SHORT COMMUNICATIONS

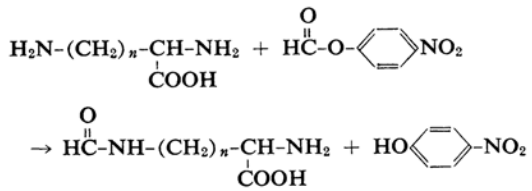
*The Synthesis of N_ω-Formyl Basic Amino Acid**

By Kenji OKAWA and Satoe HASE

(Received March 6, 1963)

It is a well-known fact that Sheehan's method[1], using formic acid and acetic anhydride, is the most convenient procedure for the formylation of α-amino acid because the reaction proceeds relatively well under mild conditions. This method can, however, be used for the *N*-formyl blocking of the α-amino acid; it can not be used for the selective formylation of one of two amino groups in such basic amino acids as ornithine or lysine.

The authors attempted to introduce a formyl group into the end amino group of ornithine or lysine selectively and found that the *p*-nitrophenyl formate was a useful reagent for this purpose, as is shown in the following scheme:



(n=3 or 4)

The formylation of arginine or histidine are now being investigated.

Experimental. — *p-Nitrophenyl Formate.* — A solution of 10.3 g. of *N, N'*-dicyclohexylcarbodiimide[2] in 30 ml. of tetrahydrofuran was added drop by drop into a stirred solution of 6.95 g. of *p*-nitrophenol and 2.76 g. of formic acid in 60 ml. of tetrahydrofuran in an ice bath. After the addition was over, the reaction mixture was allowed to stand for 1 hr. at room temperature. The urea produced was filtered off, and the filtrate was concentrated under reduced pressure until crystals appeared. From the mother solution, other crops of the crystals were obtained. The total yield was 5.3 g. (63.4%). Recrystallization from the mixed solution of tetrahydrofuran and ether gave 4.3 g. (51.4%) of fine crystals; m. p., 72~74°C.

Found: C, 50.48; H, 3.15; N, 8.26. Calcd. for $C_7H_5O_4N$: C, 50.30; H, 3.02; N, 8.38%.

N_δ-Formyl-L-ornithine.—An aqueous solution of 10.1 g. of L-ornithine mono-hydrochloride was neutralized with an equivalent amount of a 1 N aqueous sodium hydroxide solution. Into the above solution was added drop by drop 15.0 g. of *p*-nitrophenyl formate in tetrahydrofuran in an ice bath, while the solution was stirred. The stirring was continued for 6 hr. at room temperature; then the reaction mixture was extracted with ether to remove *p*-nitrophenol, and concentrated in vacuo, and the remaining solution was passed through a column of Amberlite IRC-50 to remove unreacted basic amino acid. The effluent was concentrated in vacuo, and methanol was added until the mixture became a little turbid. The mixture was then allowed to stand in a refrigerator. The crystals produced were filtered and dried. The yield was 5.0 g. (52%). Recrystallization from water methanol gave a pure compound; m. p. 217°C (decomp.); $[\alpha]_D^{15}$ +2.8° (3.97% in water); $[\alpha]_D^{15}$ +17.1° (2.17% in satd. sodium bicarbonate):

Found: C, 44.52; H, 7.64; N, 17.81. Calcd. for $C_6H_{12}O_3N_2$: C, 44.98; H, 7.55; N, 17.49%.

N_ε-Formyl-L-lysine[3].—L-Lysine monohydrochloride was treated with *p*-nitrophenyl formate as above; yield, 35%; m. p., 225~226°C (decomp.); $[\alpha]_D^{15}$ +3.0° (4.27% in water); $[\alpha]_D^{15}$, +17.7° (2.12% in satd. sodium bicarbonate):

Found: C, 48.74; H, 8.22; N, 16.22. Calcd. for $C_7H_{14}O_3N_2$: C, 48.27; H, 8.10; N, 16.08%.

Department of Chemistry
Faculty of Science
Kwansei Gakuin University
Nishinomiya

* Reported in part at the First Peptide Seminar of the Institute for Protein Research (Osaka University), November, 1962.

1) J. C. Sheehan and D-D. H. Yang, *J. Am. Chem. Soc.*, **80**, 1154 (1958).

2) E. Schmidt, F. Hitzler and E. Lahde, *Ber.*, **71**, 1933 (1938).

3) K. Hofmann, E. Stutz, G. Spühler, H. Yajima and E. T. Schwartz, *J. Am. Chem. Soc.*, **82**, 3727 (1960).