Picrate : Yellow prisms recrystallized from EtOH, m.p. 188~189°.

Isomerization of IV-A to IV-B——A sample of IV-A (m.p. 78~80°, 37 mg.) was refluxed in 3.5 ml. of pyridine for 9 hr. The solvent was removed *in vacuo*, and benzene was added and distilled off. This treatment was repeated three times to leave an oily substance which was chromatographed on alumina. Elution with benzene-Et_2O (1:1) yielded 19 mg. of solid m.p. 72~73°, affording the picrate, m.p. 201~202°, identical with that of IV-A. Elution with AcOEt afforded 15 mg. of colourless prisms, m.p. 92~93°, which was identified with IV-B by mixed melting point determination.

1-Methylspiro[indoline-3,1′-indolizidine] (XXVI)——To a suspension of 100 mg. of $LiAlH_4$ in 10 ml. of dioxan, a solution of 80 mg. of IV in 10 ml. of dioxan was added. The whole mixture was stirred and refluxed under a stream of N_2 for 3.5 hr. After the reaction, it was cooled by ice, to which was added 1.5 ml. of water and stirred for 1.5 hr. Furthermore, Et_2O (50 ml.) was added and the whole was stirred for 10 min., separating white solid at the bottom of the reaction flask. After decantation of the Et_2O layer, the white deposit was washed with Et_2O twice. The combined Et_2O solution was dried over Na_2SO_4, and the solvent was removed to afford XXVI as pale yellow oil, which solidified on stimulating with a glass rod. Yield, 80 mg. Recrystallization from petr. ether furnished colourless prisms, m.p. 58~60°. *Anal.* Calcd. for $C_{16}H_{22}N_2$: C, 79.33; H, 9.09; N, 11.57. Found : C, 79.11; H, 9.39; N, 11.34.

The authors wish to express their deep gratitude Professors S. Sugasawa and S. Yamada for their valuable advices and hearty encouragement throughout this work. Thanks are also due to Mr. K. Narita of the Central Analysis Room of this Institute for elemental analyses.

The authors are indebted to the Ministry of Education for Grant-in-Aid for Institutional Reaseach (1960~1961) in aid of this work.

Summary

The syntheses of 1-methyl spiro[indoline-3,1′-pyrrolizidine and -indolizidine]-2-one are described. The latter was obtained as two diastereoisomers, the stereochemistry of which was discussed mainly by their infrared absorption spectra.

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UDC 547.759.07

81. Yoshio Ban and Takeshi Oishi : The Synthesis of 3-Spirooxindole Derivatives. III.[1] Stereospecific Syntheses of *rac*-N-Methylrhynchophyllane for Stereochemistry of Rhynchophylline and Isorhynchophylline.*[1]

(*Faculty of Pharmaceutical Sciences, School of Medicine, Hokkaido University*[*2])

Rhynchophylline ($C_{22}H_{28}O_4N_2$) is an alkaloid of *Uncaria rhynchophylla* Miq. (*Ouroparia rhynchophylla* Matsum.) which was first isolated and named by Kondo.[2]

In the recent years, Marion, *et al.*[3a,c] proposed the plane formula (I) for rhynchophylline, and independently Nozoye[4] reached the same formula (I) and suggested the partial stereostructure (II) for the same alkaloid.

*1 For preliminary communication of this work see Y. Ban and T. Oishi : Tetranedron Letters, No. 22, 791 (1961).

*2 Kita-12-jo, Nishi-5-chome, Sapporo, Hokkaido (伴 義雄, 大石 武).

1) Part II : This Bulletin, **11**, 446 (1963).

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

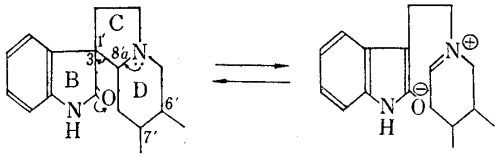
3) *a*) J.C. Seaton, L. Marion : Can. J. Chem. **35**, 1102 (1957). *b*) J.C. Seaton, R. Tondeur, L. Marion: *Ibid.*, **36**, 1031 (1958). *c*) J.C. Seaton, M.D. Nair, O.E. Edwards, L. Marion : *Ibid.*, **38**, 1035 (1960).

4) T. Nozoye : This Bulletin, **6**, 300, 306, 309 (1958).

The other alkaloid, isorhynchophylline, was isolated from the same plant by Kondo and Ikeda.[5] As this alkaloid is a stereoisomer of rhynchophylline, it should be also represented by the same plane formula (I).

Isorhynchophylline is known to partially isomerize to rhynchophylline on boiling with acetic anhydride.[5] This isomerization has been found to take place under a milder condition which is heated in dilute acetic acid[4] or in pyridine.[3c] Similar isomerization has been observed with a pair of uncarine-A and uncarine-B,[4] and also with the other pair of mitraphylline[3b,4] and isomitraphylline,[3c] all of which are the closely related series of alkaloids to rhynchophylline and are represented by the same plane formula (III).

The fact that isomerization readily occurs under relatively mild conditions, suggested that it must be due to the conversion of configurations at $C_{3(1')}$ and/or $C_{8'a}$, but not at $C_{6'}$ and $C_{7'}$. As to the mechanism of this isomerization, Wenkert[6] and Marion[3c] proposed that it is effected by fission and recombination of the bond between $C_{3(1')}$ and $C_{8'a}$, as shown in the following.



That this isomerism is concerned with $C_{3(1')}$ and/or $C_{8'a}$, should be supported by an example that the compound (VII) of no substituents at $C_{6'}$ and $C_{7'}$ synthesized by us[1] exist as two isomers, the one of which isomerizes to the other under the similar conditions.

On the other hand, rhynchophylline is converted with dilute hydrochloric acid into rhynchophyllal (IV) and then by the Wolff-Kishner-Huang reduction to rhynchophyllane (V),[3a] which is readily derived to N-methyl derivative (VI).[3c]

Also, isorhynchophylline is converted into isorhynchophyllane (V)[3c] via isorhynchophyllal (IV) in the similar way, but isorhynchophyllane was found to be identical with rhynchophyllane,*3 which indicates that isomerization occurred during the Wolff-Kishner-Huang reduction process. As this reduction was carried out in potassium hydroxide solution under a rather drastic condition, it was cared that isomerizations might occur not only at $C_{3(1')}$ and/or $C_{8'a}$, but also at $C_{6'}$ and $C_{7'}$. Meanwhile, Janot *et al.*[7] converted corynantheine (VIIIa) and corynantheidine (VIIIb) into dihydrocorynantheane (IXa) and corynantheidane (IXb), respectively, by the Wolff-Kishner-Huang reduction of the corresponding intermediary aldehydes. These products are oxidized with $Pb(OAc)_4$ to afford the dehydrocompounds, Xa and Xb[8], respectively, which suggests that these isomers are different only at the configuration of C_{15} and C_{20}. Later, van Tamelen[9] elucidated that the relative configuration of these positions of dihydrocorynantheane is *trans*, and that of corynantheidane is *cis*. These works provided an evidence that the Wolff-Kishner-Huang reduction has no effect on the configuration at C_{15} and C_{20} of these

*3 Marion *et al.* prefer the name "isorhynchophpllane" to "rhynchophyllane" for this compound (V), because the isobase always predominates at the equilibrium of isomerization between rhynchophyllin and isorhynchopylline.[3c] But we adopt the name "rhynchophyllane" till the stereochemistry of this base is elucidated.

5) H. Kondo, T. Ikeda: J. Pharm. Soc. Japan, **57**, 881 (1937).
6) E. Wenkert, J.H. Udelhofen, N.K. Bhattacharyya: J. Am. Chem. Soc., **81**, 3763 (1959).
7) M.M. Janot, R. Goutarel: Bull. soc. chim. France, 588 (1951).
8) M.M. Jannt, R. Goutarel, A. LeHir, G. Tsatsas, V. Prelog: Helv. Chim. Acta, **38**, 1073 (1955).
9) E.E. van Tamelen, P.E. Aldrich, T.J. Katz: J. Am. Chem. Soc., **79**, 6426 (1957).

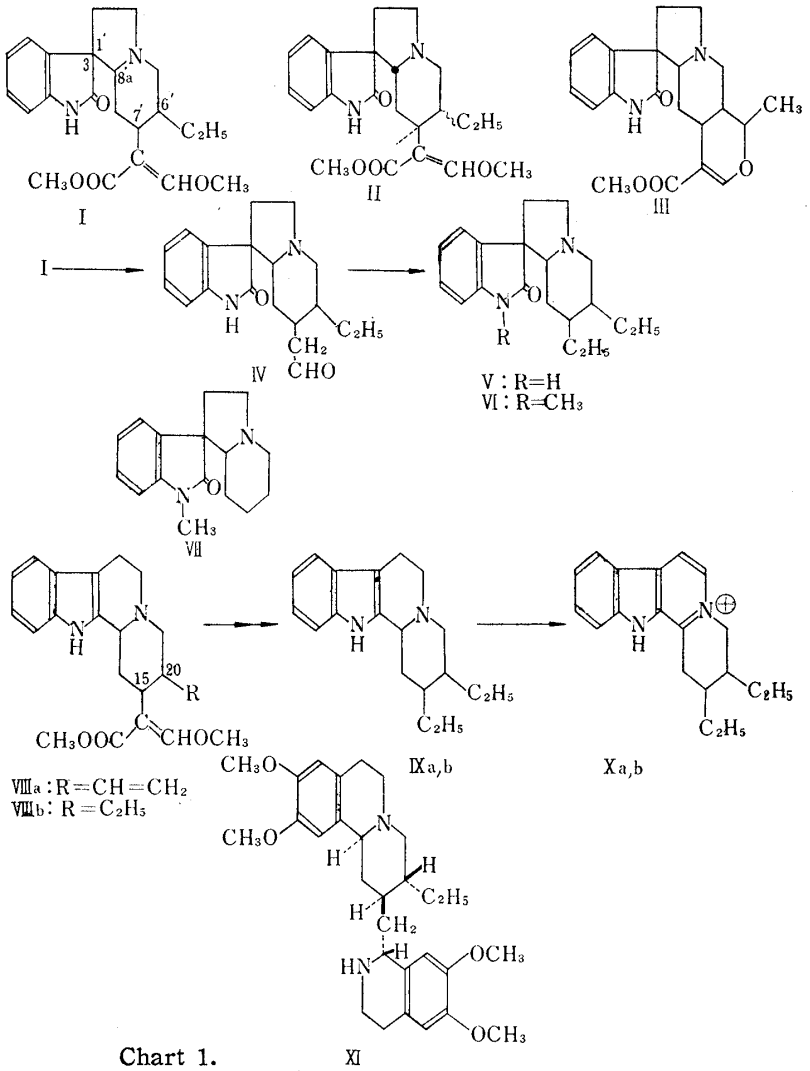


Chart 1.

products. Furthermore, Battersby[10] demonstrated that emetine (XI) was recovered unchanged when it was treated under the Wolff-Kishner reduction's condition, without conversion of any configuration.

Therefore, it might be accepted by all these data that the isomerization occurring at the Wolff-Kishner reduction stage of rhynchophyllal (VI) to rhynchophyllane (or isorhynchophyllane) (V) is concerned with the change of the configuration at $C_{3(1')}$ and/or $C_{8'a}$, but has no effect on the configuration of $C_{6'}$ and $C_{7'}$. Accordingly, the latter configuration is considered to be same as that of the initial alkaloid. Thus, we can discuss the arrangement at $C_{6'}$ and $C_{7'}$ of rhynchophylline and isorhynchophylline in terms of that at the corresponding positions of rhynchophyllane (V), which made us attempt the stereospecific syntheses of *rac*-N-methylrhynchophyllane (VI).

As was shown in the preliminary works,[1] it may be expected that these compounds will be obtained by the condensation of 5-chloro-3,4-diethylvaleraldehyde (XVIa,b) with 1-methyl-2-hydroxytryptamine hydrochloride (XVII). The *threo* compound (XVIa) will yield *rac*-1-methylrhynchophyllane containing *trans*-6',7'-diethyl groups (XIX), and the *erythro* form (XVIb) will afford the corresponding *cis*-6',7'-diethyl compound (XX). These aldehydes could be derived from the lactones (XIIIa,b) whose preparation had been already reported by van Tamelen[9] and by Battersby,[10] independently.

10) A.R. Battersby, S. Garratt : J. Chem. Soc., 3512 (1959).

Thus, at first we had the recourse to the Koelsch and Stratton's method[11] preparing *trans*- and *cis*-diethylcyclopentanone (XIIa, b), which were subjected to the Baeyer-Villiger's oxidation to afford the lactones of *threo*- and *erythro*-5-hydroxy-3,4-diethyl valeric acids (XIIIa, b), respectively.

After the lactone of *threo*-5-hydroxy-3,4-diethylvaleric acid (XIIIa) was heated with phosphorus pentachloride on a water bath for one hour, the produced phosphoryl chloride was removed *in vacuo* leaving brown black oil, which without purification, was condensed with N-methylaniline in pyridine to yield *threo*-anilide (XVa), b.$p_{2.5}$ 158°, as pale yellow glassy substance (IR 1650 cm^{-1} (>N-CO-), no absorption due to NH or OH

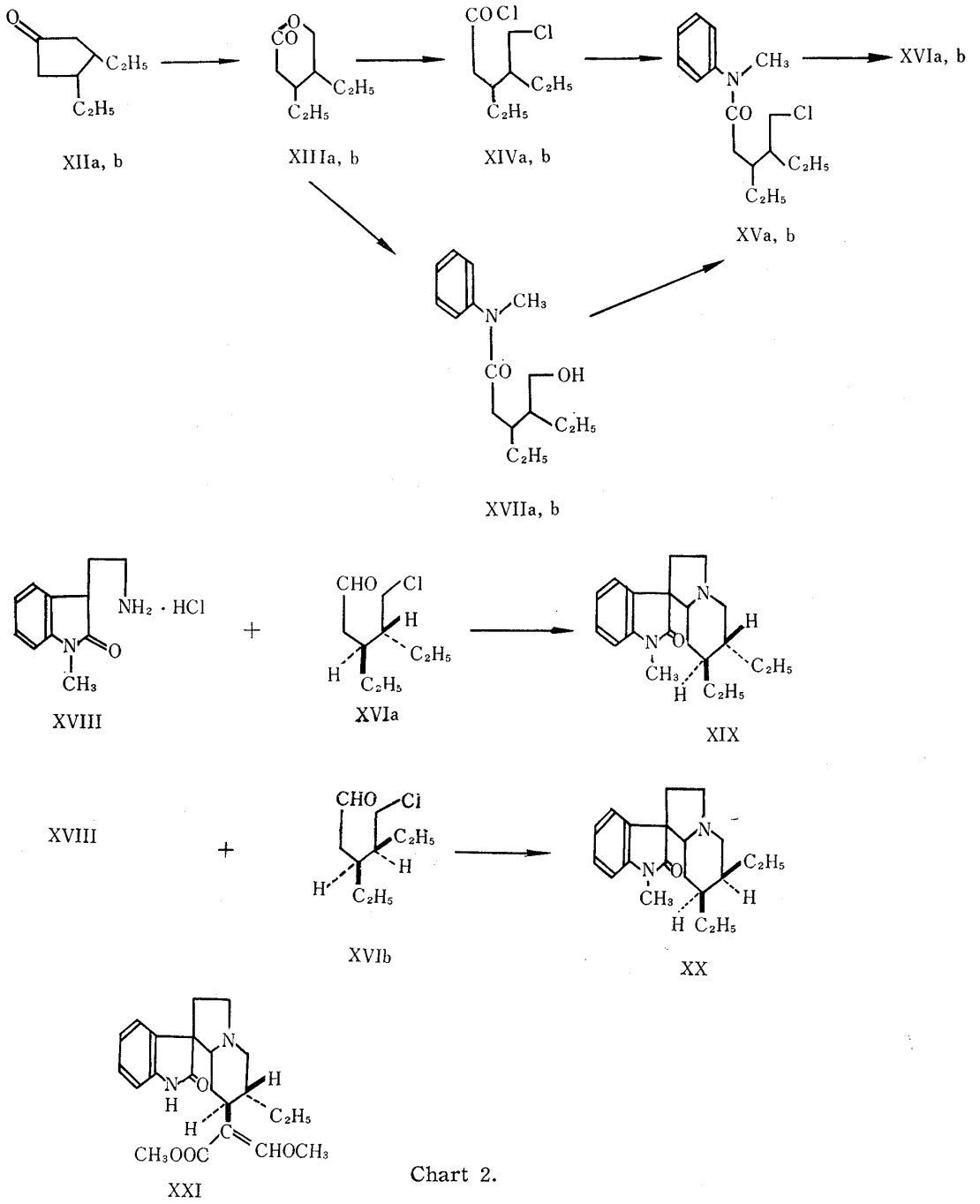


Chart 2.

11) C. F. Koelsch, C. H. Stratton: J. Am. Chem. Soc., **66**, 1881 (1944).

groups) in 24.4 % yield from XIIIa. This anilide (XVa) was reduced with lithium aluminum hydride to afford *threo*-5-chloro-3,4-diethylvaleraldehyde (XVIa) as colourless oil (b.$p_{14\sim15}$ 110～112° Yield, 14.2 %), which was characterized as 2,4-dinitrophenylhydrazone, m.p. 77～78°. Moreover, in order to confirm that any change of configuration has not occurred during the course of this reaction sequence, the compound (XIIIa) was reacted with methylanilinomagnesium iodide[12] under a much milder condition than the above mentioned way to furnish *threo*-anilide (XVIIa) as pale yellow glass (b.p_4 170～173°. Yield, 60 %), which was treatd with thionyl chloride to yield XVa, identical with the product obtained via the above route.

On the other hand, the lactone of *erythro*-5-hydroxy-3,4-diethylvaleric acid (XIIIb) gave *erythro*-5-chloro-3,4-diethylvaleric acid chloride (XIVb), which was condensed with methylaniline to afford the *erythro*-anilide (XVb) (b.$p_{2\sim3}$ 105–108°. Yield, 57.5 % from XIIIb). This anilide (XVb) was also obtained from XIIIb via XVIIb, pale yellow glass (b.$p_{3\sim4}$ 173–174°) in the above-mentioned manner.[12] The compound (XVb) was reduced with lithium aluminum hydride to yield *erythro*-5-chloro-3,4-diethylvaleradehyde (XVIb) (b.p_{12} 105～108°. Yield 28 %), which was also characterized as 2,4-dinitrophenylhydrazone, m.p. 78～79°. The infrared absorption spectra of these 2,4-dinitrophenylhydrazones were quite different each other, although an appreciable depression was not observed on mixed melting point determination. The infrared spectra of the intermediary hydroxy-anilide (XVIIa,b) and chloro-anilides (XVa, b), however, were almost identical in the *erythro*- and *threo*-series, respectively; but these compounds were obtained under the above-mentioned mild conditions which could be expected to retain the arrangement. And since there are no functional groups adjacent to the asymmetric carbons of these compounds, isomerisation could not occur by heat on distillation. Therefore, these compounds might be properly assigned to the *threo*- and *erythro*-series, respectively, in spite of the remarkable resemblance in their infrared spectra of both series. Judging from the presences of weak absorptions at 1730 cm^{-1} in both hydroxyanilides (XVIIa, b) and chloroanilides (XVa, b), however, these compounds must have been contaminated with a small amount of the starting lactones (XIIIa, b), which could not be eliminated even by distillation. As a consequence, *threo*-aldehyde (XVIa) was found to be contaminated with a vesy small amount of the starting lactone (XIIIa) according to a similar weak absorption at 1730 cm^{-1}, which was not observed with *erythro*-aldehyde (XVIb).

But the *threo*-aldehyde (XVIa) without further purification was subjected to the subsequent condensation with N-methylhydroxytryptamine hydrochloride (XVIII) in ethanolic solution of sodium hydroxide at room temperature for two days to afford pale yellow oil (yield, 56.7 %), which was chromatographed on alumina. Elution with benzene yielded a main fraction of the free base (XIX), colorless oil (called *trans*-A hereafter), giving the picrate, pale yellow prisms of m.p. 182～183°. Also, ether elution afforded the free base (XIX), colorless glass (called *trans*-B hereafter), yielding the picrate, orange yellow prisms of m.p. 184°.

Similarly, condensed with 1-methyl-2-hydroxytryptamine hydrochloride (XVIII) in ethanolic solution of sodium hydroxide, the *erythro*-aldehyde (XVIb) gave the pale yellow glass (XX) (yield, 67.7 %), which was purified by chromatography on alumina. Elution with benzene yielded a main fraction of the free base, colourless prisms, m.p. 93～94° (called *cis*-A hereafter),yielding the picrate, pale yellow scales of m.p. 173～174°. Benzene-ether (1:1) elution furnished the colorless prisms, m.p. 143～144° (called *cis*-B hereafter) which gave the picrate, orange yellow prisms, m.p. 167～168°.

On the chromatography of *trans*-product (XIX), benzene-ether (1:1) elution furnished a small amount of yellow oil which gave the picrate, orange yellow prisms, m.p. 167～

12) Cf. F. Bodroux : Compt. rend., **138**, 1428 (1904).

168°. This picrate was identified with that of *cis*-B by mixed melting point determination, and the infrared spectrum of the oil was almost identical with that of crystalline *cis*-B. The reason why *trans*-product was contaminated with *cis*-B, is not clear at present, but probably it must have come from the starting *threo*-lactone partly contaminated with the *erythro*-lactone, since the conversion of arrangement could not be thought to take place in the reaction sequence.

The infrared spectra of these free bases (XIX, *trans*-A and *trans*-B; XX, *cis*-A and *cis*-B) are shown in Figs. 1~4, which are very similar, but not identical particularly in 1100~1150 cm^{-1} region. And every spectrum possesses an absorption at 2785 cm^{-1} which is characteristic of *trans*-quinolizidine type of compounds.[13]

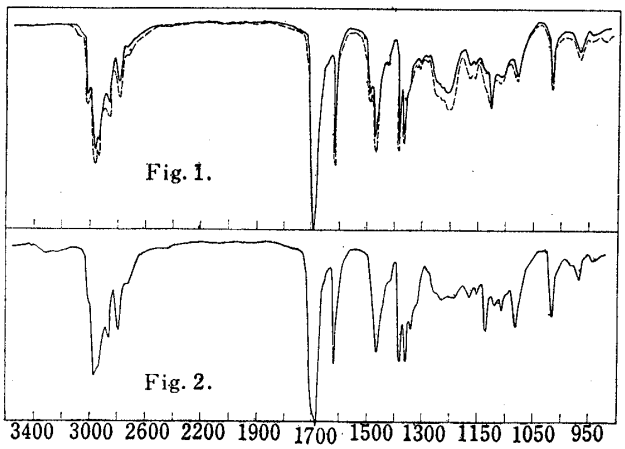


Fig. 1.
--- N-Methylrhynchophyllane derived from the natural alkaloid
—— Synthetic XIX (*trans*-A) ($CHCl_3$ solution)

Fig. 2.
XIX (*cis*-A) ($CHCl_3$ solution)

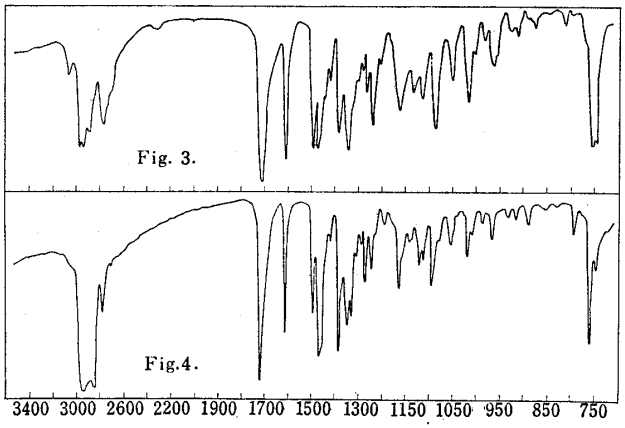


Fig. 3.
XIX (*trans*-B) (Film)

Fig. 4.
XIX (*cis*-B) (Nujol)

Rhynchophylline, identical with the authentic sample generously supplied by Professors Ochiai and Nozoye, was derived to N-methylrhynchophyllane, which after chromatography on alumina was obtained as colorless glass.*3 Its infrared absorptions in chloroform solution and in film were identical with that of the synthetic *trans*-A, but different from those of *cis*-A, *cis*-B, and *trans*-B. The *trans*-arrangement at $C_{6'}$ and $C_{7'}$ of N-methylrhynchophyllane is thus established, which means that the relative configuration of the corresponding positions of rhynchophylline and isorhynchophylline are *trans*, based on the reason mentioned above. Thus rhynchophylline and isorhynchophylline are illustrated as the partial stereoformula (XXI), in which the configurations at $C_{3(1')}$ and $C_{8'a}$ of each alkaloid remain to be determined.

*3 This base gave the picrate, m.p. 185~186°, whose infrared spectrum was completely identical with that of N-methylisorhynchophyllane, kindly supplied by Professor Marion.

13) F. Bohlmann: Chem. Ber., **91**, 2157 (1958); E. Wenkert, D.K. Roychaudhuri: J. Am. Chem. Soc., **78**, 6417 (1956).

Six possible structures of XIX (*trans*-A and -B) are delineated in Chart 3, indicating only the conformation of the *racemic* compounds, of which ii and v are *trans* in arrangement of the lone pair electrons of the bridgehead nitrogen and the axial hydrogen at $C_{8'a}$, and the others are *cis* in the same position. As has been already pointed out, the rather strong absorptions at 2785 cm^{-1} of XIX (*tranr*-A and -B) suggest that both of these stereoisomers possess the *trans*-indolizidine part in their molecules, excluding the possibility of i, iii, iv, and vi. Thus, they could be tentatively assigned to ii and v, alternatively.

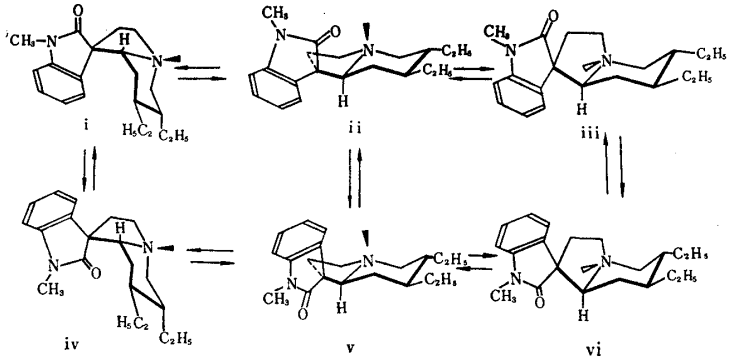


Chart 3.

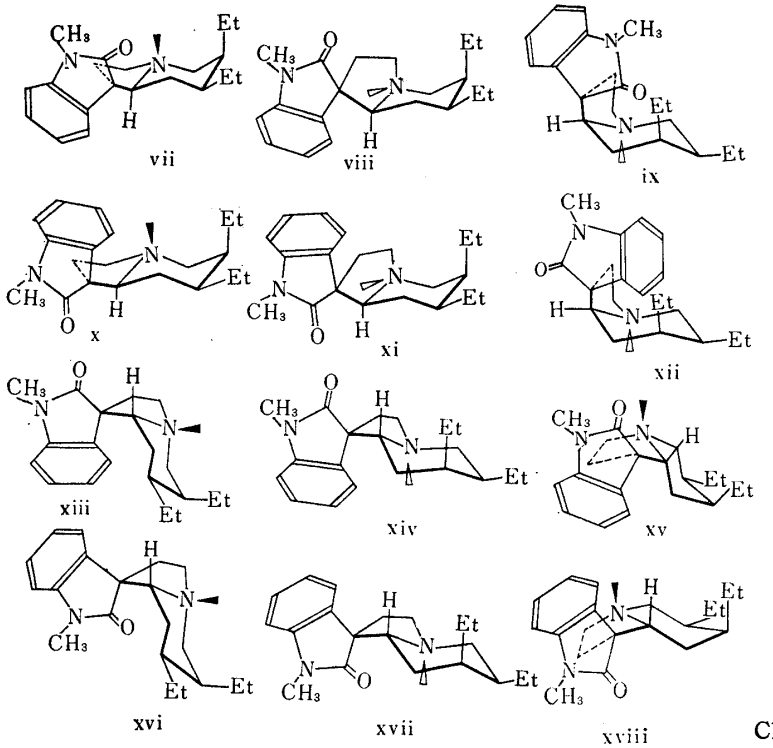


Chart 4.

As to the stereochemistry of XX (*cis*-A and *cis*-B), twelve possible stereostructures may be taken into consideration, which are shown in Chart 4. In view of the rather strong bands at 2785 cm^{-1} of our compounds (XX, *cis*-A and *cis*-B), it could be suggested that they possess the *trans*-indolizidine ring system. Therefore, XX (*cis*-A and *cis*-B) might be assigned to two of the four possible structures (vii, x, xiv, and xvii).[14] However, for the final decision, we need more experimental data, for which the further studies are in progress.

Experimental*4

***threo*-5-Chloro-3,4-diethylvaleric Acid N-Methylanilide (XVa)**——a) To 5 g. of the lactone of *threo*-5-hydroxy-3,4-diethylvaleric acid (XIIIa) was added 6.6 g. of PCl_5 in small portions under ice cooling. The mixture was slowly warmed up to room temperature, and allowed to stand for 1 hr., after which time it was heated at 60° on a water bath for an additional hour. The produced $POCl_3$ was removed *in vacuo* to leave 6 g. of a brown red oil XIVa, which without purification, was reacted with 3 g. of N-methylaniline in 2.5 g. of pyridine, by a procedure parallel to that employed for the preparation of 4-chlorobutyric acid N-methylanilide in Part II.[1] The oily material obtained above was purified by distillation to afford 2.2 g. (24.4 % from XIIIa) of the amide XVa, colorless oil, b.p_2 155~158°.

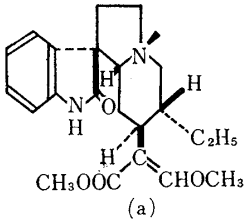
b) To an ethereal solution (ca. 60 ml.) of the Grignard reagent which was prepared from Mg (3.1 g.) and MeI (18.2 g.), a solution of N-methylaniline (13.7 g.) in 50 ml. of Et_2O was added dropwise at −15° with vigorous stirring and in a stream of N_2 gas, during which time white precipitate dsposited. The whole mixture was slowly warmed up to room temperature and stirred for 1 hr., after which it was refluxed for an additional hour, then cooled to −15°, and a solution of 10 g. of *threo*-5-hydroxy-3,4-diethylvaleric acid lactone in 50 ml. of Et_2O was added, when the white precipitate disappeared separating a black gray solid in stead. The whole was allowed to warm up to room temperature and stirred for 30 min., then boiled with stirring for an additional hour, and again cooled to −15°, to which was added 50 ml. of 10% HCl at such a rate that the temperature did not rise above 5°. At the beginning of the addition of the acid, there appeared a hard gummy material which gradually dissolved in a solvent to become clear. The Et_2O solution was separated, and the aqueous layer was extracted thrice with benzene. The combined Et_2O-benzene solution was washed twice with 10% HCl, water, dil. $NaHCO_3$, and then with water. After drying the solution over anhyd. Na_2SO_4, the solvent was removed and the residue was distilled under reduced pressure to afford 10 g. (60 %) of pale yellow glass XVIIa, b.p_4 170~173°, which even after redistillation, was recognized to be contaminated with the lactone XIIIa, judging from its IR spectrum.

To a solution of 8.7 g. of the foregoing amide XVIIa in 70 ml. of Et_2O was added a solution of 4.3 g. of $SOCl_2$ in 15 ml. of Et_2O under ice cooling, which became turbid. The ice bath was removed, and the whole was allowed to stand for 30 min., when the red brown oil collected in the bottom of the flask. When the mixture was gently refluxed with occasional shaking for 30 min., its color changed into brown black, after which the Et_2O was removed and benzene was added to dissolve the gummy material. The benzene was removed to leave the residual oil which was distilled under reduced pressure. The first fraction, collected up to 130° at 4 mm., was the white waxy material, which was identified with N-methylaniline hydrochloride. After a small intermediate fraction, the viscous oil was collected at 165~167°/4 mm., along with the accompanied white waxy material, to which mixture, after cooling, was added Et_2O. As the white wax (N-methylaniline hydrochloride) did not dissolve in Et_2O, it was filtered off; the solvent of the filtrate was removed to furnish the residual oil which was redistilled. The first fraction of white wax was again distilled off, and 5 g. (53.7 %) of the *threo*-chloroamide XVa distilled at 158°/2.5 mm., was collected, the IR spectrum of which was identical with that of the amide XVa prepared by the a) method. The *threo*-amide XVa prepared bythe b) method was found to be contaminated with a small amount of the starting lactone XIIIa as well as by the a) method, but this was subjected to the following reaction.

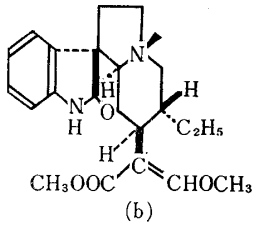
***threo*-5-Chloro-3,4-diethylvaleraldehyde (XVIa)**——Using the procedure previously described for the preparation[1] of 4-chlorobutylaldehyde, the foregoing *threo*-5-chloro-3,4-diethylvaleric acid N-methylanilide (XVa, 3.8 g.) was reduced with 214 mg. of $LiAlH_4$ to afford the crude oil which was purified by

*4 See the footnote of "Experimental" of Part I, This Bulletin, **11**, 443 (1963).

14) Recently, J. B. Hendrickson deduced the structure (a) for rhynchophylline by conformational analysis which is mainly based upon the known results appeared in the literature. (J. Am. Chem. Soc., **84**, 650 (1962)).
Also, N. Einch and W. I. Taylor succeeded in the conversion of dihydrocorynantheine into rhynchophylline, thereby proposing (b) for this alkaloid. (J. Am. Chem. Soc., 84, 1318 (1962), Also, see J. Shavel and H. Zinnes : *Ibid.*, **84**, 1321 (1962)).



(a)



(b)

distillation. The fraction boiled at 95~105°/12 mm. was redistilled to furnish 340 mg. (14.2 %) of *threo*-chloroaldehyde XVIa, b.$p_{14\sim15}$ 110~112°. 2,4-Dinitrophenylhydrazone, orange thin plates, m.p. 77~78°, was obtained by crystallization from EtOH. *Anal.* Calcd. for $C_{15}H_{21}O_4ClN_4$: C, 50.49; H, 5.89; N, 15.71. Found: C, 50.56; H, 5.95; N, 16.05.

***trans*-1-Methyl-6′,7′-diethylspiro[indoline-3,1′-indolizidine]-2-one (XIX)**——To a solution of 0.515 g. of 1-methyl-2-hydroxytryptamine hydrochloride in 2 ml. of water and 6 ml. of EtOH, 2.2 ml. of *N* NaOH (F. 1.044) was added, to which after ice cooling, a solution of 0.4 g. of the foregoing *threo* aldehyde in 7 ml. of EtOH was added. After 45 min., 2.1 ml. of *N* NaOH was added, and the whole mixture was allowed to stand at room temperature for a week. Worked up in the same way as the case of preparation of the model compounds,[1] the *trans* diethyl compound XIX was obtained as 403 mg. (56.7 %) of orange yellow oil, which was chromatographed on 30 g. of alumina. Elution with benzene yielded 159 mg. of colorless glass (called *trans*-A hereafter), which was characterized as the picrate, pale yellow prisms recrystallized from EtOH, m.p. 182~183°. *Anal.* Calcd. for $C_{26}H_{31}O_8N_5$: C, 57.67; H, 5.73; N, 12.93. Found: C, 57.51; H, 5.63; N, 12.78.

Benzene-Et_2O (1:1) eluted 43 mg. of impure yellow oil which gave the picrate, orange yellow prisms recrystallized from EtOH, m.p. 167~168°, being identical with that of *cis*-B (vide infra) by mixed melting point determination. And also the IR spectrum of the yellow oil was almost identical with that of *cis*-B (see Fig. 4).

Elution with Et_2O afforded 67 mg. of colorless glass (called *trans*-B hereafter) which was characterized as the picrate, orange yellow prisms recrystallized from EtOH, m.p. 184°. *Anal.* Calcd. for $C_{26}H_{31}O_8N_5$: C, 57.67; H, 5.73; N, 12.93. Found: C, 57.95; H, 5.70; N, 12.84.

Elution with AcOEt yielded a fraction of 39 mg. of orange oily material, which was not further examined on account of its deep coloration.

***erythro*-3,4-Diethylvaleric Acid N-Methylanilide (XVb)**——a) The lactone of *erythro*-5-hydroxy-3,4-diethylvaleric acid (12.6 g.) was reacted with PCl_5 (16.5 g.) by a procedure parallel to that employed for the preparation of XVa to afford 17 g. of black oil XIVb, which without purification, was condensed with N-methylaniline (8.6 g.) in 7 g. of pyridine in the usual manner to give 13.05 g. (57.5 %) of oil XVb, b.$p_{2\sim3}$ 156~157°.

b) An ethereal solution of MeMgI prepared from Mg (0.93 g.) and MeI (5.5 g.), was reacted with a solution of N-methylaniline (4.22 g.) in 20 ml. of Et_2O, which mixture was further reacted with a solution of *erythro*-5-hydroxy-3,4-diethylvaleric acid lactone (XIIIb) (3 g.) in 20 ml. of Et_2O, in the same way as the preparation of *threo* compoud XVIIa, to give 3.0 g. (60 %) of *erythro*-hydroxy amide XVIIb, b.$p_{3\sim4}$ 173~174°. This was found to be contaminated with a small amount of the lactone XIIIb, judging from its IR spectrum.

To a solution of the foregoing amide (XVIIb, 2.5 g.) in 10 ml. of benzene was added 0.75 g. of pyridine, to which under ice cooling, was added a solution of $SOCl_2$ (1.24 g.) in 5 ml. of benzene. Then, the whole mixture was kept at 35° for 1 hr., during which time the precipitate which seemed to be pyridine hydrochloride deposited on the bottom of the flask, and was removed by decantation. The solvent was removed *in vacuo* to give the residual oil, to which was added Et_2O, separating the insoluble material. This was filtered off, the Et_2O was removed, and the residue was purified by distillation. The first fraction accompanied by N-methylaniline hydrochloride was distilled off, and the main fraction (1.2 g.) was collected at 163°/4 mm., whose IR spectrum was identical with that of XVb obtained by the a) method. Yield, 45 %. A similar chlorination of XVIIb was carried out without pyridine to afford XVb in the almost same yield as the above-mentioned procedure. This amide XVb was also recognized to be contaminated with a very small amount of the starting lactone XIIIb by its IR spectrum, but it was subjected to the next reaction without further purification.

***erythro*-5-Hydroxy-3,4-diethylvaleraldehyde (XVIb)**——Using the procedure identical with that applied to the preparation of XVIa, the foregoing *erythro* amide XVb, (5.7 g.) was reduced with $LiAlH_4$ (350 mg.) to give an oil, b.p_{12} 95~100°, which was purified by redistillation affording XVIb, colorless oil, b.p_{12} 105~106°. Yield, 1.0 g. (23 %).

2,4-Dinitrophenylhydrazone: Orange thin plates (from EtOH). *Anal.* Calcd. for $C_{15}H_{21}O_4ClN_4$: C, 50.49; H, 5.89; N, 15.71. Found: C, 50.39; H, 5.94; N, 15.84.

***cis*-1-Methyl-6,7-diethylspiro[indoline-3,1′-indolizidine]-2-one (XX)**——To a solution of 0.9 g. of 1-methyl-2-hydroxytryptamine hydrochloride (XVIII) in 4 ml. of water and 12 ml. of EtOH, 3.8 ml. of *N* NaOH (F. 1.044) was added, to which under ice cooling, a solution of the foregoing *erythro* aldehyde (0.7 g.) in 1.4 ml. of EtOH was added. After 45 min., further 3.7 ml. of *N* NaOH (F. 1.044) was added and the whole was allowed to stand at room temperature for a week. Worked up in the same way as the case of preparation of the model compounds, the *cis* diethyl compound XX was obtained as 839 mg. (67.7 %) of orange yellow oil, which was chromatographed on 35 g. of alumina. Elution with benzene yielded 359 mg. of colorless, glass, which readily solidified on standing, The solid was recrystallized from hexane to afford colorless needles, m.p. 93~94° (called *cis*-A hereafter). *Anal.* Calcd. for $C_{20}H_{28}ON_2$: C, 76.92; H, 8.97; N, 8.97. Found: C, 76.71; H, 9.12; N, 8.59.

Picrate: Pale yellow scales (from EtOH), m.p. 173~174°. *Anal.* Calcd. for $C_{26}H_{31}O_8N_5$: C, 57.67; H, 5.73; N, 12.93. Found: C, 57.47; H, 5.63; N, 12.74.

Benzene-Et_2O (1:1) eluted 228 mg. of colorless oil, which solidified on long standing. The solid was recrystallized from hexane to give colorless needles, m.p. 143~144° (called *cis*-B hereafter). *Anal.* Calcd. for $C_{20}H_{28}ON_2$: C, 76.92; H, 8.97; N, 8.97. Found: C, 76.74; H, 9.07; N, 9.12.
Picrate: Orange yellow prisms (from EtOH), m.p. 167~168°. *Anal.* Calcd. for $C_{26}H_{31}O_8N_5$: C, 57.67; H, 5.73; N, 12.93. Found: C, 57.59; H, 5.88; N, 12.72.

Elution with AcOEt afforded 85 mg. of orange oily material, which was not further examined on account of its strong coloration tendency.

Isomerization of *cis*-A (XX) to *cis*-B (XX)——A solution of *cis*-A (m.p. 93~94°, 50 mg.) in 8 ml. of pyridine was gently refluxed for 10 hr. The pyridine was removed *in vacuo* and benzene was added and again distilled off. In order to remove the pyridine as completely as possible, this treatment was repeated three times yielding the residual oil which was chromatographed on 20 g. of alumina. Elution with benzene yielded 35 mg. of the recovered *cis*-A, and elution with Et_2O afforded 12 mg. of colorless needles, m.p. 136~137°, whose IR absorption spectrum was identical with that of *cis*-B. Also, the isomerized *cis*-B gave the picrate, orange yellow prisms, m.p. 165°, which was undepressed on admixture with the authentic sample.

Extraction of Rhynchophylline——The dried hooked stalks of *Uncaria rhynchophylla* Miq (*Ouroparia rhynchophylla* Matsum.) (1 kg.) on market, were pulverized and were extracted with 3 L. of EtOH at 60~70° for 20 hr. The insoluble material was filtered off, and the EtOH was evaporated *in vacuo* to leave a brown black resinous oil, to which 1 L. of 2% HCl was added and well shaken. The insoluble material was filtered off, and the filtrate was extracted twice with Et_2O. The aqueous layer was made basic with conc. NH_4OH, extracted with Et_2O, and the ethereal solution of fluorescence was dried over Na_2SO_4. The Et_2O was removed to leave 2.4 g. of a yellow brown oil, which was dissolved in 20 ml. of Et_2O and was allowed to stand in an ice box separating 340 mg. of white crystalls. The crystalls were recrystallized from Me_2CO to furnish 150 mg. of white prisms, m.p. 213~214°, which was identical with the authentic sample (m.p. 215~216°) kindly supplied by Professors Ochiai and Nozoe, by their superimposable IR spectra and mixed melting point determination. The mother liquors of recrystallizations were combined and the solvent was evaporated to dryness. The residue was dissolved in AcOH and treated with active charcoal. The solution was boiled for 8 hr, and after cooling, it was made basic with solid K_2CO_3, extracted with Et_2O, and the Et_2O extract was dried over Na_2SO_4. The solvent was removed to yield white crystals accompanied by oily material, of which the crystals were recrystallized from Me_2CO to give colorless prisms, m.p. 210~213° (120 mg.), whose IR spectrum was identical with that of the authentic sample of rhynchophylline. This operation was repeated to give the total 540 mg. of rhynchophylline.

N-Methylrhynchophyllane from Rhynchophylline——Following the method of Marion, rhynchophylline (I, 250 mg.) was boiled with 8% HCl to give rhynchophyllal (IV), as oily material (135 mg.) which in turn, was subjected to the Wolff-Kishner-Huang reduction to afford rhynchophyllane (V, 72 mg.). This was dissolved in MeOH, to which was added MeOH solution of MeONa (20 mg. of Na in 5 ml. of MeOH) and MeI (0.5 ml.). The whole mixture was gently refluxed on the water bath for 1 hr., after which the solvent was removed to dryness. The residue was extracted with Et_2O, the extract was dried over Na_2SO_4 and the solvent was removed to leave the relatively mobile oil, which was chromatographed on 20 g. of alumina. Elution with benzene, yielded the first fraction of colorless oily material which was discarded, and then gave 15 mg. of colorless glass as the second fraction, whose picrate was recrystallized from EtOH to give pale yellow prisms, m.p. 185~186°. The IR absorption spectrum of this picrate was identical with that of the authentic sample kindly supplied by Professor Marion. This free base had the IR absorption in film and in $CHCl_3$ solution identical with that of the synthetic *trans*-A, but different from those of *cis*-A, *cis*-B and *trans*-B. (See Fig. 1).

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Summary

N-Methylrhynchophyllane which is derived from the alkaloids, rhynchophylline and isorhynchophylline, was stereospecifically synthesized and was isolated as two pairs of stereoisomers, thereby establishing the *trans*-arrangement at $C_{6'}$ and $C_{7'}$ of these alkaloids.

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