NOTES

Benzyl Esters of α-Amino Acids

By Yoshio IWAKURA, Katsumi HAYASHI, Sanam KANG and Kunio NAKAOJI

(Received May 14, 1964)

It has well been known that benzyl esters of α-amino acids provide versatile intermediates for the polypeptide synthesis.[1-3] Various methods have been reported for the preparation of hydrochlorides or other salts of α-amino acid benzyl esters; the treatment of α-amino acid with benzyl alcohol saturated with dry hydrogen chloride,[4-6] the reaction of α-amino acid chloride hydrochloride and benzyl alcohol,[7-9] the treatment of *p*-toluenesulfonic

1) B. F. Erlanger and E. Brand, *J. Am. Chem. Soc.*, **73**, 3508 (1951).
2) B. F. Erlanger and R. H. Hall, ibid., **76**, 5781 (1954).
3) K. Miller and H. Waelsch, ibid., **74**, 1092 (1952).
4) E. Abderhalden and S. Suzuki, *Z. physiol. chem.*, **176**, 101 (1928).
5) R. E. Neuman and E. L. Smith, *J. Biol. Chem.*, **193**, 97 (1951).
6) H. Sachs and E. Brand, *J. Am. Chem. Soc.*, **75**, 4608 (1953).
7) E. Fischer, *Ber.*, **38**, 2914 (1905).
8) R. Ruggli, R. Ratti and E. Henzi, *Helv. Chim. Acta*, **12**, 361 (1929).
9) C. R. Harrinton and T. H. Mead, *Biochem. J.*, **30**, 1958 (1936).

TABLE I. BENZYL ESTER HYDROCHLORIDES OF α-AMINO ACIDS

Amino acid	Benzyl ester hydrochlorides of α-amino acids				
	M. p., °C.	Yield, %	Formula	Nitrogen, %	
				Calcd.	Found
Glycine	129	28	$C_9H_{12}O_2NCl$	6.97	6.99
L-Valine	138	78	$C_{12}H_{18}O_2NCl$	5.85	5.91
DL-Valine	91	95	$C_{12}H_{18}O_2NCl$	5.75	5.91
L-Leucine	145	62	$C_{13}H_{20}O_2NCl$	5.45	5.72
L-Phenylalanine	202	96	$C_{16}H_{18}O_2NCl$	4.80	4.82

acid or the benzenesulfonic acid salt of α-amino acid with benzyl alcohol,[3,10-13] and the reaction of α-amino acid and benzyl alcohol in polyphosphoric acid.[14]

Erlanger and Brand have synthesized benzyl ester hydrochlorides of glycine, D- and L-alanines by causing the corresponding *N*-carboanhydrides (NCAs) to react with benzyl alcohol in the presence of dry hydrogen chloride in ether.[1] In this preparation, the NCAs have been made by the reaction of *N*-carbobenzoxy α-amino acid with phosphorus pentachloride.

During the course of our investigation of poly-α-amino acid synthesis, we have found that the preparation from NCAs makes a convenient method for benzyl ester hydrochlorides of α-amino acids when it is combined with the phosgenation process of α-amino acids, which is now recognized as the most useful route to NCAs. The synthesis of L-alanine benzyl ester hydrochloride by this process has been briefly reported by Rudinger and Pravda.[15]

The phosgenation was carried out in an inert solvent, such as tetrahydrofuran, dioxane, benzene and toluene, at a temperature between 40 and 80°C. When the solvent was removed after the phosgenation was completed, a curde NCA was obtained; this was further treated with a solution of benzyl alcohol in dry ether containing dry hydrogen chloride. The reaction proceeded smoothly at room temperature; carbon dioxide was evolved, and the benzyl ester hydrochloride was precipitated out of the solution. The ether-soluble benzyl ester hydrochloride of L-leucine was isolated by removing the solvent and then recrystallizing it from chloroform/cyclohexane.

In the phosgenation, a prolonged reaction time and a large excess of phosgene decreased the yield of product, mainly because of the formation of *N*-carbonyl α-amino acid chloride.[16] In order to shorten the reaction time, it was necessary to use a finely powdered α-amino acid and to create an efficient agitation through the introduction of phosgene. The preparation is summarized in Table I.

Experimental

L-Phenylalanine Benzyl Ester Hydrochloride. — Into a mixture of 20.0 g (0.12 mol.) of finely powdered L-phenylalanine suspended in 200 ml. of dry tetrahydrofuran, phosgene was stirred efficiently in a thin stream at a temperature between 50 and 60°C. The mixture gave a clear solution after about forty minutes. The solution was then evaporated under reduced pressure, and the residue (crude NCA of L-phenylalanine) was dissolved in 200 ml. of ether containing 7 g. (0.19 mol.) of dry hydrogen chloride. To the solution 20 g. (0.19 mol.) of benzyl alcohol was immediately added. The evolution of carbon dioxide began approximately ten to fifteen minutes after the mixing. The mixture was then allowed to stand at room temperature overnight protected from moisture. The whole mixture became a solid mass because of the precipitation of L-phenylalanine benzyl ester hydrochloride, which was collected on a sintered glass filter and washed repeatedly with dry ether. The product weighed 33.2 g. (96%) and melted at 200~201°C. It was recrystallized from benzene. M. p. 202°C.

L-Valine Benzyl Ester Hydrochloride.—Thirty-five grams (0.30 mol.) of L-valine was phosgenated in 400 ml. of tetrahydrofuran at 50°C. The crude NCA of L-valine was treated with 65 g. (0.6 mol.) of benzyl alcohol in 500 ml. of ether containing 22 g. (0.6 mol.) of dry hydrogen chloride. The product, L-valine benzyl ester hydrochloride, weighed 57 g. (78%). It was recrystallized from ethyl acetate. M. p. 137~138°C.

L-Leucine Benzyl Ester Hydrochloride.—Twenty grams (0.153 mol.) of L-leucine was phosgenated in 200 ml. of tetrahydrofuran at 50°C. A clear solution was obtained within one hour. The crude NCA of L-leucine was treated with 25 g. (0.23 mol.) of benzyl alcohol in 200 ml. of ether containing

10) P. C. Crofts, J. H. H. Markes and H. N. Rydon, *J. Chem. Soc.*, **1959**, 3610.
11) N. Izumiya and S. Makisumi, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zassi*), **78**, 662 (1957).
12) L. Zervas, M. Winitz and J. P. Greenstein, *J. Org. Chem.*, **22**, 1515 (1957).
13) J. P. Cipera and R. V. V. Nicholls, *Chem. & Ind.*, **1955**, 16.
14) B. F. Erlanger and R. H. Hall, *J. Am. Chem. Soc.*, **76**, 5781 (1954).
15) J. Rudinger and Z. Pravda, *Chem. Listy*, **52**, 120 (1958).
16) Y. Iwakura and S. Kang, presented at the 16th Annual Meeting of the Chemical Society of Japan, Tokyo, March, 1963.

10 g. (0.27 mol.) of dry hydrogen chloride. After the solution had been allowed to stand overnight the solvent was removed by distillation. The product was dissolved in a small amount of chloroform and reprecipitated with cyclohexane. The yield was 24.5 g. (62%). M. p. 144~145°C.

Glycine and D,L-Valine Benzyl Ester Hydrochlorides. — They were prepared by the same procedure as has been described above. The results are listed in Table I.

The authors wish to thank the Ajinomoto Co. for supplying various α-amino acids.

Department of Synthetic Chemistry
Faculty of Engineering
The University of Tokyo
Hongo, Tokyo