AN ALTERNATIVE SYNTHESIS OF (±)-YOHIMBINE

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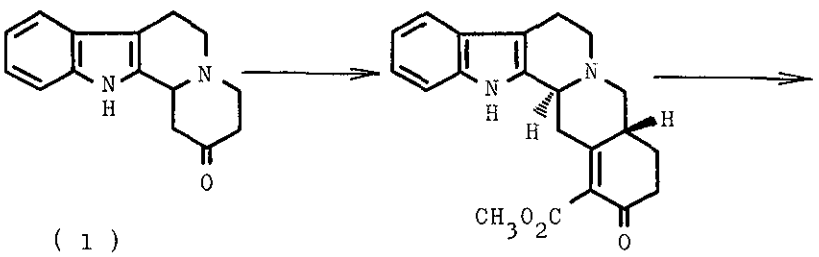
Birch reduction of 16-carboxyl-15,16,17,18,19,20-hexadehydro-17-methoxyyohimbane (8), followed by esterification gave 15,17,18,20-tetradehydro-17-methoxy-16-methoxycarbonylyohimbane (10), which was treated with oxalic acid and then hydrochloric acid to afford 15,16-dehydroyohimbinone (2) that had been already correlated with (±)-yohimbine (4).

Previously we have reported a total synthesis of (±)-yohimbine (4) from the octahydroindolo[2,3-a]quinolizin-2-one (1) by using a Robinson annalation method via 15,16-dehydroyohimbinone (2) and (±)-yohimbinone (3).[1] In this communication we wish to report an alternative total synthesis of (±)-yohimbine (4) by application of Birch reduction[2] of the 15,16,17,18,19,20-hexadehydroyohimbane derivative (8).

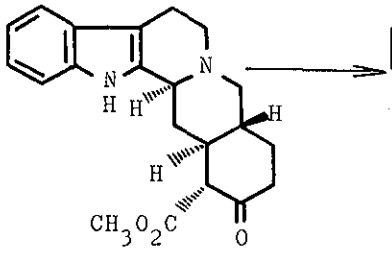
15,16,17,18,19,20-Hexadehydro-O-methylyohimbine (5), which had been synthesised in our laboratory,[3] was reduced with lithium in liquid ammonia in the presence of 2-propanol to give 15,17,18,20-tetradehydro-16-hydroxymethyl-17-methoxyyohimbane (6), mp 138 - 142° (from methanol), m/e 364 (M^+), in 32.3 % yield, which showed a typical enol ether system[2] at 1705 and 1665 cm^{-1} in ir ($CHCl_3$) spectrum and δ 3.58 (OCH_3) and 4.63 (1H, t, J 3 Hz, =CH) in nmr spectrum ($CDCl_3$). Moreover, nmr

Chart 1

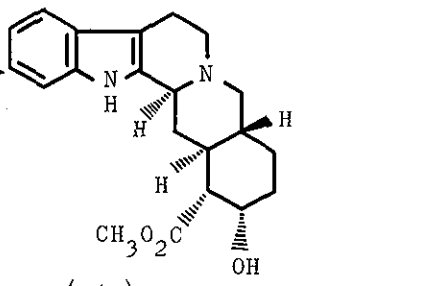


(1)

(2)



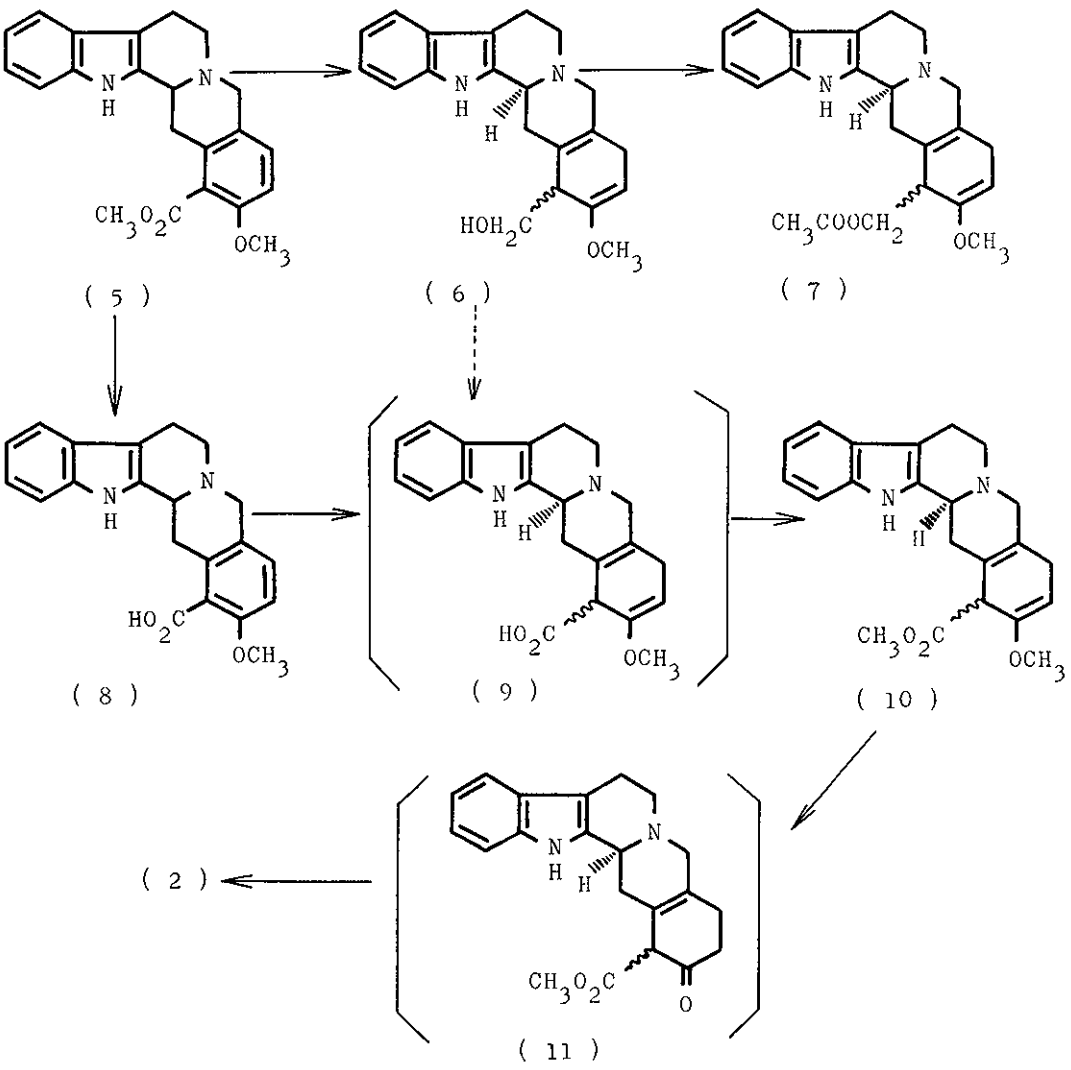
(3)



(4)

spectrum revealed a methylene resonance in a hydroxymethylene group at 3.73 as a broad signal. The stereochemistry of a hydroxymethylene residue could not be determined. Oxidation of this product (6) to the corresponding carboxylic acid (9) was examined under several conditions, but unsuccessful results were oftained. For example, oxidation of 6 with dimethyl sulphoxide and acetic anhydride at room temperature for 30 h gave the corresponding acetate (7), mp 159 - 162°, which showed 3470 (NH), 1715 ($OCOCH_3$) and 1665 ($C=C-OCH_3$) cm^{-1} in ir and δ 1.93 ($COCH_3$), 3.53 (OCH_3), 4.17 (2H, d, J 4 Hz, $C\underline{H}_2OAc$), and 4.73 (1H, t, J 3 Hz, $C=C\underline{H}-CH_2$) in nmr spectra.

Chart 2



Secondly, we examined a Birch reduction of the carboxylic acid (8) in order to get 9. Thus, hydrolysis[4] of the hexadehydro-O-methylyohimbine (5) with aqueous methanolic potassium hydroxide for 6 h under reflux gave in 62.5 % yield the corresponding carboxylic acid (8), isolated as hydrochloride, mp > 300° (from methanol), ν_{max} (KBr) 1715 cm^{-1}. This carboxylic acid was subjected to Birch reduction with lithium in liquid ammonia in the presence of 2-propanol and hexamethylphosphoric triamide (HMPT) to give the expected carboxylic acid (9), whose solution in HMPT was immediately treated with diazomethane to furnish the 15,17,18,20-tetradehydro-17-methoxy-16-methoxycarbonylyohimbane (10), mp 107 - 111°, m/e 364 (M^+), in 35.3 % yield. This product showed Bohlmann bands at 2750 - 2850, carbonyl group at 1730 and enol ether at 1705 and 1675 cm^{-1} in ir, and enolic methoxyl at δ 3.57, ester methoxyl at 3.63, methine proton at 3.80 (s) and olefinic proton at 4.87 (t, J 3.5 Hz) in nmr spectra. Hydrolysis of an enolic ether of 10 with oxalic acid in aqueous methanol at 40° for 24 h afforded the β,γ-unsaturated ketone (11) [ν_{max} ($CHCl_3$) 1735 and 1720 cm^{-1}], which without purification was treated with methanolic hydrochloric acid at room temperature for 6 h to give 15,16-dehydroyohimbine (2), mp 196 - 197° [lit., mp 189.5°,[1] mp 194 - 195°[5]], m/e 350 (M^+), in 41.5 % yield. The ir and nmr spectra of our product were superimposable upon those of the authentic sample[1] which have already been converted into (±)-yohimbine in our laboratory.[1]

Thus we have accomplished a total synthesis of (±)-yohimbine.

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