Synthesis of *N*(1)-Phosphotryptophan

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N(1)-Phospho-L-tryptophan was prepared by phosphorylation with dimethyl phosphorochloridate of benzyl N^{α}-(benzyloxycarbonyl)-*N*(1)-lithiotryptophanate followed by deprotection with CF_3SO_3H–CF_3CO_2H–Me_2S–*m*-cresol.

Tryptophan metabolites (*e.g.* kynurenine and serotonin) and indole derivatives[1] have received considerable attention in recent years owing to their physiological significance. Some indole alkaloids and mushroom constituents (*e.g.* reserpine and psilocybin) possess psychomimetic activity, and derivatives have been synthesized with antihypertensive, anti-inflammatory, and tranquillizing activity. Likewise, *C*-phosphono analogues of amino acids exhibit a wide range of biological activity; they include naturally occurring antimicrobial[2] and bactericidal[3] agents and herbicides.[4] In view of the biological significance of *N*(1)-acylindoles[1] and *C*-phosphonate derivatives of tryptophan,[5] we have undertaken studies on the synthesis of the novel amino acid *N*(1)-phosphotryptophan and synthetic peptides containing phosphorylated tryptophan. In this communication we describe the preparation of *N*(1)-phosphotryptophan by a simple and efficient three-step procedure.

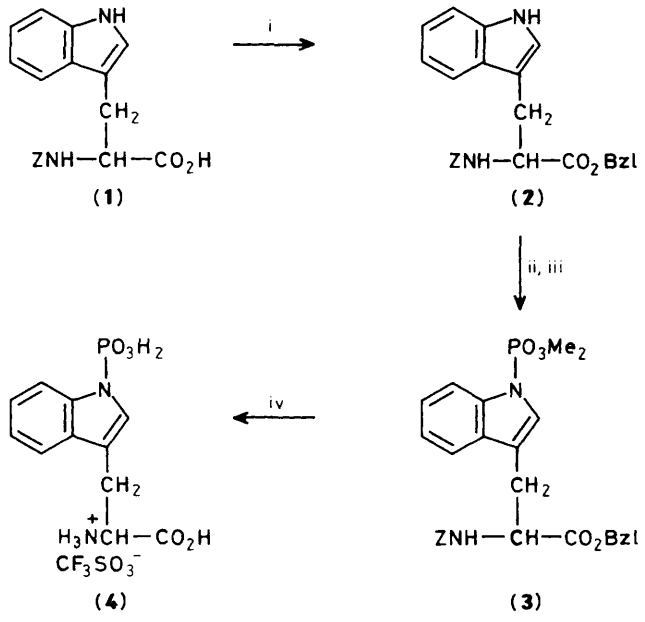
N^{α}-(Benzyloxycarbonyl)tryptophan (**1**) was converted into its benzyl ester and crystallized (m.p. 105—108 °C) after silica gel flash chromatography[6] [ethyl acetate–light petroleum (b.p. 40—60 °C) (40:60)] to remove the excess of benzyl alcohol. Successive *in situ* treatment of Z-Trp-OBzl (**2**) with lithium di-isopropylamide (LDA) (−78 °C, 10 min) in tetrahydrofuran (THF) (distilled from potassium benzophenone ketyl) and dimethyl phosphorochloridate[7] (−60 °C, 10 min; 25 °C, 3.5 h) afforded Z-Trp(PO_3Me_2)-OBzl (**3**) as a pale yellow oil {$[\alpha]_D^{22}$ +15.80° (*c* 1 in $CHCl_3$); ^{31}P n.m.r. δ −0.15 p.p.m. ($CHCl_3$,†)} in 68% yield after silica gel flash chromatography [ethyl acetate–light petroleum (b.p. 40—60 °C) (40:60)]. Treatment of Z-Trp(PO_3Me_2)-OBzl with CF_3SO_3H–CF_3CO_2H–Me_2S–*m*-cresol (1 h, 25 °C) followed by careful repeated precipitation into ether gave pure *N*(1)-phosphotryptophanium trifluoromethanesulphonate (**4**) as a white solid {m.p. 168—171 °C, $[\alpha]_D^{21.5}$ −12.22 (*c* 1 in MeOH); ^{31}P n.m.r. δ −5.60 p.p.m. (MeOH,†)}. The purity was established by amino acid analysis (single peak at 2.23 min); no peaks corresponding to *N*(1)-(*O*,*O*′-dimethylphosphono)-tryptophan‡ (6.95 min) or tryptophan (40.02 min).

^{13}C N.m.r. spectroscopy confirmed the presence of the phosphate moiety on the indole nitrogen of (**4**) (the spectrum displayed characteristic phosphorus-coupled doublet signals for the adjacent carbon atoms).§ In agreement with the bathochromic shift reported for the u.v. spectrum of *N*-alkyl-

† Reference external H_3PO_4 (0 p.p.m.).

‡ Obtained by hydrogenolysis of (**3**) over Pd/C.

§ ^{13}C n.m.r. (90 MHz; D_2O) δ 25.6, 52.8, 109.6 (d, J_{CP} 7.3 Hz), 114.0, 118.5, 121.0, 123.2, 129.0 (d, J_{CP} 6.1 Hz), 129.3 (d, J_{CP} 9.8 Hz), 137.6 (d, J_{CP} 4.8 Hz), and 171.8.



Scheme 1. *Reagents and conditions*: i, BzlOH, toluene-*p*-sulphonyl chloride, 80 °C (71%); ii, THF, LDA (1 equiv.), −78 °C; iii, $(MeO)_2P(O)Cl$, THF, −60 °C, 10 min; 25 °C, 3.5 h (68%); iv, CF_3SO_3H–CF_3CO_2H–Me_2S–*m*-cresol (100% yield by ^{13}C and ^{31}P n.m.r.).

indoles,[8] the u.v. spectra of (**3**) and (**4**) exhibited bathochromic shifts of 6 and 17 nm from the major maximum at 281 nm for (**2**).

To our knowledge, this work constitutes the first reported phosphorylation of the tryptophan indole nitrogen and the first synthesis of *N*(1)-phosphotryptophan. The synthesis of *N*(1)-phosphotryptophan-containing peptides is in progress.

H. A. G. acknowledges a Commonwealth Postgraduate Award and J. W. P. the financial support of the Australian Wool Corporation.

Received, 1st March 1988; Com. 8/00833G

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