heated on a steam-bath for one-half hour. The solid, which separated, was removed, washed with ether and recrystallized from ethanol. Although the first crop of crystals was mainly collidine hydrobromide, concentration of the mother liquor followed by addition of ethyl acetate caused the separation of 75 mg. (21%) of yellow crystals, m.p. 206–212°, as expected for dehydroquinolizinium iodide. A sample of these crystals was converted to the corresponding picrate, m.p. 179–180°, alone or mixed with an authentic sample of dehydroquinolizinium picrate.

Dehydrogenation of the 3H,4H-Quinolizinium Ion.—The results of many experiments on the dehydrogenation of the 3H,4H-quinolizinium bromide, iodide and picrate salts can be summarized: (a) N-bromosuccinimide led to the introduction of bromine and the product on treatment with triethylamine gave the dehydroquinolizinium ion (I) in 6% yield; (b) selenium dioxide gave I in 3% yield; (c) chloranil gave I in 10% yield, (d) molecular oxygen with a reduced platinum catalyst was effective in either acetic acid or nitrobenzene as solvent giving I in yields of 23 to 26%.

The most satisfactory method thus far developed, however, was that using palladium-on-charcoal as follows. A solution of 800 mg. of 3H,4H-quinolizinium picrate in 60 ml. of *n*-butyl alcohol containing 160 mg. of a 10% palladium-on-charcoal catalyst was boiled under reflux for three hours. After the hot reaction mixture had been filtered to remove tarry impurities, the filtrate on cooling deposited 450 mg. of crude yellow crystals. These after recrystallization from ethanol gave 270 mg. (34%) of yellow needles, m.p. 180–181°.

Anal. Calcd. for $C_{15}H_{10}N_4O_7$: C, 50.28; H, 2.81. Found: C, 50.26; H, 2.94.

ROCHESTER, NEW YORK

[CONTRIBUTION FROM THE CHEMISTRY DIVISION, U. S. NAVAL ORDNANCE TEST STATION]

The Acidity of Nitroguanylhydrazones

BY RONALD A. HENRY, JOHN E. DE VRIES AND ROBERT H. BOSCHAN

RECEIVED MAY 31, 1955

Acid dissociation constants for several nitroguanylhydrazones, $RCH{=}NNHC(NH_2)NNO_2$, have been determined spectrophotometrically; some salts have also been prepared. The products obtained in the methylation of potassium benzalnitroaminoguanidine lend support to the belief that these hydrazones exist in the nitrimino form.

The pK_a for nitroaminoguanidine, $NH_2NHC(NH_2)NNO_2$, was found to be 10.47 when determined by a potentiometric method,[1] and 10.60 when determined by a spectrophotometric method.[2] The acid dissociation constants for several nitroguanylhydrazones have now been measured in aqueous solution at room temperature by the spectrophotometric method. The results are summarized in Table I. These compounds are approximately 100 times more acidic than nitroaminoguanidine. The dissociation constants for the substituted benzalnitroaminoguanidines indicate a decreasing acidity with increasing electropositive character of the group; however, the pK_a's do not correlate linearly with Hammett's σ-values for groups.

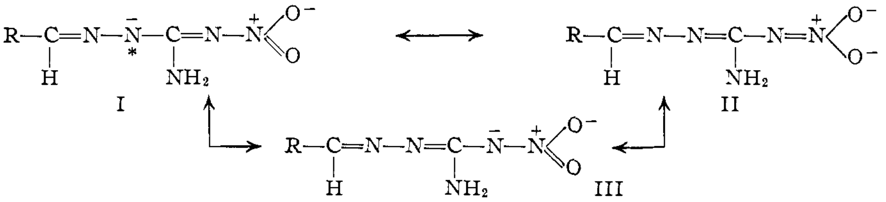
TABLE I

DISSOCIATION CONSTANTS FOR NITROGUANYLHYDRAZONES

Hydrazone derived from	λ_{max}, mμ	pK_a
Acetone	285	8.60
Cyclohexanone	287	8.80
Phenylacetaldehyde	285	8.50
Cinnamaldehyde	338	8.28
Benzaldehyde	317	8.38
2-Hydroxybenzaldehyde	342	8.50
2-Methoxybenzaldehyde	338	8.70
4-Methoxybenzaldehyde	332	8.83
4-Methylbenzaldehyde	322	8.80
4-Isopropylbenzaldehyde	323	8.90
4-Dimethylaminobenzaldehyde	363	9.2 ± 0.25[a]

[a] Substantially the same value was obtained using a small secondary peak at 273 mμ. This value is considerably less precise than the others because the peak height change on going from *p*H 6.0 to 13 is not sharp, and in the 363 mμ region is complicated by the gradual shift of the peak maximum to lower wave lengths.

If one assumes that the nitroguanylhydrazones, like nitroaminoguanidine, exist primarily in the nitrimino form,[1,3] then the following structures contribute to the resonance hybrid for the conjugate base



The stability of this anion is increased over the one derived from nitroaminoguanidine through the additional conjugation permitted by forms II and III; consequently, the hydrazones should be more acidic. In the case of the aryl derivatives the stability of the anion could be further increased by conjugation into the benzene ring. However, since the alkyl hydrazones are almost as acidic as the aryl derivatives, one has to conclude either that conjugation with the benzene ring exerts only a small influence or that hyperconjugation with the alkyl groups is causing an effect equal to that of the benzene resonance. Electropositive *ortho* and *para* substituents in the benzalnitroaminoguanidines could exert an acid weakening effect by such resonance forms as

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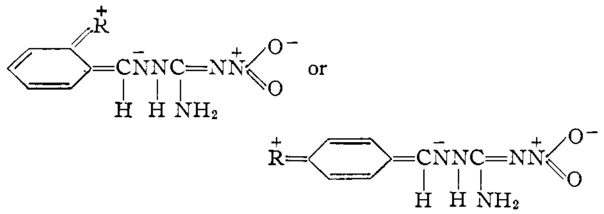
(1) W. D. Kumler and P. P. T. Sah, *J. Org. Chem.*, **18**, 669 (1953).

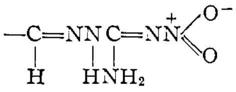
(2) J. E. De Vries and E. S. C. Gantz, THIS JOURNAL, **76**, 1008 (1954).

(3) W. D. Kumler and P. P. T. Sah, *J. Am. Pharm. Assoc., Sci. Ed.*, **41**, 375 (1952).



where R is OH, OCH_3 or $N(CH_3)_2$, which place a negative charge on the nitrogen adjacent to the nitrogen from which the proton normally leaves.

Benzalnitroaminoguanidine is sufficiently acid to form salts with aminoguanidine, benzalaminoguanidine and potassium hydroxide, which are stable dry and which can be recrystallized from 95% ethanol or methanol; nitroaminoguanidine does not give stable salts under the same conditions. As determined spectrophotometrically, the pK_a for the conjugate acid of the dimethylaminobenzalnitroaminoguanidine is 3.45. Since the pK_a for the dimethylanilinium ion is 5.1,[4] the group



$$-\underset{\mathrm{H}}{\mathrm{C}}{=}\mathrm{N}\underset{\mathrm{H}}{\mathrm{N}}\underset{\mathrm{NH_2}}{\mathrm{C}}{=}\mathrm{N}\overset{+}{\mathrm{N}}{\lessgtr}^{\mathrm{O^-}}_{\mathrm{O}}$$

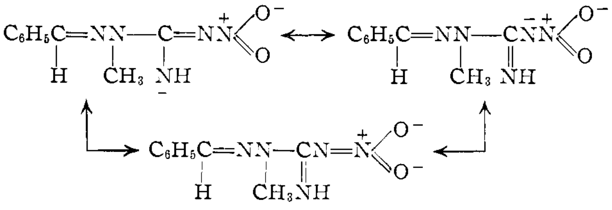
is moderately electronegative. By way of comparison the pK_a for the conjugate acid of 4-dimethylaminobenzaldehyde is 1.57.

The assumption that the nitroguanylhydrazones exist in the nitrimino form leads to the prediction that the most basic nitrogen atom (nucleophilic center) will be the hydrazino nitrogen atom adjacent to the guanyl carbon atom (asterisked in I). Direct evidence to support this prediction was obtained by alkylating the potassium salt of benzalnitroaminoguanidine with methyl iodide in absolute methanol; the principal product was the known benzal-1-methyl-1-amino-2-nitroguanidine.[5] Two other products, which corresponded to methylation on the same nitrogen atoms, were also isolated: (1) benzal-2-methylsemicarbazone, and (2) benzal-2,3-dimethylisosemicarbazone

$$C_6H_5CH{=}N{-}N(CH_3)C(OCH_3)NH$$

The formation of the latter compound represents an interesting displacement of the nitramide anion by methoxide ion. Since the total yield of these three alkylation products amounted to 97–99% of theory, it is reasonable to conclude that reaction occurs exclusively at this one center. Benzalnitroaminoguanidine and methyl iodide do not react under these conditions.

Benzal-1-amino-2-methyl-3-nitroguanidine, $C_6H_5CH{=}NNHC(NHCH_3)NNO_2$ (λ_{max} 312 mμ, ϵ_{water} 21,120, $\epsilon_{ethanol}$ 24,400), has a pK_a = 8.10. The resonance hybrid for the anion is similar to that for benzalnitroaminoguanidine and is stabilized in the same manner. The electronegative doubly bonded nitrogen of the hydrazino group has a direct effect on the dissociating proton. On the other hand, the conversion of 1-methyl-1-amino-2-nitroguanidine (pK_a = 12.60) to its benzalhydrazone, $C_6H_5CH{=}N{-}N(CH_3)C(NH_2)NNO_2$ (λ_{max} 319 mμ, $\epsilon_{ethanol}$ 31,440), produces only a tenfold increase in the acidity (pK_a = 11.45). The anion which results from the dissociation of a hydrogen from the C-amino group, although a resonance hybrid



is neither readily stabilized by conjugation with nor directly influenced by the electronegative benzal group.

Attempts to form the aminoguanidinium salt of 1-formamido-2-nitroguanidine (pK_a = 7.50) always yielded the corresponding salt of 3-nitroamino-1,2,4-triazole.

Experimental[6]

Measurement of Acid Dissociation Constants.—The nitroguanylhydrazones were prepared and purified by previously described methods.[3,7] Both benzal-1-methyl-1-amino-2-nitroguanidine and benzal-1-amino-2-methyl-3-nitroguanidine have been reported.[5]

The dissociation constants were determined by the method of Stenstrom and Goldsmith[8] using a Cary Recording Spectrophotometer, Model 11MS. The symbol ϵ refers to the molar absorptivity.

Dimethylaminobenzalnitroaminoguanidine has its maximum absorption in absolute methanol or ethanol at 370 mμ, ϵ 36,400, in 95% ethanol at 373 mμ,[9] in neutral distilled water at 363 mμ, in water, pH 1.8, at 316 mμ, ϵ 30,700, and in water, pH 12, at 355 mμ, ϵ 28,200. A secondary maximum at 273 mμ, ϵ 12,100, in neutral, aqueous or alcoholic solutions is not due to nitroaminoguanidine (λ_{max} 267 mμ, ϵ 14,000[1]) which might be present from a hydrolysis of the hydrazone since changes in the peak height with pH parallel exactly those that occur at 370 mμ. Dimethylaminobenzaldehyde has its maximum absorption at 338 mμ in absolute ethanol, and at 352 mμ in neutral or pH 12 aqueous solution. The maximum absorption for benzal nitroaminoguanidine in an aqueous solution at pH 12 occurs at 356 mμ (ϵ 20,500).

Aminoguanidinium Salt of Benzalnitroaminoguanidine.—An ethanolic solution of aminoguanidine, made from 0.125 mole of nitroguanidine by the method of Henry, Skolnik and Smith,[10] was shaken overnight with 1.5 g. of benzalnitroaminoguanidine. The golden yellow plates which gradually separated were removed by filtration and washed with two 15-ml. portions of cold 95% ethanol. The yield of air-dried salt, melting at 165–166° dec., was quantitative. One rapid recrystallization from 200 ml. of 95% ethanol raised the melting point to 169–170°.

Anal. Calcd. for $C_9H_{15}O_2N_9$: C, 38.43; H, 5.38; N, 44.82. Found: C, 38.58; H, 5.51; N, 44.88, 44.65.

This compound is moderately soluble in cold water; when the aqueous solution is acidified, benzalnitroaminoguanidine precipitates.

Benzalaminoguanidinium Salt of Benzalnitroaminoguanidine.—A solution consisting of 0.91 g. (0.0056 mole) of recrystallized benzalaminoguanidine and 1.03 g. (0.005 mole) of benzalnitroaminoguanidine in 50 ml. of absolute methanol

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[4] N. F. Hall, THIS JOURNAL, **52**, 5115 (1930); C. Golumbic and G. Goldbach, *ibid.*, **73**, 3966 (1951).

[5] R. A. Henry and G. B. L. Smith, *ibid.*, **73**, 1858 (1951).

(6) The melting points are corrected.

(7) W. F. Whitmore, A. J. Revukas and G. B. L. Smith, THIS JOURNAL, **57**, 706 (1935); G. B. L. Smith and E. P. Shoub, *ibid.*, **59**, 2077 (1937); and R. A. Henry and G. B. L. Smith, *ibid.*, **74**, 278 (1952).

(8) W. Stenstrom and N. Goldsmith, *J. Phys. Chem.*, **30**, 1683 (1926).

(9) Kumler and Sah, ref. 3, reported λ_{max} 374 mμ, ϵ 42,400, for solutions in 95% ethanol. These investigators also listed second and third absorption maxima at 273 and 268 mμ, respectively.

(10) R. A. Henry, S. Skolnik and G. B. L. Smith, THIS JOURNAL, **75**, 950 (1953).

was refluxed one hour. The deep yellow colored solution was filtered and cooled to room temperature. A crop (0.82 g.) of yellow plates, m.p. 181–182° dec., was removed; a second crop (0.58 g.) was obtained by partially evaporating and recooling to 5°. The salt, which is soluble in both ethanol and methanol, can be wastefully recrystallized from methanol.

Anal. Calcd. for $C_{16}H_{19}O_2N_9$: C, 52.02; H, 5.18; N, 34.13. Found: C, 52.84; H, 5.47; N, 34.10.

Aminoguanidine Salt of 3-Nitroamino-1,2,4-triazole.—1-Formamido-2-nitroguanidine[11] (3.76 g., 0.026 mole) was refluxed for one hour with 200 ml. of an ethanolic solution of aminoguanidine[9] derived from 0.22 mole of nitroguanidine. The solid never dissolved completely although its appearance did change; a small amount of ammonia was evolved. After the solution had been cooled in an ice-bath, the solid was removed by filtration and washed with two 20-ml. portions of cold ethanol. The yield was 3.76 g., m.p. 202° dec. Several recrystallizations from a large volume of absolute methanol gave needles which decomposed at 209–210°. A mixed melting point with 3-nitroamino-1,2,4-triazole (m.p. 217°) was 195–198°.

Anal. Calcd. for $C_3H_9O_2N_9$: C, 17.73; H, 4.46; N, 62.05. Found: C, 17.87; H, 4.36; N, 61.70.

The same salt was formed by dissolving 0.01 molar quantities of aminoguanidine bicarbonate and 3-nitroamino-1,2,4-triazole in 20 ml. of hot water, cooling and filtering.

Reaction of Methyl Iodide and the Potassium Salt of Benzalnitroaminoguanidine.—A slurry of 11.45 g. of the potassium salt[12] of benzalnitroaminoguanidine and 7.0 g. of methyl iodide in 70 ml. of absolute methanol was allowed to stand at room temperature for one month. The yellow potassium salt gradually disappeared and was replaced by a white crystalline solid. The latter was removed by filtration, washed once with a small volume of cold methanol, and then with several portions of cold water. The yield of air-dried product, melting at 188–190° dec., was 7.0 g. (68% of theory); one recrystallization from 95% ethanol gave prisms melting at 194–195° dec. Admixture with an authentic sample of benzal-1-methyl-1-amino-2-nitroguanidine[5] did not depress the melting point.

In a duplicate experiment the yield amounted to 73% of theory.

The methanolic mother liquors and washings were combined and evaporated to dryness. The oily residue which remained was extracted with eight 30-ml. portions of boiling cyclohexane; the solid insoluble residue A was retained. The extracts were cooled and 0.5 g. of white crystalline solid, m.p. 145–155°, was removed and retained (B). The cyclohexane was then evaporated to leave 1.0 g. (11.2%) of basic oil which gradually crystallized; this material did not give a positive Franchimont nitramine test. Several recrystallizations from 50% aqueous methanol gave hygroscopic white plates, melting at 54–55°, which were difficult to purify. This fraction was **benzal-2,3-dimethylisosemicarbazone.**

Anal. Calcd. for $C_{10}H_{13}ON_3$: C, 62.81; H, 6.85; N, 21.98. Found: C, 60.9; H, 6.93; N, 22.0.

The **picrate** melted at 154.5–155° after two recrystallizations from methanol.

Anal. Calcd. for $C_{16}H_{16}O_8N_6$: C, 45.71; H, 3.84; N, 20.00. Found: C, 45.87; H, 3.99; N, 20.2.

Proof for this assigned structure was obtained in the following manner: A solution consisting of 0.2 g. of the isosemicarbazone, 10 ml. of ethanol, 20 drops of concentrated aqueous ammonium hydroxide and 0.1 g. of ammonium iodide stood for two days at room temperature. The solution was then evaporated to dryness under reduced pressure, redissolved in about 10 ml. of hot aqueous ethanol, and treated with 0.3 g. of picric acid. Cooling gave a picrate which melted at 219° dec.; admixture with an authentic specimen of benzal-1-methyl-1-aminoguanidine picrate[13] did not depress the melting point. X-Ray powder patterns also were identical.

The cyclohexane-insoluble residue A was extracted with six 30-ml. portions of hot benzene; the insoluble portion was discarded. The benzene was evaporated to leave 1.1 g. of material melting at 150–160°. Fractional crystallization from benzene gave 0.6 g. (5.8%) more of benzal-1-methyl-1-amino-2-nitroguanidine and 0.5 g. of a material which was identical with fraction B. The total yield of B corresponded to approximately 12% of theory. Repeated recrystallization of this compound from benzene finally yielded long thin needles which melted at 164.5–165°. A mixture melting point with a sample of benzal-2-methylsemicarbazone was 164–165°. This semicarbazone also exists in a polymorphic form melting at 159–159.5°.

Anal. Calcd. for $C_9H_{11}ON_3$: C, 61.00; H, 6.26; N, 23.72. Found: C, 61.12, 61.02; H, 6.03, 6.14; N, 23.7, 23.8.

Benzal-2-methylsemicarbazone picrate was recrystallized from absolute ethanol as flat, orange needles, m.p. 149–150°.

Anal. Calcd. for $C_{15}H_{14}O_7N_6$: C, 46.16; H, 3.62; N, 21.53. Found: C, 45.7; H, 3.69; N, 21.6.

Benzal-1-benzyl-1-amino-2-nitroguanidine.—A slurry of benzyl chloride (1.0 g.), potassium salt of benzalnitroaminoguanidine (1.8 g.) and 50 ml. of absolute methanol was refluxed for 24 hours, cooled, diluted with 100 ml. of cold water and filtered. The solid product was washed with petroleum ether, then dried; yield 0.3 g., m.p. 189–191° dec. Recrystallization from absolute ethanol gave plates melting at 198–199° dec.

Anal. Calcd. for $C_{15}H_{15}O_2N_5$: C, 60.59; H, 5.09; N, 23.56. Found: C, 60.50; H, 5.03; N, 23.2.

Benzal-2,4-dimethylthiosemicarbazone.—2,4-Dimethylthiosemicarbazide was prepared from methylhydrazine and methyl isothiocyanate in ethanol; after recrystallization from ethanol the melting point was 138–139°; reported 138°.[14]

Anal. Calcd. for $C_3H_9N_3S$: C, 30.23; H, 7.61. Found: C, 30.35; H, 7.47.

The **benzal-2,4-dimethylthiosemicarbazone**, obtained as thick glistening plates after recrystallization from 95% ethanol, melted at 116.5–117.2°.

Anal. Calcd. for $C_{10}H_{13}N_3S$: C, 57.94; H, 6.32; S, 15.47. Found: C, 57.91; H, 6.09; S, 14.9.

Several attempts to convert this latter thiosemicarbazide to the corresponding semicarbazone by treatment with freshly precipitated mercuric oxide in 66% aqueous ethanol gave small amounts of a compound melting at 136.5–137.5° after recrystallization from methanol; admixture with 2,4-dimethylthiosemicarbazide depressed the melting point to 115–125°. The analyses were in agreement with those calculated for the substituted diguanyl disulfide formed by oxidation of the thiosemicarbazone.

Anal. Calcd. for $C_{20}H_{24}N_6S_2$: C, 58.22; H, 5.86; N, 20.37; S, 15.54. Found: C, 58.8; H, 5.5; N, 20.0; S, 15.6.

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[11] R. A. Henry, THIS JOURNAL, **72**, 5343 (1950).

[12] This salt was obtained as bright yellow plates by treating a saturated solution of benzalnitroaminoguanidine in absolute methanol at room temperature with an equivalent amount of methanolic potassium hydroxide.

[13] A. H. Greer and G. B. L. Smith, THIS JOURNAL, **72**, 874 (1950).

[14] M. Busch, E. Opfermann and H. Walther, *Ber.*, **37**, 2320 (1904).