Preparation and Reactions of 1-(Nitroguanyl)aziridines

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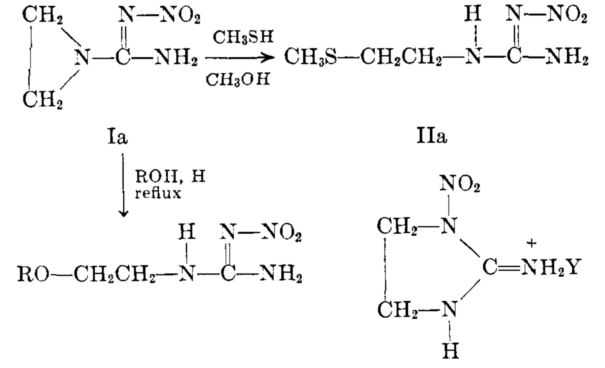
The formation of two 1-(nitroguanyl)aziridines was achieved by the reaction of 2-methyl-1-nitro-2-thiopseudourea with ethyleneimine and 2-methylaziridine. Cleavage of these aziridines in acidic media produced linear alkylnitroguanidines. The cyanobromination of 1-(nitroguanyl)aziridine (Ia) gave 3-cyano-2-imino-1-nitroimidazolidine (VIII) and 2-amino-1-nitroimidazolidinium bromide (IX) in good yields.

Amines react readily with 2-methyl-1-nitro-2-thiopseudourea to produce linear[1] and cyclic[2] guanidines. We have found that the reaction of ethylenimine and 2-methylaziridine with 2-methyl-1-nitro-2-thiopseudourea in a mixture of ether and methanol results in the formation of 1-(nitroguanyl)aziridine (Ia) and 2-methyl-1-(nitroguanyl)aziridine (Ib) in 80% and 53% yields, respectively. These compounds are white crystalline solids and are stable at room temperature in the absence of light, atmospheric carbon dioxide, and water vapor. On the other hand, the reaction of ethylenimine and 2-methyl-1-nitro-2-thiopseudourea in methanol alone gave only a low yield of 2-(methylthio)ethylnitroguanidine (IIa).

The ethanolysis of 1-(nitroguanyl)aziridine (Ia) with absolute ethanol and *p*-toluenesulfonic acid formed 1-(2-ethoxyethyl)-3-nitroguanidine (III) and 2-amino-1-nitroimidazolidine *p*-toluenesulfonate (IV). 2-Ethoxyethylamine (V) synthesized from 2-ethoxyethyl bromide[3] *via* the Gabriel method gave with 2-methyl-1-nitro-2-thiopseudourea a derivative whose properties were identical with III. The nitrate salt of 2-amino-1-nitroimidazolidine[4] was converted to IV by its reaction with *p*-toluenesulfonic acid. The alcoholysis reaction was extended to 1-pentanol and 2-methyl-2-propanol which gave the corresponding 1-(2-alkoxyethyl)-3-nitroguanidines (VI and VII). This appears to be a general method for the syntheses of 1-(2-alkoxyethyl)-3-nitroguanidines. The cleavage of Ia in methylene chloride solution with nitric, hydrochloric, and hydrobromic acids produced the corresponding 2-substituted ethylnitroguanidines. In Scheme I are summarized the general reactions of 1-(nitroguanyl)aziridine.



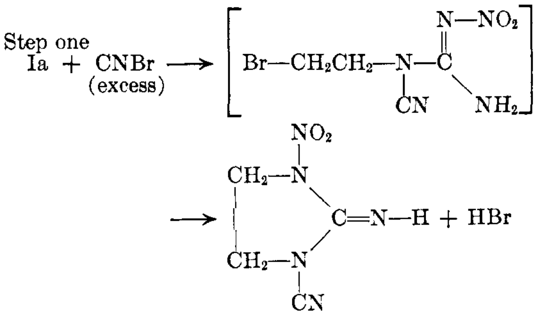
III. R = C_2H_5
VI. R = n-C_5H_{11}
VII. R = t-C_4H_9

IV. Y = p-$CH_3C_6H_4SO_3^-$

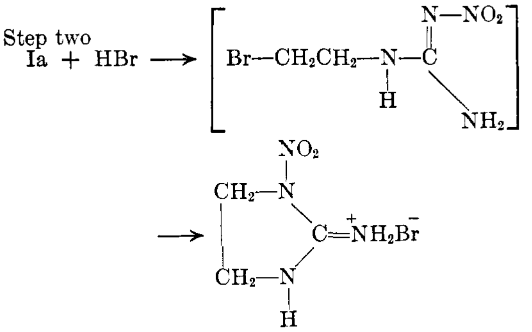
$C_2H_5OCH_2CH_2NH_2$
V

SCHEME I

The cyanobromination[5] of 1-(nitroguanyl)aziridine (Ia) in boiling benzene probably proceeds through a linear intermediate N-(2-bromoethyl)-N-cyano-nitroguanidine which cyclizes by an internal S_N2 mechanism[6] to form VIII in 43% yield. The hydrogen bromide liberated in the first step cleaves Ia to form 2-bromoethyl-3-nitroguanidine which rapidly cyclizes to IX in 41% yield.



VIII



IX

Under the cyanobromination conditions previously stated, 1-(nitroguanyl)aziridine-d_2 produced 3-cyano-2-imino-d_1-1-nitroimidazolidine (VIII*) and 2-amino-d_2-1-nitroimidazolidinium-d_1 bromide (IX*). The identity of VIII* and IX* was established by their infrared curves.

The ultraviolet absorption spectra[7,8] of the 1-(nitroguanyl)aziridines in ethanol show them to have nitrimino structures with principal absorption maxima 2700–2720 Å. All of the substituted ethylnitroguanidines had absorption curves similar to ethylnitroguanidine with maxima 2650–2740 Å. Compounds VIII and

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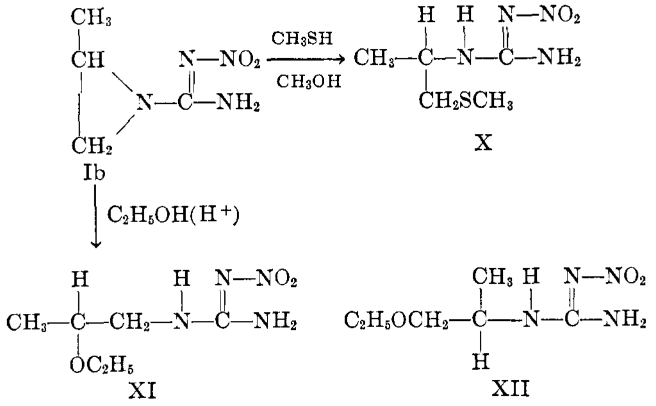
IX have nitramino structures with maxima at 2380 Å. and 2440 Å., respectively.

The infrared spectra of compounds II–XII were consistent with the proposed structures. The symmetric ν (NO_2) was located in the 1293–1270[9]-cm.$^{-1}$ region in these compounds. The asymmetric nitro group frequencies of the 1-(nitroguanyl)aziridines (Ia, Ib), 1535 cm.$^{-1}$ and 1527 cm.$^{-1}$, respectively, are in agreement with Bellamy's[9] findings for polynitramines rather than Kumler's[10] assignments for nitroguanidine derivatives.

The principal acidic cleavage products of 2-methyl-1-(nitroguanyl)aziridine (Ib) were dependent upon the strength of the acid's conjugate base. With the strong conjugate base methyl mercaptide, 1-(methylthio)-2-propylnitroguanidine (X), m.p. 79–80°, was isolated and its structure established by an independent synthesis. In the reaction with the weak conjugate base *p*-toluenesulfonate, 2-ethoxy-1-propylnitroguanidine (XI), m.p. 155–156°, was formed instead of the isomeric 1-ethoxy-2-propylnitroguanidine (XII), m.p. 88–89°. The structures of XI and XII were established by independent syntheses. The proposed structures of the derivatives of Ib are indicated in Scheme II.



Scheme II

Experimental

The melting points were determined on a micro Kofler hot stage. The infrared spectra were recorded by a Perkin-Elmer Model 21 spectrophotometer with sodium chloride or calcium fluoride optics as Nujol mulls or potassium bromide pellets. The ultraviolet spectra were recorded on a Beckman DK-2 spectrophotometer or a Beckman DU in 1-cm. silica cells.

1-(Nitroguanyl)aziridine (Ia).—Ethylenimine (6.4 g., 0.148 mole) was added to a mixture of 75 ml. of absolute ether and 75 ml. of absolute methanol. Twenty grams (0.148 mole) of 2-methyl-1-nitro-2-thiopseudourea was added, and the temperature rose from 20° to 38° with the rapid evolution of methyl mercaptan. After 15 min., 50 ml. of ether and 30 ml. of methanol were added, and the temperature was raised to 50° within a half hour. The mixture was cooled to 30° and evaporated to dryness in a stream of dry air. The solid was stirred in 150 ml. of ether and filtered. The ether extract evaporated to a gummy residue and was discarded.

The crystalline residue was dissolved in 250 ml. of absolute methanol and filtered. Upon cooling and concentration, 15.5 g. (80.2%) of 1-(nitroguanyl)aziridine (m.p. 124–126°) was obtained. An analytical sample, m.p. 129–130°, was obtained by repeated crystallization from methanol.

Anal. Calcd. for $C_3H_6N_4O_2$: C, 27.69; H, 4.60; N, 43.07. Found: C, 27.98; H, 4.60; N, 42.53. Ultraviolet spectrum in isopropyl Alcohol: λ_{max} 2710 Å., log ϵ 4.20; ν_{max} (KBr) 1625 (s), 1535 (s) cm.$^{-1}$.

2-Methyl-1-(nitroguanyl)aziridine (Ib).—To a mixture of absolute ether (200 ml.) and absolute methanol (40 ml.) was added freshly distilled 2-methylaziridine (Interchemical Corp., 5.7 g. 0.1 mole) and 2-methyl-1-nitro-2-thiopseudourea (13.5 g., 0.1 mole). The temperature was maintained at 25–27° by a water bath until a homogeneous solution occurred (1.5–2 hr.). The solution was evaporated to 20 ml. by a stream of dry air, 200 ml. of ether was added, and the mixture was evaporated to dryness. Twelve grams of 2-methyl-1-(nitroguanyl)aziridine (m.p. 102–104°, 83% yield) was isolated. Upon recrystallization from ethanol and methylene chloride a crystalline solid was obtained whose m.p. was 109–110°.

Anal. Calcd. for $C_4H_8N_4O_2$: C, 33.33; H, 5.63; N, 38.88. Found: C, 33.47; H, 5.94; N, 38.63. Ultraviolet spectrum in isopropyl alcohol: λ_{max} 2720 Å., log ϵ 4.21; ν_{max} (KBr) 1614 (s), 1527 (s) cm.$^{-1}$.

2-(Methylthio)ethylnitroguanidine (IIa). **A.**—From an equimolar quantity of ethylenimine and 2-methyl-1-nitro-2-thiopseudourea in absolute methanol at room temperature (21 hr.), white crystals of IIa were obtained. Recrystallization from methanol and water gave 18.2% of product; m.p. 115–116°; ν_{max} (KBr) 1645 (s), 1594 (s), 1535 (m, broad) 1297 (s) cm.$^{-1}$.

Anal. Calcd. for $C_4H_{10}N_4O_2S$: C, 26.96; H, 5.66; N, 31.44. Found: C, 27.44; H, 5.77; N, 31.17.

B.—A solution of 1-(nitroguanyl)aziridine (Ia) (0.417 g. 0.0032 mole) in 25 ml. of absolute ethanol was saturated with methyl mercaptan at 20° (1 hr.). The reaction flask was stoppered and allowed to stand 18 hr. at 23°. The mixture was evaporated to dryness and the residue recrystallized from ethanol and methanol–ether. The product weighed 0.301 g. (53% yield) and melted at 115–116°. A mixture melting point with a sample of material obtained from the reaction of 2-methyl-1-nitro-2-thiopseudourea with 2-(methylthio)ethylamine was not depressed.

C.—The reaction of 2-(methylthio)ethyl amine with 2-methyl-1-nitro-2-thiopseudourea. The 2-(methylthio)ethyl amine was prepared by the reaction of methyl mercaptan with ethylenimine.[11] To 2.00 g. (0.0219 mole) of the amine in 25 ml. of absolute ether and 25 ml. of absolute ethanol was added 3 g. (0.0222 mole) of finely ground 2-methyl-1-nitro-2-thiopseudourea. The reaction was allowed to stand overnight. After recrystallization from a mixture of ether and methanol, 2.89 g. (73% yield, m.p. 115–116°) of material was obtained which did not depress the melting point of the product from method A.

***p*-Toluenesulfonate of 2-Amino-1-nitroimidazolidine** (IV).—To 1-(nitroguanyl)aziridine (Ia, 1.0 g., 0.0768 mole) dissolved in 100 ml. of hot absolute ethanol was added *p*-toluenesulfonic acid (0.1 g., 0.0005 mole). The mixture was then refluxed for 4.5 hr. and allowed to stand 74 hr. at room temperature. An amorphous precipitate was removed by filtration, and the filtrate was evaporated to dryness. The residue was dissolved in 5 ml. of absolute methanol. A crystalline precipitate (0.052 g., m.p. 182–184°) was formed by the addition of 75 ml. of ether and and storage overnight at 0°. After recrystallization from absolute ethanol, the compound melted at 183–185°. A mixture melting point with an authentic sample of the compound prepared from the nitrate salt of 2-amino-1-nitroimidazolidine and *p*-toluenesulfonic acid was not depressed. The yield based on the *p*-toluenesulfonic acid was 29.6%.

Anal. Calcd. for $C_{10}H_{14}N_4O_5S$: C, 39.73; H, 4.67; N, 18.54. Found: C, 39.70; H, 5.03; N, 18.52.

1-(2-Ethoxyethyl)-3-nitroguanidine (III).—Upon evaporation the filtrate from IV gave 0.634 g. of 1-(2-ethoxyethyl)-3-nitroguanidine (m.p. 83.5–84.5°, 47% yield); ν_{max} (KBr) 1645 (vs), 1600 (vs), 1552 (m), 1272 (vs) cm.$^{-1}$.

Anal. Calcd. for $C_5H_{12}N_4O_3$: C, 34.08; H, 6.87; N, 31.81. Found: C, 34.16; H, 6.57; N, 31.76.

The reaction of 2-ethoxyethylamine (V) with 2-methyl-1-nitro-2-thiopseudourea also gave III. A mixture melting point was not depressed.

2-Ethoxyethylamine (V).—A sample of 2-ethoxyethyl bromide was converted to N-(2-ethoxyethyl)phthalimide in 57% yield. A pure sample of this compound obtained from a mixture of ether and low-boiling petroleum ether melted at 39–40°.

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.76; H, 6.65; N, 6.18.

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The 2-ethoxyethylamine was obtained in 50% yield by hydrazinolysis of the N-(2-ethoxyethyl)phthalimide.

1-[2-(1-Pentoxyethyl)]-3-nitroguanidine (VI).—To 100 ml. of freshly distilled 1-pentanol was added *p*-toluenesulfonic acid (0.1 g.) and Ia (2.6 g., 0.02 mole). The mixture was refluxed for 6 hr. and the excess 1-pentanol was removed by distillation under diminished pressure. The residue recrystallized from ethanol, methylene chloride, and finally distilled water melted sharply at 92°; ν_{max} (KBr), 1653 (vs), 1605 (s), 1542 (m, broad), 1287 (s) cm.$^{-1}$.

Anal. Calcd. for $C_8H_{18}N_4O_3$: C, 44.02; H, 8.31; N, 25.66. Found: C, 43.70; H, 7.88; N, 25.74.

2-(*t*-Butoxy)ethylnitroguanidine (VII).—A mixture of 2-methyl-2-propanol (150 ml., freshly distilled), 1-(nitroguanyl)aziridine (Ia) (1.04 g., 0.08 mole), and *p*-toluenesulfonic acid (0.1 g.) was refluxed for 18 hr. The excess alcohol was removed by distillation under reduced pressure and the residue recrystallized from ethanol to yield crude 2-(*t*-butoxy)ethylnitroguanidine (VII). An analytical sample (m.p. 150–151°) was obtained after repeated recrystallization from ethanol.

Anal. Calcd. for $C_7H_{16}N_4O_3$: C, 41.17; H, 7.89; N, 27.44. Found: C, 40.60; H, 7.33; N, 26.30, 26.70.

3-Cyano-2-imino-1-nitroimidazolidine (VIII) and 2-Amino-1-nitroimidazolidinium Bromide (IX).—When 1-(nitroguanyl)aziridine (Ia) (4 g., 0.03 mole), cyanogen bromide (6 g., 0.057 mole), and dry benzene (200 ml.) were refluxed with vigorous stirring for 110 min., VIII, m.p. 139°, was formed in 43% yield and IX, m.p. 183–185° (lit. 179.5–180°, ref. 4), was formed in 41% yield.

Anal. Calcd. for $C_4H_5N_5O_2$ (VIII): C, 30.97; H, 3.25; N, 45.15. Found: C, 30.90; H, 3.23; N, 45.21; λ_{max} 2380 Å. (ϵ 748) alcohol. ν_{max} (Nujol) 3408–3300 (2 bands, s), 2240 (s), 1707 (s), 1682 (s), 1548 (s) cm.$^{-1}$; deuterated: 2563 (m), 2470 (m), 2242 (s), 1688 (s), 1544 (s) cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_3H_7BrN_4O_2$ (IX): C, 17.07; H, 3.34; Br, 37.87; N, 26.55. Found: C, 17.35; H, 3.42; Br, 37.17; N, 26.84.

Infrared spectrum: ν_{max} (Nujol) 1707–1708 (s), 1683 (s), 1548 (s) cm.$^{-1}$.

Deuteration of 1-(Nitroguanyl)aziridine (Ia), 3-Cyano-2-imino-1-nitroimidazolidine (VIII) and 2-Amino-1-nitroimidazolidinium Bromide (IX).—Analytically pure samples of Ia, VIII, and IX (500 mg. or 1 g.) and 5–10 ml. of 99.5% deuterium oxide were heated at 50–55° (2–18 hr.) in 60-ml. stoppered cylindrical tubes. The samples were evaporated to dryness on a vacuum line and mulls of the deuterated solids prepared in the usual manner.

1-(Methylthio)-2-propylamine.—Equimolar quantities of methyl mercaptan and 2-methylaziridine in excess methanol were kept at −78° for 4 hr. and allowed to warm to room temperature overnight. The mixture was dried for several days over anhydrous sodium sulfate and fractionally distilled. An analytical fraction (16.8 g., 53%; b.p. 155–156°, $n^{20}D$ 1.4832) was collected. Mylius[12] reported that the picrate of the isomeric 2-(methylthio)-1-propylamine melted at 133–134°.

Anal. Calcd. for $C_4H_{11}NS$: C, 45.72; H, 10.48; N, 13.33. Found: C, 45.15; H, 10.43; N, 13.53.

Picrate.—*Anal.* Calcd. for $C_{10}H_{14}N_4O_7S$: C, 35.93; H, 4.19; N, 16.77. Found: C, 35.18; H, 4.24; N, 16.94; m.p. of picrate 150–151°.

1-(Methylthio)-2-propylnitroguanidine (X). A.—The condensation of 1-(methylthio)-2-propylamine (5 g., 0.048 mole) with 2-methyl-1-nitro-2-thiopseudourea (6.8 g., 0.05 mole) gave 5.3 g. of 1-(methylthio)-2-propylnitroguanidine (X) in 54% yield. Crystallization from methylene chloride gave an analytical sample, m.p. 79–80°.

Anal. Calcd. for $C_5H_{12}N_4O_2S$: C, 31.28; H, 6.29; N, 29.15. Found: C, 31.49; H, 5.97; N, 29.30.

B.—A solution of 5 g. of methyl mercaptan in 20 ml. of methyl alcohol was added to 1.44 g. (0.01 mole) of 2-methyl-1-(nitroguanyl)aziridine (Ib) at −24°. After 4 hr. the mixture was allowed to warm to room temperature and stand overnight. The mixture was evaporated to dryness and extracted with benzene. The benzene extract was concentrated, and the solid was identical to 1-(methylthio)-2-propylnitroguanidine prepared in A.

2-(Ethoxy)-1-propylnitroguanidine (XI). A.—A mixture of 2-methyl-1-(nitroguanyl)aziridine (1.44 g., 0.01 mole), 100 ml. of absolute ethanol, and 0.18 g. of *p*-toluenesulfonic acid was refluxed for 5 hr. One and nine-tenth grams of light brown, gummy residue, m.p. 120–145°, was obtained by air evaporation to dryness. After several recrystallizations from ethanol, 0.457 g. (24% yield) of white solid, m.p. 155–156°, was obtained.

Anal. Calcd. for $C_6H_{14}N_4O_3$: C, 37.88; H, 7.42; N, 29.46. Found: C, 38.00; H, 7.28; N, 29.50.

B.—To ethanol (50 ml.) were added 2-ethoxy-1-propylamine (2.0 g., 0.02 mole, b.p. 118°[13], $n^{23}D$ 1.4101) and 2-methyl-1-nitro-2-thiopseudourea (2.7 g., 0.02 mole). The mixture was refluxed for 3 hr. and evaporated to dryness by a water aspirator. After trituration with ether and recrystallization from ethanol the product was identical with 2-ethoxy-1-propyl-3-nitroguanidine (XI) prepared by method A.

1-Ethoxy-2-propylnitroguanidine (XII).—To 1.103 g. (0.0107 mole) of 1-ethoxy-2-propylamine[14] ($n^{20}D$ 1.4079, b.p. 116°; picrate m.p. 132°) was added 20 ml. of ether–ethanol (1:1).

Anal. Calcd. for $C_{11}H_{16}N_4O_8$: C, 39.76; H, 4.85; N, 16.86. Found: C, 39.74; H, 4.22; N, 16.71.

After solution had occurred, 1.44 g. (0.0107 mole) of 2-methyl-1-nitro-2-thiopseudourea and 100 ml. of ether were added. The reaction mixture was stirred 19 hr. and evaporated to dryness; 1.5 g. of 1-ethoxy-2-propylnitroguanidine (m.p. 80–82°; crude yield, 63%) was obtained. After recrystallization from water, the m.p. was 88–89°.

Anal. Calcd. for $C_6H_{14}N_4O_3$: C, 37.88; H, 7.42; N, 29.46. Found: C, 38.16; H, 7.93; N, 29.34.

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