The case of oxamide is further illustrative of the resistance of amides to HPHT change. Paracyanogen, a carbon–nitrogen polymer, has been reported to have been prepared in 30–40 % yield by heating oxamide at 270° for one week.[12] Attempts to accelerate this dehydration of oxamide, by HPHT conditions, failed. At 40 kbars and 260° for 18 min. oxamide is recovered unchanged. Elevation of the temperature to 333°, under identical pressure–time conditions, leads to extensive decomposition to a carbonaceous materials and ammonia.

A single experiment involving the HPHT reaction of urea with pyromellitic anhydride to produce a polymeric phthalocyanine also failed; ammonia was liberated as evidence of a deep-seated decomposition reaction.

(12) L. L. Bircumshaw, F. M. Taylor, and D. H. Whiffen, *J. Chem. Soc.*, 931 (1954).

Experimental

Apparatus.—The experimental apparatus used in this investigation is the "belt" high pressure–high temperature apparatus developed in this laboratory[13]; suitable modifications were made to facilitate the study of liquid and solid organic substrates. Thus, the reaction vessels are small metallic cylinders fabricated so that they are closed at one end, and capable at the other. Their dimensions (0.200-in. diameter and 0.450 in. long) permitted a sample capacity of *ca.* 0.2 ml. of liquid and 0.13 g. of solid. Cylinders fabricated of nickel, stainless steel, and lead were used; the latter soft metal is preferred for the reaction capsule since it can be opened easily with a razor blade after the reaction is completed. Liquid products and reagents were manipulated by suitable glass capillary milligram techniques.

Reactions.—The details of the HPHT reactions are summarized in Table I.

(13) H. T. Hall, *Rev. Sci. Instr.*, **31**, 125 (1960); H. T. Hall, *J. Phys. Chem.*, **59**, 1144 (1955).

The Reaction of Diketene with Glycine

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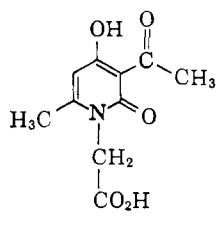
The reaction between diketene and glycine in basic solution yields 3-acetyl-1-carboxymethylene-4-hydroxy-6-methyl-2-pyridone (I).

In the course of a biosynthetic investigation, the preparation of acetoacetylglycine by the reaction of glycine with diketene was attempted. Instead, a crystalline compound was obtained in about a 15% yield which was not the desired material. We have recently re-investigated the reaction and have shown the compound to be 3-acetyl-1-carboxymethylene-4-hydroxy-6-methyl-2-pyridone (I).

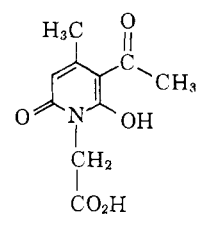
Elemental analysis gave the empirical formula $C_{10}H_{11}NO_5$ which is satisfied by the condensation of two molecules of diketene with one molecule of glycine and the elimination of one molecule of water. The compound is acidic (neutralization equivalent 112, pK_{a_1}, 3.25, pK_{a_2} 8.0) and the infrared spectrum showed three carbonyl peaks which were assigned as follows: 5.78 μ, $-CH_2CO_2H$; 6.00 μ, $>NCO-$, and 6.18 μ, α,β-unsaturated-β-hydroxy ketone.[1] There was no hydroxyl absorption. The carbonyl of the acetyl function formed a 2,4-dinitrophenylhydrazone and also gave a positive iodoform test. Kuhn Roth oxidation gave two C-methyl groups. The ultraviolet spectrum implied a pyridone rather than a pyrrolidone structure and therefore I and II were considered most probable.

The acid could be esterified easily to give the ethyl or methyl ester and the increased solubility of these compounds in deuterated chloroform enabled their n.m.r. spectra to be studied.[2] The methyl ester showed 6 singlets at τ values, −5.3 (1H); 4.2 (1H); 5.35 (2H, $-CH_2CO_2CH_3$); 6.3 (3H, $-CO_2CH_3$); 7.4 (3H, $-COCH_3$); 7.75 (3H, C—CH_3). The singlet at −5.3 τ was attributed to the hydroxyl hydrogen in the α,β-unsaturated-β-hydroxy ketone function.[3]

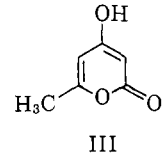
On heating with concentrated sulfuric acid, the compound was deacetylated,[4] and the acetic acid which distilled was characterized as the S-benzylthiouronium salt. The infrared spectrum of the deacetylated product lacked the band at 6.18 μ and the ultraviolet spectrum was identical with that of 1,6 dimethyl-4-hydroxy-2-pyridone and unlike that of 2,6 dihydroxypyridine. Thus structure I was assigned to the original compound and this was verified by a partial synthesis.



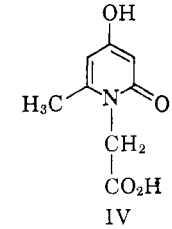
I



II



III



IV

By analogy with the well known reaction of triacetic acid lactone (III) to give 1,4 dihydroxypyridines with ammonia and amines,[5] glycine reacted with triacetic acid lactone in sodium hydroxide solution and the prod-

(1) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 124.

(2) N.m.r. spectra were taken on a Varian A60 instrument at 60 Mc. using deuterated chloroform solutions and tetramethylsilane as internal reference.

(3) L. M. Jackman, "Applications of Nuclear Magnetic Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, p. 71.

(4) O. Mumm and G. Hingst, *Ber.*, **56**, 2301 (1923).

(5) N. Collie and W. W. Myers, *J. Chem. Soc.*, 722 (1892); H. M. Woodburn and M. Hellmann, *Rec. trav. chim.*, **70**, 813 (1951).

uct obtained was identical in all respects with the deacetylated compound obtained above. Triacetic acid lactone remains unchanged when quantitatively treated with sodium hydroxide in the same manner. The deacetylated compound therefore has structure IV and this confirms the assignment of structure I to the original condensation product.

The isomer of I, which has the acetyl group at position 5 rather than at position 3, would require the rearrangement of diketene prior to or during the condensation, and is excluded by the infrared and nuclear magnetic resonance evidence.

In considering the reaction mechanism, it is unlikely that two molecules of diketene first condense to form dehydroacetic acid which then reacts with a molecule of glycine forming the pyridone (I). It has been shown[6] that under similar reaction conditions dehydroacetic acid and glycine reacted to form a compound which, although isomeric, was reported as having physical properties unlike those of the pyridone (I). We repeated this reaction and confirmed that the compound obtained was different in all respects (melting point, mixture melting point, ultraviolet, infrared, stability to acid, etc.) from the pyridone (I).

The products of the reaction of diketene on other amino acids, under the condition described here, have not been investigated. However, Lacey[7] has reported that ethyl glycinate reacts with diketene, under neutral conditions, to give the expected N-acetoacetyl derivative.

Experimental

3-Acetyl-1-carboxymethylene-4-hydroxy-6-methyl-2-pyridone (I).—Glycine (5.0 g.) was dissolved in 40% sodium hydroxide (5 ml.) and diluted with water (17 ml.). The solution was stirred at −5° and freshly distilled diketene (9.0 g.) was added in four portions during 1 hr. Stirring was continued until the reaction mixture became homogeneous. The solution was acidified to pH 2 with dilute hydrochloric acid and a white crystalline solid precipitated. The crystals were collected and washed with cold water (2.2 g.), m.p. 227–231°. Recrystallization from water gave needles (1.8 g.), m.p. 236–238°.

Anal. Calcd. for $C_{10}H_{11}NO_5$: C, 53.33; H, 4.94; N, 6.22. Found: C, 53.52; H, 4.77; N, 6.31. Ultraviolet spectrum (H_2O): λ_{max} 230 mμ (log ε 4.0), 270 mμ (log ε 3.6), and 323 mμ (log ε 4.1); (0.1 NaOH), λ_{max} 235 (log ε 4.3) and 300 mμ (log ε 3.9); infrared spectrum (Nujol): 5.78 μ (sh), 6.0 μ (sh), 6.18 μ (sh).

3-Acetyl-4-hydroxy-1-methoxycarbonylmethylene-6-methyl-2-pyridone.—The acid (I) (0.502 g.) was dissolved in 25 ml. of anhydrous methanol, a few drops of concentrated sulfuric acid were added and the solution was heated under reflux for 5 hr. The solution was evaporated to a small volume diluted with water, and extracted with ether. After drying over anhydrous magnesium sulfate, the ether was removed under reduced pressure, yielding a crystalline residue (0.514 g.), m.p. 123–124°. Recrystallization from absolute ethanol gave prisms, m.p. 125°.

Anal. Calcd. for $C_{11}H_{13}NO_5$: C, 55.22; H, 5.48; N, 5.86. Found: C, 55.17; H, 5.60; N, 6.07. Infrared (Nujol): 5.70 μ (sh), 6.06 μ (sh); 6.18 μ (sh). N.m.r. τ: −5.3 (1H), 4.2 (1H), 5.35 (2H), 6.3 (3H), 7.4 (3H), 7.75 (3H).

3-Acetyl-1-ethoxycarbonylmethylene-4-hydroxy-6-methyl-2-pyridone.—This ester was prepared from the acid (I) (0.079 g.) and absolute ethanol by the method described above. The crude ester (0.984 g.), m.p. 102–105°, was recrystallized from absolute ethanol m.p. 106–107°.

Anal. Calcd. for $C_{12}H_{15}NO_5$: C, 56.90; H, 5.97; N, 5.53. Found: C, 57.08; H, 5.84; N, 5.82. Infrared (Nujol): 5.78 μ (sh), 6.08 μ (sh), 6.18 μ (sh). N.m.r. τ: 4.2 (1H), 5.3 (2H), 5.75 (quartet 2H), 7.3 (3H), 7.75 (3H), 8.7 (triplet 3H).

Deacetylation of 3-Acetyl-1-carboxymethylene-4-hydroxy-6-methyl-2-pyridone (I).—The acid (I) (4.55 g.) was dissolved in concentrated sulfuric acid (5 ml.) and heated at 200° for 30 min. The acetic acid which distilled was converted into the S-benzylthiouronium derivative, m.p. 135°, unchanged on mixing with an authentic sample. The reaction mixture was cooled and treated with saturated barium hydroxide solution until pH 5. The precipitated barium sulfate was filtered and washed with water. The filtrate was evaporated under reduced pressure and the residue dissolved in dilute potassium carbonate solution and filtered from some insoluble material. The filtrate was acidified with dilute hydrochloric acid and evaporated to dryness leaving a residue which was extracted with absolute ethanol. Evaporation of the ethanolic extracts yielded an oil which crystallized from water (2.7 g.), m.p. 239–240°. Recrystallized from water, m.p. 248°.

Anal. Calcd. for $C_8H_9NO_4$: C, 52.48; H, 4.95; N, 7.64. Found: C, 52.68; H, 4.92; N, 7.61. Ultraviolet spectrum (95% EtOH): λ_{max} 230 (sh) (log ε 3.47) and 287 (log ε 3.70). Infrared (Nujol): 5.86 μ (sh), 6.05 μ (s).

1-Carboxymethylene-4-hydroxy-6-methyl-2-pyridone (IV).—Triacetic acid lactone (0.94 g.) was added to a solution of glycine (0.56 g.) in 0.88 *N* sodium hydroxide (8.5 ml.) and the solution warmed on a steam bath for 1 hr. After cooling, the reaction mixture was acidified with dilute hydrochloric acid and on evaporation of some of the water white needles precipitated, 0.508 g., m.p. 244–247°. It was recrystallized from water, m.p. 248°, and was identical in all respects (mixture melting point, ultraviolet spectrum, infrared spectrum) with the deacetylated product obtained above.

Acknowledgment.—This work was supported by grants from the National Institutes of Health, U. S. Public Health Service (A-1101), National Science Foundation (G-18712), and American Cancer Society (5130–870860).

(6) S. Iguchi, K. Hisatsune, M. Himeno, and S. Muraoka, *Chem. Pharm. Bull.* (Tokyo), **7**, 323 (1959).

(7) R. N. Lacey, *J. Chem. Soc.*, 851 (1954).