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A NEW SYNTHESIS OF ω-BENZOYLAMINOVALERIC ACID

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In connection with studies underway in this laboratory on some of the possible precursors or metabolites of lysine, the preparation of α-keto-ω-aminocaproic acid containing isotopic carbon in the *alpha* position became desirable. It was hoped that if ω-aminovaleric acid, suitably blocked in the amino position, could be prepared with a "tagged" carbon atom in the carboxyl group, this acid could then be converted to the desired α-keto-ω-aminocaproic acid. Although experiments run with non-isotopic material showed this approach to the desired compound was not feasible, a new synthesis of ω-benzoylaminocaproic acid has been developed. This synthesis, together with some of the reactions of the acid, is described below.

The new nitrile, ω-cyanobutylphthalimide, was obtained, although in low yield, by the action of potassium cyanide on ω-bromobutylphthalimide. The latter is readily prepared from potassium phthalimide and tetramethylene dibromide by the method Keil (1) used for preparing the analogous chloro compound. The nitrile was characterized by analysis and by acid hydrolysis to the known ω-phthalimidovaleric acid (2). Variation of the reaction conditions led to no improvement in the yield of nitrile, and because of this fact and the experience of others with similar reactions (3), attention was turned to the preparation of ω-benzoylaminovaleric acid by the reactions shown in the Figure.

The starting material for this preparation, ω-iodobutylamine hydriodide (III), was prepared in two ways; (a) from γ-phenoxypropyl cyanide (IIa) by reductive acetylation to the previously unreported N-(γ-phenoxybutyl)acetamide (IIb), followed by hydriodic acid hydrolysis, or, preferably (b) from ω-bromobutylphthalimide by hydrolysis with hydriodic acid. In the latter hydrolysis the bromine atom was replaced by iodine.

Reaction of ω-iodobutylamine hydriodide (III) with benzoyl chloride and alkali led to two products, N-benzoylpyrrolidine (IV) and N-(ω-iodobutyl)benzamide (V), either of which could be made to predominate by variation of the reaction conditions. Addition of benzoyl chloride to a mixture of the amine hydriodide and aqueous sodium hydroxide in the cold, resulted in a 49% yield of N-benzoylpyrrolidine. On the other hand, the slow addition of alkali to a mixture of amine hydriodide and benzoyl chloride led to the desired N-(ω-iodobutyl)benzamide in 54% yield.

This iodobutylbenzamide reacted with potassium cyanide to give the previously unreported N-(ω-cyanobutyl)benzamide which upon acidic hydrolysis yielded the desired ω-benzoylaminovaleric acid (VI).

This acid was converted to its chloride by the action of phosphorus pentachloride according to the procedure Bergmann, *et. al.* (4) used to prepare ω-benzyl-N-carbobenzoxyglutaroyl chloride. Since the chloride could not be puri-

fied, its presence was shown by conversion to the corresponding anilide in an over-all yield of 70% based on free acid. When the acid chloride was reacted with cuprous cyanide the only compound isolated was N-benzoyl-α-piperidone (VII).

In view of the ease with which this acid chloride reacted by ring formation, attempts were made to further benzoylate the N-benzoylaminovaleric acid using benzoyl chloride and alkali at room temperature, and by the method previously reported for the alkylation of N-substituted amides employing sodium hydride (5). In the first case only benzoic acid and starting material were isolated, whereas in the second benzoic acid and impure N-benzoyl-α-piperidone were obtained. In the light of these results this approach to the synthesis of the desired keto acid was abandoned.

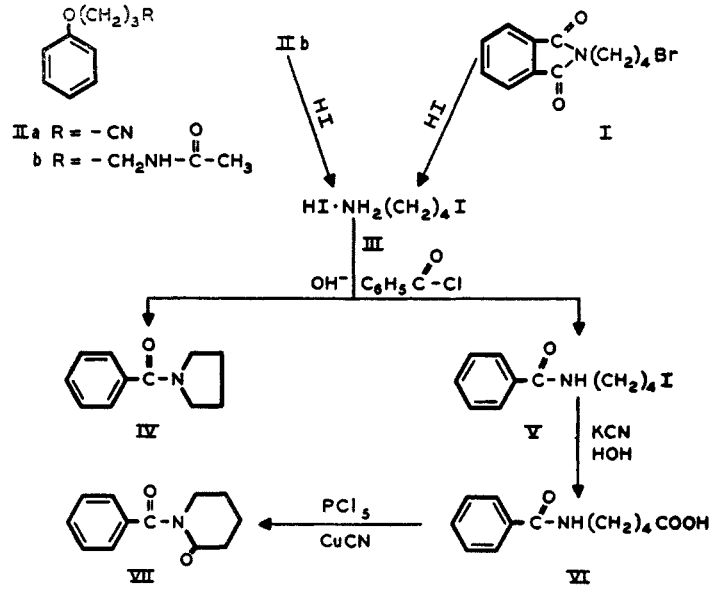

FIG. 1

The N-benzoylpyrrolidine isolated in these experiments was a solid, m.p. 46–47°. The compound had previously been described as a viscous oil which could not be crystallized (6). Repetition of the cited work led to a compound of the same melting point. A mixed melting point with the material obtained in the present experiments showed no depression. Further characterization of the material was obtained by its reaction with phosphorus pentachloride to give N-(ω-chlorobutyl)benzamide (6).

EXPERIMENTAL[1, 2]

ω-Bromobutylphthalimide. Following the procedure Keil (1) used for preparing ω-chlorobutylphthalimide, 195 g. of tetramethylene dibromide was reacted with 55 g. of potassium

[1] All melting points are corrected.

[2] Analyses by R. J. Koegel of this laboratory.

phthalimide. The product was recrystallized from alcohol, extracted with ether, and the solvent concentrated to give 70 g. (83%) of ω-bromobutylphthalimide, m.p. 78–80° [Lit. (7) 80.5°].

ω-Cyanobutylphthalimide. To a solution of 35.2 g. of ω-bromobutylphthalimide in 200 ml. of 95% alcohol was added 8.1 g. of potassium cyanide in 25 ml. of water. The mixture was refluxed 5 hours and poured on ice. There was thus obtained 14.3 g. of impure crystals, m.p. 63–65°. This material (14 g.) was placed in a liter of water. After being brought to the boiling point the supernatant was decanted and cooled in the refrigerator overnight; yield, 2 g. of white crystals, m.p. 71.8–73.8°. By concentration of the mother liquors another 0.8 g. was obtained; total yield 10%.

Anal. Calc'd for $C_{13}H_{12}N_2O_2$: N, 12.3. Found: N, 12.0, 12.1.

ω-Phthalimidovaleric acid. ω-Cyanobutylphthalimide (2.8 g.) was hydrolyzed to ω-phthalimidovaleric acid using the procedure Gabriel and Coleman (8) applied to the next lower homolog. There was obtained 2.2 g. (76%) of crude product, m.p. 102–108°. Two recrystallizations from dilute 1:1 hydrochloric acid gave a product, m.p. 115.8–117.8° [Lit. (2) 117°].

N-(ω-Phenoxybutyl)acetamide. The compound was obtained by the reductive acetylation of ω-phenoxypropyl cyanide (9) employing the general method of Carothers and Jones (10). In the Parr hydrogenation apparatus was placed 32.2 g. of nitrile, 80 ml. of acetic anhydride, and 0.8 g. of Adams' catalyst. The mixture was shaken until three moles of hydrogen was absorbed. After settling, the catalyst was removed and water was added to the filtrate followed by 30% sodium hydroxide until the solution was alkaline. The oil, which soon separated, crystallized; the resulting crystals were washed with water, and air-dried. The last traces of water were removed by taking up the product in ether and drying it over sodium sulfate. Concentration yielded 35 g. of crystals which, upon recrystallization from benzene and ligroin (b.p. 90–120°), gave 26 g. (63%) of N-(ω-phenoxybutyl)-acetamide, m.p. 61–62.5°.

Anal. Calc'd for $C_{12}H_{17}NO_2$: C, 69.6; H, 8.2; N, 6.8.
Found: C, 69.4; H, 8.5; N, 6.7.

ω-Iodobutylamine hydriodide.

(a) *From N-(ω-phenoxybutyl)acetamide.* The substituted acetamide (22 g.) and 100 ml. of 48% hydriodic acid were refluxed 24 hours. The excess acid was removed under reduced pressure and the residue was recrystallized twice from ethyl acetate to give 19 g. (57%) of ω-iodobutylamine hydriodide, m.p. 106–107° [Lit. (11) 107°].

(*b*). *From ω-bromo butylphthalimide.* There was refluxed together for 24 hours 36.8 g. of ω-bromobutylphthalimide and 150 ml. of 55–58% hydriodic acid. The reaction mixture was cooled, diluted with water, and the resulting precipitate of phthalic acid removed. The filtrate was evaporated to dryness under reduced pressure and the residue, after two recrystallizations from ethyl acetate, yielded 30 g. (82%) of ω-iodobutylamine hydriodide, m.p. 105–106.5°.

N-(ω-Iodobutyl)benzamide. To 105 g. of ω-iodobutylamine hydriodide in 320 ml. of water there was added 45 g. of benzoyl chloride. The mixture was cooled to 2° and with stirring and continued cooling there was slowly added a chilled solution of 28 g. of sodium hydroxide in 200 ml. of water. This was followed by sufficient 10% sodium hydroxide (approx. 50 ml.) to keep the reaction alkaline. The precipitate was washed with water, dried in a vacuum desiccator over phosphorus pentoxide, and recrystallized from an ether-petroleum ether (b.p. 30–60°) mixture. There was obtained 52 g. (54%) of N-(ω-iodobutyl)benzamide as white fluffy needles, m.p. 67–68.3° [Lit. (6) 58°]. Due to the discrepancy in melting points the material was analyzed.

Anal. Calc'd for $C_{11}H_{14}INO$: C, 43.6; H, 4.6; N, 4.6; I, 41.9.
Found: C, 43.8, 43.6; H, 4.7, 4.9; N, 4.6, 4.6; I, 42.3.

N-(ω-Cyanobutyl)benzamide. To 11.1 g. of potassium cyanide in 82 ml. of water there was added 51.5 g. of ω-(iodobutyl)benzamide in 500 ml. of alcohol and the resulting mixture was refluxed with stirring for two days. After filtration, the alcohol in the filtrate was removed under reduced pressure and the residue was poured in to cold water. The aqueous

solution was extracted with ether and the extract dried over sodium sulfate. The ether was removed and the residue was heated for 1½ hours on the water-bath under reduced pressure. The resulting 33 g. (97%) of light brown oil crystallized upon standing at room temperature and was sufficiently pure for hydrolysis to the acid. A small sample, recrystallized for analysis from ether, melted at 53–56°.

Anal. Calc'd for $C_{12}H_{14}N_2O$: N, 13.9. Found: N, 13.5, 13.7.

ω-Benzoylaminovaleric acid. N-(ω-Cyanobutyl)benzamide (16.5 g.) was hydrolyzed by the method Gabriel (11) used for similar nitriles. There was obtained 13 g. (72%) of ω-benzoylaminovaleric acid, m.p. 92–94° [Lit. (12) 94°, (13) 105°, (14) 106–107°]. In the last two references cited mention is made of the fact that some samples of the acid melted at 94° and were not changed by recrystallization.

ω-Benzoylaminovaleroyl chloride and ω-benzoylaminovaleranilide. ω-Benzoylaminovaleric acid (1.7 g.) was converted to the acid chloride by the use of phosphorus pentachloride in ether (4). The crude product was washed with ligroin to remove phoshporus oxychloride and the last traces of solvent were removed *in vacuo*. The residue was converted to the anilide in the usual manner. There was obtained 1.67 g. (75% based on acid used) of ω-benzoylaminovaleranilide, m.p. 167–172°. Recrystallization from alcohol gave m.p. 173.1–174.2° [Lit. (15) 170–171°].

Reaction of ω-benzoylaminovaleroyl chloride with cuprous cyanide. ω-Benzoylaminovaleroyl chloride, prepared from 1.7 g. of acid, was dissolved in dry benzene and 0.7 g. of cuprous cyanide was added. No visible reaction took place at room temperature, even with vigorous stirring; the temperature was raised slowly to 80° and kept between 70° and 80° for 18 hours. The solid material, which contained halogen, was removed and the filtrate was concentrated under reduced pressure. The residue was washed first with sodium bicarbonate solution and then with water; the oil was taken up in ether, dried, and the solvent was reduced to a small volume. Yield, 0.6 g. of N-benzoyl-α-piperidone, m.p. 112° [Lit. (16) 112°]. Kanevskoya (15) obtained this same compound in an attempt to reduce the acid chloride to the corresponding aldehyde by the Rosenmund procedure.

N-Benzoylpyrrolidine. ω-Iodobutylamine hydriodide (16.8 g.) was dissolved in 70 ml. of 10% sodium hydroxide and cooled to 5°. With stirring and continued cooling 8.4 g. of benzoyl chloride was added dropwise and the reaction mixture was allowed to warm to room temperature. The clear solution was extracted with ether, washed with water, and dried over sodium sulfate. Removal of the solvent left a heavy oil which crystallized to give 7.5 g. (49%) of N-benzoylpyrrolidine, m.p. 38–42°. Recrystallization from ether-ligroin (b.p. 90–120°) gave m.p. 46–47° for an analytical sample [Lit. (6) reports this compound as an uncry tallizable oil].

Anal. Calc'd for $C_{11}H_{13}NO$: C, 75.4; H, 7.4; N, 8.0.

Found: C, 75.5, 75.6; H, 7.2, 7.4; N, 8.0, 8.1.

A repetition of the earlier work (6), which involves isolation of pyrrolidine before the benzoylation, led to the same compound obtained above.

N-(ω-Chlorobutyl)benzamide. This compound was obtained from benzoylpyrrolidine by the method of von Braun and Beschke (6).

SUMMARY

A new synthesis of ω-benzoylaminovaleric acid is described. Results of attempts to convert this acid to α-keto-ω-benzoylaminocaproic, acid are given.

Three new compounds, ω-cyanobutylphalimide, N-(ω-cyanobutyl)benzamide, and N-(ω-phenoxybutyl)acetamide, were prepared and characterized.

N-benzoylpyrrolidine was obtained as a crystalline solid instead of an oil as previously reported.

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