Photocyclisation of Enamides. Part 27.[1] Total Syntheses of (±)-Yohimbine, (±)-Alloyohimbine, and (±)-19,20-Didehydroyohimbines[2]

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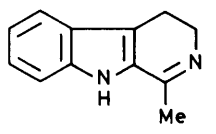
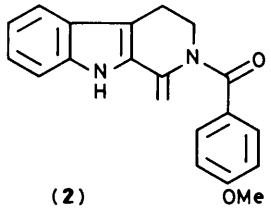
Total syntheses of five indole alkaloids, (±)-yohimbine (**10**), (±)-alloyohimbine (**11**), and three (±)-19,20-didehydroyohimbines (**15a**, **b**, and **c**) (for the first time) were completed from a single common key intermediate (**4**) *via* a route involving the stereoselective isomerisation of the double bond of (**4**) followed by regioselective functionalisation of the enones (**5a** and **b**).

There have been a number of investigations into the total syntheses of the biologically active yohimbines and related alkaloids,[3] most of which involve elaborate preparations of starting materials and are duly suitable for the target alkaloid. We now report a practical and divergent synthetic route for various indole alkaloids including yohimbines, which takes into account their common skeletal structures, with total syntheses of (±)-yohimbine, (±)-alloyohimbine, and three (±)-19,20-didehydroyohimbines from a common key intermediate (**4**) *via* the route involving the stereoselective isomerisation of an unconjugated enone (**4**) followed by regioselective acylation of the resulting conjugated enones (**5a** and **b**).

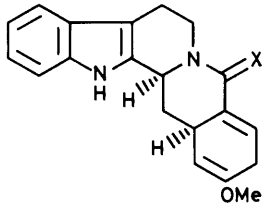
Preparation of the Unconjugated Enone (**4**) *and its Stereoselective Conversion into Alloyohimbone* (**6a**) *and Yohimbone* (**6b**).—Acylation of harmalane (**1**) with 4-methoxybenzoyl chloride in the presence of triethylamine gave the unstable enamide (**2**) in quantitative yield which was characterised by the n.m.r. spectrum [δ 4.97 and 4.40 (each 1 H, d-like, *J* 2 Hz)] and without purification was subjected to irradiation in the presence of sodium borohydride in acetonitrile–methanol[4] (9:1) to afford the photocyclised lactam (**3a**) homogeneously in 90% yield. The n.m.r. spectrum of the lactam (**3a**) exhibited two peaks due to olefinic protons at δ 6.94 (m, 19-H) and 4.56 (s-like, 16-H), respectively, and its mass spectrum



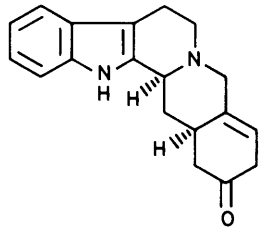
(**1**)



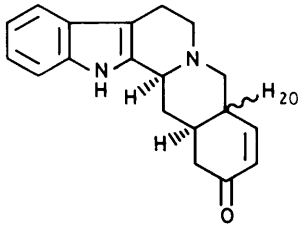
(**2**)



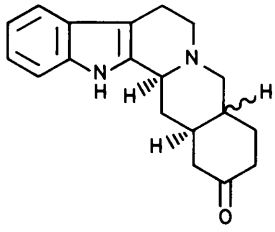
(**3a**) X = O
(**3b**) X = H_2



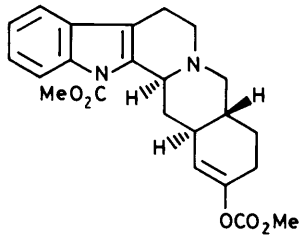
(**4**)



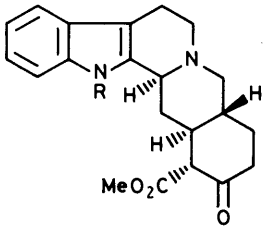
(**5a**) 20α-H
(**5b**) 20β-H



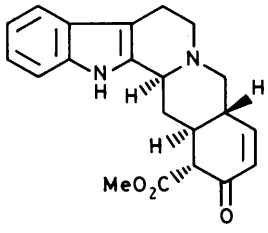
(**6a**) 20α-H (alloyohimbone)
(**6b**) 20β-H (yohimbone)



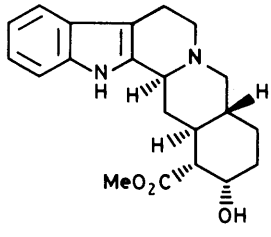
(**7**)



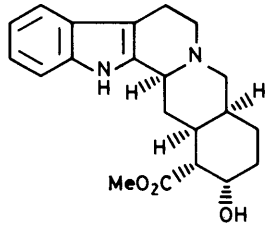
(**8a**) R = CO_2Me
(**8b**) R = H



(**9**)



(**10**) yohimbine



(**11**) alloyohimbine

Table. Isomerisation of the enone (**4**) in the presence of acid

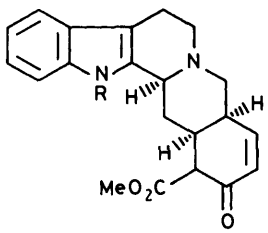
Acid	(4)	(5a)	(5b)
L-Tartaric acid			75%
L-Malic acid			75%
Lactic acid			50%
Mandelic acid	40%		40%
Succinic acid	90%		
conc. HCl			75%
p-TsOH	60%		

exhibited a molecular ion peak at *m/z* 320. These spectral data established the dihydrobenzene structure and the presence of an enol ether moiety in (**3a**). Reduction of the lactam (**3a**) by careful addition of an excess of lithium aluminium hydride in small portions during the course of reaction gave the corresponding amine (**3b**) in 90% yield. This was then treated with 10% hydrochloric acid in methanol at room temperature for 1 h to give the unconjugated enone (**4**) homogeneously in quantitative yield. The unconjugated enone (**4**) showed i.r. absorption due to a six-membered ketone at 1 720 cm^{-1} and n.m.r. peaks due to an olefinic proton at δ 5.43 (s-like, 19-H), confirming its cyclohexenone type of structure. During purification of the unconjugated enone (**4**) by preparative thin layer chromatography (p.l.c.) on silica gel, a new spot appeared. The *cis*-conjugated enone (**5a**) was thus isolated and characterised from the following spectral evidence [$\nu_{max.}$ 1 660 cm^{-1} (C=C–CO); δ 6.89 (dt, *J* 10 and 1.8 Hz, 19-H) and 6.00 (dd, *J* 10 and 2.5 Hz, 18-H)] and its structure further unambiguously established by conversion into known alloyohimbone (**6a**).[5] Thus, exclusive formation of the *cis*-enone (**5a**) from the unconjugated enone (**4**) in the presence of silica gel was established although the isomerisation of the 19,20-didehydro compound (**4**) into the *cis*-18,19-didehydro compound (**5a**) proceeded effectively only in a small-scale experiment of below 100 mg of (**4**). In order to develop the practical and stereoselective transformation of the unconjugated enone (**4**) into either the *cis*- (**5a**) or *trans*-enone (**5b**), we investigated the isomerisation under both acidic and basic conditions. Treatment of the unconjugated enone (**4**) with 10% sodium hydroxide in methanol–methylene dichloride (4:1) at 0 °C for 1 h yielded the *cis*-enone (**5a**) in 90% yield, identical with the sample obtained above. However, under acidic conditions using various acids such as hydrochloric acid, organic mono or dibasic acids, the unconjugated enone (**4**) was found to isomerise to the *trans*-enone (**5b**) selectively as shown in the Table. Thus, heating the unconjugated enone (**4**) in dioxane at 85 °C in the presence of either tartaric acid, malic acid, or conc. hydrochloric acid gave the *trans*-enone (**5b**) in 75% yield, which showed characteristic i.r. and n.m.r. spectra [$\nu_{max.}$ 1 680 cm^{-1} (C=C–C=O); δ 6.80 (dd, *J* 10 and 1.5 Hz, 19-H) and 6.08 (dd, *J* 10 and 3 Hz, 18-H)]. The *trans*-enone moiety was unambiguously established by its conversion into known yohimbone (**6b**).[5] On heating in dioxane at 85 °C in the presence of conc. hydrochloric acid, the *cis*-enone (**5a**) was isomerised into the *trans*-enone (**5b**) in 60% yield.

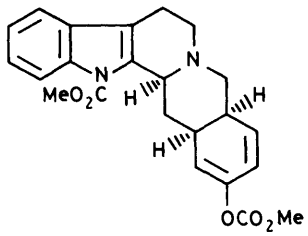
The *cis*- and *trans*-enones (**5a** and **b**) were converted into authentic alloyohimbone (**6a**) and yohimbone (**6b**),[5] respectively, by catalytic reduction of the double bonds over platinum dioxide and 10% palladium on carbon in excellent yields. Thus, two potential key intermediates, α,β-unsaturated enones (**5a** and **b**), for the synthesis of alloyohimbine and yohimbine from the common ketone (**4**) were stereoselectively prepared simply by selecting the reaction temperature.

Total Synthesis of (±)-*Yohimbine* (**10**), (±)-*Alloyohimbine* (**11**), *and* (±)-19,20-*Didehydroyohimbines* (**15a**, **b**, *and* **c**) *by Regioselective Acylation.*—The structural features of the two enones (**5a** and **b**) having one sp^3 carbon adjacent to carbonyl group at the 16-position led us to investigate the possibility of regioselective introduction of an electrophile such as a methoxycarbonyl group into the sterically hindered 16-position. Treatment of the *trans*-enone (**5b**) with an excess of lithium diisopropylamide (LDA) in tetrahydrofuran at −78 °C followed by addition of methyl chloroformate gave a mixture of the acylated products which without purification was subjected to catalytic hydrogenation over platinum dioxide at room temperature under hydrogen atmosphere to afford two isolated products, the *N*,*O*-diacylated product (**7**) and the *N*,*C*-diacylated product (**8a**) in 29 and 14% yields, respectively. The former (**7**) showed i.r. absorption at 1 760—1 730 cm^{-1} due to NCO_2Me and OCO_2Me and n.m.r. signals at δ 5.30 (s-like, 16-H) and 3.97 and 3.73 (each 3 H, s, OMe × 2). The structure of another product (**8a**) was established unambiguously from the spectral data and from its chemical conversion into authentic yohimbinone (**8b**)[6] by *N*-deacylation with potassium carbonate in methanol.[7] In order to improve the yield of the 16-acylated product (**8a**) on acylation of the enone (**5b**), we next employed two alternative reaction conditions; the magnesium enolate developed by House[8] and the soft acylating agent provided by Mander.[9] House, *et al.*,[8] suggested that the magnesium enolate prepared from ketones exists in the contact ion pair structure and reacts with an acylating agent to afford preferentially the *C*-acylated product over the *O*-acylated one. Thus, treatment of the lithium enolate, prepared *in situ* from the *trans*-enone (**5b**) and LDA at −78 °C, with freshly prepared anhydrous magnesium bromide followed by addition of methyl chloroformate gave the desired 16-acylated product (**9**) in 68% yield with no *O*-acylated product. This reaction would proceed *via* a magnesium enolate having a contact ion pair structure which would allow an electrophile to attack exclusively at the carbon atom forming the *C*-acylated product (**9**). The desired product (**9**) was thus prepared regioselectively by using the magnesium enolate of the enone (**5b**) although the tedious preparation of anhydrous magnesium bromide was a problem. We, therefore, investigated the alternative method of the regioselective *C*-acylation using the soft acylating agent, methyl cyanoformate, which has been used as an excellent reagent for the preparation of the β-keto ester from a ketone by Mander, *et al.*[9] Acylation of the lithium enolate of the *trans*-enone (**5b**) with methyl cyanoformate proceeded smoothly to give the 16-acylated product (**9**) in 70% yield as the sole product. The 16-acylated product (**9**) corresponds to 18,19-didehydroyohimbinone and was catalytically hydrogenated over platinum dioxide to give yohimbinone (**8b**) in overall 42% yield from harmalane (**1**) by a 7-step route. Since yohimbinone (**8b**) had been converted into (±)-yohimbine (**10**),[6] this synthesis completes the formal total synthesis of the parent alkaloid (±)-yohimbine (**10**).

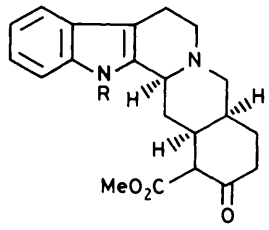
Based on the result obtained in the synthesis of (±)-yohimbine, we have also completed the total synthesis of (±)-alloyohimbine (**11**) *via* the same route involving regioselective acylation at the 16-position on the *cis*-enone (**5a**). Acylation of the lithium enolate, prepared *in situ* from the *cis*-enone (**5a**) and LDA at −78 °C, with methyl chloroformate gave a mixture of the *N*,*C*-diacylated and *N*,*O*-diacylated products (**12a**) and (**13**) in 49 and 10% yields, respectively. Acylation of either the magnesium enolate of the *cis*-enone (**5a**) with methyl chloroformate or the lithium enolate of (**5a**) with methyl cyanoformate gave the 16-acylated (**12b**) (69% yield) or the *N*,*C*-diacylated product (**12a**) (90% yield), respectively. On catalytic hydrogenation over platinum dioxide, these compounds (**12a**) and (**12b**) gave the *N*-acylalloyohimbinone (**14a**) and alloyohimbinone (**14b**), respectively; the former (**14a**) was *N*-deacylated with potassium carbonate in methanol to afford alloyohimbinone (**14b**). The keto ester (**14b**) was identical with



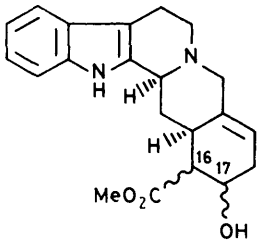
(**12a**) R = CO_2Me
(**12b**) R = H

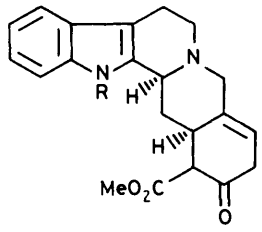


(**13**)

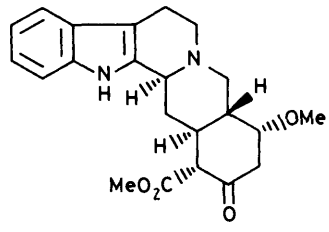


(**14a**) R = CO_2Me
(**14b**) R = H





(**16a**) R = H
(**16b**) R = CO_2Me



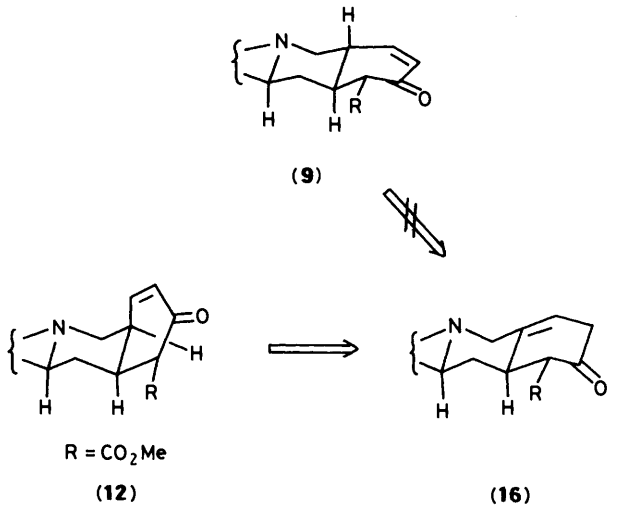
(**17**)

	16-H, 17-H		
(**15a**)	β	β	19,20-didehydroyohimbine
(**15b**)	β	α	19,20-didehydro-β-yohimbine
(**15c**)	α	β	19,20-didehydro-α-yohimbine
(**15d**)	α	α	unknown

the authentic alloyohimbinone given by Professor Szántay.[10] Thus, we have succeeded in the synthesis of alloyohimbinone (**14b**) in overall 64% yield from harmalane (**1**) by an 8-step route and also in the formal total synthesis of (±)-alloyohimbine (**11**) since alloyohimbinone (**14b**) has previously been converted into (±)-alloyohimbine (**11**) upon sodium borohydride reduction.[10]

Finally, the applicability of our synthetic methodology using the unconjugated enone (**4**) as a common key intermediate was established by the accomplishment of the first total synthesis of (±)-19,20-didehydroyohimbines (**15a**, **b**, and **c**) previously isolated from *Aspidosperma pyricollum*[11] and *oblogum*[12] and characterised only by their spectral data. So far, no synthetic work of these 19,20-didehydroyohimbines except Brown's work[13] on the chemical conversion of secologanin into 19,20-didehydroyohimbinyl acetate and Martin's work[3g] on the synthesis of 19,20-didehydro-α-yohimbine has been reported. Two 18,19-didehydro-β-keto esters (**9**) and (**12**) prepared as above would be the key intermediates for the synthesis of 19,20-didehydroyohimbines if deconjugation of the α,β-unsaturated enone system would be accomplished. Thus, we investigated their deconjugation reaction and obtained the desired 19,20-didehydro-β-keto esters (**16a** and **b**) from the *cis*-enones (**12a** and **b**). Smooth isomerisation occurred, either by stirring a methanolic solution of the *cis*-enone (**12b**) in the presence of potassium carbonate at 0 °C or by refluxing the methanolic solution in the presence of conc. sulphuric acid, to yield the desired 19,20-didehydro-β-keto ester (**16a**) in 73 or 70% yields, respectively. The structure of the 19,20-didehydro compound (**16a**) was established from the spectral data [$\nu_{max.}$ 1 740, 1 680, 1 660, and 1 620 cm^{-1} (keto and enol ester); δ 12.40 (2/3H, s, enol OH) and 5.60 (m, 19-H)]. Similarly, heating a methanolic solution of the *N*,*C*-diacylated *cis*-enone (**12a**) in the presence of conc. sulphuric acid under reflux yielded the 19,20-didehydro-β-keto ester (**16b**) in 90% yield which was carefully treated with potassium carbonate in methanol at 15 °C to give the *N*-deacylated 19,20-didehydro-β-keto ester (**16a**). Treatment of compound (**12a**) with potassium carbonate in methanol at 0 °C gave a mixture of the 19,20-didehydro compounds (**16a** and **b**) in 20 and 51% yields, respectively, the former (**16a**) of which would be formed as a result of *N*-deacylation under the basic conditions employed. On the other hand, attempted isomerisation of the *trans*-enone (**9**) to the 19,20-didehydro compound (**16a**) was unsuccessful even under acidic and basic conditions and the Michael adduct (**17**) with a methoxy group at the 19-position was obtained. Treatment of a methanolic solution of the *trans*-enone (**9**) with either potassium carbonate at 0 °C or conc. sulphuric acid at 80 °C gave no isomerised product (**16a**) but gave the methoxylated adduct (**17**) in 55 or 38% yield, respectively. The product (**17**) exhibited a molecular ion peak at *m*/*z* 382 in the mass spectrum, i.r. absorption at 1 720 cm^{-1} due to the saturated ketone, and n.m.r. signals at δ 3.34 (s, OMe) and 3.73 (q, *J* 2.5 Hz, 19-H), establishing its stereostructure. The differences in the reaction course between the *cis*- (**12a** and **b**) and *trans*-enone (**9**) can be explained as follows. The structurally less stable *cis*-enones (**12a** and **b**) with a folded conformation would be readily isomerised to the thermodynamically more stable and planar 19,20-didehydro compounds (**16a** and **b**), respectively, which exist in planar conformations as shown in the Scheme. From the spectral data, the *trans*-enone (**9**) is found to exist only in a keto ester form which would act as a Michael acceptor in the presence of methanol while the *cis*-enones (**12a** and **b**) exist in an equilibrium mixture of the keto and enol ester, thus being less reactive as a Michael acceptor and readily isomerised to the more stable 19,20-didehydro isomers (**16a** and **b**).

In the final modification of its structure, the keto ester (**16a**)



was subjected to sodium borohydride reduction at 0 °C to give a mixture of four stereoisomeric hydroxy esters (**15b**), (**15c**), (**15a**), and (**15d**) which were separated by p.l.c. on silica gel in 40, 20, 10, and 10% yields, respectively. By comparison of their n.m.r. spectra with authentic 19,20-didehydroyohimbines, the products (**15b**), (**15c**), and (**15a**) were identified as 19,20-didehydro-β-yohimbine,[12] 19,20-didehydro-α-yohimbine,[12] and 19,20-didehydroyohimbine,[11] respectively. The fourth isomer (**15d**) was found to be the 17β-hydroxy-16β-methoxycarbonyl derivative from its n.m.r. spectrum which showed signals at δ 4.32 (m, 17-H) and 3.07 (t, *J* 4 Hz, 16-H), suggesting a methoxycarbonyl group in the 16β-axial orientation and a hydroxy group in the 17β-equatorial orientation.

The application of this strategy to the synthesis of reserpine type alkaloids will be reported at a later date.

Experimental

^1H N.m.r. spectra were measured with JEOL PMX-60 and Varian XL-200 instruments for solutions in deuteriochloroform unless otherwise stated (tetramethylsilane as internal reference), mass spectra with JEOL JMSO1SG and Hitachi M-80 instruments, and i.r. spectra for solutions in chloroform on a Hitachi 215 spectrometer. M.p.s were determined with a Kofler-type hot-stage apparatus. The extracts from the reaction mixtures were dried over anhydrous sodium sulphate. Photochemical reactions were carried out by irradiation with a high-pressure (100 or 300 W) mercury lamp through a Pyrex filter (Eikosha, Osaka, Japan, PIH-100 or PIH-300); during irradiation, the solutions were kept at 5—10 °C whilst being stirred and treated with bubbling nitrogen. Ether refers to diethyl ether.

2,3,4,9-*Tetrahydro*-2-(4-*methoxybenzoyl*)-1-*methylene*-1H-*pyrido*[3,4-b]*indole* (**2**).—A solution of 4-methoxybenzoyl chloride (185 mg) in anhydrous benzene (10 ml) was added dropwise to an ice-cooled, stirred solution of harmalane (**1**) (184 mg) and triethylamine (150 mg) in anhydrous benzene (10 ml). After being stirred at room temperature for 2 h, the solution was filtered to remove triethylamine hydrochloride. The filtrate was evaporated to give the unstable enamide (**2**) (318 mg, 99%) as a pale yellow glass; δ(60 MHz) (*inter alia*) 4.97 and 4.40 (each 1 H, d-like, *J* 2 Hz, C=CH_2) and 3.77 (3 H, s, OMe) which was used for irradiation without further purification.

16,17,19,20-*Tetradehydro*-17-*methoxy-yohimban*-21-*one* (**3a**).—Sodium borohydride (350 mg) and methanol (15 ml) were added successively to a stirred solution of the enamide (**2**) (318 mg) in acetonitrile (150 ml) at room temperature. When the added sodium borohydride had dissolved, the resulting solution was cooled to 5—10 °C and irradiated for 30 min. The reaction mixture was then evaporated at room temperature under reduced pressure. Water was added to the residue to separate the colourless solid which was recrystallised from methanol to afford the lactam (**3a**) (288 mg, 90%), m.p. 248—250 °C; $\nu_{max.}$ 3 455 (NH), 1 690 and 1 655 (C=C), and 1 610 cm^{-1} (NCO); δ(200 MHz) (*inter alia*) 7.98 (1 H, s, NH), 6.94 (1 H, m, 19-H), 5.18 (1 H, m, 5-H_{eq}), 4.95 (1 H, br dd, *J* 12 and 4 Hz, 3-H), 4.56 (1 H, s-like, 16-H), 3.58 (3 H, s, OMe), 3.35 (1 H, m, 15-H), 3.04—2.74 (5 H, m, 18-H_2, 6-H_2, and 5-H_{ax}), 2.56 (1 H, ddd, *J* 12, 4, and 3.5 Hz, 14-H_{eq}), and 1.69 (1 H, q, *J* 12 Hz, 14-H_{ax}) (Found: C, 74.3; H, 6.2; N, 8.65. $C_{20}H_{20}N_2O_2 \cdot 1/6H_2O$ requires C, 74.3; H, 6.35; N, 8.65%).

16,17,19,20-*Tetradehydro*-17-*methoxy-yohimban* (**3b**).—A solution of the lactam (**3a**) (700 mg) in anhydrous THF (70 ml) was added dropwise to an ice-cooled, stirred solution of lithium aluminium hydride (1.0 g) in anhydrous ether (70 ml) under nitrogen. After being refluxed for 2 h, lithium aluminium hydride (700 mg) was added to the reaction mixture in small portions (several times) with nitrogen bubbling. Work-up afforded the *amine* (**3b**) (600 mg, 90%), m.p. 173—175 °C (from methanol); $\nu_{max.}$ 3 480 (NH) and 1 700 and 1 660 cm^{-1} (C=C); δ(200 MHz) (*inter alia*) 8.84 (1 H, br s, NH), 5.59 (1 H, m, 19-H), 4.56 (1 H, br d, *J* 3 Hz, 16-H), 3.56 (3 H, s, OMe), 3.52 (1 H, br dd, *J* 12 and 2.5 Hz, 3-H), 3.44 and 3.07 (2 H, ABq, *J* 12 Hz, 21-H_2), 3.00 (1 H, m, 15-H), 2.26 (1 H, ddd, *J* 12, 4.5, and 2.5 Hz, 14-H_{eq}), and 1.49 (1 H, q, *J* 12 Hz, 14-H_{ax}) (Found: C, 78.15; H, 7.4; N, 8.85. $C_{20}H_{22}N_2O \cdot 1/10MeOH$ requires C, 77.95; H, 7.3; N, 9.05%).

19,20-*Didehydroyohimban*-17-*one* (**4**).—10% Hydrochloric acid (18 ml) was added to a solution of the amine (**3b**) (250 mg) in methanol (15 ml). After being stirred at room temperature under a nitrogen stream for 1 h, the reaction mixture was evaporated. Water was added to the residue and the mixture was made alkaline by the addition of saturated aqueous sodium hydrogen carbonate, and then extracted with chloroform. The organic layer was washed, dried, and evaporated to give a solid which was triturated with ether to afford the unconjugated enone (**4**) (238 mg, 99%); $\nu_{max.}$ 3 480 (NH) and 1 720 cm^{-1} (C=O); δ(200 MHz) (*inter alia*) 5.43 (1 H, s-like, 19-H), 3.54 and 3.07 (2 H, ABq, *J* 12.5 Hz, 21-H_2), 3.40 (1 H, br d, *J* 12 Hz, 3-H), 2.30 (1 H, ddd, *J* 12, 5, and 3 Hz, 14-H_{eq}), and 1.54 (1 H, q, *J* 12 Hz, 14-H_{ax}). This enone (**4**) was found to be partially isomerised to the following *cis*-enone (**5a**) as detected by t.l.c. on silica gel.

(20α)-18,19-*Didehydroyohimban*-17-*one* (**5a**).—(a) *By p.l.c. on silica gel.* Purification of the crude enone (**4**) (76 mg) by p.l.c. (2 mm, Kieselgel 60F254 Art. 5735, Merck) gave the *cis*-enone (**5a**) (68 mg, 90%) as pale yellow crystals, m.p. 206—208 °C (from methanol); $\nu_{max.}$ 3 475 (NH) and 1 660 cm^{-1} (C=C–CO); δ(200 MHz) (*inter alia*) 7.86 (1 H, s, NH), 6.89 (1 H, dt, *J* 10 and 1.8 Hz, 19-H), 6.00 (1 H, dd, *J* 10 and 2.5 Hz, 18-H), 3.25 (1 H, br d, *J* 11 Hz, 3-H), 1.86 (1 H, dt, *J* 12.5 and 5 Hz, 14-H_{eq}), and 1.72 (1 H, ddd, *J* 13, 12.5 and 11 Hz, 14-H_{ax}) (Found: C, 77.9; H, 6.9; N, 9.3. Calc. for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.90, N, 9.6%).

(b) *Using sodium hydroxide.* A solution of 10% sodium hydroxide in methanol (60 mg) was added to an ice-cooled, stirred solution of the enone (**4**) (200 mg) in a mixture of methanol–methylene dichloride (4:1) (20 ml) under a nitrogen stream. After being stirred under ice-cooling for 1 h, the reaction mixture was diluted with water and extracted with methylene dichloride. The extract was washed, dried, and evaporated to give a solid which was recrystallised from methanol to afford the

cis-enone (**5a**) (180 mg, 90%) as pale yellow crystals, m.p. 206—208 °C. This enone was identical with the *cis*-enone (**5a**) obtained by treatment with silica gel as described above.

(20β)-18,19-*Didehydroyohimban*-17-*one* (**5b**).—(a) *From the unconjugated enone* (**4**). A solution of the unconjugated enone (**4**) (200 mg) and tartaric acid (100 mg) in dioxane (15 ml) was heated at 85 °C with stirring under a nitrogen stream for 8 h. Water was added and the mixture was extracted with methylene dichloride. The extract was washed, dried, and evaporated to give a solid which was recrystallised from methanol to give the *trans*-enone (**5b**) (150 mg, 75%) as pale yellow crystals, m.p. 224—226 °C (decomp.); $\nu_{max.}$ 3 500 (NH) and 1 680 cm^{-1} (C=C–CO); *m/z* 292 (M^+); δ(200 MHz) (*inter alia*) 7.80 (1 H, br s, NH), 6.80 (1 H, dd, *J* 10 and 1.5 Hz, 19-H), 6.08 (1 H, dd, *J* 10 and 3 Hz, 18-H), 3.38 (1 H, br d, *J* 12 Hz, 3-H), 2.12 (1 H, dt, *J* 12 and 3 Hz, 14-H_{eq}), and 1.60 (1 H, q, *J* 12 Hz, 14-H_{ax}) (Found: C, 78.1; H, 6.9; N, 9.55. $C_{19}H_{20}N_2O$ requires C, 78.05; H, 6.90; N, 9.6%).

(b) *From the* cis-*enone* (**5a**). Conc. hydrochloric acid (0.04 ml) was added to a solution of the *cis*-enone (**5a**) (20 mg) in dioxane (2.5 ml). After being heated at 85 °C for 8 h, the reaction mixture was diluted with water, made alkaline by the addition of saturated aqueous sodium hydrogen carbonate, and extracted with methylene dichloride. The extract was washed, dried, and evaporated to give a solid which was recrystallised from methanol to afford the *trans*-enone (**5b**) (12 mg, 60%). This enone was identical with the *trans*-enone (**5b**) by comparison of i.r. spectra and R_F values.

Isomerisation of the Unconjugated Enone (**4**) *Under Acidic Conditions.*—Following the procedure given for the isomerisation of the enone (**4**) to the *trans*-enone (**5b**) in the presence of tartaric acid, a solution of the unconjugated enone (**4**) (20 mg) in dioxane was warmed at 85 °C for 8 h in the presence of the respective acid. The results were collected in the Table. The products obtained were identified by comparison of the i.r. spectra and R_F values with those of an authentic sample.

(20α)-*Yohimban*-17-*one* (*Alloyohimbone*) (**6a**).—A solution of the *cis*-enone (**5a**) (15 mg) in anhydrous methanol (3 ml) was catalytically hydrogenated over platinum dioxide (5 mg) under a hydrogen atmosphere at room temperature for 17 h. Work-up gave a solid which was recrystallised from methanol to afford alloyohimbone (**6a**) (15 mg, 99%), m.p. 262—265 °C (decomp.) (lit.,[5] 265—267 °C). This ketone was identical with the authentic alloyohimbone prepared from alloyohimbinone by a known procedure.[5]

(20β)-*Yohimban*-17-*one* (*Yohimbone*) (**6b**).—Following the procedure given for compound (**6a**), catalytic hydrogenation of the *trans*-enone (**5b**) (20 mg) over 10% palladium–carbon (5 mg) gave yohimbone (**6b**) (20 mg, 99%), m.p. 261—264 °C (decomp.) (from methanol) (lit.,[5] 263—264 °C). This ketone was identical with the authentic (+)-yohimbone prepared from (+)-yohimbine by a known procedure.[6,14]

Acylation of the Lithium Enolate Prepared from the trans-*Enone* (**5b**) *with Methyl Chloroformate.*—A solution of the *trans*-enone (**5b**) (50 mg) in anhydrous THF (5 ml) was added with stirring at −78 °C to an LDA solution, prepared from di-isopropylamine (0.12 ml) and butyl-lithium (15% solution in hexane) (0.38 ml) at −78 °C under a nitrogen stream. After being stirred at this temperature for 1 h, methyl chloroformate (0.07 ml) was added and the resulting solution was stirred at −78 °C for a further 1 h. After being quenched by the addition of water, the reaction mixture was extracted with methylene dichloride. The extract was dried and evaporated to give a residue which, without purification, was subjected to catalytic hydrogenation over platinum dioxide (23 mg) under a hydrogen atmosphere at room temperature for 1 h. Work-up gave a residue which was purified by p.l.c. on silica gel to afford two acylated products (**7**) and (**8a**): *methyl* 16,17-*didehydro*-17-*methoxycarbonyloxy-yohimban*-1-*carboxylate* (**7**) (17.5 mg, 29%) as a yellow oil, $\nu_{max.}$ 1 760—1 730 cm^{-1} (NCO_2Me and OCO_2Me); δ(60 MHz) (*inter alia*) 7.97 (1 H, m, 12-H), 5.30 (1 H, s-like, 16-H), 4.27 (1 H, br d, *J* 12 Hz, 3-H), 3.97 (3 H, s, NCO_2Me), and 3.73 (3 H, s, OCO_2Me) (Found: M^+, 410.183. $C_{23}H_{26}N_2O_5$ requires *M*, 410.184). *Dimethyl* (16α)-17-*oxoyohimban*-1,16-*dicarboxylate* (**8a**) (8.4 mg, 14%), m.p. 166—169 °C) (from ether–methanol); $\nu_{max.}$ 1 740 (NCO_2Me and CCO_2Me) and 1 720 cm^{-1} (CO); δ(60 MHz) (*inter alia*) 8.13 (1 H, m, 12-H), 4.00 (3 H, s, NCO_2Me), and 3.77 (3 H, s, CCO_2Me) (Found: M^+, 410.183. $C_{23}H_{26}N_2O_5$ requires *M*, 410.184).

Methyl (16α)-17-*Oxoyohimban*-16-*carboxylate* (*Yohimbinone*) (**8b**).—A mixture of the *N,C*-diacylated product (**8a**) (8.4 mg), potassium carbonate (15 mg), and methanol (5 ml) was stirred under a nitrogen stream at room temperature for 3 h. After being diluted with water, the reaction mixture was extracted with methylene dichloride, then washed, dried, and evaporated to give a solid which was recrystallised from methanol to afford yohimbinone (**8b**) (7 mg, 97%), m.p. 226—227 °C (decomp.) (lit.,[6] 239 °C); $\nu_{max.}$ 3 500 (NH), 1 745 (CO_2Me), and 1 720 cm^{-1} (CO); *m/z* 352 (M^+); δ($CDCl_3$–CD_3OD) (200 MHz) (*inter alia*) 3.84 (3 H, s, CO_2Me), 3.28 (1 H, d, *J* 12 Hz, 16-H), 3.29 (1 H, br d, *J* 11 Hz, 3-H), and 1.42 (1 H, q, *J* 11 Hz, 14-H_{ax}) (Found: C, 70.65; H, 6.85; N, 7.95. Calc. for $C_{21}H_{24}N_2O_3 \cdot 1/4H_2O$: C, 70.65; H, 6.9; N, 7.85%). This ketone (**8b**) was identical with authentic yohimbinone, provided by Professor Szántay,[6] by comparison with their i.r. and n.m.r. spectra and R_F values and mixed m.p.

Acylation of the Magnesium Enolate of the trans-*Enone* (**5b**) *with Methyl Chloroformate.*—A solution of freshly prepared anhydrous magnesium bromide (35 mg) was added to a solution of the lithium enolate, prepared from the *trans*-enone (**5b**) (50 mg), di-isoproylamine (0.05 ml), and butyl-lithium (15% solution in hexane) (0.16 ml) according to the procedure described above, with stirring under a nitrogen stream at −78 °C. After being stirred at −78 °C for 40 min, methyl chloroformate (0.029 ml) was added and the reaction mixture was stirred under a nitrogen stream at −78 °C for 1 h. Water was then added and the reaction mixture was extracted with methylene dichloride. The extract was dried and evaporated to give a residue which was purified by p.l.c. on silica gel to afford *methyl* (16α)-18,19-*didehydro*-17-*oxoyohimban*-16-*carboxylate* (**9**) (41 mg, 68%) as pale yellow crystals, m.p. 216—218 °C (from methanol); $\nu_{max.}$ 3 495 (NH), 1 740 (CO_2Me), 1 680 (C=C–CO), and 1 620 cm^{-1} (C=C); δ(200 MHz) (*inter alia*) 7.88 (1 H, br s, NH), 6.82 (1 H, dd, *J* 10 and 2 Hz, 19-H), 6.12 (1 H, dd, *J* 10 and 3 Hz, 18-H), 3.89 (3 H, s, CO_2Me), 3.41 (1 H, br d, *J* 12 Hz, 3-H), 2.13 (1 H, dt, *J* 12 and 3 Hz, 14-H_{eq}), and 1.56 (1 H, q, *J* 12 Hz, 14-H_{ax}) (Found: C, 71.95; H, 6.45; N, 7.85. $C_{21}H_{22}N_2O_3$ requires C, 72.0; H, 6.35; N, 8.0%).

Acylation of the Lithium Enolate of the trans-*Enone* (**5b**) *with Methyl Cyanoformate.*—Acylation of the lithium enolate, prepared from the *trans*-enone (**5b**) (50 mg) and LDA, with methyl cyanoformate (32 mg), and purification of the crude product by p.l.c. on silica gel afforded the ester (**9**) (42 mg, 70%) which was identical with the sample obtained above.

Catalytic Hydrogenation of the C-*Acylated Compound* (**9**).—A solution of the ester (**9**) (30 mg) in anhydrous methanol (10 ml) was subjected to catalytic hydrogenation over platinum

dioxide (10 mg) under a hydrogen atmosphere at room temperature for 1 h. Work-up gave a solid which was recrystallised from methanol to afford yohimbinone (**8b**) (30 mg, 99%). This ester (**8b**) was identical with the sample prepared by *N*-deacylation of (**8a**) prepared above.

Acylation of the cis-*Enone* (**5a**).—(a) *By acylation of the lithium enolate with methyl chloroformate.* Following the procedure given for (**5b**), acylation of the lithium enolate of the *cis*-enone (**5a**) (50 mg) with methyl chloroformate (0.029 ml) followed by purification of the crude product by p.l.c. on silica gel afforded the *N,C*-diacylated product (**12a**) (34 mg, 49%) and the *N,O*-diacylated product (**13**) (7 mg, 10%); *dimethyl* (20α)-18,19-*didehydro*-17-*oxoyohimban*-1,16-*dicarboxylate* (**12a**) as a yellow oil, $\nu_{max.}$ 1 735, 1 680, 1 660, 1 620, and 1 590 cm^{-1} (NCO_2Me and C=CCOCHCO_2Me); δ(200 MHz) (*inter alia*) 11.94 (3/5 H, br s, enolic OH), 6.95 (2/5 H, dt, *J* 10 and 2 Hz, 19-H of keto form), 6.34 (3/5 H, dt, *J* 10 and 2 Hz, 19-H of enol form), 6.07 (2/5 H, dd, *J* 10 and 2.5 Hz, 18-H of keto form), 5.99 (3/5 H, dd, *J* 10 and 3 Hz, 18-H of enol form), 4.08 (6/5 H, NCO_2Me of keto form), 4.04 (9/5 H, s, NCO_2Me of enol form), 3.86 (9/5 H, s, CCO_2Me of enol form), 3.76 (6/5 H, s, CCO_2Me, of keto form), 2.10 (2/5 H, br d, *J* 11 Hz, 14-H_{eq} of keto form), 2.03 (3/5 H, ddd *J* 11, 4, and 2 Hz, 14-H_{eq} of enol form), 1.68 (2/5 H, td, *J* 12 and 11 Hz, 14-H_{ax} of keto form), and 1.47 (3/5 H, td, *J* 12 and 11 Hz, 14-H_{ax} of enol form) (Found: M^+, 408.169. $C_{23}H_{24}N_2O_5$ requires *M*, 408.168). *Methyl* (20α)-16,17,18,19-*tetradehydro*-17-*methoxycarbonyloxy*-*yohimban*-1-*carboxylate* (**13**) as a yellow oil, $\nu_{max.}$ 1 760—1 730 cm^{-1} (NCO_2Me and OCO_2Me); δ(60 MHz) (*inter alia*) 7.90 (1 H, m, 12-H), 5.78 (2 H, br s, 18- and 19-H), 5.50 (1 H, br d, *J* 4 Hz, 16-H), 4.00 (3 H, s, NCO_2Me), and 3.77 (3 H, s, OCO_2Me) (Found: M^+, 408.171. $C_{23}H_{24}N_2O_5$ requires *M*, 408.168).

(b) *By acylation of the magnesium enolate with methyl chloroformate.* According to the procedure given for (**5b**), acylation of the magnesium enolate of the *cis*-enone (**5a**) (50 mg) with methyl chloroformate followed by purification of the crude product by p.l.c. on silica gel afforded *methyl* (20α)-18,19-*didehydro*-17-*oxoyohimban*-16-*carboxylate* (**12b**) (41.5 mg, 69%) as a pale yellow oil, $\nu_{max.}$ 3 490 (NH), 1 735, 1 680, 1 655, 1 620, and 1 585 cm^{-1} (C=CCOCHCO_2Me); δ(200 MHz) (*inter alia*) 11.98 (1/2 H, br s, enolic OH), 8.10 and 7.83 (each 1/2 H, br s, NH), 6.93 (1/2 H, dt, *J* 10.5 and 2 Hz, 19-H of keto form), 6.36 (1/2 H, dt, *J* 10 and 1.5 Hz, 19-H of enol form), 6.07 (1/2 H, dd, *J* 10.5 and 3 Hz, 18-H of keto form), 6.00 (1/2 H, dd, *J* 10 and 3 Hz, 18-H of enol form), 3.87 and 3.74 (each 3/2 H, s, CO_2Me), 3.30 and 3.16 (each 1/2 H, br d, *J* 12 Hz, 3-H), 1.96 (1/2 H, dt, *J* 12 and 3 Hz, 14-H_{eq}), 1.90 (1/2 H, dt *J* 12 and 4 Hz, 14-H_{eq}), and 1.71 and 1.57 (each 1/2 H, q, *J* 12 Hz, 14-H_{ax} (Found: M^+, 350.163. $C_{21}H_{22}N_2O_3$ requires *M*, 350.163).

(c) *By acylation of the lithium enolate with methyl cyanoformate.* Following the procedure given for (**5b**), acylation of the lithium enolate of the *cis*-enone (**5a**) (100 mg) with methyl cyanoformate (62 mg) followed by purification by p.l.c. on silica gel afforded the *N,C*-diacylated product (**12a**) (126 mg, 90%) identical with the sample (**12a**) obtained in (*a*).

Methyl (20α)-17-*Oxoyohimban*-16-*carboxylate* (*Alloyohimbinone*) (**14b**).—Following the procedure given for (**9**), catalytic hydrogenation of the *C*-acylated product (**12b**) followed by purification by p.l.c. on silica gel afforded the keto ester (**14b**) (30 mg, 97%) as a yellow oil which was identical with the authentic alloyohimbinone (**14b**) provided by Professor Szántay [10] by comparison of their i.r. and n.m.r. spectra and R_F values; $\nu_{max.}$ 3 490 (NH), 1 750, 1 720, 1 660, and 1 620 cm^{-1} (COCHCO_2Me); δ(200 MHz) (*inter alia*) 12.37 (4/7 H, s, enolic OH), 7.80 (1 H, br s, NH), 3.87 (3 H, s, CO_2Me), 3.28 (1 H, br d, *J* 12 Hz, 3-H), and 1.53 (1 H, q, *J* 12 Hz, 14-H_{ax}) (Found: M^+, 352.180. Calc. for $C_{21}H_{24}N_2O_3$: *M*, 352.179).

Dimethyl (20α)-17-*Oxoyohimban*-1,16-*dicarboxylate* (**14a**).—Following the procedure given for (**9**), catalytic hydrogenation of (**12a**) (30 mg) followed by purification by p.l.c. on silica gel afforded the keto ester (**14a**) (29.5 mg, 98%) as a yellow oil, $\nu_{max.}$ 1 740—1 720, 1 655, and 1 610 cm^{-1} (NCO_2Me and $COCHCO_2Me$); δ(200 MHz) (*inter alia*) 12.33 (4/3 H, s, enolic OH), 8.07 (1 H, dd, *J* 8 and 2 Hz, 12-H), 4.03 (3 H, s, NCO_2Me), 3.83 (3 H, s, CCO_2Me), 3.72 (1 H, br d, *J* 10.5 Hz, 3-H), 2.38 (1 H, br d, *J* 12 Hz, 14-H_{eq}), and 1.30 (1 H, td, *J* 12 and 10.5 Hz, 14-H_{ax}) (Found: M^+, 410.183. $C_{23}H_{26}N_2O_5$ requires *M*, 410.184).

N-*Deacylation of the* N,C-*Diacylated Compound* (**14a**).—According to the procedure given for (**8a**), treatment of the *N,C*-diacylate (**14a**) (20 mg) with potassium carbonate in methanol gave the keto ester (**14b**) (17 mg, 99%), identical with authentic alloyohimbinone prepared by catalytic hydrogenation of (**12b**).

Methyl 19,20-*Didehydro*-17-*oxoyohimban*-16-*carboxylate* (**16a**).—(a) *Using potassium carbonate.* A mixture of the keto ester (**12b**) (25 mg), potassium carbonate (25 mg), and methanol (4 ml) was stirred at 0 °C under a nitrogen stream for 2 h. Water was then added and the mixture was extracted with methylene dichloride. The extract was washed, dried, and evaporated to give a residue which was purified by p.l.c. on silica gel to afford the unconjugated enone (**16a**) (18.3 mg, 73%) as a yellow oil, $\nu_{max.}$ 3 500 (NH), 1 740, 1 680, 1 660, and 1 620 cm^{-1} (COCHCO_2Me and C=C); δ(200 MHz) (*inter alia*) 12.40 (2/3 H, s, enolic OH), 7.80 (1 H, br s, NH), 5.60 (1 H, m, 19-H), 3.94 (2 H, s, CO_2Me of enol form), 3.90 (1 H, s, CO_2Me of keto form), 3.64 (1 H, br d, *J* 12 Hz, 3-H), 3.51 and 3.41 (2 H, ABq, *J* 11 Hz, 21-H_2), 2.68 (1 H, dt, *J* 12 and 3 Hz, 14-H_{eq}), and 1.43 (1 H, q, *J* 12 Hz, 14-H_{ax}) (Found: M^+, 350.164. $C_{21}H_{22}N_2O_3$ requires *M*, 350.163).

(b) *Using conc. sulphuric acid.* A solution of the keto ester (**12b**) (10 mg) and conc. sulphuric acid (40 mg) in methanol (5 ml) was refluxed under a nitrogen stream for 7 h. During the course of reaction, conc. sulphuric acid (*ca.* 40 mg) was added to the mixture; the reaction rate was checked by t.l.c. on silica gel. After being cooled, the reaction mixture was diluted with water, made alkaline by the addition of saturated aqueous sodium hydrogen carbonate, and extracted with methylene dichloride. The extract was washed, dried, and evaporated to give a residue which was purified by p.l.c. on silica gel to afford the 19,20-didehydro compound (**16a**) (7 mg, 70%), identical with the sample obtained in (*a*).

Dimethyl 19,20-*Didehydro*-17-*oxoyohimban*-1,16-*dicarboxylate* (**16b**).—Following the procedure given for (**12b**), treatment of the 18,19-didehydro compound (**12a**) (50 mg) with conc. sulphuric acid followed by purification by p.l.c. on silica gel afforded the 19,20-didehydro compound (**16b**) (45 mg, 90%) as a yellow oil, $\nu_{max.}$ 1 730, 1 655, and 1 620 cm^{-1} (NCO_2Me, C=C, and $COCHCO_2Me$); δ(200 MHz) (*inter alia*) 12.36 (1 H, s, enolic OH), 8.08 (1 H, dd, *J* 8 and 2 Hz, 12-H), 5.49 (1 H, br s, 19-H), 4.67 (1 H, br d, *J* 12 Hz, 3-H), 4.09 (3 H, s, NCO_2Me), 3.86 (3 H, s, CCO_2Me), 3.74 (1 H, br d, *J* 13 Hz, 21-H_{eq}), 3.38 (1 H, d, *J* 13 Hz, 21-H_{ax}), 3.38 (1 H, m, 15-H), 2.69 (1 H, ddd, *J* 12, 4, and 3 Hz, 14-H_{eq}), and 1.45 (1 H, q, *J* 12 Hz, 14-H_{ax}) (Found: M^+, 408.167. $C_{23}H_{24}N_2O_5$ requires *M*, 408.168).

Isomerisation of the N-*Acyl*-18,19-*didehydro Compound* (**12a**) *with Potassium Carbonate.*—Following the procedure given for (**12b**), treatment of the *N*-acylate (**12a**) (35 mg) with potassium carbonate followed by p.l.c. on silica gel gave the *N*-acyl-19,20-didehydro compound (**16b**) (18 mg, 51%) and the 19,20-didehydro compound (**16a**) (6 mg, 20%) which were identical with the respective samples (**16b**) and (**16a**) obtained by isomerisation of the 18,19-didehydro compounds (**12a**) and (**12b**).

N-Deacylation of the N-Acyl-19,20-didehydro Compound (**16b**).—A mixture of the *N*-acyl-19,20-didehydro compound (**16b**) (20 mg), potassium carbonate (20 mg), and methanol (3 ml) was stirred at 15 °C for 5 h. The reaction mixture was diluted with water and extracted with methylene dichloride. The extract was washed, dried, and evaporated to give a residue which was purified by p.l.c. on silica gel to afford the 19,20-didehydro compound (**16a**) (3 mg, 17%) and the starting material (**16b**) (5 mg). The 19,20-didehydro compound (**16a**) was identical with the sample obtained by isomerisation of (**12b**).

Methyl (16α,19α)-19-*Methoxy*-17-*oxoyohimban*-16-*carboxylate* (**17**).—Following the procedure given for (**12b**), treatment of the keto ester (**9**) (between 10 and 12 mg) with either potassium carbonate or conc. sulphuric acid in methanol followed by purification by p.l.c. on silica gel afforded the identical 19-methoxy adduct (**17**) (6 mg, 55% with potassium carbonate) or (5 mg, 38% with conc. sulphuric acid), m.p. 165—167 °C (from methanol); $\nu_{max.}$ 3 490 (NH), 1 740 (CO_2Me), and 1 720 cm^{-1} (C=O); δ(200 MHz) (*inter alia*) 7.92 (1 H, br s, NH), 3.86 (3 H, s, CO_2Me), 3.73 (1 H, q, *J* 2.5 Hz, 19-H), 3.36 (1 H, br d, *J* 12.5 Hz, 3-H), 3.34 (3 H, s, OMe), 2.94 (1 H, dd, *J* 13.5 and 2.5 Hz, 18-H_{eq}), 2.43 (1 H, dd, *J* 13.5 and 2.5 Hz, 18-H_{ax}), 2.20 (1 H, dt, *J* 12.5 and 3.5 Hz, 14-H_{eq}), 2.12 (1 H, tdd, *J* 11, 4, and 2.5 Hz, 20-H), and 1.44 (1 H, q, *J* 12.5 Hz, 14-H_{ax}) (Found: M^+, 382.187. $C_{22}H_{26}N_2O_4$ requires *M*, 382.189).

Reduction of the 19,20-*Didehydro Compound* (**16a**) *with Sodium Borohydride*.—A solution of the 19,20-didehydro compound (**16a**) (20 mg) and sodium borohydride (15 mg) in methanol (5 ml) was stirred at 0 °C for 30 min. Water was added to the reaction mixture and the mixture was extracted with methylene dichloride. The extract was washed, dried, and evaporated to give a residue which was purified by p.l.c. on alumina to afford a mixture of four stereoisomeric hydroxy esters which were separated; *methyl* 19,20-*didehydro*-17-*hydroxy*-*yohimban*-16-*carboxylates* (**15b**) (8 mg, 40%), (**15c**) (4 mg, 20%), (**15a**) (2 mg, 10%), and (**15d**) (2 mg, 10%) all as yellow oils. The hydroxy esters (**15b**) and (**15c**) were identical with 19,20-didehydro-β-yohimbine and 19,20-didehydro-α-yohimbine, respectively, both of which were provided by Professor Potier[12] by comparisons of the i.r. and n.m.r. spectra. I.r. and n.m.r. spectral data of the third hydroxy ester (**15a**) were consistent with those of 19,20-didehydroyohimbine reported by Professor Djerassi.[11] Compound (**15b**), $\nu_{max.}$ 3 600 (OH), 3 500 (NH), and 1 720 cm^{-1} (CO_2Me); δ(200 MHz) (*inter alia*) 7.82 (1 H, br s, NH), 5.56 (1 H, br d, *J* 5.5 Hz, 19-H), 4.08 (1 H, td, *J* 10.5 and 5.5 Hz, 17-H), 3.86 (3 H, s, CO_2Me), 3.44 (1 H, d, *J* 12 Hz, 21-H_{eq}), 3.38 (1 H, br d, *J* 12 Hz, 3-H), 2.44 (1 H, t, *J* 10.5 Hz, 16-H), 2.24 (1 H, ddd, *J* 12, 5, and 3 Hz, 14-H_{eq}), 2.14 (1 H, m, 18-H_{ax}), and 1.46 (1 H, q, *J* 12 Hz, 14-H_{ax}) (Found: M^+, 352.179. Calc. for $C_{21}H_{24}N_2O_3$: *M*, 352.179). Compound (**15c**), $\nu_{max.}$ 3 500 (NH) and 1 720 cm^{-1} (CO_2Me); δ(200 MHz) (*inter alia*) 7.80 (1 H, br s, NH), 5.60 (1 H, br s, 19-H), 4.31 (1 H, td, *J* 5 and 3 Hz, 17-H), 3.78 (3 H, s, CO_2Me), 3.46 (1 H, d, *J* 12 Hz, 21-H_{eq}), 3.46 (1 H, br d, *J* 12 Hz, 3-H), 3.00 (1 H, dd, *J* 7 and 3 Hz, 16-H), 2.36 (2 H, m, 18-H_2), and 1.94 (2 H, m, 14-H_2) (Found: M^+, 352.178). Compound (**15a**), $\nu_{max.}$ 3 500 (NH) and 1 730 cm^{-1} (CO_2Me); δ(200 MHz) (*inter alia*) 7.80 (1 H, br s, NH), 5.58 (1 H, br s, 19-H), 4.37 (1 H, br s, 17-H), 3.84 (3 H, s, CO_2Me), 3.51 (1 H, br d, *J* 12 Hz, 3-H), 3.46 (1 H, d, *J* 12.5 Hz, 21-H_{eq}), 2.48 (1 H, dd, *J* 10.5 and 1.5 Hz, 16-H), 2.36 (3 H, m, 14-H_{eq} and 18-H_2), and 1.41 (1 H, q, *J* 12 Hz, 14-H_{ax}) (Found: M^+, 352.180). Compound (**15d**), $\nu_{max.}$ 3 500 (NH) and 1 720 cm^{-1} (CO_2Me); δ(200 MHz) (*inter alia*) 7.76 (1 H, br s, NH), 5.74 (1 H, br d, *J* 5 Hz, 19-H), 4.32 (1 H, m, 17-H), 3.76 (3 H, s, CO_2Me), 3.30 (1 H, br d, *J* 12 Hz, 3-H), 3.07 (1 H, t, *J* 4 Hz, 16-H), 2.00 (1 H, dt, *J* 12 and 3.5 Hz, 14-H_{eq}), and 1.78 (1 H, q, *J* 12 Hz, 14-H_{ax}) (Found: M^+, 352.180).

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