DL-3-Methyl-4-phenyl-2,5-oxazolidinedione.—DL-2-Phenylsarcosine (34 g.) was treated with phosgene in 1.5 l. of dioxane for 4 hr. at 40–45°. The product was crystallized from ethyl acetate, yielding 32 g. (81%), m.p. 65–75°. Recrystallized material had m.p. 73–75°, λ_{max}^{KBr} 5.42 and 5.65 μ.

Anal. Calcd. for $C_{10}H_9NO_2$: C, 62.85; H, 4.74; N, 7.33; equiv. wt., 191.19. Found: C, 62.97; H, 4.70; N, 7.35; equiv. wt., 191.3.

N-Hydroxyalkyl-2,4-diamino-*sym*-triazines from Guanamines

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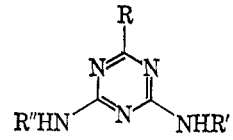
Received April 24, 1964

In connection with another investigation, a convenient method was needed for preparation of N-hydroxylalkyl-substituted guanamines[1] in large quantities and in good yield. Although such compounds would in principle be available from the guanamines and alkylene oxides, work in these laboratories showed that these reactants lead to different products. The use of amines and of chlorotriazines,[2] on the other hand, seemed unsuitable because of unavailability of the required chlorotriazines.

Examination of the literature revealed several instances of the so-called transamination or exchange amination of heterocyclic nitrogen compounds. One of the earliest examples of this reaction is recorded in a patent[3] in which melamine is converted to N-alkyl-substituted melamines by heating it with primary or secondary amines in the presence of hydrogen chloride. Similarly, melamine, ammeline, and ammelide have been converted to the corresponding N-aryl-substituted compounds by heating them with arylamine hydrochlorides.[4] Exchange amination was also successfully applied to pyrimidines and purines.[5]

In all of these transaminations amines having no other functional groups were used. The method, however, because of its simplicity and potential adaptability to a larger scale, was admirably suited to our purposes, and in this paper we describe our work which resulted in the introduction of an N-hydroxyalkyl chain into guanamines by use of amino alcohols.

When benzoguanamine hydrochloride was heated at reflux (165–175°) with an excess of ethanolamine a vigorous evolution of ammonia occurred which stopped after about 14 hr. The same result could be obtained when 1 mole of ethanolamine hydrochloride was used for one mole of benzoquanamine and the reaction mixture was heated in an excess of ethanolamine. However, because the guanamine hydrochlorides could be prepared and handled more easily than the amino alcohol hydrochlorides, the former were used nearly exclusively in the later work. Removal of the excess of ethanolamine and pouring the product into water or dilution of the crude product with water gave a good yield of a crystalline compound which analyzed correctly for N,N′-bis(2-hydroxyethyl)benzoguanamine (I) dihydrate. Attempts to obtain crystalline anhydrous I were without success, although various solvents and methods of drying were used. Oily solids or semisolids were obtained which in the presence of water reverted to the crystalline dihydrate. However, crystalline hydrochloride and picrate salts and a dibenzoyl derivative could be prepared.



I, R = Ph; R′ = R″ = CH_2CH_2OH
II, R = Ph; R′ = H; R″ = CH_2CH_2OH
III, R = CH_3; R′ = R″ = CH_2CH_2OH
IV, R = $PhCH_2$; R′ = R″ = CH_2CH_2OH
V, R = $NHCH_2CH_2OH$; R′ = R″ = CH_2CH_2OH
VI, R = $NHCH_2CH_2OH$; R′ = R″ = H
VII, R = Ph; R′ = R″ = $CH_2CH_2CH_2OH$

The hydrogen chloride to guanamine base ratio strongly affected the product composition. At a 1:1 ratio I was obtained in high yield, while at a 1:20 ratio the major product was N-(2-hydroxyethyl)benzoguanamine (II). At still lower ratios the reaction was impractically slow. Compound II was obtained in anhydrous crystalline form and was characterized as the hydrochloride salt. Further reaction of II with ethanolamine hydrochloride in boiling ethanolamine gave I.

After obtaining compounds I and II, it was of interest to determine the scope of the reaction with respect to other amino-*sym*-triazines. Thus, under the conditions used with benzoguanamine, ethanolamine and aceto- and phenylacetoguanamine gave compounds III and IV, respectively, but they were difficult to purify. The reaction of ethanolamine and melamine hydrochloride, however, was more complicated. Although the reaction went smoothly, the product was a water-soluble sirup which resisted all attempts at crystallization. From the analysis of the crude product, however, it did appear that it was mostly N,N′,N″-tris(2-hydroxyethyl)melamine[6] (V), probably contaminated to some degree by mono and bis compounds as well as by melamine itself. Under certain conditions (see Experimental) the crystalline N-(2-hydroxyethyl)melamine (VI) and N,N′,N″-tris(2-hydroxyethyl)melamine hydrochloride could be obtained in low yields from the reaction of melamine and ethanolamine.

The reaction with ethanolamine was extended to 3-amino-1-propanol. Thus, benzoguanamine hydrochloride and this amino alcohol gave under the usual conditions a good yield of N,N′-bis(3-hydroxypropyl)-benzoguanamine (VII). Although compound VII was a sirup which could not be obtained crystalline, it was adequately characterized by preparation of crystalline hydrochloride.

The attempts to extend the reaction of hydroxyalkylation of guanamines to secondary amines were fruitless. Thus, under the conditions used with primary

(1) Guanamine is a trivial name for 6-alkyl or -aryl-2,4-diamino-*sym*-triazine.

(2) J. T. Thurston, *et al.*, *J. Am. Chem. Soc.*, **73**, 2981 (1951), and papers following this.

(3) W. Zerweck and K. Keller, U. S. Patent 2,228,161 (Jan. 7, 1941).

(4) I. Honda, and Y. Oshima, *Yuki Gosei Kagaku Kyokai Shi*, **20**, 756 (1962); *Chem. Abstr.*, **58**, 5687 (1963).

(5) C. W. Whitehead and J. J. Traverso, *J. Am. Chem. Soc.*, **82**, 3971 (1960).

(6) N,N′,N″-Tris(2-hydroxyethyl)melamine has been prepared previously; see ref. 2.

alkanolamines there was very little evolution of ammonia, and work-up of the reaction mixture gave only the starting compounds. For example, from the reaction of benzoguanamine hydrochloride with N-methylethanolamine and with diethanolamine, benzoguanamine was the only solid product isolated.

Experimental

Microanalyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

Starting Materials.—The guanamines as well as melamine were commercial materials. The hydrochlorides were prepared by adding the solid triazines to a 1:2 mixture of concentrated acid and water (200 ml. of concentrated acid per mole of the triazine), warming on the steam bath for 0.5 hr., cooling, filtering the solid, washing with cold water, and drying *in vacuo*.

Benzoguanamine hydrochloride[7] melted at 244–248°.

Anal. Calcd. for $C_9H_{10}N_5Cl$: Cl, 15.9. Found: Cl, 16.3.

Acetoguanamine hydrochloride did not melt below 300°.

Anal. Calcd. for $C_4H_8N_5Cl$: Cl, 22.6. Found: Cl, 21.1.

Phenylacetoguanamine hydrochloride melted at 207–209°.

Anal. Calcd. for $C_{10}H_{12}N_5Cl$: Cl, 14.9. Found: Cl, 15.6.

Melamine hydrochloride did not melt below 300°.

Anal. Calcd. for $C_3H_7N_6Cl$: N, 51.7; Cl, 21.9. Found: N, 50.3; Cl, 22.0.

Ethanolamine hydrochloride,[8] m.p. 85–87°, was prepared by saturation of the methanol solution of the base with hydrogen, chloride, cooling, adding ether, and filtering.

2,4-Bis(2-hydroxyethylamino)-6-phenyl-*s*-triazine (I) Dihydrate.—A mixture of 895 g. (4.00 mole) of benzoguanamine hydrochloride and 733 g. (12.0 mole) of ethanolamine was stirred and heated to reflux (166°). Heating was continued for 14 hr. during which ammonia was evolved vigorously and the temperature was rising so that at the end of 14 hr. it was 175°. The mixture was allowed to cool and was diluted with 1.5 l. of water whereupon a solid crystallized. Filtration of the solid (m.p. 67–77°) and two recrystallizations from water containing a small amount of methanol gave 857 g. (68.9%) of the guanamine I dihydrate, m.p. 77–80°. The analytical sample was prepared by several recrystallizations from a mixture of ethanol and water and by drying in air, m.p. 79–80°, λ_{max}^{EtOH} 224 (ε 32,500) and 241 mμ (28,000) [reported[9] for benzoguanamine, λ_{max}^{EtOH} 249 mμ (ε 25,000)].

Anal. Calcd. for $C_{13}H_{21}N_5O_4$: C, 50.15; H, 6.80; N, 22.50; H_2O, 11.58. Found: C, 50.40; H, 6.35; N, 22.66; H_2O, 11.05 (K. Fischer reagent).

Drying the analytical sample *in vacuo* at room temperature gave material melting at 70–120° which on crystallization from a mixture of water and ethanol reverted to the dihydrate, m.p. 79–80°. Drying the dihydrate at 50° at 0.1 mm. and recrystallizing from various solvents only gave oily products. Direct recrystallization of the dihydrate from 1,2-dimethoxyethane and ethanol also gave materials of wide melting range.

The **hydrochloride** was prepared from I dihydrate and aqueous hydrochloric acid and was obtained, after recrystallization from a mixture of methanol and acetone, as a white solid, m.p. 200–201° (dec.).

Anal. Calcd. for $C_{13}H_{18}ClN_5O_2$: C, 50.08; H, 5.82; Cl, 11.37; N, 22.47. Found: C, 50.11; H, 5.65; Cl, 11.87; N, 22.19.

The **picrate** was recrystallized from methanol, m.p. 163–165°.

Anal. Calcd. for $C_{19}H_{20}N_8O_9$: C, 45.24; H, 4.00; N, 22.22. Found: C, 44.82; H, 3.99; N, 21.83.

The **dibenzoyl** derivative was prepared from benzoyl chloride and I hydrate in pyridine solution. Recrystallization of the product from a mixture of benzene and ether gave the analytical sample as a white solid, m.p. 124.5–125.5°.

Anal. Calcd. for $C_{27}H_{25}N_5O_4$: C, 67.07; H, 5.21; N, 14.49. Found: C, 67.10; H, 5.23; N, 14.40.

2-Amino-4-(2-hydroxyethylamino)-6-phenyl-*s*-triazine (II).—A mixture of 36.5 g. (0.19 mole) of benzoguanamine, 2.23 g. (0.010 mole) of benzoguanamine hydrochloride, and 37.0 g. (0.60 mole) of ethanolamine was stirred and heated at 175–180° for 14 hr. during which time ammonia was evolved vigorously. After cooling, the caked reaction mixture was diluted with aqueous ethanol and reheated to give a clear solution. Cooling and filtration gave 38.5 g. of a solid, m.p. 153–165°, and gradual evaporation of the filtrate gave three fractions (4.0 g., m.p. 115–190°; 7.0 g., m.p. 70–130°; 3.0 g. of a semisolid). The melting points of these fractions could not be improved by numerous recrystallizations. The main fraction was recrystallized from a mixture of ethanol and water to obtain 31.0 g. (60%) of the benzoguanamine II, m.p. 174–176°. An additional recrystallization from aqueous ethanol gave the analytical sample as a white solid, m.p. 176–178°, λ_{max}^{EtOH} 219 (ε 24,600) and 242 mμ (22,900).

Anal. Calcd. for $C_{11}H_{13}N_5O$: C, 57.13; H, 5.66; N, 30.29. Found: C, 57.24; H, 5.78; N, 30.12.

The **hydrochloride** was prepared as in the case of I hydrate and was recrystallized from a mixture of methanol and acetone, m.p. 201–202°.

Anal. Calcd. for $C_{11}H_{14}ClN_5O$: C, 49.35; H, 5.27; Cl, 13.25; N, 26.16. Found: C, 49.36; H, 5.22; Cl, 13.30; N, 26.13.

Reaction of II and Ethanolamine Hydrochloride.—A mixture of 25.9 g. (0.10 mole) of the benzoguanamine II, 9.8 g. (0.10 mole) of ethanolamine hydrochloride, and 12.4 g. (0.20 mole) of ethanolamine was heated at 175° for 13 hr. The brown-colored product was poured into water; the resulting mixture was filtered to give 10.0 g. of a solid, m.p. 60–71°. Several recrystallizations from a mixture of water and methanol gave 5.5 g. of the disubstituted guanamine I dihydrate, m.p. 75–77°, which did not depress the melting point of the authentic compound.

Reaction of Melamine Hydrochloride and Ethanolamine.—A mixture of 642 g. (4.00 mole) of melamine hydrochloride and 977 g. (16.0 mole) of ethanolamine was heated at 175° for 14 hr. during which time there was a vigorous evolution of ammonia. The mixture was cooled, diluted with 500 ml. of water, and treated with a cold solution of 160 g. (4.00 mole) of sodium hydroxide in 200 ml. of water. Water was removed by distillation *in vacuo*, followed by azeotropic distillation with benzene, to obtain 1304 g. of a semisolid. This was dissolved in hot methanol and the resulting mixture was filtered. The filtrate was evaporated *in vacuo* to obtain 911 g. (88.5%) of a dark viscous oil.

Anal. Calcd. for $C_9H_{18}N_6O_3$: N, 32.6. Found: N, 27.7.

N-(2-Hydroxyethyl)melamine (VI) was obtained as follows. A mixture of 34.0 g. (0.27 mole) of melamine, 4.88 g. (0.030 mole) of melamine hydrochloride, and 61.1 g. (1.00 mole) of ethanolamine was heated at 175° for 14 hr. Most of the ethanolamine was removed *in vacuo* and the residue was recrystallized from water to obtain, in addition to a large amount of high-melting solid, apparently melamine, 5.5 g. of a white solid, m.p. 220–228°. Several recrystallizations from water gave the analytical sample of VI as a white solid, m.p. 219–223°.

Anal. Calcd. for $C_5H_{10}N_6O$: C, 35.29; H, 5.92; N, 49.39. Found: C, 35.24; H, 5.92; N, 48.82.

N,N′,N″-Tris(2-hydroxymethyl)melamine Hydrochloride.—A mixture of 40.2 g. (0.25 mole) of melamine hydrochloride and 77.4 g. (1.25 mole) of ethanolamine was refluxed (175°) for 12 hr., then evaporated *in vacuo*. The residue, 81.3 g., was dissolved in water and passed through a column of ion-exchange resin Amberlite XE-89 (Rohm and Haas Co.) to obtain, on evaporation of the eluate, 51.0 g. of a yellow-colored sirup. Recrystallization from butanol containing a small amount of methanol gave 9.0 g. of a solid, m.p. 100–133°, and a large amount of a semisolid. Two additional recrystallizations of the solid from the same solvent gave the analytical sample, m.p. 132–134°.

Anal. Calcd. for $C_9H_{19}ClN_6O_3$: C, 36.67; H, 6.50; Cl, 12.03; N, 28.25. Found: C, 36.78; H, 6.56; Cl, 11.89; N, 27.49.

2,4-Bis(3-hydroxypropylamino)-6-phenyl-*sym*-triazine (VII).—A mixture of 44.7 g. (0.20 mole) of benzoguanamine hydrochloride and 45.0 g. (0.60 mole) of 3-amino-1-propanol was heated at 174° for 14 hr. The mixture was then cooled and poured into 200 ml. of water; the resulting semisolid was dissolved by addition of methanol and heating. The mixture did not crystallize (methanol, ethyl acetate, petroleum ether and ethyl acetate, benzene and methanol, ether and methanol, butanol, acetone, and xylene failed to give crystalline material). The solvent was evaporated and the semisolid was washed several times with water. Drying *in vacuo* at 50° gave 39.9 g. (66%) of the sirupy VII.

Anal. Calcd. for $C_{15}H_{21}N_5O_2$: N, 23.1. Found: N, 23.0.

(7) F. Nachod and E. Steck, *J. Am. Chem. Soc.*, **70**, 2818 (1948).

(8) J. H. Jones, *J. Assoc. Offic. Agr. Chemists*, **27**, 467 (1944); *Chem. Abstr.*, **38**, 6275 (1944).

(9) C. G. Overberger and S. L. Shapiro, *J. Am. Chem. Soc.*, **76**, 1855 (1954).

The **hydrochloride** was prepared from aqueous hydrochloric acid and was recrystallized from a mixture of methanol and acetone, m.p. 152.5–153.5°.

Anal. Calcd. for $C_{15}H_{22}ClN_5O_2$: C, 53.01; H, 6.53; Cl, 10.43; N, 20.61. Found: C, 53.75; H, 6.20; Cl, 10.34; N, 20.21.

4-Methyl-1,2,5,6-tetrahydrobenzo[*f*]quinolin-3(4H)-one. The Cyclization Product Derived from Methyl 3-[(3,4-Dihydro-2-naphthyl)methylamino]propionate

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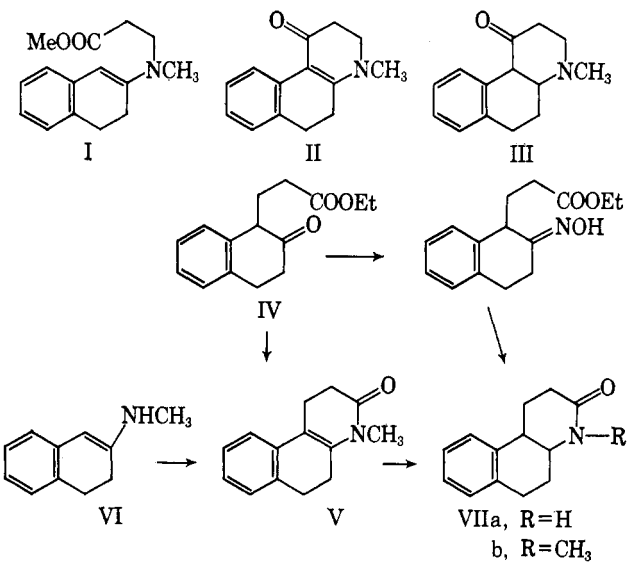
Received March 24, 1964

Several years ago it was reported[2] that the condensation of 2-tetralone and methyl β-methylaminopropionate gives the enamine I which, on heating in ethylene glycol, undergoes an intramolecular acylation reaction[3] to give 4-methyl-3,4,5,6-tetrahydrobenzo[*f*]quinolin-1(2H)-one (II). The structure II was based on the infrared and ultraviolet spectra of the product, the reductive removal of the carbonyl group of the vinylogous amide with lithium aluminum hydride[4] yielding the corresponding enamine, and further chemical transformations consistent with the enamine structure.

More recently, we had occasion to reduce the cyclization product derived from I by catalytic means and obtained a product which has a carbonyl absorption maximum in the infrared at 1620 cm.$^{-1}$ (chloroform). This carbonyl absorption is incompatible with structure III unless such a structure is capable of invoking a nitrogen–carbonyl interaction.[5,6] That this is not the case is indicated by the failure of the hydrogenation product to form a methiodide, picrate, or other stable salts,[7] thus demonstrating the feebly basic character of the product. In a review of this work, Dr. S. Archer suggested that the enamine cyclization product might, in fact, have structure V.[8] Such a structure would explain all of the accumulated physical and chemical data. This paper describes a detailed study which establishes the cyclization product as V and clarifies the step at which the chemical rearrangement occurs.[9] (See Scheme I.)

SCHEME I



Our first indication that the cyclization product has structure V came when we found that a mild treatment of 1-(β-carbethoxyethyl)-2-tetralone (IV) with methylamine gave the same product obtained by heating I in ethylene glycol. The possibility of IV undergoing a reverse Michael reaction and the fragments recombining in a different manner was considered unlikely. However, to further verify that no rearrangement occurred in the conversion of IV to V, the keto ester was converted to the corresponding oxime which in turn was catalytically reduced in the presence of Adams catalyst. The reduction product underwent a spontaneous ring closure to one isomer of the lactam VIIa. N-Methylation of the lactam gave the same product as that derived by catalytic reduction of the cyclization product V. The mutual identity of the products is based on mixture melting point behavior and identical infrared spectra, and thin layer and gas chromatographic results.

In an attempt to determine at what stage rearrangement occurred in the original preparation of V from I, 2-tetralone was treated with methylamine in boiling toluene to generate the intermediate VI and/or the corresponding imino form. The crude mixture was then treated with methyl acrylate to give a complex mixture containing 30–40% of the cyclization product V. When 2-tetralone is treated with methyl β-methylaminopropionate under essentially the same conditions,[2] no cyclization product V could be detected in the crude product I by infrared analysis. Thus, the integrity of structure I appears to be sound.

(1) To whom inquiries should be sent at Department of Chemistry, The Upjohn Company, Kalamazoo, Mich.

(2) N. A. Nelson, J. E. Ladbury, and R. S. P. Hsi, *J. Am. Chem. Soc.*, **80**, 6633 (1958).

(3) The acylation of enamines with reactive carbonyl reagents is well known; see J. Szmuszkovicz, "Advances in Organic Chemistry," Vol. 4, R. A. Raphael, E. C. Taylor, and H. Wynberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p. 1; G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963). While esters are normally unreactive toward enamines, there is no reason to believe that they will not react under more strenuous conditions.

(4) See, for example, N. G. Gaylord, *Experientia*, **10**, 166 (1954); C. F. Koelsch and D. L. Ostercamp, *J. Org. Chem.*, **26**, 1104 (1961). The lithium aluminum hydride reduction of vinylogous amides may also lead to amino alcohols or amino ketones: see J. M. Osbond, *J. Chem. Soc.*, 4711 (1961); K. T. Potts and D. R. Liljegren, *J. Org. Chem.*, **28**, 3202 (1963); G. de Stevens and A. Halamadais, *ibid.*, **26**, 1614 (1961).

(5) See M. R. Bell and S. Archer, *J. Am. Chem. Soc.*, **82**, 151 (1960), and references contained therein for examples of nitrogen–carbonyl interactions.

(6) One isomer of structure III has been prepared by the authors (Osaka group) and it has normal spectral properties.

(7) On treatment with concentrated perchloric acid or anhydrous hydrogen chloride, an ethereal solution of the hydrogenation product gave the corresponding salts as precipitates. However, the salts thus formed are extensively hydrolyzed by water and the free amides can be extracted easily with ether from a dilute aqueous acidic solution.

(8) We are indebted to Dr. Archer for his comments regarding this problem.

(9) This paper has prompted work on the revision of some previously published structures [Z. Horii, C. Iwata, and Y. Tamura, *Chem. Pharm. Bull.* (Tokyo), **10**, 940 (1962)], the results of which will be published in the near future.