potentially advantageous in the determination of trace amounts of penicillin.

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JOSEPH E. SINSHEIMER
DONALD D. HONG*
JOSEPH H. BURCKHALTER
College of Pharmacy
University of Michigan
Ann Arbor, MI 48104

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* Present Address: Drug Standards Laboratory, American Pharmaceutical Association Foundation, Washington, DC 20037

Rapid Peptide Synthesis: Synthesis of the Heptapeptide A_{65}-A_{71} of Abnormal Human α-Hemoglobin

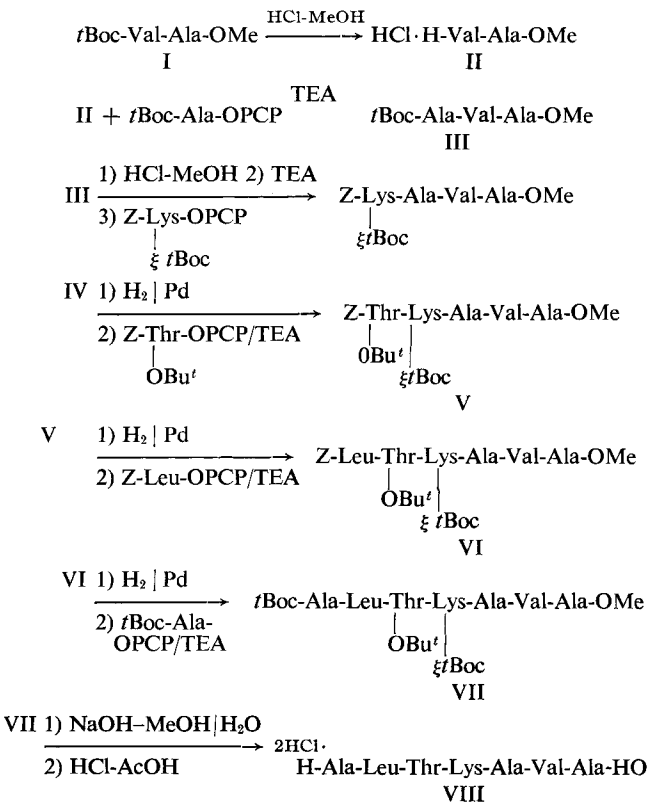
Keyphrases ☐ Peptide synthesis ☐ Heptapeptide A_{65}-A_{71} synthesis—abnormal α-hemoglobin component ☐ IR spectrophotometry—reaction monitoring

Sir:

Recently the *N*-carbobenzoxy and *N*-*t*-butyloxycarbonyl-L-amino acid pentachlorophenyl esters have been described.[1,2] We wish to report the utility of these intermediates for extremely rapid peptide synthesis. For this purpose the synthesis of the heptapeptide, L-alanyl-L-leucyl-L-threonyl-L-lysyl-L-alanyl-L-valyl-L-alanine corresponding to the sequence A_{65}–A_{71} of α-hemoglobin having a point motation at position 68[3–6] is described. The synthesis is shown in Scheme I, its rapidity being due to the minimal necessity to purify the intermediate peptides which is a result of the ease of purification of the starting amino acid pentachlorophenyl esters and their high activity toward aminolysis.

The *N*-*t*-butyloxycarbonyl protecting group was removed from the Dipeptide I using HCl in methanol. Evaporation of the solvent gave the Dipeptide Hydrochloride II, which was coupled to *N*-*t*-butyloxycarbonyl-L-alanine pentachlorophenyl ester in methylene chloride containing one equivalent of triethylamine. By following the IR absorption spectrum of the pentachlorophenyl ester peak at 1775 cm.$^{-1}$ it was observed that the coupling reaction was essentially over after 4 hr. at room temperature. Removal of the solvent gave the crude Tripeptide III. The Tetrapeptide IV was obtained by repeating the cycle of deprotection and coupling with *N*-carbobenzoxy-ξ-*N*-*t*-butyloxycarbonyl-L-lysine pentachlorophenyl ester.

The *N*-carbobenzoxy protecting group was removed from the Tetrapeptide IV by catalytic hydrogenolysis in



Scheme I

dimethylformamide until no further evolution of carbon dioxide was observed. Addition of *N*-carbobenzoxy-L-threonine pentachlorophenyl ester and triethylamine yielded the Pentapeptide V in solution. This cycle of hydrogenolysis and coupling was continued until the protected Heptapeptide VII was obtained. The methyl ester was hydrolysed from VII by use of 1 *N* NaOH in methanol and the remaining protecting groups were removed by HCl in glacial acetic acid, to give the crude free Heptapeptide VIII. Purification of this material was obtained by passage through a column of synthetic polysaccharide (Sephadex G-25) (100 × 2.5 cm.) using water as eluent at a flow rate of 8 ml./hr. The pure heptapeptide $[\alpha]^{26}$ − 34.0° (c 2.2 in water) was eluted as the first major fraction (30% overall yield) as shown by amino acid analysis: Ala, 3.01; Leu, 1.02; Lys, 0.98; Thr, 0.95; Val, 1.01.

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BRIAN J. JOHNSON
Dept. of Chemistry
Tufts University
Medford, MA 02155

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