[CONTRIBUTION OF THE DEPARTMENT OF RESEARCH AND DEVELOPMENT, U. S. NAVAL POWDER FACTORY]

The Cyclization of 1-(Hydroxyalkyl)guanidines and Nitroguanidines to Cyclicpseudoureas[1]

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Received December 23, 1955

1-(β-Hydroxyethyl)-, 1-(β-hydroxypropyl)-, and 1-(γ-hydroxypropyl)-guanidines and nitroguanidines have been found to undergo cyclization, upon heating, to the corresponding cyclicpseudourea. In the former case ammonia is split off; in the latter instance cyclization is accomplished with the loss of nitrous oxide and water. The cyclicpseudoureas, characterized as their picrate, nitrate, and salicylate salts, were found to be identical with those prepared by the method of Gabriel.[2]

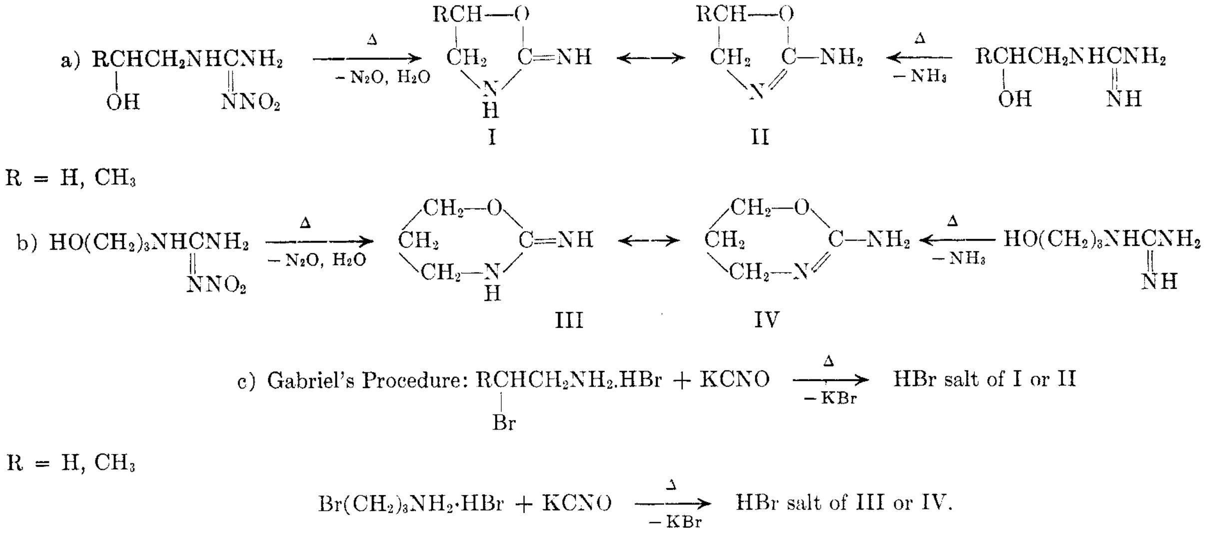
The cyclization of 1-(β-substituted ethyl)- and 1-(β-nitroxypropyl)-3-nitroguanidine to salts of 1-nitro-2-amino-Δ^2-1,3-diazacyclopentene and 1-nitro-2-amino-5-methyl-Δ^2-1,3-diazacyclopentene nitrate respectively, has been extensively investigated in recent years.[3]

Fishbein and Gallaghan[4] reported the cyclization of 1-(γ-nitroxypropyl)-3-nitroguanidine to the corresponding six-membered ring, 1-nitro-2-amino-Δ^2 1,3-diazacyclohexene nitrate.

In the present paper, the cyclizations of 1-(β-hydroxyethyl)-, 1-(β-hydroxypropyl)-, and 1-(γ-hydroxypropyl)-derivatives of guanidine and nitroguanidine to the corresponding cyclicpseudoureas, *viz.*, ethylene, propylene and trimethylene pseudoureas, are described. These cyclicpseudoureas proved to be identical with those prepared by the procedure of Gabriel.[2]

The picrate, nitrate, and salicylate salts of the cyclicpseudoureas[5] are summarized in Table I. Mixture melting points of the cyclicpseudouronium salts prepared *via* the cyclization reactions with those prepared by the procedure of Gabriel were undepressed. In addition, the infrared spectra of ethylenepseudouronium nitrate prepared by the three different methods were identical.

Earlier work by the authors[4] has shown the failure of 1-(ω-nitroxybutyl)-3-nitroguanidine to cyclize to the corresponding seven-membered ring (1-nitro-2-amino-Δ^2-1,3-diazacycloheptene). Analogous reactions with 1-(ω-hydroxybutyl)-3-nitroguanidine failed to yield the corresponding seven-membered cyclicpseudourea. The failure of cyclization in both instances could be attributed to the relatively greater strain present in a seven-membered ring.



$$\underset{\displaystyle Br}{RCHCH_2NH_2}.HBr + KCNO \xrightarrow[-KBr]{\Delta} \text{HBr salt of I or II}$$

$$Br(CH_2)_3NH_2\cdot HBr + KCNO \xrightarrow[-KBr]{\Delta} \text{HBr salt of III or IV.}$$

EXPERIMENTAL

PREPARATION OF INTERMEDIATES

Ethylene-, propylene-, and trimethylene-pseudoureas. Method of Gabriel: The cyclicpseudoureas were prepared according to the procedure of Gabriel[2] utilizing potassium cyanate and the corresponding bromoalkylamine hydrobromide salt.

1-(Hydroxyalkyl)-3-nitroguanidines: 1-(β-Hydroxyethyl)-,

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(2) Gabriel, *Ber.*, **22**, 1150, 2984 (1889); *Ber.*, **23**, 87 (1890); *Ber.*, **50**, 826 (1917).

(3) (a) McKay and Milks, *J. Am. Chem. Soc.*, **72**, 1616 (1950); (b) McKay, *Chem. Revs.*, **51**, 340 (1952); (c) Hall, McKay and Wright, *J. Am. Chem. Soc.*, **73**, 2205 (1951); (d) McKay, *J. Org. Chem.*, **16**, 1846 (1951).

(4) Fishbein and Gallaghan, *J. Am. Chem. Soc.*, **76**, 3217 (1954).

(5) The tautomers (I) and (II) are named as 2-oxazolines and tautomers (III) and (IV) as Δ^2-dihydro-1,3-oxazines.

TABLE I

CYCLICPSEUDOURONIUM SALTS

Pseudouronium salts	M.p., °C.	Formula	Carbon Calc'd	Carbon Found	Analyses[a] Hydrogen Calc'd	Hydrogen Found	Nitrogen Calc'd	Nitrogen Found
Picrate								
Ethylene	190–191	$C_9H_9N_5O_8$	34.29	34.59	2.86	3.13	22.25	21.95
Propylene	187–189	$C_{10}H_{11}N_5O_8$	36.47	36.51	3.34	3.63	21.21	21.59
Trimethylene	188–200	$C_{10}H_{11}N_5O_8$	36.47	36.42	3.34	3.32	21.21	21.67
Nitrate								
Ethylene	124–126	$C_3H_7N_3O_4$	24.16	24.09	4.72	4.63	28.19	27.98
Propylene	153–156	$C_4H_9N_3O_4$	29.44	29.37	5.52	5.55	25.76	25.49
Trimethylene	155–157	$C_4H_9N_3O_4$	29.44	29.24	5.52	5.25	25.76	25.66
Salicylate[b]								
Ethylene	139–141	$C_{10}H_{12}N_2O_4$	53.57	53.72	5.35	5.15	12.50	12.17
Propylene	140–141	$C_{11}H_{14}N_2O_4$	55.48	55.00	5.92	5.69	11.76	12.00
Trimethylene	139–140	$C_{11}H_{14}N_2O_4$	55.48	55.10	5.92	5.62	11.76	12.10

[a] Analysis of derivatives produced by cyclization of 1-(hydroxyalkyl)-3-nitroguanidine. [b] Salicylate salts were prepared by the procedure of Basterfield and Powell, *Can. J. Research*, **1**, 261 (1929).

1-(β-hydroxypropyl)-, 1-(γ-hydroxypropyl)-, and 1-(ω-hydroxybutyl)-3-nitroguanidine were prepared according to the method of Fishbein and Gallaghan[6] utilizing 2-methyl-1 (or 3)-nitro-2-thiopseudourea (S-methyl-N-nitro-thiopseudourea) and the respective alkanolamine.

CYCLIZATIONS

Ethylenepseudourea from 1-(β-hydroxyethyl)-3-nitroguanidine: 1-(β-Hydroxyethyl)-3-nitroguanidine (5.0 g., 0.034 mole) was heated in a flask connected consecutively to two weighed U-tubes (one packed with Ascarite and the other with magnesium perchlorate), a cold trap cooled with liquid nitrogen, and a vacuum pump. The temperature of the flask was maintained at 55° for 1 hour and then at 100° for 55 minutes. A viscous residue (2.8 g., 85%) was recovered in the flask. A portion of this basic oil was converted to the picrate salt, (m.p. 190–191° (see Table) by addition of aqueous picric acid. The drying tube contained 0.45 g. of water, and no measurable amount of carbon dioxide. Infrared analysis of the cold trap products indicated a predominance of nitrous oxide.

Ethylenepseudourea from 1-(β-hydroxyethyl)-3-guanidine: 1-(β-Hydroxyethyl)-3-guanidine (3.0 g., 0.03 mole), obtained by treating the corresponding guanidinium sulfate salt with an equivalent amount of barium hydroxide, was heated at 80° until the evolution of ammonia ceased (6 hours). The yield of oily residue was 2.1 g. (85%). The product was converted to the ethylenepseudouronium picrate salt melting at 190–191° after two recrystallizations from ethanol.

Ethylenepseudouronium nitrate from the picrate salt: To 3.0 g. (0.01 mole) of ethylenepseudouronium picrate was added 14 ml. of 20% nitric acid with stirring. The mixture was stirred at room temperature for 10 minutes, then allowed to stand for 15 minutes. The solid picric acid formed (2.1 g.) was removed by suction. The filtrate was extracted three times with 50-ml. portions of anhydrous ether until a colorless solution was obtained. The bottom layer (aqueous nitric acid) was evaporated on a steam-bath to dryness; 100 ml. of absolute ethanol-anhydrous ether (1:1) was added to the residue, yielding 1.3 g. of product (87.2%). The melting point of 120–122° was raised to 125–126° after one crystallization from ethanol-water (1:1).

Propylenepseudourea from 1-(β-hydroxypropyl)-3-nitroguanidine: 1-(β-Hydroxypropyl)-3-nitroguanidine (3.3 g., 0.02 mole) was refluxed with 75 ml. of *n*-butanol for 16 hours. The product (1.1 g., 56%) was isolated by distilling the solvent under a vacuum. The picrate salt melted at 187–189° after one crystallization from ethanol.

Propylenepseudourea from 1-(β-hydroxypropyl)-3-guanidine: The cyclization of 1-(β-hydroxypropyl)-3-guanidine was performed in an analogous manner to that described for the cyclization of 1-(β-hydroxyethyl)guanidine. An oily residue was recovered in yield of 45%; it was not analyzed, but was converted at once to the picrate salt, m.p. 188–190°.

Trimethylenepseudourea from 1-(γ-hydroxypropyl)-3-nitroguanidine: The cyclization was accomplished by refluxing 1-(γ-hydroxypropyl)-3-nitroguanidine (1.1 g., 0.0067 mole) with 45 ml. of *n*-butanol for 20 hours. The product, which was isolated by distilling the *n*-butanol under a vacuum, weighed 0.5 g. (70%). The picrate salt melted at 198–200° after one recrystallization from ethanol.

Trimethylenepseudourea from 1-(γ-hydroxypropyl)-3-guanidine: The procedure followed was identical to that described above for the cyclization of 1-(β-hydroxyethyl)-3-guanidine. A 90% yield of oily residue was obtained which was converted to the picrate salt, m.p. 199–200°.

Attempted cyclization of 1-(ω-hydroxybutyl)-3-nitroguanidine: All attempts to form a seven-membered cyclicpseudourea by analogous procedures were unsuccessful. The starting material was recovered unchanged.

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(6) Fishbein and Gallaghan, *J. Am. Chem. Soc.*, **76**, 1877 (1954).