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The Synthesis of 3-Spirooxindole Derivatives. VII.*,[1] Total Synthesis of Alkaloids (±)-Rhynchophylline and (±)-Isorhynchophylline

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The total synthesis of (±)-rhynchophylline (Ia) and (±)-isorhynchophylline (Ib) which are oxindole alkaloids of *Uncaria rhynchophylla* Miq (*Ourouparia rhynchophylla* Matsum), has been completed through eight stages starting from the condensation of 2-hydroxytryptamine hydrochloride (III) with ethyl sodium formyl acetate (IV). The success in the first-stage condensation is significant since ethyl sodium formyl acetate (IV) is rather unstable and has not been existent as the liberated ester. The stereostructures of the intermediates are discussed and mostly assigned.

Rhynchophylline (Ia)[3] and Isorhynchophylline (Ib)[4] are oxindole alkaloids of *Uncaria rhynchophylla* Miq (*Ourouparia rhynchophylla* Matsum.), which were first isolated and named by Kondo. Later, Marion *et al.* presented the plane formula (I) for rhynchophylline by their brilliant chemical studies,[5] and Nozoye in Kondo's school contributed to the establishment of the same formula.[6]

It has been known that isomerization between both alkaloids occurs on treatment with acid[6] or base.[5c] In the equilibration reaction, the former (Ia) is predominant in the resulting mixture (Ia: Ib=7: 3) on an acid catalyzed isomerization,[6] and the latter (Ib) is preferential on a base treatment[5c] without exception.

As for the stereochemistry of these alkaloids, the present workers (Y.B. and T.O.) provided the first evidences that the substituents at C_{15} and C_{20} should be *trans* and diequatorial by the stereospecific syntheses of four isomeric N-methylrhynchophyllanes.[7] They also proposed that the C/D ring juncture should be *trans* due to the strong absorptions at 2785 cm^{-1} in the infrared spectra[8] of these compounds.[7] On the other hand, Finch and Taylor succeeded in the conversion of dihydrocorynantheine to rhynchophylline with *t*-butylhypochlorite, proposing the reasonable mechanism of this conversion which includes the isomerization of the normal series (Ia) into the iso series (Ib), based upon the correct assignment to the stereochemistry of these isomers.[9] (See Chart 1). Further experiments to elucidate the stereochemistry of this isomerism were made by Maeno who supported the conclusion of Finch and Taylor.[10]

* Dedicated to the memory of Prof. Eiji Ochiai.

1) *a*) Part V: Y. Ban, M. Seto, and T. Oishi, *Tetrahedron Letters*, **1972**, 2113; *b*) Part VI: Y. Ban, N. Taga, and T. Oishi, *ibid.*, 187 (1974). A part of this work was published as a communication in Part V.

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3) H. Kondo, T. Fukuda, and M. Tomita, *J. Pharm. Soc. Japan*, **48**, 321 (1928).

4) H. Kondo and T. Ikeda, *J. Pharm. Soc. Japan*, **57**, 881 (1937).

5) *a*) J.C. Seaton and L. Marion, *Can. J. Chem.*, **35**, 1102 (1957); *b*) J.C. Seaton, R. Tondeur, and L. Marion, *ibid.*, **36**, 1031 (1958); *c*) J.S. Seaton, M.D. Nair, O.E. Edwards, and L. Marion, *ibid.*, **38**, 1035 (1960).

6) T. Nozoye, *Chem. Pharm. Bull.* (Tokyo), **6**, 300, 306, 309 (1958).

7) Y. Ban and T. Oishi, *Tetrahedron Letters*, **1961**, 791; Y. Ban and T. Oishi, *Chem. Pharm. Bull.* (Tokyo), **11**, 441, 446, 451 (1963).

8) F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958).

9) N. Finch and W.I. Taylor, *J. Am. Chem. Soc.*, **84**, 3871 (1962).

10) S. Maeno, *Ph. D. dissertation in Hokkaido University*, 1965. *cf*) T. Oishi, S. Maeno, and Y. Ban, *Chem. Pharm. Bull.* (Tokyo), **11**, 1195 (1963).

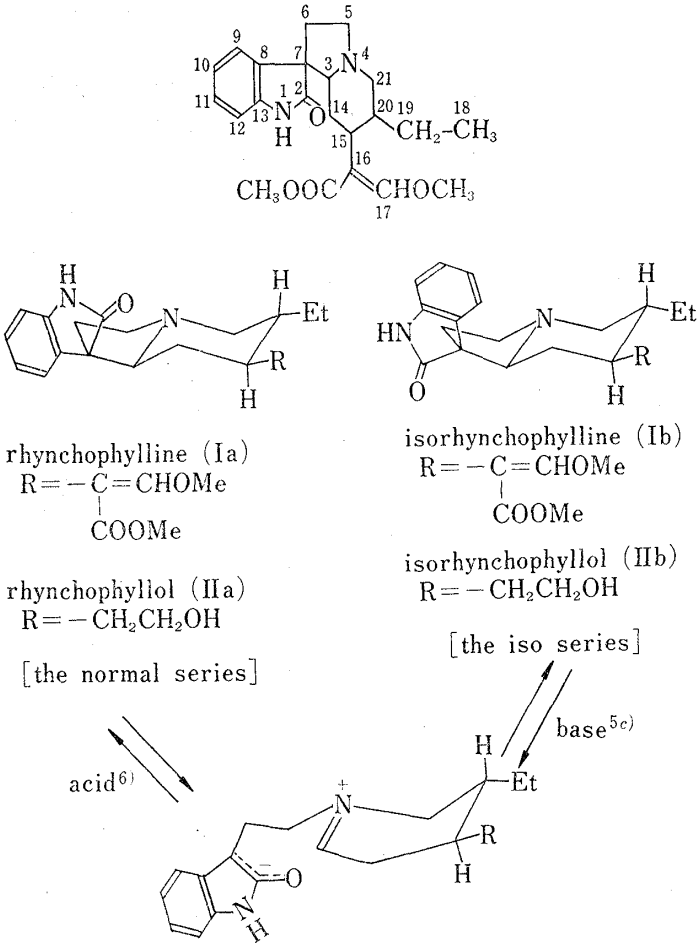

Chart 1

Although the partial synthesis of rhynchophylline (Ia) from dihydrocorynantheine was thus reported by Finch and Taylor,[9] and the ingenious biogenetic type of synthesis of (±)-rhynchophyllol (IIa) and (±)-isorhynchophyllol (IIb) was published by van Tamelen,[11] the total synthesis of these alkaloids has not yet been described, while it is only noticed that a brief reference to an incomplete work has appeared.[12]

The total synthesis of (±)-rhynchophylline (Ia) and (±)-isorhynchophylline (Ib) starting from condensation of 2-hydroxytryptamine hydrochloride (III) with ethyl sodium formyl acetate (IV), which was published in a preliminary form,[1b] is now described in the present full paper.

In the initial experiment for the above condensation when an equimolar mixture of III and IV was refluxed with sodium acetate in the mixed solvent of ethanol and water (2: 1) for one day, the decarboxylated compound [V, mp 150—151°, M^+=202: The infrared spectrum (IR) contains no ester absorption, and the nuclear magnetic resonance spectrum (NMR in $CDCl_3$) indicates a proton signal (3H, d, J=7 Hz, $C\underline{H}_3$) at τ 8.97.] was generated as a sole product in 56.5% yield after purification by column chromatography on alumina. Since formation of the compound (V) was assumed to be the result of hydrolysis of the initially formed Schiff's base or of the starting material (IV), followed by decarboxylation, the condensation was carried out in the presence of triethylamine as a base instead of sodium acetate, but the compound (V) was again obtained as a single spot on thin-layer chromatography (TLC). Subsequently,

11) E.E. van Tamelen, J.P. Yardley, M. Miyano, and W.B. Hinshaw, Jr., *J. Am. Chem. Soc.*, **91**, 7333 (1969).
12) J.E. Saxton, "The Alkaloids, Chemistry and Physiology, Vol. X (1968)" edited by R.H.F. Manske, p. 535 (Academic Press, New York); A.H. Warfield, *Dissertation Abstr.*, **26**, 1357 (1965).

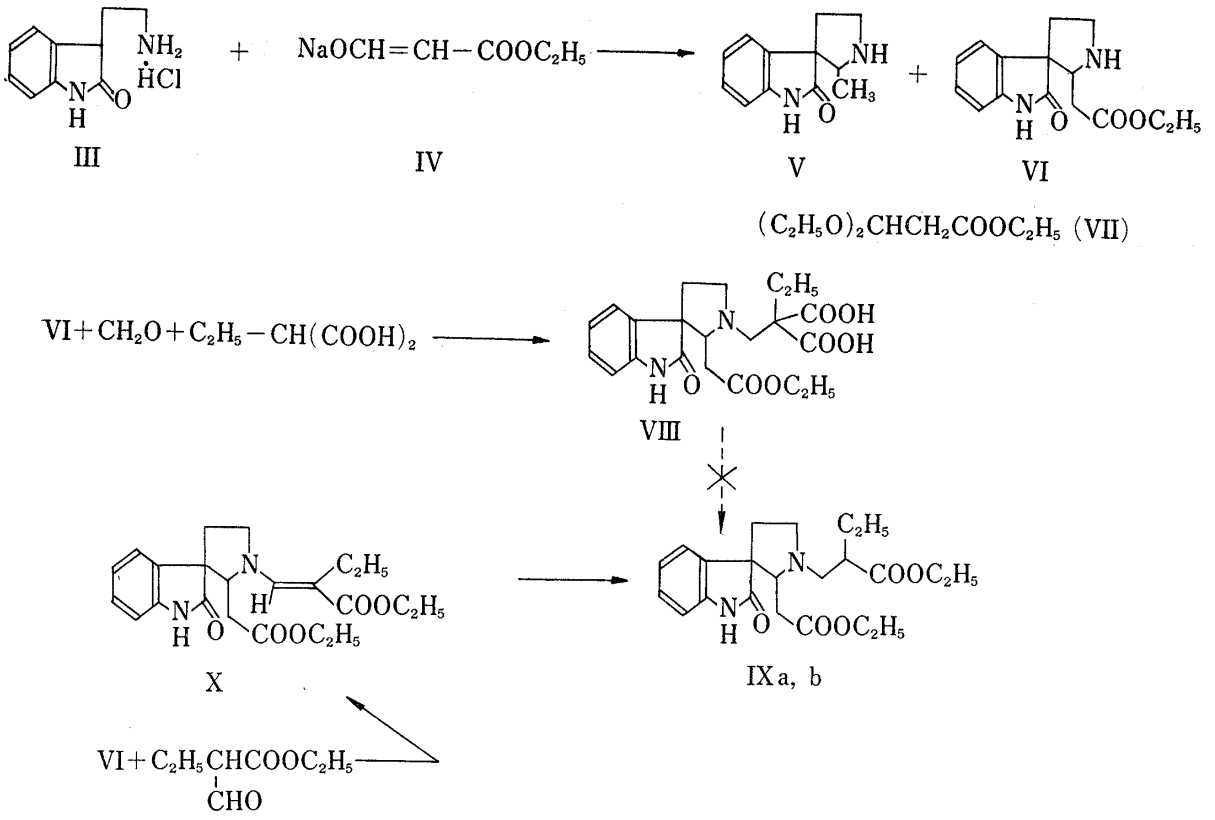

Chart 2

condensation of III with the acetal (VII)[13] was attempted, but no reaction occurred. Incidentally, an equimolar mixture of III and IV in aqueous ethanol was left at room temperature for two weeks to afford the objective compound (VI) in a very low yield. After many experiments, an optimum result was obtained by the procedure that a mixture of III and IV in the molar ratio of 1 : 1.8 in aqueous ethanol was kept at 45—48.5° for 2 days to afford almost exclusively VI as an oil [M^+=274; NMR ($CDCl_3$) τ 8.83 (3H, t, J=8 Hz, $OCH_2\underline{CH}_3$) and 6.07 (2H, q, J=8 Hz, $O\underline{CH}_2CH_3$); UV λ_{max}^{EtOH} 252—253 and 283 nm] in 63.0% yield. In this reaction was observed the generation of a negligible amount of the decarboxylated compound (V) on TLC. When the mixture was heated at higher temperatures than 60°, the ratio of V in the products increased. Even when the relative amount of ethyl sodium formyl acetate (IV) was raised up to 5 mol to III, the yield of VI was not improved. Therefore, the above reaction condition might be strictly followed.

In order to prepare the diester (IX) from the aminoester (VI), the Mannich reaction of VI with formalin and ethyl malonic acid[14] was carried out in water by leaving the whole mixture at room temperature for one night to furnish the product (mp 113—114°, M^+-CO_2= 374), which was assumed to be VIII and submitted to decarboxylation and esterification in ethanol saturated with hydrogen chloride. The products were complicated on TLC, and generation of the initial material (VI) as a result of the retro-Michael reaction was observed, but the objective diester (IX) was not recognized. Accordingly, condensation of the ester (VI) with ethyl α-formyl butyrate[15] was executed by heating a mixture in benzene in a Dean-Stark apparatus to afford the enamine (X) as an oil, which without isolation, was hydrogenated with

13) S. Sugasawa, *J. Pharm. Soc. Japan*, **47**, 551 (1927).
14) *a*) S. Sugasawa and T. Fujii, *Proc. Japan Acad.*, **30**, 877 (1954); *b*) *Idem*, *Pharm. Bull.* (Japan), **3**, 47 (1955); *c*) S. Sugasawa and Y. Ban, *Proc. Japan Acad.*, **31**, 31 (1955); *d*) Y. Ban, *Pharm. Bull.* (Japan), **3**, 53 (1955); *e*) T. Fujii, *Chem. Pharm. Bull.* (Tokyo), **6**, 591 (1958).
15) A.R. Battersby, H.T. Openshaw, and C.S. Wood, *J. Chem. Soc.*, **1953**, 2463.

Adams' catalyst in acetic acid in a Parr apparatus to furnish the diester (IXa, b) as two isomers after chromatography on silica gel. The first ether fraction furnished an isomer (IXa, M^+=402) as colorless needles, mp 113—114°, and the subsequent fraction provided an oil as a main product [IXb, M^+=402; the hydrochloride, mp 199—200° (decomp.)]. In this reaction, the reason why a single aminoester (VI) provided two isomeric diesters (IXa and IXb) might be ascribed to the result that the spiro-isomerization must have occurred during hydrogenation in acetic acid. The diester (IXb) was submitted to the Dieckmann condensation with sodium hydride in toluene heated at 110° under stirring for two hours to afford the ketoester, which in turn, was heated in hydrochloric acid at reflux for 2.5 hr with evolution of carbon dioxide, providing the ketone (XI) in 52% yield as a crude substance. A part of this product solidified

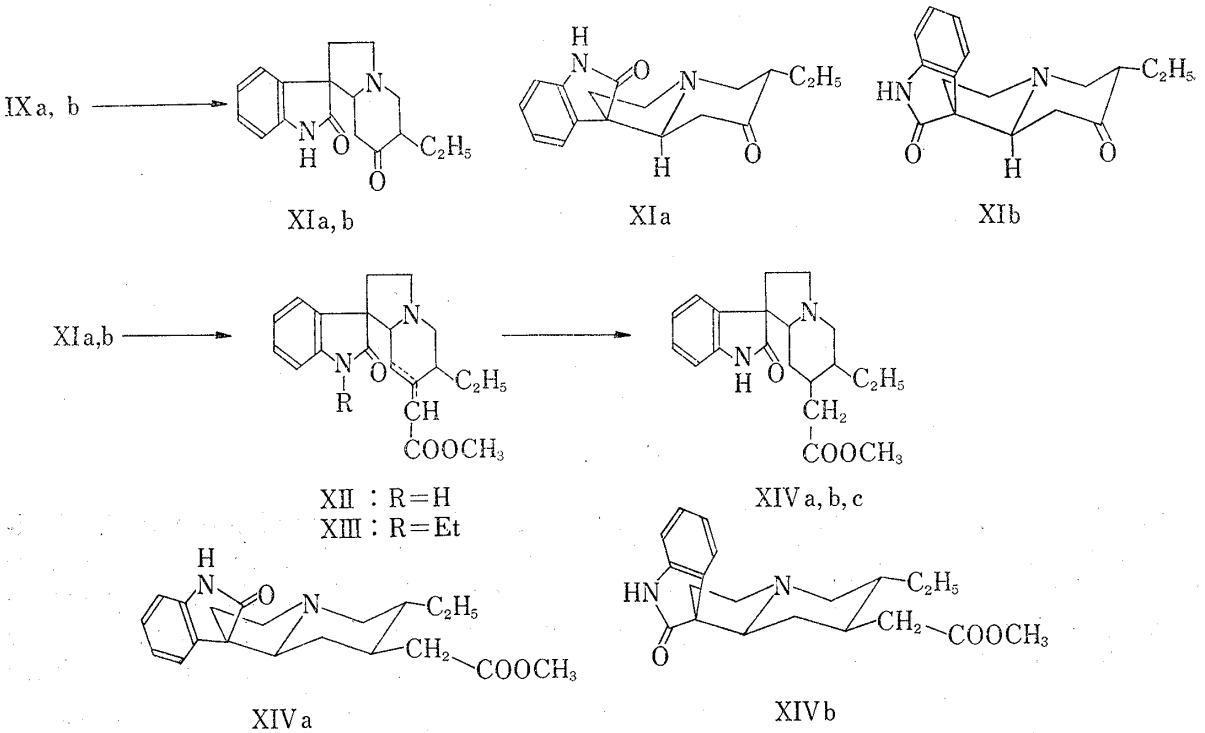

Chart 3

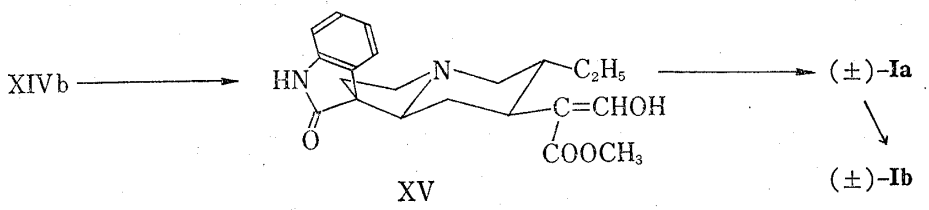

Chart 4

on standing to furnish one isomer (XIb, M^+=284, mp 162—163°) and the material from the mother liquor on filtration of XIb, was purified by chromatography on silica gel to give the other isomer (XIa, M^+=284, mp 153—154°, 43.3% yield) with a further crop of the former (XIb, totally 17.1% yield). A mixture of IXa and IXb was similarly reacted to afford the same compounds (XIa and XIb). The stereostructures of these compounds are deduced to involve the *trans*-indolizidine based on the Bohlmann's absorptions at 2800 cm^{-1} in their infrared spectra.[8] The *Rf* value of XIb was greater than that of XIa, and XIa was isomerized to XIb with alumina in methylene chloride solution. Since a proton signal of C-9 in the aromatic ring of XIb is in the lower magnetic field (τ 2.40) than that (τ 2.65) of XIa, these isomers are due to isomerism at the spiro-position, and XIb is in the iso series and XIa is in the normal

series.[10] Consequently, it might be concluded that ethyl substituent should be a stable equatorial, and the stereochemistry of these isomers could be delineated as XIa and XIb. The fact that the isomer (XIa) was predominantly produced in this reaction, could be readily explained as the result that the compound (IXb) in the iso series was converted into the normal series during the decarboxylation with hydrochloric acid.

The iso ketone (XIb) was condensed with methyl diethylphosphonoacetate[16] in the presence of sodium hydride in monoglyme kept at 50° for5 hr to afford an oil (XII, $M^+=340$) in 60.6% yield after purification by chromatography on alumina, in which a byproduct that could be assumed to be the N-ethyl derivative (XIII), was isolated as an oil in *ca.* 10% yield. Also, the normal ketone (XIa) gave the same products (XII and XIII). The product (XII) could be a mixture of geometric isomers related to the double bond (exo-cyclic Z or E or endocyclic isomers) associated with the orientation of ethyl substituted at C-20, since the O-methyl proton signals appear as two singlets at τ 6.46 and 6.51, which did not change at all when the compound (XII) was treated with sodium methoxide. This experiment suggests that XII should be in the iso series, as it was produced under an alkaline condition during the Wittig reactions of either XIa or XIb, which must have concurrently induced the complete shift of the exocyclic to the endocyclic double bond in the initially formed product.[17] This assumption might be supported by observation of the olefinic proton signal at τ 4.45 (1H, s).

The double bond of XII exhibiting these properties was hydrogenated with palladium on charcoal in neutral ethanol in a Parr apparatus to give the saturated ester (XIV), which was proved to consist of two isomers (XIVb and XIVc) on TLC, in 80% yield. The crude product was submitted to chromatography on silicagel to afford three isomers (XIVc, mp 136—137°, $M^+=342$, 36.6% yield), (XIVb, oil 26% yield) and (XIVa, mp 167—168°, 6.4% yied), of which XIVa was generated as a consequence of isomerization of XIVb on chromatography, because XIVa was converted to a mixture of XIVa and XIVb when a solution of the former (XIVa) was left with alumina at room temperature overnight. The hydrogenation was also carried out with Adams' catalyst in an acidic solution of acetic acid under several atmospheric pressure of hydrogen to afford the crude product (XIV), which was purified in a similar manner to furnish the above three isomers in a different ratio (XIVc: XIVb: XIVa=22: 28: 38). Accordingly, based upon the same ground as the above discussion about the stereochemistry of XIa and XIb, XIVa should be in the normal series at the spiro-position (C-7), and XIVb must be the corresponding iso base, both of which involve the *trans*-indolizidine part with *trans*-diequatorial substituents at C-15 and C-20 (Chart 3). Although the stereochemistry of XIVc has remained to be decided, it would be assumed to be the stereoisomer involving the *cis*-substituents at C-15 and C-20.

The compound (XIVb) was formylated with ethyl formate in the presence of sodium bistrimethylsilylamide [$\langle(CH)_3Si\rangle_2NNa$][18] to provide the formyl derivative (XV) as yellow caramel (positive on the $FeCl_3$ test), which was methylated with diazomethane in ether and methanol to yield (±)-isorhynchophylline [(±)-Ib] as colorless fine crystals, mp 225—227° (decomp.) after recrystallization from ether–*n*–hexane. The infrared ($CHCl_3$) and mass ($M^+=384$) spectra of the synthetic sample were completely identical with those of the natural isorhynchophylline (Ib) on direct comparison (Fig. 1).

Furthermore, the synthetic (±)-isorhynchophylline [(±)-Ib] was converted on treatment with dilute acetic acid to (±)-rhychophylline [(±)-Ia], mp 197—198° (decomp), colorless pillars, on recrystallization from ethyl acetate–ether. The spectral data of the synthetic sample [(±)-Ia] were identical with those of the authentic specimen of the natural alkaloid (Ia). The total synthesis of the entitled alkaloids has been completed.

16) R.J. Sundberg and F.O. Holcombe, Jr., *J. Org. Chem.*, **34**, 3273 (1969).
17) J.A. Weisbach, J.L. Kirkpatrick, K.R. Williams, E.L. Anderson, N.C. Yim, and B. Douglas, *Tetrahedron Letters*, **1965**, 3457.
18) U. Wannagat and H. Niederprum, *Chem. Ber.* **94**, 1500 (1961).

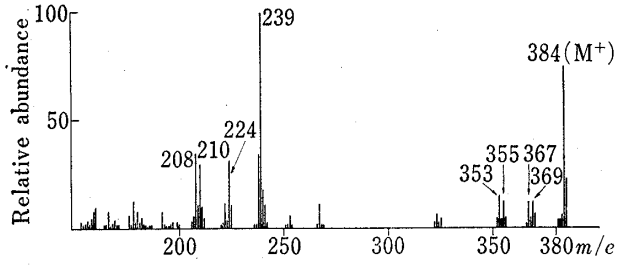

Fig. 1a. Mass Spectrum of synthetic (±)-Isorhynchophylline

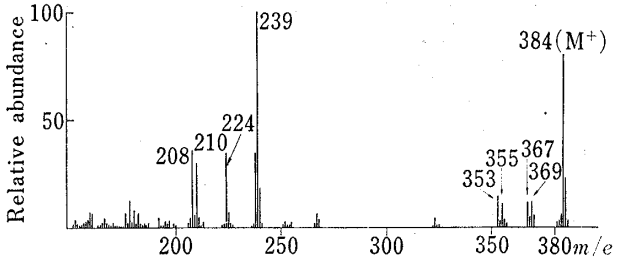

Fig. 1b. Mass Spectrum of Natural Isorhynchophylline (Ib)

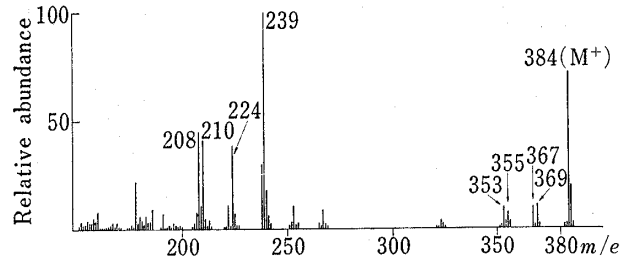

Fig. 1c. Mass Spectrum of Synthetic (±)-Rhynchophylline

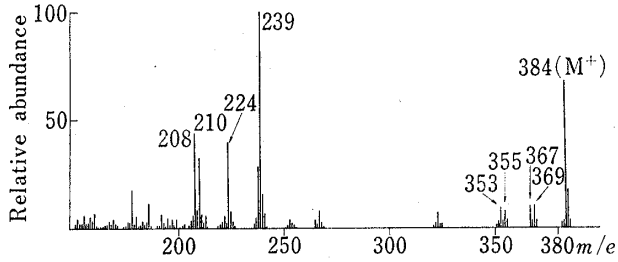

Fig. 1d. Mass Spectrum of Natural Rhynchophylline (Ia)

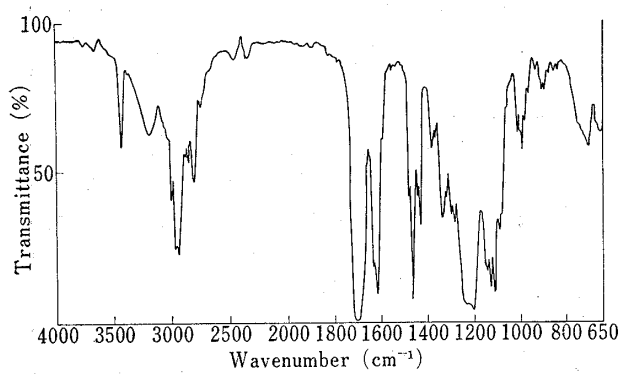

Fig. 2a. IR Spectrum (in $CHCl_3$) of Synthetic (±)-Isorhynchophylline

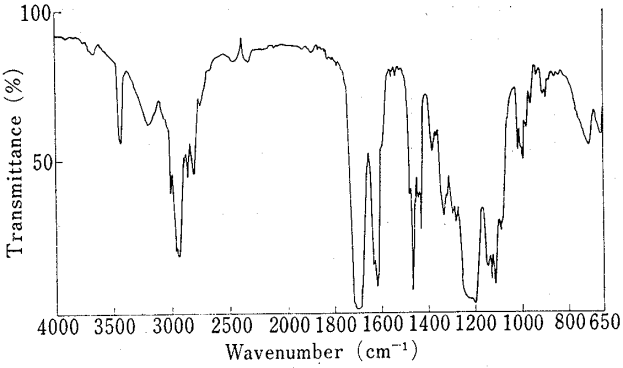

Fig. 2b. IR Spectrum (in $CHCl_3$) of Natural Isorhynchophylline (Ib)

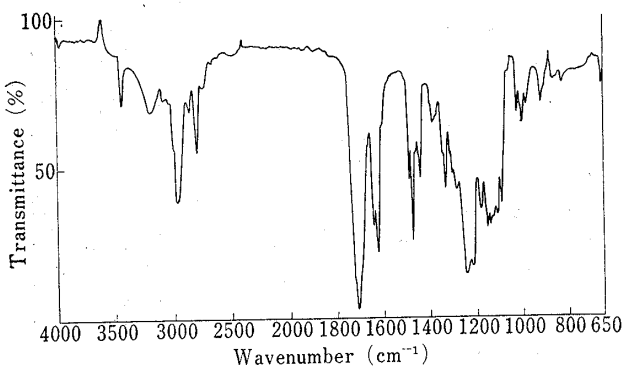

Fig. 2c. IR Spectrum (in $CHCl_3$) of Synthetic (±)-Rhynchophylline

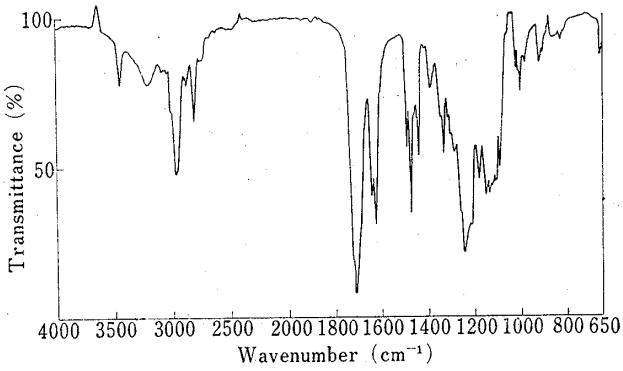

Fig. 2d. IR Spectrum (in $CHCl_3$) of Natural Rhynchophylline (Ia)

Experimental[19]

2′-Methylspiro[indoline-3,3′-pyrrolidine]-2-one (V)[20]——A solution of 2-hydroxytryptamine hydrochloride[III, 1.06 g(5 mmoles.), sodium acetate trihydrate[0.816 g(6 mmoles.)] and ethyl sodium formyl acetate [IV, 0.69 g (5 mmoles.)] in aqueous ethanol (water: ethanol=1: 2) was heated at reflux for 24 hr. The solvent was removed by concentration *in vacuo*, and the residue was extracted with chloroform. The extract was washed with water, dried over sodium sulfate and concentration at the water aspirator afforded an oil (810 mg), which was purified by chromatography on alumina. Elution was carried out with chloroform to afford 571 mg (56.5%) of V, which was recrystallized from a mixed solvent of methanol and ethyl acetate to give colorless prisms, mp 150—151°. Mass Spectrum *m/e*: 202 (M^+). UV λ_{max}^{EtOH} 253 nm. NMR ($CDCl_3$) τ: 8.97 (3H, d, J=7 Hz, CH–C<u>H</u>$_3$). *Anal.* Calcd. for $C_{12}H_{14}ON_2$ (202.25): C, 71.26; H, 6.98; N, 13.85. Found: C, 71.31; H, 6.94; N, 13.71.

2′-Ethoxycarbonylmethylspiro[indoline-3,3′-pyrrolidine]-2-one (VI)——A solution of 2-hydroxytryptamine hydrochloride[III, 10.5 g (0.05 mole.)] and ethyl sodium formyl acetate [V, 12.5 g (0.09 mole.)] in 200 ml of aqueous ethanol was stirred at 48.5° for 24 hr, and the whole solution was left at room temperature overnight. The residue obtained after solvent evaporation *in vacuo*, was extracted with chloroform, and the extract was washed with water. The chloroform solution was extracted with 10% HCl to take up the base in the aqueous layer, which was made alkaline with NH_4OH, and extracted again with chloroform. The chloroform extract was washed with water, dried over Na_2SO_4, and the solvent was removed by evaporation to leave 9.69 g of the crude oil, which was purified by chromatography on silica gel. Elution with a mixed solvent of $CHCl_3$ and EtOH (9: 1) gave VI as an oil (8.63 g, 63.0%). Mass Spectrum *m/e*: 274 (M^+). UV λ_{max}^{EtOH} 253 nm. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450 (NH), 1720 (ester CO), and 1705 (oxindole CO). NMR ($CDCl_3$) τ: 6.07 (2H, q, J=8 Hz, –OC<u>H</u>$_2$CH$_3$) and 8.88 (3H, t, J=8 Hz, –OCH$_2$C<u>H</u>$_3$). Picrate: mp 187—188°, yellow needles on recrystallization from EtOH. *Anal.* Calcd. for $C_{21}H_{21}O_{10}N_5$: C, 50.10; H, 4.20; N, 13.91. Found: C, 50.04; H, 4.17; N, 13.70.

1′-(2,2-Dicarboxybutyl)-2′-ethoxycarbonylmethylspiro[indoline-3,3′-pyrrolidine]-2-one (VIII)——To a solution of ethyl malonic acid [390 mg (3 mmoles.)] in 3 ml of water, was added the aminoester [VI, 300 mg (1.1 mmoles.)] and formalin (2 ml). The whole solution was left at room temperature for one night. The colorless crystals deposited, which were collected by filtration to furnish fine crystals [115 mg (25.1%)], mp 113—115° (decomp.). Mass Spectrum *m/e*: 374 (M^+-CO_2). IR: ν_{max}^{Nujol} cm^{-1}: 1720, 1700.

1′-(2-Ethoxycarbonyl butyl)-2′-ethoxycarbonylmethylspiro[indoline-3,3′-pyrrolidine]-2-one (IXa, b)——To a solution of the aminoester[VI, 7.14 g (26 mmoles.)] in benzene (150 ml) was added ethyl α-formylbutyrate [5.76 g (40 mmoles.)]. The whole solution was heated at reflux in a Dean-Stark apparatus to eliminate the water generated from the azeotropic mixture. The benzene was evaporated, and the other 150 ml of anhydrous benzene was added. The benzene was again removed by evaporation to leave the residue (X), which indicated the ultraviolet (UV) absorption at 290 nm in neutral ethanol, and it was shifted to 254 nm on acidification. A solution of the above residue (X) in acetic acid (70 ml) was hydrogenated in the presence of $PtO_2 \cdot H_2O$ (300 mg) in a Parr apparatus at room temperature. One mole equivalent of hydrogen was absorbed. After filtration of the catalyst and distillation of the solvent, the residue was dissolved in water, made alkaline with NH_4OH, and extracted with ether. The ether solution was extracted with 10% HCl to take up the base in the aqueous layer as the hydrochloride, 600 mg of which [IXb-HCl, mp 199—200°, colorless needles recrystallized from EtOH). The mother liquor on filtration of the hydrochloride was made alkaline with NH_4OH, extracted with ether, washed with water and dried over Na_2SO_4. The ether was evaporated to leave 7.95 g of the residue, which was submitted to chromatography on silica gel. The first fraction eluted with ether gave the diester (IXa, mp 113—114° recrystallized from ether–*n*-hexane, 572 mg). The second fraction eluted with ether gave a mixture of IXa and IXb (6.04 g), of which IXb was proved to be a main product on TLC. The last fraction eluted with ether afforded the diester (IXb, oil, 859 mg; the hydrochloride, colorless needles, mp 199—200°). The total yield of IXa and IXb was 76.6% (8.03 g). The isomer (IXa). Mass Spectrum *m/e*: 402 (M^+). IR ν_{max}^{neat} cm^{-1}:1740, 1720, 1705. NMR (CCl_4) τ: 0.10 (N<u>H</u>), 5.87, 6.15 (2H, q, J=7 Hz, OC<u>H</u>$_2$CH$_3$, respectively) and 8.73, 8.98 (3H, t, J=7 Hz, OCH$_2$C<u>H</u>$_3$, respectively). *Anal.* Calcd. for $C_{22}H_{30}O_5N_2$ (402.48): C, 65.65; H, 7.51; N, 6.96. Found: C, 65.52; H, 7.46; N, 6.71. The isomer (IXb).

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19) Melting points were measured with a hot stage microscope (Yanaco MP-J2). Spectra reported herein were measured on a Hitachi EPS-3T spectrophotometer, JASCO DS-701G and 215 Hitachi grating infrared spectrophotometers, a Hitachi R-20B (NMR, 60 MHz), and a Hitachi RMU-7M double focussing mass spectrometer. The authors are indebted to Misses H. Kakizaki, M. Satoh, A. Maeda, and C. Ohara for microanalyses, to Mrs. M. Ohnuma for obtaining NMR spectra and to Miss Masako Takahashi for mass spectral measurements.

20) The numberings which are shown in formula (I), are used for the natural alkaloids. The general numberings are used for the intermediates. To avoid the confusion between them, however, discussions are made by using the former numberings. The following abbrebiations are used: b=broad, d=doublet, m=multiplet, q=quartet, s=singlet, t=triplet.

Mass Spectrum *m/e*: 402 (M^+). IR ν_{max}^{neat} cm^{-1}: 1740, 1720, 1700. NMR (CCl_4) τ: 0.15 (NH), 5.85, 6.20 (2H, q, $J=7$ Hz, OCH_2CH_3, respectively), 8.70, 8.97 (3H, t, $J=7$ Hz, OCH_2CH_3, respectively). The hydrochloride (IXb·HCl), colorless needles, mp 199—200°, recrystallized from EtOH. *Anal.* Calcd. for $C_{22}H_{30}O_5N_2 \cdot HCl$ (438.94): C, 60.19; H, 7.12; N, 6.41. Found: C, 60.06; H, 7.25; N, 6.19.

6′-Ethyl-7′-oxospiro[indoline-3,1′-indolizidine]-2-one (XIa, b)——A suspension of 65% NaH [620 mg (16.8 mmoles.)] in anhydrous toluene (30 ml) was kept at 50°, to which a mixture of IXa and IXb [338 mg (8.4 mmoles.)] in toluene (20 ml) was added over a period of 30 min. The whole mixture was refluxed for 3 hr, during which time orange crystals deposited. On cooling, water (50 ml) was added, the aqueous layer was separated, and washed with ether. The aqueous solution was acidified with concentrated hydrochloric acid (16 ml) and the whole solution was heated at reflux for 5 hr, during which time evolution of carbon dioxide was observed. On cooling, the reaction mixture was washed with ether, made alkaline with NH_4OH, and then extracted with CH_2Cl_2. The methylene chloride solution was washed with water, dried over Na_2SO_4, and the solvent was removed by evaporation to give the residual liquid (1.65 g), which was submitted to chromatography on silica gel. The first fraction eluted with benzene: ethyl acetate (3: 1) gave the aminoketone (XIb), which was recrystallized from ether–*n*-hexane to afford 396 mg (17.1%) of colorless plates, mp 153—154°. Mass Spectrum *m/e*: 284 (M^+). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420, 2800, 1700. NMR ($CDCl_3$) τ: 1.40 (NH), 2.40—3.25 (4H, m, aromatic protons). *Anal.* Calcd. for $C_{17}H_{20}O_2N_2$ (284.35): C, 71.80; H, 7.09; N, 9.87. Found: C, 72.03; H, 7.10; N, 9.91. The second fraction eluted with the same solvdnt (benzene: ethyl acetate=3: 1) furnished the other aminoketone (XIa), which was recrystallized from ethyl acetate to give 1004 mg (43.3%) of colorless needles, mp 162—163°. Mass Spectrum *m/e*: 284 (M^+). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3425, 2790, 1700. NMR ($CDCl_3$) τ: 0.97 (NH), 2.65—3.25 (4H, m, aromatic protons). *Anal.* Calcd. for $C_{17}H_{20}O_2N_2$ (284.35): C, 71.80; H, 7.09; N, 9.87. Found: C, 71.76; H, 7.08; N, 9.72.

The Isomerization of the Aminoketone (XIa)——To a solution of the aminoketone (XIa) in CH_2Cl_2 was added Al_2O_3, and the whole mixture was left to stand at room temperature overnight to give a mixture of XIa and XIb, which was recongnized on TLC over Al_2O_3 eluted with ether. The relative *Rf* values of XIa and XIb were approximately 1: 2.5.

6′-Ethyl-7′-methoxycarbonylmethylidene spiro[indoline-3,1′-indolizidine]-2-one (XII) and 1-Ethyl-6′-ethyl-7′-methoxycarbonylmethylidenespiro[indoline-3,1′-indolizidine]-2-one (XIII)——A suspension of 65% NaH [37 mg (1.0 mmole.)] in 1,2-dimethoxyethane (2 ml) was kept below 20°, to which was added methyl diethylphosphonoacetate [210 mg (1.0 mmole.)]. The whole mixture was stirred at room temperature for 1.5 hr. The aminoketone [XIb, 142 mg (0.5 mmole.)] in a crystalline form was added to the mixture, which was kept at 50° for 5 hr. On cooling, the reaction mixture was poured onto ice, extracted with ether, and the ether solution was extracted with 10% HCl to take up the base in the aqueous phase. The acidic solution was washed with ether, and made alkaline with NH_4OH. The alkaline solution was again extracted with ether, and the ether solution was dried over Na_2SO_4. The solvent was evaporated to leave 161 mg of the residual oil, which was submitted to chromatography on alumina. The first fraction eluted with ether afforded 103 mg (60.6%) of the olefinic ester (XII) as an oil. Mass Spectrum *m/e*: 340 (M^+). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3425, 2800, 1702, 1640. NMR (CCl_4) τ: −0.31, −0.03 (NH), 2.55—3.25 (4H, m, aromatic protons), 4.45 (1H, s, a vinyl proton), 6.46, 6.51 (3H, s, OCH_3). The other fraction eluted with ether gave 6.0% of the N-ethyl derivative (XIII) as an oil. Mass Spectrum *m/e*: 368 (M^+). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2800, 1700, 1640. NMR (CCl_4) τ: 2.5—3.4 (4H, m, aromatic protons), 4.45 (1H, s, a vinyl proton), 6.44, 6.46 (3H, s, OCH_3).

6′-Ethyl-7′-methoxycarbonylmethylspiro[indoline-3,1′-indolizidine]-2-one (XIVa, b, c)——A solution of XII [1.31 g (3.85 mmoles.)] in ethanol (30 ml) was hydrogenated in the presence of 10% palladium on charcoal in a Parr apparatus at room temperature. One mole equivalent of hydrogen was absorbed. After filtration of the catalyst and distillation of the solvent, the residual oil (1.30 g) which was recognized to consist of two substances on TLC, was submitted to chromatography on silica-gel. The fractions eluted with a mixed solvent of ethyl acetate and benzene (4: 1) gave XIVc (36.6%), XIVb (26.0%) and XIVa (6.4%) in these orders. The starting material [180 mg (13.7%)] was recovered. The isomer (XIVa) was generated as a result of isomerization of XIVb on chromatography. The isomer (XIVa, colorless needles recrystallized from EtOH–AcOEt, mp 167—168°). Mass Spectrum *m/e*: 342 (M^+). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3430, 2790, 1720, 1695. NMR ($CDCl_3$) τ: 0.95 (NH), 2.7—3.2 (4H, m, aromatic protons), 6.47 (3H, s, OCH_3). *Anal.* Calcd. for $C_{20}H_{26}O_3N_2$ (342.42): C, 70.5; H, 7.66; N, 8.18. Found: C, 70.17; H, 7.69; N, 8.35. The isomer (XIVb, oil). Mass Spectrum *m/e*: 342 (M^+). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3440, 2800, 1720, 1695. NMR ($CDCl_3$) τ: 0.49 (NH), 2.55—3.25 (4H, m, aromatic protons), 6.49 (3H, s, OCH_3). The picrate was recrystallized from ethanol to afford yellow prisms, mp 200—203°. *Anal.* Calcd. for $C_{26}H_{29}O_{10}N_5$: C, 54.64; H, 5.11; N, 12.25. Found: C, 54.50; H, 5.12; N, 11.98. The isomer (XIVc, colorless prisms recrystallized from ether–AcOEt, mp 136—137°). Mass Spectrum *m/e*: 342 (M^+). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3440, 2800, 1720, 1692. NMR ($CDCl_3$) τ: 1.30 (NH), 2.55—3.25 (4H, m, aromatic protons), 6.43 (3H, s, OCH_3). *Anal.* Calcd. for $C_{20}H_{26}O_3N_2$ (342.42): C, 70.15; H, 7.66; N, 8.18. Found: C, 70.39; H, 7.65; N, 8.12.

Hydrogenation in an Acidic Solution: A solution of XII [370 mg (1.09 mmoles.)] in 15 ml of acetic acid was hydrogenated with $PtO_2 \cdot H_2O$ (50 mg) in a Parr apparatus at room temperature. One molar equivalent of hydrogen was absorbed. The chromatography of the crude product on silica gel afforded the three isomers (XIVa, XIVb and XIVc) in the yields of 38.1%, 28.1% and 21.6%, respectively.

The Isomerization of the Ester (XIVa)——To a solution of the ester (XIVa) in CH_2Cl_2 was added Al_2O_3, and the whole mixture was left to stand at room temperature overnight to give a mixture of XIVa and XIVb, which was recognized on TLC over silica gel eluted with AcOEt, where the relative *Rf* values of XIVa and XIVb were approximately 1: 10.

6′-Ethyl-7′-(formyl)(methoxycarbonyl)methylspiro[indoline-3,1′-indolizidine]-2-one (XV)——A suspension of $[(CH_3)_3Si]_2NNa$ [915 mg (4.8 mmoles.)] in 20 ml of 1,2-dimethoxyethane and ether (1: 1) was cooled to 0—5°, to which was added a solution of the ester [XIVb, 560 mg (1.6 mmoles.)] in 5 ml of ether. The mixture was stirred at 0—5° for 5 min, ethyl formate [600 mg (8.1 mmoles.)] was added, and stirred at the same temperature for 1 hr and then at room temperature for 24 hr. On cooling, 10 ml of water was added, the aqueous phase was separated, acidified with acetic acid, and made alkaline with NH_4OH. The alkaline solution was extracted with ether, dried over Na_2SO_4, and the solvent was evaporated to leave 83 mg (13.7%) of the residue as a yellow caramel. Mass Spectrum *m/e*: 370 (M^+). $FeCl_3$ test: positive with red color. The starting material (435 mg) was recovered from the organic phase.

(±)-Isorhynchophylline (Ib)——To a solution of the formyl derivative [XV, 80 mg (0.22 mmole.)] in 5 ml of the mixed solvent [ether: MeOH (1: 1)] was added at room temperature an ethereal solution (10 ml) of CH_2N_2 which was prepared from 70 mg of nitrosomethylurea. The whole solution was stirred for 3 hr, and the solvent was evaporated *in vacuo* to leave the residue, which was submitted to chromatography on silica gel. The fraction eluted with benzene: AcOEt (6: 4) afforded 22 mg (26.5%) of (±)-isorhynchophylline (Ib) which was recrystallized from ether: *n*-hexane to furnish colorless prisms, mp 225—227°. Mass Spectrum *m/e*: 384 (M^+). (See Fig. 1a, b). IR: See Fig. 2a, b. NMR ($CDCl_3$) τ: 1.17 (NH), 6.32, 6.42 (3H, s, OCH_3). *Anal.* Calcd. for $C_{22}H_{28}O_4N_2$ (384.46): C, 68.72; H, 7.34; N, 7.29. Found: C, 68.47; H, 7.48; N, 7.15.

(±)-Rhynchophylline (Ia)——A solution of (±)-isorhynchophylline (55 mg) in AcOH: H_2O (1.6: 20) was heated in a water bath for 8.5 hr. On cooling, the solution was made alkaline with NH_4OH, and extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried over Na_2SO_4, and the solvent was removed *in vacuo* to leave the residue (54 mg), which solidified on addition of ether. The deposited substance was recrystallized from AcOEt–ether to afford 20 mg (36.4%) of (±)-rhynchophylline (Ia) as colorless prisms, mp 197—199°. Mass Spectrum *m/e*: 384 (M^+). See Fig. 1c, d. IR: See Fig. 2c, d. *Anal.* Calcd. for $C_{22}H_{28}O_4N_2$ (384.46): C, 68.72; H, 7.34; N, 7.29. Found: C, 68.81; H, 7.38; N, 7.24.

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