When the two reactants were fused on the steam bath without solvent, oxides of nitrogen were evolved. On the other hand, when phenol and II were heated to 115°, a mild exothermic reaction occurred (the temperature rose to 125°), but no oxides of nitrogen were noted. Benzyl phenyl ether contaminated with carbamyl azide was recovered in less than 20% yield when the mixture was heated for 1 hr. at 120–130° and worked up in the same manner as described above.

Decomposition of 1-Cyclohexyl-2-guanyl-1-nitrosohydrazine (I) in Concentrated Hydrochloric Acid.—The nitroso compound I (0.93 g., 0.005 mole) was dissolved in 5 ml. of concentrated hydrochloric acid. The solution was heated on a steam bath for 5 min., then evaporated to dryness at room temperature and reduced pressure. The distillate was collected in a Dry Ice cooled trap. The residue from the evaporation was extracted with two 25-ml. portions of ether. Evaporation of the ether left 0.16 g. (37.2%) of carbamyl azide, m.p. and m.m.p. 95.5–98.5°. When the ether-insoluble residue was extracted with acetone, there remained 0.25 g. (93.6%) of solid residue, identified by X-ray powder pattern as ammonium chloride. The distillate from the original evaporation was warmed to room temperature and extracted with three 25-ml. portions of methylene chloride. After drying with magnesium sulfate, the methylene chloride solution was evaporated, leaving 0.55 g. (93.2%) of cyclohexyl chloride, which was identified by its infrared spectrum; carbamyl azide was also identified as an impurity.

Decomposition of 1-Benzyl-2-(4,5-dihydro-2-imidazolyl)-1-nitrosohydrazine in Concentrated Hydrochloric Acid.—1-Benzyl-2-(4,5-dihydro-2-imidazolyl)-1-nitrosohydrazine (1.1 g., 0.005 mole) was dissolved in 3 ml. of concentrated hydrochloric acid and allowed to stand at room temperature until the solution turned colorless. The water-insoluble phase was extracted with pentane, yielding, after evaporation, 0.35 g. (55.7%) of benzyl chloride, identified by infrared spectroscopy. The aqueous hydrochloric acid solution was evaporated to dryness at reduced pressure and room temperature. The residue, 0.83 g. (100%) of **N-(β-aminoethyl)carbamyl azide hydrochloride**, melted at 164.5–165.5° dec. after recrystallization from 2-propanol. An infrared spectrum showed carbonyl absorption at 5.9, azide absorption at 4.65, and NH absorption at 3.0 and 3.1 μ.

Anal. Calcd. for $C_3H_8ClN_5O$: C, 21.76; H, 4.87; Cl, 21.41; N, 42.30. Found: C, 21.97; H, 4.97; Cl, 21.58; N, 42.27.

3-Cyclohexyl-5-imino-1,2,3,4-oxatriazoline Hydrochloride (III).—The nitroso compound I (1.86 g., 0.01 mole) was dissolved with cooling in 5 ml. of concentrated hydrochloric acid and the solution was allowed to stand at room temperature. Precipitation of solid material was noted in 2 hr. and the solution became almost solid in 4 hr. The precipitated solid was recovered by filtration, washed with 5 ml. of acetonitrile, and dried to yield 1.31 g. (65.3%) of 3-cyclohexyl-5-imino-1,2,3,4-oxatriazoline hydrochloride (III), m.p. 130–134° dec. Recrystallization from 200 ml. of acetonitrile raised the melting point to 138–139° dec. An infrared spectrum shows strong C=N absorption at 5.9 μ, and an absorption at 4.6 μ attributed to ammonium ion,[17] since the compound gives no qualitative test for the azido group with potassium iodide in trifluoroacetic acid.[18]

Anal. Calcd. for $C_7H_{13}ClN_4O$: C, 41.08; H, 6.40; Cl, 17.32; N, 27.38. Found: C, 41.03; H, 6.27; Cl, 17.29; N, 27.62.

In another experiment, 0.93 g. (0.005 mole) of I was dissolved in 10 ml. of 1 *N* hydrochloric acid and heated to 50° for 30 min. The solution turned colorless and an odor of cyclohexyl chloride was noted. The solution was evaporated to dryness at reduced pressure and 40–50° within 15 min. The residue was dissolved in 200 ml. of hot acetonitrile and the solution was filtered to remove ammonium chloride. On cooling overnight 0.53 g. (51.8%) of III precipitated, m.p. 134° dec. The filtrate was concentrated to 10 ml. and recooled, yielding an additional

(16) L. C. Raiford and J. C. Colbert, *J. Am. Chem. Soc.*, **48**, 2652 (1926).
(17) W. P. Norris and R. A. Henry, *J. Org. Chem.*, **29**, 650 (1964).
(18) W. R. Carpenter, unpublished results.

0.18 g., m.p. 130–131° dec. The total yield of crude product amounted to 76.8%.

Attempted Decomposition of 1-Benzyl-2-guanyl-2-methyl-1-nitrosohydrazine in Concentrated Hydrochloric Acid.—The title compound (1 g., 0.0048 mole) was dissolved in 5 ml. of concentrated hydrochloric acid; the solution was heated for 10 min. on a steam bath, then evaporated to dryness at reduced pressure. The residue was dissolved in 15 ml. of hot ethanol and 1 g. of picric acid was added. On cooling, 1.04 g. (49.3%) of 1-benzyl-2-guanyl-2-methyl-1-nitrosohydrazinium picrate, m.p. and m.m.p. 169–170°, was obtained. The moderate recovery of picrate is perhaps due to its solubility in ethanol, but the excellent melting point of the unrecrystallized derivative infers that it was uncontaminated with derivatives of potential decomposition products such as ammonium picrate, benzal 1-methyl-1-aminoguanidinium picrate, or 1-benzyl-2-guanyl-2-methylhydrazinium picrate.

When 1-benzyl-2-(N-methylguanyl)-2-methyl-1-nitrosohydrazinium picrate was heated with excess concentrated hydrochloric acid on the steam bath for 10 min., no nitrogen dioxide was evident. Complete stripping of the water and acid under reduced pressure at ambient temperature left a gummy picrate which could not be crystallized but whose infrared spectrum was essentially the same as that for the starting material; no absorption due to the azido group was present. The sample, however, rapidly liberated iodine in the sodium iodide–trifluoroacetic acid test (a behavior typical of a nitrosoamino group).

Cyclohexylidene 3-Cyclohexyl-1,2,3,4-oxatriazolon-5-hydrazone.—Three grams (0.01 mole) of monocyclohexylidene 1,2-diamino-3-(cyclohexylamino)guanidinium chloride was slurried in 35 ml. of ethanol, 25 ml. of water, and 2 ml. of concentrated hydrochloric acid and cooled to 3°. Sodium nitrite (1.4 g., 0.02 mole) in 5 ml. of water was added dropwise with stirring while the temperature was held below 5°. The nitrite was consumed rapidly during the early stages of the addition, but more slowly near the end. When the solution no longer gave a positive nitrite test, it was filtered to remove 1.0 g. (after drying) of white solid which melted 185–186° dec. and which was not further investigated. The yellow filtrate was diluted with 25 ml. of water and treated with 2 g. of sodium bicarbonate. The bright yellow oil which separated crystallized when allowed to stand overnight at 5°. The solid was filtered, washed with cold water, and dried, 1.05 g., m.p. 68–70°. One recrystallization from 200 ml. of pentane gave yellow-orange plates, m.p. 78–79°. The compound was readily soluble in benzene, acetone, and ethanol; it did not give a positive test for nitrosoamine. The infrared spectrum revealed no absorption due to the azido group; the ultraviolet spectrum showed absorptions at 240 mμ (ε 23,300) and 357 mμ (ε 7100). An acetone solution treated with copper acetate gave an intense olive-green color.

Anal. Calcd. for $C_{13}H_{21}N_5O$: C, 59.29; H, 8.04; N, 26.60. Found: C, 59.33; H, 8.20; N, 26.76.

Evidence consistent with the structure assigned to this compound was obtained as follows. Approximately 200 mg. of the compound was added to 2 ml. of concentrated hydrochloric acid at ambient temperature. The almost colorless solution developed a turbidity within 10 min.; after standing overnight, droplets of oil had separated. The latter were extracted into a small volume of *n*-pentane and the resulting pentane solution was chromatographed (vapor phase). Based on a comparison of retention times, it was concluded that the main product was cyclohexyl chloride contaminated with small amounts of cyclohexene and cyclohexanone. The presence of the latter was confirmed in an infrared spectrum.

The acidic mother liquor remaining after the pentane extraction was adjusted to pH 8.5, and the solution was extracted with diethyl ether. Evaporation of the latter gave a gum whose infrared spectrum agreed with that expected for the structure of $C_6H_{10}{=}NNHCON_3$.

3-Benzyl-1,2,3,4-oxatriazolin-5-one (VI).—Benzoic acid (2.44 g.; 0.02 mole) and V (1.94 g., 0.01 mole) were intimately mixed in a large test tube, then heated for 1 hr. in an oil bath at 100°. After about 40 min. of the heating period, an exothermic reaction began and the temperature of the semisolid mix rose to 107°; within 5 min. the temperature dropped back to 100°. Work-up in the same manner as for the reaction of II with benzoic acid yielded 1.44 g. of ether-insoluble material (ammonium acid benzoate plus ammonium benzoate), 1.05 g. of benzoic acid from the sodium bicarbonate wash of the ether-soluble portion, and 1.56 g. (88%) of solid, m.p. 40–45°. The compound was purified by solution in benzene and fractional precipitation with hexane giving felted, flat needles, m.p. 46.5–47.5°.

Anal. Calcd. for $C_8H_7N_3O_2$: C, 54.23; H, 3.99; N, 23.72; mol. wt., 177.2. Found: C, 54.64; H, 3.99; N, 23.32; mol. wt., 186.

The infrared spectrum showed an intense carbonyl absorption at 5.63 μ; there was no absorption in the region 4.5–4.7 μ which would correspond to N_3 or NCO.

Denitroxylation of 1-Benzyl-2-carbamyl-2-methyl-1-nitrosohydrazine in Acetic Acid.—A solution of the title compound (0.31 g., 0.004 mole) in 5 ml. of glacial acetic acid was heated on a steam bath for 5 min., then poured into 25 ml. of 2,4-dinitrophenylhydrazine reagent. The immediate precipitation of benzaldehyde 2,4-dinitrophenylhydrazone, 0.4 g. (100%), m.p. 237°, indicated complete denitroxylation.

Solutions of the title compound in concentrated hydrochloric acid at ambient temperature, or in 6 *N* hydrochloric acid at steam-bath temperature, rapidly evolved oxides of nitrogen.

Decomposition of 1-Benzyl-2-carbamyl-1-nitrosohydrazine (V) in Water.—The title compound V (2 g.) was refluxed for 1 hr. in 20 ml. of water; some amine (ammonia or hydrazine) was evolved in the early stages of the heating. The product, which separated as an oil but which crystallized when the mixture was cooled to 5°, was filtered and washed with cold water, then with three 20-ml. portions of diethyl ether–pentane (1:1). The yield of dried material, whose melting point by itself or admixed with authentic 1-benzylurea was 149–150°, was 1.0 g. (64.5%). The infrared spectrum was also identical with that for authentic 1-benzylurea.

When either VI or 1-benzyl-2-guanyl-2-methyl-1-nitrosohydrazine was similarly treated, only unchanged starting compound was recovered and no amine was evolved. Although trace amounts of nitrogen dioxide were detected by starch–iodide paper when 0.5 g. of 1-benzyl-2-carbamyl-2-methyl-1-nitrosohydrazine was refluxed for 1 hr. in 10 ml. of water, the product which was recovered melted at 102–103° both by itself and when admixed with starting material.

Decomposition of 1-Benzyl-1-nitroso-2-(N-phenylcarbamyl)-hydrazine (VII) in Water.—The title compound VII (0.58 g.) was refluxed for 2 hr. in 50 ml. of water. The solid in suspension softened and partially melted during the early stages of the reaction, then resolidified. After cooling, the product was removed by filtration, washed with cold water, and dried: yield, 0.38 g. (75.7%), m.p. 155–165°. Its infrared spectrum was essentially the same as that for an authentic sample of 1-benzyl-3-phenylurea. One recrystallization from benzene raised the melting point to 171–172°; admixture with an authentic sample of 1-benzyl-3-phenylurea did not depress its melting point.

Basic Decomposition of 3-Benzyl-1,2,3,4-oxatriazolin-5-one (VI).—The benzyloxatriazolin-5-one VI (0.5 g.) was refluxed for 2 hr. in 10 ml. of water plus 2 ml. of concentrated ammonium hydroxide. Some oily material was present during the entire heating period; it did not crystallize when the reaction mixture was cooled and seeded with starting compound. The aqueous phase, after the oil had been removed by ether extraction, was evaporated to dryness and furnished 0.1 g. of white solid. After two recrystallizations from water the compound was obtained as white plates or flat needles, m.p. 71–72°, reported[11] for 1-benzyl-1-nitrosohydrazine, 71°.

Anal. Calcd. for $C_7H_9N_3O$: C, 55.62; H, 6.00; N, 27.80. Found: C, 55.68, 55.51; H, 5.70, 5.97; N, 27.51.

An absorption characteristic of carbonyl was lacking in the infrared spectrum; NH was indicated. The compound gave a positive test for nitrosoamine with potassium iodide in trifluoroacetic acid.[18]

A much better conversion of VI to 1-benzyl-1-nitrosohydrazine could be effected as follows. One gram was mixed with 32 ml. of 3.3 *N* ammonium hydroxide and allowed to stand at ambient temperature in a stoppered flask until the oil which was initially present had been replaced completely by crystalline material. The yield of crude product melting at 65–68° was 0.85 g.

Decomposition of 1-Benzyl-2-(N,N-dimethylcarbamyl)-1-nitrosohydrazine in Water.—When 1-benzyl-2-(N,N-dimethylcarbamyl)-1-nitrosohydrazine was boiled in water for 1 hr., the principal product (53%) which was isolated and characterized was 1-benzyl-1-nitrosohydrazine, m.p. 71–72°. A lower melting material with an intense carbonyl absorption at 5.6 μ was also recovered, but was not further purified or identified; most likely it was the intermediate 3-benzyl-1,2,3,4-oxatriazolin-5-one (VI).

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Quaternization of *cis*- and *trans*-1,2-Dimethyl-3-isopropylaziridine with Methyl Iodide[1a-c]

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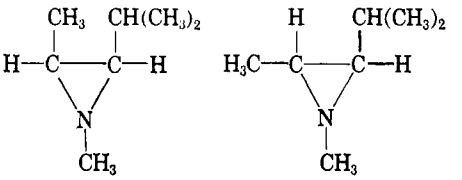
Treatment of *cis*- or *trans*-1,2-dimethyl-3-isopropylaziridine (**1** and **2**) with methyl iodide was found to give the corresponding 1,1,2-trimethyl-3-isopropylaziridinium iodide (**3** and **4**). Characterization of the aziridinium compounds was accomplished by elemental analysis, n.m.r. spectroscopy, vapor pressure osmometry, and examination of their reactions with thiosulfate ion. *trans*-1,2-Dimethyl-3-isopropylaziridine (**2**), which exists as an 80%–20% mixture of rapidly interconverting diastereomers (**2a** and **2b**) in which the isomer with *cis* methyl groups predominates, gives with methyl-d_3 iodide a nearly equal mixture of the two diastereomeric *trans*-1,1,2-trimethyl-3-isopropylaziridinium-1-d_3 iodides (**4a** and **4b**) as indicated by n.m.r. spectroscopy. *cis*-1,2-Dimethyl-3-isopropylaziridine (**1**), which we estimate is ~99% of the *trans*-, *cis*-diastereomer (**1b**), has also been quaternized with methyl-d_3 iodide; approximately half of the product is formed by quaternization of the *cis*-diastereomer (**1b**) of **1**.

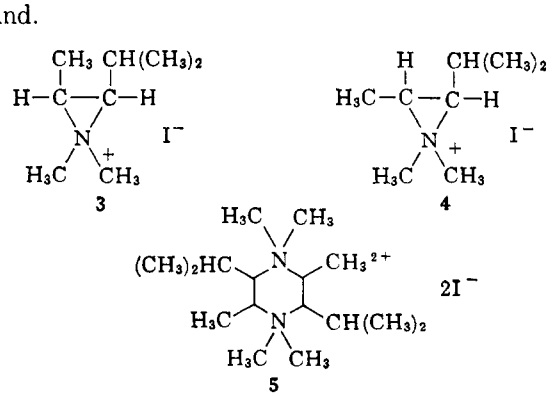
Since their implication as intermediates in the mechanism of biological action of nitrogen mustards (β-haloalkylamines),[2] a substantial number of aziridinium compounds have been prepared and characterized.[3,4] In addition, reactions with nucleophiles of other aziridinium compounds, which were generated from aziridines in the presence of acid but not isolated, have been studied.[5] Interestingly, although the large majority of known aziridinium compounds are highly reactive toward nucleophiles, there are notable exceptions, and these exceptions are aziridinium compounds that possess two secondary ring carbons.[3e]

We report here our study of the formation of aziridinium compounds by quaternization of *cis*- and *trans*-1,2-dimethyl-3-isopropylaziridine (**1** and **2**, respectively) with methyl iodide and methyl-d_3 iodide. This work was undertaken not only because of our desire to learn more of the chemistry of these potentially biologically useful compounds but also because the static geometrical requirements of the three-membered aziridinium ring make study of their formation and reactions particularly suitable for assessing the role of steric effects on reactivity.



1 **2**

Treatment of *cis*-1,2-dimethyl-3-isopropylaziridine[1b] (**1**) in benzene with an equal molar amount of methyl iodide gave *cis*-1,1,2-trimethyl-3-isopropylaziridinium iodide (**3**) as white needles in over 50% yield after recrystallization from anhydrous ethanol–ethyl acetate. The yield of crude **3** was greater than 90%. The elemental analysis of the product indicated that it was either an aziridinium compound or a polymer thereof, the most likely polymer being the dimer having the bispiperazinium structure **5**. The number average molecular weight (NAMW) of the product was determined in ethanol using the vapor pressure osmometry technique, and the value found (125 ± 3) was in accord with the aziridinium structure **3**, NAMW = 127.6, and inconsistent with the dimer structure **5**, NAMW = 170.1. The reaction of thiosulfate with **3** under conditions that did not affect N,N,N′,N′-tetramethylpiperazinium diiodide provided convincing proof that the compound was indeed an aziridinium compound.



3 **4**

5

(1) (a) Structure–Activity Relationships of Ethylenimines. IV. Presented at the 148th National Meeting of the American Chemical Society, Chicago, Ill., Aug.–Sept. 1964. (b) Previous paper in the series: A. T. Bottini, R. L. VanEtten, and A. J. Davidson, *J. Am. Chem. Soc.*, to be published. (c) This research was supported by Grant CA-05528 from the National Cancer Institute of the Public Health Service. (d) Public Health Service Predoctoral Fellow, 1963–1964.

(2) A leading reference is W. C. J. Ross, "Biological Alkylating Agents," Butterworth and Co. (Publishers) Ltd., London, 1962. See also the papers cited in footnotes 9–18 or ref. 3b.

(3) Reports describing aziridinium compounds include (a) N. J. Leonard and K. Jann, *J. Am. Chem. Soc.*, **82**, 6418 (1960); (b) N. J. Leonard and K. Jann, *ibid.*, **84**, 4806 (1962); (c) N. J. Leonard, K. Jann, J. V. Paukstelis, and C. K. Steinhardt, *J. Org. Chem.*, **28**, 1499 (1963); (d) N. J. Leonard, E. F. Kiefer, and L. E. Brady, *ibid.*, **28**, 2850 (1963); (e) P. E. Fanta, L. J. Pandya, W. R. Groskopf, and H.-J. Su, *ibid.*, **28**, 413 (1963); (f) R. D. Clark and G. K. Helmkamp, *ibid.*, **29**, 1316 (1964); (g) V. B. Schatz, Ph.D. Thesis, Brown University (1954) (cited in 3f); (h) L. M. Trefonas and R. Towns, *J. Heterocyclic Chem.*, **1**, 19 (1964). See also the papers cited in footnotes 10, 20, 22, 24, 25, and 28 of ref. 3b.

(4) The number of known aziridinium compounds seems quite small when compared with the number of known nitrogen mustards and aziridines. *Cf.* R. P. Bratzel, R. B. Ross, T. H. Goodridge, W. T. Huntress, M. T. Flather, and D. E. Johnson, *Cancer Chemotherapy Rept.*, **26**, 1 (1963), and T. H. Goodridge, W. T. Huntress, and R. B. Bratzel, *ibid.*, **26**, 341 (1963).

(5) See especially (a) J. E. Earley, C. E. O'Rourke, L. B. Clapp, J. O. Edwards, and B. C. Lawes, *J. Am. Chem. Soc.*, **80**, 3458 (1958); (b) G. J. Buist and H. J. Lucas, *ibid.*, **79**, 6157 (1957).