[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF DELAWARE]

Condensation of α-Carbethoxy-γ-butyrolactones with Amidines and Guanidine

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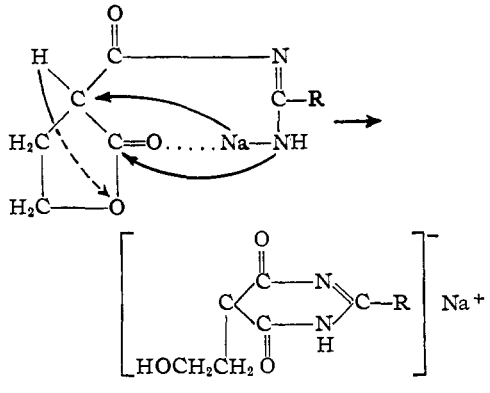
It has been previously reported[1] that an α-alkyl-α-carbethoxy-γ-butyrolactone does not condense with an amidine to yield a tetrahydropyrimidine derivative but a product whose formation could be explained by the hydrolysis of an intermediate in which the lactone ring had remained intact.

By rapid and intimate mixing of the alkaline reaction product with a freezing mixture of ice and hydrochloric acid there is obtained the intermediate lactone amidine containing a small amount of the inner salt that is formed through the initial splitting of the lactone ring by aqueous alkali. A better procedure for the isolation of the pure lactone amidine involves the prior removal of the sodium as sodium chloride under anhydrous conditions.

The unalkylated lactone ester, however, readily condenses with amidines to yield the tetrahydropyrimidine derivatives. The greater reactivity of the unalkylated lactone ester is probably due to the residual active hydrogen atom. The formation of the sodium derivative of the intermediate that is made possible by the tautomerism of the amidine residue in the intermediate can then lead by the 1 → 3 shift mechanism to a more stable sodium derivative involving ring closure.



Due to the fact that an α-carbethoxy-γ-butyrolactone may be decarboxethylated[1] and that amidines may lose ammonia to form nitriles, some study was made to find the optimum conditions for the formation of the tetrahydropyrimidine derivative. In general, the best yields were obtained by heating the mixture of reactants at 45° (Table I). In the case of the 2-ethyl- and 2-phenyl- derivatives it was also shown that the yield was raised from 55.4 and 53.6 per cent. to 66.3 and 65.5 per cent., respectively, by the very slow addition of an alcohol solution of the lactone ester to the mixture as it was stirred at 45°. This is confirmation that one of the difficulties lies in the decarboxethylation of the ester.

(1) Skinner, Stokes and Spiller, THIS JOURNAL, 69, 3083 (1947).

TABLE I

2-ALKYL-5-β-HYDROXYETHYL-4,6-DIKETO-3,4,5,6-TETRAHYDROPYRIMIDINES

R–	Yield, %	M. p., °C.[a]	Nitrogen, % Calcd.	Found
H–	67.9	247–248[b]	17.94	17.88
CH_3–	68.7	275–276	16.46	16.48
C_2H_5–	55.4[c]	267–268	15.21	15.12
n-C_4H_9–	75.9	259–260	13.20	13.10
iso-C_5H_{11}–	66.4	244	12.38	12.37
C_6H_5–	53.6[d]	248–249	12.06	12.10

[a] Except where noted all melted with decomposition. [b] Decomposed without melting. [c] Yield 66.3% by slow addition of lactone ester. [d] Yield 65.5% by slow addition of lactone ester.

Attempts to isolate the intermediate disodium derivative from the condensation of an α-alkyl-α-carbethoxy-γ-butyrolactone with guanidine gave evidence that such a compound is formed, but a set of conditions whereby a constant weight could be obtained for the sample to be analyzed was not found. The 5-alkyl-5-β-hydroxyethyl-2-iminobarbituric acids can be isolated in fair yields (Table II).

TABLE II

5-ALKYL-5-β-HYDROXYETHYL-2-IMINOBARBITURIC ACIDS

Alkyl	M. p., °C., dec.	Yield, %	Nitrogen, % Calcd.	Found
C_2H_5–	248–249		21.10	20.82
n-C_3H_7–	252	88.7	19.70	19.64
n-C_4H_9–	263–264	51.4	18.49	18.43
n-C_5H_{11}–	242	86.5	17.42	17.51
iso-C_5H_{11}–	247		17.42	17.27

Experimental

Lactone Amidine.—A solution of sodium ethoxide was prepared from 0.243 mole of sodium and 100 cc. of alcohol. To the cooled (22°) and mechanically stirred solution were added 0.0866 mole of benzamidine hydrochloride and 0.0693 mole of α-isoamyl-α-carbethoxy-γ-butyrolactone. The bath was then heated rapidly to 45°. Heating was continued at this temperature for twenty-four hours and it was then heated three hours at 70°. The mixture was cooled in an ice-bath, and with good mixing, made just acid with 15.7 cc. of hydrochloric acid. The sodium chloride (13.3 g.) was filtered and washed with absolute alcohol. After concentration of the filtrate by distillation of the alcohol *in vacuo* from a bath, not heated above 50°, 5.4 g. of the lactone–amidine separated in the form of white crystals, m. p. 117–118°.

A mixture of the lactone–amidine and the inner salt resulting from the hydrolysis was prepared by the following procedure. To a stirred solution of sodium ethoxide prepared from 7.6 g. of sodium and 100 cc. of absolute alcohol there was added at 0° 18.8 g. of benzamidine hydrochloride and then 22.8 g. of α-isoamyl-α-carbethoxy-γ-butyrolactone. The temperature was allowed to rise to 23° in one hour. The mixture was heated two hours at 40° and

then two hours at 47°. Stirring was stopped and the mixture was heated twelve hours longer at 47°. Most of the alcohol (82 cc.) was removed by distillation under diminished pressure at this bath temperature. The residue was quickly and vigorously shaken with a mixture of 19 cc. of hydrochloric acid (1.19) and 80 g. of finely crushed ice. The cold mixture was filtered with suction and washed with ice-cold water and petroleum ether. The mixture weighed 22.24 g., m. p. 112–122° (dec.). Upon standing an additional 1.33 g. of impure inner salt separated from the filtrate, m. p. 132–134° (dec.).

Lowering the initial and final reaction temperatures to −10 and 23°, respectively, for a total reaction period of thirty-four hours decreased the yield to 6.85 g. Increasing the heating period to twenty-four hours at 45–48° followed by heating three hours at 70° decreased the yield to 7.34 g. When the temperature of the reaction mixture was allowed to rise to 89° in two hours and the mixture was then heated six hours longer at 89° the yield was decreased to 7.12 g.

To separate the lactone–amidine from the inner salt, 1 g. of the product was placed in a beaker cooled in a salt–ice mixture. To this was added with good stirring a precooled mixture of 2 cc. of hydrochloric acid (1.19) and 10 cc. of water. To the cold filtrate from a very small amount of undissolved material concentrated aqua ammonia was added from a buret until the maximum precipitation was obtained. Constant mixing and a temperature below 0° should be maintained. It is preferable to operate at −5°. The crystals were filtered with suction and washed with ice-cold water and a mixture of ether and ligroin, m. p. 114–115°. By dissolving this product in alcohol at 35° and crystallizing by cooling in a freezing mixture the melting point rose to 117°.

Anal. Calcd. for $C_{17}H_{22}O_3N_2$: N, 9.27. Found: N, 9.16.

The inner salt was best obtained by crystallizing from alcohol the product from those preparations in which no precautions were taken against hydrolysis of the lactone–amidine, m. p. 140–141 (dec.). The salt previously prepared under more vigorous conditions decomposed at 147°.

Anal. Calcd. for $C_{17}H_{24}N_2O_4$: C, 63.73; H, 7.55; N, 8.75. Found: C, 63.46; H, 7.49; N, 8.73.

The inner salt, by heating at its decomposition point, gave one equivalent of ammonia, benzonitrile and nonvolatilized material which behaved as a lactone but was not further identified.

2-Alkyl-5-β-hydroxyethyl-4,6-diketo-3,4,5,6-tetrahydropyrimidines.—In a typical experiment valeramidine hydrochloride (0.1250 mole) and α-carbethoxy-γ-butyrolactone (0.100 mole) were rapidly and thoroughly mixed at room temperature with a solution of sodium ethoxide prepared from 6.9 g. of sodium and 100 cc. of absolute alcohol. The mixture was brought rapidly to 45° and maintained at that temperature for twenty-five hours. After standing at room temperature for twelve hours the mixture was treated with 20 cc. of acetic acid mixed with 125 g. of ice and water. The yield was 16.1 g. (75.9%). Recrystallization from hot 50% alcohol gave nearly white crystals, m. p. 259–260° (dec.).

To isolate all of the compounds containing smaller radicals it was found necessary to concentrate the mother liquor. The pure products possess a faint yellow color.

5-Alkyl-β-hydroxyethyl-2-iminobarbituric Acids.—In a typical preparation, 18.0 g. of guanidine carbonate was added to a solution of sodium ethoxide prepared from 8.0 g. of sodium and 125 cc. of absolute alcohol. After stirring for ten minutes the mixture was cooled to 5° and 11.4 g. of α-*n*-amyl-α-carbethoxy-γ-butyrolactone was added dropwise with stirring. At the end of three hours at this temperature the mixture was allowed to stand twenty-four hours at room temperature. One liter of cold water was added and the filtered solution was made neutral to litmus with acetic acid. The crude acid was recrystallized by dissolving in a boiling mixture of 800 cc. of ethyl alcohol and 650 cc. of water; yield 9.86 g., m. p. 242° (dec.).

In attempts to isolate the intermediate complex salt the alcohol solution of guanidine and sodium ethoxide, after removal of the sodium carbonate, was mixed with 11.4 g. of α-isoamyl-α-carbethoxy-γ-butyrolactone at 19°. The temperature rose to 28° in two minutes and a precipitate began to form in twelve minutes. After twenty-four hours at room temperature the salt was filtered and washed with alcohol. The yield was 5.66 g. The filtrate gave 5.58 g. of crude 5-isoamyl-5-β-hydroxyethyl-2-iminobarbituric acid, m. p. 240–244°. After recrystallization from a mixture of 550 cc. of ethanol and 350 cc. of water the yield was 5.3 g., m. p. 248–249°. The salt continued to decompose under various conditions in attempts to get a constant weight for the sample. A sample after heating intermittently at 76° for fifty-six hours gave the following analysis: Calcd. for $C_{13}H_{23}O_4N_3Na_2$: Na, 13.89; N, 12.69. Found: Na, 16.29; N, 7.45. The substance had therefore suffered extensive decomposition.

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Summary

1. A comparison is made between the action of alkylated and unalkylated α-carbethoxy-γ-butyrolacetones on amidines. The intermediate lactone–amidine has been isolated.

2. The alkylated lactone esters have been condensed with guanidine.

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