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AMINO ACIDS AND PEPTIDES—II[1]

CYCLODEHYDRATION OF SOME TRYPTOPHAN-DIPEPTIDES AND THEIR DERIVATIVES WITH POLYPHOSPHATE ESTER*

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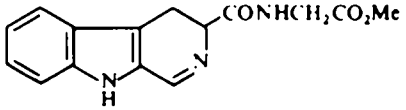
Abstract N-Formyl-DL-tryptophylglycine ester was cyclized to form 3,4-dihydro-β-carboline derivative (II) by means of polyphosphate ester (PPE). In contrast with this, N-acylglycyl-tryptamine (IIIa, b) or -DL-tryptophan ester (IIIc) underwent two-fold cyclodehydration to yield 5H-imidazo[1',5':1,2]pyrido-[3,4-b]indole derivatives (V), probably by way of 3,4-dihydro-β-carboline-type intermediate (IV).

IT HAS been reported that polyphosphate ester (PPE) is a good dehydrating agent in condensation reactions[2,3] as well as a mild agent in some acid-catalyzed rearrangements.[4,5] For example, N-formyl- or -acetyl-DL-tryptophan and their esters were cyclized in the presence of PPE under mild conditions to afford corresponding 3,4-dihydro-β-carboline-3-carboxylic acid derivatives, some of which have not been isolated nor characterized by other conventional methods.[3]

An extension of the above work was undertaken with some dipeptides containing tryptophan and glycine and their related amides as substrates. The present paper is concerned with a facile cyclodehydration of these substrates by means of PPE, some of which led to the formation of imidazopyridoindole derivatives as a result of double cyclodehydration.

N-Formyl-DL-tryptophylglycine methyl ester (I) was first subjected to reaction with PPE. As observed previously with N-formyl-DL-tryptophan ester,[3] I was readily cyclized to yield the 3-substitued 3,4-dihydro-β-carboline derivative II. With regard to the possible application of PPE as a special dehydrating agent for chemical modification in the peptide field, it should be noted that the glycine part of the peptide remained intact during the treatment with PPE.

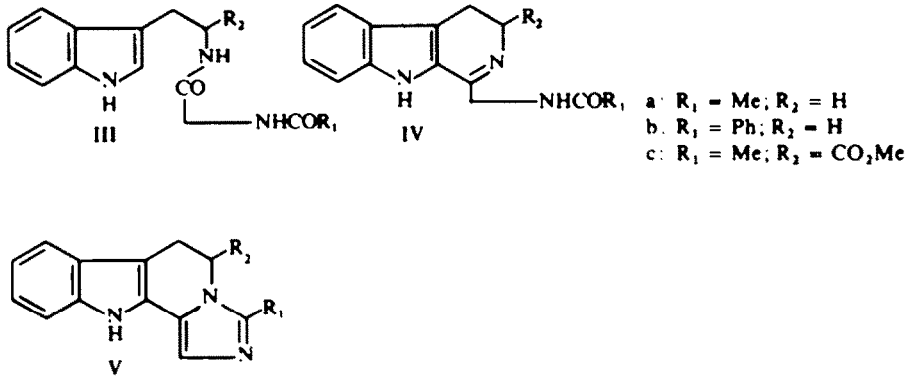


II

The dehydration reaction of glycyl-tryptamine derivatives was examined in order to determine the influence of neighbouring groups surrounding the indole nucleus in the peptide chain. When N-(N-acetylglycyl)tryptamine (IIIa) was refluxed with PPE in chloroform solution for 4 hr, a basic product was isolated as a monoperchlorate in 57% yield, from which a free base (Va) having the composition $C_{14}H_{13}N_3$ (2 moles of water lost from IIIa) was obtained in a pure form. The UV spectrum of

* Part VIII in the series *Polyphosphate Ester as a Synthetic Agent*; for a preceding paper see Ref 5

Va was typical for indoles substituted in the 2-position by an aryl group,[6] being clearly distinguishable from the chromophore of the 3,4-dihydro-β-carboline system, a product initially expected from the cyclization.[3] The assignment of the 5H-imidazo(1′.5′:1.2)pyrido(3.4-b)indole structure for Va was further confirmed by the fact that the analogous benzoyl amide IIIb was also converted by a similar treatment to the known compound Vb of the same tetracyclic structure, synthesized from IIIb by Elliott with phosphoryl chloride.[7]



During the course of the reaction, the absorption band of the UV spectrum of IIIb was readily replaced by the new band at 354 mμ, which was further transformed into the absorption of Vb. In attempting to trap an intermediate of the conversion (IIIb → Vb), IIIb was treated with PPE under milder conditions. As expected, the isolated product was IVb, a primary product of the Bischler-Napieralski cyclization of IIIb, the absorption of which was identical with that observed intermediately. Therefore, the use of PPE may generally permit isolation of a product at a primary stage of reaction if desired, in advantage over phosphoryl chloride. Further, milder reactivity of the reagent without active chlorine atoms would be suitable for application to peptides to minimize side reactions involving amide bonds.

In general, only a few limited observations may be found in the literature on the chemical features of peptides in non-aqueous or dehydrating media.[8] Very little is known about intramolecular dehydration of tryptophan-peptides. For example, attempted dehydration of glycyltryptophan with trifluoroacetic acid, the only attempt of this kind reported as far as we are aware, was unsuccessful despite the fact that the reagent effected the Bischler-Napieralski reaction of acetyltryptophan.[9]

Acetylglycyl-DL-tryptophan methyl ester (IIIc) was similarly heated with PPE to produce Vc in 71% yield. Compound IVc, the most probable intermediate, apparently underwent subsequent cyclization as a result of interaction between the newly formed azomethine group and a neighbouring amide bond. Since this observation on the dipeptide level would suggest that the two-fold cyclodehydration of this type could possibly be a general behaviour of the peptide system involving the indole nucleus, this technique is expected to be used for the purpose of some chemical modification of tryptophan-containing peptides.

EXPERIMENTAL*

* All m.p. are uncorrected.

N-(3,4-Dihydro-β-carboline-3-carbonyl)glycine methyl ester (II). To a soln of N-formyl-DL-tryptophan[3] (1·16 g) and Et_3N (555 mg) in THF (60 ml) ethyl chloroformate (596 mg) was added in several portions under stirring and cooling during 30 min, followed by addition of powdered glycine methyl ester hydrochloride (613 mg). A soln of Et_3N (550 mg) in THF (20 ml) was added under cooling during 30 min and stirring was continued for an additional 2 hr at 0° to −5°. After standing overnight at a room temp, the reaction mixture was filtered and the filtrate evaporated *in vacuo*. The residue was extracted into $CHCl_3$, the extract washed with 10% HCl, 10% Na_2CO_3 aq, water, dried (Na_2SO_4) and evaporated *in vacuo* to leave crude I as a viscous oil; 900 mg. This material gave a single spot in TLC (silicagel; acetone:benzene = 1:0·6); IR cm^{-1} (Nujol): 1750 (ester); 1650 (broad) (amine I).

A mixture of crude I (1199 mg), $CHCl_3$ (10 ml) and PPE[1] (5 g) was stirred at a room temp for 1 hr, and the mixture was evaporated *in vacuo* at a room temp. Cold water (50 ml) was added with cooling and after stirring for 2 hr the soln was applied to a column of cation exchange resin (IR-120; 1·5 g), which was washed with MeOH (150 ml) then eluted with MeOH (1·4 l) containing 70% $HClO_4$ (9·8 g). The eluate was evaporated *in vacuo* below 30° and the residue was recrystallized from MeOH–ether to give the perchlorate of II as pale yellow needles of m.p. 155–156°; 529 mg or 35%; IR cm^{-1} (Nujol): 1745 (ester C=O); 1625 (conjugated C=N⁺). UV λ_{max}^{EtOH} mμ (log ε): 245 (4·12); 364 (4·25). (Found: C, 46·75; H, 4·31; N, 10·60. $C_{15}H_{13}O_3N_3 \cdot HClO_4$ (perchlorate of II) requires: C, 46·95; H, 4·15; N, 10·90%.)

N-(N-Acetylglycyl)tryptamine (IIIa). A suspension of acetylglycine (1·17 g) in THF (50 ml) was mixed with Et_3N (1·00 g) with stirring and ethyl chloroformate (1·00 g) was added at −5° to 0° and stirring continued for 30 min, followed by dropwise addition of a soln of tryptamine (1·60 g) in THF (50 ml). After stirring for 3 hr at room temp, the mixture was evaporated *in vacuo* and the residue dissolved in $CHCl_3$, washed successively with sat. $NaHCO_3$ aq, 10% HCl, sat NaCl aq and dried with Na_2SO_4 and evaporated *in vacuo*. The residue was recrystallized from THF to give IIIa as colourless fine needles, m.p. 145–146°; 1·70 g or 66%; IR cm^{-1} (Nujol): 1645 (amide I). (Found: C, 64·74; H, 6·74; N, 16·27. $C_{14}H_{17}O_2N_3$ (IIIa) requires: C, 64·84; H, 6·61; N, 16·21%).

N-Hippuryltryptamine (IIIb). Hippuric acid (3·60 g) was reacted with tryptamine (3·20 g) as above to give IIIb as colourless needles, m.p. 179–180° from EtOH; 87% (lit.[7] m.p. 180–181°); IR cm^{-1} (Nujol): 1670, 1630 (amide I).

N-Acetylglycyl-DL-tryptophan methyl ester (IIIc). Compound IIIc was prepared from acetylglycine and DL-tryptophan methyl ester as in the case of IIIa yielding colourless plates, m.p. 158–159° from acetone. (Found: C, 60·36; H, 6·00; N, 13·01. $C_{16}H_{19}O_4N_3$ (IIIc) requires: C, 60·55; H, 6·04; N, 13·24%.)

1-(N-Benzoylaminomethyl)-3,4-dihydro-β-carboline (IVb). A mixture of IIIb (964 mg) and PPE (5 g) in $CHCl_3$ (10 ml) was refluxed for 1 hr; cold water (2 ml) was added and most of $CHCl_3$ removed *in vacuo* below 40° and the whole stirred after addition of cold water (20 ml) for 2 hr to decompose excess of PPE, while a viscous oil separated. The supernatant aqueous layer was decanted and the oil dissolved in MeOH (10 ml) and treated with 70% perchloric acid soln (450 mg), then evaporated *in vacuo* to leave a solid residue. The water layer was also treated with 70% perchloric acid (50 mg) to deposit crude perchlorate. Upon recrystallization of the combined solid from MeOH–ether, the perchlorate of IVb was obtained as dark yellow needles, m.p. 216–217° (dec); 996 mg or 80%; UV λ_{max}^{EtOH} mμ (log ε): 232 (4·29); 354 (4·35); IR cm^{-1} (Nujol): 1665 (amide I), 1645 (conjugated C=N⁺). (Found: C, 56·65; H, 4·46; N, 10·39. $C_{19}H_{17}ON_3 \cdot HClO_4$ (perchlorate of IVb) requires: C, 56·55; H, 4·46; N, 10·41%).

6,11-Dihydro-3-methyl-5H-imidazo [1′.5′; 1.2] *pyrido*[3.4-b]*indole* (Va). A mixture of IIIa (777 mg) and PPE (4 g) in $CHCl_3$ (10 ml) was refluxed for 4 hr. The solvent was evaporated *in vacuo* and cold water (30 ml) was added to the residue followed by stirring for 3 hr. The additon of 70% perchloric acid (450 mg) and storage in the cold gave a ppt, which was recrystallized from MeOH to form pale yellow needles, m.p. 303° (dec); 556 mg or 57%; λ_{max}^{EtOH} mμ (log ε): 242 (4·31); 315 (4·38). IR cm^{-1} (Nujol): 1660 (ring C=N⁺). (Found: C, 51·85; H, 4·35; N, 12·95. $C_{14}H_{13}N_3 \cdot HClO_4$ (perchlorate of Va) requires: C, 51·93; H, 4·35; N, 12·98%.)

The free base (Va) was obtained by suspending the perchlorate in EtOAc and treating the suspension with 10% Na_2CO_3 aq. The base, recrystallized from EtOH, formed colourless needles, m.p. 278–279° (dec). IR cm^{-1} (Nujol): 1650 (w) (ring C=N). (Found: C, 75·38; H, 5·85; N, 18·95. $C_{14}H_{13}N_3$ (Va) requires: C, 75·31; H, 5·87; N, 18·82%.)

6,11-Dihydro-3-phenyl-5H-imidazo[1′.5′; 1.2]*pyrido*[3.4-b]*indole* (Vb). Compound IIIb (643 mg) was mixed with PPE (7 g) and the mixture was heated at 120° (oil-bath temp) for 30 min in the atmosphere of

N_2. After decomposition with cold water (100 ml) the reaction mixture was made alkaline with conc NH_4OH and the ppt was collected, dried and recrystallized from MeOH containing a small amount of pyridine to give pale yellow needles, m.p. 307–309° (dec); 349 mg or 61% (lit.[7] m.p. 309–310°); UV λ_{max}^{EtOH} mμ (log ε): 253 (4·23); 332 (4·32). Perchlorate of Vb forms dark yellow needles of m.p. 265–266° (dec) from MeOH–ether. (Found: C, 58·84; H, 4·17; N, 10·94. $C_{19}H_{15}N_3 \cdot HClO_4$ (perchlorate of Vb) requires: C, 59·14; H, 4·15; N, 10·89%.)

6,11-*Dihydro*-3-*methyl*-5-*methoxycarbonyl*-5H-*imidazo*[1′,5′; 1,2]*pyrido*[3,4-b]*indole* (Vc). A soln of IIIc (634 mg) and PPE (7 g) in $CHCl_3$ (10 ml) was refluxed for 4 hr, the solvent was evaporated *in vacuo*, cold water was added and the reaction mixture made alkaline with excess of $NaHCO_3$ and extracted with EtOAc. The extract was washed with sat NaCl aq and dried with Na_2SO_4 and evaporated *in vacuo*. The resultant residue was dissolved in MeOH (5 ml), mixed with 70% perchloric acid (300 mg), evaporated *in vacuo* and the residual solid recrystallized from MeOH to give the perchlorate of Vc as pale yellow needles, m.p. 277–278°, 543 mg or 71%; UV λ_{max}^{EtOH} mμ (log ε): 244 (4·34); 249 (4·32); 316 (4·40); IR cm^{-1} (Nujol): 1750 (ester C=O); 1660 (ring C=N⁺). (Found: C, 50·24; H, 4·39; N, 11·21. $C_{16}H_{15}O_2N_3 \cdot HClO_4$ (perchlorate of Vc) requires: C, 50·32; H, 4·20; N, 11·01%.)

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