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63. Shun-ichi Yamada and Takehisa Kunieda : Studies on Indole Series. I. Studies on the Synthesis of Optically Active Indole Derivatives.*1

(*Faculty of Pharmaceutical Sciences, University of Tokyo**2)

R(+)- and S(−)-1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizine (Ⅲa, b), and R(+)- and S(−)-5,7,8,13,13b,14-hexahydrobenz[*b*]indolo[2,3-*a*]quinolizine (Ⅳa, b) were synthesized by the application of the Fischer indole synthesis on optically active hexahydro-2*H*-quinolizin-1(6*H*)-one (Ia, b) and 3,4,11,11a-tetrahydro-2*H*-benzo[*b*]quinolizin-1(6*H*)-one (Ⅱa, b) of known absolute configuration.

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A number of indole alkaloids have been isolated hitherto and their structures and stereochemistry seem to have almost been established. However the absolute configurations at 3-position*3 of such indole alkaloids as yohimbine, reserpine etc. and the related compounds have not been "chemically" determined yet, except the case of (+) tetrahydroharman (Ⅷ) which was correlated with D-alanine.[1]

From both the above point of view and synthetic interest, it appeared to be of significance to establish the synthetic route from optically active compounds of known absolute configuration to optically active indole derivatives with the only asymmetric center at 3-position.*3 Although the Fischer indole synthesis[2] may be the most widely employed method for the synthesis of indole derivatives, there seem to be few cases[3] applied to optically active ketones with an exception of the case of ketosteroids[4] and camphor derivatives.[5] Therefore, the present investigation was undertaken to examine the applicability of the Fischer indole synthesis to the optically active cyclic α-amino-ketones such as hexahydro-2*H*-quinolizin-1(6*H*)-one (Ⅰ) and 3,4,11,11a-tetrahydro-2*H*-benzo[*b*]-quinolizin-1(6*H*)-one (Ⅱ), which have only the asymmetric carbon atom at the position adjacent to the carbonyl group.

The facts, pointed out in an earlier paper,[6] that Ⅰ was racemized very slowly in EtOH alone or ethanol-triethylamine system and gave optically active oxime, suggested that the application of the Fischer indole synthesis to active α-amino-ketones Ⅰ and Ⅱ could afford optically active indole derivatives. The absolute configurations of these ketones were chemically determined as follows[7]; Ⅰ was correlated through 1-methylene-quinolizidine (Ⅴ) with lupinine of known absolute configuration and Ⅱ through hexahydro-2*H*-benzo[*b*]quinolizine (Ⅵ) with L-phenylalanine.

Reactions of racemic Ⅰ and Ⅱ with *d*-3-bromo-8-camphorsulfonic acid in acetone as previously described,[6,7] afforded the corresponding 3-bromo-8-camphorsulfonates,

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*2 Hongo 7, Tokyo (山田俊一, 国枝武久).

*3 In this report, for a convenience the trivial numbering for yohimbane skeleton is employed.

1) J. Trojanek, Z. Koblicova, K. Blaha : Chem. & Ind. (London), **1965**, 1261.

2) *a*) E. Fischer, O. Hess : Ber., **17**, 559 (1884). *b*) B. Robinson : Chem. Revs., **63**, 373 (1963).

3) Chang-Pai Chen, R. P. Erstigneava, N. A. Preobrazhenskii : Zhur. Obshchei Khim., **30**, 2085 (1960) (C. A., **55**, 6511b (1961)).

4) C. Doree : J. Chem. Soc., **1909**, 638; Y. Ban, Y. Sato : This Bulletin, **13**, 1073 (1965) and the references cited therein; M. G. Lester, V. Petrow, O. Stephenson : Tetrahedron, **21**, 1761 (1965).

5) S. Kuroda : J. Pharm. Soc. Japan, **493**, 131 (1923); F. Sparatore : Gazz. Chim. Ital., **88**, 755 (1958) (C. A., **53**, 22054d (1959)).

6) T. Kunieda, K. Koga, S. Yamada : This Bulletin, **15**, 337 (1967).

7) S. Yamada, T. Kunieda : *Ibid.*, **15**, 490 (1967).

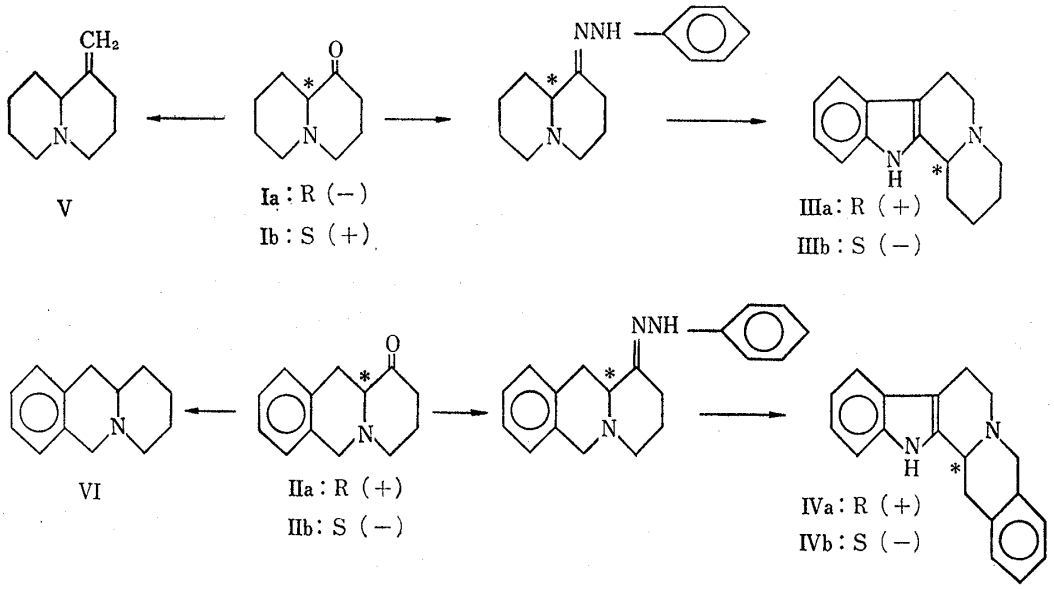


Chart 1.

m.p. 190~193°, $[\alpha]_D$ +61.2° (H_2O) and m.p. 188~190°, $[\alpha]_D$ +84.2° (H_2O) as one of the diastereomeric salts, respectively. The free bases Ia and IIa recovered from the corresponding salt, had the rotation of $[\alpha]_D$ −31.2° (EtOH), and $[\alpha]_D$ +88.4° (EtOH), respectively. The enantiomeric ketones Ib, $[\alpha]_D$ +17.7° (EtOH) and IIb, $[\alpha]_D$ −43° (EtOH), were also obtained from mother liquor. These active α-amino-ketones were converted to the corresponding phenylhydrazones in ethanol, which were subjected without purification to the Fischer indole synthesis, using hydrogen chloride as a catalyst. Racemic or nearly racemic indole derivatives were readily isolated as hydrochlorides from crude products because of their less solubility in cold water. Optically active compounds separated from water soluble layer were purified by chromatography on neutral alumina. Ia and Ib afforded optically active indole derivatives, IIIa, $[\alpha]_D$ +73° (EtOH) and IIIb, $[\alpha]_D$ −62.5° (EtOH), respectively. Similarly IIa and IIb gave the corresponding indole compounds with high optical rotation IVa, $[\alpha]_D$ +303.4° (pyridine)

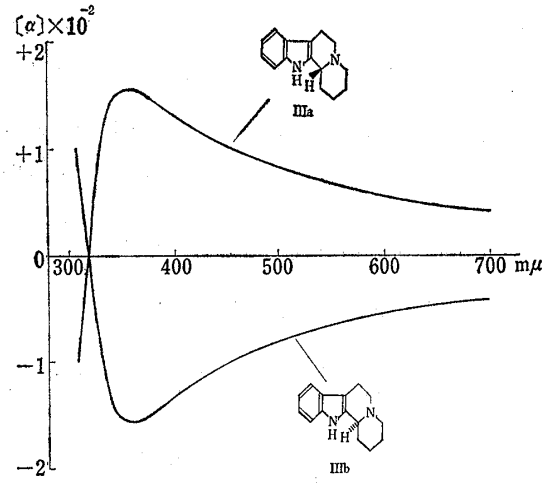


Fig. 1. Optical Rotatory Dispersion Curves of IIIa and IIIb in EtOH

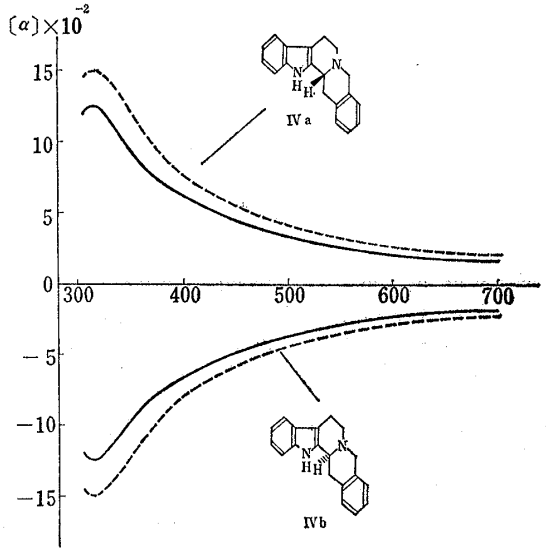
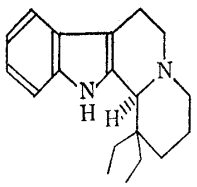


Fig. 2. Optical Rotatory Dispersion Curves of IVa and IVb

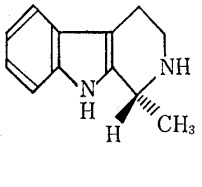
——— : in EtOH -------- : in pyridine

and Ⅳb, $[\alpha]_D$ −312° (pyridine), respectively. As shown in Fig. 1 and Fig. 2, Ⅰ and Ⅱ exhibit the first extremities of the Cotton effect at 350 mμ and 315 mμ, respectively, which are near to the wave-length of inflection at 289 mμ of indole chromophore.

The above facts are of considerable interest not only to support the mechanism of this reaction proposed by Robinson, *et al.*[8] suggesting at least the passing through no symmetrical intermediates but also to show the establishment of synthetic route to optically active indole derivatives represented generally by Ⅲ and Ⅳ.



Ⅶ



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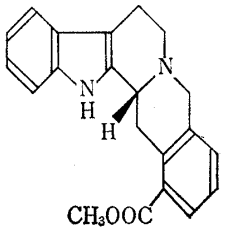

Ⅸ

Recently, Trojanek and co-workers[1] reported that with an aid of optical rotatory dispersion (ORD) curves, the indole compound Ⅶ transformed from (−)-eburnamonine was enantiomeric to (+)-tetrahydroharman (Ⅷ) which was related to D-alanine and *S*-configuration was ascribed. The result obtained as comparison with Ⅲb, which seems to be more reasonable, also supports the reported absolute configurations of vincamine series.

Further, optically active Ⅸ having only asymmetric center was obtained in sodium methoxide treatment of deserpideine by Smith, *et al.*[9] and its rotation is in agreement with that of Ⅳa, which seems to support the reported absolute configuration of deserpideine and related alkaloids.

Experimental*4

R(−) and S(+)-Hexahydro-2*H*-quinolizin-1(6*H*)-one (Ia and Ib)——To a solution of 13.2 g. (0.086 mole) of *dl*-Ⅰ, prepared from *dl*-pipecolic acid, according to the reported method,[10] in 25 ml. of acetone was added a solution of 2.7 g. (0.087 mole) of *d*-3-bromo-8-camphorsulfonic acid[6] (BCS) in 25 ml. of acetone and the mixture was allowed to stand at room temperature for 2 days. The separated colorless crystals were collected by filtration and washed with 50 ml. of hot acetone. After drying, they weighed 14.5 g. Recrystallization from acetone-EtOH afforded an analytical sample of m.p. 190~193°, $[\alpha]_D^{20}$ +61.2° (c=2.0, H_2O), as colorless prisms. The IR spectrum (KBr) was identical with that of an authentic sample.[6]

In 4 ml. of cold water was dissolved 3.5 g. of the above salt and the solution was basified with saturated aqueous potassium carbonate and extracted with benzene. After drying (Na_2SO_4) and removal of the benzene under N_2 stream, the resulting oil was distilled under N_2 atmosphere to yield 0.9 g. of colorless liquid, $b.p_3$ 78°, $[\alpha]_D^{28}$ −31.2° (c=3, EtOH). The IR spectrum (cap.) was identical with that of an authentic sample,[6] showing ketone carbonyl at 1723 and Bohlmann band[11] at 2680, 2735, 2775 cm^{-1}.

The same treatment of the combined mother liquor and the washings afforded the enantiomeric α-amino-ketone as a colorless liquid, $b.p_4$ 81°, $[\alpha]_D^{21}$ +17.7° (c=1.5, EtOH).

R(+)-1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizine (IIIa)——The mixture of 0.9 g. (0.006 mole) of the above Ia, ($[\alpha]_D$ −31.2°) and 0.69 g. (0.0064 mole) of phenylhydrazine in 13 ml. of EtOH was heated

*4 All melting points were uncorrected. Optical rotations in ultra violet region were measured with ORD/UV-5 spectrophotometer of Nihon Bunko and $[\alpha]_D$ with a Yanagimoto Photo-Magnetic Polarimeter, Model OR-20.

8) G. M. Robinson, R. Robinson : J. Chem. Soc., **1918**, 639; *Idem* : *Ibid.*, **1927**, 827; R. B. Carlin : J. Am. Chem. Soc., **70**, 3421 (1948); *Idem* : *Ibid.*, **74**, 1077 (1952).
9) E. Smith, R. S. Taret, M. Shamma, R. J. Shine : J. Am. Chem. Soc., **86**, 2083 (1964).
10) G. R. Clemo, F. R. Rawag : J. Chem. Soc., **1931**, 437; N. J. Leonard, S. Swann, J. Figueras : J. Am. Chem. Soc., **74**, 4620 (1952).
11) F. Bohlmann : Ber., **91**, 2157 (1958).

under reflux for 1 hr. on a water-bath. A removal of EtOH afforded pale yellow crystals, m.p. 116~121°, whose IR spectrum showed the absence of a carbonyl group.

The crystals were dissolved by warming in 20 ml. of abs. EtOH, the solution cooled in ice and saturated with hydrogen chloride. After having been kept for 30 min. at room temperature, the solution was refluxed for 3 hr. Alcohol was distilled off *in vacuo* and the residue was washed with a little volume of cold water. The insoluble pale yellow solid (310 mg.) was collected by filtration and recrystallization yielded slightly yellow prisms, m.p. 307~308°(lit.,[12] 311°), which was proved to be identical with racemic octahydroindolo-[2,3-*a*]quinolizine (III) hydrochloride. It was confirmed by optical rotatory dispersion.

On the other hand, the combined washings were made alkaline with potassium carbonate and extracted with benzene. The benzene was removed *in vacuo* from the dried (Na_2SO_4) extract to give 1 g. of orange yellow oil. The product was purified by chromatography on neutral alumina (100 g., Woelm activity grade III) with benzene as an eluent to yield 0.48 g. as a pale yellow solid, m.p. 128~131°. Sublimation at 140~150°/0.08 mm., followed by several recrystallizations from hexane afforded colorless needles, m.p. 146~149°, $[\alpha]_D^{30}$ +73°(c=0.44, EtOH), $[\alpha]_D^{28}$ +110.5°(c=0.69, pyridine). ORD (EtOH, c=0.81), $[\alpha]_{350}$ +160, $[\alpha]_{316}$ ±0, $[\alpha]_{310}$ −110 (Fig. 1). UV λ_{max}^{EtOH} mμ (log ε): 225 (4.56), 282 (3.86), 289 (3.78) (lit., (a)[13]: 226 (4.58), 283 (3.91), 290 (3.84); (b)[14]: 226 (4.67), 283 (3.88), 290 (3.80)). *Anal.* Calcd. for $C_{15}H_{18}N_2$: C, 79.60; H, 8.02; N, 12.38. Found: C, 79.46; H, 8.12; N, 12.31.

S(−)-1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizine (IIIb)——Analogously to the procedure described above, from 1 g. of the above Ib ($[\alpha]_D$ +17.7), 0.2 g. of S(−)-octahydroindolo[2,3-*a*]quinolizine (IIIb) was obtained as colorless prisms in addition to 0.4 g. of *dl*-hydrochloride. IIIb had m.p. 140~143°, $[\alpha]_D^{26}$ −62.3° (c=1.06, EtOH). ORD (EtOH, c=1.06), $[\alpha]_{350}$ −145, $[\alpha]_{315}$ ±0, $[\alpha]_{313}$ +40 (Fig. 1). The IR spectrum (KBr) was identical with that of IIIa.

The picrate was prepared in EtOH and obtained as yellow needles from EtOH, m.p. 225~226.5°. *Anal.* Calcd. for $C_{21}H_{21}O_7N_5$: C, 55.38; H, 4.65; N, 15.38. Found: C, 55.44; H, 4.57; N, 14.97.

R(+) and S(−)-3,4,11,11a-Tetrahydro-2*H*-benzo[*b*]quinolizin-1(6*H*)-one (IIa and IIb)——To a solution of 4.0 g. (0.02 mole) of *dl*-III, prepared from phenylalanine in the method reported,[15] in 20 ml. of acetone was added a solution of 6.4 g. (0.02 mole) of *d*-3-bromo-8-camphorsulfonic acid in acetone. A little volume of ether was added and the mixture was kept to stand in the refrigerator overnight. The colorless crystals separated were collected by filtration and washed with acetone. Recrystallization from EtOH yield 2.2 g. of diastereomeric salt as colorless prisms, m.p. 188~190° (decomp.), $[\alpha]_D$ +84.2° (c=0.94, H_2O). The IR spectrum (KBr) was identical with that of an authentic sample.[7]

In 5 ml. of water was suspended 2.2 g. of the aforementioned salt and the mixture was basified with saturated aqueous potassium carbonate and extracted with benzene. The extract was dried and evaporated *in vacuo* under N_2 stream. The product weighing 0.8 g. was obtained as an orange yellow solid, which was recrystallized from a little volume of EtOH as yellow small needles, m.p. 60~64°, $[\alpha]_D^{28}$ +88.4°(c=0.6, EtOH). The IR spectrum (KBr) was virtually identical with that of an authentic sample.[7] With the same treatment of mother liquor as IIa, the enantiomeric amino-ketone, IIb, was also obtained, $[\alpha]_D^{30}$ −43°(c=1). This was used without purification for the next procedure.

R(+)-5,7,8,13,13b,14-Hexahydrobenz[*b*]indolo[2,3-*a*]quinolizine (IVa)——The mixture of 0.8 g. (0.004 mole) of the above IIa ($[\alpha]_D$ +88.4°) and 0.45 g. (0.0042 mole) of phenylhydrazine in 15 ml. of EtOH was refluxed for 1 hr. on a water-bath and then evaporated to dryness *in vacuo*. The resulting pale yellow crystals having m.p. 107~115° were dissolved in 15 ml. of EtOH, the mixture was cooled in ice and saturated with hydrogen chloride. Then the mixture was kept for 20 min. at room temperature and refluxed for 1.5 hr. Alcohol was distilled off and the residue was washed with cold water. The pale yellow insoluble solid was obtained by filtration weighing 0.1 g. and recrystallized from EtOH–ether as pale yellow prisms, m.p. 285~287°, $[\alpha]_D^{18}$ +15.5°(c=0.2, EtOH). This value suggests that the product was almost racemic or at most of 8% optical purity, since free base IVa with the rotation, $[\alpha]_D$ +286.5°, was converted to the corresponding hydrochloride with $[\alpha]_D$ +195°.

The washing was made basic with potassium carbonate and extracted with benzene. After drying (Na_2SO_4) and removal of the solvent, the resulting black oil (0.5 g.) was chromatographed on neutral alumina (70 g., Woelm activity III) with benzene as an eluent to give 0.1 g. as pale yellow crystals which had m.p. 157~160°. Further purification from benzene–hexane afforded slightly yellow prisms, m.p. 159~161°, $[\alpha]_D^{31}$ +303.4°(c=0.36, pyridine). ORD (pyridine, c=0.36), $[\alpha]_{318}$ +1500 (Fig. 2); (EtOH, c=0.25), $[\alpha]_{313}$ +1220, $[\alpha]_{305}$ +1140 (Fig. 2). UV λ_{max}^{EtOH} mμ (log ε): 224 (4.63), 272 (3.90), 282 (3.90), 289 (3.81), (lit.,[16]

12) L. H. Groves, G. A. Swan: J. Chem. Soc., **1952**, 650; cf. K. B. Prasad, G. A. Swan: *Ibid.*, **1958**, 2024.
13) R. C. Elderfield, J. M. Lagowski, D. L. McCurdy, S. L. Wythe: J. Org. Chem., **23**, 435 (1958).
14) Y. Ban, M. Seo: Chem. & Ind. (London), **1960**, 235.
15) G. R. Clemo, G. A. Swan: J. Chem. Soc., **1946**, 617; S. Archer: J. Org. Chem., **16**, 430 (1951); N. J. Leonard, S. Swan, G. Fuller: J. Am. Chem. Soc., **76**, 3193 (1954).
16) J. W. Huffman: J. Am. Chem. Soc., **80**, 5193 (1958).

226 (4.85), 274 (3.97), 284 (3.97), 292 (3.86)). *Anal.* Calcd. for $C_{19}H_{18}N_2$: C, 83.17; H, 6.61; N, 10.21. Found: C, 82.89; H, 6.61; N, 10.06.

S(−)-5,7,8,13,13b,14-Hexahydrobenz[*b*]indolo[2,3-*a*]quinolizine (IVb)——In the same procedure described above, 1.6 g. (0.0086 mole) of IIb ($[\alpha]_D$ −43°) was subjected to the Fischer indole synthesis using hydrogen chloride as a catalyst. The hydrochloride of crude product was washed with cold water. 450 mg. of the less soluble racemic hydrochloride was obtained by filtration, m.p. 280~283°) (lit.,[17] 288~289°). UV λ_{max}^{EtOH} mμ (log ε): 220(4.63), 272 (3.90), 277 (3.89), 287 (3.77) (lit.,[17] 225 (4.54), 270 (4.00), 289 (3.86)). The racemic free base IV recovered from the hydrochloride had m.p. 192~195° from benzene-hexane (lit.,[16] 196~197°).

On the other hand, 0.15 g. of optically active indole derivative (IVb) was isolated from the combined aqueous washings in the same way as IVa. Several recrystallizations from benzene-hexane yielded slightly yellow prisms, m.p. 163~165°, $[\alpha]_D^{30}$ −312° (c=0.38, pyridine). ORD (pyridine, c=0.38), $[\alpha]_{320}$ −1570 (Fig. 2); (EtOH, c=0.39), $[\alpha]_{350}$ −1000, $[\alpha]_{310}$ −1340 (Fig. 2). The IR spectrum (KBr) was identical with that of IVa.

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17) K. T. Potts, R. Robinson: J. Chem. Soc., **1955**, 2675. In this ref., 208~209° read 288~289°.