[Chem. Pharm. Bull. 23(11)2634—2642(1975)]

UDC 547.94.057 : 547.571.04

Studies on the Syntheses of Heterocyclic Compounds. DCXLI*,[1] A Convenient Synthesis of Hexadehydroyohimbine and a Total Synthesis of Yohimbine

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(Received April 28, 1975)

A total synthesis of (±)-yohimbine (I) has been achieved from 1,2,3,4,5,6,7,12b-octahydroindolo[2,3-*a*]quinolizin-2-one(XXXIV)*via* 15,16-dehydroyohimbinone (XXXVII) and yohimbinone (XXXVIII). Moreover, hexadehydroyohimbine (XXIX) was synthesized from 2-bromo-5-methoxybenzaldehyde (VIII). α-Cyanophenylpropionic acid (X), prepared from VIII through the α-cyanocinnamic acid (IX), was cyclized to the indanone (XI), which was converted into 6-bromo-3-methoxy-2-methoxycarbonylphenylpropionic acid (XIV) *via* the corresponding dicarboxylic acid (XII) and diester (XIII). Debromination of XIV, followed by cyclization, gave the indanone (XXIII), which was transformed into the indan-1,2-dione (XXV) through the α-hydroxyimino ketone (XXIV). Pictet-Spengler reaction of XXV with tryptamine afforded the spirobenzyl-β-carboline (XXVI), whose photolysis yielded the decadehydroyohimbane (XXVII) and the decadehydroyohimban-21-one (XXVIII). Reduction of both products gave O-methylhexadehydroyohimbine (XXIX).

The yohimbine-type alkaloids[3] have received much attention in the synthetic areas,[4] because of the pharmacological activity of reserpine and yohimbine (I). We have been interested in the synthesis and chemical modification of alkaloids of yohimbane group in order to get pharmacologically active compounds and reported a synthesis of methyl O-(4-hydroxy-3-methoxycinnamoyl) reserpate (II), which showed the strongest antihypertensive activity and lower side effect[5] rather than reserpine. Recently, we have developed three new synthetic methods of the hexadehydrohimbane (V and VI) ring system, thus the first method was an intramolecular thermolysis of the 1-benzocyclobutenyl-3,4-dihydro-β-carboline (III)[6] and the second one was an intermolecular cycloaddition of the benzocyclobutenes to 3,4-dihydro-β-carboline. The third method was a photolysis of the spiro[indene-2,1′-β-carbolin]-1-one (IV) derived from (III).[7,8]

Our methods would be specially useful for the synthesis of the yohimbanes having an electron withdrawing group on the ring E, because this type of compounds could not be obtained by a usual Mannich reaction of the 1-benzyl-1,2,3,4-tetrahydro-β-carboline with formalin,[9] but in our synthesis the key starting materials have already a "berberine bridge carbon" in

* Dedicated to the memory of Prof. Eiji Ochiai.

1) Part DCXL: T. Kametani, K. Fukumoto, F. Satoh, K. Kigasawa, and H. Sugi, *Heterocycles*, 3, 921 (1975).
2) Location: *Aobayama, Sendai.*
3) H.J. Monteiro, "The Alkaloids," ed. by R.H.F. Manske, Vol. XI, Academic Press, New York, 1968, p. 145.
4) J.P. Kutney, "Alkaloids-Organic Chemistry Series One," ed. by K. Wiesner, Vol. IX, Butterworths, London, 1973, p. 27.
5) T. Kametani, M. Ihara, T. Suzuki, T. Takahashi, R. Iwaki, H. Takei, N. Miyake, M. Yoshida, Y. Hasegawa, and H. Kitagawa, *J. Med. Chem.*, **15**, 686 (1972).
6) T. Kametani, M. Kajiwara, and K. Fukumoto, *Chem. Ind.*, **1973**, 1165; *Tetrahedron*, **30**, 1053 (1974).
7) T. Kametani, M. Kajiwara, T. Takahashi, and K. Fukumoto, *J. Chem. Soc. Perkin I*, **1975**, 737.
8) T. Kametani, H. Takeda, Y. Hirai, F. Satoh, and K. Fukumoto, *J. Chem. Soc. Perkin I*, **1974**, 2141.
9) W.M. Whaley and T.R. Govindachari, *Organic Reactions*, **6**, 151 (1971).

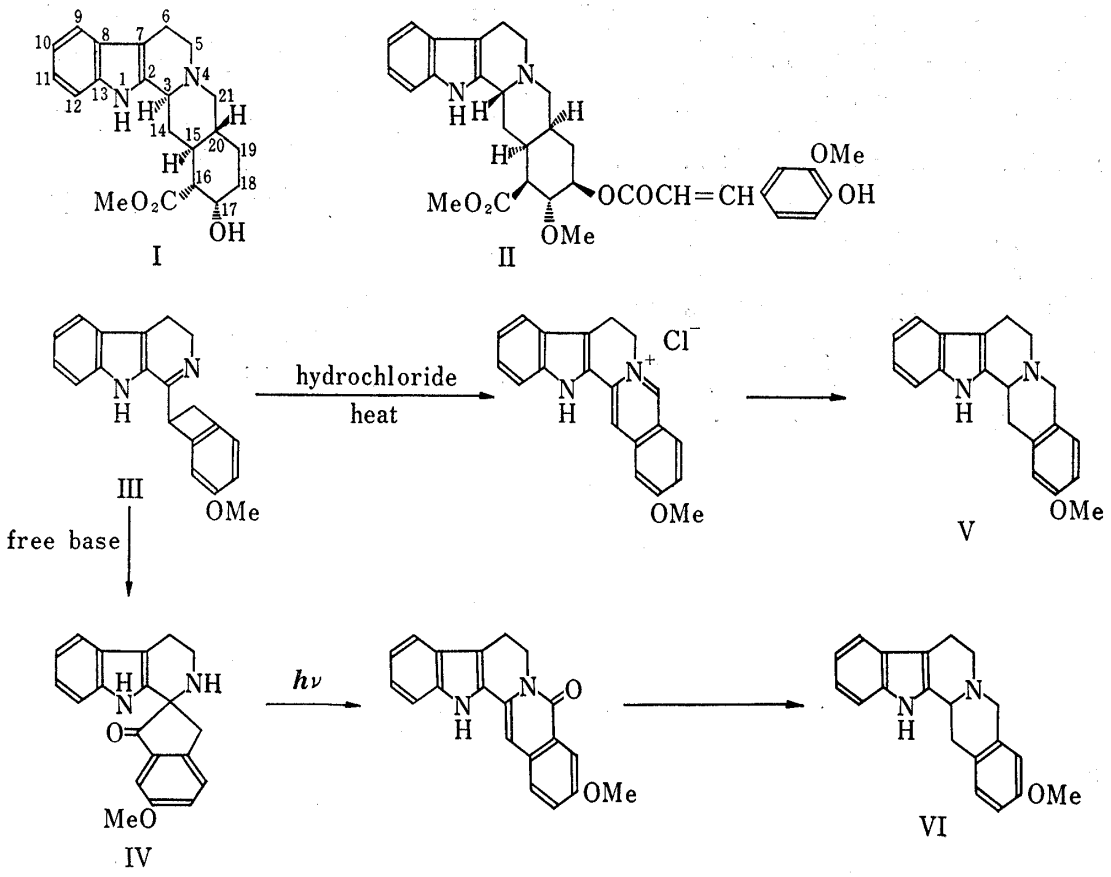

Chart 1

the molecule. On the ground of this, we have examined a synthesis of the O-methylhexadehydroyohimbine (XXIX), which would be a potential precursor for yohimbine, by our method and a total synthesis of yohimbine has been accomplished by a modification of Stork's yohimbine synthesis.[10] Here we wish to report these successful results.

The first trial is a synthesis of the decadehydroyohimbane (XXVII) by the thermolysis of the benzocyclobutene derivative (XXI), which would be a key intermediate to dehydroyohimbinone (XXXVII), by our third method[8] described above as shown in Chart 2. The synthesis of a key intermediate, 4-methoxy-3-methoxycarbonylbenzocyclobutene-1-carboxylic acid (XX), was examined by usual method[11] as follows. Bromination of *m*-methoxybenzaldehyde (VII) gave 2-bromo-5-methoxybenzaldehyde (VIII), mp 76—78° (lit.,[12] mp 75—76°) and the position of the introduced bromine atom was determined by the nuclear magnetic resonance (NMR) spectrum (δ in $CDCl_3$) showing three aromatic protons at 6.95 as a double doublet (J=6 and 3 Hz), at 7.32 as a doublet (J=3 Hz) and at 7.43 as a doublet (J=6 Hz). The condensation[6] of this aldehyde with cyanoacetic acid in the presence of pyridine and ammonium acetate gave the cinnamic acid (IX), mp 227—228°, in 85% yield [δ ($CDCl_3$) 8.52 (s, –CH=C〈); ν_{max}^{KBr} cm^{-1}: 2220 (CN) and 1700 (CO_2H)], whose reduction with sodium borohydride in the presence of sodium bicarbonate in methanol afforded the α-cyanopropionic acid (X), mp 111—112°, in 76% yield [*m/e* 283 and 285 (M^+); $\nu_{max}^{CHCl_3}$ cm^{-1}: 2240 (CN) and 1720 (CO_2H); δ ($CDCl_3$): 3.10—4.20 (3H, $C\underline{H}_2C\underline{H}$〈)]. The cyclization of this carboxylic acid with polyphosphoric acid[14] at 100° for 30 min afforded, in 79% yield, 4-bromo-2-carbamoyl-7-

10) G. Stork and R.N. Guthikonda, *J. Am. Chem. Soc.*, **94**, 5109 (1972).
11) T. Kametani and K. Fukumoto, *Heterocycles*, **3**, 29 (1975).
12) R. Pschorr, *Ann.*, **391**, 25 (1912).
14) Y. Tamura, *J. Pharm. Soc. Japan*, **76**, 739 (1956).

methoxyindan-1-one (XI), mp 243—245° [ν_{max}^{KBr} cm^{-1}: 1710 (CO) and 1660 ($CONH_2$); δ ($CDCl_3$+CF_3CO_2H): 6.70 (1H, d, J=9 Hz, C_6–H) and 7.70 (1H, d, J=9 Hz, C_5–H)], by accompanying a partial hydrolysis of the cyano group. Acid hydrolysis[14] of this product with boiling 10% potassium hydroxide gave the dicarboxylic acid (XII), mp 175—176°, in 80% yield [ν_{max}^{KBr} cm^{-1}: 1715 and 1725; δ ($CDCl_3$): 2.6—3.4 (4H, m, $ArC\underline{H}_2C\underline{H}_2CO_2H$)], which on treatment with diazomethane afforded the diester (XIII), bp_3 168° [δ ($CDCl_3$): 3.70, 3.80, and 3.92 (each 3H, s, OMe)]. The selective hydrolysis of the diester was carried out with an equimolar amount of 2.5% methanolic sodium hydroxide solution to give the 2-methoxycarbonylphenylpropionic acid (XIV), mp 108—109°, in 80% yield [$\nu_{max}^{CHCl_3}$ cm^{-1}: 1705 and 1725; δ ($CDCl_3$) 3.80 and 3.90 (each 3H, s, OMe)], whose acid chloride (XV) was treated with concentrated ammonia to furnish the amide (XVI) in 93% yield, mp 157—158° [$\nu_{max}^{CHCl_3}$ cm^{-1}: 3540 and 3415 (NH_2), 1725 (CO_2Me) and 1680 ($CONH_2$)].

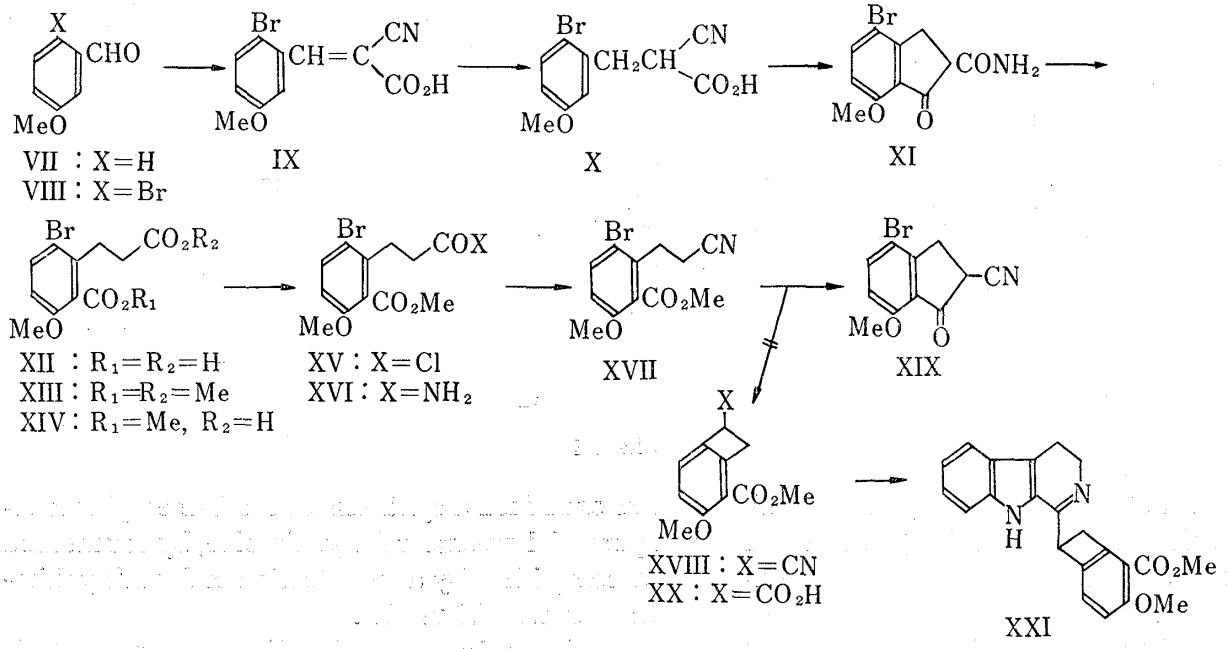

Chart 2

Dehydration[15] of the amide with phosphoryl chloride in boiling benzene gave the nitrile (XVII) in 84% yield, mp 112—113° [$\nu_{max}^{CHCl_3}$ cm^{-1}: 2250 (C≡N) and 1725 (CO_2Me)], which was treated with sodium amide in liquid ammonia[6,13] to give no expected 1-cyanobenzocyclobutene (XVIII) but Dieckmann cyclization proceeded to afford the 2-cyanoindan-1-one (XIX), mp 192.5—194.5°, whose structure was determined by IR [ν_{max}^{KBr} cm^{-1}: 2250 (CN) and 1720 (CO)] and NMR [δ ($CDCl_3$): 3.70 (1H, dd, J=8 and 6 Hz, >CHCN)] spectra.[13] This product also showed a positive Beilstein test. Since we could not obtain the expected benzocyclobutene derivatives (XVIII and XX), the other method, which was developed by us[7] and Irie,[16] independently, was investigated in order to get the compound having a dehydrohimbane system.

Debromination of XIV by a hydrogenolysis with palladium on carbon in the presence of sodium acetate in acetic acid afforded 2-carbomethoxy-3-methoxyphenylpropionic acid (XXII), mp 113—114°, in 90% yield [δ ($CDCl_3$): 6.76 (2H, dd, J=8 and 2.5 Hz, C_4–H and C_6–H) and 7.45 (1H, t, J=8 Hz, C_5–H)], which was cyclised with polyphosphoric acid at 110° for 10 min to give the indan-1-one (XXIII), mp 112.5—113.5°, in 72% yield [δ ($CDCl_3$): 6.87

15) C.F. Koelsch, *J. Org. Chem.*, **26**, 1003 (1961).
16) J. Tanaka, T. Omori, J. Fukumoto, and H. Irie, "The Abstract of the 95th Annual Meeting of Japanese Pharmaceutical Society," Vol. 2, 1975, p. 222.

and 7.70 (each 1H,d J=8 Hz, C_6–H and C_7–H)]. Hydroximination[17] of this indanone (XXIII) with isoamyl nitrite and hydrochloric acid in methanol, followed by hydrolysis in the presence of 37% formalin of the resulting 2-hydroxyiminoindanone (XXIV), mp 246—249° [δ ($CDCl_3$): 4.00 (2H, s, CH_2)], afforded the indan-1,2-dione (XXV), mp 204—205°, in 72% yield [$\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 and 1760; δ ($CDCl_3$): 3.67 (2H, s, CH_2)]. Pictet-Spengler reaction[17] of tryptamine hydrochloride with indan-1,2-dione (XXV) in boiling ethanol furnished, in 89.6% yield, the spiro[indene-2,1′-β-carbolin]-1-one (XXVI), mp 132—136° [ν_{max}^{KBr} cm^{-1}: 1705; δ ($CDCl_3$): 3.43 and 3.53 (each 1H, d, J=3 Hz, $ArCH_2C\langle$)].

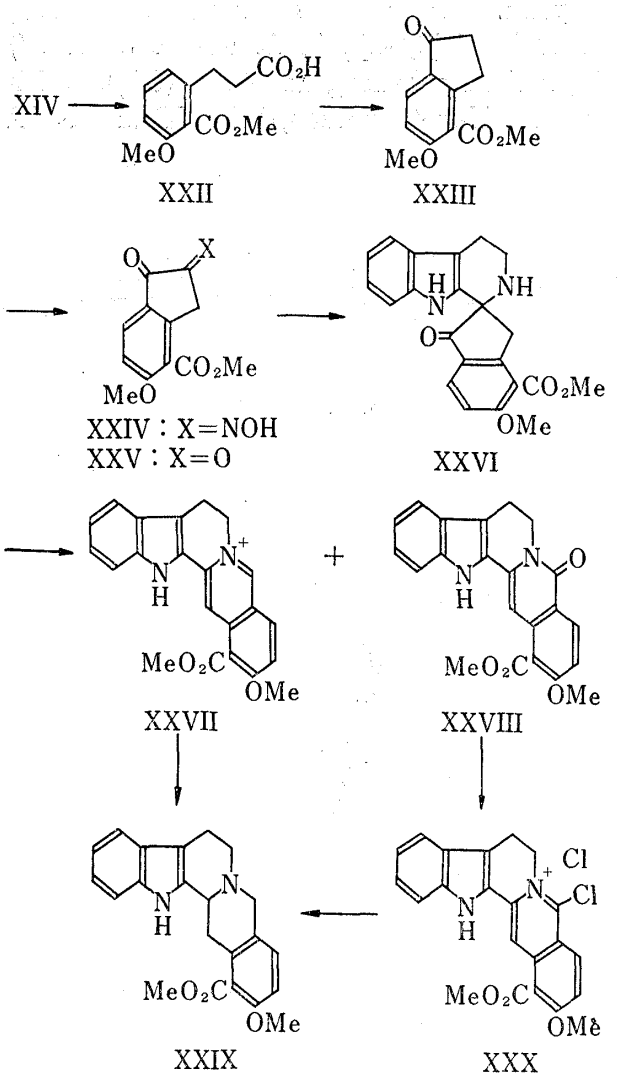

Chart 3

Photolysis[7,18] of this spiro-compound (XXVI) with a Hanovia 450 W mercury lamp in dry tetrahydrofuran in a current of nitrogen at room temperature for 3 hr gave a separable mixture of the decadehydroyohimbane (XXVII), mp 245—248°, m/e 359 (M^+), in 20% yield and decadehydroyohimban-21-one (XXVII), mp >300°, m/e 374 (M^+), in 13% yield, whose structures were determined by spectroscopic methods. The infrared (IR) spectrum (KBr) of the second compound showed an amide carbonyl band at 1645 cm^{-1} in addition to an indole NH group at 3300 and an ester carbonyl group at 1700 cm^{-1}, and the ultraviolet (UV) spectrum [λ_{max}^{MeOH} nm: 378, 359, 345^{sh}, 295, 284, and 257] revealed the decadehydroyohimban-21-one system.[19] The NMR spectrum ($CDCl_3$) showed C_{14}–H at 6.53 as a singlet and two aromatic protons at 6.80 and 8.40 as a doublet having J=9 Hz. The IR [ν_{max}^{KBr} cm^{-1}: 1638 ($C{=}\overset{+}{N}\langle$)] and UV [$\lambda_{max}^{MeOH}$ nm: 355, 342, 319, and 260] spectra of the first product suggested the presence of the decadehydroyohimbane skeleton[6] and this fact was also supported by the NMR spectrum ($CDCl_3$+CF_3CO_2H) showing C_{14}–H and C_{20}–H at 8.30 and 9.30 as each singlet. Chlorination of the decadehydroyohimban-21-one (XXVIII) with boiling phosphoryl chloride, followed by treatment of the chloride of the crude 21-chloroyohimbane (XXX) with sodium borohydride, gave the O-methylhexadehydroyohimbine (XXI), mp 185°, m/e 362 (M^+), in 84% yield, which was characterised by IR [ν_{max}^{KBr} cm^{-1}: 3400 (NH), 2725—2850 (Bohlmann bands) and 1720 (CO_2-Me)], UV [λ_{max}^{MeOH} nm: 291 and 284] and NMR [δ ($CDCl_3$): 4.05 (1H, d, J=15 Hz, C_{21}–H)] spectra.[6] This product could be obtained in 76% yield by direct reduction of the decadehydroyohimbane (XXVII) with sodium borohydride.

17) H. Irie, T. Kishimoto, and S. Uyeo, *J. Chem. Soc.* (*C*), **1968**, 3051.
18) H. Irie, K. Akagi, S. Tani, K. Yabusaki, and H. Yamane, *Chem. Pharm. Bull.* (Tokyo), **21**, 855 (1973).
19) L. Merlini, R. Mondelli, and G. Nasini, *Tetrahedron*, **23**, 3219 (1967).

The conversion of the hexadehydroyohimbine into dehydroyohimbinone (XXXVII) was examined under several conditions by Birch reduction but unsuccessful result was obtained. Therefore, a synthesis of dehydroyohimbinone (XXXVII) by other method[10] was examined as follows.

1-Ethoxycarbonylmethyl-1,2,3,4-tetrahydro-β-carboline (XXXI)[20] was condensed with acrylonitrile on a water bath for 20 hr to give in 97% yield the corresponding 2-cyanoethyl derivative (XXXII) [$\nu_{max}^{CHCl_3}$ cm^{-1}: 3340 (indole NH), 2245 (CN), and 1717 (CO)][21] which was subjected to Dieckmann condensation with sodium hydride in boiling benzene for 2 hr to afford 3-cyano-1,2,3,4,5,6,7,12b-octahydroindolo[2,3-a]quinolizin-2-one (XXXIII) [$\nu_{max}^{CHCl_3}$ cm^{-1}: 2250 (CN) and 1720 (CO), *m/e* 265 (M$^+$)] in 87.9% yield. Treatment of this nitrile with 10% sulfhuric acid under reflux furnished the decyanated indolo[2,3-*a*]quinolizin-2-one (XXXIV) in 75% yield [$\nu_{max}^{CHCl_3}$ cm^{-1}: 3475 (NH), 2760—2850 (Bohlmann bands), and 1717 (CO)], which was identical with the authentic sample, prepared by Kline's method,[20] by IR and NMR spectral comparisons.

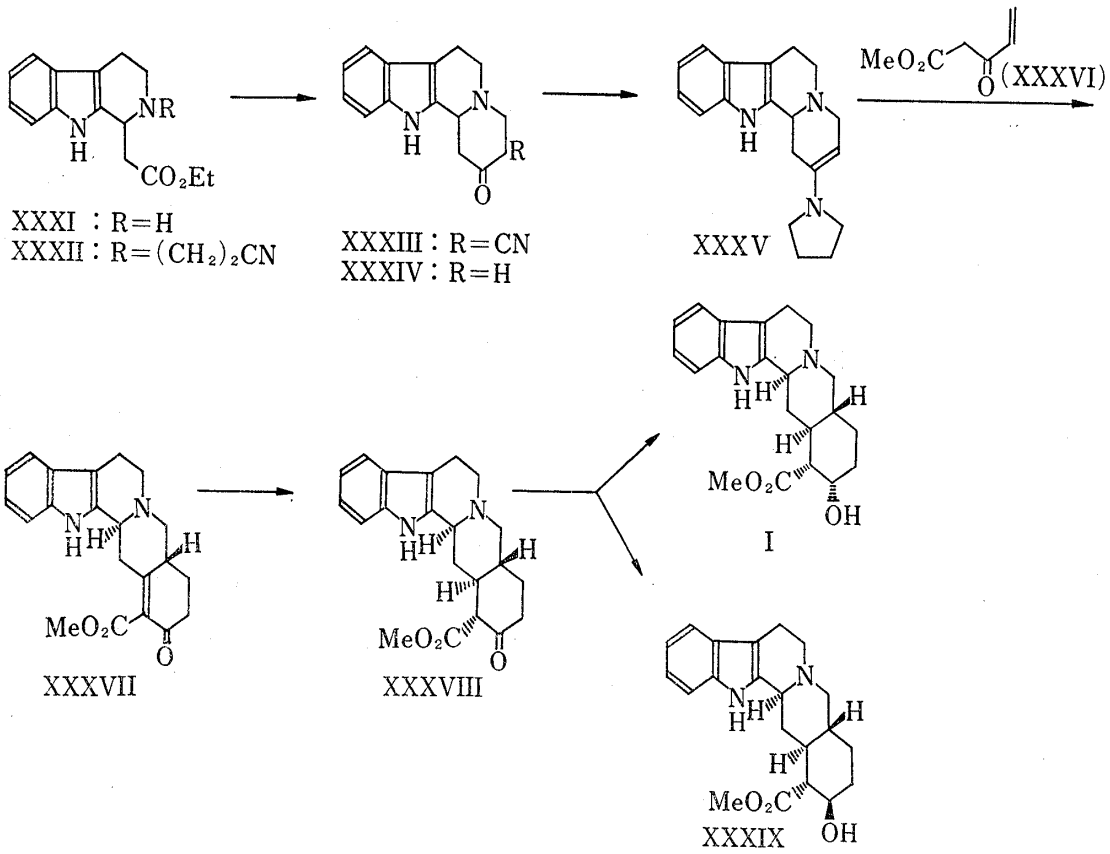

Chart 4

Reaction of the pyrrolidine enamine (XXXV) of this ketone (XXXIV), prepared by usual way,[22] with methyl 3-oxo-4-pentenoate (XXXVI)[23] in boiling benzene for 10 min by Stork's method[10] gave the 15,16-dehydroyohimbinone (XXXVII), mp 192—193° (lit.,[24] mp 188—189°) in 17.2% yield [$\nu_{max}^{CHCl_3}$ cm^{-1}: 3475 (NH), 2760—2850 (Bohlmann bands), 1725 (CO), 1675 (CO),

20) G.B. Kline, *J. Am. Chem. Soc.*, **81**, 2251 (1959).
21) L.H. Groves and G.A. Swan, *J. Chem. Soc.*, **1952**, 650.
22) *a*) J.D. Albright and L. Goldman, *J. Med. Chem.*, **17**, 296 (1974); *b*) K. Mori, I. Takemoto, and M. Matsui, *Agric. Biol. Chem. Japan*, **36**, 2605 (1972).
23) *a*) E. Wenkert, A. Afonso, J.B. Bredenberg, C. Kaneko, and A. Tahara, *J. Am. Chem. Soc.*, **86**, 2038 (1964); *b*) S.W. Pelletier, R.L. Chappell, and S. Prabhakar, *J. Am. Chem. Soc.*, **90**, 2889 (1968).
24) L. Töke, K. Honty, and Cz. Szántay, *Chem. Ber.*, **102**, 3248 (1969).

1625 (C=C); λ_{max}^{MeOH} nm: 291, 283, and 247; *m/e* 350 (M^+); δ ($CDCl_3$): 3.93 (3H, s, CO_2Me)]. The stereochemistry[10,22b] of the C_3- and C_{20}-hydrogens of this compound was revealed by the identity of the reduction product, (±)-yohimbinone (XXXVIII), with the known yohimbinone derived from yohimbine (I). Thus, catalytic hydrogenation[25] of dehydroyohimbinone (XXXVII) on 30% palladium on carbon in methanol at room temperature gave (±)-yohimbinone (XXXVIII), mp 239° (lit.,[24] mp 238—239°) [*m/e* 352 (M^+)], whose IR [$\nu_{max}^{CHCl_3}$ cm^{-1}: 3480 (NH) and 1740 (CO)] and NMR [δ ($CDCl_3$): 3.83 (3H, s, CO_2Me)] spectra were superimposable upon those of the yohimbinone[26] prepared from natural yohimbine. This fact also indicates that the reduction could proceed stereospecifically. (±)-Yohimbinone (XXXVIII) was converted into (±)-yohimbine (I) [mp 218—220°; *m/e* 354 (M^+); δ ($CDCl_3$): 3.81 (3H, s, CO_2Me), 4.23 (1H, broad s, CHOH), and 7.80 (1H, broad s, NH); $\nu_{max}^{CHCl_3}$ cm^{-1}: 3475 (NH) and 1705 (CO_2-Me)] in addition to β-yohimbine (XXXIV) by sodium borohydride reduction according to Szántay method.[25] Thus, a total synthesis of (±)-yohimbine (I) has been accomplished.

Experimental[27]

2-Bromo-5-methoxybenzaldehyde (VIII)——To a mixture of *m*-methoxybenzaldehyde (VII) (45 g), sodium acetate trihydrate (45 g) and chloroform (350 ml) was added dropwise a solution of bromine (58 g) in chloroform (175 ml) with stirring and then refluxed for 30 min. The reaction mixture was washed successively with 5% $NaHCO_3$ aqueous solution, 5% $Na_2S_2O_3$ aqueous solution and water, dried over Na_2SO_4, and evaporated to give the bromide (VIII) (72 g) as colorless plates, mp 76—78° (from *n*-hexane).[12] IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1675 (C=O). NMR ($CDCl_3$) ppm: 3.79 (3H, s, OMe), 6.95 (1H, dd, J=6 and 3 Hz, C_4–H), 7.32 (1H, d, J=3 Hz, C_6–H), 7.43 (1H, d, J=6 Hz, C_3–H), and 10.02 (1H, s, CHO).

α-Cyano-2-bromo-5-methoxycinnamic Acid (IX)——A mixture of the aldehyde (VIII) (28 g), cyanoacetic acid (12 g), ammonium acetate (1 g), benzene (80 ml) and pyridine (40 ml) was refluxed using a Dean-Stark apparatus. After a calculated amount of water had separated, the mixture was cooled to give a yellow solid (35 g), which was treated with an excess of 10% HCl to afford the cinnamic acid (IX) (30 g; 85%) as pale yellow needles, mp 227—228° (from methanol). IR ν_{max}^{KBr} cm^{-1}: 2220 (CN) and 1700 (CO_2H). NMR [$CDCl_3$+$(CD_3)_2SO$] ppm: 3.84 (3H, s, OMe), 6.95—7.75 (3H, m, ArH), and 8.52 (1H, s, –CH=C〈). *Anal.* Calcd. for $C_{11}H_8O_3NBr$: C, 46.81; H, 2.84; N, 4.96. Found: C, 46.93; H, 3.08; N, 4.87.

α-Cyano-β-(2-bromo-5-methoxyphenyl)propionic Acid (X)——To a suspension of the cinnamic acid (24 g) in methanol (200 ml) and saturated $NaHCO_3$ aqueous solution (100 ml) was added in small portions sodium borohydride (6 g) with stirring at 18° during 0.5 hr and the mixture was then stirred for 0.5 hr at room temperature. After evaporation of methanol, the residue was acidified with 10% HCl and extracted with ether. The extract was washed with water, dried over Na_2SO_4, and evaporated to afford the phenylpropionic acid (X) (18.7 g; 76%) as colorless prisms, mp 111—112° (from benzene). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2240 (CN) and 1720 (CO_2H). NMR ($CDCl_3$) ppm: 3.10—4.20 (3H, m, CH_2CH) and 6.75—7.33 (3H, m, ArH). Mass Spectrum *m/e*: 285 and 283 (M^+). *Anal.* Calcd. for $C_{11}H_{10}O_3NBr$: C, 46.04; H, 3.52; N, 4.93. Found: C, 45.97; H, 3.67; N, 4.86.

4-Bromo-2-carbamoyl-7-methoxyindan-1-one (XI)——A mixture of the phenylpropionic acid (X) (10 g) and polyphosphoric acid (100 g) was heated at 100° for 0.5 hr and the reaction mixture was then poured into ice-water. The separated solid was collected by filtration and recrystallized from methanol to give the indanone (XI) (7.9 g; 79%) as colorless needles, mp 243—245°. IR ν_{max}^{KBr} cm^{-1}: 3410, 3310, and 3220 (NH_2), 1710 (CO) and 1660 ($CONH_2$). NMR ($CDCl_3$+CF_3CO_2H) ppm: 3.20—3.80 (3H, m, CH_2CH), 3.90 (3H, s, OMe), and 6.70, 7.70 (each 1H, d, J=9 Hz, C_6–H, and C_5–H). *Anal.* Calcd. for $C_{11}H_{10}O_3NBr$: C, 46.50, H, 3.55, N, 4.93. Found: C, 46.15; H, 3.72; N, 4.96.

6-Bromo-2-carboxy-3-methoxyphenylpropionic Acid (XII)——A mixture of the indanone (XI) (3 g) and 10% KOH aqueous solution was refluxed for 50 hr and washed with ether. The aqueous layer was acidified with 10% HCl and extracted with ether. The extract was washed with water, dried over Na_2SO_4, and evaporated to give the dicarboxylic acid (XII) (2.6 g; 80%) as colorless needles, mp 175—176° (from chloroform). IR ν_{max}^{KBr} cm^{-1}: 1715 (CO_2H) and 1725^{sh} (CO_2H). NMR ($CDCl_3$) ppm: 2.6—3.4 (4H, m, CH_2CH_2),

25) Cs. Szántay, K. Hony, L. Töke, A. Buzas, and J.P. Gacquet, *Tetrahedron Letters*, **1971**, 4871.
26) J.D. Albright and L. Goldman, *J. Am. Chem. Soc.*, **87**, 4214 (1965).
27) All melting points are uncorrected and were measured with a Yanagimoto micro melting point apparatus (MP-22). IR spectra were measured with a Hitachi 215 grating spectrophotometer, NMR spectra with a JEOL PMX spectrometer with Me_4Si as an internal standard, mass spectra with a Hitachi RMU-7 spectrometer, and UV spectra with a Hitachi 124 spectrometer.

3.90 (3H, s, OMe), and 6.76, 7.60 (each 1H, d, J=7 Hz, C_4–H and C_5–H). *Anal.* Calcd. for $C_{11}H_{11}O_5Br$: C, 43.58; H, 3.66. Found: C, 43.91; H, 4.10.

Methyl 6-Bromo-3-methoxy-2-methoxycarbonylphenylpropionate (XIII)——An excess of diazomethane in ether was added to the dicarboxylic acid (XII) (1 g) in ether (50 ml), and the resulting mixture was stirred for 1 hr, washed with 5% $NaHCO_3$ aqueous solution, and water, dried over Na_2SO_4, and evaporated to give the diester (XIII) (950 mg; 87%) as a colorless syrup, bp_3 168°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725 (CO_2Me). NMR ($CDCl_3$) ppm: 2.43—3.23 (4H, m, $C\underline{H}_2C\underline{H}_2$), 3.70 (3H, s, OMe), 3.80 (3H, s, OMe), 3.92 (3H, s, OMe), and 6.73, 7.50 (each 1H, d, J=8 Hz, C_5–H and C_4–H).

6-Bromo-3-methoxy-2-methoxycarbonylphenylpropionic Acid (XIV)——A solution of the diester (XIII) (2 g) in 2.5% methanolic NaOH solution (10 ml) was refluxed for 4 hr and then methanol was removed by distillation. The residue was diluted with water, whose solution was washed with ether, acidified with 10% HCl, and extracted with ether. The extract was washed with saturated NaCl aqueous solution, dried over Na_2SO_4, and evaporated to afford the monocarboxylic acid (XIV) (1.6 g; 80%) as colorless needles, mp 108—109° (from benzene). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725 (CO_2H) and 1705 (CO_2Me). NMR ($CDCl_3$) ppm: 2.43—3.27 (4H, m, $C\underline{H}_2C\underline{H}_2$), 3.80 (3H, s, OMe), 3.90 (3H, s, OMe) and 6.69, 7.50 (each 1H, d, J=8 Hz, C_5–H and C_4–H). *Anal.* Calcd. for $C_{12}H_{13}O_5Br$: C, 45.44; H, 4.13. Found: C, 45.55; H, 4.36.

6-Bromo-3-methoxy-2-methoxycarbonylphenylpropionamide (XVI)——A solution of the monocarboxylic acid (4 g) and thionyl chloride (4 g) in dry benzene (40 ml) was refluxed for 0.5 hr, and the excess of reagent and benzene were distilled off. The residue was dissolved in ether (5 ml), to a solution of which was added concentrated ammonia (20 ml) with stirring under cooling. The separated solid was extracted with chloroform, and the extract was washed with 10% HCl, saturated $NaHCO_3$ aqueous solution, and saturated NaCl aqueous solution, dried over Na_2SO_4, and evaporated to afford the amide (XVI) (3.7 g; 93%) as colorless needles, mp 157—158° (from ethanol). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3540, 3415 (NH_2), 1725 (CO_2Me) and 1680 ($CONH_2$). NMR ($CDCl_3$) ppm: 2.35—3.20 (4H, m, $C\underline{H}_2C\underline{H}_2$), 3.85 (3H, s, OMe), 3.94 (3H, s, OMe), 5.1—5.6 (2H, broad, NH_2) and 6.70, 7.55 (each 1H, d, J=9 Hz, C_5–H and C_4–H). *Anal.* Calcd. for $C_{12}H_{14}O_4NBr$: C, 45.58; H, 4.46; N, 4.43. Found: C, 46.07; H, 4.77; N, 4.38.

6-Bromo-3-methoxy-2-methoxycarbonylphenylpropiononitrile (XVII)——A mixture of the amide (XVI) (4 g), phosphoryl chloride (4 ml), and dry benzene (10 ml) was refluxed for 3 hr, and the excess of reagent and benzene were removed by distillation. The residue was treated with water and extracted with chloroform. The extract was washed with saturated $NaHCO_3$ aqueous solution and NaCl aqueous solution, dried over Na_2SO_4, and evaporated to give the nitrile (XVII) (3.18 g; 84%) as colorless prisms, mp 112—113° (from ethanol). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2250 (CN) and 1725 (CO_2Me). NMR ($CDCl_3$) ppm: 2.40—3.25 (4H, m, $C\underline{H}_2C\underline{H}_2$), 3.80 (3H, s, OMe), 3.94 (3H, s, OMe) and 6.73, 7.54 (each 1H, d, J=8 Hz, C_5–H and C_4–H). *Anal.* Calcd. for $C_{12}H_{12}O_3NBr$: C, 48.34; H, 4.06; N, 4.70. Found: C, 48.34; H, 4.20; N, 4.65.

4-Bromo-2-cyano-7-methoxyindan-1-one (XIX)——To a suspension of sodium amide in liquid ammonia [prepared from liquid ammonia (150 ml) and sodium (0.5 g) in the presence of a catalytic amount of ferric chloride hexahydrate] the nitrile (XVII) (1 g) was added in small portions with stirring and the resulting mixture was stirred for further 3 hr. After evaporation of ammonia, the residue was decomposed with crystalline NH_4Cl (2 g) and water (20 ml) and extracted with chloroform. The extract was washed with saturated NaCl aqueous solution, dried over Na_2SO_4, and evaporated to give the indanone (XIX) (100 mg; 11.2%) as yellow prisms, mp 192.5—194.5° (from benzene). IR ν_{max}^{KBr} cm^{-1}: 2250 (CN) and 1720 (CO). NMR ($CDCl_3$) ppm: 3.70 (1H, dd, J=8 and 6 Hz), 3.98 (3H, s, OMe), and 6.81, 7.70 (each 1H, d, J=9 Hz, C_5–H and C_4–H). *Anal.* Calcd. for $C_{11}H_8O_2NBr$: C, 49.65; H, 3.03; N, 5.26. Found: C, 49.64; H, 3.24; N, 5.30.

3-Methoxy-2-methoxycarbonylphenylpropionic Acid (XXII)——A solution of the monocarboxylic acid (XIV) (25 g) and sodium acetate (7 g) in acetic acid (250 ml) was shaken in a current of hydrogen in the presence of 30% palladium on carbon (3 g) at room temperature. After a calculated amount of hydrogen had been absorbed, an undissolved material was filtered off and the filtrate was evaporated *in vacuo* to give a syrup, which was extracted with ether. The extract was washed with saturated NaCl aqueous solution, dried over Na_2SO_4, and evaporated to afford the debrominated carboxylic acid (XXII) (16.8 g; 90%) as colorless plates, mp 113—114° (from benzene). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1715 (CO_2Me and CO_2H). NMR ($CDCl_3$) ppm: 2.40—3.07 (4H, m, $C\underline{H}_2C\underline{H}_2$), 3.80 (3H, s, OMe), 3.88 (3H, s, OMe), 6.76 (2H, dd, J=8 and 2.5 Hz, C_4–H and C_6–H), and 7.45 (1H, t, J=8, C_5–H). *Anal.* Calcd. for $C_{12}H_{14}O_5$: C, 60.06; H, 5.92. Found: C, 60.22; H, 5.93.

5-Methoxy-4-methoxycarbonylindan-1-one (XXIII)——A mixture of the carboxylic acid (XXII) (10 g) and polyphosphoric acid (150 g) was heated at 110° for 10 min. The resulting mixture was poured into ice-water and extracted with chloroform. The extract was washed with saturated $NaHCO_3$ aqueous solution and saturated NaCl aqueous solution, dried over Na_2SO_4, and evaporated to give the indanone (XXIII) (6.6 g; 72%) as colorless needles, mp 112.5—113.5° (from ether). IR ν_{max}^{KBr} cm^{-1}: 1715 (CO) and 1710 (CO_2Me). NMR ($CDCl_3$) ppm: 2.50—3.36 (4H, m, $C\underline{H}_2C\underline{H}_2$), 3.90 (3H, s, OMe), 3.93 (3H, s, OMe), and 6.87, 7.70, (each 1H, d, J=8 Hz, C_6–H and C_7–H). *Anal.* Calcd. for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49. Found: C, 65.73; H, 5.57.

2-Hydroxyimino-5-methoxy-4-methoxycarbonylindan-1-one (XXIV)——To a solution of the indanone (XXIII) (100 mg) in methanol (10 ml) was added isoamyl nitrite (120 ng), and, after heating at 50—60°, concentrated HCl (0.1 ml) was added to this mixture to separate a solid which was collected by filtration

and recrystallized from ethanol to give the hydroxyimino compound (XXIV) (90 mg; 80%) as a pale brown powder, mp 246—249°. IR ν_{max}^{KBr} cm^{-1}: 1725 (CO_2Me) and 1730 (CO). NMR ($CDCl_3$) ppm: 4.00 (8H, s, $C\underline{H}_2$ and 2×OMe) and 7.12, 8.08 (each 1H, d, J=9 Hz, C_6–H and C_7–H). *Anal.* Calcd. for $C_{12}H_{11}O_5N$: C, 57.83; H, 4.45; N, 5.62. Found: C, 58.30; H, 4.60; N, 5.47.

5-Methoxy-4-methoxycarbonylindan-1,2-dione (XXV)——A mixture of the α-hydroxyimino ketone (XXIV) (1 g), 37% formalin (5 ml) and concentrated HCl (1 ml) was heated at 60° for 10 min with stirring, and then diluted with water to separate a solid, which was collected by filtration and recrystallized from benzene to give the indan-1,2-dione (XXV) (1.85 g; 90%) as pale yellow needles, mp 204—205°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1760 and 1720 (CO). NMR ($CDCl_3$) ppm: 3.67 (2H, s, CH_2), 3.90 (3H, s, OMe), 4.00 (3H, s, OMe), and 7.07, 8.00 (each 1H, d, J=8 Hz, C_6–H and C_7–H). *Anal.* Calcd. for $C_{12}H_{10}O_5$: C, 61.54; H, 4.30. Found: C, 61.47; H, 4.23.

1′,2,2′,3,3′,4′-Hexahydro-5-methoxy-4-methoxycarbonylspiro[indene-2,1′-carbolin]-1-one (XXVI)——A solution of the diketone (XXV) (6.0 g) and tryptamine hydrochloride (5.03 g) in ethanol (50 ml) was refluxed for 0.5 hr and the solvent was then distilled off *in vacuo*. The residue was recrystallized from methanol to give the β-carboline (XXVI) hydrochloride (8.5 g; 89.6%) as colorless needles, mp 132—136°. IR ν_{max}^{KBr} cm^{-1}: 1705 (CO). NMR ($CDCl_3$) ppm: 2.9—3.25 (4H, m, $ArC\underline{H}_2C\underline{H}_2N\langle$), 3.43, 3.53 (each 1H, d, J=3 Hz, $ArC\underline{H}_2C\langle$). 3.77 (3H, s, OMe), 6.90, 7.80 (each 1H, d, J=8 Hz, C_6–H and C_7–H), and 7.00—7.57 (4H, m, ArH). *Anal.* Calcd. for $C_{22}H_{20}O_4N_2\cdot HCl$: C, 64.00; H, 5.13; N, 6.79. Found: C, 64.23; H, 5.33; N, 6.64.

Photolysis of the Spirobenzyl-β-carboline (XXVI)——A solution of the spirobenzyl-β-carboline (XXVI) (500 mg) in dry tetrahydrofuran (500 ml) was irradiated with a Hanovia 450 W mercury lamp in a current of nitrogen at room temperature for 3 hr, and the separated material was collected by filtration. Recrystallization from methanol gave the decadehydroyohimbane (XXVII) (90 mg; 20%) as yellow needles, mp 245—248°. IR ν_{max}^{KBr} cm^{-1}: 3350 (NH), 1720 (CO_2Me), and 1638 (C=N). NMR ($CDCl_3+CF_3CO_2H$) ppm: 3.30—3.80 (4H, m, $C\underline{H}_2C\underline{H}_2$), 4.17 (6H, s, 2×OMe), 7.17—7.87 (6H, m, ArH), 8.30 (1H, s, C_{14}–H), and 9.30 (1H, s, C_{20}–H). Mass Spectrum *m/e*: 359 (M^+). UV λ_{max}^{MeOH} nm: 355, 342, 319 and 260. The mother liquor in case of collection of the separated material was evaporated *in vacuo* and the resulting residue was extracted with chloroform. The extract was washed with 10% HCl and water, dried over Na_2SO_4, and evaporated to afford the decadehydroyohimban-21-one (XXVIII) (400 mg; 13%) as yellow needles, mp>300° (from methanol). IR ν_{max}^{KBr} cm^{-1}: 3300 (NH), 1700 (CO_2Me), and 1645 (CON). UV λ_{max}^{MeOH} nm: 378, 359, 345^{sh}, 295, 284, and 257. NMR ($CDCl_3$) ppm: 3.03 (2H, t, J=7 Hz, $ArC\underline{H}_2CH_2N$), 3.73 (3H, s, OMe), 4.10 (3H, s, OMe), 4.40 (2H, t, J=7 Hz, $ArCH_2C\underline{H}_2N$), 6.53 (1H, s, C_{14}–H), 6.80, 8.40 (each 1H, d, J=9 Hz, C_{18}–H and C_{19}–H), 7.07—7.67 (4H, ArH), and 8.8 (1H, broad s, NH). Mass Spectrum *m/e*: 374 (M^+). *Anal.* Calcd. for $C_{22}H_{18}O_4N_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.22; H, 5.06; N, 6.98.

15,16,17,18,19,20-Hexadehydro-O-methylyohimbine (XXIX)——a) From Lactam (XXVIII): A solution of the lactam (XXVIII) (120 mg) in phosphoryl chloride (5 ml) was refluxed for 1 hr. After evaporation of the excess of reagent, the residue (XXX) was dissolved in dry methanol (10 ml), to a solution of which was added sodium borohydride (20 mg) with stirring at 0°. The mixture was stirred for 0.5 hr at 0° and then methanol was removed by distillation. The residue was decomposed with water and extracted with chloroform. The extract was washed with water, dried over Na_2SO_4, and evaporated to give the hexadehydroyohimbine (XXIX) (95 mg; 84%) as pale yellow needles, mp 185° (from methanol). IR ν_{max}^{KBr} cm^{-1}: 3400 (NH), 2725—2850 (Bohlmann bands), and 1720 (CO_2Me). UV λ_{max}^{MeOH} nm: 291 and 284. NMR ($CDCl_3$) ppm: 3.47 (3H, s, OMe), 3.93 (3H, s, OMe), 4.05 (1H, d, J=15 Hz, C_{21}–H), 6.60 (1H, d, J=8 Hz, C_{18}–H), and 8.50 (1H, broad s, NH). Mass Spectrum *m/e*: 362 (M^+). *Anal.* Calcd. for $C_{22}H_{20}O_3N_2\cdot 1.5H_2O$: C, 67.85; H, 6.47; N, 7.19. Found: C, 67.93; H, 5.98; N, 6.89.

b) From the Decadehydroyohimbane (XXVII): To a solution of the decadehydroyohimbane (XXVII) (80 mg) in methanol was added in small portions sodium borohyride (80 mg) with stirring at 0° and the mixture was stirred for 10 min at 0°. After evaporation of methanol, the residue was worked up as above to give hexadehydroyohimbine (XXIX) (57.7 mg; 76%), mp 185°, which was identical in all aspects with the sample prepared by the method (a).

1,2,3,4,5,6,7,12b-Octahydro-3-cyanoindolo[2,3-*a*]quinolizin-2-one (XXXIII)——To a solution of the nitrile (XXXII) (1.735 g, 5.6 mmole) in dry benzene (10 ml) was added 50% NaH (535 mg; 11.1 mmole), and the mixture was refluxed for 2 hr under a current of nitrogen. After decomposition of the excess of reagent with water, the resulting mixture was neutralized with 4% acetic acid, and the organic layer was separated and evaporated to leave a residue (1.2 g), which was chromatographed on silica gel (50 g) by elution with chloroform–methanol to give the ketone (XXXIII) as a syrup. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2250 (CN) and 1720 (CO). Mass Spectrum *m/e*: 265 (M^+).

1,2,3,4,5,6,7,12b-Octahydroindolo[2,3-*a*]quinolizine-2-one (XXXIV)——A mixture of the nitrile (XXXIII) (265.3 mg, 1 mmole) and 10% H_2SO_4 (10 mg) was refluxed for 20 hr under a current of nitrogen. After the reaction, an equal volume of ice and water was added to the resulting mixture, and an insoluble material was removed by filtration. The filtrate was basified with 12 N NaOH aqueous solution and extracted with ether. The extract was washed with water, dried over Na_2SO_4, and evaporated *in vacuo* to give the ketone (XXXIV) (180.2 mg; 75%) as a colorless powder, mp 177—180° (from benzene). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3475

(NH), 2760—2850 (Bohlmann bands), and 1717 (CO). NMR ($CDCl_3$) ppm: 8.07 (1H, NH). Mass Spectrum *m/e*: 240 (M^+). *Anal.* Calcd. for $C_{15}H_{16}ON_2$: C, 74.97; H, 6.71; N, 11.66. Found: C, 75.25; H, 6.59; N, 11.36.

15, 16-Dehydroyohimbinone (XXXVII)——A solution of the ketone (XXXIV) (1 g, 4.2 mmole) and pyrrolidine (2 g, 28.1 mmole) in dry benzene (20 ml) was refluxed for 7.5 hr in a current of nitrogen, and the reagent and solvent were distilled off *in vacuo* to leave the enamine (XXXV) as a reddish brown syrup [IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1640; NMR ($CDCl_3$) ppm: 4.2—4.6 (>C=CH)], to a solution of which in dry benzene (20 ml) was added methyl 3-oxo-4-pentenoate (XXXVI)[23] (586.2 mg, 4.6 mmole). The resulting mixture was refluxed for 10 min under a current of nitrogen, and then a mixture of sodium acetate (5 g), acetic acid (10 ml) and water (10 ml) was added to the above reaction mixture and this solution was refluxed for additional 4 hr under a current of nitrogen. The reaction mixture was made basic with saturated $NaHCO_3$ aqueous solution and concentrated ammonia and extracted with benzene and then with chloroform. The extracts were washed with saturated NaCl solution, dried over Na_2SO_4, and evaporated to leave a reddish brown syrup (758 mg from benzene extract and 789 mg from chloroform extract, respectively). Both materials were combined and subjected to preparative thick layer chromatography on silica gel developed by chloroform–methanol (v/v 9: 1) to give the 15,16-dehydroyohimbinone (XXXVII) (251.2 mg; 17.2%) as colorless crystals, mp 192—193° (lit.,[25] 188—189°) (from methanol). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3475 (NH), 2760—2850 (Bohlmann bands), 1725 (CO), 1675 (CO), and 1625 (C=C). UV λ_{max}^{MeOH} nm: 291, 283, and 274. NMR ($CDCl_3$) ppm: 3.93 (3H, s, CO_2Me). Mass Spectrum *m/e*: 350 (M^+). *Anal.* Calcd. for $C_{21}H_{22}O_3N_2 \cdot 0.25H_2O$: C, 71.06; H, 6.39; N, 7.89. Found: C, 71.31; H, 6.17; N, 7.60.

(±)-Yohimbinone (XXXVIII)——A mixture of dehydroyohimbinone (XXXVII) (124.6 mg) and 30% palladium on carbon (60 mg) in dry methanol (30 ml) was shaken in a current of hydrogen at room temperature and atmospheric pressure for 24 hr. After separation of the catalyst, methanol was distilled off *in vacuo* and the residue was extracted with chloroform. The extract was washed with saturated $NaHCO_3$ aqueous solution and saturated NaCl aqueous solution, dried over Na_2SO_4, and evaporated to leave a residue (120.3 mg), which was subjected to preparative thick layer chromatography on silica gel developed by chloroform–methanol (v/v 9: 1) to give (±)-yohimbinone (XXXVIII) as yellow needles, mp 239° (lit.,[25] 238—239°) (from methanol). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3480 (NH) and 1740 (CO). NMR ($CDCl_3$) ppm: 3.83 (3H, s, CO_2Me). Mass Spectrum *m/e*: 352 (M^+). *Anal.* Calcd. for $C_{21}H_{24}O_3N_2 \cdot 0.25H_2O$: C, 70.66; H, 6.91; N, 7.85. Found: C, 70.77; H, 6.68; N, 7.71.

Acknowledgement We thank Mrs. A. Sato, Mrs. C. Koyanagi, Miss R. Kato, Miss R. Suenaga, Miss E. Nagaoka, Miss Y. Yokohama, and Mr. K. Kawamura, Pharmaceutical Institute, Tohoku University, for microanalyses and spectral measurements and Dr. K. Okui, Research Laboratories, Chugai Pharmaceutical Co., Ltd., Tokyo and Dr. N. Koga, Research Laboratories, Daiichi Seiyaku Co., Ltd., Tokyo, for providing natural yohimbine and tryptamine. We also thank Takeda Science Foundation for the financial support.