[FROM THE RESEARCH LABORATORIES OF THE BUREAU OF DAIRY INDUSTRY, UNITED STATES DEPARTMENT OF AGRICUL-TURE]

Some Derivatives of α, α -Bis-benzoylaminopropionic Acid

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In view of the interesting results obtained by Bergmann and Grafe¹ in the synthesis and application to amino acid problems of α , α -bisacetylaminopropionic acid and its derivatives, an investigation of the corresponding benzoyl derivatives seemed worth while.

The bis-benzoylamino acid, $CH_3C(NHCOPh)_2$ -COOH (I), was readily prepared from benzamide and pyruvic acid. The use of less than two moles of benzamide resulted merely in a decreased yield, and did not give appreciable amounts of α -benzoylaminoacrylic acid (II). The latter was formed in the usual way¹ from the acid I, but is apparently somewhat less easy to obtain than the corresponding acetyl derivative.

The azlactone (JII) CH_sC(NHCOPh)CO de-| | | | N=CPh----O

rived from the acid I is unusually stable, as the writer has previously shown² in connection with its failure to yield a thiohydantoin derivative. It can, however, be readily condensed with glycine, and presumably with amino acids generally.

The amide of the acid I showed no indications of dehydration to form a cyclic compound when heated with acetic anhydride.

Experimental Part

 α, α -Bis-benzoylaminopropionic Acid (I).³—Twenty grams of pyruvic acid was heated with two moles of benzamide for one and one-half hours at a pressure of 20-30 mm. under an air condenser. The oil-bath temperature was 110–120°, and water distilled over continuously. The residue, which solidified on cooling, was crystallized from alcohol. Some 30 g. of material was obtained which melted fairly sharply, though with obvious decomposition, at 181–186°, according to the rate of heating.

Anal. (Kjeldahl) Calcd. for $C_{17}H_{16}O_4N_2$: N, 8.99. Found: N, 8.80, 8.85.

From the residues, much impure benzamide separated. On extraction with bicarbonate solution, some of this material dissolved, and on acidification an oil separated. On purification, only the acid I was obtained (N, 8.88, 8.90).

 α -Benzoylaminoacrylic Acid (II).—Five grams of the acid I was boiled under reflux with 20 cc. of glacial acetic acid for twelve minutes. Ten minutes was required for complete solution. On cooling, and on moderate dilution with water,

(1) M. Bergmann and K. Grafe, Z. physiol. Chem., 187, 183, 187, 196 (1930).

(2) B. H. Nicolet, J. Biol. Chem., 99, 429 (1933).

(3) C. Böttinger, Ber., 14, 1599 (1881), prepared this compound from pyruvic acid and benzonitrile in concentrated sulfuric acid. His product melted at 172° with effervescence. considerable amounts of unaltered material were recovered. The residues were evaporated to dryness (vacuum) and extracted with bicarbonate solution, leaving behind 1.5 g. of benzamide. On acidification, a solid separated which after two crystallizations from hot water melted at $137-138^\circ$.

Anal. (Kjeldahl) Calcd. for $C_{10}H_9O_8N$: N, 7.34. Found: N, 7.72.

Azlactone of α, α -Bis-benzoylaminopropionic Acid (III). — Ten grams of the acid I in 65 cc. of acetic anhydride was warmed on the water-bath until solution was complete (one and one-half hours). On standing at room temperature, about half of the product crystallized; the remainder was obtained after distillation of the solvent under reduced pressure. The azlactone, after crystallization from benzene, melted fairly sharply at 203–205°, the temperature depending on the rate of heating.

Anal. (Kjeldahl) Calcd. for $C_{17}H_{14}O_3N_2$: N, 9.52. Found: N, 9.45, 9.60.

A portion of the material, recrystallized from hot methyl alcohol, melted somewhat lower, but still contained 9.40% of nitrogen.

 α, α -Bis-benzoylaminopropionamide.—One gram of the azlactone was treated with 25 cc. of absolute alcohol to which had been added 3 cc. of concentrated ammonium hydroxide, and the mixture warmed until solution was complete. The amide, crystallized from 40–50 parts of hot alcohol, m. p. 212–213° with only slight decomposition.

Anal. (Kjeldahl) Calcd. for $C_{17}H_{17}O_8N_3$: N, 13.15. Found: N, 13.32, 13.12.

When this amide (0.3 g.) was heated fifteen minutes at 100° with 5 cc. of acetic anhydride, only unaltered amide could be isolated.

Ethyl $\alpha_i \alpha$ -Bis-Benzoylaminopropionate.—Three grams of the azlactone was warmed gently with 20 cc. of absolute alcohol containing 3 cc. of diethylamine⁴ until solution was complete. The product, crystallized from benzene and then from diluted alcohol, m. p. 132–133°.

Anal. (Kjelďahl) Calcd. for $C_{19}H_{20}O_4N_2$: N, 8.24. Found: N, 8.16, 8.31.

 α, α -Bis-benzoylaminopropionylglycine.—Three grams of the azlactone in 20 cc. of acetone was added to 0.8 g. of glycine in 10 cc. of water containing 1.7 cc. of 6 N sodium hydroxide. The mixture was shaken until solution was complete, and then acidified with an equivalent amount of hydrochloric acid. The yield was 3.5 g. of material of m. p. 197° with effervescence.

Anal. (Kjeldahl) Calcd. for $C_{19}H_{19}O_6N_3$: N, 11.39. Found: N, 10.91.

Summary

The preparation of α, α -bis-benzoylaminopropionic acid and a number of its derivatives has been described.

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(4) B. H. Nicolet, J. Biol. Chem., 100, 287 (1933).