Photocyclisation of Enamides. Part 29.[1,2] A General Strategy for the Synthesis of Ipecac and Heteroyohimbine Alkaloids

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The synthesis of the ester (**12**) and lactone (**19**) *via* reductive photocyclisation of the enamide (**3**), kinetically controlled alkylation of the furopyridone (**4**), and reductive cleavage of the γ-lactones (**10**) and (**14**) illustrates a new general method for the preparation of the ipecac and heteroyohimbine alkaloids.

The 2,3-disubstituted benzo- or indolo-quinolizine structure is a common skeleton for most of the monoterpenoid alkaloids which are known to be biogenetically derived from the same secologanin and β-arylethylamines.[3-5] Aiming at the exploration of a practical and divergent synthetic route for monoterpenoid alkaloids *via* an unnatural common intermediate, we focused our attention on the furopyridone (A) (Scheme 1) which would be a versatile starting block for the construction of the partial structure of alkaloids derived from secologanin unit, since it is a bifunctionalised bicyclic heterocycle with a lactam carbonyl and an enol ether group.[6]

We now report a general strategy applicable to the practical and total synthesis of benzo- and indolo-quinolizine alkaloids by the efficient synthesis of two key intermediates, the ester (**12**) and the δ-lactone (**19**), *via* the furopyridone (**4**) as a common key precursor. Our strategy is based on the following three key reactions: reductive photocyclisation of an enamide,[7] kinetically controlled alkylation or acylation α to a lactam carbonyl group, and reductive cleavage of a γ-lactone ring.

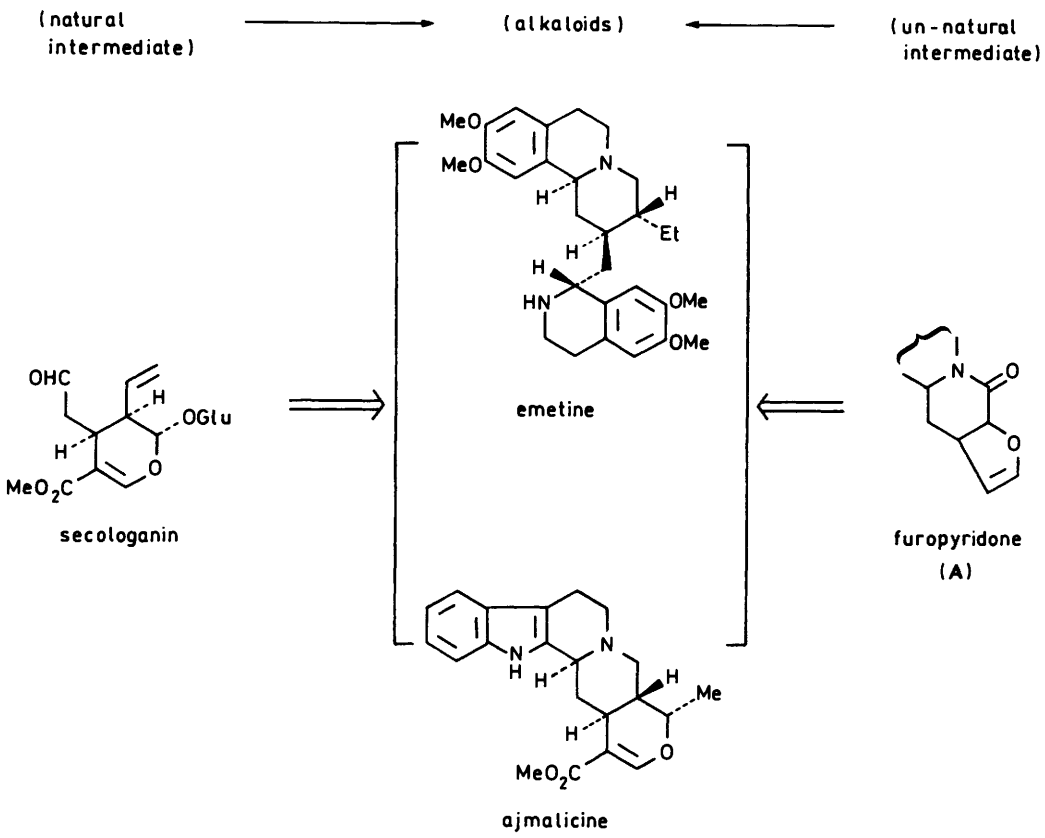
Preparation of the Furopyridones (**4**)–(**8**).—Acylation of the 1-methyl-3,4-dihydroisoquinoline (**1**) with furan-2-carbonyl chloride (**2**) in the presence of triethylamine gave the unstable enamide (**3**) in quantitative yield which was characterised by its NMR spectrum [δ 5.40 and 4.75 (each 1 H, br s, $C{=}CH_2$)] and without purification was subjected to irradiation in the presence of sodium borohydride in acetonitrile–methanol (9:1) to afford the desired furopyridone (**4**) in 77% yield after low-pressure column chromatography on silica gel of the crude product. The mass spectrum of the furopyridone (**4**) exhibited a molecular ion peak at *m/z* 301 and its NMR spectrum exhibited a peak due to the 12-axial proton at δ 1.44 (br q, *J* 12.5 Hz) and two peaks due to olefinic protons at δ 6.44 (dd, *J* 2.5 and 1.5 Hz) and 5.10 (t, *J* 2.5 Hz). These spectral data suggested that (**4**) included a hydrogenated dihydrofuran structure containing an enol ether moiety. The *cis–syn*-stereostructure of the product (**4**) was unambiguously established not only by the nuclear Overhauser enhancement (NOE) between 11a- and 8a-H but also by its X-ray analysis, as shown in the Figure. In order to investigate the chemical reactivity of the lactam carbonyl group of the furopyridone (**4**), we treated (**4**) with lithium di-isopropylamide (LDA) in tetrahydrofuran (THF) at −78 °C and then added methan[^{2}H]ol. The 8a-deuteriated lactam (**5**) was obtained in quantitative yield and characterised by its NMR spectrum [disappearance of the peak due to 8a-H and a less complicated signal pattern (br dm, *J* 12 Hz) of the peak due to 11a-H]. On the basis of this study of the reactivity of the lactam carbonyl group, introduction of a carbon unit into the 8a-position was investigated by employing an appropriate electrophile.

Lithiation of (**4**) with LDA in THF at −78 °C followed by quenching with ethyl iodide, acetic anhydride, or methyl chloroformate led successfully to exclusive formation of the 8a-ethyl (**6**), 8a-acetyl (**7**), or 8a-methoxycarbonyl derivatives (**8**) in 86, 80, or 89% yield respectively. Stereoisomers of (**6**), (**7**), and (**8**), epimeric at the 8a-position, were not isolated from the above kinetically controlled alkylation or acylation reactions. Products (**7**) and (**8**) showed IR absorptions at 1 720 cm^{-1} (acetyl) and 1 760 and 1 730 cm^{-1} (methoxycarbonyl), in addition to an absorption at 1 650 cm^{-1} (lactam carbonyl). The stereochemistry of all the products (**5**)–(**8**) was deduced from comparison of their NMR spectra, particularly signals due to protons in the C- and D-rings, with the spectrum of the starting lactam (**4**), whose stereostructure had been firmly established by its X-ray analysis as just described. The chemical shifts and signal patterns for 8a-, 10-, 11-, 11a-, 12-, and 12a-H in compounds (**5**)–(**8**) are quite similar. The NOE (12%) between 11a-H and the methylene proton of the ethyl group firmly established the C/D-*cis*-ring fusion of the lactam (**6**). Therefore, the other products (**5**), (**7**), and (**8**) were deduced to have the same C/D-*cis*-stereochemistry.

Reaction of the furopyridone (**4**) with electrophiles proceeded smoothly to give the C/D-*cis* compounds (**5**)–(**8**) as a result of the stereoselective addition of the electrophile from the α-face, avoiding steric repulsion between itself and the 12β-axial hydrogen.

Thus, we achieved the stereoselective preparation of the 8a-substituted furopyridones (**6**)–(**8**); (**6**) and (**7**) contain a versatile benzoquinolizine skeleton bearing C_2-unit at both the 2- and 3-positions of the quinolizine unit appropriate for preparation of a key precursor for conversion into ipecac alkaloids such as emetine.

Preparation of the Known Key Intermediates (**11**) *and* (**12**) *for the Total Synthesis of* (±)*-Emetine and of the* δ*-Lactone* (**19**) *as an Essential Fragment for the Total Synthesis of* (±)*-Ajmalicine and Other Heteroyohimbine Alkaloids.*—Since the furopyridones (**6**) and (**7**) have a stereochemical configuration of the substituents at the 2-, 3-, and 11b-positions of the benzoquinolizine nucleus appropriate for the synthesis of monoterpenoid alkaloids, they were converted into the well known synthetic intermediates[8,9] (**11**) and (**12**) and the related compound (**19**). We first investigated the conversion of the ethyl-lactam (**6**) into the ester (**12**) *via* a route involving reductive cleavage of the γ-lactone (**10**). Direct conversion of



Scheme 1.

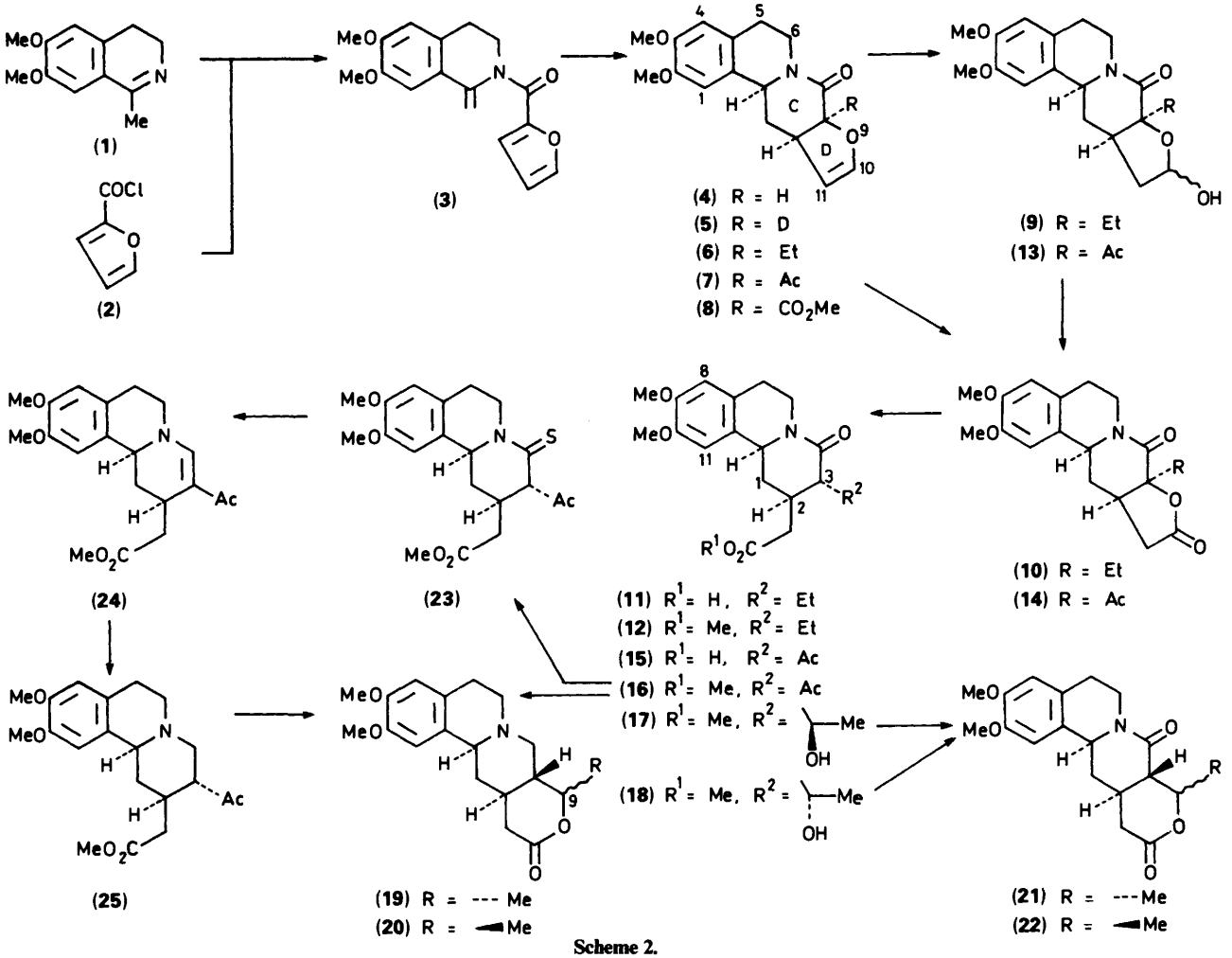
Table 1. ^{1}H NMR data of (**4**)—(**8**): δ (*J* in Hz).

	(4)	(5)	(6)	(7)	(8)
8a-H	4.84 (d, *J* 10.5)	—	—	—	—
10-H	6.44 (dd, *J* 2.5, 1.5)	6.43 (br t, *J* 2.5)	6.36 (dd, *J* 2.5, 1.5)	6.52 (dd, *J* 3, 1.5)	6.50 (dd, *J* 3, 1.5)
11-H	5.10 (t, *J* 2.5)	5.10 (t, *J* 2.5)	4.95 (t, *J* 2.5)	5.09 (t, *J* 3)	5.08 (t, *J* 3)
11a-H	3.37 (m)	3.38 (br dm, *J* 12)	3.13 (dddd, *J* 12, 5.5, 2.5, 1.5)	3.64 (dddd, *J* 12, 5.5, 3, 1.5)	3.55 (m)
12-H_{eq}	2.39 (ddd, *J* 13, 5, 2.5)	2.41 (ddd, *J* 13, 5, 2.5)	2.39 (ddd, *J* 12, 5.5, 2.5)	2.48 (ddd, *J* 12.5, 5.5, 2.5)	2.47 (ddd, *J* 13, 5.5, 2.5)
12-H_{ax}	1.44 (br q, *J* 12.5)	1.44 (br q, *J* 12)	1.41 (q, *J* 12)	1.44 (br q, *J* 12)	1.47 (q, *J* 13)
12a-H	4.64 (br dd, *J* 11.5, 2.5)	4.66 (br d, *J* 12)	4.57 (br dd, *J* 12, 2.5)	4.84 (br d, *J* 12)	4.85 (br d, *J* 13)

the dihydrofuran ring in (**6**) into the γ-lactone by oxidation with pyridinium chlorochromate (PCC)[10] was attempted and gave only a 14% yield of the desired γ-lactone (**10**) with poor recovery. We then investigated the stepwise oxidation of the dihydrofuran (**6**) *via* the corresponding hemiacetal (**9**) which was readily prepared by treatment of (**6**) with 15% sulphuric acid in THF at room temperature in quantitative yield. The hemiacetal (**9**) showed a characteristic IR spectrum and NMR signals [ν_{max} 3 400 cm^{-1} (OH); δ 5.73–5.50 (1 H, m, 10-H)], thus confirming its structure except the relative configuration of the hydroxy group at the 10-position. Oxidation of the hemiacetal (**9**) with PCC (1 equiv) in methylene dichloride afforded the desired γ-lactone (**10**) in 60% yield which was identical with the sample prepared by direct oxidation of the dihydrofuran (**6**). The structure of the γ-lactone (**10**) was established from spectral data [ν_{max} 1 790 cm^{-1} (γ-lactone): δ 3.00 (1 H, dd, *J* 17.5 and 9 Hz, 11-H) and 2.36 (1 H, br d, *J* 17.5 Hz, 11-H)]. Reductive cleavage of the oxo-γ-lactones with aluminium amalgam, calcium in liquid ammonia, or chromium(II) chloride has been investigated by various groups including those of Grieco,[11] Cairns,[12] and House.[13] Of the various attempts at the reductive cleavage of the γ-lactone (**10**), only the reaction with calcium in liquid ammonia[12,14] at −70 °C proceeded smoothly to give the desired carboxylic acid (**11**) as the sole product in 62% yield, while other procedures using aluminium amalgam, chromium(II) chloride, and zinc in acetic acid led to complete recovery of the starting γ-lactone (**10**). The carboxylic acid (**11**) was characterised as its methyl ester (**12**) which was prepared by treatment with diazomethane [ν_{max} 1 735 (CO_2Me) and 1 625 cm^{-1} (NCO): δ 3.75 (3 H, s, CO_2Me) and 0.91 (3 H, t, *J* 7.5 Hz, CH_2CH_3)]. Both the acid (**11**) and the methyl ester (**12**) were identical with authentic samples[8] provided by Professor Takano. Thus, we have succeeded in the formal total synthesis of (±)-emetine and related alkaloids such as protoemetine, protoemetinol, and tubulosine since the ester (**12**) had been converted into respective alkaloids.[3,8,9]

The generality and potential of our synthetic methodology using the furopyridone (**4**) as a common key intermediate were further illustrated by successful conversion of the 8a-acetylfuropyridone (**7**) into the δ-lactone (**19**) which is a fragment including the C, D, and E rings of a key intermediate for the total synthesis of monoterpenoid indole alkaloids such as ajmalicine and related compounds.

Ajmalicine, a representative heterocyclic indole alkaloid,[5] is a



Scheme 2.

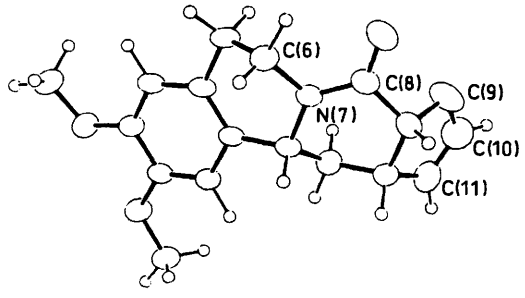
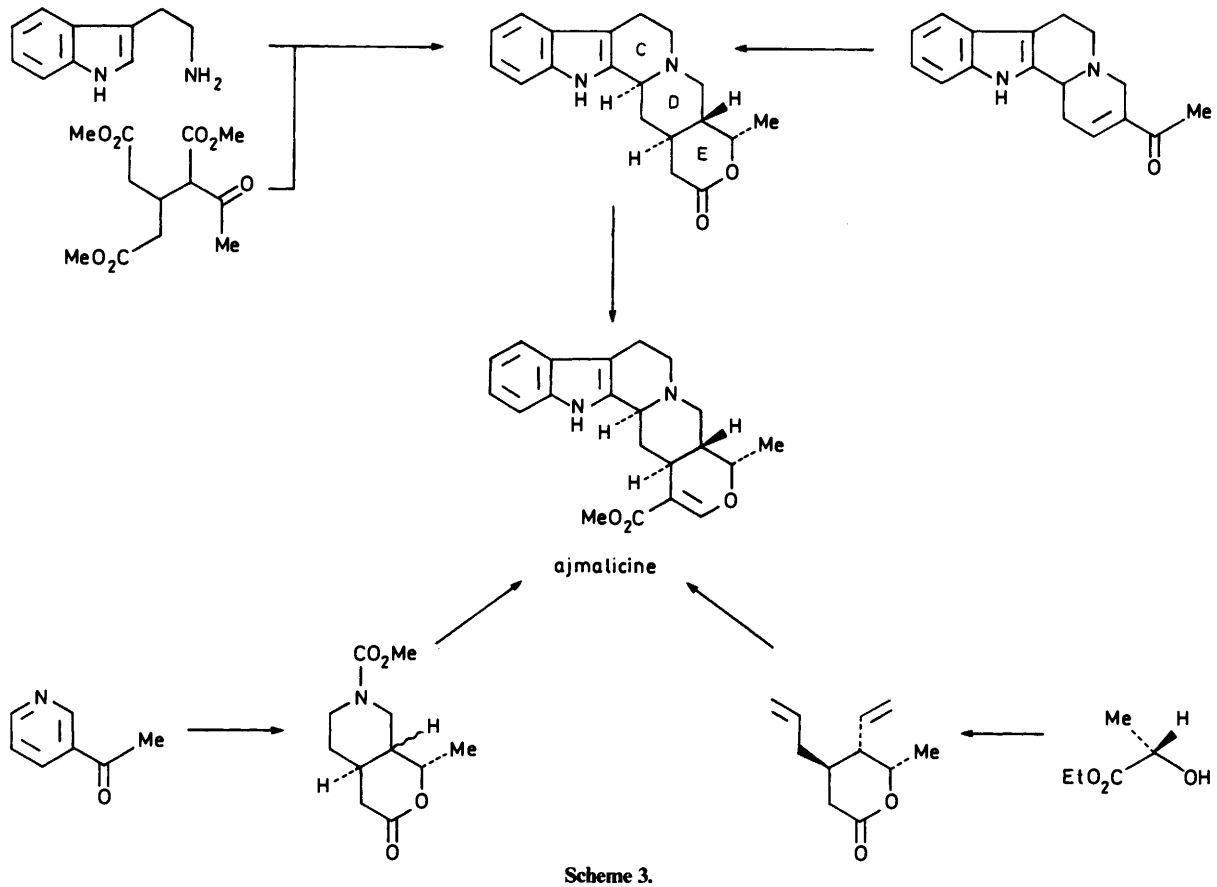


Figure. Crystal structure of (**4**).

drug for increasing cerebral blood flow, and has been clinically used most frequently in combination with ergot alkaloids in Europe.[4] Since the first total synthesis by van Tamelen[15] in 1961, many groups[16,17] including Hoffmann–La Roche's group have reported synthetic studies on ajmalicine and related derivatives in searching for new medicinals and have demonstrated that the δ-lactone sub-unit has the most potential as a key intermediate for constructing the E ring of these alkaloids (Scheme 3).

Thus, we investigated a synthetic route for ajmalicine by preparing the tetracyclic δ-lactone (**19**) as a model compound from the 8a-acetylfuropyridone (**7**). Hydration of (**7**) with 15% sulphuric acid in THF gave the hemiacetal (**13**) in quantitative yield which showed an IR absorption at 3 400 cm^{-1} (OH) and NMR signals at δ 5.90–5.67 (1 H, m, 10-H) and 2.47 (3/2 H, s) and 2.35 (3/2 H, s) (Ac), thus suggesting that the hemiacetal was a 1:1 epimeric mixture. We investigated the oxidation of the hemiacetal (**13**) with three types of reagent: PCC, Jones reagent (CrO_3–H_2SO_4), and dimethyl sulphoxide–acetic anhydride, and obtained the identical γ-lactone (**14**) in 51, 58, and 77% yields, respectively. Reductive cleavage of the lactone ring in the 8a-acetyl-lactone (**14**) with aluminium amalgam in aqueous ethanolic THF[11] proceeded more smoothly than in the case of the ethyl-lactone (**10**) to afford the desired carboxylic acid (**15**) in 95% yield which was also prepared by reductive cleavage with zinc in refluxing acetic acid in 85% yield. Upon esterification with diazomethane, the carboxylic acid (**15**) was readily converted into the corresponding methyl ester (**16**) which exhibited IR absorption at 1 740–1 720 cm^{-1} due to the ester and ketone carbonyl groups and NMR signals at δ 3.72 (3 H, s, CO_2Me) 2.45 (3 H, s, Ac), 3.46 (1 H, d, *J* 11 Hz, 3-H), and 1.49 (1 H, q, *J* 12 Hz, 1-H_{ax}), establishing its *trans–syn* stereostructure. In order to convert the acetyl ester (**16**) into the δ-lactone (**19**), chemoselective reduction of two (acetyl and lactam) of the three carbonyl groups in (**16**) was investigated as follows.

Treatment of the acetyl ester (**16**) with diborane in THF at −10 °C afforded a mixture of two epimeric aminolactones (**19**) and (**20**) which was readily separated by preparative TLC, (PLC) to give the components in 15 and 40% yield respectively. Thus, the first method for reduction of the acetyl and lactam carbonyl groups at the same time in (**16**) resulted in the formation of the desired δ-lactone (**19**) as a minor product only. A two-step method involving reduction of the acetyl group by sodium borohydride or other related borohydride agents



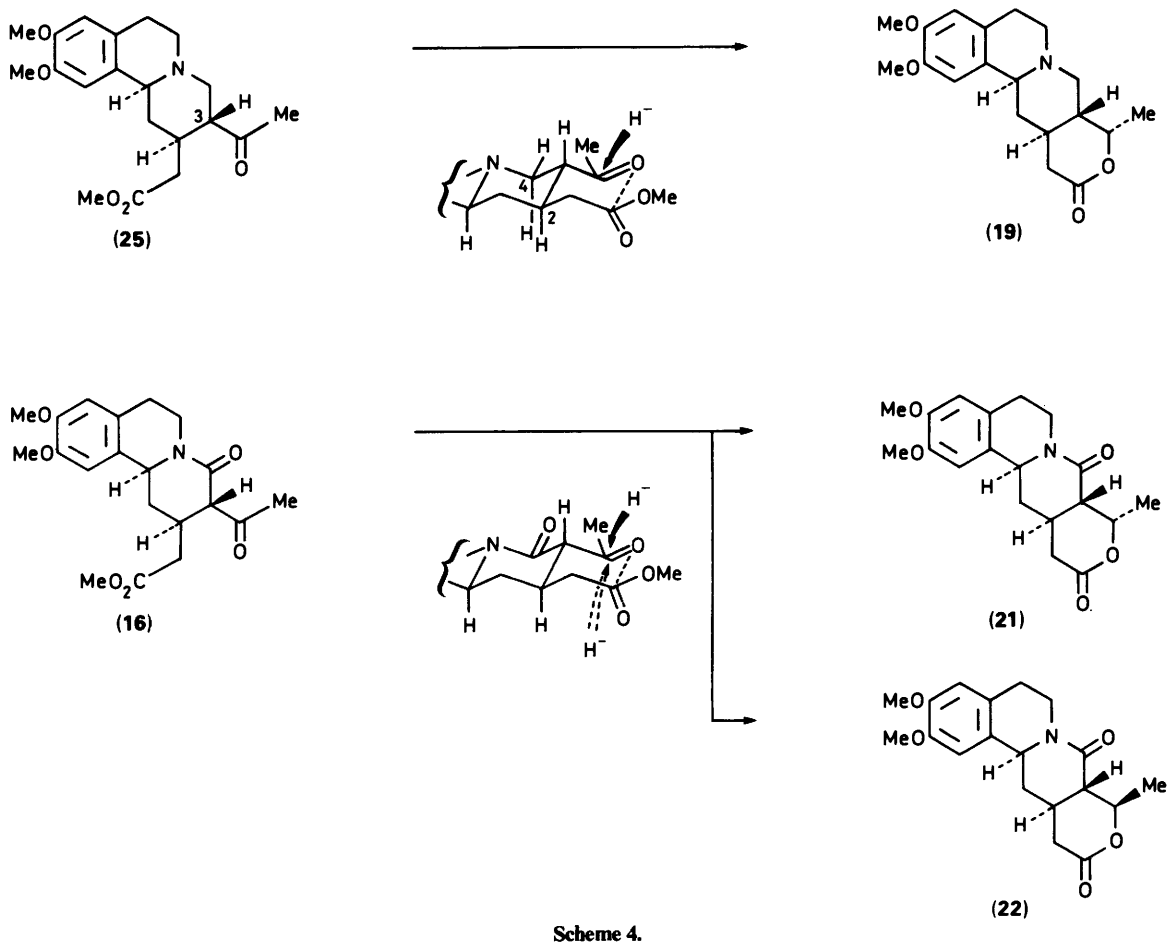
Scheme 3.

followed by reduction of the lactam carbonyl group *via* the imino ether[17] or imino chloride[8] was then investigated but gave unsatisfactory results as the latter step was unsuccessful. Hydride reduction of (**16**) by sodium borohydride, tetrabutylammonium borohydride, or lithium borohydride gave a mixture of two hydroxy compounds (**17**) and (**18**) in quantitative yield which was separated by PLC and, without establishment of their stereostructures, converted into the respective δ-lactones (**21**) and (**22**) by treatment with toluene-*p*-sulphonic acid in refluxing benzene. Attempted chemoselective reduction of the lactam carbonyl group in the α-methyl-lactone (**21**) *via* the corresponding imino ether[17] or imino chloride[8] was unsuccessful though a TLC spot corresponding to the product (**19**) was observed. Finally, the following two-step method involving reduction of the lactam carbonyl group followed by the acetyl group accomplished an effective synthesis of the desired δ-lactone (**19**). We thus investigated reduction of the corresponding thiolactam (**23**) which was readily prepared in 95% yield by treatment of (**16**) with Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,2,3,4-dithiadiphosphetane 2,4-disulphide].[18] Treatment of the thiolactam (**23**) with Raney nickel (W-2) in refluxing methanol gave the unstable enamine (**24**) in 98% yield which showed a characteristic IR spectrum and NMR signals [ν_{max} 1 580 cm^{-1} (NC=CCO); δ 7.30 (1 H, s, 4-H)]. Sundberg[19] has reported similar results in desulphurisation of thiolactams and thioamides, substituted α to thiocarbonyl group with an electron-withdrawing group, with Raney nickel which gave the enamine instead of the amine. Reduction of the unstable enamine (**24**) with sodium cyanoborohydride in the presence of hydrochloric acid gave the acetyl amine (**25**) in 60% yield which according to the known method[15,20] was reduced with sodium borohydride in methanol followed by treatment of the resulting hydroxy compound with toluene-*p*-sulphonic acid to afford the desired α-methyl-δ-lactone (**19**) in quantitative yield. The lactone (**19**) thus obtained was identical with the sample prepared by direct reduction of (**16**) with diborane. The stereostructures of the δ-lactones (**19**) and (**20**) were established by comparison of their NMR spectra with those of known related δ-lactones.[20]

As shown in Table 2, signals due to the 19-protons in α-methyl lactones appear at lower field (δ ~4.62) with a smaller coupling constant (*J* 4.5 Hz) to the 20-proton than those (δ ~4.15; *J* 10 Hz) of the β-methyl isomers. Thus, the lactone (**19**) showing an NMR signal at δ 4.76 (br qd, *J* 7 and 4 Hz) due to 9-proton is the α-methyl lactone while the lactone (**20**) showing an NMR signal at δ 4.23 (dq, *J* 10 and 6 Hz) due to the same proton is the β-methyl congener. The difference between the stereoselective reduction of the acetyl amine (**25**) and the nonstereoselective reduction of the acetyl-lactam (**16**) could be explained as follows (Scheme 4).

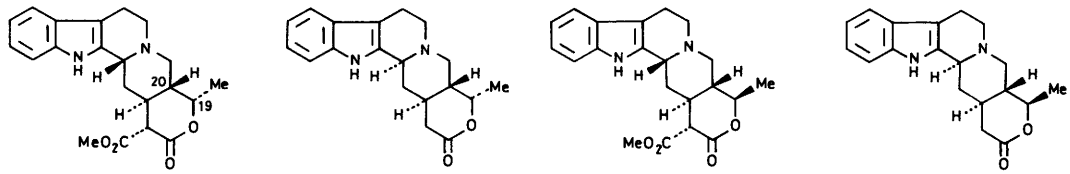
In both transition states, rotation of single bond between C-3 and the acetyl group would be inhibited by electrostatic interaction between the acetyl oxygen and ester carbonyl carbon atoms. In the case of the amine (**25**), attack of hydride from the α-side would be sterically hindered owing to the presence of two axial hydrogens at the 2- and 4-positions while in the case of the lactam (**16**), attack from both α- and β-sides would be allowed owing to the absence of hydrogen at the 4-position. A similar explanation has been described in the reduction of an indole series of compounds by Winterfeldt.[20] These two lactones (**19**) and (**20**) contain the essential skeletal structure of the C, D, and E rings of heteroyohimbine alkaloids such as ajmalicine[15] and corynantheine.[21]

Thus, we have established a useful new method for preparing a common potential intermediate for ipecac and heteroyohimbine alkaloid synthesis.



Scheme 4.

Table 2. ^{1}H NMR data of δ-lactones [$(CD_3)_2SO$]: δ (*J* in Hz).



19-H	4.62 (m, $J_{19,20}$ 4.5)	4.65 (m)	4.08 (m, $J_{19,20}$ 10)	4.18 (m)
Me	0.95 (d, *J* 5.5)	1.23 (d, *J* 6.5)	1.27 (d, *J* 6)	1.28 (d, *J* 6.5)

Experimental

^{1}H NMR 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 Hitachi M-80 instruments, and IR 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 nitrogen bubbled through. All other reactions were carried out in a nitrogen stream. TLC was performed on precoated silica gel 60F-254 (0.25 mm thick, Merck) and preparative TLC (PTLC) on precoated silica gel 60F-254 (0.5 mm thick, Merck), with UV detection at 254 and 300 nm. Low-pressure column chromatography (LCC) was undertaken on a 530-4-10V apparatus (Yamazen) using Lobar grösse B (310–25, Lichroprep Si60, Merck) as a column. Ether refers to diethyl ether.

2-(2-*Furoyl*)-6,7-*dimethoxy*-1-*methylene*-1,2,3,4-*tetrahydroisoquinoline* (**3**).—A solution of furan-2-carbonyl chloride (1.50 g) in anhydrous benzene (50 ml) was added dropwise to an ice-cooled, stirred solution of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline (**1**) (2.05 g) and triethylamine (2.0 g) in anhydrous benzene (100 ml). After being stirred at room temperature for 1 h, the solution was filtered to remove triethylamine hydrochloride. The filtrate was evaporated to give the unstable enamide (**3**) (2.90 g, 97%) as a pale yellow glass which was used for irradiation without further purification; ν_{max} 1 630 cm^{-1} (NCO); δ_H(60 MHz) 7.40 (1 H, br s, furan 3-H), 7.10 (1 H, s, 8-H), 6.90 (1 H, d, *J* 3 Hz, furan 5-H), 6.63 (1 H, s, 5-H), 6.40 (1 H, dd, *J* 3 and 1 Hz, furan 4-H), 5.40 and 4.75 (each 1 H, br s, C=CH_2), 4.10 (2 H, t, *J* 6 Hz, 3-H_2), 3.95 and 3.90 (each 3 H, s, OMe × 2), and 2.97 (2 H, t, *J* 6 Hz, 4-H_2).

(8aα,11aα,12aα)-(±)-2,3-*Dimethoxy*-5,6,8a,11a,12,12a-*hexahydrobenzo*[a]*furo*[2,3-g]*quinolizin*-8-*one* (**4**).—Sodium borohydride (3.0 g) and methanol (100 ml) were added successively to a stirred solution of the enamide (**3**) (2.6 g) in acetonitrile (900 ml) at 0 – 5 °C. When the sodium borohydride had dissolved, the solution was irradiated for 2 h, and then evaporated at room temperature under reduced pressure. Water was added to the residue and the separated oil was extracted with methylene dichloride. The extract was washed, dried, and evaporated to give a residue which was purified by LCC (ethyl acetate) to afford the *furopyridone* (**4**) (2.02 g, 77%) as pale yellow crystals, m.p. 146–147 °C (from ether–methanol); ν_{max} 1 640 cm^{-1} (NCO); *m/z* 301 (M^+); δ_H(200 MHz) 6.66 and 6.64 (each 1 H, s, 1- and 4-H), 6.44 (1 H, dd, *J* 2.5 and 1.5 Hz, 10-H), 5.10 (1 H, t, *J* 2.5 Hz, 11-H), 4.94 (1 H, m, 6-H_{eq}), 4.84 (1 H, d, *J* 10.5 Hz, 8a-H: 32.0% intensity increase upon irradiation at δ 3.37), 4.64 (1 H, br dd, *J* 11.5 and 2.5 Hz, 12a-H), 3.90 (6 H, s, OMe × 2), 3.37 (1 H, m, 11a-H: 18.8% intensity increase upon irradiation at δ 4.84), 2.39 (1 H, ddd, *J* 13, 5, and 2.5 Hz, 12-H_{eq}), and 1.44 (1 H, br q, *J* 12.5 Hz, 12-H_{ax}) (Found: C, 67.8; H, 6.4; N, 4.6. $C_{17}H_{19}NO_4$ requires C, 67.8; H, 6.4; N, 4.65%).

(8aα,11aα,12aα)-(±)-8a-*Deuterio*-2,3-*dimethoxy*-5,6,8a,11a,-12,12a-*hexahydrobenzo*[a]*furo*[2,3-g]*quinolizin*-8-*one* (**5**).—A solution of the furopyridone (**4**) (53 mg, 0.18 mmol) in anhydrous THF (3 ml) was added at −78 °C to a stirred solution of LDA, prepared from di-isopropylamine (0.03 ml, 0.22 mmol) and butyl-lithium (15% solution in hexane) (0.1 ml, 0.22 mmol) at −78 °C. After being stirred at −78 °C for 10 min, at −30 °C for 40 min, and again at −78 °C for 10 min, methan[^{2}H]ol (0.5 ml) was added and the resulting solution was stirred at −78 °C for 1 h. After addition of water, the reaction mixture was extracted with methylene dichloride. The extract was washed, dried, and evaporated to give the deuteriated lactam (**5**) (50 mg, 94%) as a yellow oil, which was characterised by its NMR spectrum; δ_H(200 MHz) 6.68 and 6.66 (each 1 H, s, 1- and 4-H), 6.43 (1 H, br t, *J* 2.5 Hz, 10-H), 5.10 (1 H, t, *J* 2.5 Hz, 11-H), 4.90 (1 H, m, 6-H_{eq}), 4.66 (1 H, br d, *J* 12 Hz, 12a-H), 3.90 (6 H, s, OMe × 2), 3.38 (1 H, br dm, *J* 12 Hz, 11a-H), 2.41 (1 H, ddd, *J* 13, 5, 2.5 Hz, 12-H_{eq}), and 1.44 (1 H, br q, *J* 12 Hz, 12-H_{ax}).

(8aα,11aα,12aα)-(±)-8a-*Ethyl*-2,3-*dimethoxy*-5,6,8a,11a,12,-12a-*hexahydrobenzo*[a]*furo*[2,3-g]*quinolizin*-8-*one* (**6**).—Following the procedure given for (**5**), alkylation of the lithium enolate, prepared from the furopyridone (**4**) (300 mg, 1.0 mmol), di-isopropylamine (0.18 ml, 1.3 mmol), and butyl-lithium (15% solution in hexane) (0.56 ml, 1.3 mmol), with ethyl iodide (0.4 ml, 4 mmol), followed by purification of the crude product by LCC (ethyl acetate–hexane, 1:1) afforded the 8a-*ethyl-lactam* (**6**) (280 mg, 86%) as pale yellow crystals, m.p. 118–120 °C (from benzene–hexane); ν_{max} 1 640 cm^{-1} (NCO); *m/z* 329 (M^+); δ_H (200 MHz) 6.66 and 6.64 (each 1 H, s, 1- and 4-H), 6.36 (1 H, dd, *J* 2.5 and 1.5 Hz, 10-H), 4.95 (1 H, t, *J* 2.5 Hz, 11-H), 4.92 (1 H, m, 6-H_{eq}), 4.57 (1 H, br dd, *J* 12 and 2.5 Hz, 12a-H), 3.89 (6 H, s, OMe × 2), 3.13 (1 H, dddd, *J* 12, 5.5, 2.5, and 1.5 Hz, 11a-H: 12.0% intensity increase upon irradiation at δ 1.94), 2.39 (1 H, ddd, *J* 12, 5.5, and 2.5 Hz, 12-H_{eq}), 1.94 (2 H, q, *J* 7.5 Hz, CH_2CH_3: 2.7% intensity increase upon irradiation at δ 3.13), 1.41 (1 H, q, *J* 12 Hz, 12-H_{ax}), and 0.96 (3 H, t, *J* 7.5 Hz, CH_2CH_3) (Found: C, 69.25; H, 7.1; N, 4.3. $C_{19}H_{23}NO_4$ requires C, 69.3; H, 7.0; N, 4.25%).

(8aα,11aα,12aα)-(±)-8a-*Acetyl*-2,3-*dimethoxy*-5,6,8a,11a,12,-12a-*hexahydrobenzo*[a]*furo*[2,3-g]*quinolizin*-8-*one* (**7**).—Following the procedure given for (**5**), acetylation of the lithium enolate, prepared from the furopyridone (**4**) (600 mg, 2.0 mmol), di-isopropylamine (0.56 ml, 4.0 mmol), and butyl-lithium (15% solution in hexane) (1.7 ml, 4.0 mmol) with acetic anhydride (0.38 ml, 4.0 mmol) followed by purification of the crude product by LCC (ethyl acetate–hexane, 1:1) afforded the 8a-*acetyl-lactam* (**7**) (550 mg, 80%) as colourless crystals, m.p. 130–132 °C (from benzene–hexane); ν_{max} 1 720 (Ac) and 1 650 cm^{-1} (NCO); *m/z* 343 (M^+); δ_H(200 MHz) 6.68 (2 H, s, 1- and 4-H), 6.52 (1 H, dd, *J* 3 and 1.5 Hz, 10-H), 5.09 (1 H, t, *J* 3 Hz, 11-H), 4.84 (1 H, m, 6-H_{eq}), 4.84 (1 H, br d, *J* 12 Hz, 12a-H), 3.91 (6 H, s, OMe × 2), 3.64 (1 H, dddd, *J* 12, 5.5, 3, and 1.5 Hz, 11a-H), 2.49 (3 H, s, Ac), 2.48 (1 H, ddd, *J* 12.5, 5.5, and 2.5 Hz, 12-H_{eq}), and 1.44 (1 H, br q, *J* 12 Hz, 12-H_{ax}) (Found: C, 66.0; H, 6.1; N, 4.0. $C_{19}H_{21}NO_5$ requires C, 66.5; H, 6.2; N, 4.1%).

(8aα,11aα,12α)-(±)-2,3-*Dimethoxy*-8a-*methoxycarbonyl*-5,6,8a,11a,12,12a-*hexahydrobenzo*[a]*furo*[2,3-g]*quinolizin*-8-*one* (**8**).—Following the procedure given for (**5**), acylation of the lithium enolate, prepared from the furopyridone (**4**) (60 mg, 0.2 mmol), di-isopropylamine (0.056 ml, 0.4 mmol), and butyl-lithium (15% solution in hexane) (0.17 ml, 0.4 mmol) with methyl chloroformate (0.03 ml, 0.4 mmol) followed by purification of the crude product by LCC (ethyl acetate–hexane, 3:1) afforded the 8a-*methoxycarbonyl-lactam* (**8**) (72 mg, 89%) as colourless crystals, m.p. 202–203 °C (from benzene–hexane); ν_{max} 1 760, 1 730 (CO_2Me), and 1 650 cm^{-1} (NCO); *m/z* 359 (M^+); δ_H(200 MHz) 6.66 and 6.64 (each 1 H, s, 1- and 4-H), 6.50 (1 H, dd, *J* 3 and 1.5 Hz, 10-H), 5.08 (1 H, t, *J* 3 Hz, 11-H), 4.90 (1 H, m, 6-H_{eq}), 4.85 (1 H, br d, *J* 13 Hz, 12a-H), 3.89 (6 H, s, OMe × 2), 3.87 (3 H, s, OMe), 3.55 (1 H, m, 11a-H), 2.47 (1 H, ddd, *J* 13, 5.5, and 2.5 Hz, 12-H_{eq}), and 1.47 (1 H, q, *J* 13 Hz, 12-H_{ax}) (Found: C, 63.25; H, 5.8; N, 3.8. $C_{19}H_{21}NO_6$ requires C, 63.5; H, 5.9; N, 3.9%).

(8aα,10α,11aα,12aα)- *and* (8aα,10β,11aα,12aα)-(±)-8a-*Ethyl*-10-*hydroxy*-2,3-*dimethoxy*-5,6,8a,10,11,11a,12,12a-*octahydrobenzo*[a]*furo*[2,3-g]*quinolizin*-8-*one* (**9**).—A solution of the dihydrofuran (**6**) (200 mg) in THF (20 ml) containing 15% sulphuric acid (4 ml) was stirred at room temperature for 2 h. Methylene dichloride and anhydrous potassium carbonate were added to the resulting solution cooled in ice and the separated organic layer was dried and evaporated to give a residue which was purified by LCC (ethyl acetate) to afford the *hemiacetal* (**9**) (208 mg, 99%) as colourless crystals, m.p. 178–179 °C (from benzene–hexane); ν_{max} 3 400 (OH) and 1 640 cm^{-1} (NCO); *m/z* 347 (M^+); δ_H(60 MHz) 6.57 (2 H, s, 1- and 4-H), 5.73–5.50 (1 H, m, 10-H), 5.13–4.13 (2 H, m, 6-H_{eq} and 12a-H), 3.85 (6 H, s, OMe × 2), and 1.00 (3 H, t, *J* 7 Hz, CH_2CH_3) (Found: C, 65.3; H, 7.30; N, 3.9. $C_{19}H_{25}NO_5$ requires C, 65.7; H, 7.25; N, 4.0%).

(8aα,11aα,12aα)-(±)-8a-*Ethyl*-2,3-*dimethoxy*-5,6,8a,11a,12,-12a-*hexahydrobenzo*[a]*furo*[2,3-g]*quinolizine*-8,10(11H)-*dione* (**10**).—(*a*) *By direct oxidation of the dihydrofuran* (**6**) *with PCC.* A solution of the dihydrofuran (**6**) (66 mg, 0.2 mmol) in anhydrous methylene dichloride (5 ml) was added dropwise to a solution of PCC (94.8 mg, 0.44 mmol) in anhydrous methylene dichloride (45 ml) at room temperature. After being stirred at room temperature for 10 h, the solution was left at 4–5 °C for 14 h. Methanol (2 ml) was added and the resulting solution was stirred at room temperature for 30 min. Evaporation gave a residue which was purified by PLC (ethyl acetate) to afford the lactone (**10**) (10 mg, 14%) as crystals, m.p. 192–193 °C (from benzene–hexane); ν_{max} 1 790 (γ-lactone) and 1 650 cm^{-1} (NCO); *m/z* 345 (M^+); δ_H(200 MHz) 6.68 and 6.63 (each 1 H, s, 1- and 4-H), 4.88 (1 H, m, 6-H_{eq}), 4.68 (1 H, br d, *J* 13 Hz, 12a-H), 3.90 and 3.89 (each 3 H, s, OMe × 2), 3.00 (1 H, dd, *J* 17.5 and 9 Hz, 11-H), 2.40 (1 H, ddd, *J* 13, 5, and 3 Hz, 12-H_{eq}), 2.36 (1 H, br d, *J* 17.5 Hz, 11-H), 2.28 and 1.86 (each 1 H, dq, *J* 13.5 and 7.5 Hz, CH_2CH_3), 1.62 (1 H, br q, *J* 13 Hz, 12-

H_{ax}), and 0.99 (3 H, t, *J* 7.5 Hz, CH_2CH_3) (Found: C, 65.65; H, 6.65; N, 4.30. $C_{19}H_{23}NO_5$ requires C, 66.1; H, 6.7; N, 4.1%).

(*b*) *By oxidation of the hemiacetal* (**9**). A solution of the hemiacetal (**9**) (60 mg, 0.17 mmol) in anhydrous methylene dichloride (12 ml) was added dropwise to a solution of PCC (41 mg, 0.19 mmol) in anhydrous methylene dichloride (18 ml) at room temperature. The mixture was stirred at room temperature for 3 h, methanol (2 ml) was added, and the solution was stirred at room temperature for 30 min. Evaporation gave a residue which was purified by LCC (ethyl acetate–hexane, 1:1) to give the lactone (**10**) (36 mg, 60%) which was identical with the sample obtained in (*a*).

(2α,3β,11bβ)-(±)-3-*Ethyl*-9,10-*dimethoxy*-4-*oxo*-1,3,4,6,7,-11b-*hexahydro*-2H-*benzo*[a]*quinolizin*-2-*ylacetic Acid* (**11**).—Calcium (10 mg) was added to liquid ammonia (50 ml). A solution of the γ-lactone (**10**) (100 mg) in anhydrous THF (10 ml) was added dropwise to the resulting blue solution at −70 °C. The mixture was stirred at the same temperature for 30 min, methanol (2 ml) was added, and the solution was stirred for further 30 min; ammonium chloride (10 mg) was then added. After evaporation of ammonia, water was added to the residue and the mixture was acidified by the addition of 10% hydrochloric acid and then extracted with methylene dichloride. The organic layer was washed, dried, and evaporated to give a solid which was recrystallised from ether–methanol to give the acid (**11**) (64 mg, 62%) as pale yellow crystals, m.p. 186.5–188 °C (lit.,[8] 187–188 °C); ν_{max} (Nujol) 3 200–2 500 and 1 720 cm^{-1} (CO_2H); δ_H(60 MHz) 6.70 and 6.65 (each 1 H, s, 8- and 11-H), 6.03–5.53 (2 H, m, 6-H_{eq} and 11b-H), 3.97 (6 H, s, OMe × 2), and 0.97 (3 H, t, *J* 7 Hz, CH_2CH_3) (Found: M^+, 347.173. Calc. for $C_{19}H_{25}NO_5$: *M*, 347.173). This acid was identical (IR) with the authentic acid,[8] provided by Professor Takano.

Methyl (2α,3β,11bβ)-(±)-3-*Ethyl*-9,10-*dimethoxy*-4-*oxo*-1,3,4,6,7,11b-*hexahydro*-2H-*benzo*[a]*quinolizin*-2-*ylacetate* (**12**).—Esterification of the acid (**11**) (60 mg) with diazomethane in the usual manner, followed by purification by PLC (methylene dichloride–methanol) gave the methyl ester (**12**) (61 mg, 98%) as pale yellow crystals, m.p. 54–55 °C (from ether–methanol) (lit.,[8] 56–57 °C); ν_{max} 1 735 (CO_2Me) and 1 625 cm^{-1} (NCO); δ_H(200 MHz) 6.68 and 6.64 (each 1 H, s, 8- and 11-H), 4.88 (1 H, m, 6-H_{eq}), 4.67 (1 H, br dd, *J* 12 and 4 Hz, 11b-H), 3.88 (6 H, s, OMe × 2), 3.75 (3 H, s, CO_2Me), 2.61 (1 H, dd, *J* 15 and 3.5 Hz, $CHHCO_2Me$), 2.56 (1 H, dt, *J* 12 and 4 Hz, 1-H_{eq}), 2.37 (1 H, m, 2-H), 2.20 (1 H, dd, *J* 15 and 8.5 Hz, $CHHCO_2Me$), 1.63 (1 H, m, CH_2CH_3), 1.44 (1 H, q, *J* 12 Hz, 1-H_{ax}), and 0.91 (3 H, t, *J* 7.5 Hz, CH_2CH_3) (Found: M^+, 361.190. Calc. for $C_{20}H_{27}NO_5$: *M*, 361.189). This ester was identical (IR) with the authentic ester,[8] provided by Professor Takano.

(8aα,10α,11aα,12aα)- *and* (8aα,10β,11aα,12aα)-(±)-8a-*Acetyl*-10-*hydroxy*-2,3-*dimethoxy*-5,6,8a,10,11,11a,12,12a-*octahydrobenzo*[a]*furo*[2,3-g]*quinolizin*-8-*one* (**13**).—Following the procedure given for (**9**), treatment of the dihydrofuran (**7**) (200 mg) with 15% sulphuric acid (4 ml) followed by purification of the crude product by LCC (ethyl acetate) afforded the hemiacetal (**13**) (209 mg, 99%) as pale yellow crystals, m.p. 137–139 °C (from benzene); ν_{max} 3 400 (OH), 1 710 (Ac), and 1 640 cm^{-1} (NCO); *m*/*z* 361 (M^+); δ_H(60 MHz) 6.60 (2 H, br s, 1- and 4-H), 5.90–5.67 (1 H, m, 10-H), 5.12–4.53 (2 H, m, 6-H_{eq} and 12a-H), 3.87 (6 H, s, OMe × 2), 2.47 (1.5 H, s, Ac), and 2.35 (1.5 H, s, Ac) (Found: C, 64.5; H, 6.5; N, 3.7. $C_{19}H_{23}NO_6 \cdot 1/6C_6H_6$ requires C, 64.35; H, 6.5; N, 3.7%). The NMR spectrum shows that this hemiacetal is a 1:1 mixture of two epimers at the 10-position.

(8aα,11aα,12aα)-(±)-8a-*Acetyl*-2,3-*dimethoxy*-5,6,8a,11a,12,-12a-*hexahydro*-8H-*benzo*[a]*furo*[2,3-g]*quinolizine*-8,10(11H)-*dione* (**14**).—(*a*) *By oxidation with PCC.* Following the procedure given for (**10**), oxidation of the hemiacetal (**13**) (240 mg, 0.66 mmol) with PCC (213 mg, 0.99 mmol) followed by LCC of the crude product (ethyl acetate–hexane, 1:1) afforded the γ-lactone (**14**) (121 mg, 51%) as crystals, m.p. 217–219 °C (from benzene–hexane); ν_{max} 1 800 (γ-lactone), 1 720 (Ac), and 1 660 cm^{-1} (NCO); *m*/*z* 359 (M^+); δ_H(200 MHz) 6.68 and 6.66 (each 1 H, s, 1- and 4-H), 4.86 (1 H, dd, *J* 12 and 3 Hz, 12a-H), 3.91 (6 H, s, OMe × 2), 3.36 (1 H, m, 11a-H), 2.86 (1 H, dd, *J* 19 and 9 Hz, 11-H), 2.55 (1 H, ddd, *J* 12, 6, and 3 Hz, 12-H_{eq}), 2.52 (3 H, s, Ac), 2.34 (1 H, dd, *J* 19 and 3 Hz, 11-H), and 1.62 (1 H, br q, *J* 12 Hz, 12-H_{ax}) (Found: C, 64.6; H, 6.0; N, 3.7. $C_{19}H_{21}NO_6 \cdot 1/6C_6H_6$ requires C, 64.5; H, 5.95; N, 3.8%).

(*b*) *By oxidation with Jones reagent.* A solution of Jones reagent (30 mg) was added dropwise to a stirred solution of the hemiacetal (**13**) (75 mg) in anhydrous acetone (10 ml) at −30 °C. After being stirred at −30 °C for 30 min, propan-2-ol (2 ml) was added and the mixture was made alkaline by the addition of saturated sodium hydrogen carbonate and then filtered. The filtrate was evaporated to give a residue which was recrystallised from ether–methanol to afford the γ-lactone (**14**) (43 mg, 58%), identical with the sample obtained in (*a*). (*c*) *By oxidation with dimethyl sulphoxide–acetic anhydride.* A mixture of the hemiacetal (**13**) (350 mg), anhydrous dimethyl sulphoxide (3.6 ml), and acetic anhydride (2.4 ml) was stirred at room temperature overnight. Water was added and the mixture was extracted with methylene dichloride. The extract was washed, dried, and evaporated to a residue which was purified by LCC (ethyl acetate–hexane, 1:1) to give the γ-lactone (**14**) (270 mg, 77%), identical with the sample obtained in (*a*).

Methyl (2α,3β,11bβ)-(±)-3-*Acetyl*-9,10-*dimethoxy*-4-*oxo*-1,3,4,6,7,11b-*hexahydro*-2H-*benzo*[a]*quinolizin*-2-*ylacetate* (**16**).—(*a*) *By reduction with aluminium amalgam.* A solution of the lactone (**14**) (100 mg) in THF–ethanol–water (10:3:3) (16 ml) was added to aluminium amalgam, prepared from aluminium (110 mg) and 5% mercury(II) dichloride (5 ml), and the resulting solution was refluxed. During the reaction, newly prepared aluminium amalgam, prepared from aluminium (200 mg), was added with monitoring by TLC. After filtration of the mixture, the filtrate was evaporated and acidified by the addition of dilute hydrochloric acid, and then extracted with methylene dichloride. The organic layer was washed, dried, and evaporated to give the crude carboxylic acid (**15**) which was, without purification, esterified with diazomethane according to the procedure given for (**12**) to give the ester (**16**) (99 mg, 95%) as crystals, m.p. 128–130 °C (from benzene–hexane). The acid (**15**) had ν_{max} 3 600–2 500 (CO_2H), 1 720 (CO_2H and Ac), and 1 635 cm^{-1} (NCO); *m*/*z* 361 (M^+); δ_H (60 MHz) 6.55 and 6.51 (each 1 H, s, 8- and 11-H), 3.80 (6 H, s, OMe × 2), 3.47 (1 H, d, *J* 10 Hz, 3-H), and 2.40 (3 H, s, Ac); the *ester* (**16**) had ν_{max} 1 740–1 720 (CO_2Me and Ac) and 1 630 cm^{-1} (NCO); *m*/*z* 375 (M^+); δ_H (200 MHz) 6.68 and 6.66 (each 1 H, s, 8- and 11-H), 4.80 (1 H, m, 6-H_{eq}), 4.74 (1 H, dd, *J* 12 and 5 Hz, 11b-H), 3.90 (6 H, s, OMe × 2), 3.72 (3 H, s, CO_2Me), 3.46 (1 H, d, *J* 11 Hz, 3-H), 2.45 (3 H, s, Ac), 2.40 (1 H, dd, *J* 16.5 and 2 Hz, $CHHCO_2Me$), 2.30 (1 H, dd, *J* 16.5 and 7.5 Hz, $CHHCO_2Me$), and 1.49 (1 H, q, *J* 12 Hz, 1-H_{ax}) (Found: C, 63.6; H, 6.7; N, 3.6. $C_{20}H_{25}NO_6$ requires C, 64.0; H, 6.7; N, 3.7%).

(*b*) *By reduction with zinc in acetic acid.* A mixture of the γ-lactone (**14**) (120 mg), freshly prepared zinc powder (3 g), and anhydrous acetic acid (70 ml) was refluxed for 10 h. After being filtered, the filtrate was evaporated to give a residue, the chloroform-soluble part of which was made alkaline by the addition of saturated aqueous sodium hydrogen carbonate, and then extracted with benzene. The aqueous layer was acidified by the addition of hydrochloric acid and then extracted with

methylene dichloride. The extract was washed, dried, and evaporated to give the carboxylic acid (**15**) which was also characterised as its methyl ester (**16**) (106 mg, 85%) according to the procedure given for (**12**). This ester (**16**) was identical with the sample obtained in (*a*).

Reduction of the Acetyl Ester (**16**).—(*a*) *With diborane.* A solution (1.5 ml) of freshly prepared diborane in THF was added dropwise to a solution of the acetyl ester (**16**) (60 mg) in anhydrous THF (5 ml) at −10 °C. The mixture was stirred at the same temperature for 1 h, 10% hydrochloric acid (10 ml) was added at −10 °C, and then the mixture was stirred at room temperature for 1 h. The mixture was diluted with water and extracted with methylene dichloride. The aqueous layer was 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 PLC (ethyl acetate–methanol, 95:5) to afford two lactones (**19**) and (**20**). (8aα,9β,12aβ,13aβ)-(±)-2,3-*dimethoxy*-9-*methyl*-5,6,8a,9,12,12a,13,13a-*octahydro*-8H-*benzo*[a]*pyrano*[3,4-g]*quinolizin*-11-*one* (**19**) (8 mg, 15%) was a yellow oil, ν_{max} 2 840 and 2 775 (Bohlmann) and 1 725 cm^{-1} (δ-lactone); δ_H(200 MHz) 6.68 and 6.62 (each 1 H, s, 1- and 4-H), 4.76 (1 H, br dq, *J* 7 and 4 Hz, 9-H), 3.89 and 3.88 (each 3 H, s, OMe × 2), 3.20 (1 H, br d, *J* 11.5 Hz, 13a-H), 2.42 (1 H, dt, *J* 13 and 3 Hz, 13-H_{eq}), 1.42 (1 H, br q, *J* 12 Hz, 13-H_{ax}), and 1.36 (3 H, d, *J* 7 Hz, Me) (Found: M^+, 331.177. $C_{19}H_{25}NO_4$ requires *M*, 331.178). The 9-*epimer* (**20**) (21 mg, 40%) was a yellow oil, ν_{max} 2 840 and 2 760 (Bohlmann) and 1 730 cm^{-1} (δ-lactone); δ_H (200 MHz) 6.69 and 6.62 (each 1 H, s, 1- and 4-H), 4.23 (1 H, dq, *J* 10 and 6 Hz, 9-H), 3.89 and 3.88 (each 3 H, s, OMe × 2), 3.23 (1 H, br d, *J* 11 Hz, 13a-H), 3.08 (1 H, dd, *J* 11 and 4 Hz, 8-H_{eq}), 2.81 (1 H, dd, *J* 18 and 5 Hz, 12-H_{eq}), 2.36 (1 H, dt, *J* 13 and 4 Hz, 13-H_{eq}), 2.26 (1 H, dd, *J* 18 and 12 Hz, 12-H_{ax}), 2.15 (1 H, t, *J* 11 Hz, 8-H_{ax}), 1.88 (1 H, br qt, *J* 11 and 5 Hz, 12a-H), 1.68 (1 H, br qd, *J* 11 and 4 Hz, 8a-H), 1.42 (3 H, d, *J* 6 Hz, Me), and 1.24 (1 H, dt *J* 13 and 11 Hz, 13-H_{ax}) (Found: M^+, 331.176).

(*b*) *With sodium borohydride.* Sodium borohydride (10 mg) was added to a stirred solution of the acetyl ester (**16**) (20 mg) in methanol (2 ml) at −10 °C. The mixture was stirred at −10 °C for 30 min, water was added at −10 °C, and the mixture was acidified with 10% hydrochloric acid and then extracted with methylene dichloride. The organic layer was washed, dried, and evaporated to give a residue which was purified by PLC (ethyl acetate) to give two hydroxy esters (**17**) and (**18**): *methyl* [2α,3β(*R**),11bβ]-(±)-3-(1-*hydroxyethyl*)-9,10-*dimethoxy*-4-*oxo*-1,3,4,6,7,11b-*hexahydro*-2H-*benzo*[a]*quinolizin*-2-*ylacetate* (**17**) (12 mg, 55%) was an oil, ν_{max} 3 400 (OH), 1 730 (CO_2Me), and 1 610 cm^{-1} (NCO); δ_H(200 MHz) 6.67 and 6.65 (each 1 H, s, 8- and 11-H), 4.87 (1 H, m, 6-H_{eq}), 4.68 (1 H, dd, *J* 11 and 3.5 Hz, 11b-H), 4.20 [1 H, m, C*H*(OH)Me], 3.88 (6 H, s, OMe × 2), 3.72 (3 H, s, CO_2Me), 3.47 (1 H, br s, OH), 1.46 (1 H, br q, *J* 13 Hz, 1-H_{ax}), and 1.41 [3 H, d, *J* 6.5 Hz, CH(OH)*Me*] (Found: M^+, 377.183. $C_{20}H_{27}NO_6$ requires *M*, 377.184). The 3β(S*)-*epimer* (**18**) (8 mg, 40%) was an oil, ν_{max} 3 400, (OH), 1 730 (CO_2Me), and 1 610 cm^{-1} (NCO); δ_H (200 MHz) 6.66 (2 H, s, 8- and 11-H), 5.33 (1 H, d, *J* 10.5 Hz, OH), 4.84 (1 H, m, 6-H_{eq}), 4.69 (1 H, dd, *J* 11.5 and 4.5 Hz, 11b-H), 3.98 [1 H, m, C*H*(OH)Me], 3.94 (6 H, s, OMe × 2), 3.75 (3 H, s, CO_2Me), 1.44 (1 H, q, *J* 11.5 Hz, 1-H_{ax}), and 1.26 [3 H, d, *J* 6.5 Hz, CH(OH)*Me*] (Found: M^+, 377.185).

(*c*) *With tetrabutylammonium borohydride.* Tetrabutylammonium borohydride (10 mg) was added to a stirred solution of the acetyl ester (**16**) (20 mg) in methanol (2 ml) at −20 °C and the mixture was stirred at the same temperature for 30 min. The same work-up as that described in (*b*) gave a 4:3 epimeric mixture of the hydroxy esters (**17**) and (**18**) which was characterised by the NMR spectrum (60 MHz) showing two peaks at δ 3.71 (12/7 H, s) and 3.74 (9/7 H, s) due to the ester methyl protons. These esters (**17**) and (**18**) were identical with the samples obtained in (*b*) by comparison of their R_F values.

(*d*) *With lithium borohydride.* Lithium borohydride (10 mg) was added to a stirred solution of the acetyl ester (**16**) (20 mg) in anhydrous THF (2 ml) at −20 °C and the mixture was stirred at the same temperature for 30 min. The same work-up as that described in (*b*) gave a 1:1 mixture of the hydroxy esters (**17**) and (**18**) which was characterised by the NMR spectrum (60 MHz) showing two peaks at δ 3.71 (3/2 H, s) and 3.74 (3/2 H, s) due to the ester methyl protons. These esters (**17**) and (**18**) were identical with the authentic samples obtained in (*b*) and (*c*) by comparison of their R_F values.

(8aα,9β,12aβ,13aβ)-(±)-2,3-*Dimethoxy*-9-*methyl*-5,6,8a,9,12,-12a,13,13a-*octahydrobenzo*[a]*pyrano*[3,4-g]*quinoli-zine*-8,11-*dione* (**21**).—A solution of the hydroxy ester (**17**) (20 mg) and toluene-*p*-sulphonic acid (5 mg) in anhydrous benzene (5 ml) was refluxed for 30 min. After addition of saturated aqueous sodium hydrogen carbonate, the mixture was extracted with benzene. The extract was washed, dried, and evaporated to give a residue which was purified by PLC (ethyl acetate) to afford the lactam (**21**) (17 mg, 94%) as a yellow oil, ν_{max} 1 725 (δ-lactone) and 1 640 cm^{-1} (NCO); δ_H(200 MHz) 6.68 and 6.67 (each 1 H, s, 1- and 4-H), 5.29 (1 H, dq, *J* 7 and 6 Hz, 9-H), 4.88 (1 H, m, 6-H_{eq}), 4.78 (1 H, dd, *J* 11 and 5 Hz, 13a-H), 3.91 and 3.90 (each 3 H, s, OMe × 2), 2.30 (1 H, dd, *J* 18 and 11 Hz, 12-H_{ax}), and 1.42 (3 H, d, *J* 6 Hz, CMe) (Found: M^+, 345.157. $C_{19}H_{23}NO_5$ requires *M*, 345.157).

(8aα,9α,12aβ,13aβ)-(±)-2,3-*Dimethoxy*-9-*methyl*-5,6,8a,9,12,12a,13,13a-*octahydrobenzo*[a]*pyrano*[3,4-g]*quinoli-zine*-8,11-*dione* (**22**).—Following the procedure given for (**21**), lactonisation of the hydroxy ester (**18**) (15 mg) gave the *lactone* (**22**) (13 mg, 95%) as a yellow oil, ν_{max} 1 725 (δ-lactone) and 1 640 cm^{-1} (NCO); δ_H (200 MHz) 6.67 (2 H, s, 1- and 4-H), 4.87 (1 H, m, 6-H_{eq}) 4.78 (1 H, br d, *J* 11 Hz, 13a-H), 4.71 (1 H, dq, *J* 10 and 6 Hz, 9-H), 3.89 and 3.88 (each 3 H, s, OMe × 2), 2.13 (1 H, dd, *J* 17 and 12 Hz, 12-H_{ax}), and 1.79 (3 H, d, *J* 6 Hz, CMe) (Found: M^+, 345.157).

Methyl (2α,3β,11bβ)-(±)-3-*Acetyl*-9,10-*dimethoxy*-4-*thioxo*-1,3,4,6,7,11b-*hexahydro*-2H-*benzo*[a]*quinolizin*-2-*ylacetate* (**23**).—A mixture of the acetyl ester (**16**) (70 mg, 0.19 mmol), Lawesson's reagent (50 mg, 0.12 mmol), and anhydrous toluene (30 ml) was stirred at 100 °C for 3 h. The mixture was then immediately subjected to LCC (ethyl acetate–hexane, 1:1) to give the *thiolactam* (**23**) (69 mg, 95%) as a yellow oil, ν_{max} 1 735 (CO_2Me) and 1 710 cm^{-1} (Ac); δ_H(200 MHz) 6.70 and 6.66 (each 1 H, s, 8- and 11-H), 5.53 (1 H, dt, *J* 13 and 4.5 Hz, 6-H_{eq}), 4.83 (1 H, br dd, *J* 11.5 and 4.5 Hz, 11b-H), 4.01 (1 H, d, *J* 8.5 Hz, 3-H), 3.90 (6 H, s, OMe × 2), 3.72 (3 H, s, CO_2Me), 2.68 (1 H, dt, *J* 13.5 and 4.5 Hz, 1-H_{eq}), 2.48 (3 H, s, Ac), 2.46 (1 H, dd, *J* 17 and 5 Hz, CH*H*CO_2Me), 2.31 (1 H, dd, *J* 17 and 8.5 Hz, C*H*HCO_2Me), and 1.55 (1 H, dt, *J* 13.5 and 11.5 Hz, 1-H_{ax}) (Found: M^+, 391.144. $C_{20}H_{25}NO_5S$ requires *M*, 391.145).

Methyl trans-3-*Acetyl*-9,10-*dimethoxy*-1,6,7,11b-*tetrahydro*-2H-*benzo*[a]*quinolizin*-2-*ylacetate* (**24**).—Freshly prepared Raney nickel (W-2) (1 ml) was added in small portions to a refluxing solution of the thiolactam (**23**) (50 mg) in methanol (20 ml) during the course of 1 h. The catalyst was filtered off and the filtrate was evaporated to give the unstable enamine (**24**) (45 mg, 98%) as a yellow oil, ν_{max} 1 730 (CO_2Me) and 1 580 cm^{-1} (NC=CCO); δ_H(60 MHz) 7.30 (1 H, s, 4-H), 6.67 and 6.55 (each 1 H, s, 8- and 11-H), 3.83 (6 H, s, OMe × 2), 3.63 (3 H, s,

Table 3. Fractional atomic co-ordinates with esd's in parentheses.

Atom	x/a	y/b	z/c
C(1)	0.957 5(3)	0.471 3(2)	0.332 4(2)
C(2)	0.826 1(3)	0.469 0(2)	0.365 9(2)
C(3)	0.765 2(3)	0.555 2(2)	0.395 5(2)
C(4)	0.838 1(3)	0.642 3(2)	0.388 8(2)
C(5)	1.048 2(3)	0.740 0(2)	0.346 2(3)
C(6)	1.215 3(3)	0.722 6(2)	0.365 5(3)
N(7)	1.240 1(3)	0.652 0(1)	0.281 7(2)
C(8)	1.326 9(3)	0.677 8(2)	0.212 9(3)
O(9)	1.349 0(4)	0.633 5(2)	0.028 5(2)
C(10)	1.304 0(5)	0.553 7(3)	−0.039 2(3)
C(11)	1.279 8(4)	0.475 9(3)	0.014 7(3)
C(12)	1.152 2(3)	0.506 8(2)	0.170 5(3)
C(13)	1.176 0(3)	0.554 6(2)	0.286 0(2)
C(14)	1.030 5(3)	0.559 7(2)	0.323 3(2)
C(15)	0.969 2(3)	0.644 8(2)	0.350 5(2)
C(16)	1.376 0(3)	0.600 1(2)	0.143 1(3)
C(17)	1.300 9(3)	0.500 1(2)	0.137 4(3)
O(2′)	0.747 2(2)	0.386 8(1)	0.374 5(2)
C(2′)	0.812 8(3)	0.297 9(2)	0.350 4(3)
O(3′)	0.638 2(2)	0.545 7(1)	0.432 1(2)
C(3′)	0.592 9(3)	0.629 3(2)	0.486 0(3)
O(8′)	1.372 1(3)	0.760 9(2)	0.209 4(2)

CO_2Me), and 2.17 (3 H, s, Ac), which was used for the subsequent reduction without further purification.

Methyl (2α,3β,11bβ)-(±)-3-*Acetyl*-9,10-*dimethoxy*-1,3,4,6,7,-11b-*hexahydro*-2H-*benzo*[a]*quinolizin*-2-*ylacetate* (**25**).—Methanol saturated with dry hydrogen chloride gas was added to a stirred solution of the enamine (**24**) (45 mg) and sodium cyanoborohydride (50 mg) in methanol (10 ml) at room temperature until the pH of the solution reached 1. After being kept at room temperature overnight, the mixture was made alkaline by the addition of saturated sodium hydrogen carbonate and then extracted with methylene dichloride. The extract was washed, dried, and evaporated to give a residue which was purified by PLC (ethyl acetate) to afford the amine (**25**) (27 mg, 60%) as a yellow oil, ν_{max} 2 850 (Bohlmann), 1 730 (CO_2Me), and 1 710 cm^{-1} (Ac); δ_H(60 MHz) 6.58 and 6.50 (each 1 H, s, 8- and 11-H), 3.80 (6 H, s, OMe × 2), 3.63 (3 H, s, CO_2Me), and 2.20 (3 H, s, Ac) (Found: M^+, 361.190. $C_{20}H_{27}NO_5$ requires M, 361.189).

Conversion of the Acetyl Amine (**25**) *into the Lactone* (**19**).—A solution of the acetyl amine (**25**) (15 mg) and sodium borohydride (10 mg) in methanol (2 ml) was stirred at 0 °C for 30 min. Water was added and the mixture was extracted with methylene dichloride. The extract was washed, dried, and evaporated to give the alcohol which, without purification, was subjected to lactonisation by treatment with toluene-*p*-sulphonic acid, according to the procedure given for (**21**) and (**22**), to give the lactone (**19**) (13 mg, 95%). This lactone (**19**) was identical with the sample obtained by the reduction of the acetyl ester (**16**).

Crystal Data of the Furopyridone (**4**).—$C_{17}H_{19}NO_4$, M = 301.3, monoclinic, space group $P2_1/n$, a = 9.184(1), b = 13.828(1), c = 12.206(1) Å, β = 105.32(2)°, V = 1 495.1(4) $Å^3$, D_c = 1.339 g cm^{-3}, F(000) = 640, Z = 4, μ(Cu-K_α) = 7.441 cm^{-1}. Intensity data were collected on a Rigaku AFC-5 diffractometer with graphite-monochromated Cu-K_α radiation (λ = 1.5418 Å) using the ω–2θ scanning technique. A total of 2 542 independent reflections were measured (h, −10 to 0; k, 0 to 16; l, −13 to 14; sin θ/λ < 0.588 $Å^{-1}$) of which 2 423 [independent reflections $I \geqslant 3\sigma(I)$] were used in the structure determination and refinement.

Solution and Refinement.—The structure was solved by direct methods with the MULTAN78 programs.[22] The non-hydrogen atoms were refined by full-matrix least-squares with isotropic thermal parameters and by block-diagonal least-squares with anisotropic thermal parameters, minimising $\Sigma w(|F_o| - |F_c|)^2$ where $w = 1.0/[\sigma(F_o)^2 + c_1|F_o| + c_2|F_o|^2]$. Hydrogen atoms were placed in calculated positions (C–H 1.08 Å) and assigned isotropic thermal parameters in the calculation of the structure factors. The final R value was 0.091 (R_w 0.135) using the weighing scheme c_1 = 0.021 36 and c_2 = 0.008 34. Atomic scattering factors were obtained from ref. 23. All crystallographic calculations were carried out on ACOS computer using UNICS library[24] in Osaka University. Atomic co-ordinates for non-hydrogen atoms are in Table 3. Hydrogen atom co-ordinates, thermal parameters, bond distances, and bond angles have been deposited at the Cambridge Crystallographic Data Centre.*

* For details, see Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1990, Issue 1.

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