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SYNTHETIC ENTRY INTO YOHIMBINOID ALKALOIDS AND NOVEL SYNTHESIS OF (±)-17-METHOXY-HEXADEHYDROYOHIMBANE

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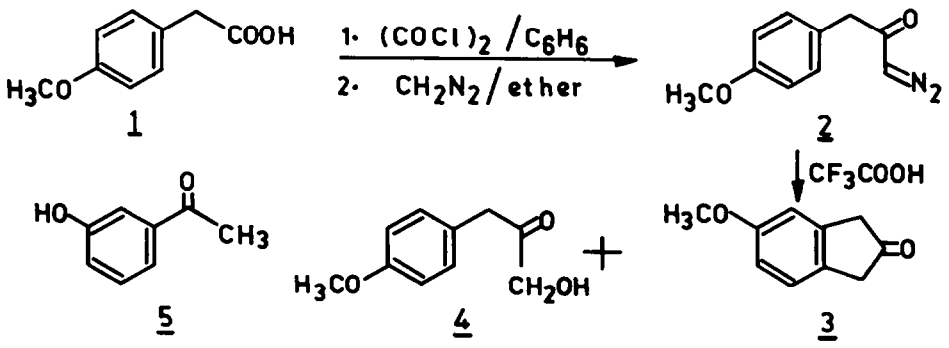
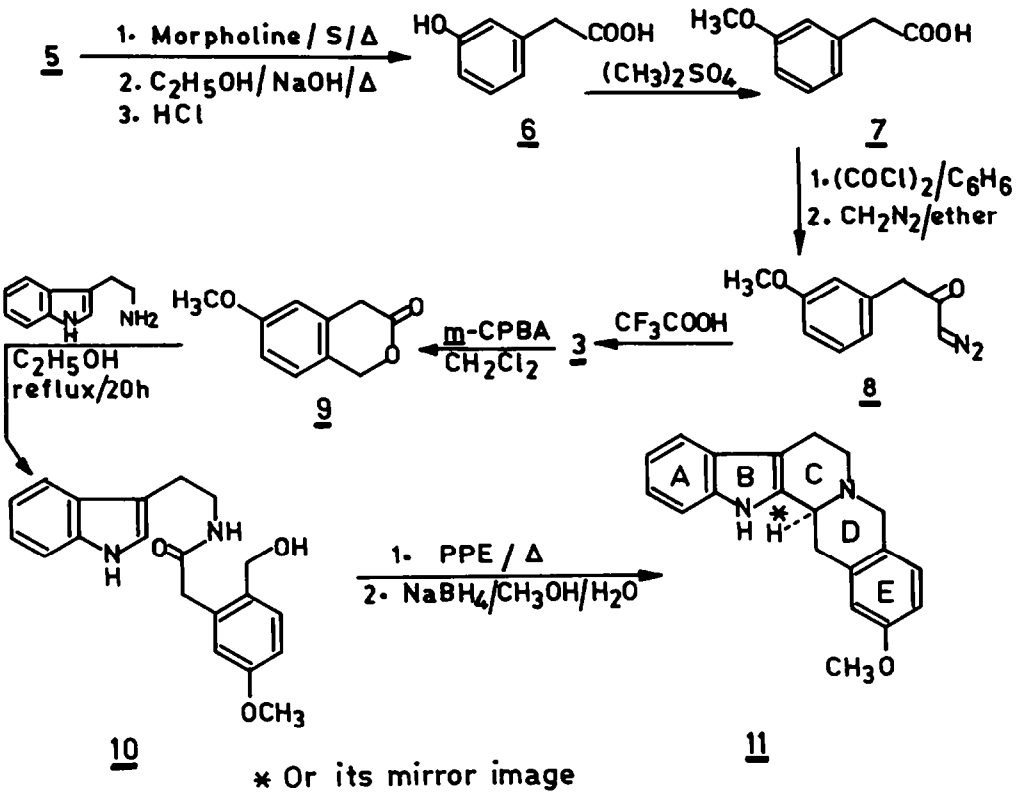
Abstract - A novel method has been developed for the synthesis of (±)-17-methoxy-hexadehydroyonimbane (11) which could be converted to yohimbinoid alkaloids through a sequence of reactions. The approach for the desired synthesis was based on the choice of 6-methoxy-3-isochromanone (9) as a suitable synthon for the construction of non-nitrogeneous moiety. The nitrogeneous portion was developed from tryptamine. An appropriate condensation of 9 and tryptamine yielded (±)-17-methoxy-hexadehydroyohimbane. 6-Methoxy-3-isochromanone (9) which is a δ-lactone was prepared from 5-methoxy-2-indanone (3) by Baeyer-Villiger oxidation. A simple procedure for the synthesis of 3 has been developed by a unique acid catalysed diazoketone cyclisation. It deserves mention in this connection that the acid catalysed cyclization was facile with 3-methoxybenzyl diazomethyl ketone (8) but 4-methoxybenzyl diazomethyl ketone (2) was reluctant to cyclise. All attempts in this direction resulted in the formation of a hydroxy ketone (4) as a major product.

17-Methoxy-hexadehydroyohimbane (11) a key synthon in the synthesis of (±)-alloyohimbine[1] and (±)-rauwolscine[1] has been synthesised by a novel procedure.

6-Methoxy-3-isochromanone (9) was used as an intermediate species for the desired synthesis. It was obtained from 5-methoxy-2-indanone (3) by Baeyer-Villiger oxidation with *m*-chloroperbenzoic acid (Scheme 1).

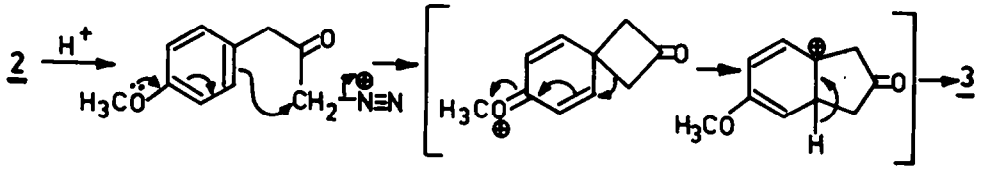


Scheme 1 (contd.)



Scheme 1

The indanone derivative 3 was prepared via a unique diazoketone cyclization procedure. For this purpose 4-methoxy-phenylacetic acid (1) was converted into its diazoketone (2) in good yield. The diazoketone 2 on treatment with trifluoroacetic acid at -20° afforded the hydroxy ketone 4 as a major product, the desired indanone (3) being obtained in very poor yield. Thus the conventional mechanism of diazoketone cyclization through the spiro intermediate as observed by Mander et al[2], could not operate to the desired extent in this system (Scheme 2).



Scheme 2

In order to improve the yield of the indanone derivative (3), 3-methoxy-phenylacetic acid (7) and the intermediate diazoketone 8 were used. The latter on cyclization with TFA resulted in the synthesis of 3 in good yield. The cyclization proceeded through Friedel-Crafts type mechanism with the direct participation of methoxyl group which increases the electron density at the para position

as a result of which cyclization was facile with good yield (Scheme 3).

Scheme 3

3-Methoxy-phenylacetic acid (7) was prepared from 3-hydroxy-acetophenone (5) by Willgerodt reaction followed by the methylation of the corresponding 3-hydroxy-phenylacetic acid (7) with dimethyl sulphate. Indanone derivative 3 on Baeyer-Villiger oxidation with m-CPBA in dry dichloromethane at 0° afforded 6-methoxy-3-isochromanone (9) [ν_{max}(KBr) 1740 cm^{-1}] as only isolable product in 43% yield out of two theoretically possible isochromanones. The structure of the lactone (9) was confirmed from its spectral data and also by comparison with the authentic sample[3]. For the synthesis of 11, the intermediate substituted hydroxy amide 10 was obtained by condensing tryptamine with lactone (9) in refluxing absolute ethanol in 83% yield. The structure was proved by mass [m/z 338 (M^+), 320 (M^+-H_2O)], IR [ν_{max}(KBr) 3280 (OH), 3200 and 3060 (NH) and 1610 cm^{-1} (C=O)], UV [λ_{max}(EtOH) 290, 282 and 224 nm] and 80 MHz ^{1}H-NMR spectra [δ(d_6-DMSO) 3.64 (3H, s, OMe), 4.38 (2H, d, J = 5 Hz, $-CH_2OH$, collapses to a singlet on shaking with D_2O), 5.03 (1H, t, J = 5 Hz, $-CH_2OH$), 10.71 (1H, s, for indole -NH)]. With D_2O -NH proton is found to be missing in the pmr spectra.

(±)-17-Methoxy-hexadehydroyohimbane (11) was synthesized from the hydroxy amide (10) by Bischler-Napieralski cyclization with polyphosphate ester followed by sodium borohydride reduction. The double cyclization of 10 with the formation of C and D rings occurred possibly via the imide intermediate. The latter was not isolated. The reaction mixture was directly reduced with sodium borohydride which afforded a gummy mass. From the reduction product only 11 could be obtained. Such polyphosphate ester cyclization to an imine is known in the literature[4,5]. Double cyclization as observed in our case has also been reported with $POCl_3$[6]. In our case we presume that prior to the cyclization of ring C (through Bischler-Napieralski reaction) cyclization of D ring occurred followed by the ring closure of C. The IR spectrum of the compound (11) showed the characteristic absorption band of indole NH at 3440 cm^{-1} while the UV [λ_{max}(EtOH) 290, 284 and 225 nm and mass spectra m/z 304 (M^+), 169, 144 and 134] indicated the presence of hexadehydroyohimbane system[7]. The structure was further supported by its 200 MHz ^{1}H-NMR spectrum [δ($CDCl_3$) 3.62-3.77 (1H, m, C_3-H), 3.71 (1H, d, J = 15.0 Hz, C_{21}-H), 3.79 (3H, s, OMe), 4.05 (1H, d, J = 15.0 Hz, C_{21}-H), 7.85 (1H, s, disappears with D_2O, indole NH)]. The same conclusion was arrived by comparison with an authentic sample provided by Professor T. Kametani[7].

EXPERIMENTAL

M.ps were recorded in a Koffler block and are uncorrected. I.R. spectra were measured with a Perkin-Elmer IR 782 and UV spectra with a Varian-634 spectrophotometer. ^{1}H-NMR spectra were measured on 80 MHz, 100 MHz and on 200 MHz spectrometers respectively using TMS as an internal standard. Petroleum ether used has the boiling range 60-80°.

4-Methoxybenzyl diazomethyl ketone (2)

To a mixture of (1) (4.98g) and dry benzene (60 ml) a soln of oxalyl chloride (10 ml) in dry benzene (40 ml) was added dropwise at room temp. The mixture was stirred vigorously during addition and stirring was continued for another 1 h. The solvent and excess reagents were removed in vacuo. The oily acid chloride thus obtained was dissolved in dry benzene (30 ml) and added dropwise with stirring to an ice-cold soln of ethereal diazomethane (large excess). After 2 h

the solvent was removed by distillation. The residue so obtained was subjected to chromatography over neutral alumina eluted by petroleum ether : ether (v/v 60:40) to afford 2 (4.0g, 70%) as a yellow oil. I.R. (neat) 2100 (CH=N=N), 1630 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$, 100 MHz)δ3.56 (2H, s, $ArCH_2$-), 3.84 (3H, s, OMe), 5.16 (1H, s, -CH=N_2), 6.88 (2H, d, J_o= 10 Hz, C_3-H and C_5-H), 7.12 (2H, d, J_o = 10 Hz, C_2-H and C_6-H). (Calc. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.26; N, 14.73. Found : C, 63.09; H, 5.45; N, 14.54%).

5-Methoxy-2-indanone (3).

To a well stirred and cooled (-20°) soln of trifluoroacetic acid (40 ml) in dry CH_2Cl_2 (30 ml), a soln of 2 (3.8g) in dry CH_2Cl_2 (30 ml) was added dropwise under N_2 atm during a period of 1h. The whole soln was stirred subsequently for another 10 mins, the excess reagent and solvents were removed under vacuo. The residue on chromatography over silica gel afforded the desired indanone 2 (100mg, 1.9%) as a gummy mass with benzene as eluent, R_f 0.51 (benzene : ethyl acetate = 4:1); I.R. (neat) 1740 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$; 80 MHz)δ3.66 (2H, s, $C_1<\frac{H}{H}$), 3.71 (2H, s, $C_3<\frac{H}{H}$), 3.79 (3H, s, OMe), 6.75 (1H, d, J_o = 8Hz, C_6-H, m-coupling ill resolved), 6.80 (1H, m-coupling ill resolved, C_4-H), 7.15 (1H, d, J_o = 8Hz, C_7-H). (Calc. for $C_{10}H_{10}O_2$: C, 74.07; H, 6.17. Found : C, 73.93; H, 6.29). Further elution with the same solvent furnished 4-methoxybenzyl hydroxymethyl ketone (4) (2.3g; 64%) as a crystalline solid, m.p.75°; R_f 0.19 (benzene : ethylacetate = 4:1) I.R. (KBr) 3360-3440 (br, OH), 1720 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$, 100 MHz)δ3.00 (1H, t, J = 5 Hz, -OH, disappears with D_2O), 3.52 (2H, s, $ArCH_2$-), 3.64 (3H, s, OMe), 4.24 (2H, d, J = 5 Hz, -CH_2OH, collapses to a singlet on shaking with D_2O), 6.88 (2H, d, J_o= 10Hz, C_3-H and C_5-H), 7.16 (2H, d, J_o= 10Hz, C_2-H and C_6-H). (Calc. for $C_{10}H_{12}O_3$: C, 66.66; H, 6.66. Found : C, 66.43; H, 6.84).

3-Hydroxy-phenylacetic acid (6).

A mixture of 3-hydroxy-acetophenone (5) (19.04g), sulphur (6.75g) and morpholine (18 ml, 18.25g) was refluxed for 5 h. The reaction mixture was cooled and poured into ice-cold water. The semisolid mass appeared. It was separated and dissolved in 10% ethanolic NaOH soln (200 ml) and refluxed for 8 h. Ethanol was distilled off and the residue was poured into water (100 ml), cooled in an ice-bath and acidified with 6N HCl. It was extracted with EtOAc. The extract was washed with little ice-cold water, dried (Na_2SO_4) and evaporated. The residue was poured slowly into saturated soln of $NaHCO_3$ with constant stirring. It was then extracted with ether to remove unreacted 5. The aqueous part containing sodio salt of 6 was acidified with 6N HCl, extracted with ether, washed with little water and dried (Na_2SO_4). Evaporation of the solvent afforded a semisolid mass which solidified on cooling. It was crystallized from petroleum ether : ether mixture to give 6 (7.6 g, 36%), m.p.124-126° (lit.[8] 129°); I.R. (KBr) 3000-3400 (br. OH), 1690 cm^{-1} (C=O). (Calc. for $C_8H_8O_3$: C, 63.15; H, 5.26. Found : C, 63.29; H,5.04)

3-Methoxy-phenylacetic acid (7).

3-Hydroxy-phenylacetic acid (6) (7.5g) was dissolved in 10% aqueous NaOH soln (50 ml) and stirred at room temp. To this soln $(CH_3)_2SO_4$ (15.6g, 12ml) was added dropwise. After addition it was heated at 50-60° for 10 mins and then further 10% aqueous NaOH soln (50 ml) was added with constant stirring. The mixture was further heated for 1h at the above temp. It was cooled and poured into 100ml of ice-cold water and acidified with 6N HCl and kept at 0° for 1h when 7 was precipitated out. It was filtered, washed with ice-cold water and dried in vacuo. Then it was chromatographed over silica gel. The fraction eluted with petroleum ether: ether (v/v 3:1) afforded crystalline 7 (6g, 73%), m.p.67-68° (lit.[8] 68-69°); I.R. (KBr) 3000-3200 (OH), 1700 cm^{-1} (C=O). (Calc. for $C_9H_{10}O_3$: C, 65.06; H, 6.02. Found : C, 65.32; H, 6.21).

3-Methoxybenzyl diazomethyl ketone (8)

3-Methoxy-phenylacetic acid (7) (3.8g) was converted to 8 by the same procedure applied for the synthesis of 2. The reaction products on chromatography over neutral alumina afforded 8 as a yellow oil on elution with petroleum ether : ether (v/v 60:40), Yield : 3.98g (69%). I.R. (neat) 2100 (CH=N=N), 1640 cm^{-1}(C=O); ^{1}H-NMR ($CDCl_3$, 80 MHz)δ3.59 (2H, s, $ArCH_2$-), 3.80 (3H, s, OMe), 5.13 (1H, s, -CH=N_2), 6.76-6.85 (3H, m, C_2-H, C_4-H and C_6-H), 7.15-7.24 (1H, m, C_5-H). (Calc. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.26; N, 14.73. Found : C, 63.33; H,5.04; N,14.91).

5-Methoxy-2-indanone (3).

8 (3.8g) was converted to 3 following the procedure for the synthesis of 3 from 2. The reaction product was chromatographed over silica gel and eluted by benzene to yield 3 (1.75g, 54%) as a semi-solid mass.

5-Methoxy-3-isochromanone (9).

A soln of 3 (1.62 g) in dry CH_2Cl_2 (15 ml) was cooled in an ice-bath. To it an ice-cold soln of m-CPBA (2.59g) in dry CH_2Cl_2 (70ml) was added dropwise and the mixture was stirred vigorously at 0° for 1h. It was kept at this temp for 10days. Excess peracid was decomposed by 2% aq. Na_2SO_3 soln and the precipitated m-chlorobenzoic acid was filtered off and washed with a little CH_2Cl_2. The combined organic layers were washed with 2% aq $NaHCO_3$ soln, water and dried (Na_2SO_4). The residue obtained after removal of the solvent was chromatographed over silica gel. Benzene : ethyl acetate (v/v 9:1) eluate furnished 9 (0.765g, 43%) which was

crystallized from ethanol, m.p.74-76° (lit.[3] 74-78°), R_f 0.41 (benzene : ethyl acetate = 4:1) I.R. (KBr) 1740 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$, 80 MHz) δ 3.64 (2H, s, $C_4<\underline{H}$), 3.78 (3H, s, OMe), 5.22 (2H, s, $C_1<\underline{H}$), 6.71 (1H, m-coupling ill resolved, C_5-$\underline{H}$), 6.76 (1H, d, J_o = 8Hz, C_7-$\underline{H}$), 7.11 (1H, d, J_o = 8Hz, C_8-$\underline{H}$). (Calc. for $C_{10}H_{10}O_3$: C, 67.41; H, 5.61. Found : C, 67.59; H, 5.52).

N-[2-(3-Indolyl)-ethyl]-5-methoxy-2-(hydroxymethyl)-phenylacetamide (10).

A mixture of tryptamine (0.8g) and 9 (0.89g) was refluxed in absolute ethanol (80ml) under N_2 atm for 20h. The residue thus obtained after removal of ethanol was chromatographed over silica gel and the fraction eluted with benzene : ethyl acetate (v/v 1:1) afforded 10 (1.4g, 83%), m.p.120-124°; R_f 0.35 (ethyl acetate). It was crystallized from benzene : ethyl acetate mixture; I.R. (KBr) 3280 (OH), 3200 (NH), 3060 (NH), 1610 cm^{-1} (C=O); UV λ_{max} (EtOH) 290, 282, 224 nm; m/z 338 (M^+), 320 (M^+-H_2O), 143, 130; ^{1}H-NMR (d_6-DMSO, 80 MHz) δ 2.42-2.82 (4H, m, -NHC$\underline{H}_2$C$\underline{H}_2$-), 3.40 (2H, s, ArC$\underline{H}_2$CO-), 3.64 (3H, s, OMe), 4.39 (2H, d, J = 5 Hz, collapses to a singlet on shaking with D_2O, -C$\underline{H}_2$OH), 5.03 (1H, t, J = 5Hz, disappears with D_2O, -CH$_2$O$\underline{H}$), 6.63-7.50 (8H, m, aromatic), 8.10 (1H, t, J = 5Hz, D_2O-exchangeable, -N$\underline{H}$CO-), 10.71 (1H, s, disappears with D_2O, indole N$\underline{H}$) (Calc. for $C_{20}H_{22}N_2O_3$: C, 71.00; H, 6.50; N, 8.28. Found:C, 71.17; H, 6.63; N, 8.12).

(±)-17-Methoxy-hexadehydroyohimbane (11).

Hydroxy amide 10 (1.014g) was heated with polyphosphate ester[5] (PPE) (8g) at 80° under N_2 atm for 1.5h. The reaction mixture was cooled and poured into 100ml of water and the mixture was stirred at room temp for 0.5h and was extracted with ether. The aqueous part was made basic with ammonia and was extracted with $CHCl_3$, washed (H_2O) and dried (Na_2SO_4). Removal of solvent afforded a yellow semisolid which was subjected to chromatography over silica gel.The fraction eluted by $CHCl_3$: MeOH (v/v 99:1) afforded 11 (90mg; 10%), m.p.160° (lit.[9] 168°); R_f 0.60 (benzene : ethyl acetate = 7.3); I.R.(KBr) 3440 cm^{-1} (NH); UV λ_{max} (EtOH) 290(sh), 284, 225 nm; m/z 304 (M^+), 169, 144 and 134; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 2.64-2.88 (2H, m, $C_6<\underline{H}$), 2.90-3.30 (4H, m, $C_5<\underline{H}$ and $C_{14}<\underline{H}$), 3.62-3.77 (1H, m, C_3-$\underline{H}$), 3.71 (1H, d, J = 15Hz, C_{21}-$\underline{H}$), 3.79 (3H, s, OMe), 4.05 (1H, d, J = 15Hz, C_{21}-$\underline{H}$), 6.65-7.51 (7H, m, aromatic), 7.85 (1H, s, N_1-$\underline{H}$, D_2O-exchangeable). (Calc. for $C_{20}H_{20}N_2O$: C, 78.94; H, 6.57; N, 9.21. Found : C, 78.81; H, 6.71; N, 9.08).

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