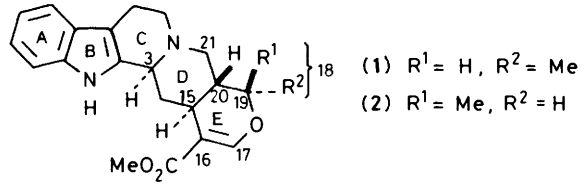
Heteroyohimbine Alkaloids. Stereospecific Conversion of Ajmalicine into 19-Epiajmalicine

Giovanni Palmisano,* Bruno Danieli, Giordano Lesma, and Renata Riva
Istituto di Chimica Organica della Facoltà di Scienze, Università degli Studi di Milano – Centro di Studio per le Sostanze Organiche Naturali del C.N.R., Via Venezian 21, 20133 Milano, Italy

An efficient four-step sequence to 19-epiajmalicine, a rare heteroyohimbane alkaloid, which requires mild conditions and utilises ajmalicine as an easily accessible starting material, is described.

Pentacyclic heteroyohimbane alkaloids represent an important group of natural products arising from the cyclisation of corynantheine aldehyde and/or geissoschizine. All compounds of this type possess a 15α-H configuration and, apart from the chirality at C-19, the eight possible stereoisomers at C-3 and C-20 occur in Nature. The four possible configurations are defined as *normal* (3α-H, 20β-H), *pseudo* (3β-H, 20β-H), *allo* (3α-H, 20α-H), and *epiallo* (3β-H, 20α-H).[1,†]

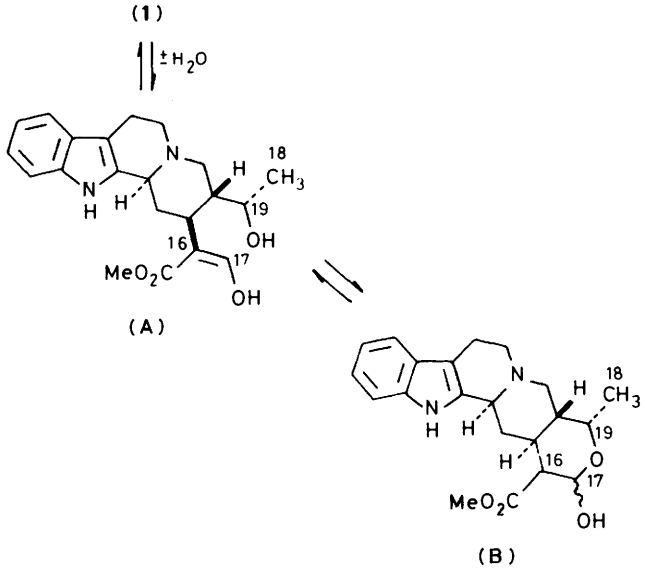
The most important member of heteroyohimbane alkaloids is ajmalicine (**1**) (raubasine, δ-yohimbine). Because of its valuable pharmacological activity, ajmalicine has found clinical use, being effective as an adrenergic blocking agent both alone and in combination therapy with reserpine.[2] On the other hand, the C-19 epimer of (**1**), 19-epiajmalicine (**2**), is very rare. It was isolated from *Pseudocinchona mayumbensis* (syn. *Corynanthe mayumbensis*) (R. Good) N. Halle and named mayumbine.[3] Mayumbine was long thought to have the *epiallo* structure but has recently shown to be 19-epiajmalicine.[4] This alkaloid was obtained, together with stereoisomeric compounds, as a racemate from total synthesis or in optically active form by partial synthesis from demethylcorynantheine.[5]



(**1**) R^1 = H, R^2 = Me
(**2**) R^1 = Me, R^2 = H

The paucity of the natural product, and the lack of a general and satisfactory method of permitting a direct and stereocontrolled access to compound (**2**), precluded extensive pharmacological studies. In view of the possible interest in compound (**2**) and in pursuance of our programme on the synthesis of indole alkaloids, we chose as the next goal 19-epiajmalicine (**2**) and we have devised a preparative route to (**2**) from (**1**). This method seemed attractive since the starting material, ajmalicine (**1**), is readily available and the obtained 19-epiajmalicine (**2**) was uncontaminated by stereoisomers, thus avoiding tedious and time-consuming chromatographic separations. Examination of the structure of compound (**1**) reveals the presence of a latent carbonyl function (C-17) as a result of dehydration of the acetal linkage between C-17 and C-19. It became evident that compound (**1**) could exist in equilibrium with the 'open'-chain carbonyl compound (**A**) and/or its equivalent (**B**) (Scheme 1).

Our initial aim in the present work was to examine the possibility of intercepting the 'open' intermediate (**A**) in order to

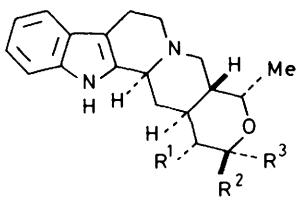


Scheme 1.

effect the inversion at C-19 and the resulting 19-epi derivative should yield the target molecule by intramolecular cyclisation–dehydration. Our synthetic plan was designed to exploit the reactivity of the ring E in ajmalicine (**1**) and this required that the carbonyl function in (**A**) must be protected, prior to the inversion step, to prevent the ring closure. However, the most misleading aspect of the chemistry of ajmalicine (**1**) was the complete resistance of ajmalicine itself to undergo E-ring cleavage with concomitant protection of the transient carbonyl group. The ineffectiveness of this strategy was exposed throughout many trials under diverse reaction conditions (*e.g.*, trimethyl orthoformate, methanol, catalytic toluene-*p*-sulphonic acid; propane-1,3-diol–Amberlyst-15, tetrahydrofuran; propane-1,3-dithiol–trifluoroacetic acid;[6] n-propanethiol–trimethylchlorosilane[7]). The presence of a *trans* D/E ring junction and axial orientation of the methyl group at C-19 could apparently cause the reactions of a heteroyohimbine to be modified. For example, alstonine and tetrahydroalstonine, the *allo* isomer of ajmalicine (**1**), are reported [8] to give, under the usual reaction conditions, the derivatives (*e.g.*, 2,4-DNP) of their 'open'-chain compounds.

At the inception of our work, Chatterjee *et al.*[9] reported that treatment of ajmalicine (**1**) with 5% sulphuric acid afforded a yellow crystalline hemiacetal (m.p. 167—168 °C) (40% yield), which was identified from its ^{1}H n.m.r. spectrum as compound (**3**). We envisaged that this compound could provide the starting point for a relatively brief synthesis of 19-epiajmalicine (**2**), as outlined in Scheme 2. We therefore repeated the acid-catalysed

† The numbering system is one based on the biogenetic interrelationship of the indole alkaloids as proposed by J. Le Men and W. I. Taylor, *Experientia*, 1965, **21**, 508.

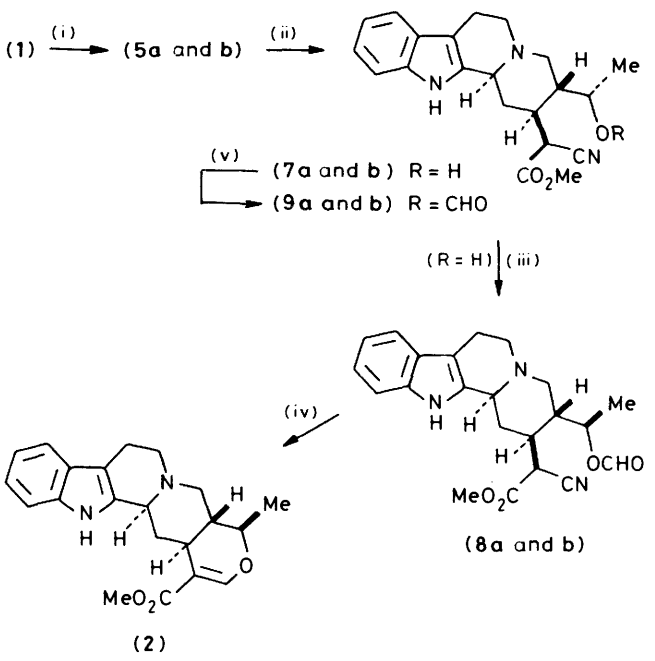


(3) $R^1 = CO_2Me$, $R^2 = H$, $R^3 = OH$
(4)a; $R^1 = R^3 = H$, $R^2 = OH$
b; $R^1 = R^2 = H$, $R^3 = OH$
(5)a; $R^1 = CO_2Me$, $R^2 = OH$, $R^3 = H$
b; $R^1 = CO_2Me$, $R^2 = H$, $R^3 = OH$
(6) $R^1 = CN$, $R^2R^3 = O$

treatment of ajmalicine (**1**) under the conditions used by Chatterjee: the resulting mixture contained, besides starting material, the desired hemiacetal and ajmalicial (**4**) as a 4:1 mixture (by ^1H n.m.r.) of two anomers (**4a** and **b**), respectively.* The recrystallised hemiacetal (m.p. 165—166 °C), obtained in 42% yield, appeared to be homogeneous on t.l.c. and its properties corresponded to those reported. However, the 200-MHz ^1H n.m.r. spectrum of this material was not consistent with Chaterjee's structure and showed that the product was actually a mixture of two epimers at C-17 in the approximate ratio 9:1. Even though the stereochemistry of this centre is ultimately unimportant with regard to the target molecule, we have ascertained (see Experimental section) that the major compound of the above mixture must be represented stereochemically as in structure (**5a**), in which the methoxycarbonyl and hydroxy groupings are *trans* and equatorial.

Preliminary attempts to protect the C-17 atom in the hydroxy esters (**5a** and **b**), according to the above mentioned procedures, led almost entirely to ajmalicine (**1**). Such acid catalysis was incompatible with the survival of the strategically important hemiacetal group in (**5a** and **b**). Our inability to protect C-17 in (**5a** and **b**) prompted us to attempt functional modification of this carbon. Specifically, the transformation of compounds (**5a** and **b**) into the cyano esters (**7a** and **b**) was explored. We opted for the cyano group as the aldehyde-masking group on the grounds that this did not require protection during the C-19 inversion stage. Furthermore, it could be reduced conveniently to the requisite aldehyde at the very last stage of the synthetic procedure. The value of this approach to 19-epiajmalicine (**2**) was enhanced by the fact that (**7a** and **b**) could be cleanly obtained (91% yield) when the hydroxy esters (**5a** and **b**) were treated with 2.0 equiv. of hydroxylamine-*O*-sulphonic acid (HSA)[10] in water at room temperature for 24 h. Attempts to convert ajmalicine (**1**) directly into the cyano esters (**7a** and **b**) by HSA proved to be unrewarding as expected. The cyano and ester groups in compounds (**7a** and **b**) gave rise to bands at 2 250 and 1 740 cm^{-1} in the i.r. spectrum. The ^1H n.m.r. spectrum indicated the compounds to be a 2:1 mixture of two epimers at C-16, which could not be separated by chromatography or crystallisation.† It showed two singlets at δ 3.89 and 3.77 and two doublets at δ 4.43 (*J* 3.5 Hz) and 4.18 (*J* 2.8 Hz), due to the CO_2Me and 16-H protons in compounds (**7a**) and (**7b**), respectively. The ^{13}C n.m.r. spectrum lent further support to structure (**7**), showing the replacement of the hemiacetal carbon atom with a cyano group at δ_C 115.3 p.p.m. for both diastereoisomers. The precise structure of these two compounds, namely the chirality at the C-16, was not ascertained and both products were carried out through the synthetic sequence.

Epimerisation of hydroxy groups is often effected by S_N2 displacement of the mesylate or tosylate of the alcohols by



Scheme 2. *Reagents and conditions:* (i) 2.3M-H_2SO_4, water, reflux, 15 min; (ii) HSA, water, 24 h, room temp.; (iii) DEAD, TPP, benzene–DMF, room temp., 2 h; (iv) $NaH_2PO_2 \cdot H_2O$, W-2 Ra-Ni, Py–AcOH–water, 50 °C; then, TFA, room temp., 15 min; (v) HCO_2H, DCC, −78 °C, CH_2Cl_2

suitable nucleophiles. We have tested various reagents, including tetraethylammonium acetate,[11] tetra-n-butylammonium acetate,[12] tetra-n-butylammonium formate,[13] potassium superoxide,[14] and potassium nitrite.[15] Although initial attempts to effect the desired inversion at C-19 according to these reagents were unsuccessful, further investigations revealed a two-step sequence that resulted in the transformation (**7a** and **b**) ⟶ (**2**).

The intramolecular formation of esters from alcohols under Mitsunobu's conditions[16] is well known to proceed smoothly with inversion at the hydroxy carbon. Thus, when the cyano esters (**7a** and **b**) were allowed to react with formic acid, diethyl azodicarboxylate (DEAD), and triphenylphosphine (TPP) in benzene–*NN*-dimethylformamide (DMF) at room temperature, the formates (**8a** and **b**) were isolated in 89% yield. The 200-MHz ^1H n.m.r. spectrum of compounds (**8a** and **b**) revealed two doublets in the ratio 2:1 at δ 3.94 (*J* 3.0 Hz) and 3.83 (*J* 2.5 Hz), respectively, the peaks being ascribed to the epimeric 16-hydrogens. Assignment of the *R*-configuration to C-19 in compounds (**8a** and **b**) was based on conversion of the 19*S*-cyano esters (**7a** and **b**) into the 19*R*-formates (**9a** and **b**) by a route of definable stereochemistry. Treatment of (**7a** and **b**) with formic anhydride [generated *in situ* from formic acid and *NN'*-dicyclohexylcarbodi-imide (DCC)][17] gave, in 87% yield, the formates (**9a** and **b**) as a mixture (2:1) of 16-epimers. Although these isomers were separable by careful h.p.l.c., t.l.c. on silica gel was not effective for separation, showing a single spot with a variety of solvent systems. However, the formates (**9a** and **b**) and (**8a** and **b**) showed distinctly different R_F values on t.l.c. The ^1H n.m.r. spectra of compounds (**9a** and **b**) were the same in character but different in chemical shift values from the spectra of (**8a** and **b**). For example, the 16-H and 18-H_3 groups in compound (**9a**) appeared at δ 4.27 and 1.37, as compared with δ 3.94 and 1.30 in its isomer (**8a**). The Figure shows lowest-energy conformations for (**8a** and **b**) and (**9a** and **b**), which accommodate the observed spin–spin coupling constants between vicinal protons ($J_{15,16}$ 2.5—3.5 Hz, $J_{19,20}$ 2.0—3.0 Hz). In the

* The major and minor component of compounds (**4**)—(**9**) are designated a and b respectively.

† Attempts to induce crystallisation of (**5a** and **b**) by prolonged heating in benzene–ethyl acetate resulted in the formation of a beautifully crystalline compound which was shown to be the diastereoisomerically pure cyano lactone (**6**).

molecular models of compounds (**9a** and **b**) and (**8a** and **b**), the 16-proton is situated in dissimilar environments, lying in the proximity of the formate group and the 19-Me group, respectively, thus establishing the reason for the observed difference in chemical shifts. Therefore, it is reasonable to conclude that the diastereoisomeric pair of formates (**8a** and **b**), produced under Mitsunobu's conditions, possessed the requisite 19*R*-configuration and differed only at C-16.

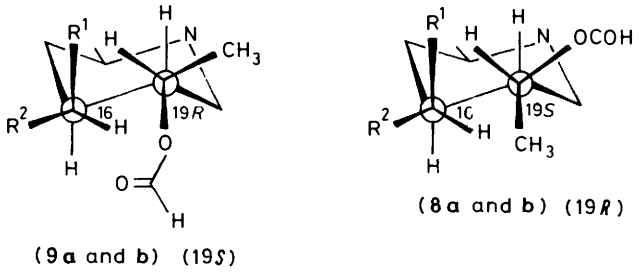


Figure. R^1, R^2 = CN, CO_2Me

Having completed the preparation of the cyano formates (**8a** and **b**), we then studied their chemoselective reduction to aldehyde and subsequent cyclisation to yield 19-epiajmalicine (**2**).

Although the choice of the Backeberg–Staksun method[18] was initially made on the basis of compatibility with the other functionality, the acid-lability of the formate group proved ideal for the final step of the sequence. Compounds (**8a** and **b**) were dissolved in water–acetic acid–pyridine (1:1:2) in the presence of sodium hypophosphite and deactivated Raney nickel, and the mixture was stirred for 3 h at 50 °C and subjected to acid treatment (trifluoroacetic acid, room temperature) to give 19-epiajmalicine (**2**) (78%) as the sole stereoisomer present in the reaction mixture, as shown by h.p.l.c. and t.l.c. This compound was shown to be identical, by all available analytical procedures, with an authentic sample of 19-epiajmalicine kindly provided by Dr. P. Potier.

Experimental

I.r. spectra were recorded on a Perkin-Elmer 681 spectrophotometer for chloroform solutions, u.v. spectra on a Perkin-Elmer model 554 spectrophotometer in methanol. ^{1}H N.m.r. spectra were recorded on a Bruker WP-80 (80 MHz) or a Varian XL-200 (200 MHz) spectrometer with deuteriochloroform as solvent, unless otherwise stated, and tetramethylsilane as internal standard. ^{13}C N.m.r. spectra were taken in deuteriochloroform on a Varian XL-100 spectrometer at 25.2 MHz, using tetramethylsilane as internal reference. Mass spectra (electron impact) were determined using Varian 112 (mode 212 for high-resolution spectra) and CH-7 spectrometers. Optical rotations were measured on a Perkin-Elmer 141 polarimeter for solutions in chloroform. Compounds were detected on developed chromatograms by fluorescence quenching (λ 254 or 365 nm) or visualised with cerium(IV) ammonium sulphate (CAS, 1% in 85% phosphoric acid); R_F and colour (CAS spray on t.l.c.) of products are given. Flash chromatography was carried out as described by Still *et al.*[19] and performed with silica gel S (Merck) 230—400 mesh. All solvents were purified by standard procedures before use.

Preparation of Ajmalicine Hemiacetal (**5a** *and* **b**) *from Ajmalicine* (**1**).—Ajmalicine (**1**) (10 g, 28.4 mmol) and 2.3M-sulphuric acid (1.5 l) were heated under reflux for 15 min under nitrogen and the resulting solution was made alkaline with concentrated aqueous ammonia. The mixture was extracted with chloroform (3 × 250 ml). The combined extracts were washed with water (500 ml), dried (Na_2SO_4), and evaporated to furnish a crystalline yellowish residue (9.55 g) which was chromatographed. Elution with ethyl acetate afforded recovered ajmalicine (**1**) (485 mg). Further elution with ethyl acetate–methanol (49:1) gave a (9:1) mixture (by 200-MHz ^{1}H n.m.r.) of *epimeric* 17-*hydroxy*-16,17-*dihydroajmalicines* (**5a** and **b**) (4.53 g, 42%) as a single spot on t.l.c. [R_F 0.40 (green)]; $[\alpha]_D^{20}$ −27.3° (*c* 0.2); m.p. 165—166 °C (decomp.) (from benzene–ethyl acetate) {lit.,[9] 167—168 °C [for compound erroneously assigned structure (**3**)]}; $\nu_{max.}$ 3 580, 3 470, 1 728, and 1 730 cm^{-1}; $\lambda_{max.}$ (log ε) 226 (4.65), 283 (3.87), and 290 nm (3.80). For (**5a**): δ_H [200 MHz; $(CD_3)_2SO$] 1.22 (d, $J_{18,19}$ 7.0 Hz, 18-H_3), 2.12 (dd, $J_{15,16}$ 11.5, $J_{16,17}$ 6.4 Hz, 16-H), 3.22 (br d, *J* 11.0 Hz, 3-H), 3.74 (s, CO_2Me), 4.13 (dq, $J_{18,19}$ 6.5, $J_{19,20}$ 5.0 Hz, 19-H), 4.96 (br t, $J_{16,17}$ 6.4 Hz, 17-H), 6.58 (br d, *J* 6.4 Hz, OH), 6.94 (dt, *J* 7.0 and 1.3 Hz, 10-H), 7.04 (dt, *J* 7.0 and 1.3 Hz, 11-H), 7.31 (dd, *J* 7.0 and 1.3 Hz, 12-H), 7.37 (br dd, *J* 7.0 and 1.3 Hz, 9-H), and 10.80 (br s, NH); δ_H (80 MHz) 1.22 (d, $J_{18,19}$ 6.4 Hz, 18-H_3), 3.80 (s, CO_2Me), 4.19 (br dq, $J_{18,19}$ 6.4, $J_{18,20}$ 2.7 Hz, 19-H), 5.02 (br d, *J* 7.8 Hz, 17-H), and 7.87 (br s, NH). For (**5b**): δ_H [200 MHz; $(CD_3)_2SO$] 1.30 (d, $J_{18,19}$ 7.0 Hz, 18-H_3), 3.68 (s, CO_2Me), 5.29 (m, 17-H), and 6.40 (br d, *J* 3.2 Hz, OH); *m/z* 370 ($M^{+\cdot}$, 18%), 369 (20), 352 (25), 351 (22), 338 (35), 337 (30), 311 (14), 309 (11), 184 (75), 169 (60), and 156 (100).

Elution with ethyl acetate–methanol (19:1) gave a (4:1) mixture of epimeric hemiacetals (**4a** and **b**) (3.43 g, 38%) as a single spot with R_F 0.26 (yellow-green); $\nu_{max.}$ 3 580, 3 470, and 1 630 cm^{-1}; $\lambda_{max.}$ (log ε) 227 (4.51), 283 (3.88), and 290 nm (3.74). For the major epimer (**4a**); δ_H [$CDCl_3$–$(CD_3)_2SO$ (1:1)] 1.10 (d, $J_{18,19}$ 6.4 Hz, 18-H_3), 4.00 (m, $w_{\frac{1}{2}}$ 14 Hz, 19-H), 4.86 (m, $w_{\frac{1}{2}}$ 7 Hz, 17-H), 5.86 (br d, *J* 7.5 Hz, 17β-OH), and 10.08 (br s, NH). For (**4b**): δ_H [$CDCl_3$–$(CD_3)_2SO$ (1:1)] 1.10 (d, $J_{18,19}$ 6.4 Hz, 18-H_3), 5.11 (m, $w_{\frac{1}{2}}$ 7 Hz, 17-H), and 5.32 (br s, 17α-OH); *m/z* (150 °C) 312 ($M^{+\cdot}$ 84%), 311 (100), 294 (22), 293 (19), 269 (50), 184 (59), 170 (51), 169 (61), and 156 (48).

Preparation of the Cyano Ester (**7a** *and* **b**) *from Ajmalicine Hemiacetal* (**5a** *and* **b**).—The anomeric mixture of compounds (**5a** and **b**) (2.5 g, 6.75 mmol) was finely ground and suspended in water (250 ml) containing HSA (1.52 g, 13.5 mmol) and the mixture was stirred in the dark under nitrogen at room temperature for 24 h. The resulting solution was brought to pH 8 with 5% aqueous sodium hydrogen carbonate and extracted with ethyl acetate (3 × 100 ml). Evaporation of the dried (Na_2SO_4) extracts left a glass (2.62 g). Flash chromatography with ethyl acetate as eluant yielded the cyano ester (**7a** and **b**) (2.52 g, 91%), R_F 0.46 [ethyl acetate–methanol (9:1); green], as an inseparable mixture of 16-*epimeric nitriles* in a 2:1 ratio, respectively (^{1}H n.m.r.); $\nu_{max.}$ 3 600, 3 470, 2 250, and 1 740 cm^{-1}; $\lambda_{max.}$ (log ε) 227 (4.49), 282 (3.78), and 290 (3.81). For (**5a**): δ_H (200 MHz) 1.37 (d, $J_{18,19}$ 6.3 Hz, 18-H_3), 2.02 (br s, OH), 3.89 (s, CO_2Me), 4.00 (dq, $J_{18,19}$ 6.3, $J_{19,20}$ 2.5 Hz, 19-H), 4.43 (d, $J_{15,16}$ 3.5 Hz, 16-H), and 7.94 (br s, NH); δ_C($CDCl_3$) 115.3 (CN) and 166.9 (C-22). For the minor epimer (**5b**): δ_H (200 MHz) 1.37 (d, $J_{18,19}$ 6.5 Hz, 18-H_3), 3.77 (s, CO_2Me), 4.0 (dq, $J_{18,19}$ 6.5, $J_{19,20}$ 2.5 Hz, 19-H), 4.18 (d, $J_{15,16}$ 2.8 Hz, 16-H), and 8.06 (br s, NH); *m/z* (150 °C) 367 ($M^{+\cdot}$, 12%), 366 (11), 335 (93), 334 (100), 223 (22), 184 (53), 169 (36), and 156 (35) (Found: $M^{+\cdot}$, 367.183 19. $C_{21}H_{25}N_3O_3$ requires *M*, 367.183 27).

Prolonged heating of above mixture in benzene–ethyl acetate resulted in the formation of a nicely crystalline compound which was shown to be the cyano lactone (**6**), m.p. 229 °C (decomp.); R_F 0.46 [ethyl acetate–methanol (9:1)] (yellow-green); $[\alpha]_D^{20}$ −35.1° (*c* 0.2); $\nu_{max.}$ 3 470, 2 250, and 1 735 cm^{-1}; $\lambda_{max.}$ (log ε) 227 (4.51), 282 (3.82), and 289 nm (3.81); δ_H [200 MHz; $(CD_3)_2SO$] 1.28 (d, $J_{18,19}$ 6.7 Hz, 18-H_3), 4.38 (d, $J_{15,16}$ 11.4 Hz, 16-H), 4.78 (dq, $J_{18,19}$ 6.7, $J_{19,20}$ 3.5 Hz, 19-H), 6.92 (dt, *J* 8.0 and 2.0 Hz, 10-H), 7.02 (dt, *J* 8.0 and 2.0 Hz, 11-H), 7.27

(1 H, dd, *J* 8.0 and 2.0 Hz, 12-H), and 7.35 (dd, *J* 8.0 and 2.0 Hz, 9-H); *m/z* (200 °C) 335 ($M^{+\bullet}$, 100%), 334 (98), 310 (11), 251 (22), 249 (16), 223 (40), 183 (93), 169 (60), 156 (58), and 155 (20).

Formylation of Compounds (**5a** *and* **b**) *under Mitsunobu's Conditions*.—A dry round-bottomed flask (50 ml), fitted with a magnetic follower and protected by a serum cap, was flushed with nitrogen and charged with the nitriles (**5a** and **b**) (390 mg, 1.06 mmol) dissolved in benzene-DMF (19:1) (20 ml). Anhydrous formic acid (120 μl, 3.18 mmol) and triphenylphosphine (833 mg, 3.18 mmol) were added, after which the solution was stirred at room temperature whilst diethyl azodicarboxylate (500 μl, 3.18 mmol) was added dropwise during 15 min. The mixture was then kept in the dark for 2 h. The serum cap was removed and 0.5M-hydrochloric acid (25 ml) was added dropwise, and the mixture was diluted with water (50 ml) and extracted with ethyl acetate (3 × 25 ml). The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated to give a residue (350 mg). Flash chromatography [ethyl acetate–hexane (65:35)] yielded the formate (**8a** and **b**) (373 mg, 89%), R_F 0.57 (ethyl acetate; yellow-green) as an inseparable mixture of epimers in a 2:1 ratio; $\nu_{max.}$ 3 740, 2 250, 1 740, and 1 730 cm^{-1}; $\lambda_{max.}$ (log ε) 225 (4.50), 282(3.71), and 290 (3.81). For the major epimer (**8a**): δ_H (200 MHz) 1.30 (d, $J_{18,19}$ 6.0 Hz, 18-H_3), 3.90 (s, CO_2Me), 3.94 (d, $J_{15,16}$ 3.0 Hz, 16-H), 5.21 (dq, $J_{18,19}$ 6.0, $J_{19,20}$ 3.0 Hz, 19-H), 8.02 (br s, NH), and 8.04 (s, OCHO). For the minor epimer (**8b**); δ_H 1.28 (d, $J_{18,19}$ 6.0 Hz, 18-H_3), 3.78 (s, CO_2Me), 3.83 (d, $J_{15,16}$ 2.5 Hz, 16-H), 5.33 (dq, $J_{18,19}$ 6.0, $J_{19,20}$ 2.5 Hz, 19-H), 8.02 (s, OCHO), and 8.20 (br s, NH); *m/z* (80 °C) 395 ($M^{+\bullet}$, 20%), 394 (17), 352 (10), 297 (18), 184 (11), 176 (100), 170 (27), and 169 (21).

Direct Conversion of the Cyano Formates (**8a** *and* **b**) *into* 19-*Epiajmalicine* (**2**).—The mixture of formates (**8a** and **b**) (300 mg, 0.76 mmol) was added to a vigorously stirred suspension of W-2 Raney nickel (2.5 g), previously deactivated by being boiled (0.5 h) in acetone, in a solution of sodium hypophosphite hydrate (700 mg, 7.94 mmol) in a mixture of pyridine–acetic acid–water (2:1:1) (25 ml). The mixture was stirred at 50 °C under nitrogen for 3 h and then filtered on Celite. The solvents were evaporated off under reduced pressure and the dark residue was taken up in trifluoroacetic acid (5 ml) and the mixture was set aside at room temperature for 15 min. The solution was poured into ice–water, neutralised with aqueous sodium hydrogen carbonate, and extracted with ethyl acetate (100 ml). The extract was dried ($MgSO_4$) and evaporated to give a crystalline residue. Recrystallisation from methanol gave pure 19-*epiajmalicine* (**2**) (209 mg, 78%), m.p. 213 °C (decomp.); R_F 0.33 [ethyl acetate–hexane (7:3); green spot]; $\nu_{max.}$ 3 480, 2 850, 2 750, 1 698, 1 620, and 1 465 cm^{-1}; $\lambda_{max.}$ (log ε) 227 (4.60), 280 (3.84), and 2.92 nm (3.80); δ_H (200 MHz) 1.33 (d, *J* 6.5 Hz, 18-H_3), 3.69 (s, CO_2Me), 3.81 (m, $w_{\frac{1}{2}}$ 10 Hz, 19-H), 7.53 (d, *J* 1 Hz, 17-H), and 8.10 (br s, NH); *m/z* (120 °C) 352 ($M^{+\bullet}$, 8%), 351 (67), 295 (38), 281 (48), 221 (100), 207 (33), 184 (41), 170 (33), 169 (33), and 156 (67). This product proved to be identical with an authentic sample kindly provided by Dr. Potier (Gif-sur-Yvette); its spectroscopic properties were also virtually identical with the reported values.[20]

Formylation of the Cyano Esters (**7a** *and* **b**) *to give Cyano Formates* (**9a** *and* **b**).—To a solution of anhydrous formic acid (40 μl, 1.10 mmol) in dry dichloromethane (20 ml), cooled at −78 °C under nitrogen, was added DCC (115 mg, 0.55 mmol) followed, after 10 min, by a solution of the anomeric mixture of compounds (**7a** and **b**) (200 mg, 0.54 mmol) in dichloromethane (50 ml). After 1 h at room temperature, t.l.c. (ethyl acetate) showed complete conversion of (**7a** and **b**) into cyano formates (**9a** and **b**) (R_F 0.53). The mixture was then diluted with dichloromethane (20 ml) and the solution was washed with 0.5M-sodium hydrogen carbonate (3 × 10 ml) and water, and dried ($MgSO_4$). The dichloromethane was evaporated off under reduced pressure and the residue was chromatographed on silica gel. Elution with ethyl acetate–hexane (7:3) gave the formate (187 mg, 87%) as a (2:1) mixture of 16-epimers (**9a** and **b**), $\nu_{max.}$ 3 470, 1 740, and 1 730 cm^{-1}; $\lambda_{max.}$ (log ε) 225 (4.48), 282 (3.70), and 290 nm (3.78). For the major epimer (**9a**): δ_H (200 MHz) 1.37 (d, $J_{18,19}$ 6.5 Hz, 18-H_3), 3.91 (s, CO_2Me), 4.27 (d, $J_{15,16}$ 3.5 Hz, 16-H), 5.35 (dq, $J_{18,19}$ 6.5, $J_{19,20}$ 2.0 Hz, 19-H), 7.78 (br s, NH), and 8.10 (s, OCHO). For the minor epimer (**9b**): δ_H (200 MHz) 1.36 (d, $J_{18,19}$ 6.5 Hz, 18-H_3), 3.76 (s, CO_2Me), 4.14 (d, $J_{15,16}$ 2.8 Hz, 16-H), 5.40 (dq, $J_{18,19}$ 6.5, $J_{19,20}$ 2.0 Hz, 19-H), 7.93 (br s, NH), and 8.08 (s, OCHO); *m/z* (100 °C) 395 ($M^{+\bullet}$, 64%), 394 (42), 297 (100), 184 (20), 170 (25), 169 (42), and 156 (45).

Acknowledgements

Grateful acknowledgement is made to Dr. P. Potier, Gif-sur-Yvette, for a sample of natural 19-epiajmalicine.

References

1 For an excellent review on heteroyohimbane alkaloids, see R. T. Brown, in 'The Monoterpenoid Indole Alkaloids,' ed. J. E. Saxton, Wiley, New York, 1983, vol. 25, part 4, p. 63.
2 N. Neuss, in 'Indole and Biogenetically Related Alkaloids,' eds. J. D. Phillipson and M. H. Zenk, Academic Press, London, 1980, p. 293.
3 M. Raymond-Hamet, *C.R. Hebd. Seances, Acad. Sci.*, 1951, **232**, 2354.
4 J. Melchio, A. Bouquet, M. Païs, and R. Goutarel, *Tetrahedron Lett.*, 1977, 315.
5 Belg. P. 780,729 (*Chem. Abstr.*, 1973, **78**, 84630b); L. A. Djakouré, F. X. Jarreau, and R. Goutarel, *Tetrahedron*, 1975, **31**, 2695; R. T. Brown and L. Chapple, *J. Chem. Soc., Chem. Commun.*, 1974, 740; E. Winterfeldt, A. J. Gaskell, T. Korth, H. E. Radunz, and M. Walkowiak, *Chem. Ber.*, 1969, **102**, 3558; J. Gutzwiller, G. Pizzolato, and M. Uskoković, *J. Am. Chem. Soc.*, 1971, **93**, 5907; R. T. Brown and T. Leonard, *J. Chem. Soc., Chem. Commun.*, 1979, 877; E. Winterfeldt, H. E. Radunz, and T. Korth, *Chem. Ber.*, 1968, **101**, 3172; E. Wenkert, C. J. Chang, H. P. S. Chawla, D. W. Cochran, E. W. Hagaman, J. C. King, and K. Orito, *J. Am. Chem. Soc.*, 1976, **98**, 3645; R. T. Brown, C. L. Chapple, D. M. Duckworth, and R. Platt, *J. Chem. Soc., Perkin Trans. 1*, 1976, 160; F. A. MacKellar, R. C. Kelly, E. E. van Tamelen, and C. Dorschel, *J. Am. Chem. Soc.*, 1973, **95**, 7155.
6 M. Ihara, K. Noguchi, T. Ohsawa, K. Fukumoto, and T. Kametani, *Heterocycles*, 1982, **19**, 1835.
7 B. S. Ong and T. H. Chan, *Synth. Commun.*, 1977, **7**, 283.
8 R. C. Elderfield and A. P. Gray, *J. Org. Chem.*, 1951, **16**, 506; F. E. Bader, *Helv. Chim. Acta*, 1953, **36**, 215.
9 A. Chatterjee, S. Bandyopadhyay, and J. N. Shoolery, *J. Org. Chem.*, 1982, **47**, 3113.
10 C. Fizet and J. Streith, *Tetrahedron Lett.*, 1974, 3187.
11 A. C. Cope and D. L. Nealy, *J. Am. Chem. Soc.*, 1965, **87**, 3122.
12 R. Baker, J. Hudec, and K. L. Rabone, *J. Chem. Soc. C*, 1969, 1605.
13 E. J. Corey and S. Terashima, *Tetrahedron Lett.*, 1972, 111.
14 E. J. Corey, K. C. Nicolaou, and M. Shibasaki, *J. Chem. Soc., Chem. Commun.*, 1975, 658.
15 R. Lattrell and G. Lohaus, *Justus Liebigs Ann. Chem.*, 1974, 901.
16 For the use of the DEAD–TPP system, see O. Mitsunobu, *Synthesis*, 1981, 1.
17 G. A. Olah, Y. D. Vankar, M. Arvanaghi, and J. Sommer, *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 614.
18 O. G. Backeberg and B. Staksun, *J. Chem. Soc.*, 1962, 3961.
19 W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.
20 M. Lounasmaa and S. K. Kan, *Tetrahedron*, 1980, **36**, 1607; R. Uusvuori and M. Lounasmaa, *Planta Med.*, 1981, **41**, 406.

Received 20*th July* 1984; *Paper* 4/1253