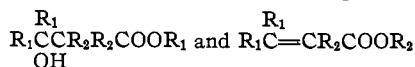


[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NEW YORK UNIVERSITY]

A New Reaction of Nitriles. IV. Synthesis of N-Benzoylamino Acids¹BY LAWRENCE W. HARTZEL² WITH JOHN J. RITTER

Previous work in this Laboratory³ has shown that nitriles interact with certain alkenes and alcohols in the presence of sulfuric acid to form substituted amides. In order to extend the scope of this reaction, the reaction of benzonitrile with a number of unsaturated acids and esters, and hydroxy esters, has now been investigated. This paper describes the preparation of N-benzoylamino acids by this novel procedure. Table I lists the reactants used and the products obtained, together with yields, melting points and analyses.

It was found that only certain of the acids and esters examined would undergo reaction with benzonitrile under the conditions of these experiments; compounds of the general types



where $R_1 = \text{alkyl}$ and $R_2 = \text{H or alkyl}$

were found to be very reactive, while certain other types showed less reactivity. Among the compounds which failed to react with benzonitrile under a variety of conditions were methyl acrylate, methyl methacrylate, methyl crotonate, ethyl lactate, vinyl acetic acid, allyl acetic acid, maleic acid, diethyl fumarate and citraconic acid.

Two of the products obtained, β -benzoylamino- β -methylbutyric acid and β -benzoylamino- β -phenylpropionic acid, have been prepared previously by conventional methods.⁴ A comparison of the physical properties found with those recorded in the literature established their identity. Hydrolysis of β -benzoylamino- α -ethyl- β -methylbutyric acid and β -benzoylamino- β -methylbutyric acid yielded β -amino- α -ethyl- β -methylbutyric acid and β -valine, respectively. The latter compound has been described by Slimmer.^{4a} No attempt has been made to determine the position of the benzoylamino group on benzoylaminoheptadecanoic acid.

Experimental

Certain of the unsaturated and hydroxy esters were prepared by means of the Reformatsky reaction; two of the hydroxy esters, ethyl β -hydroxy- β -methylcaprylate and ethyl β -hydroxy- β -methyl- γ -phenylbutyrate have not been previously described.

All reactions were carried out in concentrated sulfuric acid with no other solvent. The same general procedure was followed in most cases; detailed directions are given

(1) Based upon the thesis submitted by Lawrence W. Hartzel in February, 1948, to the Graduate School of New York University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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(3) Ritter and Minieri, *THIS JOURNAL*, **70**, 4045 (1948); Benson with Ritter, *ibid.*, **70**, 4128 (1949).

(4) (a) Slimmer, *Ber.*, **35**, 400 (1902); (b) Pesner, *Ber.*, **38**, 2322 (1905).

for only a few typical preparations. Most of the products were recrystallized from benzene; in a few cases mixed solvents were used.

Analyses were performed in the Laboratory of Microchemistry at New York University. Nitrogen determinations were carried out by the Kjeldahl method.

Ethyl β -Hydroxy- β -methylcaprylate.—Reaction of methyl *n*-amyl ketone and ethyl bromoacetate in the presence of zinc using the Natelson and Gottfried⁵ modification of the Reformatsky reaction gave a colorless oil in 71% yield; b. p. 93–95° (3 mm.), n_D^{25} 1.4350, d_4^{25} 0.941.

Anal. Calcd. for $C_{11}H_{20}O_3$: C, 65.3; H, 11.0. Found: C, 65.4; H, 11.1.

Ethyl β -Hydroxy- β -methyl- γ -phenylbutyrate.—Reaction of methyl benzyl ketone and ethyl bromoacetate as described above gave a viscous oil in 61% yield; b. p. 118–119° (2 mm.), n_D^{25} 1.5041, d_4^{25} 1.051.

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.3; H, 8.2. Found: C, 70.9; H, 8.2.

Reaction of Benzonitrile with Unsaturated and Hydroxy Esters.—The following procedure is typical of that used throughout the work. A mixture of 14.6 g. (0.1 mole) of ethyl β -hydroxy- β -methylbutyrate and 10.3 g. (0.1 mole) of benzonitrile was cooled in an ice-bath and 20 ml. of concentrated sulfuric acid was added with stirring so that the temperature remained below 20°. When all the acid had been added, the temperature was allowed to rise to 40–45° until the exothermic reaction subsided. The mixture was allowed to stand at room temperature overnight and was then poured into 200 ml. of ice-water. The crude ester so precipitated was hydrolyzed to the benzoylamino acid by refluxing for two hours with 50 ml. of ethanol and 10 ml. of 50% aqueous potassium hydroxide solution. The hydrolysis mixture was poured into 400 ml. of water, non-acidic impurities were removed by extraction with ether; the free acid was precipitated by acidification with hydrochloric acid and recrystallized from benzene. The data on this compound and on the others prepared in this work are given on Table I.

β -Valine.—A mixture of 3.0 g. (0.0135 mole) of β -benzoylamino- β -methylbutyric acid, 20 g. (approximately 0.1 mole) of dried C. p. barium hydroxide and 180 ml. of distilled water was refluxed for one hundred and twenty hours, the condenser being fitted with a soda lime tube to exclude carbon dioxide. The hot solution was filtered, acidified with dilute sulfuric acid, and allowed to stand overnight. The heavy barium sulfate precipitate was filtered and washed thoroughly with distilled water. The filtrate and washings, approximately 400 ml. in all, were combined and made slightly alkaline with aqueous barium hydroxide. After standing overnight the mixture was filtered and washed. The filtrate and washings were combined and evaporated on a water-bath to a 50-ml. volume. This solution was again acidified with dilute sulfuric acid and allowed to stand overnight. The precipitate was filtered and washed. The filtrate and washings were combined and extracted with four 30-ml. portions of hexane. The aqueous solution was then shaken for ten minutes with 10 g. of Amberlite IR-4B⁶ resin, which had previously been purified by shaking for ten minutes with six successive portions of distilled water. The mixture was filtered and washed. The filtrate was treated with further portions of resin until the pH of the solution no longer changed (approximately 5.9–6.1 as measured by indicator paper). The clear filtrate was heated with charcoal on a water-bath, filtered, and evap-

(5) Natelson and Gottfried, *THIS JOURNAL*, **61**, 970 (1939).

(6) This material was kindly supplied by the Resinous Products Division, Rohm and Haas Company.

TABLE I

N-BENZOYLAMINO ACIDS FROM BENZONITRILE AND UNSATURATED ACIDS AND ESTERS, AND HYDROXY ESTERS

Starting compound	Formula of product	M. p., °C. ^a	Yield, %	Nitrogen, %	
				Calcd.	Found
β,β -Dimethylacrylic acid	C ₁₂ H ₁₆ O ₃ N	141-142 ^b	72	6.33	6.49
Ethyl β -hydroxy- β -methylbutyrate	C ₁₂ H ₁₈ O ₃ N	141-142.5	62
Ethyl β -hydroxy- β -methylvalerate	C ₁₃ H ₁₇ O ₃ N	103-104.5	76.5	5.99	5.82
Ethyl β -hydroxy- β -methylcaproate	C ₁₄ H ₁₉ O ₃ N	76-78	72	5.62	5.77
Ethyl β -hydroxy- β -methylcaprylate	C ₁₇ H ₂₅ O ₃ N ^c	113.5-114	67	4.81	4.49
Ethyl β -ethyl- β -hydroxyvalerate	C ₁₄ H ₁₉ O ₃ N	125-126.5	78	5.62	5.66
Ethyl α -ethyl- β -methylbutenoate	C ₁₄ H ₁₉ O ₃ N	108-109.5	72	5.62	5.70
Ethyl β -hydroxy- α -isopropyl- β -methylbutyrate	C ₁₇ H ₂₅ O ₃ N ^d	99-100	62	4.81	4.65
Ethyl β -hydroxy- α,α,β -trimethylbutyrate	C ₁₄ H ₁₉ O ₃ N	150-152	80	5.62	5.47
Ethyl 1-hydroxycyclopentylacetate	C ₁₄ H ₁₇ O ₃ N	185-187	40	5.66	5.51
Ethyl α -(1-hydroxycyclopentyl)-propionate	C ₁₅ H ₁₉ O ₃ N	133-134	44	5.36	5.47
Ethyl 1-hydroxycyclohexylacetate	C ₁₅ H ₁₉ O ₃ N	167-168	65	5.36	5.37
Ethyl α -(1-hydroxycyclohexyl)-propionate	C ₁₆ H ₂₁ O ₃ N	160-161.5	58	5.09 ^e	4.94
Ethyl β -hydroxy- β -methyl- γ -phenylbutyrate	C ₁₈ H ₁₉ O ₃ N ^f	179-181	9	4.71	4.32
Ethyl cinnamate	C ₁₆ H ₁₅ O ₃ N ^g	195-196	26	5.20	5.23
Methyl undecylenate	C ₁₈ H ₂₇ O ₃ N ^h	103-105	16	4.59	4.56

^a All melting points uncorrected. ^b Slimmer^{4a} reported m. p. 141.5°. ^c *p*-Tolunitrile used in place of benzonitrile in this experiment. Calcd.: C, 70.1; H, 8.7. Found: C, 70.6; H, 8.7. ^d Isolated as the ethyl ester since standard alkaline hydrolysis failed. Calcd.: C, 70.1; H, 8.7. Found: C, 70.3; H, 8.9. ^e Calcd.: C, 69.8; H, 7.7. Found: C, 69.7; H, 7.6. ^f Crude acid dissolved in benzene and reprecipitated with hexane. Recrystallized from benzene-ethanol. Calcd.: C, 72.7; H, 6.4. Found: C, 72.7; H, 6.6. ^g Posner^{4b} reported m. p. 194-196°. Excess cinnamic acid removed by dissolving in hot benzene. Residue dissolved in alkali, reprecipitated with acid and recrystallized from water. ^h Saponification mixture acidified with acetic acid; crude acid recrystallized twice from diisopropyl ether-acetone and finally from benzene. Calcd.: C, 70.8; H, 8.9. Found: C, 70.9; H, 8.7.

orated to dryness under reduced pressure. The residue was washed from the flask with 30 ml. of absolute ethanol and allowed to stand overnight. The mixture was filtered and the precipitate dried for two weeks under vacuum, then two hours at 110°; yield 0.50 g. (32%), m. p. 215-217°. Slimmer^{4a} reported the melting point of β -valine to be 217° (cor.).

Anal. Calcd. for C₈H₁₁O₃N: N, 12.0. Found: N, 12.0.

The absolute alcohol filtrate was diluted with 200 ml. of ether, allowed to stand overnight and filtered. The white solid obtained after drying and heating melted at 205-207° and weighed 0.47 g.

β -Amino- α -ethyl- β -methylbutyric Acid.—This material was obtained from 3.0 g. (0.0120 mole) of β -benzoylamino-

α -ethyl- β -methylbutyric acid by hydrolysis with barium hydroxide as described above; yield, 0.40 g. (23%), m. p. 228-229°.

Anal. Calcd. for C₇H₁₃O₂N: N, 9.65. Found: N, 9.41.

Summary

The preparation of a number of benzoylamino acids by the interaction of benzonitrile with certain unsaturated acids and esters and hydroxy esters, has been described.

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[CONTRIBUTION FROM THE P. R. INDUSTRIAL DEVELOPMENT LABORATORY AT THE UNIVERSITY OF PUERTO RICO]

Nitric Acid Oxidation of 2,4:3,5-Dimethylene-D-gluconic Acid; Some Derivatives of 2,4-Methylene-D-gluconolactone-3,6

BY I. A. COLÓN, R. FERNÁNDEZ-GARCÍA, LUIS AMORÓS AND HILDA BLAY

In a previous communication¹ from this Laboratory a modification of Zief and Scattergood's preparation of 2,4:3,5-dimethylene-D-gluconic acid was recorded. This paper deals with the nitric acid oxidation of dimethylene-D-gluconic acid as well as with the preparation and properties of derivatives of monomethylene gluconolactone, the oxidation product.

The oxidation of 2,4:3,5-dimethylene-D-gluconic acid was carried out with concentrated nitric acid. No spontaneous reaction could be noticed when dilute nitric acid was used at room temperature. Using the minimum amount of

concentrated nitric acid required to dissolve all the dimethylene gluconic acid, a yield of 56% of the theoretical amount was obtained. A higher proportion of concentrated nitric acid led to slightly higher yields (67%).

The oxidation product crystallized directly from the reaction solution on cooling. The physical properties of this substance and of its monoethyl ester, dimethyl ester, monomethyl ester and diamide agreed with the values reported^{2,3} for 2,4-methylene-D-gluconolactone-3,6 and its corresponding derivatives.

The stability of the 2,4-methylene acetal ring

(1) Colón, Fernández, Amorós and Blay, *THIS JOURNAL*, **71**, 1493 (1949).

(2) Henneberg and Tollens, *Ann.*, **292**, 40 (1896).

(3) Haworth and Jones, *J. Chem. Soc.*, 66 (1944).