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Studies on the Syntheses of Heterocyclic Compounds. DCLXXI.[1] An Alternative Total Synthesis of Yohimbine

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Birch reduction of 16-carboxy-15,16,17,18,19,20-hexadehydro-17-methoxyyohimbane (XII), followed by esterification with diazomethane, gave 15,17,18,20-tetradehydro-17-methoxy-16-methoxycarbonylyohimbane (XIII), which was converted into 15,16-dehydroyohimbinone (II). This was correlated with yohimbine (IV) by the present authors.

The synthetic challenge of indole alkaloids[3] has attracted much attention for many workers. A crucial step in a synthesis of yohimbine (IV), a typical example of indole alkaloids, is the introduction of two functionalized groups at C-16 and C-17 positions with keeping *trans* fused D—E ring under an appropriate stereochemical control. Before we started our work on the synthesis of yohimbine, stereoselective total synthesis of yohimbine had been reported by three groups.[4-6] In 1975, we also achieved a total synthesis of yohimbine from the octahydroindolo[2,3-*a*]quinolizin-2-one (I) by using Robinson annelation method *via* 15,16-dehydroyohimbinone (II) and yohimbinone (III).[7] Furthermore, we investigated an alternative synthesis of IV, and here wish to report a formal total synthesis of yohimbine by an application of Birch reduction, whose synthetic approach had been initiated by Swan in 1950.[8]

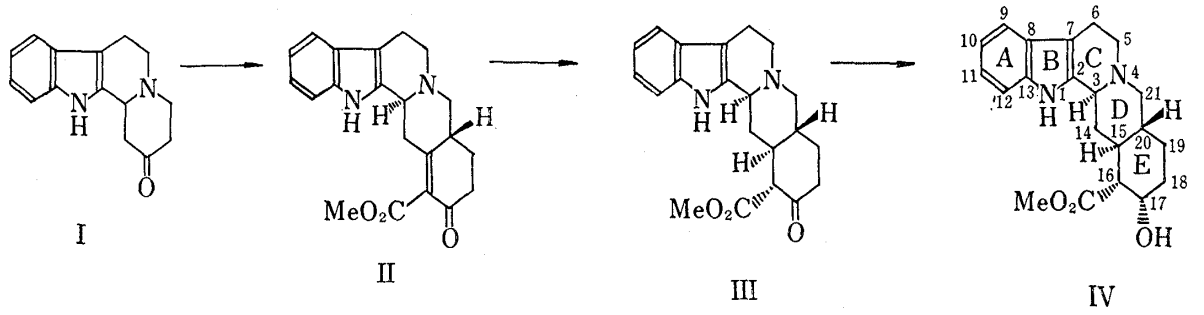

Chart 1

Previously, we have developed three new synthetic methods of 15,16,17,18,19,20-hexadehydroyohimbane ring system,[9-11] whose methods have an advantage over the usual Mannich reaction method for the synthesis of the yohimbanes having an electron withdrawing group on

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ring E, and recently, we have reported a synthesis of O-methyl-15,16,17,18,19,20-hexadehydroyohimbine (VIII) by our method[11] from the spirobenzyl-β-carobline (VII) derived from tryptamine (V) and the indandione (VI).[7] This product has all functional groups in yohimbine (IV), and, therefore, we examined a conversion of O-methylhexadehydroyohimbine (VIII) into yohimbine (IV) as follow.

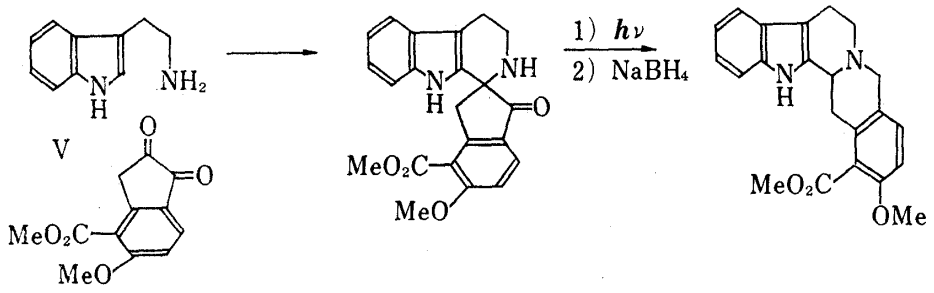

Chart 2

O-Methylhexadehydroyohimbine (VIII) was treated with lithium and liquid ammonia in the presence of 2-propanol as proton source and dry tetrahydrofuran as cosolvent at −78° to give 15,17,18,20-tetradehydro-16-hydroxymethyl-17-methoxyyohimbane (IX), mp 138—142°, *m/e* 336 (M^+), in 32.3% yield, which showed a typical enol ether system[10] at 1705 and 1665 cm^{-1} and lacked a carbonyl absorption in the infrared (IR) spectrum. Moreover, the nuclear magnetic resonance (NMR) spectrum (δ in $CDCl_3$) revealed a methylene resonance in a hydroxymethylene group and a methyl resonance in enolic methyl ether[10] at 3.73 and 3.57 in addition to olefinic proton at 4.77 as a triplet having J=3 Hz.[10] The stereochemistry of a hydroxymethylene group could not be determined. Oxidation of this product (IX) to the corresponding carboxylic acid (X) was examined under several methods, but unsuccessful results were obtained. For example, an oxidation of IX with dimethyl sulfoxide and acetic

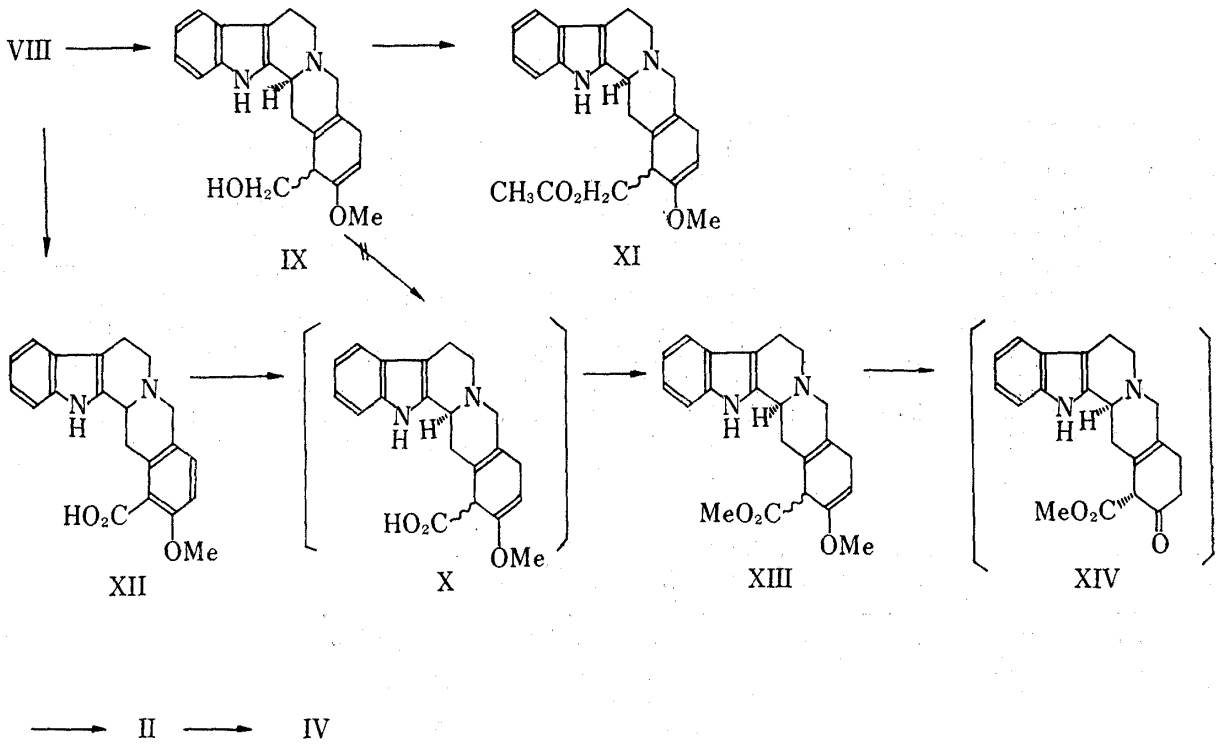

Chart 3

acid[12] for 30 hr at room temperature gave the corresponding acetate (XI), which was unstable in the air and showed a carbonyl absorption at 1715 cm^{-1} in IR spectrum and acetyl methyl and methylene protons at δ 1.93 and 4.17 in NMR spectrum.

Secondly, we examined a Birch reduction of the carboxylic acid (XII) in order to get our expected carboxylic acid (X) directly. Thus, hydrolysis[13,14] of the O-methylhexadehydroyohimbine (VIII) with aqueous methanolic potassium hydroxide under reflux for 6 hr gave, in 62.5% yield, the corresponding carboxylic acid (XII), which was isolated easily as its hydrochloride, mp>300°, *m/e* 348 (M^+—HCl), showing carboxyl absorption at 1715 cm^{-1} in its IR spectrum. This carboxylic acid was subjected to Birch reduction[14] with lithium and liquid ammonia in the presence of 2-propanol and hexamethylphosphoric triamide as a cosolvent at −78° to give the expected carboxylic acid (X), which, without isolation, was treated immediately with diazomethane to afford 15,17,18,20-tetradehydro-17-methoxy-16-methoxycarbonylyohimbane (XIII), mp 117—119°, *m/e* 364 (M^+), in 35.3% yield based on the starting carboxylic acid (XII). This product showed Bohlmann bands[15] at 2850—2725, carbonyl group at 1730 and enol ether at 1705 and 1668 cm^{-1} in IR spectrum and two methoxyl resonances at δ 3.55 and 3.60, methine proton on C-16 at 3.80, and olefinic proton at 4.83 as a triplet having J=3.5 Hz in NMR spectrum. Hydrolysis of the enol ether of this product with oxalic acid in aqueous methanol at 40° for 24 hr gave the β,γ-unsaturated ketone (XIV)[16] [$\nu_{max}^{CHCl_3}$ 1735 and 1720 cm^{-1}], which without purification was treated with concentrated hydrochloric acid in methanol at room temperature for 6 hr to afford 15,16-dehydroyohimbinone (II), mp 196—197° (lit., mp 192—193°,[7] mp 194—195°[5]), *m/e* 350 (M^+), in 41.5% yield. The IR [ν_{max}^{KBr} 3475 (NH), 2850—2725 (Bohlmann bands), 1720 (CO_2Me), 1668 (CO), and 1622 cm^{-1} (C=C)] and NMR [δ ($CDCl_3$), 3.93 (3H, s, Me) and 8.05 (1H, broad s, NH)] spectra of this product were superimposable upon those of the authentic sample,[7] which has already been converted into yohimbine (IV) through two steps in our laboratory.[7] Recently, Szántay[16] converted 15,20-dehydroyohimbinone (XIV), prepared by a different method from our route, into alloyohimbinone and epi-alloyohimbinone by catalytic reduction on palladium.

Thus we have accomplished an alternative total synthesis of yohimbine by a Birch reduction method which has long been expected.

Experimental[17]

15,17,18,20-Tetradehydro-16-hydroxymethyl-17-methoxyyohimbane (IX)——A solution of O-methyl-15,16,-17,18,19,20-hexadehydroyohimbine[7] (VIII) (500 mg) in dry tetrahydrofuran (10 ml) and 2-propanol (2 ml) was added to liquid ammonia (300 ml), to a mixture of which was added metallic Li (200 mg) in three portions with stirring at −78°. After stirring for 5 hr at −78°, an excess of Li was decomposed with crystalline NH_4Cl (1 g) and ammonia was evaporated with stirring. The residue was extracted with chloroform, and the extract was washed with water, dried over Na_2SO_4, and evaporated *in vacuo* to leave a viscous syrup, which was purified on silica gel column chromatography by elution with chloroform-benzene (1 : 4 v/v) to give the tetradehydroyohimbane (IX) (150 mg, 32.3% yield) as colorless needles, mp 138—142° (from methanol). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3470 (NH), 1705 and 1665 (enol ether). NMR ($CDCl_3$) ppm: 3.57 (3H, s, >C=C–OMe), 3.73 (2H, broad s, $C\underline{H}_2OH$), 4.77 (1H, t, J=3 Hz, >C=CH–) and 8.07 (1H, broad s, NH). Mass Spectrum *m/e*: 336 (M^+), 318 (M^+ −18, 100%). *Anal.* Calcd. for $C_{21}H_{24}O_2N_2 \cdot 0.33H_2O$: C, 73.65; H, 7.26; N, 8.18. Found: C, 74.09; H, 7.42; N, 8.15.

Oxidation of the Tetradehydroyohimbane (IX)——A mixture of IX (33 mg), dry dimethyl sulfoxide (0.3 ml) and acetic anhydride (0.2 ml) was stirred for 30 hr at room temperature in a current of nitrogen, and dilut-

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17) All melting points are uncorrected and were measured with a Yanagimoto micro melting point apparatus (MP-22). IR spectra were taken with a Hitachi 215 grating spectrophotometer, NMR spectra with a JEOL PMX-60 spectrometer with Me_4Si as internal standard, and mass spectra with a Hitachi RMU-7 spectrometer.

ed with water (5 ml), and then extracted with ether. The extract was washed with 5% $NaHCO_3$ aqueous solution and saturated NaCl aqueous solution, dried over Na_2SO_4, and evaporated *in vacuo* to give the O-acetate (XI) as a yellow powder [IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3475 (NH), 2760—2850 (Bohlmann bands), 1715 (OCOMe), and 1662 (enol ether); NMR ($CDCl_3$) ppm: 1.93 (3H, s, $MeCO_2$), 3.52 (3H, s, OMe), 4.17 (2H, d, J=4 Hz, $C\underline{H}_2OCO$-Me), and 4 73 (1H, t, J=3 Hz, >C=CH-)], which was unstable in the air and could not be purified by recrystallization or chromatographic method.

16-Carboxy-15,16,17,18,19,20-hexadehydro-17-methoxyyohimbane (XII)——A mixture of VIII (135 mg) and 40% KOH aqueous solution (3 ml) and methanol (5 ml) was refluxed for 6 hr in a current of nitrogen. After cooling, the reaction mixture was acidified with conc. HCl and the separated solid was filtered off. The filtrate was evaporated *in vacuo* and the residue was extracted with anhydrous methanol. The extract was evaporated to give the hydrochloride of XII (90 mg, 62.5%) as a colorless powder, mp>300° (from methanol). IR ν_{max}^{KBr} cm^{-1}: 3340 (NH) and 1715 (CO_2H). Mass Spectrum *m/e*: 348 (M^+). *Anal.* Calcd. for $C_{21}H_{21}O_3N_2Cl \cdot 0.6H_2O$: C, 63.58; H, 5.49. Found: C, 63 48; H, 5·61.

15,17,18,20-Tetradehydro-17-methoxy-16-methoxycarbonylyohimbane (XIII)——To an anhydrous liquid ammonia (150 ml) was added a solution of the carboxylic acid (120 mg) in dry hexamethylphosphoric triamide (10 ml) and 2-propanol (1 ml), to a mixture of which metallic Li (200 mg) was added in three portions with stirring at −78°. After stirring for 3 hr at −78°, an excess of Li was decomposed with crystalline NH_4Cl (3 g) and ammonia was evaporated under stirring. To a residue was added diazomethane in ether [prepared form *p*-tolylsulfonylmethylnitrosamide (7 g)][18] and a mixture was stirred for 1 hr at room temperature. After evaporation of ether, the residue was extracted with benzene The extract was washed with water, dried over Na_2SO_4, and evaporated *in vacuo* to leave a caramel, which was subjected to silica gel column chromatography and eluted with chloroform–benzene (1: 4 v/v) to give the ester (XIII) (40 mg, 35.3%) as colorless plates, mp 117—119° (from methanol). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3480 (NH), 2850—2725 (Bohlmann bands), 1730 (CO_2Me), and 1705 and 1668 (enol ether). NMR ($CDCl_3$) ppm: 3.55 (3H, s, C=C-OMe), 3.60 (3H, s, CO_2Me), 3.80 (1H, s, $C\underline{H}CO_2Me$), 4.83 (1H, t, J=3.5 Hz,=$C\underline{H}$-CH_2), and 7.96 (1H, broad s, NH). Mass Spectrum *m/e*: 364 (M^+). *Anal.* Calcd. for $C_{22}H_{24}O_3N_2 \cdot H_2O$: C, 69. 09; H, 6.85; N, 7.33. Found: C, 69.45; H, 7.04; N, 7.01.

15,16-Dehydroyohimbinone (II)——A solution of oxalic acid (200 mg) in water (5 ml) and methanol (15 ml) was added to a solution of XIII (20 mg) in methanol (5 ml), and the resulting mixture was stirred for 24 hr at 40°, and then methanol was evaporated *in vacuo* The residue was extracted with chloroform. The extract was washed with 5% $NaHCO_3$ aqueous solution and then saturated NaCl aqueous solution, dried over Na_2SO_4, and evaporated *in vacuo* to leave a viscous syrup [$\nu_{max}^{CHCl_3}$ cm^{-1}: 1735 and 1720]. This was taken in methanol (20 ml), to a solution of which was added conc. HCl (0.5 ml) and stirred for 6 hr at room temperature. After evaporation of methanol at room temperature, the residue was basified with 10% NH_4OH and extracted with chloroform. The extract was washed with water, dried over Na_2SO_4, and evaporated *in vacuo* to leave a viscous syrup, which was chromatographed on silica gel by elution with chloroform–benzene (1: 4 v/v) to give 15,16-dehydroyohimbinone (II) (8 mg, 41.5%) as colorless needles, mp 196—197° (from methanol). IR ν_{max}^{KBr} cm^{-1}: 3475 (NH), 2850—2725 (Bohlmann bands), 1720 (CO_2Me), 1668 (CO), and 1622 (>C=C<). NMR ($CDCl_3$) ppm: 3.93 (3H, s, OMe) and 8.05 (1H, broad s, NH). Mass Spectrum *m/e*: 350 (M^+). The IR and NMR spectra of this product were identical with those of the authentic sample.[7]

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