[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OREGON STATE COLLEGE]

Pyrimidines VII: Cyclization of Ethyl Oxalate and Ethyl α-Oxalylpropionate with Urea and Certain of Its Analogs[1]

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Procedures have been established for the preparation of parabanic acid and thioparabanic acid by the condensation reactions of diethyl oxalate. Guanidine does not cyclize with diethyl oxalate but yields a linear product when reacted under the conditions cited above.

Guanidine and ethyl α-oxalylpropionate have been condensed in an alkaline medium to yield a noncyclic guanide. The guanide has been cyclized to an imidazoline derivative and that in turn enlarged to the pyrimidine-4-carboxylic acid.

The structure of the imidazoline derivative, and consequently the isomeric pyrimidine as well as the guanide, has been determined on the basis of: (1) the ease of hydrogenation of the olefinic unsaturation in ethyl-5(4)-[2-amino-4(5)-oxo-Δ^2-imidazolineidene]-2-propionate, (2) analytical data, and (3) the ultraviolet spectral data.

The condensation of urea with ethyl α-oxalylpropionate, in an acidic medium, yielded ethyl hydantoidene-2-propionate which was hydrolyzed to the acid and then rearranged to the isomeric pyrimidine-4-carboxylic acid. The analytical data and ultraviolet curves are given.

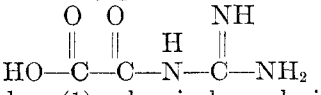
Condensations of the ester with formamidine and acetamidine were attempted yielding oils which were not characterized. Thiourea gave such a small amount of product that it did not seem feasible to continue work on that phase of the problem.

It is common knowledge that urea, thiourea, guanidine, and amidines condense readily with β-keto ester, β-diketones, cyanoacetates and malonates to yield linear condensation products or substituted pyrimidines. Numerous reactions of this type have been described in the more recent literature. Furthermore, the study of the condensation of these nitrogenous bases has also been extended to glyoxal and certain α-diketones.[2]

Condensations involving diethyl oxalate, on the other hand, have received scant attention, which is surprising in view of the importance of parabanic acid. Michael does mention its condensation with urea but reports no yields and fails to give detailed directions.[3]

In this laboratory, the reaction product of urea, diethyl oxalate, and sodium ethoxide was found to be an alcohol-insoluble salt which, when suspended in absolute alcohol and treated with sulfuric acid, yielded pure parabanic acid.

2-Thioparabanic acid was obtained by the corresponding sequence of reactions. However, the same experiment repeated with guanidine gave a linear product oxalylguanidine



as judged by (1) chemical analysis, (2) the fact that it reacted with ammonium hydroxide to yield a stable ammonium salt, and (3) it's failure to lose water when heated under 1-mm. pressure at 110° for 48 hr. Similar experiments in which acetamidine was substituted for urea gave a sodium salt which upon further treatment with sulfuric acid hydrolyzed to yield oxalic acid.

In case of intermediates in which the carbonyl is both alpha and beta to a carbethoxy such as exists in ethyl oxalacetate, there is a possibility of both ring systems being formed on cyclization. Some confusion as to the products of such cyclizations is to be noted in the earlier literature.[4] Apparently condensations under basic conditions yielded pyrimidine derivatives, while an acid medium gave a substituted hydantoin.

Recently, Mitchell, and Nyc[5] observed the cyclizations under acidic conditions which yielded hydantoins could rearrange, when treated with base, to yield pyrimidines. These workers hypothesized that the hydantoin opened to form an unsaturated hydantoic acid which was followed by ring closure to give a pyrimidine derivative. The validity of this hypothesis was confirmed by several supporting experiments.[6]

Condensations using diethyl α-oxalylpropionate were first reported by Johnson[7] who noted that the reaction product obtained from an alkaline medium using pseudomethylthiourea was either the salt or ester of 5-methyl-2-methylmercapto-6-oxopyrimidine-4-carboxylate depending on the amount of alkali employed; this compound was converted to thymine-4-carboxylic acid. Since the condensation was carried out in a basic medium it may be likely that the pyrimidine, in this instance, did not arise

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(2) H. Pauly, and H. Sauter, *Ber.*, **63B**, 2063–9 (1930). H. Biltz and Rinspel, *Ber.*, **41**, 1379 (1908). A. P. N. Franchimont and E. A. Klobbie, *Rec. trav. chim.*, **7**, 236 (1888). I. Bengelsdorf, *J. Am. Chem. Soc.*, **75**, 3138–40 (1953).

(3) A. Michael, *J. prakt. Chem.*, **35**, 458 (1887).

(4) H. L. Wheeler, *Am. Chem. J.*, **38**, 358 (1907).

(5) H. K. Mitchell and J. F. Nyc, *J. Am. Chem. Soc.*, **69**, 674 (1947).

(6) H. K. Mitchell and J. F. Nyc, *J. Am. Chem. Soc.*, **69**, 1382 (1947).

(7) T. B. Johnson, *J. Biol. Chem.*, **3**, 299 (1907).

from a rearrangement of a hydantoin but by direct cyclization.

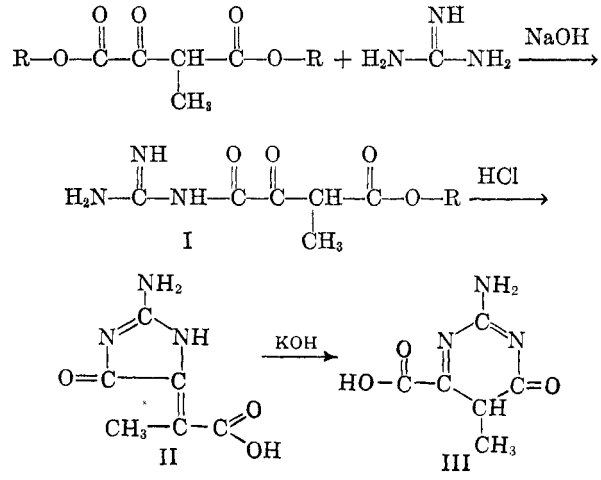
In 1949 Mentzer and Billet,[8] using Muller's[9] procedure, studied the condensation of diethyl α-oxalylpropionate with urea, which was reported to yield ethyl thymine-4-carboxylate. The saponification of the ester to the acid gave a product which was identical with the acid prepared by Johnson.[7] These workers, however, carried out their initial condensations in an acid medium in contrast to the basic conditions employed by Johnson. Although their acids were identical, the ester which Mentzer and Billet isolated was not the same as the one prepared by the esterification of thymine-4-carboxylic acid. On the basis of spectral studies and by making comparison to the 5-carbethoxymethylenehydantoin reported by Mitchell and Nyc,[6] these workers concluded that their initial condensation product was a hydantoin which, under the influence of alkali, opens and recyclizes to a pyrimidine.

The condensation of diethyl α-oxalylpropionate with amidines, guanidines or thiourea has received scant attention. Johnson[10] attempted the condensation with guanidine in aqueous media and reports a small yield which he did not characterize. In view of the interest which has since arisen in derivatives of orotic acid, as a result of the discovery of its presence in milk, it appeared worthwhile to investigate these reactions.

Initial experiments involving the condensation of amidines with diethyl α-oxalylpropionate resulted in an oily product which was not characterized. However the condensation in anhydrous methanolic medium with guanidine free base in absence of a condensing agent yielded an insoluble product which was found to be a noncyclic guanide (I) rather than the expected cyclic derivative. The treatment of this guanide with hydrochloric acid effected cyclization as judged by the solubility characteristics and melting point behavior of the product II. The ultraviolet spectrum of the compound II was similar to the hydantoin which had been described earlier by Mitchell and Nyc.[5] Furthermore, compound II was esterified and hydrogenated at low pressures with Adams catalyst. The relatively mild conditions of hydrogenation indicated olefinic unsaturation which would not have been possible if a six-membered ring had been formed in the cyclization. This observation not only confirmed the structure of the imadazoline but also fixed that of the guanide, compound I (see Fig. 1).

Since pyrimidines had been reported as cyclization products of like condensations carried out in the presence of inorganic bases, compound II was heated in the presence of aqueous potassium hydroxide. Acidification of the reaction mixture yielded an acid product, III, which had a considerably higher melting point. The ultraviolet absorption spectrum of III closely resembled that reported for orotic acid[5] (see Fig. 2). On this basis the pyrimidine structure was assigned to compound III.

Fig. 1



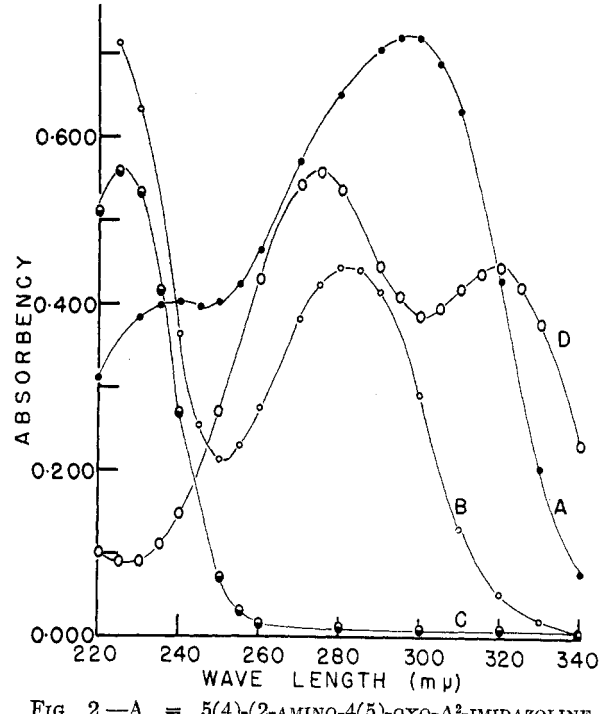


FIG. 2.—A = 5(4)-(2-AMINO-4(5)-OXO-Δ^2-IMIDAZOLINEIDENE)-2-PROPANOIC ACID (II). B = 2-AMINO-5-METHYL-6-OXO-PYRIMIDINE-4-CARBOXYLIC ACID (III). C = ETHYL-5(4)-(2-AMINO-4(5)-OXO-Δ^2-IMIDAZOLINE)-2-PROPIONATE. D = ETHYL-5(4)-(2-AMINO-4(5)-OXO-Δ-IMIDAZOLINEIDENE)-2-PROPIONATE

The condensation of urea with diethyl α-oxalylpropionate has been effected recently by Mentzer and Billet[8] who employed an acidic medium and used hydrogen chloride as the condensing agent. Their reaction product yielded an ester which was

(8) C. Mentzer and D. Billet, *Compt. rend.*, 288, 402 (1949).

(9) R. Muller, *J. prakt. Chem.*, 56, 475 (1897).

(10) T. B. Johnson, *Am. Chem. J.*, 49, 287 (1913).

saponified in basic medium and then acidified to yield a product to which they assigned the structure thymine-4-carboxylic acid.

Although these workers also identified their initial condensation product (the ester) as a hydantoin, no analytical data were given to support this conclusion.

This condensation has been confirmed in this laboratory, and the existence of a hydantoin intermediate has been established on the basis of analytical data and spectral data (see Fig. 3). Although the condensations with guanidine and urea gave similar products which rearranged to pyrimidine derivatives it is interesting to note that no noncyclic intermediate was observed in condensations involving urea. The tendency of guanidine to form noncyclic guanides under like conditions has been observed in other reactions.

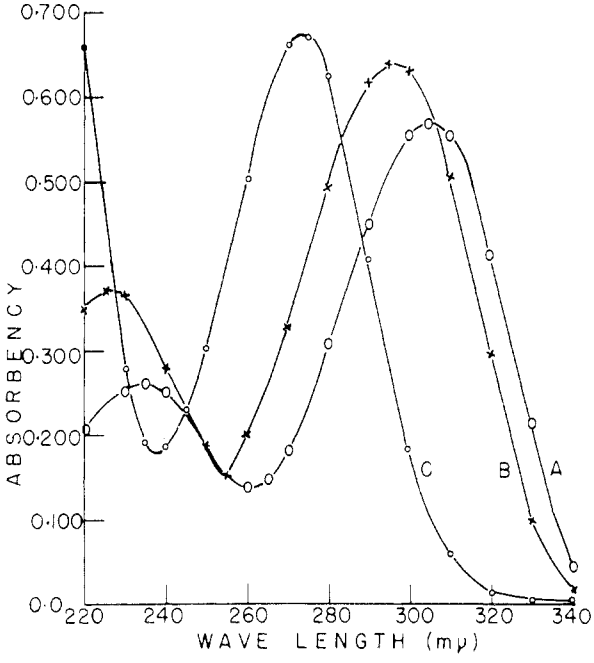


FIG. 3.—A = ETHYL (HYDANTOIDENE)-2-PROPIONATE. B = (HYDANTOIDENE)-2-PROPIONIC ACID. C = 2,6-DIOXO-5-METHYLPYRIMIDINE-4-CARBOXYLIC ACID.

Since condensations with thiourea and diethyl α-oxalylpropionate have not been run under the conditions here employed, this work was repeated with thiourea. Using sodium ethoxide as a condensing agent in ethanolic medium gave such a small yield of reaction product that it did not seem feasible to pursue the problem further. Condensations attempted using Muller's[9] procedure likewise failed to yield appreciable product.

EXPERIMENTAL

Parabanic acid. Into a 250-ml. three-necked flask equipped with reflux condenser and stirrer were placed, in this order, 100 ml. of absolute ethanol, 7.9 g. (0.34 mole) of sodium, and 10.3 g. (0.17 mole) of urea. As this stirred mixture was slowly brought to a reflux temperature 25 g. (0.17 mole) of diethyl oxalate was added dropwise; the mixture was then refluxed for 2 hr. and cooled. The product, a white sodio salt was filtered and dried. Yield, 29 g.

Anal. Calcd. for $C_3H_2N_2O_4Na_2$: Na, 25.7. Found: Na, 26.2.

The sodio salt was resuspended in absolute alcohol and 0.17 mole of concentrated sulfuric acid was added dropwise with stirring which was continued for several hours. After cooling, the insoluble sodium sulfate was removed and the alcohol then evaporated. This yielded a white crystalline product which was in turn recrystallized from a minimum quantity of hot water. Yield, 13.9 g. (72%); neut. equiv. 112; m.p. 247°.

Anal. Calcd. for $C_3H_2N_2O_3$: C, 31.59; H, 1.77. Found: C, 31.3; H, 1.93.

Thioparabanic acid. To 25 ml. of an anhydrous alcoholic solution containing 2 g. (0.09 mole) of sodium and 3.35 g. (0.044 mole) of thiourea were slowly added with stirring and heating 6.42 g. (0.044 mole) of diethyl oxalate. This mixture was then refluxed for 2 hr. and cooled. The yellow sodio salt was removed by filtration and dried.

Anal. Calcd. for $C_3H_2N_2O_3SNa_2$: Na, 32.3. Found: Na, 32.5.

The yellow salt was resuspended in absolute alcohol and 0.045 mole of concentrated sulfuric acid was added. The mixture was stirred for several hours, then cooled, and the insoluble sodium sulfate removed. The alcohol was then evaporated, yielding a yellow residue. This residue was extracted with 35 ml. of hot water, filtered, and then concentrated to 5 ml. and cooled in a refrigerator. Yield of yellow crystals, 4.1 g. (72%); m.p. 174–175° (dec.).

Anal. Calcd. for $C_3H_2N_2O_2S$: C, 27.7; H, 1.54; N, 21.61. Found: C, 27.8; H, 2.15; N, 21.9.

Oxalylguanidine. To 25 ml. of anhydrous alcohol was added 3.04 g. (0.133 mole) of sodium and then 4.2 g. (0.044 mole) of guanidine hydrochloride. The salt which precipitated was removed and 6.46 g. (0.044 mole) of diethyloxalate was added to the alcoholic filtrate. This mixture was refluxed for 2 hr., then cooled, filtered, and the insoluble product removed.

Anal. Calcd. for $C_3H_3N_3O_3Na_2$: Na, 26.3. Found: Na, 26.4.

The salt was dissolved in water and then treated with an equivalent amount of concentrated sulfuric acid. A white solid separated which was insoluble in all the common solvents. Yield, m.p. 237° (in sealed tube).

Anal. Calcd. for $C_3H_5N_3O_3$: C, 27.5; H, 3.82. Found: C, 27.6; H, 3.85.

Ammonium oxalylguanide. Solution of oxalylguanidine in concentrated ammonium hydroxide and evaporation of the excess ammonium hydroxide solution gave a quantitative yield of the ammonium salt.

Anal. Calcd. for $C_3H_6N_4O_2$: C, 27.7; H, 4.62. Found: C, 27.8; H, 4.73.

3-Carbethoxy-2-oxobutanguanide (I). Two solutions, one containing 4.75 g. (0.04 mole) of guanidine hydrochloride in 30 ml. of absolute methanol and the other 1.15 g. (0.05 mole) of sodium in 30 ml. of absolute methanol were mixed, then filtered to remove the sodium chloride. To this solution was added 10 g. (0.05 mole) of diethyl α-oxalylpropionate and the mixture was refluxed for 3 hr. Upon returning to room temperature, 3 ml. of glacial acetic acid was added and the reaction product was set aside in the refrigerator overnight. The crystalline product was removed by filtration, washed with a small amount of anhydrous methanol, and then recrystallized from hot water; yield, 5.5 g. (51%) of a white crystalline material which had no definite melting point.

Anal. Calcd. for $C_8H_{13}N_3O_4$: C, 44.64; H, 6.09. Found: C, 44.5; H, 6.08.

5(4)-(2-Amino-4(5)-oxo-Δ²-imadazolineidene)-2-propanoic acid (II). Two grams of 3-carbethoxy-2-oxobutanguanide (I) was dissolved in 60 ml. of 6*N* hydrochloric acid and the solution was refluxed for 1.5 hr. The solution was then set

in a refrigerator overnight, and the product removed by filtration, yield, 580 mg. of silky needles melting with decomposition from 200–212°. A second crop of 50 mg. was obtained upon concentrating the mother liquors and allowing them to stand in a refrigerator overnight. The crude product upon recrystallization from water yielded a white crystalline powder which melted with effervescence at 234.5–235.5°. Total yield of recrystallized product 380 mg. (24.2%).

Anal. Calcd. for $C_6H_7N_3O_3$: C, 42.61; H, 4.17. Found: C, 42.6; H, 4.40.

Ethyl 5(4)-(2-amino-4(5)-oxo-Δ^2-imidazolineidene)-2-propionate. 5(4)-(2-Amino-4(5)-oxo-Δ^2-imidazolineidene)-2-propionic acid (II) (200 mg.) was dissolved in 9.1 ml. of 50% ethanol–concentrated sulfuric acid solution and the mixture then heated at 100° for approximately 20 min. The reaction vessel was then placed in an ice bath and upon cooling the *p*H was adjusted to approximately 8 with 6*N* ammonium hydroxide whereupon the ester precipitated. The product was removed by filtration and washed with several portions of cold water. Recrystallization of the crude material from 95% ethanol gave a yield of 120 mg. (51%) of a white crystalline material m.p. 275° dec.

An analytical sample was prepared by recrystallization from absolute ethanol. The sample was dried in an Abderhalden over phosphorus pentoxide at 110° for 2 hr.

Anal. Calcd. for $C_8H_{11}N_3O_3$: C, 48.71; H, 5.62. Found: C, 48.6; H, 5.7.

Ethyl 5(4)-(2-amino-4(5)-oxo-Δ^2-imidazoline)-2-propionate. Ethyl 5(4)-(2-amino-4(5)-oxo-Δ^2-imadazolineidene)-2-propionate (490 mg.) was dissolved in 100 ml. of glacial acetic acid. The solution was then hydrogenated at approximately 40 p.s.i. for 8 hr. using 100 mg. of Adams catalyst. Upon completion of the hydrogenation the solution was filtered and then concentrated to a syrup *in vacuo* (water pump). The *p*H was then adjusted to approximately 8 with 6*N* ammonium hydroxide whereupon the ester precipitated. The product was removed by filtration and the mother liquors when replaced in the refrigerator yielded a second crop.

The crude material was recrystallized from 95% ethanol yielding 220 mg. (45%) of a white crystalline material m.p. 227–229°.

Anal. Calcd. for $C_8H_{13}N_3O_3$: C, 48.23; H, 6.58. Found: C, 48.1; H, 6.74.

2-Amino-5-methyl-6-oxopyrimidine-4-carboxylic acid (III). To 7.5 ml. of 1*N* potassium hydroxide was added 340 mg. of 5(4)-(2-amino-4(5)-oxo-Δ^2-imidazolineidene)-2-propanoic acid and the mixture was heated on a steam bath for 30 min. After the heating period the solution was cooled, acidified with 6*N* hydrochloric acid, and set in the refrigerator to crystallize. The product was removed by filtration and recrystallized from hot water. The first crop of crystals weighed 130 mg. By concentrating the mother liquor a second crop of 80 mg. was obtained; total yield 62%. When a sample was placed on a melting point block at 285° and the temperature raised 0.5° per minute the melting point was 302° (dec.). An analytical sample was dried in an Abderhalden over phosphorus pentoxide at 110°.

Anal. Calcd. for $C_6H_7N_3O_3$: C, 42.61; H, 4.17. Found: C, 42.5; H, 4.31.

Ethyl hydantoidene-2-propionate. Ten grams (0.05 mole) of diethyl α-oxalylpropionate, 3 g. (0.05 mole) of urea, and 3.8 ml. of glacial acetic acid were placed in a flask equipped with a reflux condenser and a tube for introducing hydrogen chloride gas. The flask was heated on a steam bath while hydrogen chloride was bubbled through the mixture for 0.5 hr. The product was removed by filtration and washed with a small amount of water. The product was recrystallized from water yielding 4.3 g. (44%) of white powder melting at 181–181.5°.

Anal. Calcd. for $C_8H_{10}N_2O_4$: C, 48.48; H, 5.09. Found: C, 48.5; H, 5.17.

Hydantoidene-2-propanoic acid. Ethyl hydantoidene-2-propionate (340 mg.) was placed in 7.5 ml. of 1*N* potassium hydroxide and heated for 0.5 hr. at 100°. The solution was then cooled, neutralized with 6*N* hydrochloric acid and set aside to crystallize. The product after two recrystallizations from water yielded small white needles 175 mg. (61%) which melted at 278–280°. An analytical sample was dried in an Abderhalden over phosphorus pentoxide at 138° for 6 hr.

Anal. Calcd. for $C_6H_6N_2O_4$: C, 42.36; H, 3.56. Found: C, 42.1; H, 3.63.

2,6-Dioxo-5-methylpyrimidine-4-carboxylic acid. Hydantoidene-2-propanoic acid (1 g.) was dissolved in 23 ml. of 1*N* potassium hydroxide and the solution was then evaporated almost to dryness at 100° C. Upon cooling, the concentrate was acidified with 6*N* hydrochloric acid and allowed to stand in a refrigerator for several hours. The product (710 mg.) was removed by filtration and mother liquors were concentrated and cooled, yielding 270 mg. additional.

The two crops were combined and recrystallized from water yielding white crystalline needles. The first crop contained 405 mg., the second 200 mg. giving 60% over-all yield. The melting point depends upon the rate of heating of the melting point block. When a sample was placed on the block at 290° and the temperature raised 4°/minute, the sample decomposed with effervescence at 326.5–327.5°.

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