SYNTHESES OF SUBSTITUTED GUANIDINES[1]

PAUL E. GAGNON, JEAN L. BOIVIN,[2] AND JOSEPH ZAUHAR[3]

ABSTRACT

Ethyl-, propyl-, and benzyl-guanidine nitrates were prepared from amine nitrates and calcium cyanamide or dicyandiamide. Carboxyalkylguanidines were made by condensing the corresponding amino acids with guanidine carbonate in aqueous medium. All the guanidine nitrates, except the benzyl derivative, were converted into the corresponding nitroguanidines by treatment with concentrated sulphuric acid. Esters and metal salts of 1-(α-carboxyalkyl)-2-nitroguanidines were also prepared.

INTRODUCTION

Guanidine nitrate is prepared by heating ammonium nitrate with calcium cyanamide in aqueous solution (1, 2) or in the presence of urea (3), or with dicyandiamide (4, 5). Carboxyalkylguanidines have been previously made from amino acids and cyanamide in aqueous solution (6, 7) and by the action of haloaliphatic acids on guanidine (8). A more recent method for the preparation of carboxyalkylguanidines involves the use of methylisothiourea in an ammoniacal medium (9, 10). Carboxymethylguanidine was synthesized by the direct condensation of guanidine carbonate and glycine in aqueous medium (11).

RESULTS

Alkylguanidines

The methods of preparation of guanidine nitrate were extended to the syntheses of substituted guanidine nitrates in view of their nitration into the corresponding 1-substituted 2-nitroguanidines. The reaction of aqueous solutions of amine nitrates with calcium cyanamide gave the corresponding guanidine nitrates in yields ranging from 35 to 41%, as recorded in Table I.

TABLE I

ALKYLGUANIDINE NITRATES AND 1-ALKYL-2-NITROGUANIDINES

	Alkyl substituent		
	Ethyl	Propyl	Benzyl
	Nitrates		
M.p. °C	108–109	93–94	164–165
Yield, %: 1	41	38	35
2	86	67	51
3	41	41	40
4	88	67	45
	Nitroguanidines		
M.p. °C	147–148	99–100	—
Yield, %	30	57	—

1. Calcium cyanamide and amine nitrates in aqueous solution.
2. Dry mixtures of calcium cyanamide and amine nitrates.
3. Dry mixtures of calcium cyanamide, amine nitrates, and urea.
4. Dicyandiamide and amine nitrates.

[1]*Manuscript received June 2, 1958.*
Contribution from the Department of Chemistry, Laval University, Quebec, Que., with financial assistance from the Defence Research Board of Canada in 1955–56. This paper constitutes part of a thesis submitted to the Graduate School, Laval University, in partial fulfillment of the requirements for the degree of Doctor of Science.
[2]*Defence Research Board, C.A.R.D.E., Valcartier, Que.*
[3]*Graduate Student, holder of National Research Council of Canada Studentships in 1956–58.*

$$3RNH_2.HNO_3 + CaCN_2 \longrightarrow RHNC(=NH)NH_2.HNO_3 + 2RNH_2 + Ca(NO_3)_2$$

R = C_2H_5, C_3H_7, and $C_6H_5CH_2$

By heating the reactants in the solid state, instead of in aqueous solution, an increased yield was observed, namely, 86% for ethylguanidine nitrate, 67% for propylguanidine nitrate, and 51% for benzylguanidine nitrate. By adding urea to the dry reagents to depress the melting point of the mixtures, yields of about 40% were obtained. This behavior was unexpected because Wright obtained increased yields of guanidine nitrate from cyanamide (3) by using urea.

Ethyl-, propyl-, and benzyl-guanidine nitrates were also successfully synthesized by heating the amine nitrates with dicyandiamide. The over-all reaction can be expressed by the equation:

$$NCNHC(=NH)NH_2 + 2RNH_2.HNO_3 \longrightarrow 2RHNC(=NH)NH_2.HNO_3.$$

The latter method of preparation of ethyl-, propyl-, and benzyl-guanidine nitrates from amine nitrates and dicyandiamide gave yields up to 88% in some cases. In the preparation of guanidine hydrochloride from dicyandiamide and ammonium chloride (5), a biguanide hydrochloride is formed and ammonolyzed. A similar mechanism applies to the preparation of substituted guanidine nitrates from amine nitrates and dicyandiamide in which a substituted biguanide nitrate is the intermediate.

Carboxyalkylguanidines

Carboxyethylguanidine and carboxypropylguanidine were prepared from the corresponding amino acids and guanidine carbonate.

$$2H_2NCHRCOOH + [H_2NC(=NH)NH_2]_2.2H_2CO_3 \longrightarrow 2H_2NC(=NH)NHRCOOH + 2NH_3 + CO_2 + H_2O.$$

Cyclization of carboxyalkylguanidines can also take place (7, 12) in aqueous medium to form anhydro compounds.

$$2C_6H_5CH_2CH(NH_2)COOH + [H_2NC(=NH)NH_2]_2.H_2CO_3 \longrightarrow 2C_5H_5CH_2CH(HN)C(=NH)NHC(=O) + CO_2 + 3H_2O + 2NH_3$$

Carboxyalkylguanidines when treated with a slight excess of dilute nitric acid gave the corresponding carboxyalkylguanidine nitrates. The nitrates slowly decomposed on heating in aqueous solution at temperatures above 100° C. Anhydrocarboxyphenylethylguanidine nitrate was obtained in the same manner.

Substituted Nitroguanidines

Ethyl- and propyl-nitroguanidines were obtained by a method similar to the production of nitroguanidine from guanidine nitrate using sulphuric acid (13, 14) but benzylnitroguanidine could not be obtained by this method, which confirms the results of other investigators (15). The results are shown in Table I.

Nitroguanidines substituted with an acid function were obtained by treating the corresponding carboxyalkylguanidine nitrates with concentrated sulphuric acid. The results are shown in Table II. To obtain 1-(α-carboxypropyl)-2-nitroguanidine, which was soluble in dilute sulphuric acid, the sulphate ions were eliminated and the compound was isolated as the dihydrate of the barium salt.

$$HNO_3.H_2NC(=NH)NHRCOOH \longrightarrow H_2NC(=NNO_2)NHCHRCOOH + H_2O$$

1-(α-Carboxymethyl)-2-nitroguanidine was also identified by its lead salt; it was prepared by treating an aqueous solution of the nitroguanidine with lead oxide.

The esters of 1-(α-carboxyalkyl)-2-nitroguanidines were prepared by esterification with absolute ethanol in the presence of dry hydrogen chloride. The results are shown in Table II.

TABLE II

CARBOXYALKYLGUANIDINES, NITRATES, AND NITRO DERIVATIVES

Compound	Formula	M.p., °C	Yield, %	Calculated C	Calculated H	Calculated N	Found C	Found H	Found N
Carboxyalkylguanidines									
Ethyl	$C_4H_9O_2N_3$	225–226	31	36.64	6.87	32.06	36.9	7.0	32.1
Anhydro β-phenylethyl	$C_{10}H_{11}O_1N_3$	234–235	28	63.44	5.82	22.22	63.2	5.6	21.8
Propyl	$C_5H_{11}O_2N_3$	234–235	29	41.45	7.59	28.95	41.6	7.6	29.2
Carboxyalkylguanidine nitrates									
Methyl	$C_3H_8O_5N_4$	180–181	52	(Calc. for HNO_3: 34.42. Found for HNO_3: 34.8)					
Ethyl	$C_4H_{10}O_5N_4$	149–150	51	[Ramsay, H. Ber. **41**, 4385 (1908).]					
Anhydro β-phenylethyl	$C_{10}H_{12}O_4N_4$	134–135	65	47.61	4.76	22.22	47.8	4.8	22.4
Propyl	$C_5H_{12}O_5N_4$	146–147	58	28.81	5.77	26.92	28.8	5.7	27.0
1-(α-Carboxyalkyl)-2-nitroguanidines									
1-(α-Carboxymethyl)	$C_3H_6O_4N_4$	166–167	60	22.42	3.70	34.60	22.4	3.6	34.7
1-(α-Carboxyethyl)	$C_4H_8O_4N_4$	155–157	55	27.22	4.54	31.80	27.1	4.6	31.6
Ethyl esters of 1-(α-carboxyalkyl)-2-nitroguanidines									
1-(α-Carbethoxymethyl)	$C_{15}H_{10}O_4N_4$	149–150	29	31.58	5.26	29.47	31.8	5.3	29.2
1-(α-Carbethoxyethyl)	$C_6H_{12}O_4N_4$	175–176	32	35.30	5.88	27.40	35.2	6.0	27.6

DISCUSSION

The present study has shown that the methods of syntheses of guanidine nitrate apply as well to the substituted guanidine nitrates with the difference that lower yields resulted with the use of amine nitrates. Guanidines substituted by a carboxylic group are monobasic in character and form the lead and barium salts. The solubilities of the nitro derivatives were greater than that of nitroguanidine itself or of the alkyl nitroguanidines. The esterification of 1-(α-carboxyalkyl)-2-nitroguanidines in the presence of hydrogen chloride did not yield the corresponding hydrochloride salts, which supports the view that acids combine with the free amino group to form salts.

EXPERIMENTAL PART

Alkylguanidine Nitrates

1. Syntheses from calcium cyanamide and amine nitrates in aqueous solution.—The amine nitrate (0.29 mole) was dissolved in water (100 ml) and the resulting solution was evaporated until it reached a boiling point of 100° C. Calcium cyanamide (55%, 0.05 mole) was added slowly while stirring and at that temperature the reaction occurred with frothing while some free amine was evolved. The guanidine nitrate salt crystallized from the solution on cooling. The results are shown in Table I.

2. Syntheses from amine nitrates and calcium cyanamide in the dry state.—Dry solid mixtures of amine nitrates (0.21 mole) and calcium cyanamide were heated at 110° C for 1 hour (55%, 0.05 mole), during which time free amine was liberated. The fluid

reaction products were diluted with hot water (40 ml) and the mixtures filtered while hot. On cooling, the guanidine nitrate salts crystallized and were separated by filtration. The experimental results obtained are given in Table I.

3. Syntheses from calcium cyanamide, amine nitrates, and urea.—Calcium cyanamide (55%, 0.05 mole), amine nitrates (0.21 mole), and urea (0.13 mole) were heated at 90° C for 1 hour, during which time some free amine was evolved. Hot distilled water (40 ml) was added and the mixtures were filtered while hot. The guanidine nitrate salts crystallized from the cooled filtrate and were isolated by filtration. The results are listed in Table I.

4. Syntheses from amine nitrates and dicyandiamide.—Mixtures of dicyandiamide (0.22 mole) and amine nitrates (0.44 mole) were heated in an oil bath. Fusion began at 70° C, was complete at 130–133° C, and the temperature was gradually raised to 170° C and kept there for 3 hours. Upon cooling, the crude guanidine nitrate salts crystallized from the solution and were recrystallized from water. The results obtained are given in Table I.

Alkylnitroguanidines

The substituted guanidine nitrate (0.46 mole) was slowly added to sulphuric acid (98%, 2.1 mole) and cooled to 5° C. After all the solid was added, the mixture was stirred at that temperature for 3 hours, and afterwards poured over cracked ice. A small amount of the product precipitated from the solution. The compound was separated by filtration, the filtrate neutralized with barium hydroxide, and the barium sulphate formed was filtered through charcoal. The resulting filtrate was evaporated under vacuum and a second crop of crystals was obtained. The compound was then recrystallized from ethanol. The results obtained are shown in Table I.

Carboxyalkylguanidines

An aqueous solution of guanidine carbonate (0.06 mole) was added to an aqueous solution of amino acid (0.12 mole) and the reaction vessel was heated on a sand bath for 24 hours, during which time ammonia was liberated. Upon cooling, the resulting liquid was filtered, and the filtrate evaporated under reduced pressure until a yellow viscous product remained. A mixture of absolute alcohol (50 ml) and acetone (50 ml) was added, with stirring, and the resulting solution was stored in a cool place for several hours. The carboxyalkylguanidine soon separated from the solution and after filtration and washing with ethanol, the crude product was recrystallized from water. The results are given in Table II.

Carboxyalkylguanidine Nitrates

Dilute nitric acid (0.06 mole) was added slowly to an aqueous solution of the carboxyalkylguanidine (0.05 mole) while it was being cooled and stirred, and the resulting solution was evaporated to dryness under vacuum. The product was recrystallized from water. The results are listed in Table II.

1-(α-Carboxyalkyl)-2-nitroguanidines

Concentrated sulphuric acid (98%, 0.06 mole) was cooled to 5° C and the carboxyalkylguanidine nitrate (0.01 mole) was added in small portions with continuous stirring and cooling whenever necessary. After all the nitrate salt was added, the mixture was further stirred for 15 minutes at the above temperature and then allowed to reach 20° C, where the mass was stirred for 3 hours. The sulphuric acid solution was then

poured over cracked ice, which effected precipitation, after 15 minutes, of the crude product, which separated by filtration and was recrystallized from water. The compounds prepared are shown in Table II.

Salts of 1-(α-Carboxyalkyl)-2-nitroguanidines

1-(α-Carboxymethyl)-2-nitroguanidine was also identified by its dihydrate lead salt obtained by treating 1-(α-carboxymethyl)-2-nitroguanidine with an excess of lead oxide (litharge). The compound had no melting point but decomposed above 300° C. Calc. for $C_6H_{14}O_{10}N_6Pb$: Pb, 38.50%. Found: 38.8%. 1-(α-Carboxypropyl)-2-nitroguanidine, which was soluble in sulphuric acid, was isolated by precipitating the sulphate with barium hydroxide, filtering off the barium sulphate, and evaporating the resulting filtrate under reduced pressure. The dihydrate barium salt of 1-(α-carboxypropyl)-2-nitroguanidine crystallized from the concentrated solution in colorless needles: m.p. 183–184° C. Yield, 27%. Calc. for $C_{10}H_{22}O_{10}N_8Ba$: C, 21.76; H, 4.00; N, 20.31%. Found: C, 22.2; H, 4.2; N, 19.9%.

Esters of 1-(α-Carboxyalkyl)-2-nitroguanidines

Pulverized samples of 1-(α-carboxyalkyl)-2-nitroguanidines (0.06 mole) were added to absolute ethanol (70 ml), and dry hydrogen chloride was added until the solution was saturated. The mixtures were then refluxed for 1 hour, filtered, and left to stand in a cool place. The crude esters which separated from the filtrates were recrystallized from ethanol. The compounds obtained were slightly soluble in water. The results are given in Table II.

REFERENCES

1. BURNS, R. and GAY, P. F. Brit. Patent No. 507,498 (1939).
2. DHOMMEE, R. Compt. rend. **134**, 1313 (1902).
3. WRIGHT, G. F. U.S. Patent No. 2,431,301 (1947).
4. WERNER, F. A. and BELL, J. J. Chem. Soc. **117**, 1133 (1920); **121**, 1790 (1922).
5. BLAIR, J. S. and BRAHAM, J. M. J. Am. Chem. Soc. **44**, 2342 (1922).
6. STRECKER, A. Compt. rend. **52**, 1212 (1861).
7. DUVILLIER, E. Compt. rend. **91**, 171 (1880).
8. RAMSAY, H. Ber. **41**, 4385 (1908).
9. MOURQUE, M. Bull. soc. chim. France, 181 (1948).
10. BENGERLSDORF, I. S. J. Am. Chem. Soc. **75**, 3138 (1953).
11. NENCKI, M. and SEIBER, N. J. prakt. Chem. **17**, 478 (1878).
12. ABDERHALDEN, E. and SICKEL, H. Z. physiol. Chem. **173**, 51 (1928).
13. THIELE, J. Ann. **270**, 1 (1892).
14. EWAN, T. and YOUNG, J. H. J. Chem. Ind. **40**, 109 (1921).
15. DAVIS, T. L. and ELDERFIELD, R. C. J. Am. Chem. Soc. **55**, 731, 735 (1933).