UDC 547.831.1.07 : 547.491

80. Yoshio Ban and Takeshi Oishi : The Synthesis of 3-Spiro-oxindole Derivatives. II.[1] Syntheses of 1-Methylspiro-[indoline-3,1′-pyrrolizidine and Indolizidine]-2-one.

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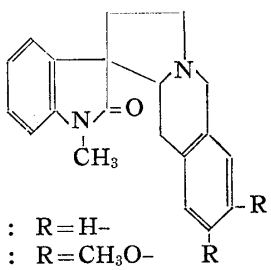
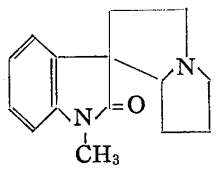
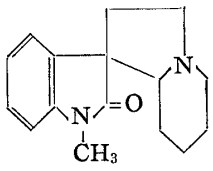
In the preceding paper,[1] we described a synthesis of 1-methyl-2′,3′,10′,10′a-tetrahydrospiro[indoline-3,1′(5′*H*)-pyrrolo[1,2-*b*]isoquinoline]-2-one (I) and its homolog (II) by condensation of 1-methyl-2-hydroxytryptamine with phenylacetaldehyde and with 3,4-dimethoxyphenylacetaldehyde, followed by the formation of "berberine bridge." These preliminary works suggested that 1-methyl-2-hydroxytryptamine could be generally condensed with various aldehydes to afford 3-spiro-oxindole derivatives.



I : R=H-
II : R=CH_3O-



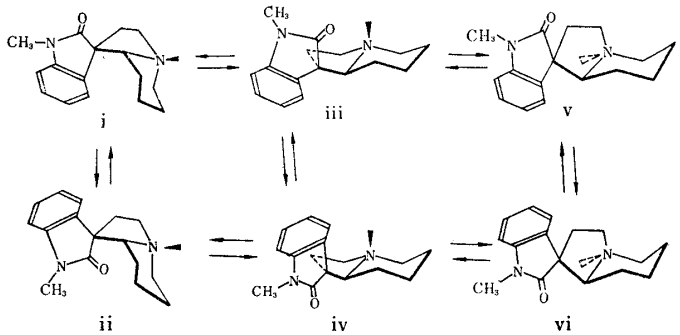
III



IV

At this time we attempted with success the syntheses of III and IV by one-step reactions of 1-methyl-2-hydroxytryptamine hydrochloride (XVII) with chloroaldehyde (XI) and with (XII), respectively. The latter product (IV) possesses the fundamental ring system of oxindole alkaloids, and the former (III) constitutes the closely related ring system to that of the same alkaloids.

4-Chlorobutyraldehyde (XI) was already prepared by Loftfield[2] who applied the Rosenmund reduction to the corresponding acid chloride (VII). Although 5-chlorovaleraldehyde (XII) is unknown in the literature, it should be prepared by the same method, which has been substantiated by us. And so far as the preparation of these aldehydes is concerned, the Rosenmund method is quite satisfactory, but this reaction generally requires the high purity of the starting acid chloride, limiting to some extent the scope of application of this method. Thus, in order to have further information as to preparation of this type of aldehydes, the other methods have been surveyed, particularly since it was not so easy to get the corresponding acid chloride of high purity for the



Chrat 1.

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

1) Part I : This Bulletin, **11**, 441 (1963).
2) R.B. Loftfield : J. Am. Chem. Soc., **73**, 1365 (1951).

stereospecific syntheses of *rac*-N-methylrhynchophyllane which will be described in the following paper.

Meanwhile, Weygand[3] obtained some aldehydes by partial reduction of N-methylanilides with 1/3~1/4 molar equivalent of lithium aluminum hydride. By applying Weygand method to the present synthesis, the aldehydes, XI and XII, were also synthesized by the scheme shown in the Chart 2.

γ-Butyrolactone was heated with thionyl chloride in the presence of zinc chloride, yielding 4-chlorobutyryl chloride (VII)[4], which was reacted with N-methylaniline to afford the anilide (IX). This anilide was reduced with 1/3 molar equivalent of lithium aluminum hydride in tetrahydrofuran at −15° to yield 4-chlorobutyraldehyde in 24.5 % yield, whose 2,4-dinitrophenylhydrazone, m.p. 130~131°, was in good agreement with Loftfield's description. On the other hand, cyclopentanone was oxidized with potassium persulfate to afford the lactone (VI),[5] which was converted into the chloroanilide (X), via VIII.

The chloroanilide (X) was reduced with lithium aluminum hydride in the same way

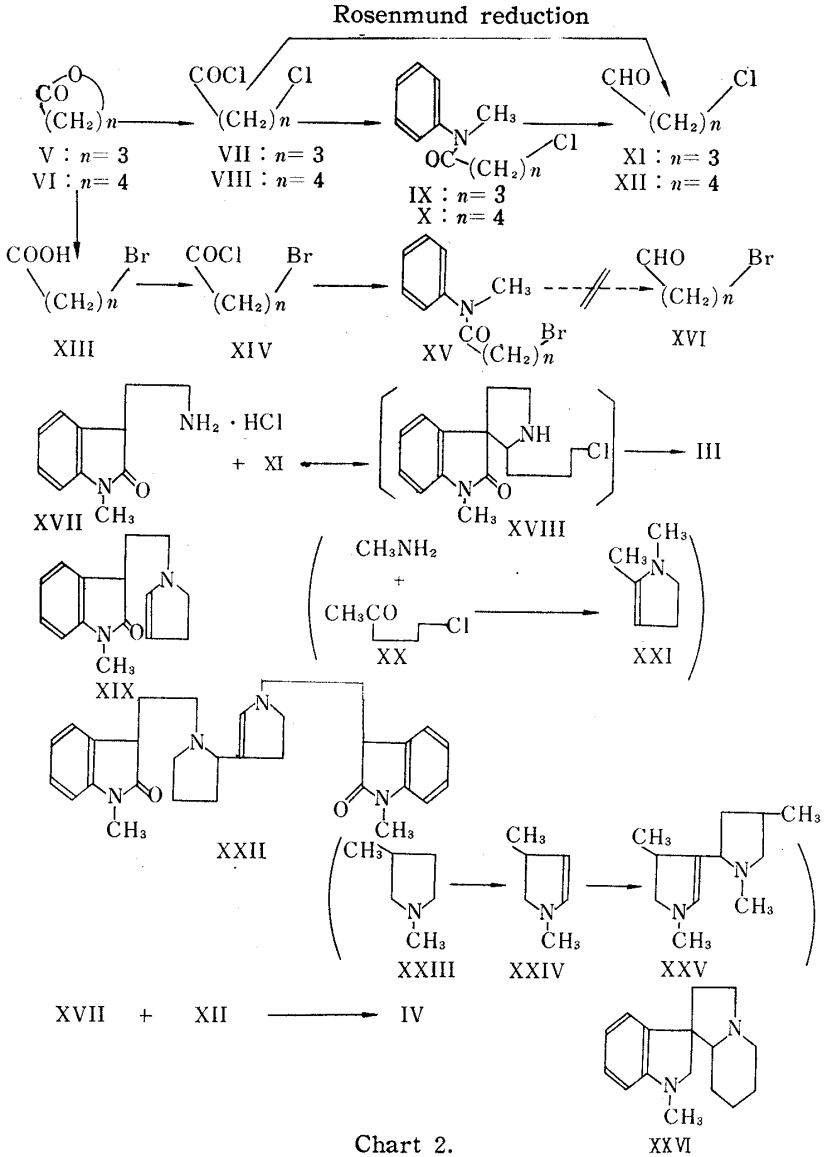


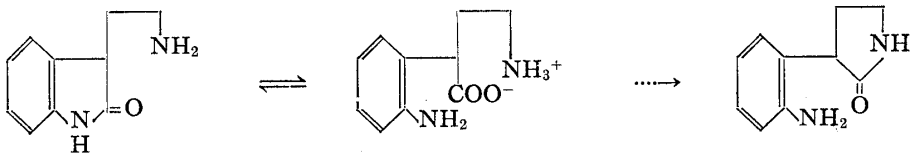
Chart 2.

3) F. Weygand, G. Eberhardt, H. Linden, F. Schäfer, I. Eigen : Angew. Chem., **65**, 525 (1953).
4) W. Reppe *et al.* : Ann., **596**, 190 (1955).
5) cf. G. Büchi, O. Jegar : Helv. Chim. Acta, **32**, 538 (1949).

to afford 5-chlorovaleraldehyde (XII), whose infrared spectrum and 2,4-dinitrophenylhydrazone (m.p. 108~109°) were identical with those of the compound obtained by the Rosenmund method.

The attempt of obtaining 5-bromovaleraldehyde by the same method (XIII→XIV→XV→XVI), however, resulted in failure, because the final step over-reduced the bromo-compound to yield the none-halogenated one. As has been already pointed out, the Rosenmund method is preferable to the Weygand method for preparation of these chloroaldehydes in respects of the yield and the facile treatment in a large scale.

Thus, the condensations of these aldehydes with 1-methyl-2-hydroxytryptamine hydrochloride (XVII) were carried out. The reason why 1-methyl-derivative (XVII) was selected in place of 2-hydroxytryptamine (XXVII), was dependent upon the assumption that the latter (XXVII) will be readily hydrolyzed with caustic alkali to yield XXVIII or XXIX.[6,7]



XXVII XXVIII XXIX

A solution of 1-methyl-2-hydroxytryptamine hydrochloride (VII) in a small amount of water was neutralized with an equimolar *N*-sodium hydroxide solution, to which was added a solution of the aldehyde (XI) in ethanol and the whole was allowed to stand at room temperature for a week. After removal of ethanol a small amount of the base was obtained as brown syrup, which contained no halogen and had a strong absorption at 1720 cm^{-1} (cyclic >N-CO-) but no absorptions due to NH or OH groups. Its ultraviolet absorption spectrum is characteristic of oxindole. These facts suggested that the product would be represented by one of III, XIX and XXII, but it should not be XVIII which had been expected to obtain before the experiments. The possibility of XIX is exemplified by the known condensation of methyl amine with chloroketone (XX) affording 1,2-dimethyl-2-pyrroline (XXI).[8] The compound (XXII) would be formed by bimolecular self-condensation of XIX, an anlogous example of which is seen in the oxidation of 1,3-dimethylpyrrolidine (XXIII) yielding XXV via XXIV.[9]

Our basic product is a tertiary amine since it is recovered unchanged by treating with *p*-toluenesulfonyl chloride in a sodium hydroxide solution. Moreover, as it is indifferent to the hydrogenation with platinum catalyst and also stable to 10% hydrochloric acid, the presence of enamine type of double bond was taken impossible. Finally it does not reduce the Tollens reagent, indicating that it should be 3-spiro-oxindole derivative. 3-Monosubstituted oxindole derivatives generally reduce the same reagent[10], which has been confirmed in many examples by ourselves. These facts undoubtedly excluded the possibility of XIX or XXII, thereby strongly suggesting that it should be represented by III. Thus, this condensation was effected in two molar equivalents of *N*-sodium hydroxide solution to afford III in 82% yield.

Similarly, 1-methyl-2-hydroxytryptamine hydrochloride (XVII) was condensed with 5-chlorovaleraldehyde (XII) to afford IV as pale yellow oil, which was chromatographed on alumina to furnish two substances, m.p. 81~82° (eluted with benzene and referred as

6) K. Freter, H. Weissbach, B. Redfield, S. Udenfrend, B. Witkop : J. Am. Chem. Soc., **80**, 983 (1958).
7) E. Wenkert, B.S. Bernstein, J.H. Udelhofen : *Ibid.*, **80**, 4899 (1958).
8) R. Hielscher : Chem. Ber., **31**, 277 (1898).
9) N.J. Leonard, A.G. Cook : J. Am. Chem. Soc., **81**, 5627 (1959).
10) K. Brunner : Monatsh. Chem., **17**, 479 (1896). cf. B. Belleau : Chem. & Ind. (London), **1955**, 229.

IV-A hereafter) and m.p. 91~92° (eluted with benzene-ether (1:1) and referred as IV-B hereafter).

Both of them gave the satisfactory results of elemental analyses as IV, and possess the similar ultraviolet spectra being characteristic of oxindole. They are also quite similar in their infrared absorption spectra, particularly in the region of 1200~1700 cm^{-1}, suggesting that they are stereoisomers in respect of positions $C_{1(3')}$ and/or C_{8a}. This assumption was confirmed by isomerizing the former (IV-A) into the latter (IV-B) in boiling pyridine.[11] Also, the full reduction of IV-A with lithium aluminum hydride gave the base (XXVI), m.p. 58~60°, which had no absorption due to a lactam group in its infrared spectrum and its ultraviolet absorption spectrum was characteristic of indoline. If the compound assigned to IV had been a monosubstituted oxindole derivative, it would have afforded an indole derivative by this reduction.[12,13]

All these results have established the structures of 3-spiro-oxindole, III and IV, for our condensation products.

As for the stereochemistry of IV-A and IV-B, six structures in all possibilities are taken into consideration, which are depicted in Chart 1. All of them might be interconvertible, indicating only the conformation of the *racemic* compound.

In regard to choice of these structures, we need more experimental data for final decision, but it is noteworthy to find out that the infrared spectra of IV-A and IV-B in chloroform, exhibit rather strong bands at 2800 cm^{-1}. As is well known, these bands are characteristic of *trans*-quinolizidine type of compound,[14,15] which are considered to be due to the interaction between the lone pair electrons of nitrogen and at least two axial C-H bonds at the neighboring positions of the nitrogen atom.[14] If this interpretation is accepted in this case,[16] both of these isomers must have *trans*-indolizidine system, excluding the possibility of i, ii, v, and vi, and thus they could be tentatively assigned to iii and iv, alternatively. Further experiments for solution of this problem are in progress.

Experimental*2

4-Chlorobutyraldehyde (XI)——To a solution of 12.8 g. of N-methylaniline and 9.5 g. of pyridine in 25 ml. of benzene was added a solution of 17 g. of chlorobutyryl chloride in 20 ml. of benzene at 3~4° under mechanical stirring. The whole was stirred at the same temperature for 1 hr. and then at room temperature for 3 hr., during which time pyridine hydrochloride deposited; this was filtered off and washed well with benzene. The combined filtrate and washings were washed with dil. AcOH, water, dil. $NaHCO_3$ sol. and then water. After drying the benzene solution over anhyd. $MgSO_4$, the benzene was removed to furnish the amide (IX), $b.p_{1\sim2}$ 129~132°, in 74.5% yield. To a solution of 4.23 g. of this amide (IX) in 30 ml. of anhyd. peroxide-free tetrahydrofuran which was cooled to −15°, was added 0.315 g. of $LiAlH_4$ (1/3 molar equivalent of the amide (IX) and assumably ca. 80% pure). The whole was stirred at −15° for 1.5 hr. and then at −5~1° for 4 hr. The tetrahydrofuran was concentrated *in vacuo* at room temperature to about one-third of its volume, to which was added 50 ml. of Et_2O under ice-cooling. Twenty ml. of water was added dropwise to the whole mixture at such a rate that the temperature did not rise above 5°, when amorphous white solids deposited. To this mixture was added 10 ml. of 10% HCl, which was shaken well so that the deposit might be dissolved. The Et_2O layer was separated and the aqueous layer was extracted with Et_2O three times. The combined Et_2O solution was washed with 10 ml. of 10% HCl, satd. NaCl sol., dil. $NaHCO_3$ sol. and with satd. NaCl sol. twice; this solution was dried over $MgSO_4$, and distilled. The colourless aldehyde (XI), $b.p_{40}$ 74°, was obtained

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

11) J.C. Seaton, M.D. Nair, O.E. Edwards, L. Marion: Can. J. Chem., **38**, 1035 (1960).
12) P.L. Julian, H.C. Printy: J. Am. Chem. Soc., **71**, 3206 (1949).
13) M. Kates, L. Marion: Can. J. Chem., **29**, 37 (1951).
14) F. Bohlmann: Chem. Ber., **91**, 2157 (1958).
15) E. Wenkert, D.K. Roychaudhuri: J. Am. Chem. Soc., **78**, 6417 (1956).
16) Cf. Y. Sato, N. Ikekawa: J. Org. Chem., **26**, 1945 (1961).

in 24.5% yield, which was characterized as 2,4-dinitrophenylhydrazone, orange-yellow needles, m.p. 130~131°, recrystallized from EtOH. These are in good agreement with the description by Loftfield[2] who synthesized the same aldehyde by the Rosenmund method.

1-Methylspiro[indoline-3,1'-pyrrolizidine]-2-one (III)——To a solution of 2.1 g. of 1-methyl-2-hydroxytryptamine hydrochloride (XVII) in 6 ml. of water was added 9.4 ml. of *N* NaOH sol. and 30 ml. of EtOH under ice cooling. To this solution was added a solution of 1 g. of chloroaldehyde (XI) in 30 ml. of EtOH, which was allowed to warm up to room temperature. After 45 min. 9.3 ml. of *N* NaOH sol. was added. The whole mixture was allowed to stand at room temerature for one week. The ethanol was removed *in vacuo* to produce the suspension of oil, which was extracted with benzene. The benzene solution was extracted with 10% HCl three times to transfer the basic product to the aq. layer, which was separated, washed with benzene twice, treated with active charcoal, and made basic with solid K_2CO_3 under ice cooling. The liberated oil was extracted with benzene, which was washed with water and dried over $MgSO_4$. The solvent was removed *in vacuo* to afford 1.88 g. (82%) of the crude pyrrolizidine (III), orange-yellow viscous oil, which was charcterized as the picrate, yellow prisms, m.p. 183°, recrystallized from EtOH. *Anal.* Calcd. for $C_{21}H_{21}O_8N_5$: C, 53.50; H, 4.45; N, 14.86. Found: C, 53.36; H, 4.35; N, 14.93. The crude free base was negative in Beilstein test.

Hydrogenation Test of III——To a solution of 1 g. of the crude base (III) in 30 ml. of EtOH was added 1 ml. of HCl, which was subjected to hydrogenation with 50 mg. of Adams' catalyst at room temperature in an atmospheric pressure of H_2. Only less than 3.5 ml. of H_2 was absorbed. After the usual worked up, there was obtained 0.89 g. of the yellow oily base, which was identified with the starting material by IR spectral comparison and by mixed melting point determination (182°) of its picrate.

Reaction of III with Tosyl Chloride——To a solution of 0.18 g. of III in 1 ml. of 10% HCl and 3 ml. of water was added 0.3 g. of tosyl chloride, to which was added 5 ml. of 10% NaOH under ice cooling. The whole mixture was allowed to warm up to room temperature and vigorously shaken for 15 min. Another 3 ml. of 10% NaOH was added and the whole was further shaken for 10 min., and extracted with benzene. The basic substance was transferred to 10% HCl layer, which was treated with active charcoal, made basic with solid K_2CO_3 and extracted with benzene. The benzene was removed to leave pale yellow oil which was identical with the starting material (III) in every respect.

5-Chlorovaleryl Chloride (VIII)——To 47 g. of δ-valerolactone which was prepared by Büchi's method,[5] was added 67 g. of $SOCl_2$ and 0.5 g. of freshly prepared anhyd. $ZnCl_2$. The whole mixture was stirred at 60~70° for 20 hr., during which time the colour of the reaction mixture became black brown. On distillationthere, was obtained 5-chlorovaleryl chloride (44%), b.$p_{10\sim11}$ 80~82°. *Anal.* Calcd. for $C_5H_8OCl_2$: C, 38.71; H, 5.16. Found : C, 39.18; H, 5.51.

5-Chlorovaleraldehyde (XII)——a) The foregoing acid chloride (32 g.) was reacted with N-methylaniline in the same way as the prerarration of IX to furnish 41 g. (88%) of the corresponding N-methylanilide (X), b.p_3 154~156°. Ten grams of this anilide was reduced with 0.7 g. of $LiAlH_4$ by following the procedure for preparation of XI to yield 1.46 g. (27.3%) of 5-chlorovaleraldehyde (XII), b.p_{12} 70~72°. *Anal.* Calcd. for C_5H_9OCl : C, 49.79; H, 7.46. Found : C, 49.62; H, 7.68. 2,4-Dinitrophenylhydrazone, orange needles recrystallized from EtOH, m.p. 108~109°. *Anal.* Calcd. for $C_{11}H_{13}N_4O_4Cl$: C, 43.92; H, 4.32; N, 18.63. Found : C, 44.10; H, 4.44; N, 18.27.

b) A mixture of 50 ml. of dry toluene, 2 g. of Pd-$BaSO_4$ and 0.2 g. of quinoline S was heated under passing of dry H_2 gas. When the toluene began to boil, 12.2 g. of the acid chloride (VIII) was added. Under a constant passing of H_2, heating and stirring were continued to proceed the reaction, during which time the evolved gas was absorbed into cold water, and the produced hydrochloric acid was titrated with *N* NaOH. The reaction was continued for 9 hr., until the evolution of HCl gas ceased, reaching 82.7% of the theoretical amount. After cooling, the catalyst was filtered off, and the toluene solution was washed with water, with $NaHCO_3$ sol. and then with water. After drying, the solvent was removed to leave the oil, which was purified by distillation to give 4.2 g. (44.2 %) of the colourless oil, being identical with the aldehyde (XII) obtained by the (a) method in every respect.

1-Methylspiro[indoline-3,1'-indolizidine]-2-one (IV)——To a solution of 2.63 g. of 1-methyl-2-hydroxytryptamine hydrochloride (XVII) in 9 ml. of water and 40 ml. of EtOH was added 11.5 ml. of *N* NaOH, to which a solution of 1.4 g. of 5-chlorovaleraldehyde (XII) in 30 ml. of EtOH was added dropwise under ice cooling. After 45 min., another 11.6 ml. of *N* NaOH was added, and the whole mixture was allowed to stand at room temperature for one week. In a similar manner to the case of preparation of III, there was obtained 1.24 g. (41%) of the crude brown yellow oil, 740 mg. of which was chromatographed on alumina. Elution with benzene yielded 380 mg. of colourless viscous oil which solidified on standing. Recrystallization from hexane gave colourless prisms (IV-A), m.p. 81~82°. *Anal.* Calcd. for $C_{16}H_{20}N_2O$: C, 75.00; H, 7.81; N, 10.94. Found : C, 74.66; H, 7.84; N, 10.90. Picrate, yellow prisms purified from EtOH, m.p. 200~201°. *Anal.* Calcd. for $C_{22}H_{23}N_5O_8$: C, 54.43; H, 4.74; N, 14.41. Found : C, 54.74; H, 4.73; N, 14.03. Elution with benzene-Et_2O (1:1) afforded 100 mg. of colourless oil which also solidified on standing. Recrystallized from hexane, it furnished colourless prisms (IV-B), m.p. 91~92°. *Anal.* Calcd. for $C_{16}H_{20}N_2O$: C, 75.00; H, 7.81; N, 10.94. Found : C, 74.81; H, 7.68; N 10.40.

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.

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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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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]

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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).