The Reaction of Harmaline with Cyclohexanone-Oxalyl Chloride Adduct - A One Step Synthesis of Reserpine Analogues.

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Summary: The reaction of cyclohexanone with oxalylchloride affords the adduct (3). Reaction of (3) with harmaline (1) affords a high yield one step synthesis of the pharmacologically interesting skeletal system(5) which bears the carbon frame-work of reserpine.

A large number of indole alkaloids possess a β-carboline nucleus or some variation of it as an integral part of their structure. The occurrence of the major β-carboline alkaloids harmine (2) and harmaline (1) in the seeds of Peganum harmala, [1,2] a plant which grows abundantly in Pakistan, has led us to investigate the potentials of the utilization of these alkaloids for the synthesis of pharmacologically interesting indole alkaloidal systems. Our earlier studies on the enamine chemistry of harmaline [3-5](1) has led to the synthesis of a number of novel indoloquinolizidines and derivatives of indole alkaloids of medicinal repute[3-11]. We now report the reaction of harmaline (1) with the adduct (3)obtained on reaction of cyclohexanone with oxalyl chloride.

Cyclohexanone when refluxed with oxalyl chloride in undried benzene or carbon tetrachloride was found to be smoothly converted into a single reaction product. After 2 hours reflux a whitish solid crystallised out of the reaction mixture which was filtered off.

Microanalysis indicated the absence of chlorine in the substance. The IR spectrum showed a strong absorption in the carbonyl region at 1765 cm^{-1}. The mass spectrum afforded the molecular ion at m/z = 358. The appearance of a base peak in the mass spectrum at m/z = 179 was in agreement with the cleavage of the dimer. The proton NMR and C-13 NMR appeared to be very simple and showed only half the peaks corresponding to the number of protons and carbons in the substance. The above spectral data is consistent with the symmetrical dimeric structure(3) assigned to the cyclohexanone derivative and its possible mode of formation is given in Scheme-1.

The cyclohexanone derivative (3) was allowed to react with harmaline (1) in methanol/benzene (1:1) for 72 hours at room temperature. The reaction mixture gradually turned deep red in colour. t.l.c.(15% MeOH-85% $CHCl_3$) showed complete conversion of the starting material into one major and four minor reaction products. The major product crystallised out of the reaction mixture as a red solid on concentrating the reaction mixture (95% yield). The solid was filtered off and further purified by recrystallisation from a methanol/ethylacetate mixture. The strong absorption in the IR spectrum at 1740 cm^{-1} corresponded to the ester carbonyl group in the molecule. The UV spectrum of the substance afforded peaks at 218 nm, 267 nm, 335 nm, and 455 nm which

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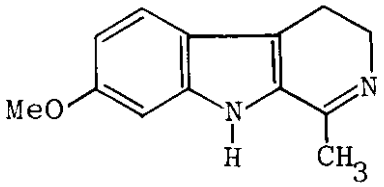
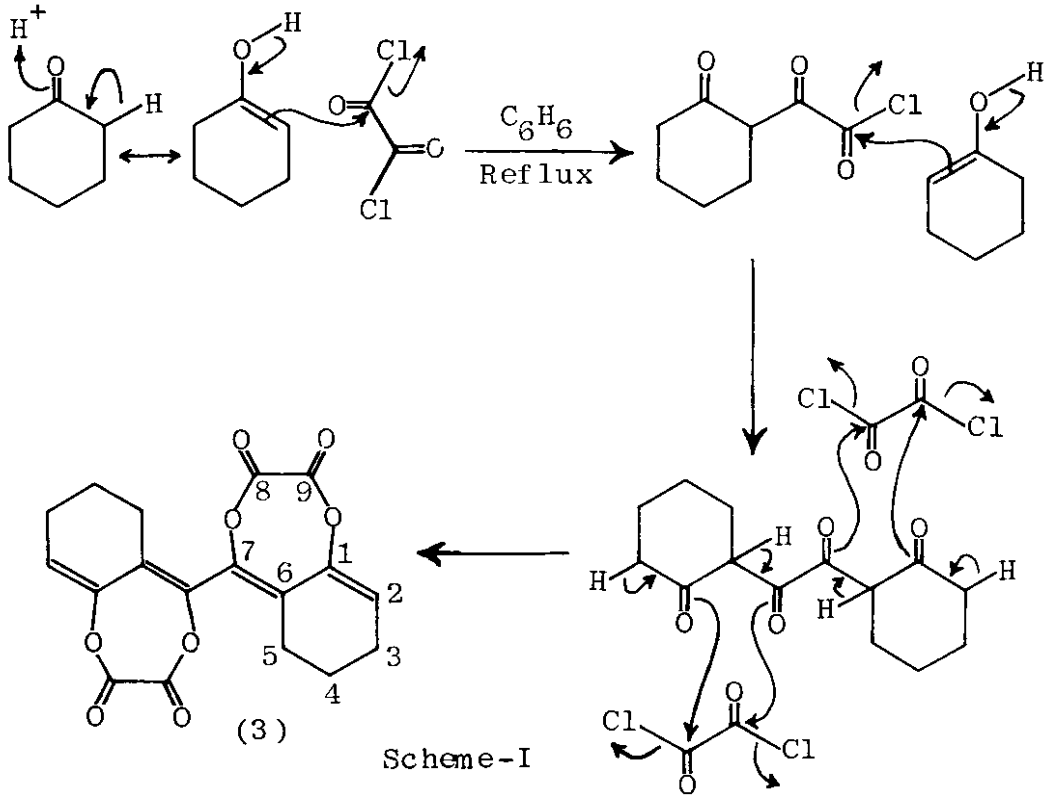


(1): Harmalin

(2): Harmine, $\Delta^{5,6}$



Scheme-I

shifted to 220 nm, 280 nm, 335 nm and 403 nm on basification. The original peaks appeared on acidification of the methanolic solution. Such shifts are characteristics of compounds bearing a C=N grouping in conjugation with the indole-2-position[4,5].

The mass spectrum of the substance afforded the molecular ion peak at m/z = 362. The substance showed a facile loss of a methyl from the methoxy group and underwent decarboxylation affording a prominent peak at m/z=303 with other major fragments appearing at m/z = 361,347, 319 and 303. Further confirmation of the molecular ion peak came from the mass spectrum recorded using a field ionisation source in which the M^+ peak was observed at m/z = 362. The exact masses of the M^+ peak and a major fragment at m/z = 303 were determined by peak matching with a standard E.I. source to be 362.1637 and 303.1491 which were consistent with the molecular formula $C_{22}H_{22}N_2O_3$ and $C_{20}H_{19}N_2O$ respectively.

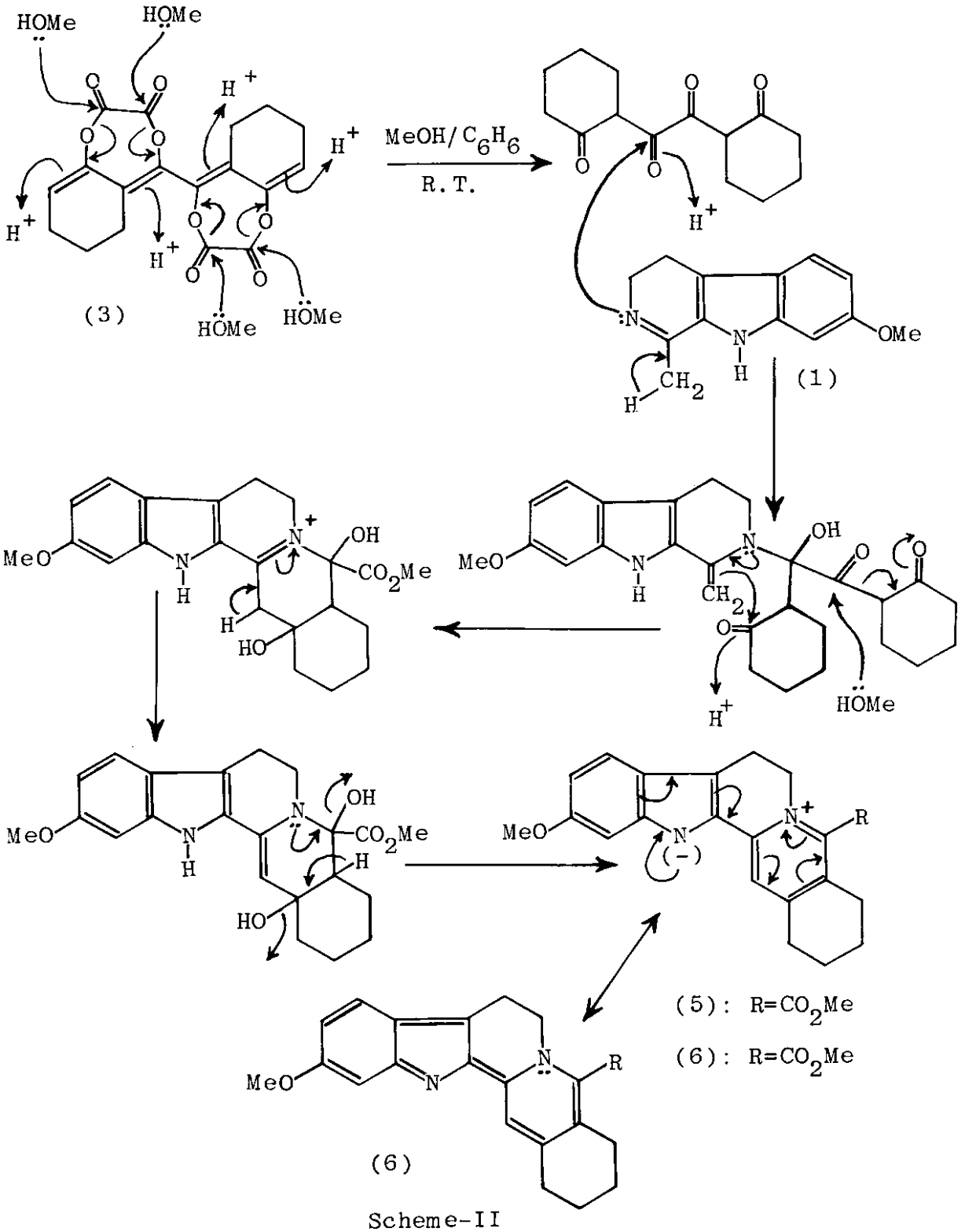
The proton NMR spectrum of the substance in tetradeutromethanol showed a three proton singlet at δ 4.01 corresponding to the ester methyl group

while another singlet integrating for 3-protons resonated at δ 3.71 which was assigned to aromatic methoxyl group in the molecule. A one proton double-doublet was found to be centred at δ 6.64 and was assigned to proton B in ring A (Fig.8) (J_{AB}=9.0 Hz, J_{BC}=2.5 Hz), a one proton doublet centred at δ 6.76 corresponded to proton C (J_{BC}=2.5 Hz). Proton A resonated as a doublet at δ 7.38 (J_{AB}=9.0 Hz). The aromatic proton in ring D was strongly deshielded by the quaternary nitrogen and appeared as a one-ptoton singlet at δ 8.05. A two-proton triplet at δ 4.47 (J=8.0Hz) was assigned to H_E the methylenic protons also being deshielded by the adjacent quaternary nitrogen atom. On the basis of the above spectral data structure (5) is assigned to the red compound.

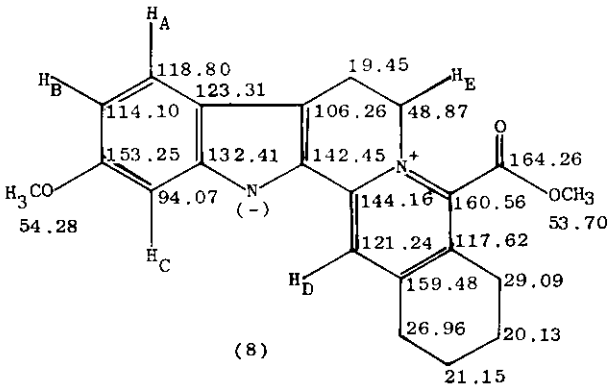
The C-13 NMR spectrum was consistent with the assigned structure. In the aliphatic region, the six methylenes appeared at δ 19.45, δ 20.13, δ 21.15, 26.95. δ 29.09 and δ 48.87 which were split into the corresponding triplets in the off-resonance spectrum. Two singlets observed at δ 54.28 and δ 53.70 were assigned to the carbons of the methoxy group attached to ring A and the methoxyl group of the ester moiety respectively. The corresponding quartets were present in the off-resonance spectrum. A peak at δ 121.24 was assigned to the tertiary carbons of ring D, which was split into a doublet in the off-resonance spectrum. The carbonyl carbon of the carbomethoxyl group resonated at δ 164.26. Peaks at δ 94.07, δ 114.10 and δ 118.80 in the broad band decoupled spectrum were assigned to the tertiary aromatic carbons of ring A. These were seen to be split into the corresponding doublets in the off-resonance spectrum. The C-13 values assigned[12,14] to the various carbon atoms are shown in Fig 8.

The alternative structure (6) could be ruled out by (a) the presence of a singlet at δ 8.05 in the proton NMR spectrum which was consistent with the C-14 proton in structure (6).This proton would have been expected to resonate further upfield in the structure (6). Moreover the triplet at δ 4.47 ascribed to the methylene protons adjacent to the nitrogen was also consistent with structure (5) instead of structure (6) in which these protons would have been expected to resonate further upfield. Further support for this was provided by the carbonyl absorption in the IR spectrum which appeared at 1740 cm^{-1}, and on reduction to (9) and (10) underwent a shift to 1720 cm^{-1}. In the case of the alternative structure (6), absorption would have been expected at a lower value, and a shift in the opposite direction on reduction would have been expected.

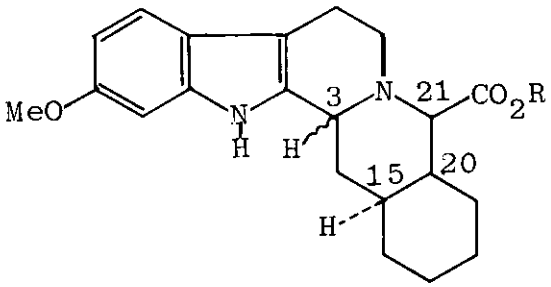
The red substance (5) was reduced with sodium borohydride in ethanol at O°C. It was observed that the reduction proceeded smoothly and quickly and the initially red solution turned pale yellow within a few minutes. t.l.c. of the reaction mixture showed complete conversion of the starting material into two major and a minor faster moving products. Both the major products were isolated by column chromatography as white crystalline solids, which were unstable in solution. Both reduction products afforded almost identical spectral data with minor differences. The UV spectra of both substances showed absorption maxima at 226 nm and 295 nm. The IR spectra of both showed ester carbonyl absorption at 1720 cm^{-1} due to the carbomethoxy group. The shift of the carbonyl absorption in IR spectrum of the reduction products from that of the starting material which showed strong absorption at 1740 cm^{-1} was consistent with the absence of strong electron withdrawing effect of


HOMe
HOMe
H+
H+
H+
H+
(3)
HOMe
HOMe
MeOH/C6H6
R.T.
OMe
(1)
MeO
OH
CO2Me
HO
CH2
HOMe
(5): R=CO2Me
(6): R=CO2Me
(6)

Scheme-II



(8)



(9): C_3-Hα, R=CH_3, $\Delta^{15,20}$

(10): C_3-Hβ, R=CH_3, $\Delta^{20,21}$

(11): C_3-Hα, R=Et, $\Delta^{15,20}$

(12): C_3-Hβ, R=Et, $\Delta^{20,21}$

the neighbouring quaternary nitrogen atom. A characteristic difference in the IR spectra of the two products was observed in the absorption pattern between 2900-2700 cm^{-1} i.e.(3.4-3. 7μ) region [15,16]. The IR spectrum of the faster moving reduction product afforded distinct Bohlmann bands at 2750, 2810 and 2850 cm^{-1} which provided evidence for the existence of a C-3 axial proton i.e. the presence of a C/D trans fused system. The absence of Bohlmann bands in the slower moving reduction product suggested that the C-3 proton was equatorial i.e. a C/D cis fused ring junction was present. The mass spectrum of both reduction products afforded molecular ion peaks at m/z = 366 and both exhibited almost identical fragmentation patterns. The exact mass of the molecular ion of the slower moving material was found by peak matching to be 366.1943 which was consistent with the molecular formula $C_{22}H_{26}N_2O_3$. The major mass fragments appeared at m/z = 365,307,199 and 200. In the proton NMR spectra two sharp singlets at δ 3.83 and δ 3.74 integrating for the three proton each were assigned to the aromatic methoxy and to the carbomethoxyl groups respectively. A downfield singlet corresponding to the indole NH proton appeared at δ 7.66 while a one-proton doublet centred at δ 7.36 (J_{AB}=9.0Hz) was assigned to the proton A. Proton B appeared as a double-doublet centred at δ 6.75 (J_{AB}=9.0 Hz, J_{BC}=2.5 Hz) a part of which was overlapped by a singlet at δ 6.81 corresponding to proton C. The methylene protons appeared as complex multiplets between δ 2.0-3.5. The absence of olefinic absorption in the NMR spectra of the two products favours a C_{15}-C_{20} or a C_{20}-C_{21} double bond in the molecule.

The major difference in the proton NMR spectra of the two products was observed in the absorption pattern of the C-3 proton. This appeared as a double-doublet centred at δ 4.10 (J=5.0 Hz) in the C/D trans fused product while it appeared as a double-doublet centred at δ 4.07 (J_{ax-ax}=9.0 Hz, J_{ax-eq}=3.5 Hz) in the NMR spectrum of the cis fused product. The broad band C-13 NMR spectrum of the slower moving product showed singlets at δ 55.92 and δ 51.34 corresponding to the methyl carbon atom of aromatic methoxyl and the carbomethoxy groups respectively. These were found to be split into the corresponding quartets in the off-resonance spectrum. Downfield singlets at δ 168.61 and δ156.38 were assigned to the carbonyl carbon atom and to the olefinic (C-20) carbon atom respectively.

The tertiary aromatic carbon atoms of ring A appeared at δ 118.68, δ 108.90 and δ 105.39 which resonated as doublet in the off-resonance spectrum. The methylene carbons appeared in the region between δ 21.80- δ 48.46 as singlets in the broad band decoupled spectrum each singlet underwent splitting into the corresponding triplet in the off-resonance spectrum. On the basis of the above spectral data structure (10)is assigned to the slower moving product. The C-13 values assigned to various carbon atoms in the molecule are shown in Table 1.

Table-1:- C-13 Chemical Shifts of 11-methoxy-15,20-didehydro-yohimbane (9) and 11-methoxy-20, 21-didehydro yohimbane (10)

Carbon	9	10
C-2	133.70	133.99
C-3	54.72	64.33
C-5	49.03	48.46
C-6	22.13	21.80
C-7	108.47	108.63
C-8	121.87	121.98
C-9	118.71	118.68
C-10	108.86	108.90
C-11	151.20	152.26
C-12	95.35	95.39
C-13	137.18	137.29
C-14	30.81	28.86
C-15*	120.41	47.30
C-16	30.94	32.02
C-17	27.71	28.95
C-18*	25.61	25.75
C-19	31.97	32.81
C-20	133.59	156.38
C-21	65.45	121.98
-OMe(aromatic)	55.89	51.34
-OMe(ester)	169.02	168.61

The spectra were determined at 25.2 MHz in Fourier transform mode in $CDCl_3$ solutions. The data for each carbon are shown in ppm downfield from TMS.

*These assignments can be reversed.

The C-13 broad band spectrum of the faster moving product was very similar to that of the slower moving product, the main difference being the appearance of signals corresponding to olefinic carbon atoms at δ 120.41 and 133.59 in the C-13 NMR spectrum of the faster moving product which favours a C_{15}-C_{20} double bond in ring D. The C-13 values assigned to the various carbon atoms of the faster moving product are given in Table 1. The above spectral data are consistent with structures (9) and (10) assigned to the faster and slower moving products respectively.

The reaction of cyclohexanone-oxalyl chloride adduct (3)was then repeated in ethanol/benzene (1:1) under identical reaction conditions in order to confirm that the solvent has participated during the reaction. It was observed that the red compound similarly obtained from this reaction exhibited the molecular ion peak at m/z = 376 instead of 362, indicating the presence of carboethyoxy group instead of carbomethoxy in the reaction product (7). The other prominent peaks in the spectrum appeared at m/z=375, 347 and 305. The molecular ion was further confirmed by recording the mass spectrum using F.I. source, which afforded the molecular ion peak at m/z=376. The results clearly demonstrate the participation of solvent during the reaction.

The sodium borohydride reduction of the red product (7) obtained from the ethanol/benzene reaction provided identical results and the two isomeric reduced products (11) and (12) having the same molecular weight (m/z = 380) were isolated by preparative t.l.c.exhibiting almost identical fragmentation patterns. The major mass fragments appeared at m/z = 307,200 and 199.

The proposed mechanism of the reaction of harmaline (1) with cyclohexanone-derivative (3) is presented in

Scheme (II). It involves the attack of solvent on the carbonyl carbons resulting in the loss of dimethyl oxalate. Attack of the basic nitrogen of harmaline (1) on the ketoester followed by cyclisation and subsequent dehydration affords the red compound (5).

Experimental

Preparation of cyclohexanone-oxalyl chloride adduct(3).

Cyclohexanone (3),(50 ml, 0.4836 mole) was mixed with undried benzene or carbon tetrachloride (40 ml). Oxalyl chloride (34 ml, 0.3960 mole) was added to the magnetically stirred solution and the reaction mixture was refluxed on a boiling water bath for 2 hours. The initially colourless solution gradually turned orange and after 2 hours reflux a pale white solid crystallised out of the reaction mixture. The reaction was allowed to cool at room temperature. The solid was filtered off and washed thoroughly with benzene, whitish solid cyclohexanone-oxalyl chloride adduct (3) was obtained (11.4 gms, 8% yield) m.p. 250°C. UV (MeOH): λ_{max} 209, 283 nm., λ_{min} 226 nm; IR (KBr): ν_{max} 1765 cm^{-1} (C = O), 1650 cm^{-1} (C = C, str.). ^1H NMR (CF_3CO_2D): δ 196(2 H_A,quintet, $J_{AB}=J_{AC}=6.0$ Hz), δ 2.54 ($2H_B$, quartet, $J_{ABD}=5.5 - 6.0$ Hz), δ 2.84 ($2H_C$,t, $J_{AC}=6.0$ Hz), 6.37 (H_D,t, $J_{BD}=5.5$ Hz) C-13 NMR (CF_3CO_2D): δ 26.89 (C-4 t), δ 27.91 (C-5,t), δ 28.84 (C-3 t), δ 122.12 (C-2, d), δ 130.78 (C-6 s), δ 144.85 (C-1 s), δ 147.34 (C-7 s), δ 153.01 (C-8, C = O, s), δ 167.83 (C-9 C=O,s), Analysis: Calcd: C = 60.32%, H = 3.94%, O = 35.74% Obsd: C=59.15%, H=4.50%, O = 34.86%: MS (70 ev): (m/z, %) = 358 (M^+,2), 207 (26), 180 (10), 179 (100), 152 (7), 135 (7),107 (20), 96 (10), 95 (6), 79 (11), 77 (40), 68 (7), 67 (10), 66 (5), 65 (7), 55 (30), 53 (6). F.I.: M^+,m/z = 358, High Resolution MS: 358.0711 (Calcd. for $C_{18}H_{14}O_8$: 358.0690), 207.0305 (Calcd. for $C_{10}H_7O_5$: 207.0293).

Preparation of 11-methoxy-21-carbomethoxy-3,14,15,20-tetradehydroyohimbane (5)

Harmaline (1) (4 gms, 0.0190 mole) was dissolved in methanol/benzene (1:1) (35 ml). Cyclohexanone-oxalyl chloride adduct (3) (4.139 gms,0.0116 mole) was also added and the reaction mixture was magnetically stirred at room temperature for 72 hours. The colour of the reaction mixture gradually turned deep red and after 72 hours a red solid crystallised out of the solution. The solid was filtered off and purified by recrystallising from a methanol/ethyl acetate mixture. 11-methoxy-21-carbomethoxy-3,14,15,20-tetradehydro-yohimbane (5) was obtained (3.99 gms,yield 95%).m.p.319°C. (UV (MeOH): λ_{max} 218,267,335,455 nm. ε_{max} 20727, 6182, 13836, 12364, λ_{min} 293,370 nm. ε_{min} 5454, 5818. On basification: λ_{max} 220,280, 335, 403 nm. ε_{max} 34545, 9090, 9455, 13090, λ_{min} 298, 370 nm. ε_{min} 6909,9090. IR (KBr): ν_{max} 1740 cm^{-1} (C = O, ester), 1280 cm^{-1}(C - O,str.). ^1H NMR (CD_3OD): δ 4.01 (3H, s, -OMe aromatic), δ 3.71 (3H, s, -OMe ester), δ 6.64 (H_B, d.d, J_{AB} = 9.0 Hz, J_{BC} = 2.5 Hz), δ 6.76 (Hc, d, J_{BC} = 2.5 Hz), δ 7.38 (H_A, d, J_{AB} = 9.0 Hz), 8.05 (H_D,s, aromatic), δ 4.47 ($2H_E$, t, J = 8.0 Hz) C-13 NMR ($CDCl_3$+5 drops CF_3CO_2D):δ 19.45 (C-6,t,), δ 20.13 (C-18,t),δ 21.15 (C-17

t,)δ 26.96 (C-16, t,), δ 29.09(C-19,t), δ48.87 (C-5,t), δ53.70 (-OCH_3 ester,q), δ54.28 (OMe aromatic, q), δ 94.07 (C-12, d), δ 106.26 (C-7,s), δ 114.10 (C-10,d), δ117.62 (C-20,s), δ 118.80 (-9,d), δ 121.24 (C-14,d), δ 123.31 (C-8,s) δ 132.41 (C-13,s), δ 142.45 (C-2 s), δ 144.16 (C-3 s), δ 153.25 (C-11 s), δ 159.48 (C-15 s), δ 160.56 (C-21 s) δ 164.26 (C=O,s). MS (70 ev): M/z, %) = 364 (12), 363 (13), 362 (M^+,46), 361 (65), 349 (5), 347 (6), 319 (5), 317 (6), 307 (6), 303 (35), 181 (9), 152 (5), 128 (5), 122 (5), 85 (16), 83 (26), 77 (6), 60 (17), 59 (100), 50 (14), 47 (10), 45 (81), 44 (52), 43 (13), 41 (5). FI: M^+, m/e = 362. High Resolution MS: 362.1636 (calcd. for $C_{22}H_{22}N_2O_3$: 362.1630), 303.1491 (calcd. for $C_{20}H_{19}N_2O$:303.1498).

Reduction of 11-methoxy-21-carbomethoxy-3,14,15,20-tetrahydroyohimbane(5) to 11-methoxy-21-carbomethoxy-15,20-didehydro-yohimbane (9) and 11-methoxy-21-carbomethoxy-20,21-didehydro-yohimbane (10)

11-methoxy-21-carbomethoxy-3,14, 15,20-tetrahydro-yohimbane (5) (0.2 gms, 0.0006 mole) was dissolved in ethanol (5 ml). Sodium borohydride (0.0416 gms, 0.0011 mole) was added to the red solution at O°C. Brisk effervescence was observed on addition of sodium borohydride into the reaction mixture and the red solution readily turned pale yellow within a few minutes. The reaction mixture was filtered off and washed with ethanol (3 ml). The filterate was quenched with cold water (5 ml) and ethanol was evaporated under reduced pressure to a pale aqueous concentrate which was then extracted with chloroform (25 ml). The chloroform extract, after drying with anhydrous sodium sulphate, was evaporated to a pale concentrate containing the crude reduction mixture. The reduction mixture on t.l.c. showed complete conversion of the starting material into two major and one minor faster moving products. The two major products were isolated by column chromatography on silica gel and eluted with increasing percentage of chloroform in pet ether. A faster moving substance, 11-methoxy-21-carbomethoxy-15,20-didehydroyohimbane (9) was obtained as a white crystalline material (0.0769 gm, yield 35%). m.p. 210°C. A slower moving 11-methoxy-21-carbomethoxy-20,21-didehydroyohimbine(10) was obtained also as a white crystalline material (0.0878 gm, yield 40%) m.p. 198°C.

i)Spectral data 11-methoxy-21-carbomethoxy-15,20-didehydro-yohimbane (9):

UV (MeOH): λ_{max} 226, 295 nm. λ_{min} 280 nm. IR(KBr): ν_{max} 1720 cm^{-1} (C = O, ester), 1630 (C = C, str.), 2750, 2810, 2850 cm^{-1} (Bohlmann's bands) H^1 NMR ($CDCl_3$): δ 8.83 (3H, s, -OMe aromatic), δ 3.78 (3H, s, -OMe ester), δ 4.10 (H, d, C-3, J = 5.0 Hz), δ 7.35 (H_A, d, J_{AB} = 9.0 Hz), δ 7.70 (H_B, s, indole). C-13 NMR ($CDCl_3$): δ 22.13 (C-6,t), δ 25.16 (C-18,t,), δ 27.71 (C-17,t), δ 30.81 (C-14,t), δ 30.94 (C-16,t), δ 31.97 (C-19,t), δ 49.03 (C-5, t), δ 51.45 (-OM ester,q), δ54.72 (C-3,d), δ 55.89 (-OMe aromatic, q) δ 65.45 (C-21,d), δ 95.35 (C-12,d), δ108.47 (C-7,s), δ 108.86 (C-10,d) δ 118.71 (C-9,d), δ 120.41 (C-15,s), δ 121.87 (C-8,s), δ 133.59 (C-20, s), δ 137.18 (C-13,s), δ 151.20 (C-11,s) MS (70 ev): (m/z,%) 367 (5), 366 (M^+,20), 365 (6), 307 (6), 201 (18), 200 (100), 199 (27), 173 (5), 153(6), 85 (6), 83 (10), 81 (5), 79 (7), 71 (10), 69 (11), 67 (5), 57 (18), 55 (14).

ii) Spectral data of 11-methoxy-21-carbomethoxy-20,21-didehydroyohimbane (10):

UV (MeOH): λ_{max} 227, 297 nm, λ_{min} 280 nm. IR (KBr): ν_{max} 1720 cm^{-1}

(C=O, ester), 1630 cm^{-1} (C=C str.) ^1H NMR ($CDCl_3$): δ 3.83 (3H, s, -OMe aromatic), δ 3.74 (3H, s, -OMe ester), δ 4.07 (H, d.d, C-3, J_{ax-ax}=9.0 Hz, J_{ax-eq}=3.5 Hz), δ6.75(H_B,dd, J_{AB}=9.0 Hz, J_{BC}=2.5 Hz), δ 6.81 (H_c,s), δ 7.36 (H_B ,d, J_{AB}=9.0 Hz), δ 7.66 (H,s, indole) C-13 NMR ($CDCl_3$):δ21.80 (C-6,t), δ 25.75 (C-18,t), δ28.86 (C-14), δ 28.95(C-17,t) δ 32.02 (C-16,t),δ 32.81 (C-19,t),δ 47.30 (C-15,d),δ48.46 (C-5,t), δ 51.34 (-OM ester ,q), δ 55.92 (-OMe aromatic, q), δ 64.33 (C-3,d), δ 95.39(C-12,d), 108.63 (C-7,s), 108.90 (C-10,d)δ118.68 (C-9,s), δ 121.98(C-8,s), δ 133.99 (C-2,s), δ 127.29 (C-13,s), δ152.26 (C-11, s), δ 156.38 (C-20,s), δ168.61 (C=O,s) MS (70 ev): m/z %) = 367 (7), 366 (17), 365 (6), 307 (5), 201 (14), 200 (100), 199 (27), 174 (7), 153 (7), 87 (6), 85 (38), 83 (63), 81 (5), 79 (5), 71 (5), 69 (6), 57 (11). High Resolution MS: 366.19430 (calcd. for $C_{22}H_{26}N_2O_3$: 366.1493).

Preparation of 11-methoxy-21-carboethyoxy-3,14,15,20-tetradehydroyohimbane (7):

Harmaline (1) (0.5 gm, 0.0023 mole) was dissolved in ethanol/benzene (1:1) (10 ml), oxalyl chloride (0.564 gm,0.0015 mole) was added and the reaction was allowed to stir at room temperature for 72 hours. The colour of the reaction mixture gradually turned deep red and after 72 hours, a red solid crystallised out of the reaction mixture. The solid was filtered off and further purified by recrystallisation from an ethanol/ethyl acetate mixture. 11-methoxy-21-carboethoxy-3,14,15,20-tetradehydroyohimbane(7) was obtained (0.41 gm, yield 73%):UV (MeOH): λ_{max} 215, 332, 458 nm. λ_{min}277, 376 nm; IR (KBr): ν_{max}1735 cm^{-1} (C=O, ester), 1280 cm^{-1} (C-O,str.); MS (70 ev): m/z,%) = 378 (9), 377 (24), 376 M^+,(89), 375 (100), 374 (13), 361 (6), 348 (6), 347 (24), 333(5) 332 (7), 331 (8), 317 (5), 306 (8), 305 (33), 304 (7), 303 (16), 301 (5), 198 (11), 167 (8), 152 (5), 66 (12), 64 (38), 57 (6), 55 (5), F.I.: M^+,m/z = 376.

Reduction of 11-methoxy-21-carboethoxy-3,14,15,20-tetrahydroyohimbane (7) to 11-methoxy-21-carboethoxy-15,20-didehydro-yohimbane (11) and 11-methoxy-21-carboethoxy-20,21-didehydro-yohimbane (12).

11-methoxy-21-carboethoxy-3,14,15,20-tetradehydro-yohimbane (7) (0.2 gm, 0.0005 mole) was dissolved in ethanol (6 ml). Sodium borohydride (0.0404 gm, 0.0011 mole) was added to the red soltuion at O°C. Brisk effervescence commenced on addition of sodium borohydride and the red solution readily turned pale yellow within a few minutes. The reaction mixture was filtered off and sodium borohydride was washed with ethanol(1 ml). Ethanol was evaporated under vacuum to a pale concentrate. The sodium borohydride reduction of (7) resulted in the formation of two major and one minor faster moving reduction products visible on t.l.c. The two major products were isolated by preparative t.l.c. on silica gel (PF-254). The faster moving material, 11-methoxy-21-carboethoxy-15,20-didehydroyohimbane (11) was obtained as a white crystalline solid (0.0665 gm, yield 35%) while the slower moving substance, 11-methoxy-21-carboethoxy-20,21-didehydro-yohimbane (12), was also obtained as a white crystalline material (0.076 gm, yield 40%).

i)Spectral data of 11-methoxy-21-carboethoxy-15,20-didehydro-yohimbane(11):

UV(MeOH): λ_{max} 226, 295 nm.λ_{min} 285 nm. IR (KBr): ν_{max} 1720 cm^{-1} (C=O ester), 1630 (C=C, str.); MS (70

ev): (m/z,%) = 396 (4), 381 (3), 380 (M^+,13), 379 (5), 232(5), 307 (6), 201 (17), 200 (100), 199 (24), 174 (7), 154 (7), 79(4), 77 (4), 57 (5), 55 (5).

iii) Spectral data of 11-methoxy-21-carboethoxy-20,21-didehydro-yohimbane (12):

UV (MeOH): λ_{max} 225, 297 nm. λ_{min} 280 nm. IR(KBr) $_{max}$ 1720 cm^{-1} (C=O,ester), 1650 cm^{-1} (C=C,str.) MS (70 ev):(m/z,%) = 381 (4), 380 (M^+,15), 379 (4), 307 (7), 201 (17), 200 (100), 199 (25), 174 (6), 154 (7), 97 (4), 83 (6), 81 (5), 71 (8), 69 (8), 67 (5), 57 (15), 55 (10).

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References

1. F.Goebel, *Ann*, **38**, *363 (1841)*.
2. R.H.F.Manske,W.H.Perkins and R.Robinson, *J.Chem.Soc.*, **1**, *(1927)*.
3. Atta-ur-Rahman and Tayyaba Burney, *Pakistan J.Sci.Ind.Res.*, **15(1)**, *9 (1972)*.
4. Atta-ur-Rahman, *J.Chem.Soc.(Perkin I),731 (1972)*.
5. Atta-ur-Rahman, *J.Chem.Soc.(Perkin 1),736 (1972)*
6. Atta-ur-Rahman,E.Foresti Serantoni and L.Riva di Sanserverino, *Pak.J.Sci.Ind.Res.*, **14**, *490 (1971)*.
7. Atta-ur-Rahman and Fatima Zehra, *Pak.J.Sci.&.Ind.Res.*, **15**, *9,(1972)*.
8. Atta-ur-Rahman,A.Basha and V.U.Ahmad, *Z.Naturforsch.*, **30b**, *653, (1975)*.
9. Atta-ur-Rahman,S.Firdous and A.Basha, *Z.Naturforsch.*, **31b**, *533 (1975)*.
10. Atta-ur-Rahman and Maryam Ghazala, *Synthesis*, **5**, *372 (1980)*.
11. Atta-ur-Rahman and Maryam Ghazala, *Heterocycles*, **16**(2), *261 (1981)*.
12. A.H.Heckendrof, K.C.Mattes,C.R.Hutchinson and E.H.Hagaman and E.Wenkert, *J.Org.Chem.*, **41**, *2045 (1976)*.
13. C-13 NMR Shift Assignments of Amines and Alkaloids, Maurice Shamma and David M.Hindenlang, *Plenum Press, N.Y. & London.*
14. Special Periodical Reports *The Alkaloids vol.5 P 186-190 The Chemical Society.*
15. E.Wenkert and D.K.Roy Chaudhuri, *J.Am.Chem.Soc.*, **78**. *6417 (1956)*.
16. F.Bohlmann, *Ber.*, **92**, *1798 (1959)*.