[Chem. Pharm. Bull. 19(3) 545—551 (1971)]

UDC 547.757.04 : 542.951

Indoles. I. Syntheses of 1-Acetyltryptophan and Its Derivatives, and Their Friedel-Crafts Reaction

SADAO OHKI and TATSUO NAGASAKA

Tokyo College of Pharmacy[1]

(Received September 1, 1970)

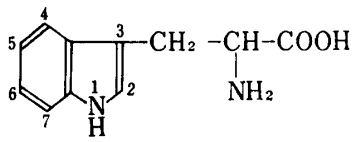
1-Acetyltryptophan and its derivatives were synthesized in good yields from *dl*-tryptophan.

Reduced nucleophilic activity in the indole ring by 1-acetylation was examined in the reaction of 1-acetyl derivatives with *o*-nitrophenylsulfenyl chloride (NPS–Cl) and the Friedel–Crafts reaction of them. In the reaction with NPS–Cl, **7**, **10**, and **12** did not show the activity of 2-position in the indole ring, but the Friedel–Crafts reaction of **12** (chloride) afforded **15** cyclized to 2-position of the indole, different from only one example reported previously by Szmuszkovicz of the same reaction of 1-acetyl indole derivatives which cyclized to 4-position.

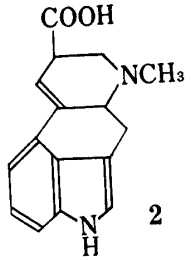
Tryptophan (**1**) is a biologically important material which is one of the essential amino acids in animals and a precursor of various alkaloids in plants. Hence, it seemed of significant to convert **1** into a variety of indole derivatives in connection with a search for new pharmacologically active materials. Further, *dl*-tryptophan is an easily available material today.

An attempt was first made to acylcyclize the carboxyl group in **1** to 4-position of the indole ring to prepare a lysergic acid (**2**) type compound.

In general, 2(and 3)-position of indole exhibits a strong nucleophilic activity. For example, it is well known that when tryptophan peptide (**3**) with *o*-nitrophenylsulfenyl substituent protecting the amino group is treated with dilute hydrochloric acid, sulfenyl chloride is liberated which immediately attacks the 2-position of indole to afford **4** quantitatively.[2] Therefore, it is necessary at least to inhibit the activity of this 2(and 3)-position for acylation of the 4-position. Some time ago, Szmuszkovicz[3] reported the acylcylization of 4-position in 1-acetyl-3-indolesuccinic anhydride (**5**) by the Friedel–Crafts reaction to obtain 1-acetyl-1,3,4,5-tetrahydro-5-oxobenz[*c*,*d*]indole-3-carboxylic acid (**6**). This result showed inhibition of the activity in its 2(and 3)-position by 1-acetyl group. In view of this fact it would seem that 4-position, being very inactive, had become more reactive to some extent as a result of 1-acetylation. Then, by application of the above example, we synthesized 1-acetyltryptophan (**7**) and its N-protected derivatives to examine the reactivity in 2(and 3)-position, and to examine their intramolecular acylation.

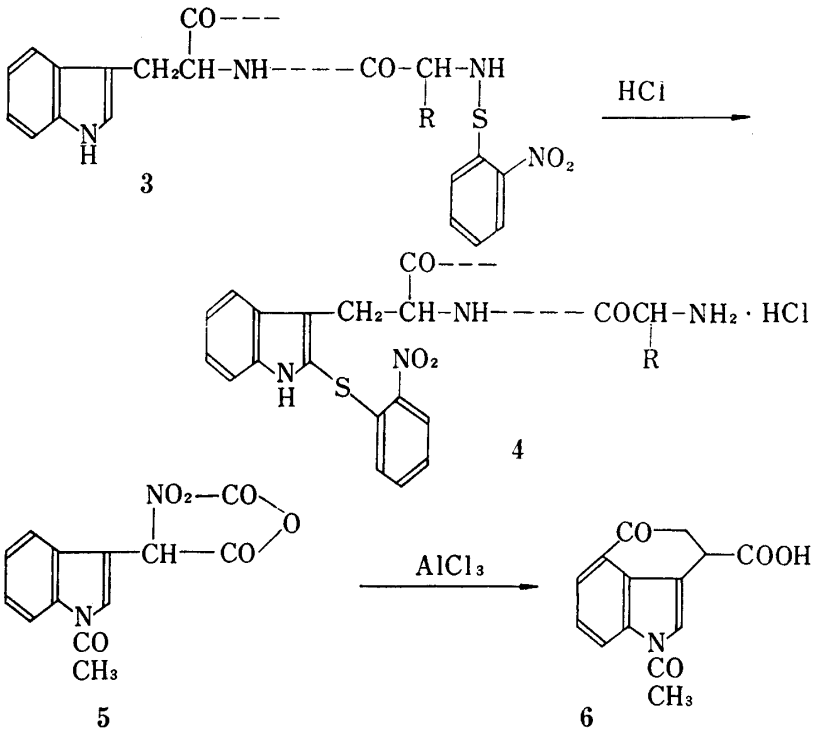


1



2

1) Location: *Women's Division, Ueno Sakuragi, Taito-ku, Tokyo.*
2) E. Wünsch, A. Fontana, and F. Drees, *Z. Naturforschg*, **22b**, 607 (1967).
3) J. Szmuszkovicz, *J. Org. Chem.*, **29**, 843 (1964).



Syntheses of 1-Acetyltryptophan and Its Derivatives

Surprisingly enough, the 1-acetyl derivative of tryptophan had not been synthesized yet and we synthesized it by the following method (Chart 1).

With due regard to the subsequent acetylation, phthaloyl group was used an as amino-protecting group. The N-phthaloyl derivative (**9**) was obtained in a good yield by the condensation of the methyl ester hydrochloride (**8**) with phtalic anhyride in the presence of triethylamine. Though 1–acetylation of indole is frequently difficult, N-phthaloyl-1-acetyltryptophan methyl ester (**10**) was obtained in a fair yield by acetylation of **9** with acetic anhydride and sodium acetate. However, it was not possible to prepare **12** or **7** from **10** by saponification or by the removal of phthaloyl group by saponification, respectively, becausethse 1-acetyl group

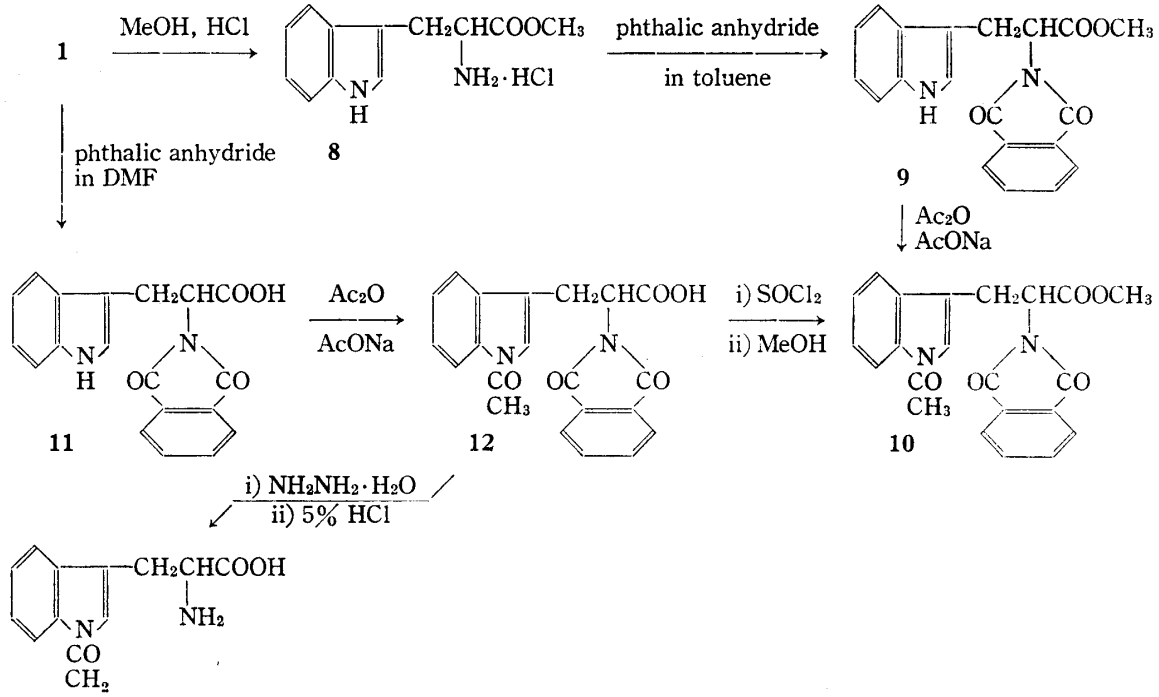
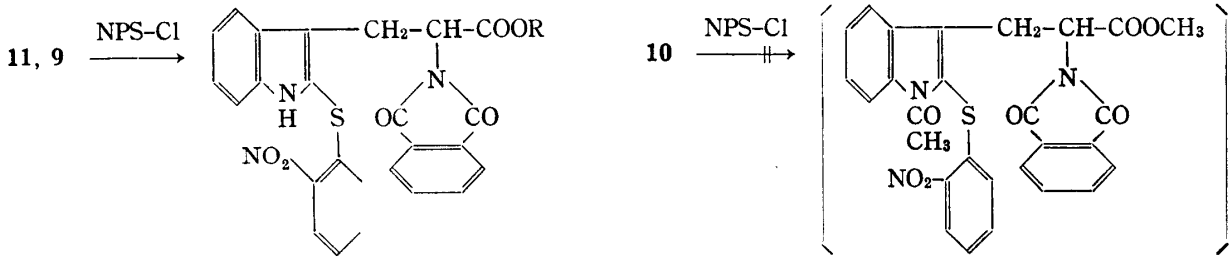


Chart 1

was easily saponified by alkali or acid. Examination was then made on several condition for N-phthaloylation of **1**, and N-phthaloyl tryptophan (**11**) was obtained in a fair yield by heating **1** with phthalic anhydride in dimethyl formamide. Acetylation of **11** in a maner analogous to that of **9** afforded the 1-acetyl derivative (**12**) in 67% yield.[4] Treatment of **12** with thionyl chloride, followed with methanol, afforded **10** obtained previously. Thus, its structure was confirmed. The removal of phthaloyl group from **12** was effected by its reaction with exactly equivalent hydrazine hydrate in ethanol and then its hydrolysis with 5% hydrochloric acid. In this case, the use of 1.1 mole of hydrazine hydrate afforded tryptophan quatitatively with the removal of 1-acetyl group in addition to phthaloyl group.

Reaction of 1-Acetyltryptophan and Its Derivatives with *o*-Nitrophenylsulfenyl Chloride

As an example of the nucleophilic activity of 2-position in the indole ring, we previously described the occurrence of **4** from **3**. Similarly, we examined the reaction of **11**, **9**, **1**, **7**, and **10** with *o*-nitrophenylsulfenyl chloride (Chart 2).



13: R=H
14: R=CH_3

Chart 2

The reaction of **11** and **9** with *o*-nitrophenylsulfenyl chloride afforded 2-sulfenyl compounds (**13** and **14**) in 81% and 100% yield, respectively. The 1-acetyl derivative (**10**), however, did not react at all and was recovered unchanged. On the otherhand, when the reaction of **1** or **7** with *o*-nitrophenylsulfenyl chloride in acetic acid was followed from the amount of *o*-nitrophenylsulfenyl chloride comsumed it was found that **1** had almost quantitatively reacted after 3 or 4 hours (Fig. 1) but **7** reacted only within the limit of an observation error (0.2—0.6%). Consequentry, it was clarified that the 1-acetyl group of tryptophan had controlled the activity in 2-position. Therefore, **7**, which is a chemically more stable tryptophan, indicates the possibility for use in the syntheses of tryptophan peptides.

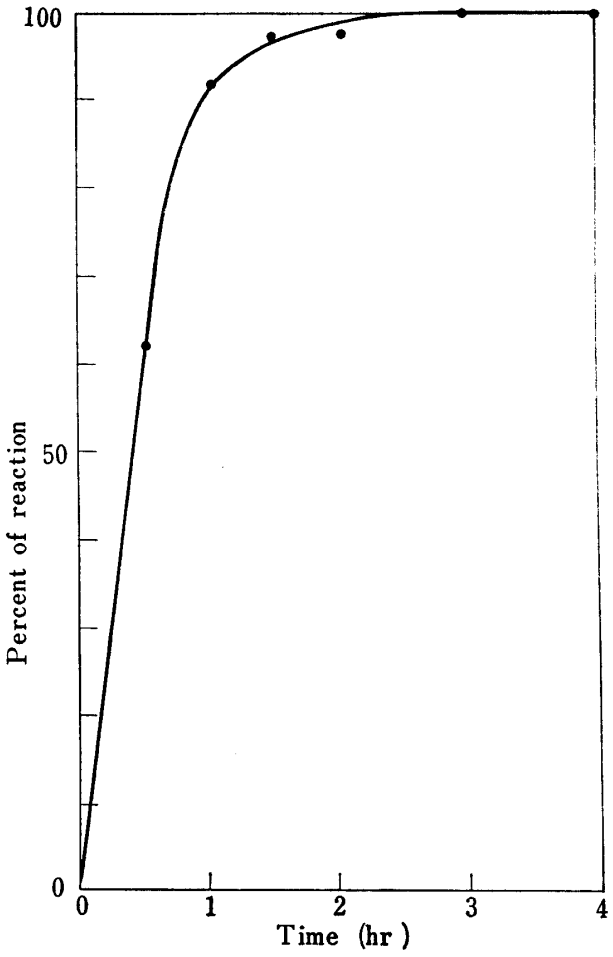


Fig. 1. Reaction of NPS-Cl with Tryptophan in Glacial Acetic Acid

Friedel–Crafts Reactions of 1-Acetyltryptophan Derivatives

After **12** was converted into acid chloride with phosphorus pentachloride, the Friedel–Crafts reaction of acid chloride with aluminum chloride in dichlo-

roethane gave two kinds of crystals, one of mp 264—268° (colorless plates) (yield, 20—24%) and the other of mp290—293° (decomp.) (colorless prisms) (yield, 2.2%). The former was easily hydrolyzed by weak alkali to afford the latter, which exhibited a strong NH band (3400 cm^{-1}) in its infrared (IR) spectrum. The structure of these two products was determined as **15** and **16**, respectively, from elemental analytical values and by spectroscopic methods, **15** showed a significantly deshielded signal in its nuclear magnetic resonance (NMR) spectrum (in $CDCl_3$) at 7.10 τ (3H, $COCH_3$) which was observed in a lower field than the corresponding signal of **12** at 7.50 τ. This result indicates the anisotropic effect of the acyl group cyclized to 2-position of the indole. Further,a signal of C_7-H of **15** (1.34 τ) was observed in a lower field than that of **12** (1.54 τ). Heating of **15** with concentrated hydrochloric acid in acetic acid gave **17** quantitatively, which exhibited characteristic band of 2-acylindole in its ultraviolet (UV) spectrum (in EtOH) at 236 and 306 mμ, and the signal for 2-postion of the indole in its NMR spectrum disappeared, though the four mutually coupling aromatic protons were observed in the region of 2.0—2.8 τ.

It is known that the intramolecular acylation of 3-indolylpropionic acid, *etc.*, by polyphosphoric acid affords derivatives cyclized to 2-position,[5] so that a similar treatment of **11** by polyphosphoric acid gave **16** prepared previously, though in a very poor yield. It was thereby confirmed that **16** was a compound acylcyclized to 2-position. It was rather surprising that the cyclization of **11** was effected in a much lower yield than that of **12**.

As mentioned above, cyclization to 2-position and not to the 4-position of indole had occurred unexpectedly in our case, different from that of Szmuszkovicz's. Then the mixed anhydride of 1-acetyltryptophan (**18**) similar to **5** was synthesized. Treatment of **18** with aluminum chloride did not give the compound cyclized to 4-position and only an amorphous material was produced. Heating of **18** in methanol or its ultraviolet irradiation in dioxan easily gave a clear polymerized white powder. As it is known that this type of compound forms models of peptides and proteins, **18** must have formed a polymer (**19**) before the Friedel–Crafts reaction.

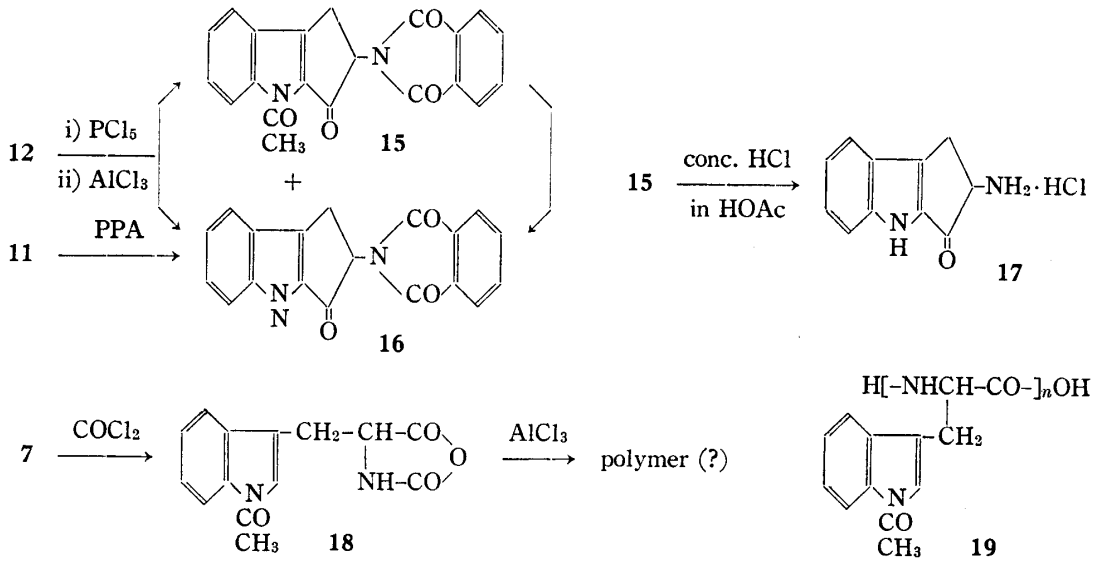


Chart 3

4) The same acylation of 3-indolylpropionic acid was unsuccessful.

5) K. Ishizumi, T. Shioiri, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **15**, 863 (1967).

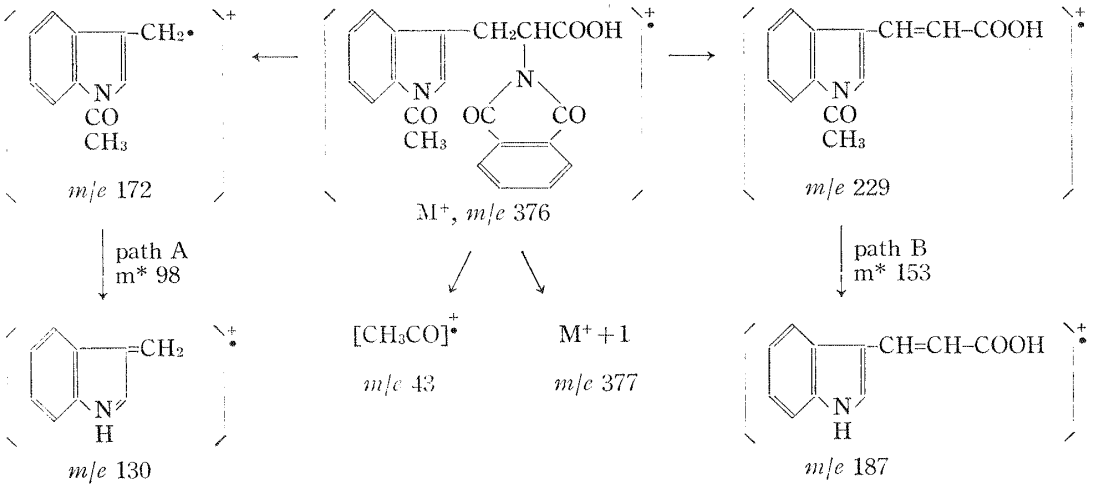


Chart 4

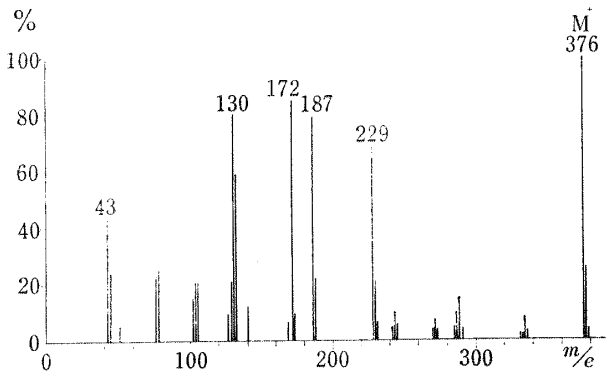


Fig. 2. Mass Spectrum of **12**

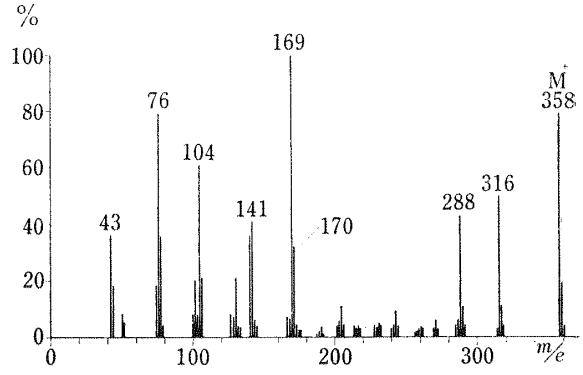


Fig. 3. Mass Spectrum of **15**

Differences in the Friedel–Crafts reaction of **5**, **12** (chloride), and **18** will be investigated further.

Mass Spectra of 1, 7, 11, 12, and 15

Comparison of the mass spectra of **1** and **7** and those of **11** and **12** (Fig.2) showed that **7** and **12** exhibit fragment ion species of 1-acetylated **1** and **11**, respectively. Namely, the 1-acetyl

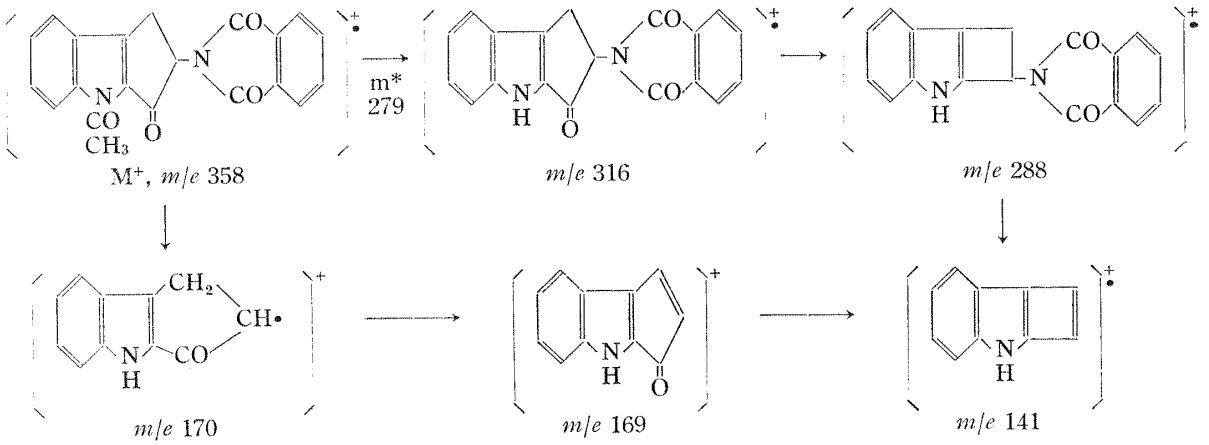


Chart 5

derivatives (**7** and **12**) exhibited strong ion peaks *m/e* 172 and 187, while the N-acyltryptophans (**11** and N-acetyltryptophan) only the strong ion peak, *m/e* 187, but these peaks were not found in tryptophan (**1**) itself. Main fragment ion peaks of **12** can be explained as shown in Chart 4. Furthermore, two metastable ions, *m/e* 98 and 153 showed the possibility of A and B routes, respectively, as shown. From these facts, it seems that elimination of 1-acetyl group is not easy, while in **15** (Fig.3) the fragment ion peaks containing 1-acetyl group was not found. It is likely that 1-acetyl group of 1,2-diacylindole derivatives are easily eliminated. Main fragmentation of **15** was observed as shown in Chart 5.

Experimental[6]

N-Phthaloyltryptophan (11)——A mixture of **1** (20 g, 9.8×10^{-2} mole), phthalic anhydride (14.5 g, 9.8×10^{-2} mole), and Et_3N (20 ml) in Me_2NCHO was refluxed for 6 hr. After removal of Me_2NCHO *in vacuo*, the residual brown viscous oil was dissolved in EtOAc (250 ml). The solution was washed with 5% HCl and H_2O, dried over Na_2SO_4, and evaporated. To the residue dissolved in EtOH (50 ml), H_2O (350 ml) was added, the solution was shaken gently, and then the oil solidified. The crude solid product was collected by filtration, washed with H_2O, and dried. Recrystallization of the solid from EtOH–H_2O gave yellow needles, mp 194—196°. Yeild, 31 g (95%). *Anal.* Calcd. for $C_{19}H_{14}O_4N_2$: C, 68.25; H, 4.20; N, 8.38. Found: C, 67.85; H, 4.30; N, 8.41. IR ν_{max}^{KBr} cm^{-1}: 3420 (NH), 1750 (broad), 1710.

N-Phthaloyltryptophan Methyl Ester (9)——By the procedure described above, except for the use of toluene in place of Me_2NCHO, from 1-methyl ester hydrochloride **9** was obtained as yellow prisms, mp 119—120° (from MeOH). Yield, 88%. *Anal.* Calcd. for $C_{20}H_{16}O_4N_2$: C, 68.96; H, 4.63; N, 8.04. Found; C, 68.53; H, 4.52; N, 8.32. UV λ_{max}^{EtOH} mμ: 241, 283, 291. IR ν_{max}^{KBr} cm^{-1}: 3400 (NH), 1775, 1705 (phthalimide), 1750 (ester), 750, 718. NMR ($CDCl_3$)τ: 6.24 (3H, singlet,), 6.32 (2H, doublet), 4.78 (1H, triplet).

N-Phthaloyl-1-acetyltryptophan (12)——A mixture of **11** (30 g), AcONa (16 g), and Ac_2O (100 ml) was refluxed for 6 hr. After majority of Ac_2O was evaporated, ice water (100 g) was added, and the reaction mixture was extracted with $CHCl_3$ (200 ml). The $CHCl_3$ extract was washed several times with H_2O and shaken with saturated $NaHCO_3$ solution (200 ml). Sodium salt that separated out fromthe solution, was collected, washed with a small quantity of cold H_2O, and dissolved in hot H_2O (100 ml). When the aqueous solution was acidified with conc. HCl, yellow solid was obtained. Recrystallization from MeOH gave colorless prisms, mp 220—222°. *Anal.* Calcd. for $C_{21}H_{16}O_5N_2$: C, 67.01; H, 4.29; N, 7.44. Found: C, 66.87; H, 4.57; N, 7.64. UV λ_{max}^{EtOH} mμ; 241, 293, 302. IR ν_{max}^{KBr} cm^{-1}: 1770, 1750, 1705. NMR ($CDCl_3$) τ: 7.50 (3H, singlet).

N-Phthaloyl-1-acetyltryptophan Methyl Ester (10)——1) From **9**: By the analogous procedure described above, **10** was obtained as yellow needles, mp 152—153° (from MeOH). Yield, 78%. *Anal.* Calcd. for $C_{22}H_{18}O_5N_2$: C, 67.68; H, 4.65; N, 7.18. Found: C, 67.76; H, 4.87; N, 7.35. UV λ_{max}^{EtOH} mμ: 241, 293, 302. IR ν_{max}^{KBr} cm^{-1}: 1770, 1750, 1720, 1705 (sh), 750, 720. NMR ($CDCl_3$)τ: 7.51 (3H, singlet), 6.20 (3H, singlet). GLC (column 1.5% SE-30 on Anakrom, temp. 230°. N_2, 34 ml/min), t_R: 22.5.

2) From **12**: $SOCl_2$ (1 ml)was added slowly to **12** (100 mg), and the mixture was warmed at 50—60° (bath temp.) for 10 min, and evaporated. When the residue was dissolved in MeOH and then the solution was allowed to stand in a refrigerator for several days, yellow crystal was obtained (yield, 20%) and identified with the above sample through IR spectra and admixture.

1-Acetyltryptophan (7)——After **12** (10 g, 2.65×10^{-2} mole) was completely dissolved in boiling EtOH (140 ml), an EtOH solution (40 ml) of 80% $NH_2NH_2\cdot H_2O$ (1.60 g, 2.56×10^{-2} mole) was gradually added dropwise into the refluxing solution during about 1 hr. Heating was continued for 5 hr, and the solution was allowed to stand at room temperature overnight. After evaporation of EtOH, 1.2% HCl (110 ml) was added to the residual white solid and stirred for 2 hr in a boiling water bath. When cooled, the solid was collected by filtration and washed with 5% HCl, which was combined with filtrate. The filtrate was basified to pH 8 with 28% NH_3, concentrated to about 30 ml under reduced pressure, and allowed to stand, and then white crystals precipitated. Yield, 3.1 g (49%) of mp 222—224° (decomp.) (from MeOH). *Anal.* Calcd. for $C_{13}H_{14}O_3N_2\cdot H_2O$ (one molecule of water was confirmed by NMR measurement): C, 59.08; H, 6.10; N, 10.60. Found: C, 59.21; H, 6.22; N, 10.34. UV (H_2SO_4salt) λ_{max}^{EtOH} mμ: 240, 262, 291, 300. IR ν_{max}^{KBr} cm^{-1}: 1730, 1600, 750. NMR (CF_3COOH)τ: 7.25 (3H, singlet), 1.54 (1H, doublet, C_7–H).

N-Phthaloyl-2-(*o*-nitrophenylsulfenyl) tryptophan (13)——N-Phthalyltryptophan (**11**) (1.0 g,3×10^{-3}mole) was dissolved in hot AcOH (25 ml), *o*-nitrophenylsulfenyl chlolide (0.6 g, 3.1×10^{-3} mole) was added at room temperature, and the solution was allowed to stand for 4.5 hr. When H_2O (100 ml) was added, yellow powder came out and its recrystallization from MeOH afforded yellow prisms, mp 284—288° (decomp.). Yield,

6) All melting points are uncorrected.

1.18 g (81%). *Anal.* Calcd. for $C_{25}H_{17}O_6N_3S$: C, 61.60; H, 3.44; N, 8.62. Found: C, 61.55; H, 3.25; N, 8.48. IR ν_{max}^{KBr} cm^{-1}: 3400 (NH), 1775 (weak), 1750 (strong, carbonyl), 1510, 1390 (NO_2).

N-Phthaloyl-2-(*o*-nitrophenylsulfenyl) tryptophan Methyl Ester (14)——By the analogous procedure described above, **14** was obtained from **9** as yellow powder, mp 207—208° (from EtOH). Yield, 100%. *Anal.* Calcd. for $C_{26}H_{19}O_6N_3S$: C, 62.27; H, 3.82; N, 8.38. Found: C, 62.34; H, 4.22; N, 8.10. UV λ_{max}^{EtOH} mμ: 285, 360. IR ν_{max}^{KBr} cm^{-1}: 3400 (NH), 1775, 1750, 1710 (carbonyl), 1510, 1390 (NO_2). NMR ($CDCl_3$)τ: 6.24 (3H, singlet), 4.86 (1H, quartet), 2.35 (4H, singlet).

Friedel-Crafts Reaction of N-Phthaloyl-1-acetyltryptophan (12)——Abs. ether solution (150 ml) of **12** (1.89 g, 5×10^{-3} mole) and PCl_5[7] (1.2 g, 5.8×10^{-3} mole) was stirred at room temperature for one day. After removal of ether under reduced pressure, abs. ether (20 ml) was added to the residue and evaporated. This procedure was repeated twice in order to remove HCl completely. The residual white solid was suspended in dry $ClCH_2CH_2Cl$ (50 ml), $AlCl_3$ (2.6 g, 2×10^{-2} mole) was added, and the solution was refluxed for 2 hr. When cooled, ice water (250 g) was added and the product was extracted with $CHCl_3$. The extract was washed with 10% $NaHCO_3$ and H_2O, dired over Na_2SO_4, and evaporated. A yellow viscous oil (1.5 g) was obtained, which afforded three kinds of crystals after chromatography (on silica gel–$CHCl_3$): colorless plates (A)(from EtOAc) mp 264—268°. Yield, 430 mg. (24%); colorless prisms (B) (from MeOH), mp 290—293° (decomp.), Yield, 35 mg (2.2%); and starting materials, 190 mg (10%). A (**15**): *Anal.* Calcd. for $C_{21}H_{14}O_4N_2$: C, 70.38; H, 3.94; N, 7.82. Found: C, 70.55; H, 4.13; N, 7.94. UV λ_{max}^{KBr} mμ: 223, 239 (sh), 302. IR ν_{max}^{KBr} cm^{-1}: 1710 (broad). NMR ($CDCl_3$)τ: 7.10 (3H, singlet), 6.60 (2H, sextet), 4.57 (1H, quartet), 2.04—2.63 (7H, multiplet), 1.34 (1H, doublet). B (**16**): *Anal.* Calcd. for $C_{19}H_{12}O_3N_2$: C, 72.14; H, 3.82; N, 8.86. Found: C, 71.33; H, 3.93; N, 9.09. IR ν_{max}^{KBr} cm^{-1}: 3400 (NH), 1705 (broad). NMR (d_6-Me_2SO)τ: 6.42 (2H, sextet), 4.62 (1H, quartet), 2.10—2.90 (multiplet).

1-Oxo-5-phthaloylimidocyclopenta[2,3-*b*]indole (16)——1) From **15**: To a solution of **15** (30 mg) dissolved in EtOAc (20 ml), 10% $NaHCO_3$ (1 ml) and MeOH (5 ml) were added, the mixture was warmed in a boiling water bath for 2.5 hr, concentrated to small volume under reduced pressure, and allowed to stand in a refrigerator. Colorless prisms were obtained quantitatively and identified with the above sample B through IR spectra and admixture.

2) From **11**: To polyphosphoric acid (2 g) heated to 90—100°, **11** (80 mg) was added and the mixture was allowed to stand for 30 min at the same temperature. Ice water(30g) was added and the solution was extracted with benzene (30 ml). Benzene extract was washed with H_2O, 10% $NaHCO_3$, and H_2O, dried over Na_2SO_4, and evaporated. Colorless prisms (3 mg) were obtained from the residual oil by crystallization from EtOH and identified with the above sample through IR spectra and admixture.

1-Oxo-5-amino-cyclopenta[2,3-*b*]indole Hydrochloride (17)——A mixture of **15** (50 mg), glacial AcOH (3 ml), and conc. HCl (2 ml) was allowed to stand for 3 hr in a boiling water bath, conc. HCl (2 ml) was added and stood for further 6 hr at the same temperature. After evaporation of solvent *in vacuo*, the residual solid was dissolved in a small quantity of H_2O and filtered from undissolved materials. When the filtrate was evaporated, a white solid (67 mg) was obtained, whose recrystallization from abs. EtOH–abs. ether afforded colorless needles, mp above 300°. *Anal.* Calcd. for $C_{11}H_{10}ON_2\cdot HCl$: N, 12.58. Found: N, 12.34. UV λ_{max}^{EtOH} mμ: 236, 306. IR ν_{max}^{KBr} cm^{-1}: 3200 (NH), 3020—2600 (N^+H_3), 1700, 735. NMR (d_6-Me_2SO)τ: 5.51 (1H, quartet), 2.10 (1H, doublet), 2.30—2.85 (3H, multiplet), 0.96 (3H, broad singlet).

4-(1-Acetyl-3-indolylmethyl)-2,5-oxazolidinedion (18)——$COCl_2$ gas was bubbled through a suspension of **7** (300 mg) in dioxan (20 ml) for 2 hr at room temperature. The solution was allowed to stand overnight and filtered from undissolved solids (170 mg) which were starting material and its hydrochloride. The filtrate was evaporated *in vacuo*, the brown viscous oil (220 mg) so obtained afforded colorless needles (140 mg), mp 172—173° from $CHCl_3$. *Anal.* Calcd. for $C_{14}H_{12}O_4N_2$: C, 61.76; H, 4.44; N, 10.29. Found: C, 61.40; H, 4.43; N, 10.24. UV λ_{max}^{EtOH} mμ: 240, 292, 301. IR ν_{max}^{KBr} cm^{-1}: 1850, 1775, 1700.

Comparison of Tryptophan (1) with 1-Acetyltryptophan (7) toward Reaction with *o*-Nitrophenylsulfenyl Chloride (NPS-Cl)——The quantitative determination of NPS–Cl was performed by the same techniques used by Scoffone, *et al.*[8]

Polymer (19)——When the MeOH solution of **18** was refluxed for 30 min or its dioxan solution was irradiated for 20 hr by UV lamp, the clear white powder was obtained.

Acknowledgement The authors are grateful to Mrs. Y. Baba, Mrs. A. Shimada, Mr. S. Suzuki, Mr. A. Wakamatsu, and Miss S. Suzuki for the elemental analyses, Mr. T. Ono for the NMR spectrum, and Mr. Y. Shida for the mass spectrum.

7) Acid-chlorination with PCl_5–CH_2Cl_2(reflux, 2 hr) afforded amorphous products and with PCl_5–THF (room temperature, 23 hr) much of starting material, but **15** was obtained in 9% yield with $SOCl_2$.

8) E. Scoffone, A. Fontana, and R. Rocchi, *Biochemistry*, **7**, 971 (1968).