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14. Yuichi Kanaoka, Eisuke Sato and Yoshio Ban : Polyphosphate Ester as a Synthetic Agent. Ⅵ.*1 The Bischler-Napieralski Reaction of Tryptamine and Tryptophan Derivatives by Means of Polyphosphate Ester.*2

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Polyphosphate ester (PPE) was shown to be a good agent of the Bischler-Napieralski reaction for the synthesis of 3,4-dihydro-β-carboline derivatives. 3,4-Dihydro-β-carboline-3-carboxylic acid system, a key intermediate in the cyclization of acyltryptophan series, could be isolated and characterized by this procedure.

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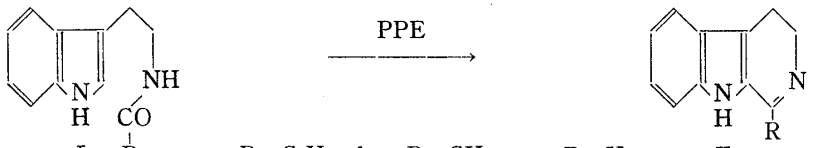
It was previously shown that polyphosphate ester (PPE) is a good agent of the Bischler-Napieralski reaction in the synthesis of dihydroisoquinoline, and further dihydro-5*H*-2-benzazepine, a homologous heterocyclic system.[1] The present paper deals with the extensive application of this agent to the synthesis of β-carboline derivatives.

The cyclization of N-acyltryptamine by the Bischler-Napieralski reaction[2,3] as well as the reaction of tryptamine with carbonyl component by the Pictet-Spengler reaction[4] represents a major synthetic route to a number of β-carboline derivatives,[5,6] an important indole family related to natural products. This well-known cyclodehydration has been customarily conducted employing such a common reagent as phosphorus oxychloride, phosphorus pentoxide or polyphosphoric acid in the range from room temperature to 200°.[5~7] Here may be also added analogous cyclodesulfurization of thioamide derivatives recently reported by Yamada and Omar.[8]

Upon refluxing in chloroform solution with PPE, N-benzoyltryptamine (I-a) was cyclized to 1-phenyl-3,4-dihydro-β-carboline (Ⅱ-a) in 68% yield. Although the same treatment of N-acetyltryptamine (I-b) gave a rather impure product, warming I-b in the presence of PPE without solvent afforded 1-methyl-3,4-dihydro-β-carboline (Ⅱ-b) as expected. These results suggest that 2-position of indole ring is activated to a com-



I a : R=C_6H_5 b : R=CH_3 c : R=H Ⅱ

Chart 1.

*1 Part Ⅴ : Chem. & Ind. (London), **1965**, 473; This Bulletin, **14**, 934 (1966).
*2 Presented at the 85th Annual Meeting of the Pharmaceutical Society of Japan, October, 1965, Tokushima.
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1) Y. Kanaoka, E. Sato, O. Yonemitsu, Y. Ban : Tetrahedron Letters, No. 35, 2419 (1964).
2) W. M. Whaley, T. R. Govindachari : "Organic Reactions," **6**, 74 (1951), J. Wiley, N. Y.
3) R. A. Abramovitch, I. D. Spenser : "Advances in Heterocyclic Chemistry," **3**, 107 (1964), Academic Press, N. Y.
4) Ref. 2), p. 151.
5) W. O. Kermack, J. E. McKail : "Heterocyclic Compounds (Elderfield, ed.)," **7**, 237 (1961), J. Wiley, N. Y.
6) Ref. 3), p. 79.
7) Ref. 2), p. 142.
8) S. Yamada, A.-M. M. E. Omar : This Bulletin, **12**, 738 (1964).

parable extent to the benzenoid ring having methoxyl group which facilitates an electrophilic attack on the position of ring closure.[1]

A survey of the literatures revealed that the yields tend to be somewhat less with formyl group as an acyl moiety, though the influence of the acyl residue on the ease of cyclization of this type is usually of a minor order.[9] It is noteworthy, therefore, that the cyclization of N-formyltryptamine (I-c) took place even at room temperature in the presence of PPE. The synthetic data of 3,4-dihydro-β-carboline in this fashion are listed in the Table I, along with the best yields reported in literatures in the Bischler-Napieralski reaction carried out with other conventional condensing agents.

Table I. 3,4-Dihydro-β-carboline (IIa~c)

Conditions		Product	Yield[a] (%)	Lit.[b]
Temp. (°C)	Time (min.)			
refl. $CHCl_3$	60	IIa	68	36%; P_2O_5, 140°[10]
80°[c]	15	IIb	51	56%; P_2O_5, 140°[11]
refl. $CHCl_3$	60	IIb	34	
room temp.	60	IIc	73	50%; P_2O_5, 110°[12]
refl. $CHCl_3$	30	IIc	68	

a) Yield of purified product
b) Best yields and conditions in literatures
c) Without solvent

As a further application of this method to indole derivatives, simultaneously in line with another series of our study of amino acid, the cyclization of N-acyltryptophan by means of PPE was examined.

Many examples of the Pictet-Spengler reaction of tryptophan have been recorded,[5,13,14] whereas successful reports on the Bischler-Napieralski reaction of N-acyltryptophan have been rarely encountered in literatures. The attempted cyclization by means of classical agents failed to yield corresponding 3,4-dihydro-β-carboline-3-carboxylic acid derivatives.[15] The use of PPA and phosphorus oxychloride brought about the ring closure of N-formyl- (III-a) and N-acetyl-DL-tryptophan (III-b), but this was invariably accompanied by the loss of carbon dioxide and hydrogens to give β-carboline (IV-a) and 1-methyl-β-carboline (IV-b), respectively, as only isolable product in low yields.[16,17] Reaction of PPA with the ethyl esters of III-b and N-phenylacetyl-DL-tryptophan again gave the decarboxylated and aromatized products.[18] Sugasawa and Yoneda recently obtained also an analogous quaternary salt by the cyclization of a N-substituted N-acyltryptophan derivative with phosphorus oxychloride as an agent.[19]

This reaction was later achieved by Tschesche, *et al.* using a mixture of PPA and phosphorus oxybromide.[20] Thus, from III-b and N-propionyl-DL-tryptophan (III:

9) Ref. 2), p. 96.
10) E. Späth, E. Lederer: Ber., **63**, 2120 (1930).
11) *Idem*: *Ibid.*, **63**, 120 (1930).
12) C. Schöpf, H. Steuer: Ann., **558**, 124 (1947).
13) Ref. 2), p. 185.
14) Ref. 3), p. 96.
15) D. G. Harvey, E. J. Miller, W. Robson: J. Chem. Soc., **1941**, 153.
16) H. R. Snyder, C. H. Hansch, L. Katz, S. M. Parmerter, E. S. Spaeth: J. Am. Chem. Soc., **70**, 219 (1948).
17) H. R. Snyder, F. X. Werber: *Ibid.*, **72**, 2962 (1950).
18) I. Murakoshi: Yakugaku Zasshi, **77**, 550 (1957); C. A., **51**, 14720 (1957).
19) S. Sugasawa, N. Yoneda: Private communication; N. Yoneda: This Bulletin, **13**, 1231 (1965).
20) R. Tschesche, H. Jenssen, P. N. Rangachari: Chem. Ber., **91**, 1732 (1958).

R=Et; R′=H), 1-methyl-3,4-dihydro-β-carboline-3-carboxylic acid (V-b)*4,20) and 1-ethyl-3,4-dihydro-β-carboline-3-carboxylic acid (V: R=Et; R′=H)23) were prepared, respectively. It must also be noted that trifluoroacetic acid could effect the cyclization of Ⅲ-b to give V-b although the yield was poor.24) In order to circumvent the difficulty in the Bischler-Napieralski reaction of this type, V-b was alternatively synthesized by the decarboxylation of 1-methyl-3,4-dihydro-β-carboline-3,3-dicarboxylic acid or the dehydration of 1-hydroxymethyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid (Ⅷ: R=CH_2OH).25)

N-Acetyl-DL-tryptophan methyl ester (Ⅲ-d) was prepared by acetylation of DL-tryptophan methyl ester (Ⅶ) or esterification of Ⅲ-b. However, a conventional esterification of Ⅲ-a with methanol and anhydrous hydrochloric acid resulted in cleavage of formyl bond, in accord with the known acid-catalyzed solvolytic behavior of N-formyl group.26) N-Formyl-DL-tryptophan methyl ester (Ⅲ-c) was obtained from DL-tryptophan methyl ester (Ⅶ) by formylation with a mixture of formic acid and acetic anhydride to form colorless plates of m.p. 121°, which is different from the reported m.p. 97~99°, for this compound.17) In order to establish the structure of Ⅲ-c, therefore, Ⅲ-a was methylated with diazomethane as described in the literature. The methyl ester thus obtained had m.p. 121° and was shown to be identical with the sample prepared from Ⅵ by way of Ⅶ. The relationship is shown in the accompanying equations.

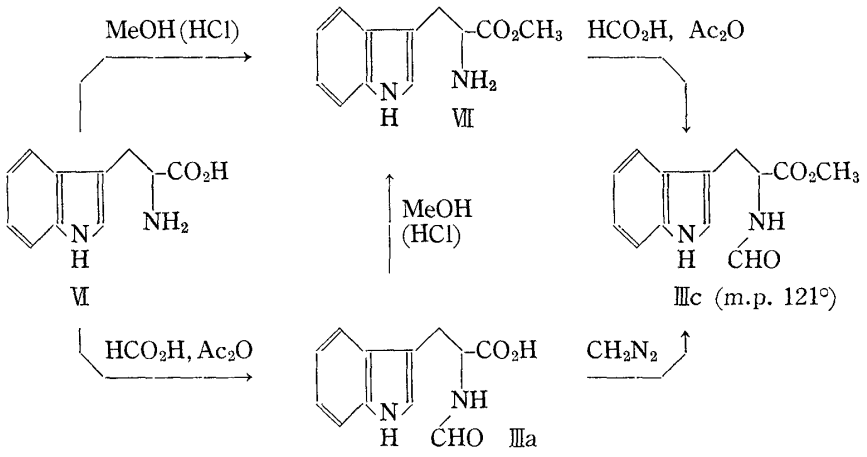


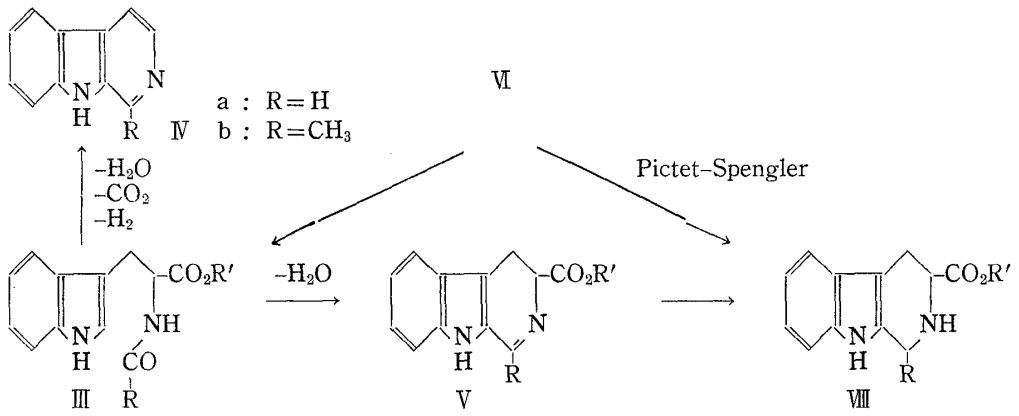
Chart 2.

By refluxing in chloroform solution with PPE for an hour, N-acetyl-DL-tryptophan (Ⅲ-b) gave 1-methyl-3,4-dihydro-β-carboline-3-carboxylic acid (V-b), purified through cation-exchange resin column, in a yield of 44%. The similar reaction with the methyl ester (Ⅲ-d), however, gave the same product (V-b) instead of the expected ester (V-d) in 20% yield, apparently due to hydrolysis during the purifying process. When the above resin column was eluted with methanol containing perchloric acid, perchlorate of the methyl ester (V-d) was eventually obtained from Ⅲ-d. The treatment of V-b with perchloric acid in methanol yielded the same perchlorate. The

*4 This compound had been obtained without recognition of the structure.21) Yamada and Omar prepared V-b by cyclodesulfurization method.22)

21) F. Wrede, G. Feierviegel: Ber., **66**, 1073 (1933).
22) S. Yamada, A.-M. M. E. Omar: Abs. 85th Annual Meeting of the Pharm. Soc. Japan, p. 247 (1965).
23) R. Tschesche, H. Jenssen: Chem. Ber., **93**, 271 (1960).
24) R. A. Uphaus, L. I. Grossweiner, J. J. Katz, K. D. Kopple: Science, **129**, 641 (1959).
25) I. D. Spenser: Can. J. Chem., **37**, 1851 (1959).
26) J. C. Sheehan, D.-D. H. Yang: J. Am. Chem. Soc., **80**, 1154 (1958).

structures of V-b and V-d were confirmed by melting points, analyses, spectra and conversion to the known tetrahydro-β-carboline derivatives.



a : R=H, R'=H, b : R=CH_3, R'=H
c : R=H, R'=CH_3, d : R=CH_3, R'=CH_3

Chart 3.

The cyclization of N-formyl-DL-tryptophan (Ⅲ-a) or the methyl ester (Ⅲ-c) was elaborated by Snyder, *et al.* Attempts to obtain 3,4-dihydro-β-carboline-3-carboxylic acid (V-a) or its ester (V-c), a possible initial product which was assumed to be transformed into Ⅳ-a, were unsuccessful under a variety of conditions.[17] Thus, V-a and V-c have not been isolated so far although the presence in the reaction mixture with PPA-phosphorus oxybromide was suggested by paper chromatography.[23]

Unusual ease of cyclization with N-formyl group at the PPE procedure was again realized in the case of tryptophan derivatives. When Ⅲ-a was subjected to reaction with PPE in chloroform solution at room temperature followed by careful treatment with perchloric acid, V-a was obtained as crystalline perchlorate in 82% yield. Ⅲ-c also gave V-c in a similar way in 91% yield. To secure good yield of V-a or V-c, reaction media must be kept acid throughout working-up. This salts, fairly stable in a purified state, are unstable especially in alkaline solution and suffer rapid oxidative change above pH 7. Thus, only the controlled cyclizing conditions by means of PPE as above permitted the successful isolation of V-a and V-c. The structures of the salts (V-a and V-c) were definitely supported by the characteristic absorption at 1620~1610 cm^{-1} in infrared and at 365~367 mμ (log ε, 4.16~4.19) in ultraviolet spectra due to 3,4-dihydro-β-carboline moiety. For further confirmation of the structure, V-a and V-c were converted by reduction with sodium borohydride to the corresponding tetrahydro-β-carboline bases (Ⅷ-a and Ⅷ-c), which were shown to be identical with the specimen prepared from Ⅵ or Ⅶ and formaldehyde by the Pictet-Spengler reaction by mixed melting point and comparison of infrared spectra.

The special properties of 3,4-dihydro-β-carboline-3-carboxylic acid system, including the marked sensitivity of V-a to oxidation, have been obviously responsible for difficulty in isolation recorded in literatures.[11~13] Furthermore, this system may possibly be concerned in part with biochemically interesting color or fluorescent reactions of tryptophan-containing proteins.[24] This chemical features will be the subject of another report.

Experimental*5

N-Benzoyltryptamine (Ia)——Prepared by benzoylation of tryptamine with benzoyl chloride in pyridine. Colorless blades from benzene, m.p. 133~135°(lit.,[10] m.p. 137~138°). IR ν_{max}^{Nujol} cm^{-1} : 1640 (amide I).

*5 Melting points are uncorrected.

N-Acetyltryptamine (Ib)——Prepared by acetylation of tryptamine with acetic anhydride. Colorless needles from ether-petroleum ether, m.p. 75～76°(lit.,[11] m.p. 77°). IR ν_{max}^{Nujol} cm^{-1} : 1640 (amide I).

N-Formyltryptamine (Ic)——A mixture of tryptamine (2056 mg.) and formamide (1.0 g.) was heated at 180°(bath-temp.) for 4 hr. Removal of formamide *in vacuo* left a brown oil, which was taken in $CHCl_3$. This extract was washed twice with 10% HCl, then with satd. aq. NaCl solution and dried (Na_2SO_4). The solvent was evaporated *in vacuo* to leave crude Ic as a reddish brown oil, 1.78 g. (74%) (lit.,[12] m.p. 76°; lit.,[27] faint yellow syrup). IR ν_{max}^{Nujol} cm^{-1} : 1660 (amide I). This product was used for cyclization without further purification.

1-Phenyl-3,4-dihydro-β-carboline (IIa)——A solution of 500 mg. of Ia and 2.5 g. of PPE[28] in $CHCl_3$ (50 ml.) was refluxed for 1 hr. After removal of the solvent *in vacuo*, cold water was added to the reaction mixture under ice-cooling and the whole was stirred for 2 hr. to effect complete decompositon of the reagent. The solution was extracted with ether to remove non-basic material, made alkaline with 10% NaOH. The extract was washed with satd. aq. NaCl and dried (Na_2SO_4). Removal of the solvent left a yellow solid, which was recrystallized from benzene to form pale yellow pillars of m.p. 211～212°, 318 mg. or 68% (lit.,[29] m.p. 213°; lit.,[10] m.p. 221～222°). IR ν_{max}^{Nujol} cm^{-1} : 1615 (conjugated C=N). UV λ_{max}^{EtOH} mμ (log ε) : 232 (4.35); 248 (4.38); 326 (4.15). Picrate, orange fine needles from EtOH, m.p. 236～238°(decomp.) (lit.,[29] m.p. 235° (decomp.); lit.,[10] m.p. 240°(decomp.)). Perchlorate, yellow needles from MeOH-ether, m.p. 233～234°. IR ν_{max}^{Nujol} cm^{-1} : 1620 (conjugated C=N^+). UV λ_{max}^{EtOH} mμ (log ε) : 256 (4.07); 277 (3.98); 375 (4.35). *Anal.* Calcd. for $C_{17}H_{14}N_2 \cdot HClO_4$ (perchlorate of IIa) : C, 58.88; H, 4.36; N, 8.08. Found : C, 59.05; H, 4.41; N, 7.85.

1-Methyl-3,4-dihydro-β-carboline (Harmalan) (IIb)——a) Without solvent : A mixture of 400 mg. of Ib and 3.0 g. of PPE was warmed at 80°(bath temp.) under occasional shaking for 15 min. After cooling, cold water (40 ml.) was added and the mixture was stirred for 3 hr., filtered, extracted with ether to remove non-basic material, made alkaline with 20% NaOH, and extracted with ether. The extract was washed with water, dried (Na_2SO_4) and evaporated to dryness, and the residue was recrystallized from 10% EtOH forming pale yellow needles of m.p. 180～181°; 173 mg. or 51% (lit.,[11] m.p. 181～182°; lit.,[30] m.p. 182～183°). IR ν_{max}^{Nujol} cm^{-1} : 1625 (conjugated C=N). UV λ_{max}^{EtOH} mμ (log ε) : 236 (4.21); 241 (shoulder) (4.19); 317 (4.19). Picrate, yellow needles from MeOH, m.p. 234～235°(decomp.). *Anal.* Calcd. for $C_{12}H_{12}N_2 \cdot C_6H_3O_7N_3$ (picrate of harmalan) : C, 52.30; H, 3.66; N, 16.94. Found : C, 52.34; H, 3.76; N, 16.74. Perchlorate, yellow needles from MeOH-ether, m.p. 208～209°. IR ν_{max}^{Nujol} cm^{-1} : 1640 (conjugated C=N^+). UV λ_{max}^{EtOH} mμ (log ε) : 246 (4.12); 354 (4.43). *Anal.* Calcd. for $C_{12}H_{12}N_2 \cdot HClO_4$ (perchlorate of harmalan) : C, 50.62 ; H, 4.60; N, 9.84. Found : C, 50.62; H, 4.63; N, 9.87.

b) In chloroform solution : Treatment of Ib with PPE in $CHCl_3$ solution as in the case of IIa gave basic product, from which 34% of IIb was isolated as perchlorate.

3,4-Dihydro-β-carboline (Norharmalan) (IIc)——a) At room temp. : PPE (3 g.) was added to a solution of Ic (563 mg.) in $CHCl_3$ (50 ml.) and the mixture was stirred at room temp. for 1 hr. Cold water was added under ice-cooling, followed by stirring for 2 hr. to decompose the excess of the reagent. Most of $CHCl_3$ was removed at room temp. *in vacuo* and the solution thus obtained was extracted with EtOAc to remove nonbasic material, made alkaline with 10% aq. NaOH and the amorphous product separated was taken in ether. The extract washed with satd. aq. NaCl and dried (Na_2SO_4). On removal of the solvent the crude product was obtained as a pale yellow solid of m.p. 91～95°; 424 mg. or 81% (lit.,[27] m.p. 93～99° for crude base). IR ν_{max}^{Nujol} cm^{-1} : 1625 (conjugated C=N). UV λ_{max}^{EtOH} mμ (log ε) : 237 (4.12); 246 (4.10); 320 (4.05). Picrate was prepared from the crude base (204 mg.) forming orange yellow fine prisms of m.p. 233～234° (decomp.) from EtOH (lit.,[12] m.p. 233°(decomp.); lit.,[31] m.p. 233～234°); yield, 420 mg. Perchlorate was obtained from the crude base (20 mg.) as pale reddish brown needles from EtOH, m.p. 205～206° (decomp.), (lit.,[12] m.p. 205°(decomp.)); yield, 29 mg. IR ν_{max}^{Nujol} cm^{-1} : 1640 (conjugated C=N^+). UV λ_{max}^{EtOH} mμ (log ε) : 245 (4.03); 361 (4.22). Yield of purified IIc in the cyclization, based on the amount of perchlorate or picrate, as purified was 73% or 71%, respectively.

b) On refluxing in chloroform solution : A solution of Ic (657 mg.) and PPE (3.5 g.) in $CHCl_3$ (50 ml.) was refluxed for 30 min. After removal of the solvent *in vacuo*, and working up as above, IIc was obtained picrate in 68% yield.

N-Formyl-DL-tryptophan (IIIa)——DL-Tryptophan (V) was formylated with 98% formic acid and acetic anhydride as in the lit.[32] Colorless needles from water or EtOH-benzene, m.p. 166～167°; lit.,[32] m.p. 167～168°; lit.,[17] m.p. 161～162.5°). IR ν_{max}^{Nujol} cm^{-1} : 1715 (C=O); 1625 (amide I).

DL-Tryptophan Methyl Ester (VII)——V was treated with MeOH·HCl as in the lit.[33] Hydrochloride of VII, colorless needles from MeOH-ether, m.p. 224～225°(decomp.) (lit.,[34] m.p. 225°(decomp.)). The similar

27) M. Onda, M. Sasamoto : This Bulletin, **5**, 305 (1957).
28) Y. Kanaoka, M. Machida, O. Yonemitsu, Y. Ban : *Ibid.*, **13**, 1065 (1965).
29) Y. Asahina, S. Osada : J. Pharm. Soc. Japan, **534**, 63 (1929).
30) R. H. F. Manske, W. H. Perkin, Jr., R. Robinson : J. Chem. Soc., **1927**, 1.
31) R. N. Gupta, I. D. Spenser : Can. J. Chem., **40**, 2049 (1962).
32) C. E. Dalgleish : J. Chem. Soc., **1952**, 137.

treatment of IIIa also gave VII-hydrochloride as a result of solvolysis. VII was liberated from the hydrochloride with K_2CO_3 and used without purification.

N-Formyl-DL-tryptophan Methyl Ester (IIIc)——a) From VII: To a solution of VII (2.47 g.) in 98% formic acid (10 ml.) was added dropwise 2 ml. of acetic anhydride at room temp. After stirring at room temp. for 2 hr., water (30 ml.) was added under ice-cooling and the whole was stirred for 3 hr. and was stood overnight. Pale yellow precipitate which had separated was collected and recrystallized from benzene to give colorless plates of m.p. 121°(lit.,[17] m.p. 97~99°); yield, 2.07 g. or 77%. IR ν_{max}^{Nujol} cm^{-1}: 1740 (ester C=O); 1670 (amide I). *Anal.* Calcd. for $C_{13}H_{14}O_3N_2$ (IIIc): C, 63.40; H, 5.73; N, 11.38. Found: C, 63.61; H, 5.59; N, 11.15.

b) From IIIa: IIIa (320 mg.) was methylated with diazomethane in ether solution.[17] The reaction mixture was stood overnight in a refrigerator and the precipitate was collected, washed with aq. $NaHCO_3$ and then aq. NaCl, dried and recrystallized from benzene or aq. MeOH; yield, 358 mg. or 81%. The product was identical with the sample obtained above.

N-Acetyl-DL-tryptophan (IIIb)——VI was acetylated in acetic acid solution with acetic anhydride. Colorless plates from 20% EtOH, m.p. 204~205° (lit.,[35] m.p. 206°). IR ν_{max}^{Nujol} cm^{-1}: 1720 (C=O), 1630 (amide I).

N-Acetyl-DL-tryptophan Methyl Ester (IIId)——A solution of VII (6450 mg.) in acetic acid (85 ml.) was rapidly heated to boil and the oil bath was removed to avoid prolonged heating. To this reaction mixture was added acetic anhydride (7 ml.) in a minute and the mixture was boiled for 2 min. and cooled immediately. Removal of acetic acid and acetic anhydride *in vacuo* left an oil, which solidified on treatment with water. The product was washed well with aq. NaCl, dried and recrystallized from MeOH to give colorless plates of m.p. 141~142°; yield, 79%. IR ν_{max}^{Nujol} cm^{-1}: 1740 (ester C=O), 1660 (amide I). *Anal.* Calcd. for $C_{14}H_{16}O_3N_2$ (IIId): C, 64.60; H, 6.20; N, 10.76. Found: C, 64.50; H, 6.12; N, 10.99.

1-Methyl-3,4-dihydro-β-carboline-3-carboxylic Acid (Vb)——a) From IIIb: A solution of IIIb (738 mg.) and PPE (4 g.) in $CHCl_3$ (30 ml.) was refluxed for 1 hr. The solvent was distilled off *in vacuo* and the residue was mixed with water (50 ml.) and 10% HCl (3 ml.). The whole was stirred for 4 hr. at room temp., filtered and the filtrate was absorbed on Amberlite IR-120 cation exchange resin (1.5 g.; 100 mesh). The resin column was washed by elution with MeOH (30 ml.) and then water (100 ml.), and eluted with 5% NH_4OH (450 ml.). The eluate was concentrated *in vacuo* below 40° to give a yellow precipitate, which was collected and recrystallized from MeOH forming yellow needles of m.p. 197~198°(decomp.); 303 mg. or 44% (lit.,[20] m.p. 198~199°; lit.,[24] m.p. 199°(decomp.); lit.,[25] m.p. 189~190°). UV λ_{max}^{EtOH} mμ (log ε): 244 (4.04); 354 (4.25) (lit.,[20] 243.5 (4.007); 350 (4.251)). Vb thus obtained was shown to be identical with the sample prepared with PPA-$POBr_3$[20] by mixed m.p. and IR comparison. Tetrachloroaurate was obtained by mixing a solution of the base (30 mg.) in 15% HCl (3 ml.) and a warm 50% aq. solution of $HAuCl_4 \cdot 4H_2O$ (70 mg.) as a precipitate, which was collected and recrystallized from 15% HCl containing a small amount of $HAuCl_4$ to form yellow-red fine needles, m.p. 181~182°(decomp.); 56 mg. (75%) (lit.,[21] m.p. 179°; lit.,[20] m.p. 175~179°). Crystallization of Vb from water gave yellow needles of m.p. 194~195° (decomp.), which gave IR spectrum slightly different from that of the sample from MeOH, indicating that they are probably in dimorphic relation. Though comparison of IR in solution was not possible due to limited solubility, mixed melting point of them showed no depression. The former was converted to the latter by recrystallization from MeOH and *vice versa*.

b) From IIId: IIId (780 mg.) was treated with PPE (4 g.) in the manner as described above. Vb was isolated in 20% yield as yellow needles of m.p. 197~198°(decomp.), identical in IR and mixed melting point with that obtained above.

Methyl 1-Methyl-3,4-dihydro-β-carboline-3-carboxylate (Vd)——a) From Vb: To a solution of Vb (126 mg.: 0.42 mmole) in MeOH (100 ml.) was added 70% aq. $HClO_4$ (120 mg.; 0.83 mmole) and MeOH was removed *in vacuo*. Yellow-brown solid which separated was collected, washed with ether, dried and recrystallized from MeOH-ether forming yellow needles of m.p. 201~202°(decomp.); 168 mg. or 89%. IR ν_{max}^{Nujol} cm^{-1}: 1740 (ester C=O); 1630 (conjugated C=N^+). UV λ_{max}^{EtOH} mμ (log ε): 245 (4.08); 358 (4.35). *Anal.* Calcd. for $C_{14}H_{14}O_2N_2 \cdot HClO_4$ (perchlorate of Vd): C, 49.05; H, 4.38; N, 8.18. Found: C, 49.25; H, 4.26; N, 8.19.

b) From IIId: IIId (691 mg.) was subjected to reaction with PPE (4 g.) as in the case of Vb and applied to column of Amberlite IR-120. After washing, the product was eluted with a solution of 70% aq. $HClO_4$ (640 mg.) in MeOH (50 ml.) six times. Concentration of the eluate at room temp. *in vacuo* gave a colored precipitate, which was recrystallized from MeOH-ether to form yellow needles of m.p. 201~202° (decomp.), shown to be identical with perchlorate of Vd by mixed m.p. and IR comparison; 307 mg. or 34%.

1-Methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic Acid (VIIIb)——a) From VI: VI (200 mg.) was reacted with acetaldehyde in aq. dil. H_2SO_4 as described in lit.[16] VIIIb was obtained as colorless needles of m.p. 247~248°(decomp.) from EtOH-dil. NH_4OH (lit.,[16] m.p. 247~248°(decomp.)); yield, 75%.

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34) A. Patchornik, M. Sela, E. Katchalski: J. Am. Chem. Soc., **76**, 299 (1954).
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b) From (Vb): Sodium borohydride (7 mg; 0.18 mole) was added to a solution of Vb (80 mg.; 0.35 mmole) in MeOH (80 ml.) under stirring, while the color of the solution soon disappeared. The solvent was evaporated *in vacuo* to leave a viscous oil, which was dissolved in water (3 ml.) and filtered. The filtrate was stood at room temp. after addition of one drop of HOAc to deposit crystals. Recrystallization from EtOH-dil. NH_4OH gave colorless needles of m.p. 247~248°(decomp.) in 87% yield, which was shown to be identical with VIIIb obtained from VI by mixed m.p. and IR comparison.

Methyl 1-Methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylate (VIIId)——a) From VIIIb: VIIIb (600 mg.) was esterified with HCl-MeOH as described in lit.[16] VIIId was obtained as pale yellow needles of m.p. 128~129° from benzene-hexane (lit.,[16] m.p. 129~130°) in 65% yield. IR ν_{max}^{Nujol} cm^{-1}: 1735 (ester C=O).

b) From Vd: The perchlorate of Vd (135 mg.; 0.394 mmole) was dissolved in MeOH (30 ml.) and to this solution was added sodium borohydride (8 mg.; 0.21 mmole) under ice-cooling. One drop of HOAc was added to this discolored solution and the solvent was removed *in vacuo* at room temp. The residue was triturated with 10% aq. HCl (2 ml.), cooled and the precipitate was collected, washed with cold water, dried and suspended in ether. The suspension was made alkaline by adding cold satd. aq. Na_2CO_3 containing 20 mg. of Na_2CO_3, extracted with ether and the extract was washed with water, dried (Na_2SO_4) and evaporated. The solid thus obtained was recrystallized from benzene-hexane to form pale yellow needles of m.p. 128~129° in 68% yield, which was shown to be identical with the sample from VIIIb by mixed m.p. and IR comparison.

3,4-Dihydro-β-carboline-3-carboxylic Acid (Va)——A solution of IIIa (493 mg.) and PPE (2.5 g.) in $CHCl_3$ (40 ml.) was stirred at room temp. for 1 hr., when the band at 280 mμ in UV of the original solution had been completely replaced by the band at 365 mμ. Cold water was added under ice-cooling followed by stirring for 2 hr. to decompose the reagent. Most of $CHCl_3$ was removed *in vacuo* at room temp. and to this solution was added excess of 70% aq. $HClO_4$ and the mixture was stood for 1 hr. The deposited perchlorate was collected, washed with a small amount of cold water and dried. This product was dissolved in warm MeOH (ca. 40 ml.), followed by addition of abs. ether to a turbid point and stood overnight. The perchlorate was obtained as yellow needles, m.p. 213~214° (decomp.), 549 mg. or 82%. IR ν_{max}^{Nujol} cm^{-1}: 1620 (conjugated C=N$^+$). UV λ_{max}^{EtOH} mμ (log ε): 245 (3.90); 365 (4.16). *Anal.* Calcd. for $C_{12}H_{10}O_2N_2 \cdot HClO_4$ (perchlorate of Va): C, 45.93; H, 3.56; N, 8.86. Found: C, 45.75; H, 3.36; N, 9.03.

1,2,3,4-Tetrahydro-β-carboline-3-carboxylic Acid (VIIIa)——To a solution of Va (100 mg.) in MeOH (20 ml.) was added powdered sodium borohydride (7 mg.) and the whole was stirred at room temp. for 5 min. MeOH was removed *in vacuo* to leave a solid, which was dissolved in small amount of water, followed by addition of HOAc (1 drop) to form a white precipitate. This crude product was collected and recrystallized from dil. NH_4OH to give VIIIa as colorless feathers of m.p. 299~300° (decomp.); 50 mg. *Anal.* Calcd. for $C_{12}H_{12}O_2N_2$ (VIIIa): C, 66.65; H, 5.59; N, 12.96. Found: C, 66.51; H, 5.67; N, 13.25. The melting point of this compound was unchanged on admixture with the sample, m.p. 298~300°(decomp.), prepared by the Pictet-Spengler reaction of VI.[6,36] IR spectra of them were superimposable.

Methyl 3,4-Dihydro-β-carboline-3-carboxylate (Vc)——A solution of IIIc (1412 mg.) in $CHCl_3$ (50 ml.) was treated with PPE (7.5 g.) as in the case of Va. Vc was obtained as perchlorate, yellow needles of m.p. 178~180°(decomp.) from MeOH-ether; yield, 1579 mg. or 91%. IR ν_{max}^{Nujol} cm^{-1}: 1610 (conjugated C=N$^+$). UV λ_{max}^{EtOH} mμ (log ε): 245 (4.06); 367 (4.19). *Anal.* Calcd. for $C_{13}H_{12}O_2N_2 \cdot HClO_4$ (perchlorate of Vc): C, 47.59; H, 4.00; N, 8.52. Found: C, 47.74; H, 3.95; N, 8.45.

Methyl 1,2,3,4-Tetrahydro-β-carboline-3-carboxylate (VIIIc)——Vc (32 mg.) was reduced with sodium borohydride (2 mg.) as in the case of VIIIa to give VIIIc as colorless blades of m.p. 190~192°(decomp.), 22 mg. *Anal.* Calcd. for $C_{13}H_{14}O_2N_2$ (VIIIc): C, 67.81; H, 6.13; N, 12.17. Found: C, 67.87; H, 6.03; N, 12.02. This was shown to be identical with the sample prepared by the Pictet-Spengler reaction of VI[6,36] (m.p. 192~193°(decomp.)) by mixed m.p. and IR comparison.

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