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THE SYNTHESIS OF D,L-PHOSPHOTRYPTOPHAN

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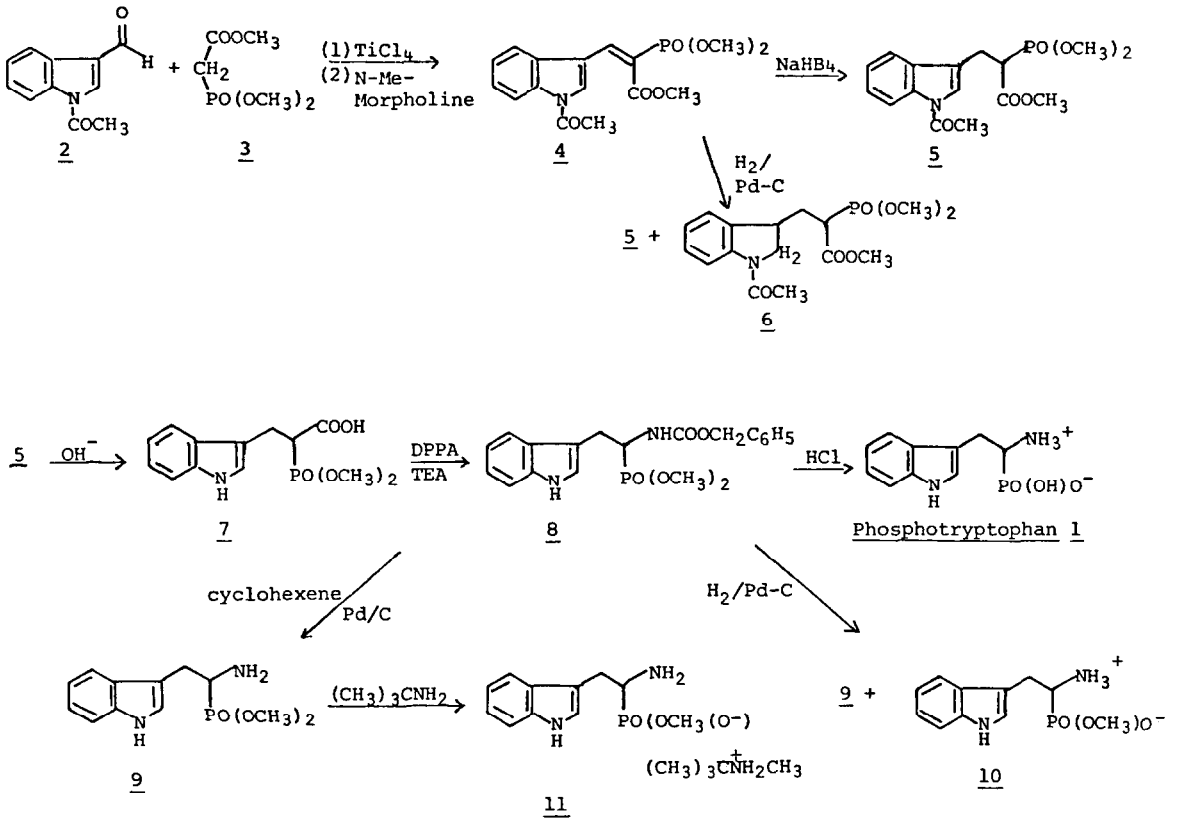
Abstract: The synthesis of phosphotryptophan and its mono methyl ester is described.

During the past several years, interest has been growing in the phosphonic acid analogs of α-amino acids due in part to the occurrence of these acids in nature[1]. While a number of α-amino phosphonic acid analogs of essential amino acids have been synthesized[2], several analogs have not been made. Since these phosphorus containing amino acids may be regarded as isosteres of α-amino acids, our objective is to prepare them and the related phosphinic acids and to determine whether they may be of biological consequence. We now wish to report a new synthesis of phosphotryptophan. A very different, somewhat more classical synthesis of phosphotryptophan, in considerably lower yield from commercially available starting material, has been recently reported[3].

Our synthesis of phosphotryptophan started with N-acetyl-3-indole carboxaldehyde 2 and the trimethyl ester of phosphonoacetic acid 3, subjecting them to the conditions of the Knoevenagel reaction. However, no reaction occurred using the usual catalysts such as piperidine, pyridine acetate and the more recently introduced aluminum oxide procedure[4], even in boiling toluene with a Dean-Stark trap for collection of water and heating for several days. Condensation did occur and produce the desired compound 4 by following essentially the procedure of Lehnert[5], consisting in our case of treating the reagents 2 and 3 first with titanium tetrachloride in scrupulously dried THF and then with either pyridine or N-methylmorpholine. While 4 was obtained using pyridine in the second phase of the reaction, yields were erratic and low ranging between 0-45%. To our surprise, we found that with N-methylmorpholine the reaction in the second phase, as indicated by silica TLC plates, was complete in 20 minutes. Working up the reaction mixture at this point consistently gave yields of 80-85% (m.p. 108-109°). Longer times 24-72 hours, as employed by Lehnert, caused destruction of the product. Condensation of 3 with unacetylated indole-3-carboxaldehyde using N-methylmorpholine in the second phase proceeded poorly. The reaction was slow and incomplete even after prolonged times. The presence of small amounts of the condensation product in the reaction mixture was established by nmr and confirmed by acetylation and isolation of 4.

Scheme



Hydrogenation of 4 with 5% palladium on charcoal at 30 psi produced a mixture of two compounds, the desired compound 5 and the over-reduced indoline 6. Compound 5 was formed exclusively, however, by reduction with $NaBH_4$ at room temperature. The reduction was complete in 10 minutes and pure 5 (m.p. 86-87°) was obtained in 80% yield.

Attempts to convert the carbomethoxy group of 5 via its hydrazide and acid azide into an amino group by the Curtius reactions were unsuccessful. This classical sequence had been effectively used with a number of substituted phosphonoacetates[6]. The objective, however, was achieved by employing the recently introduced and elegant azide transfer agent diphenylphosphoryl azide (DPPA).[7] This was done by heating an equimolecular mixture of 7, prepared from 5 by mild alkaline hydrolysis (m.p. 133-134°C), DPPA and triethylamine for 1 hour, then

adding benzyl alcohol and heating for 12 hours. Using dioxane as a solvent for the reaction, the yield of benzyl carbamate 8 (m.p. 130-131°C) was 75% whereas in benzene, the solvent used previously,[7] the yield was 50%.

The conversion of 8 into dl-phosphotryptophan 1 was accomplished by heating it in concentrated hydrochloric acid under reflux and an atmosphere of nitrogen for 6 hours, concentrating the colorless solution to dryness, dissolving the residue in methanol and neutralizing with propylene oxide. The hydrolysis went smoothly and phosphotryptophan was isolated in 95% yield (m.p. & d.c. 280-281°C). Under the conditions of hydrolysis, 8 went into solution within a half hour indicating that the benzyloxycarbonyl group was first cleaved The structure of phosphotryptophan was confirmed by elemental analysis, high resolution mass spectroscopy and 'H nmr. (It is interesting to note that reports in the literature persist in proclaiming the sensitivity of tryptophan and indole containing compounds to boiling with acids[8]).

Owing to the high polarity of phosphotryptophan it was desirable to make for biological studies a less charged derivative, namely its monomethyl ester 10 (m.p. 260°C). This compound was first isolated from the hydrogenolysis of 8 using 5% Pd/C as catalyst. A mixture of 9 and 10 was obtained from this reaction with the former predominating. Using hydrogen transfer catalysis[9], namely heating a solution of 8 in methanol containing cyclohexene and 5% Pd/C, compound 9 (oxalate m.p. 172-173°C) was obtained exclusively. Selective dealkylation of the latter by refluxing with t-butylamine produced 10 exclusively as its amine salt 11 (m.p. 272-275°C) in excellent yield. Dealkylation of 9, as expected, with concentrated hydrochloric acid readily led to phosphotryptophan. Trimethylsilyl iodide is also effective in dealkylation of 9 but the yield is quite low.[11]

References and Notes

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