Studies on the Syntheses of Heterocyclic Compounds. Part CCLXXIII (1). Synthesis of *C*-Nordihydrocorynantheol and Its Related Compounds

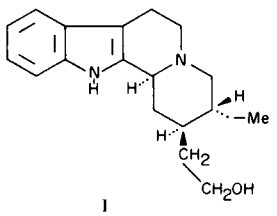
T. Kametani, M. Ihara, T. Suzuki and K. Shima

Pharmaceutical Institute, School of Medicine, Tohoku University

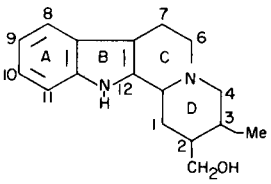
Mannich reaction of tryptamine with 3,3,4-triethoxycarbonylhexaldehyde (IV) gave the cyclized product (VIII), whose hydrolysis, followed by decarboxylation, afforded the acid (IX). After esterification of IX, reduction of ester (X) with lithium aluminum hydride gave the *C*-nordihydrocorynantheol (II). The syntheses of IV and XV were also described. Furthermore, the Mannich reaction of L-*N*-benzyl-1-methyltryptophan methyl ester (XV) with IV was also examined. This reaction gave the ester (XVII), which was hydrolyzed and decarboxylated to give the acid (XVIII). Esterification of XVIII, followed by catalytic hydrogenation, gave the lactam (III).

Dihydrocorynantheol (I), $C_{19}H_{26}ON_2$, which was isolated from both *Aspidosperma auriclatum* and *A. marcgravianum* (2), was synthesized from dihydrocorynanthein (3) by Vamvacus *et al.* (4). We now wish to report a simple synthesis of compounds II and III which have a corynanthein nucleus for the purpose examining their pharmacological activity.

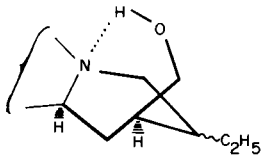
Chart I



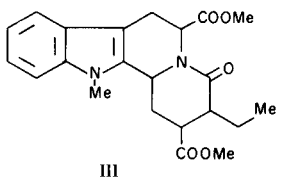
I



II



IIa

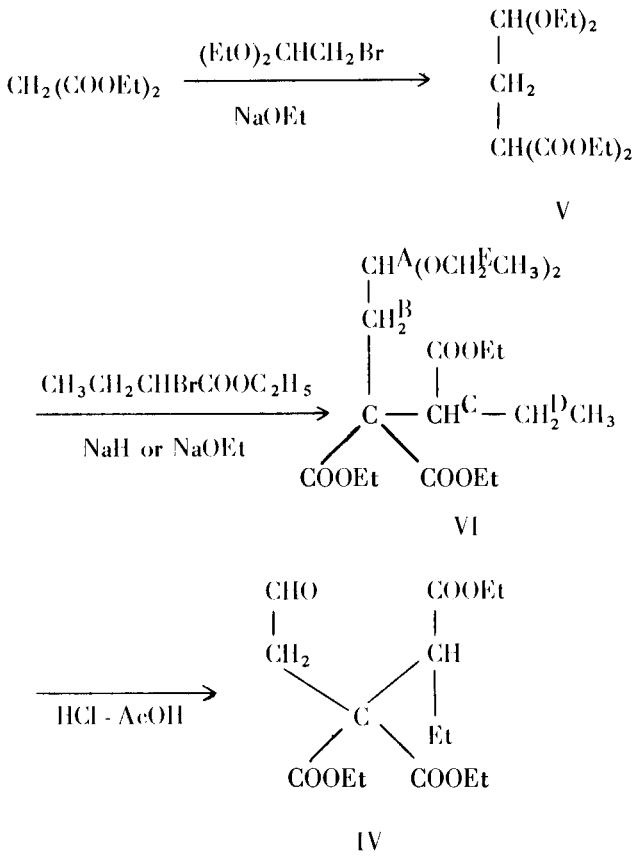


III

The aldehyde (IV, a key starting material) was synthesized as follows: condensation of the acetal (V) (obtained as shown in Chart 2) with ethyl α-bromobutyrate was carried out in the presence of sodium ethoxide or sodium hydride to give a colorless oil, b.p. 155-159° (3 mm.), to which was assigned VI on the basis of the nmr spectrum; the following signals (ppm), H^A (triplet, J = 6 cps, δ 4.61), H^B (doublet, J = 6 cps, δ 2.08), H^C (quartet, J = 6 and 7 cps, δ 2.75), and H^D (multiplet, δ 2.10-1.35) were observed. Furthermore, the proton H^E absorbed at 3.50 δ and 3.45 δ as two pairs of quartets with J = 7 cps. In this case the appearance of H^C as a quartet and H^E as two pairs of quartets support the restriction of free rotation as a result of steric hindrance. A solution of VI in hydrochloric acid and acetic acid was shaken at room temperature for 1.5 hours to give the expected aldehyde (IV), which was characterized as the semicarbazone and the 2,4-dinitrophenylhydrazone.

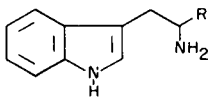
A Mannich reaction of IV with tryptamine (VII) in the presence of acetic acid afforded benzo[2,1-*a*]-β-carboline (VIII) in one step, which upon saponification followed by decarboxylation gave the compound IX. Esterification of IX afforded the ester (X), which was reduced with lithium aluminum hydride to give *C*-nordihydrocorynantheol (II). In the infrared spectrum the absorption bands attributable to lactam and ester C=O disappeared and that of the NH band was observed at 3400 cm^{-1}. In this case the absorption of an associated OH group was recognized at 3100-3400 cm^{-1}. Furthermore, in the nmr spectrum the signal due to an associated OH group was observed at a lower field (10.6-10.8 δ). These facts support the assign-

Chart 2

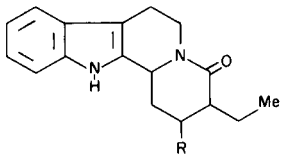


ment of a boat form (IIa) for the D ring of compound II. The other signals also support the correctness of structure II.

Chart 3



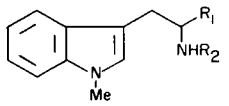
VII: R = H
VIIa: R = COOH



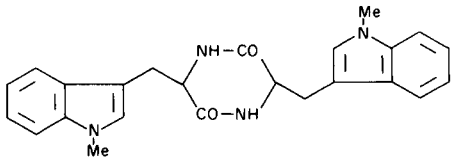
VIII: R = $(COOEt)_2$
IX: R = COOH
X: R = COOMe

The Mannich reaction of L-*N*-benzyl-l-methyl-tryptophan methyl ester (XV) with the aldehyde (IV) was carried out. The condensation product (XVII) was obtained with suppression of lactam formation. The tryptamin derivative (XV) was synthesized following Yamada's (5) and Yoneda's (6) methods as outlined below. Tryptophane (VIIa) was methylated with methyl iodide in the presence of sodium iodide to give L-1-methyl-tryptophan (XI) which in turn gave the ester (XII) upon treatment with methanolic hydrochloric acid. Compound XII with benzaldehyde gave the Schiff base (XIV) which was reduced to the ester (XV) with sodium borohydride. The use of excess sodium borohydride gave the carbinol (XVI) as a byproduct. When the free base of XII was allowed to stand at room temperature for extended periods of time, the L-diketopiperazine derivative (XIII) was formed.

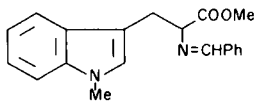
Chart 4



XI: R_1 = COOH, R_2 = H
XII: R_1 = COOMe, R_2 = H
XV: R_1 = COOMe, R_2 = CH_2Ph
XVI: R_1 = CH_2OH, R_2 = CH_2Ph



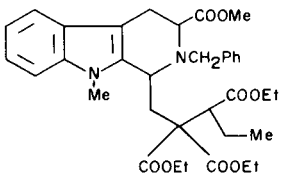
XIII



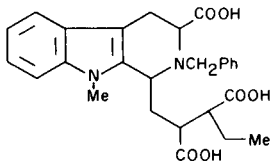
XIV

Mannich reaction of the amine (XV) with the aldehyde (IV) also gave the cyclized compound (XVII), whose purification by silica gel chromatography gave colorless needles, m.p. 148-149°. Hydrolysis with 5% ethanolic sodium hydroxide, followed by decarboxylation with acetic acid, afforded the carboxylic acid (XVIII). Esterification of XVIII with 10% methanolic hydrochloric acid gave the trimethyl ester, which was purified by silica gel chromatography to give a mixture of diastereoisomers (XIXa and XIXb), both of which showed R_f, 0.74 and R_f, 0.52 on thin layer chromatogram and appeared to be important intermediates for the synthesis of ajmaline. The formation ratio of both isomers was about 5:2.

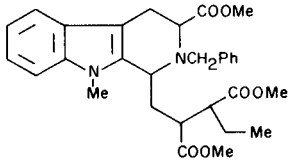
Chart 5



XVII



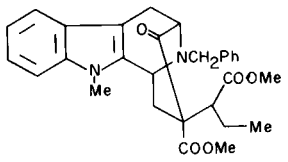
XVIII



XIXa~b

Debenzylation of XIXa by the usual catalytic hydrogenation procedures gave compound III. This fact also supports the correctness of structure XIXa. Approaches to compound XX, an apparent key intermediate for the synthesis of ajmaline derivatives is under examination.

Chart 6



XX

EXPERIMENTAL (7)

3,3-Diethoxycarbonylpropionaldehyde Diethyl Acetal (V).

To pasty sodium ethoxide (prepared from 20.6 g. of metallic sodium in the usual manner) was added dropwise with stirring a solution containing 138 g. of ethyl malonate in 300 ml. of diethyl carbonate. The reaction mixture was stirred until a clear solution resulted. After removal of the ethanol under reduced pressure, 110 g. of bromoacetal (8) was added dropwise to the above residue and the mixture was heated under reflux at 130° for 20 hours with stirring during which time sodium bromide separated. After cooling, the reaction mixture was decomposed with water and extracted with ether. The extract was washed with saturated sodium chloride solution and water, dried over potassium carbonate and evaporated to give a syrup, which was distilled *in vacuo* to give 112 g. of a colorless oil, b.p. 150-154° (15 mm.) [lit., b.p. 163-165° (20 mm.) (9)]; infrared cm^{-1} (chloroform) ν (C=O), 1722; nmr δ (carbon tetrachloride), 4.40 (1H, triplet, J = 6.0 cps, C_1-H), 4.12 (4H, quartet, J = 7.5 cps, 2 x $COOCH_2CH_3$), 3.45, 3.40 (each 2H, quartet, J = 7.0 cps, 2 x OCH_2CH_3), 2.03 (2H, quartet, J = 6.0 and 7.0 cps, C_2-H_2).

3,3,4-Triethoxycarbonylhexaldehyde Diethyl Acetal (VI).

(a) Method by Sodium Ethoxide.

A solution of 10 g. of the above acetal (V) in 25 ml. of diethyl carbonate was added gradually to sodium ethoxide [prepared from 0.83 g. of metallic sodium in the usual manner]. The mixture was stirred until it became clear. After removal of the ethanol, 7.0 g. of ethyl α-bromobutyrate was added to the residue and the resulting mixture was refluxed with stirring for 27 hours. After cooling, the reaction mixture was decomposed with water and extracted with ether. The extract was washed with saturated sodium chloride solution and water, dried over potassium carbonate and evaporated to give a yellowish brown oil, which was distilled *in vacuo* to give 11 g. of a colorless oil (VI), b.p. 155-159° (3 mm); infrared cm^{-1} (chloroform), ν (C=O), 1725; nmr δ (carbon tetrachloride), 4.61 (1H, triplet, J = 6.0 cps, C_1-H), 4.32-3.90 (6H, multiplet, 3 x $COOCH_2CH_3$), 3.50, 3.45 (each 2H, quartet, J = 7.0 cps, 2 x OCH_2CH_3), 2.75 (1H, quartet, J = 6.0 and 7.0 cps, C_4-H), 2.08 (2H, doublet, J = 6.0 cps, C_2-H_2), 2.10-1.35 (2H, multiplet, C_5-H_2).

(b) Method by Sodium Hydride.

To a suspension of 20.8 g. of sodium hydride in 200 ml. of benzene was added dropwise with stirring 143.5 g. of acetal (V). After 10 minutes, the benzene was distilled off, to give the residue, which was dissolved in 250 ml. of diethyl carbonate. To the resulting solution was added carefully 100.5 g. of ethyl α-bromobutyrate with stirring, and the mixture was then heated with stirring at 140° for 30 hours. The reaction mixture was treated by the same method as (a) to give 170.5 g. of VI, which was identical with an authentic sample.

3,3,4-Triethoxycarbonylhexaldehyde (IV).

A mixture of 10 g. of acetal (VI), 11 ml. of acetic acid, 4.5 ml. of concentrated hydrochloric acid and 1.6 ml. of water was shaken at room temperature for 1.5 hours. The reaction mixture was basified with concentrated ammonia and extracted with ether several times. The extract was washed with saturated sodium chloride solution and water, dried over sodium sulfate and evaporated to give 6.0 g. of a colorless syrup; infrared cm^{-1} (chloroform), ν (CH) 2725 (aldehyde CH), ν (C=O), 1725 (aldehyde and ester C=O), nmr δ (carbon tetrachloride), 9.60 (1H, broad singlet, C_1-H), 4.33-3.88 (6H, multiplet, 3 x $COOCH_2CH_3$), 2.88 (2H, broad singlet, C_2-H_2). Recrystallization of the semicarbazone from methanol gave colorless cubes, m.p. 121-122°.

Anal. Calcd. for $C_{16}H_{27}O_7N_3$: C, 51.46; H, 7.29; N, 11.25. Found: C, 51.14; H, 6.96; N, 11.38.

Recrystallization of the 2,4-dinitrophenylhydrazone from methanol gave yellow needles, m.p. 89-90°.

Anal. Calcd. for $C_{21}H_{28}O_{10}N_4$: C, 50.80; H, 5.68; N, 11.29. Found: C, 51.23; H, 5.65; N, 11.53.

3-Ethyl-2,2-diethoxycarbonyl-1,2,3,4,5,6,7,12b-octahydro-4-oxobenzo[2,1-*a*]-β-carboline (VIII).

A mixture of 8.3 g. of tryptamine (VII), 16.2 g. of the aldehyde (IV) and 100 ml. of acetic acid was refluxed at 130° for 9 hours.

After an excess of acetic acid had been distilled off, the residue was chromatographed on 100 g. of silica gel. Evaporation of the benzene eluate gave 16 g. of a pale yellowish residue R_f 0.68 [silica-gel, chloroform:acetone:methanol=100:20:1]; infrared cm^{-1} (chloroform), ν (NH), 3400 (indole NH), ν (CH), 2900, ν (C=O), 1720 (ester C=O), ν (C=O), 1680 (lactam C=O); nmr δ (deuteriochloroform), 0.75-1.5 (9H, multiplet, CH_2CH_3), 1.8-4.7 (13H, multiplet, methylene and methine protons), 5.0 (1H, C_{12b}-H), 7.05-7.6 (4H, multiplet, aromatic protons), 8.35-8.6 (1H, indole NH, exchanged with deuterium oxide), mass (m/e), 412 (M^+).

Anal. Calcd. for $C_{23}H_{28}O_5N_2$: C, 66.97; H, 6.84; N, 6.79. Found: C, 66.59; H, 6.92; N, 7.15.

3-Ethyl-1,2,3,4,5,6,7,12b-octahydro-2-hydroxycarbonyl-4-oxobenzo[2,1-*a*]-*β*-carboline (IX).

A mixture of 16 g. of the above diester (VIII), 14 g. of potassium hydroxide, 220 ml. of ethanol and 80 ml. of water was refluxed on a water-bath for 2 hours and removal of the solvent gave a solid, whose solution in 50 ml. of water was extracted with ether to remove non-acidic substance. The above aqueous solution was acidified with 10% hydrochloric acid and the resultant acidic solution was heated on a water-bath with evolution of carbon dioxide. After heating an additional 5 minutes, the reaction mixture was extracted with chloroform. The extract was washed with saturated sodium chloride, treated with active carbon, filtered, dried over sodium sulfate and evaporated to give 14 g. of a reddish syrup, which was chromatographed on 100 g. of silicic acid. Removal of the eluant [benzene:chloroform = 1:1] afforded the acid (IX), which was recrystallized from methanol-hexane-chloroform to give 4 g. of colorless prisms, m.p. 188°, R_f 0.55 (silica gel, chloroform:methanol = 7:31; infrared cm^{-1} (potassium bromide), ν (NH), 3320 (indole NH), ν (CH), 2900, ν (C=O), 1700 (ester C=O), ν (C=O), 1670 (lactam C=O), δ (CH) 735 (disubstituted benzene); nmr, δ [DMSO-d_6], 1.5-4.7 (10H, multiplet, methylene and methine protons), 4.8-5.2 (1H, multiplet, indole NH, exchanged with deuterium oxide).

Anal. Calcd. for $C_{18}H_{20}O_3N_2 \cdot H_2O$ (10): C, 65.44; H, 6.71. Found: C, 65.46; H, 6.81.

3-Ethyl-1,2,3,4,5,6,7,12b-octahydro-2-methoxycarbonyl-4-oxobenzo[2,1-*a*]-*β*-carboline (X).

A mixture of 200 mg. of the acid (IX) and 50 ml. of methanol containing 5 g. of dry hydrochloride gas was refluxed on a water-bath for 4 hours. After removal of the solvent, the residue was extracted with chloroform. The extract was washed with saturated sodium chloride solution, dried over potassium carbonate and evaporated to give 170 mg. of X as a pale yellowish-green syrup, R_f 0.87 [silica gel, chloroform:methanol = 7:3]; infrared cm^{-1} (chloroform), ν (NH), 3400 (indole NH), ν (CH) 2920, ν (C=O), 1725 (ester C=O), ν (C=O), 1680 (lactam C=O); nmr δ (deuteriochloroform), 1.2 (3H, triplet, J = 7 cps), 1.5-4.7 (10H, multiplet, methylene and methine protons), 3.72 (3H, singlet, OCH_3), 5.08 (1H, C_{12b}-H), 7.0-7.6 (4H, multiplet, aromatic protons), 8.7-9.0 (1H, indole NH, exchanged with deuterium oxide).

3-Ethyl-1,2,3,4,5,6,7,12b-octahydro-2-hydroxymethlbenzo-[2,1-*a*]-*β*-carboline (*C*-Nordihydrocorynantheol) (II).

To a cooled suspension of 1 g. of lithium aluminum hydride in 40 ml. of dry tetrahydrofuran was added dropwise with stirring a solution of 170 mg. of the preceding ester (X) in 10 ml. of dry tetrahydrofuran and, after addition, the mixture was refluxed at 70° for 7 hours. After the reaction mixture had been decomposed with wet ether and then water at room temperature for 30 minutes with stirring, the resultant mixture was filtered. The filtrate was evaporated *in vacuo* under a current of nitrogen to give a syrup, which was extracted with chloroform. The extract was washed twice with saturated sodium chloride solution, dried over potassium carbonate and evaporated in a current of nitrogen to give 150 mg. of II as a yellow syrup, which solidified, perhaps due to the formation of the chloroform solvate on being triturated with chloroform. In this instance trituration with the other organic solvents gave no crystals. Recrystallization from chloroform-methanol-hexane gave 100 mg. of II as colorless prisms, m.p. 134°, R_f 0.68 [silica gel, chloroform:methanol = 1:1]; infrared cm^{-1} (chloroform), ν (NH) 3400 (indole NH), ν (OH) 3100-3400 (associated OH), ν (CH) 2900; nmr δ [DMSO-d_6], 0.6-1.0 (3H, triplet, J = 7 cps, CH_2CH_3), 1.0-4.5 (14H, multiplet, methylene and methine protons), 4.7 (1H, C_{12b}-H), 6.8-7.6 (4H, multiplet, aromatic protons), 8.4-8.7 (1H, indole NH, exchanged with deuterium oxide), 10.6-10.8 (1H, associated OH, exchanged with deuterium oxide) (II), 8.1 (1H, singlet, $CHCl_3$).

Anal. Calcd. for $C_{18}H_{24}ON_2 \cdot CHCl_3 \cdot H_2O$ (12): C, 54.10; H, 6.45; N, 6.64. Found: C, 53.93; H, 6.42; N, 6.77.

L-1-Methyltryptophan (XI).

To a solution of sodium amide [prepared from a mixture of 16 g. of metallic sodium, 0.8 g. of ferric chloride and *ca.* 20 liters of liquid ammonia] was added with stirring 62 g. of L-tryptophan (VIIa) and, after 30 minutes, 57 g. of methyl iodide was added gradually to the above mixture, which was stirred until an excess of ammonia had been evaporated. The residue was mixed with 180 ml. of water and the resultant aqueous solution was siltered on heating. The filtrate was acidified with acetic acid to *p*H 5, whereupon crystals began to separate. After the addition of 180 ml. of ethanol, the mixture was allowed to stand overnight and the crystals which separated were collected by filtration. After washing with water, ethanol and ether, 63 g. of XI was obtained as colorless plates, whose recrystallization from ethanol gave colorless plates, m.p. 230-233° dec.; $[\alpha]_D^{31}$ +63.5° (c = 0.2 in acetic acid).

Anal. Calcd. for $C_{12}H_{14}O_2N_2$: C, 66.03; H, 6.47; N, 12.84. Found: C, 65.57; H, 6.04; N, 13.30.

L-1-Methyltryptophan Methyl Ester (XII).

A mixture of 62 g. of the above amino acid (XI) and 470 ml. of 10 w/v percent hydrogen chloride-methanol was refluxed for 6 hours and, on cooling, the crystals began to separate. Collection and washing with methanol and ether gave 67 g. of colorless fine needles, whose recrystallization from methanol-ether afforded colorless needles, m.p. 216-217° dec; $[\alpha]_D^{31}$ +19.0° (c = 0.16 in methanol); infrared cm^{-1} (potassium bromide); ν (C=O), 1745.

Anal. Calcd. for $C_{13}H_{16}O_2N_2 \cdot HCl$: C, 58.10; H, 6.38; N, 10.42. Found: C, 58.31; H, 6.53; N, 10.38.

This hydrochloride (65 g.) was basified with potassium carbonate solution and extracted with ether to give 51 g. of the free base (XII) as a yellow syrup; nmr δ (deuteriochloroform), 6.85 (1H, singlet, C_2-H), 3.60 (3H, singlet, OCH_3), 3.58 (3H, singlet, NCH_3), 3.02 (2H, doublet, J = 7 cps, $-CH_2$-CH).

The above free base was allowed to stand at room temperature for a few days to separate L-3,6-di-(3-*N*-methylindolyl)diketopiperazine (XIII) as colorless needles, m.p. 248-250°, $[\alpha]_D^{31}$ -93.5° (c = 0.25 in chloroform); infrared cm^{-1} (chloroform), ν(NH), 3360, ν (C=O), 1670; nmr δ (deuteriochloroform), 6.33 (2H, singlet, 2 x C_2-H), 3.66 (6H, singlet, 2 x NCH_3), mass (m/e), 400 (M^+).

Anal. Calcd. for $C_{24}H_{24}O_2N_4$: C, 71.98; H, 6.04; N, 13.99. Found: C, 72.20; H, 6.20; N, 14.40.

L-*N*-Benzyl-1-methyltryptophan Methyl Ester (XV).

To a solution of 23 g. of XII in 150 ml. of methanol was added 12.6 g. of benzaldehyde and 3 g. of sodium borohydride was added in small portions to the resulting Schiff base (XIV) with stirring at 0-5° within 3 hours. The mixture was stirred for an additional 1 hour. After 3 ml. of acetic acid had been added to the reaction mixture, methanol was distilled off to give a syrup which was basified with 10% sodium carbonate solution and extracted with benzene. The extract was washed with water, dried over potassium carbonate and evaporated to give a yellow oil, which was chromatographed on silica gel. Removal of the first chloroform eluate gave 25 g. of XV as an oil; infrared cm^{-1} (chloroform), ν (C=O), 1723; nmr, δ (deuteriochloroform), 6.85 (1H, singlet, C_2-*H*), 3.67 (3H, singlet, OCH_3), 3.59 (3H, singlet, NCH_3), 3.12 (2H, doublet, J = 7 cps, $-CH_2CH$).

Recrystallization of the hydrochloride from methanol-ether gave colorless needles, m.p. 160-161° dec.; $[\alpha]_D^{31}$ +23.7 (c = 0.35 in methanol).

Anal. Calcd. for $C_{20}H_{22}O_2N_2 \cdot HCl$: C, 66.94; H, 6.46; N, 7.80. Found: C, 67.02; H, 6.51; N, 7.89.

Evaporation of the final chloroform eluate gave a yellow powder, whose recrystallization from hexane afforded the carbinol (XVI) as colorless needles, m.p. 85-86°; $[\alpha]_D^{31}$ -31.0° (c = 0.31 in chloroform); nmr δ (deuteriochloroform), 7.55-7.05 (9H, aromatic protons), 6.77 (1H, singlet, C_2-*H*), 3.75 (2H, singlet, NCH_2Ph), 3.65 (3H, singlet, NCH_3).

Anal. Calcd. for $C_{19}H_{22}ON_2$: C, 77.51; H, 7.53; N, 9.52. Found: C, 77.40; H, 7.68; N, 9.91.

Recrystallization of the hydrochloride of XVI from methanol-ether gave colorless needles, m.p. 170-171° dec.

Anal. Calcd. for $C_{19}H_{22}ON_2 \cdot HCl$: C, 68.94; H, 7.03; N, 8.46. found: C, 68.61; H, 7.21; N, 8.25.

2-Benzyl-1-(2′,2′,3′-triethoxycarbonylpentyl)-1,2,3,4-tetrahydro-3-methoxycarbonyl-9-methylpyrido[3,4-*b*]indole (XVII).

A mixture of 5 g. of the amine (XV), 5 g. of aldehyde (IV) and 30 ml. of acetic acid was heated at 120° for 10 hours and the solvent was distilled off *in vacuo* to give a syrup, which was chromatographed on silica gel. Evaporation of the chloroform-benzene (6:94) eluate gave the compound (XVII) as a pale yellow oil, whose recrystallization from hexane afforded colorless needles, m.p. 148-149°; infrared cm^{-1} (potassium bromide), ν (C=O) 1741, 1723; δ (CH), 743 (1,2-disubstituted benzene), δ (CH) 701 (monosubstituted benzene); nmr δ (deuteriochloroform), 3.79 (3H, singlet, OCH_3), 3.57 (3H, singlet, NCH_3), 0.65 (3H, triplet, J = 7 cps, $-CH_2$-CH_3), R_f 0.60 (silica gel, hexane:ethyl acetate = 3:2).

Anal. Calcd. for $C_{35}H_{44}O_8N_2$: C, 67.72; H, 7.15; N, 4.51. Found: C, 67.35; H, 7.04; N, 4.83.

2-Benzyl-3-hydroxycarbonyl-1-(2′,3′-dihydroxycarbonylpentyl-1,2,3,4-tetrahydro-9-methylpyrido[3,4-*b*]indole (XVIII).

A solution of 4 g. of the above ester (XVII), 3.5 g. of potassium hydroxide, 60 ml. of ethanol, and 10 ml. of water was refluxed for 15 hours and the solvent was then removed by distillation to give the residue, which was dissolved in water and extracted with ether in order to remove non-acidic substances. The preceding aqueous alkaline solution was acidified with acetic acid, an evolution of carbon dioxide being observed. A brown oil precipitated and was extracted with chloroform. The extract was washed with water, dried over sodium sulfate and evaporated to give 2.5 g. of a pale yellow residue, which was recrystallized from chloroform-hexane to afford 2.3 g. of a colorless powder, R_f 0.67 (silica gel, chloroform:methanol = 1:1); nmr δ (trifluoroacetic acid), 3.73 (2H, singlet, NCH_2Ph), 3.60 (3H, singlet, NCH_3).

Anal. Calcd. for $C_{27}H_{30}O_6N_2 \cdot 2H_2O$ (dried over phosphorus pentoxide at 100° for 2 days): C, 63.02; H, 6.66; N, 5.44. Found: C, 62.74; H, 6.77; N, 5.45.

2-Benzyl-1,2,3,4-tetrahydro-3-methoxycarbonyl-1-(2′,3′-dimethoxycarbonylpentyl)-9-methylpyrido[3,4-*b*]indole (XIXa and XIXb).

A solution of 0.5 g. of XVIII and 20 ml. of 10 w/v percent hydrogen chloride-methanol was refluxed for 5 hours and then evaporated to give a brown syrup, which was basified with 10% potassium carbonate solution and extracted with chloroform. The extract was washed with water, dried over sodium sulfate and evaporated to give 0.5 g. of a pale yellow syrup, which was chromatographed on silica gel. Evaporation of the chloroform-benzene (7:93) eluate afforded 0.25 g. of a pale yellow syrup (XVIIa), R_f 0.74 (silica gel, hexane:ethyl acetate = 3:2); nmr δ (carbon tetrachloride), 0.70 (3H, triplet, J = 7 cps, $-CH_2CH_3$), 2.95 (2H, doublet, J = 8.5 cps, C_4H_2), 3.64, 3.54, 3.50, 3.44 (each 3H, 3 x OCH_3, N-CH_3), 3.72 (2H, singlet, NCH_2Ph), 6.39-7.00 (9H, aromatic protons).

Anal. Calcd. for $C_{30}H_{36}O_6N_2$: C, 69.21; H, 6.97; N, 5.38. Found: C, 69.20; H, 7.09; N, 5.38.

Evaporation of the second chloroform-benzene (20:80) eluate gave 0.1 g. of a pale yellow syrup (XIXb), R_f 0.52 (silica gel, hexane:ethyl acetate = 3:2); infrared cm^{-1} (chloroform), ν(C=O) 1725. In its infrared spectrum the absorption bands at 950-1150 cm^{-1} were different from those of XIXa. Nmr (δ) (carbon tetrachloride), 0.91 (3H, triplet, J = 7 cps, CH_2CH_3), 3.03 (2H, doublet, J = 7 cps, C_4H_2), 3.45-3.70 (14H, NCH_2Ph, 3 x OCH_3, N-CH_3), 7.03-7.24 (9H, aromatic protons).

3-Ethyl-1,2,3,4,5,6,7,12b-octahydro-2,6-dimethoxycarbonyl-12-methyl-4-oxo-benzo[2,1-*a*]-β-carboline (III).

A solution of 0.1 g. of XIXa in 10 ml. of ethanol was hydrogenated at room temperature in the presence of 0.2 g. of 10% palladium on carbon, 4.5 ml. of hydrogen being absorbed within 20 hours. After removal of catalyst by filtration, the solvent was distilled off to give a syrup, whose solution in chloroform was basified with 10% sodium bicarbonate solution. The chloroform layer was separated, washed with water, dried over sodium carbonate and evaporated to give 0.06 g. of a pale yellow oil, which was chromatographed on silica gel to give 0.04 g. of the lactam (III) as a pale viscous substance; infrared cm^{-1} (chloroform), ν (C=O) 1726 (ester C=O), 1680 (lactam C=O); nmr δ (deuteriochloroform), 0.88 (3H, triplet, J = 7 cps, $-CH_2CH_3$), 3.75, 3.63 (3H, 6H, 2 x OCH_3, NCH_3), 5.35 (1H, C_{12b}-*H*), 7.08-7.52 (4H, aromatic protons).

Anal. Calcd. for $C_{22}H_{26}O_5N_2 \cdot H_2O$: C, 63.44; H, 6.78; N, 6.73. Found: C, 63.09; N, 6.44; N, 6.50.

Acknowledgment.

We thank Mr. K. Saito, Hitachi Pharmaceutical Co. Ltd., Tokyo, for a gift of a valuable reagent. We also thank Miss R. Hasebe, Miss T. Yoshida, Miss R. Kato and Miss A. Kawakami, Pharmaceutical Institute, Tohoku University, and Miss Y. Tadano for the nmr spectral determinations.

REFERENCES

(1) Part CCLXXII: T. Kametani, S. Takano, and T. Kobari, *Tetrahedron Letters*, 4565 (1968).

(2) B. Gilbert, L. D. Antonaccio, and C. Djerassi, *J. Org. Chem.*, 27, 4702 (1962).

(3) E. E. van Tamelen, P. E. Aldrich, and T. J. Katz, *J. Am. Chem. Soc.*, 79, 6426 (1957).

(4) C. Vamvacas, W. V. Philpsborn, E. Schlittler, H. Schmid, and P. Karrer, *Helv. Chim. Acta*, 40, 1793 (1957).

(5) S. Yamada, T. Shioiri, T. Itaya, T. Hara, and R. Matsueda, *Chem. Pharm. Bull.* (Tokyo), 13, 88 (1965); S. Yamada, K. Koga, and H. Matsuo, *ibid.*, 11, 1140 (1963).

(6) N. Yoneda, *ibid.*, 12, 1478 (1964); 13, 622 (1965).

(7) All melting points were uncorrected.

(8) C. F. Koelsch, *Org. Synthesis*, Coll. Vol. 3, 123 (1955).

(9) W. H. Perkin Jun. and H. S. Pink, *J. Chem. Soc.*, 127, 191 (1925).

(10) In its nmr spectrum the signal (2H) due to water of crystallization was observed at 4.1 δ.

(11) The signal of two protons due to water of crystallization overlapped with the signal of methyl protons at 3.85 δ due to deuteriodimethylsulfoxide.

(12) This solvate was confirmed by its nmr spectrum. On drying at $> 80^{\circ}$ it became yellow perhaps due to decomposition. Therefore it was dried at 60° over phosphorus pentoxide overnight.

Received September 20, 1968 Sendai, Japan