The Reactions of Alkyl Acrylates and Acrylonitrile with Guanidine in Dimethylformamide[1,2]

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The reaction of acrylic esters or acrylonitrile with guanidine has not previously been reported. We have found that, on addition of different alkyl acrylates to a DMF solution of free guanidine, a basic compound (I′) separated in almost quantitative yield. No C=C double bond was detected by infrared analysis or by the reaction of potassium permanganate or bromine with I′. Hydrolysis of the compound with water gave the guanidinium salt II′, and further alkaline hydrolysis led to 3,3′-iminodipropionic acid.

A different compound (III) was obtained in a yield as high as 75% by adding acrylonitrile to a DMF solution of free guanidine. This product was a strongly basic, hygroscopic crystalline substance which absorbed carbon dioxide when allowed to stand in air; the ir spectrum showed neither CN group nor C=C double-bond absorption. These properties suggested the cyclic structure III. Treatment of III with 12 *N* hydrochloric acid gave the hydrochloride IV′. The base IV was hydrolyzed in water to the amino acid I which, when treated with barium hydroxide, gave the monobarium salt of iminodipropionic acid. The structures are consistent with the interconversion shown in Chart I.

For example, I′ could be converted into IV′ by treating it with 6 *N* hydrochloric acid and, by adding IV′ to a methanolic solution of guanidine, the reaction could be reversed, converting IV′ into I′. When the hydrochloride of I′ was refluxed in ethanol, IV was obtained with the liberation of 1 mol of guanidine hydrochloride; IV could also be reversely converted into I′ in the same manner as described above. Also when I′ was boiled with an equimolar amount of hydrochloric acid, it was converted into I; I was converted into II′ by boiling it with an aqueous solution of guanidine. Also II was converted into I with dehydration by boiling its aqueous solution.

Experimental Section

2-Amino-3-(3-propionic acid guanidine)-6-oxy-3,4,5,6-tetrahydropyrimidine (I′).—To a solution of 29.5 g (0.5 mol) of free guanidine in 250 ml of dimethylformamide was added 45 ml (0.5 mol) of methyl acrylate dropwise with agitation at 25–30° over 1 hr period. After 2 hr the precipitate was collected, washed successively with methanol and ether, and dried, yielding 52.0 g (92%) of I′: mp 247° dec (recrystallization from methanol gave white crystals, mp 251° dec); ultraviolet, $\lambda_{max}^{H_2O}$ 226 mμ (ε 15500), 262 (7160).

Anal. Calcd for $C_8H_{14}N_6O_2$: C, 42.47; H, 6.24; N, 37.14. Found: C, 42.51; H, 6.20; N, 37.70.

N,N-(3,3′-Dipropionic acid)guanidine (II) and Its Guanidonium Salt (II′).—A solution of 10 g of I′ in 200 ml of water was boiled for 2 hr and the resulting solution was evaporated to dryness at reduced pressure. The syrup formed was crystallized by the addition of 50 ml of isopropanol. The crystals were collected, washed with ether, and dried, yielding 10.7 g of II′ (93%), mp 167–170° (recrystallization from methanol–2-propanol mixture raised the melting point to 176°).

Anal. Calcd for $C_5H_{18}N_6O_4$: C, 36.64; H, 6.92; N, 32.05. Found: C, 36.93; H, 6.95; N, 32.30.

Removal of guanidine from II′ with an equimolar amount of 6 *N* hydrochloric acid gave II in a yield of 89%, mp 175–176° (picrate, mp 178–180°). No ultraviolet absorption appeared.

Anal. Calcd for $C_7H_{13}N_3O_4$: C, 41.38; H, 6.45; N, 20.68. Found: C, 41.90; H, 6.70; N, 20.50.

3,4,6,7,8,9-Hexahydro-2H-pyrimido[1,2-*a*]pyrimidine-2,8-diimine (III).—To a solution of 5.9 g (0.1 mol) of free guanidine in 20 ml of dimethylformamide was added 14 ml (0.2 mol) of acrylonitrile dropwise with agitation at 5–10° over a 0.5 hr period. After 3 hr the precipitate was collected, washed with 2-propanol, and dried in a vacuum desiccater provided with sodium hydroxide, yielding 12.7 g (76%) of III, mp 140–143°. It was easily converted into carbonate by absorption of carbon dioxide from air. The carbonate decomposed at 209–210°.

Anal. Calcd for $C_7H_{11}N_5 \cdot {}^1/_2H_2CO_3$: C, 45.69; H, 6.13; N, 35.49. Found: C, 45.58; H, 6.53; N, 35.47.

3,4,6,7,8,9-Hexahydro-2H-pyrimido[1,2-*a*]pyrimidine-2,8-dione (IV) and Its Hydrochloride (IV′).—III (1.7 g, 0.01 mol) was dissolved in 5 ml of 12 *N* hydrochloric acid and allowed to stand overnight. The solution was diluted with ethanol to obtain white crystals of IV′, yielding 1.1 g (54%), mp 290–292° dec (recrystallization from aqueous ethanol raised the decomposition point to 299–303°).

Anal. Calcd for $C_7H_9N_3O_2HCl$: C, 41.29; H, 4.95; N, 20.64; Cl, 17.41. Found: 41.30; H, 5.14; N, 20.47; Cl, 17.42.

Removal of hydrochloric acid from IV′ with an equimolar amount of sodium methoxide in methanol gave IV in a yield of 95%: mp 229° after recrystallization; ultraviolet, $\lambda_{max}^{H_2O}$ 226 mμ (ε 26100), 262 (6210); picrate, dp 234–238°.

Anal. Calcd for $C_7H_9N_3O_2$: C, 50.29; H, 5.43; N, 25.14. Found: C, 50.12; H, 5.46; N, 24.96.

2-Amino-3-(3-prioponic acid)-6-oxy-3,4,5,6-tetrahydropyrimidine Monohydrate (I).—A solution of 1.7 g of IV in 30 ml of water was boiled for 3 hr and then evaporated to dryness, yielding 1.8 g (90%) of I: mp 18–3186° (recrystallization from water raised the melting point to 190°); ultraviolet, $\lambda_{max}^{H_2O}$ 220 mμ (ε 6770); picrate, dp 204–205°.

Anal. Calcd for $C_7H_{11}N_3O_3 \cdot H_2O$: C, 41.38; H, 6.45; N, 20.68. Found: C, 41.47; H, 6.74; N, 20.64.

Hydrolyses of II and I with Barium Hydroxide Formation of Monoammonium Salt of 3,3′-Iminodipropionic Acid. A.—To a solution of 4.0 g (0.02 mol) of II in 200 ml of water was added 19.0 g (0.06 mol) of barium hydroxide octahydrate and the solution was boiled for 24 hr. During the reaction, the ammonia evolved was caught by a trap containing hydrochloric acid and determined by titration to be 95% of the theoretical. After the precipitate ($BaCO_3$) was filtered off and washed with hot water, the combined filtrate was saturated with carbon dioxide and the resulting barium carbonate precipitate was again filtered off and washed with hot water. The second combined filtrate was then evaporated at reduced pressure to obtain a syrup which could be crystallized by treating it with ethanol, yielding 4.3 g (91%) of monobarium salt of 3,3′-iminodipropionic acid. An aqueous solution of the crude monobarium salt was treated with an equivalent amount of ammonium sulfate, the precipitate ($BaSO_4$) was filtered off, and the filtrate was again evaporated at reduced pressure to a 50% concentration and diluted with methanol to obtain 2.5 g (70%) of monoammonium salt of 3,3′-iminodipropionic acid which melted at 172–176° after recrystallization from aqueous methanol.

Anal. Calcd for $C_6H_{14}N_2O_4$: C, 40.44; H, 7.92; N, 15.72. Found: C, 40.19; H, 7.85; N, 15.64.

A mixture melting point with an authentic sample[3] showed no depression.

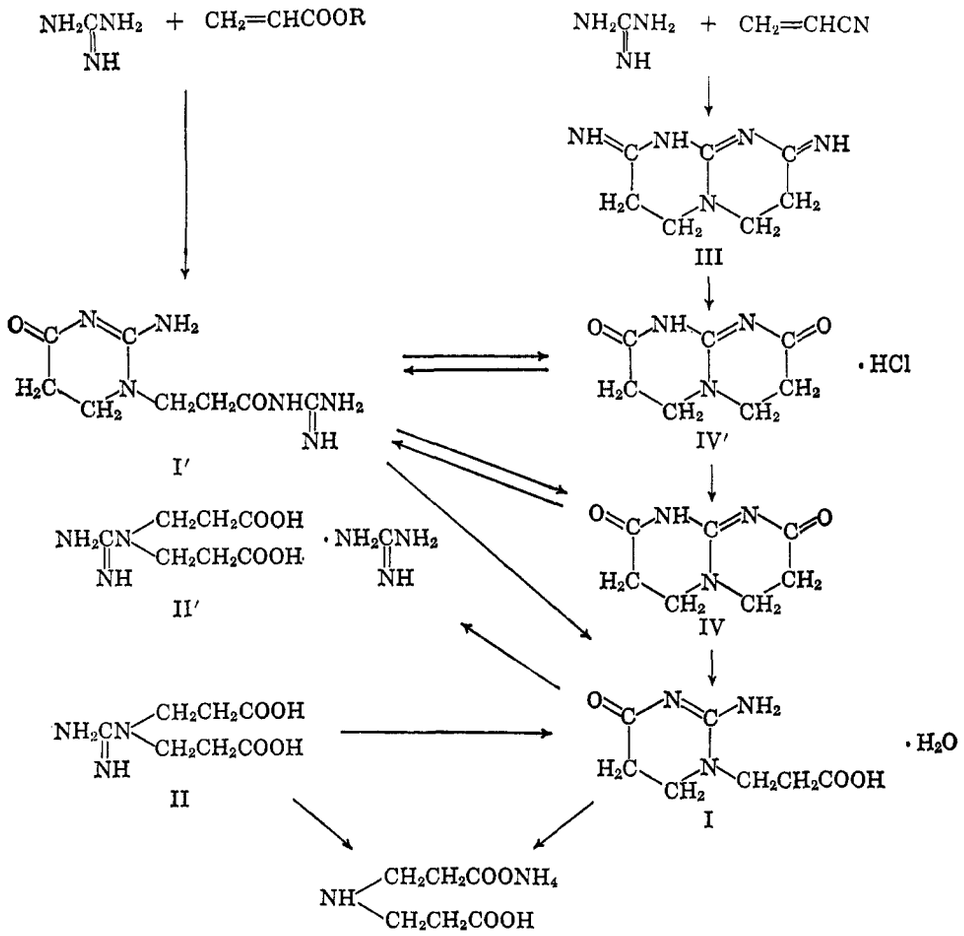
B.—To a solution of 3.5 g of I in 200 ml of water was added 19.0 g of barium hydroxide octahydrate and the mixture was boiled for 27 hr. After the reaction, the resulting mixture was

(1) Cyanamide Derivatives. LXXV. Previous paper of this series: LXXIV, K. Odo, *et al.*, *Yuki Gosei Kegaku Kyokai Shi*, **25**, 1048 (1967).

(2) Presented at the 20th Annual Meeting of the Chemical Society of Japan, Tokyo, March 31–April 4, 1967.

(3) Prepared by the procedure of J. H. Ford, *J. Amer. Chem. Soc.*, **67**, 876 (1945).

CHART I



worked up the same as in the above experiment to obtain 2.2 g (71%) of monoammonium salt of 3,3′-iminodipropionic acid.

Conversion of I′ into IV′.—A solution of 11.3 g (0.05 mol) of I′ dissolved in 17 ml of 6 *N* hydrochloric acid (0.1 mol) was allowed to stand for 3 hr to obtain 8.3 g (82%) of IV′ which melted at 299–303° dec after purification.

Conversion of the Hydrochloride of I′ into IV.—A solution of 4.0 g of the hydrochloride of I′ (prepared in ethanol) in 200 ml of ethanol was refluxed for 3 hr and concentrated at reduced pressure to obtain 1.6 g (63%) of IV which melted at 229° after recrystallization.

Conversion of IV and IV′ into I′.—To a solution of 0.6 g (0.01 mol) of free guanidine in 50 ml of methanol was added 1.7 g (0.01 mol) of IV [or 1.0 g (0.005 mol) of IV′] dissolved in 200 ml of methanol and the solution was allowed to stand for 3 hr at room temperature to obtain 2.1 g (93%) [or 0.9 g (80%)] of I′ which melted at 250° dec after purification.

Conversion of I′ into I.—A solution of 11.3 g (0.05 mol) of I′ dissolved in 100 ml of water containing 8.5 ml of 6 *N* hydrochloric acid (0.05 mol) was boiled for 3 hr and concentrated at reduced pressure to obtain 6.9 g (68%) of I which melted at 190° after recrystallization.

Conversion of I into II′.—To a solution of 0.6 g (0.01 mol) of free guanidine in 10 ml of water was added 2.0 g (0.01 mol) of I and the solution was boiled for 1 hr. The resulting solution was worked up the same as in the preparation of II′ from I′: yield 2.4 g (92%); mp 176° after recrystallization.

Conversion of II into I.—A solution of 2.0 g of II in 50 ml of water was boiled for 3 hr and evaporated to dryness to obtain 1.8 g (90%) of I which melted at 190° after recrystallization.

Registry No.—I, 16675-75-5; I picrate, 16675-76-6; I′, 16675-77-7; II, 16675-32-4; II picrate, 16675-78-8; II′, 16675-79-9; III, 16675-80-2; IV, 16675-81-3; IV picrate, 16675-82-4; IV′, 16675-31-3; monoammonium salt of 3,3′-iminodipropionic acid, 16675-33-5; acrylonitrile, 107-13-1; guanidine, 113-00-8; dimethylformamide, 68-12-2.

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Cyclizations of Substituted N-(Purin-6-yl)-2-aminoethanol System[1]

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The current interest [2–6] in the internal cyclization of suitably substituted 6-aminopurine derivatives (Ia, Ib,

(1) Presented in part at the 2nd Annual Great Lakes Regional Meeting of the American Chemical Society, Milwaukee, Wis., June 1968.

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