Photocyclisation of Enamides. Part 18.[1] Syntheses of the Basic Structures of Chelidonine and Related Alkaloids [2]

Ichiya Ninomiya, Okiko Yamamoto, and Takeaki Naito
Kobe Women's College of Pharmacy, Motoyamakita, Higashinada, Kobe 658, Japan

Oxidation of the didehydro lactam (6b), prepared by regiospecific photocyclisation of the *o*-methoxy-substituted enamide (7), with lead tetra-acetate gave exclusively the 12-acetoxy lactam (8b) which was subjected to further oxidation and reduction to develop a general and potential synthetic route for the total synthesis of the chelidonine group of alkaloids.

B/C-Hexahydrobenzo[*c*]phenanthridine alkaloids [3] are structurally divided into two classes; one is the chelidonine group of alkaloids, and the other is the corynoline group of alkaloids with an additional 10b-methyl group at the ring junction. Synthetic studies of the former group of alkaloids have been so far limited only to two total syntheses [4,5] of chelidonine; those for the latter group include rather basic studies by Onda,[6] Ninomiya,[1,7] and Cushman's [8] group.

In the course of our study aimed at the total synthesis of B/C-hexahydrobenzo[*c*]phenanthridine alkaloids involving the use of enamide photocyclisation,[9] we now report full details of a stereoselective synthetic route toward the chelidonine group of alkaloids by preparing their basic compounds (10a, b, c, g, h, and i). Before we completed this synthetic work there had been only an elegant synthesis of chelidonine by Oppolzer *et al.*[4] and a very recent total synthesis of the same alkaloid by Cushman *et al.*[5]

Upon considering the recent works [10] on the isolation of *N*-demethyl-6,7-dihydro-oxysanguinarine (1), oxysanguinarine (2), and chelamine (3), all of which are regarded as biogenetically related to the chelidonine group of alkaloids on the basis of their oxidative level of ring C, we planned to achieve a total synthesis of the chelidonine group of alkaloids by using each of the aforementioned alkaloids as key intermediates.

Formation of the 12-Acetoxybenzo[c]*phenanthridine Skeleton.*—As Oppolzer *et al.*[4] have used the 10b,11-didehydro compound (5) as a key intermediate for the introduction of the 11-hydroxy group in the total synthesis of chelidonine, we also attempted to prepare the 10b,11-didehydro lactam (5) from the 10b-carboxy lactam (4a) which had previously [7] been used as an intermediate to establish the synthetic route to the corynoline group of alkaloids.

However, neither photochemical introduction [11] by irradiation of the carboxy lactam (4a) nor the modified Hunsdiecker reaction [12] of the same acid under various conditions gave the expected didehydro lactam (5). The major product isolated was the *cis*-lactam [13] (4b) in the former reaction and the 10b-acetoxy lactam (4c) in the latter one. Attempted conversions of the 10b-acetoxy lactam (4c) into the 10b,11-didehydro lactam (5) directly or *via* the corresponding 10b-hydroxy compound (4d) were all unsuccessful, giving only the 4b,10b-didehydro lactam (6a) from both routes.

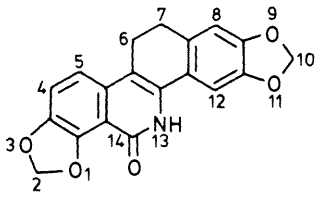
However, during the course of our study on the decarboxylation of the acid (4a) with lead tetra-acetate, we observed the formation of a small amount of the 12-acetoxy compound; this prompted our investigation of the oxidation of the 4b,10b-didehydro lactam (6b) with lead tetra-acetate since we expected to be able to develop a new methodology for the introduction of an hydroxy group into ring C. Thus, the *o*-methoxy-substituted enamide (7) was prepared from 6,7-dimethoxy-1-tetralone † and *o*-methoxybenzoyl chloride in good yield, and had $\nu_{max.}$ 1 630 cm^{-1} (NCO).

Photocyclisation [1] of the enamide (7) in methanolic solution proceeded smoothly to give the didehydro lactam (6b) in 50% yield as a result of regiospecific photocyclisation involving the *o*-methoxy-substituted carbon atom.[9]

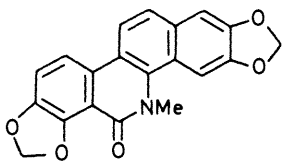
Although the application of the known [14] hydroxylation of aromatic rings to give the didehydro lactam (6b) and aromatised lactam (8a) was unsuccessful under various conditions using various reagents, an interesting result was observed when lead tetra-acetate was used as an oxidising agent. Treatment of the didehydro lactam (6b) with lead tetra-acetate in benzene at 50 °C gave the aromatised lactam (8a) in quantitative yield, while the acetoxylated lactam (8b) was obtained as the sole product in 75% yield when the didehydro lactam (6b) was oxidised in refluxing benzene. The structure of compound (8b) was established from its spectral data, particularly the i.r. absorption at 1 760 cm^{-1} (OAc), and also the n.m.r. peaks at δ_H 8.10 (1 H, m, 7-H), 7.88 (1 H, s, 11-H), 7.58 and 7.13 (each 1 H, s, together 1- and 4-H), 4.00 (9 H, s, NMe and 2 × OMe), and 2.50 (3 H, s, Ac); these peaks had a different pattern compared with that reported for the known [15] 11-acetoxy lactam (8c). Although various acetoxylations of aromatic rings with lead tetra-acetate have been reported,[16] this is the first example of direct acetoxylation of a hetero aromatic ring by the same reagent, thus providing a potential synthetic route for the total synthesis of the chelidonine group of alkaloids.

Stereoselective Introduction of the Hydroxy Group.—In order to introduce an hydroxy group into the 11-position of the benzo[*c*]phenanthridine skeleton, we investigated oxidations of the 12-acetoxy lactam (8b) under various conditions and we also found that the 12-hydroxy lactam (8d) was readily oxidised to give the red-coloured 11,12-quinone (9) in 95% yield, $\nu_{max.}$ 1 690 and 1 675 cm^{-1} (OCCO and NCO), upon treatment with lead tetra-acetate. Reduction of the quinone (9) with lithium aluminium hydride gave an unstable amine which was, without purification, subjected to catalytic hydrogenation over platinum dioxide to give the 11,12-glycol (10a) in 23% yield after careful separation by repeated preparative t.l.c. (p.l.c.). Since the stereochemistry of this glycol (10a) could not be easily established from the spectral data except for that of its B/C-*cis*-configuration which was assigned from a signal at δ_H 4.33 (d, *J* 4 Hz), hydrogenolysis of the 12-hydroxy group of the glycol (10a) with 40% palladium–charcoal was investigated according to the procedure given in the total synthesis [1,7] of corynoline. The products thus isolated were shown to be a mixture of the 11α-hydroxy amine (10b) (25%) and the 11α,12α-glycol (10c) (13%) from

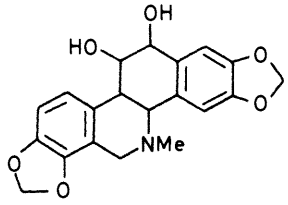
† 1,2,3,4-Tetrahydro-6,7-dimethoxynaphthalen-1-one.



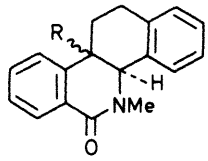
(1)



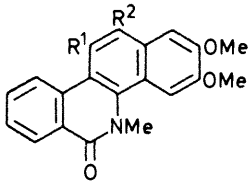
(2)



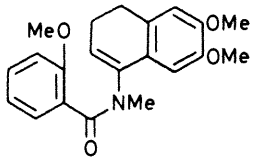
(3)



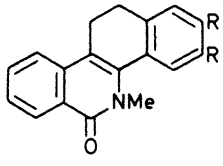
(4) a; R = ---CO_2H
b; R = ---H
c; R = ~~OAc
d; R = ~~OH



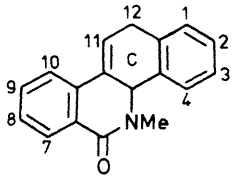
(8) a; $R^1 = R^2 = H$
b; $R^1 = H, R^2 = OAc$
c; $R^1 = OAc, R^2 = H$
d; $R^1 = H, R^2 = OH$



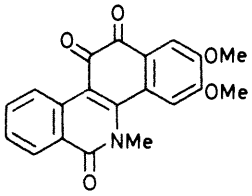
(7)



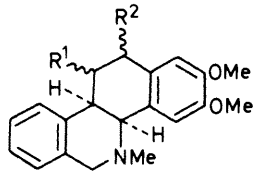
(6) a; R = H
b; R = OMe



(5)



(9)



(10) a; R^1 = ---OH, R^2 = —OH
b; R^1 = ---OH, R^2 = H
c; R^1 = ---OH, R^2 = ---OH
d; R^1 = ---OH, R^2 = —OAc
e; R^1 = ---OMs, R^2 = —OAc
f; R^1 = —OH, R^2 = ~~OMe
g; R^1 = —OH, R^2 = H
h; R^1 = —OH, R^2 = ---OH
i; R^1 = —OH, R^2 = —OH

Ms = Mesyl

their n.m.r. spectra upon comparisons with those of the related hydroxy compounds described later. Therefore, it is now established that the glycol (10a) is a B/C-*cis*-benzo[*c*]-phenanthridine with an 11α-hydroxy group.

The formation of the *cis*-glycol (10c) from the corresponding *trans*-glycol (10a) during the course of hydrogenation could be ascribed to a simple substitution at the 12-position by a solvent molecule as in the case reported in our previous work.[1]

Conversion of the 11α-hydroxy group into the desired 11β-hydroxy group was then accomplished *via* a route involving nucleophilic substitution on the corresponding 11α-methanesulphonate (10e). Acetylation of the glycol (10a) with acetic anhydride in chloroform at room temperature gave the 12-acetate (10d) which showed n.m.r. peaks at δ_H 5.93 (1 H, d, *J* 7 Hz, 12-H), 4.55 (1 H, dd, *J* 10 and 7 Hz, 11-H), and 2.10 (3 H, s, Ac) and which was then mesylated to give the unstable 12-acetoxy-11-methanesulphonate (10e) as a yellow oil. Treatment of the methanesulphonate (10e) with 5% potassium hydroxide in methanol yielded the 11β-hydroxy-12-methoxy amine (10f) as the sole product in 67% yield from the *trans*-glycol (10a). The configuration of the 11β-hydroxy group in (10f) was readily assigned from the spectral data and also from the following hydrogenolytic conversion of (10f) into the desired basic structure (10g) of the chelidonine group of alkaloids. Hydrogenolysis of the 12-methoxy group in (10f) with 40% palladium–charcoal in 10% hydrochloric acid containing a small amount of 70% perchloric acid afforded a mixture of the 11β-hydroxy amine (10g) and two glycols (10h) and (10i) in 17, 38, and 8% yield, respectively of which the 11β-hydroxy amine (10g) showed an i.r. absorption at 3 200 cm^{-1} (OH) and n.m.r. peaks at δ_H 4.34 (1 H, m, $w_{\frac{1}{2}}$ 6 Hz, 11-H), 3.64 (1 H, dd, *J* 3 and 1.5 Hz, 4b-H), 3.04 (1 H, t, *J* 3 Hz, 10b-H), and 2.29 (3 H, s, NMe). This spectral evidence indicated that (10g) had the same basic structure as the alkaloid chelidonine.[17] The two glycols (10h) and (10i) were also subjected to hydrogenolysis as in the case of (10f) and afforded the same compound (10g).

Stereochemistry of the Four Glycols (10a, c, h, *and* i) *and the Two Hydroxy Amines* (10b *and* g).—Thus, we have succeeded in the preparation of all four possible epimers of the 11,12-dihydroxy amines (10a, c, h, and i), which enabled us to determine the stereochemistry of these compounds in addition

Table 1.

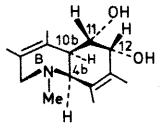
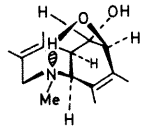
	(10c)	(10a)
Forms an acetonide	Yes	No
12-H	4.82 (d, *J* 4.5 Hz)	4.51—4.26 (m)
11-H	4.62 (dd, *J* 8, 4.5 Hz)	
4b-H	3.64 (d, *J* 5 Hz)	3.47 (d, *J* 4 Hz)
10b-H	3.30 (dd, *J* 8, 5 Hz)	3.01 (t-like, *J* 4 Hz)
Conformation		

Table 2.

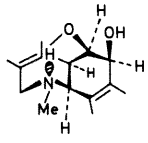
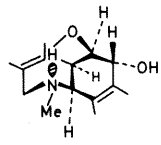
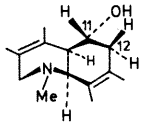
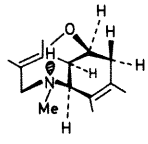
	(10i)	(10h)
Forms an acetonide	Yes	No
12-H	4.72 (d, *J* 4.5 Hz)	4.79 (d, *J* 2 Hz)
11-H	4.27 (m, $w_{\frac{1}{2}}$ 6 Hz)	4.07 (m, $w_{\frac{1}{2}}$ 5 Hz)
4b-H	3.62 (m, $w_{\frac{1}{2}}$ 5 Hz)	3.56 (m, $w_{\frac{1}{2}}$ 4 Hz)
10b-H	3.13 (t-like, *J* 2.5 Hz)	3.31 (t-like, *J* 2 Hz)
Conformation		

Table 3.

	(10b)	(10g)
11-H	4.63 (td, *J* 8, 6 Hz)	4.34 (m, $w_{\frac{1}{2}}$ 6 Hz)
4b-H	3.67 (br s)	3.64 (dd, *J* 3, 1.5 Hz)
12-H	3.24 (dd, *J* 14, 6 Hz) 2.73 (dd, *J* 14, 8 Hz)	3.21 (m)
10b-H	2.98 (dd, *J* 8, 4 Hz)	3.04 (t, *J* 3 Hz)
Conformation		

to that of the two hydroxy amines (10b and g) unambiguously upon comparison of their n.m.r. spectra.

The fact that two glycols (10c and i) afforded the corresponding acetonides strongly supported their assigned *cis*-configurations. As shown in Table 1, the n.m.r. peaks assignable to the 12-, 11-, 10b-, and 4b-hydrogen of (10c) suggested that the glycol (10c) has a conformation with 10b-H and 11-H in the axial and 12-H in the equatorial orientations with respect to ring C as shown in the Table.

On the other hand, the fact that the *trans*-glycol (10a) could not form the corresponding acetonide, together with its n.m.r. spectrum, would be reasonably explained by postulating a conformation (10a) with half-boat ring C and also with hydrogen bonding between a 12β-hydroxy group and the lone pair on nitrogen as shown in Table 1. The conformations of the remaining two glycols (10h and i) were readily assigned, as shown in Table 2, from their n.m.r. spectra which were very similar to that of chelidonine.[17]

Finally, the n.m.r. spectra of the 11α- and 11β-hydroxyamines (10b and g) are well in accord with the conformations shown in Table 3.

The synthesis of the compounds (10a, b, c, g, h, and i), which have the basic structures of the chelidonine group of alkaloids, offers a promising and potential approach to the total synthesis of natural alkaloids.

Experimental

^{1}H N.m.r. spectra were measured with Varian XL-200 and JEOL PMX-60 instruments for solutions in deuteriochloro-

form unless otherwise stated (tetramethylsilane as internal reference), i.r. spectra for solutions in chloroform, and mass spectra with a JEOL JMS-O1SG machine. M.p.s were determined with a Kofler-type hot-stage apparatus. Extracts from the reaction mixtures were dried over anhydrous sodium sulphate. Photochemical reactions were carried out by irradiation at room temperature with a high-pressure (300 W) mercury lamp (Eikosha PIH 300) unless otherwise stated.

Irradiation of the Carboxylic Acid (4a).—A solution of a mixture of the carboxylic acid (4a) (307 mg) and copper(II) acetate (20 mg) in ethanol (100 ml) was irradiated with a low-pressure mercury lamp (Eikosha PIL 60) for 7 h. The solvent was removed under reduced pressure and the residue was extracted with chloroform. The extract was washed in turn with saturated aqueous sodium hydrogen carbonate and water, dried, and evaporated to give a residue which was purified by p.l.c. on silica gel and recrystallised from methanol–diethyl ether to give the *cis*-lactam (4b) (147 mg, 56%), m.p. 160—161 °C (lit.,[13] 161—162 °C), identical with the authentic sample prepared previously.[13]

Modified Hunsdiecker Reaction of the Carboxylic Acid (4a).—To a stirred solution of the carboxylic acid (4a) (500 mg) in anhydrous benzene (120 ml) under nitrogen was added 86% lead tetra-acetate (1.25 g) and then the mixture was refluxed for 2 h. After the mixture has cooled the precipitated lead acetate was filtered off. The filtrate, diluted with benzene, was washed in turn with saturated sodium hydrogen carbonate and water, dried, and evaporated to give a solid which was recrystallised from ethanol to afford the *acetoxy lactam* (4c) (250 mg, 50%), m.p. 196—198 °C; $\nu_{max.}$ 1 740 (OAc) and 1 640 cm^{-1} (NCO); δ_H 8.08 (1 H, m, 7-H), 7.83—6.97 (7 H, m, 7 × ArH), 5.23 (1 H, s, 4b-H), 3.43 (3 H, s, NMe), 3.28—2.25 (4 H, m, 2 × CH_2), and 1.90 (3 H, s, Ac) (Found: C, 74.9; H, 6.05; N, 4.35. $C_{20}H_{19}NO_3$ requires C, 74.75; H, 5.95; N, 4.35%).

N-(3,4-*Dihydro*-6,7-*dimethoxy*-1-*naphthyl*)-2-*methoxy*-N-*methylbenzamide* (7).—Anhydrous methylamine gas was bubbled into an ice-cooled solution of 6,7-dimethoxy-1-tetralone (10.3 g) in anhydrous chloroform (50 ml) for 30 min. This mixture was then added dropwise to a stirred ice-cooled solution of titanium tetrachloride (6 ml) in anhydrous chloroform (20 ml). After the mixture had been refluxed for 1 h it was evaporated to dryness under reduced pressure. The residue was dissolved in anhydrous benzene (100 ml) and the solution was filtered. Triethylamine (13 g) was added to the filtrate, and then a solution of *o*-anisoyl chloride (8.5 g) in anhydrous benzene (50 ml) was added dropwise to the reaction mixture which was then heated under reflux for 2 h and filtered to remove triethylamine hydrochloride. The filtrate was evaporated to give a solid which was recrystallised from ethanol to afford the crystalline *enamide* (7) (15 g, 85%), m.p. 147.5—148 °C; $\nu_{max.}$ 1 630 cm^{-1} (NCO); δ_H 5.63 (1 H, t, *J* 4 Hz, olefinic H), 3.90, 3.83, and 3.63 (each 3 H, s, OMe), and 3.33 (3 H, s, NMe) (Found: C, 71.65; H, 6.6; N, 4.1. $C_{21}H_{23}NO_4$ requires C, 71.3; H, 6.55; N, 3.95%).

11,12-*Dihydro*-2,3-*dimethoxy*-5-*methylbenzo*[c]*phenanthridin*-6(5H)-*one* (6b).—A solution of the enamide (7) (3 g) in methanol (300 ml) and diethyl ether (500 ml) was irradiated for 24 h. The solvent was removed and the residual solid was recrystallised from methanol to afford the lactam (6b) (1.37 g, 50%), m.p. 186—187 °C; $\nu_{max.}$ 1 630 cm^{-1} (NCO); δ_H 8.50 (1 H, m, 7-H), 7.00 (1 H, s, 4-H), 6.83 (1 H, s, 1-H), 3.93 and 3.88 (each 3 H, s, OMe), 3.78 (3 H, s, NMe), and 2.80 (4 H, s, 2 × CH_2) (Found: C, 74.6; H, 6.0; N, 4.45. $C_{20}H_{19}NO_3$ requires C, 74.75; H, 5.95; N, 4.35%).

2,3-*Dimethoxy*-5-*methylbenzo*[c]*phenanthridin*-6(5H)-*one* (8a).—To a stirred solution of the lactam (6b) (1.3 g) in anhydrous benzene (70 ml) under nitrogen was added 86% lead tetra-acetate (2 g) at room temperature and the mixture was warmed at 50 °C for 40 min. After the mixture had cooled the precipitated lead acetate was filtered off. The filtrate was diluted with benzene, washed in turn with saturated aqueous sodium hydrogen carbonate and water, dried, and evaporated to afford the aromatic *lactam* (8a) (1.2 g, 95%) as crystals, m.p. 188—190 °C (from methanol); $\nu_{max.}$ 1 635 cm^{-1} (NCO); δ_H 8.53 (1 H, m, 7-H), 8.23 and 7.97 (each 1 H, ABq, *J* 9 Hz, together 11- and 12-H), and 4.03 (9 H, s, NMe and 2 × OMe) (Found: C, 73.65; H, 5.45; N, 4.25. $C_{20}H_{17}NO_3 \cdot 1/2MeOH$ requires C, 73.4; H, 5.7; N, 4.2%).

12-*Acetoxy*-2,3-*dimethoxy*-5-*methylbenzo*[c]*phenanthridin*-6(5H)-*one* (8b).—To a stirred solution of the lactam (6b) (2.6 g) in anhydrous benzene (150 ml) under nitrogen was added 86% lead tetra-acetate (9 g) and then the mixture was refluxed for 5 h. After the mixture had cooled the precipitated lead acetate was filtered off. The filtrate was diluted with benzene, washed with in turn with saturated aqueous sodium hydrogen carbonate and water, dried, and evaporated to give a solid which was recrystallised from methanol to afford the *acetoxy lactam* (8b) (2.3 g, 75%), m.p. 202.5—203.5 °C; $\nu_{max.}$ 1 760 (OAc) and 1 640 cm^{-1} (NCO); δ_H 8.10 (1 H, m, 7-H), 7.88 (1 H, s, 11-H), 7.58 and 7.13 (each 1 H, s, together 1- and 4-H), 4.00 (9 H, s, NMe and 2 × OMe), and 2.50 (3 H, s, Ac) (Found: C, 69.8; H, 5.2; N, 3.85. $C_{22}H_{29}NO_5$ requires C, 70.0; H, 5.05; N, 3.7%).

The acetoxylactam (8b) was also obtained from the aromatised lactam (8a) under the same conditions.

12-*Hydroxy*-2,3-*dimethoxy*-5-*methylbenzo*[c]*phenanthridin*-6(5H)-*one* (8d).—A solution of the acetoxy lactam (8b) (2 g) in 30% methanolic potassium hydroxide (60 ml) was refluxed for 2.5 h. After evaporation of methanol, the resulting residue was neutralised with concentrated hydrochloric acid. The precipitate thus formed was the *naphthol* (8d) (1.65 g, 98%) which formed pale yellow crystals, m.p. 260—265 °C (decomp.) (from chloroform–ethyl acetate); $\nu_{max.}$ (Nujol) 3 200 (OH) and 1 620 cm^{-1} (NCO) (Found: C, 71.35; H, 5.15; N, 4.3. $C_{20}H_{17}NO_4$ requires C, 71.65; H, 5.1; N, 4.2%).

2,3-*Dimethoxy*-5-*methylbenzo*[c]*phenanthridine*-6,11,12(5H)-*trione* (9).—To a stirred solution of the naphthol (8d) (1.34 g) in acetic acid (30 ml) under nitrogen, was added 86% lead tetra-acetate (3.8 g). The reaction mixture was kept at room temperature for 5 h and was then treated with water and chloroform. The aqueous layer was extracted with chloroform. The combined chloroform extracts were washed in turn with saturated aqueous sodium hydrogen carbonate and water, dried, and evaporated to give a red solid which was recrystallised from tetrahydrofuran (THF) to afford the *quinone* (9) (1.32 g, 95%) as red crystals, m.p. >300 °C; $\nu_{max.}$ (Nujol) 1 690, 1 675, and 1 660 cm^{-1} (*o*-quinone and NCO); $\lambda_{max.}$ (EtOH) 520, 353, 334, 302, 260, 242, 227, and 210 nm; *m/z* 349 (M^+) (Found: C, 68.9; H, 4.55; N, 3.65. $C_{20}H_{15}NO_5$ requires C, 68.75; H, 4.35; N, 4.0%).

(4bα,10bα,11α,12β)-4b,5,6,10b,11,12-*Hexahydro*-2,3-*dimethoxy*-5-*methylbenzo*[c]*phenanthridine*-11,12-*diol* (10a).—To a cooled solution of the quinone (9) (300 mg) in absolute THF (30 ml), was added lithium aluminium hydride (150 mg). The resulting mixture was heated under reflux for 4 h

and was then evaporated. After being cooled the resulting mixture was treated with water to decompose the excess of lithium aluminium hydride. The aqueous layer was extracted with diethyl ether. The combined ethereal layers were washed with brine, dried, and evaporated. A solution of the residue in absolute ethanol was hydrogenated over platinum dioxide (100 mg) under hydrogen at atmospheric pressure and room temperature for 3 h. The catalyst was filtered off and the filtrate was evaporated to give a solid which was recrystallised from ethanol to afford the *glycol* (10a) (70 mg, 23%) as crystals, m.p. 186—188 °C; $\nu_{max.}$ 3 600 and 3 400 cm^{-1} (OH); δ_H 7.02 and 6.83 (each 1 H, s, together 1- and 4-H), 4.51—4.26 (2 H, m, 11- and 12-H) [upon irradiation at δ_H 3.01; 4.44 (1 H, d, *J* 4 Hz, 12-H) and 4.33 (1 H, d, *J* 4 Hz, 11-H)], 4.02 and 3.62 (each 1 H, ABq, *J* 16 Hz, 6-H), 3.91 (6 H, s, 2 × OMe), 3.47 (1 H, d, *J* 4 Hz, 4b-H), 3.01 (1 H, t-like, *J* 4 Hz, 10b-H), and 2.09 (3 H, s, NMe) (Found: C, 69.95; H, 6.8; N, 4.1. $C_{20}H_{23}NO_4 \cdot 1/10H_2O$ requires C, 70.0; H, 6.8; N, 4.2%).

Hydrogenolysis of the Glycol (10a).—A solution of the glycol (10a) (100 mg) in 10% hydrochloric acid (20 ml) containing three drops of 70% perchloric acid was hydrogenated over 40% palladium–charcoal (50 mg) under hydrogen at 5.2 atm and 50 °C for 48 h. The catalyst was filtered off and the filtrate was neutralised with potassium carbonate and was then extracted with chloroform. The extract was washed with water, dried, and evaporated to give a solid. Purification by p.l.c. on silica gel afforded two products. The first product, with the higher R_F value, was (4bα,10bα,11α)-4b,5,6,10b,11,12-hexahydro-2,3-dimethoxy-5-methylbenzo-[*c*]phenanthridin-11-ol (10b) (23 mg, 25%) obtained as crystals, m.p. 134.5—135 °C (from methanol); $\nu_{max.}$ 3 600 cm^{-1} (OH); δ_H 6.88 and 6.67 (each 1 H, s, together 1- and 4-H), 4.63 (1 H, td, *J* 8 and 6 Hz, 11-H), 4.04 and 3.62 (2 H, ABq, *J* 16 Hz, 6-H), 3.67 (1 H, br s, 4b-H), 3.89 (6 H, s, 2 × OMe), 3.24 (1 H, dd, *J* 14 and 6 Hz, 12β-H), 2.98 (1 H, dd, *J* 8 and 4 Hz, 10b-H), 2.73 (1 H, dd, *J* 14 and 8 Hz, 12α-H), and 2.29 (3 H, s, NMe) (Found: M^+, 325.169. $C_{20}H_{23}NO_3$ requires *M*, 325.168).

The second product (lower R_F value) was (4bα,10bα,11α,-12α)-4b,5,6,10b,11,12-*hexahydro*-2,3-*dimethoxy*-5-*methyl-benzo*[c]*phenanthridine*-11,12-*diol* (10c) (13 mg, 13%) obtained as a yellow oil, $\nu_{max.}$ 3 600 cm^{-1} (OH); δ_H 6.92 and 6.88 (each 1 H, s, together 1- and 4-H), 4.82 (1 H, d, *J* 4.5 Hz, 12-H), 4.62 (1 H, dd, *J* 8 and 4.5 Hz, 11-H), 4.16 and 3.67 (each 1 H, ABq, *J* 17 Hz, 6-H), 3.91 and 3.90 (each 3 H, s, OMe), 3.64 (1 H, d, *J* 5 Hz, 4b-H), 3.30 (1 H, dd, *J* 8 and 5 Hz, 10b-H), and 2.26 (3 H, s, NMe) (Found: C, 69.5; H, 6.6; N, 3.85. $C_{20}H_{23}NO_4 \cdot 1/5H_2O$ requires C, 69.6; H, 6.85; N, 4.05%) (Found: M^+, 341.164. $C_{20}H_{23}NO_4$ requires *M*, 341.163).

Treatment of the glycol (10c) (20 mg) in acetone (2 ml) containing two drops of 70% perchloric acid gave the acetonide (20 mg, 93%) as a yellow oil, $\nu_{max.}$ no hydroxy group; δ_H 7.06 and 6.73 (each 1 H, s, together 1- and 4-H), 5.22 (1 H, d, *J* 6 Hz, 12-H), 4.73 (1 H, dd, *J* 8 and 6 Hz, 11-H), 4.07 and 3.58 (each 1 H, ABq, *J* 16 Hz, 6-H), 3.94 and 3.89 (each 3 H, s, OMe), 3.42 (1 H, d, *J* 3 Hz, 4b-H), 2.96 (1 H, dd, *J* 8 and 3 Hz, 10b-H), 2.11 (3 H, s, NMe), and 1.44 and 1.53 (each 3 H, s, CMe) (Found: M^+, 381.193. $C_{23}H_{27}NO_4$ requires *M*, 381.194).

(4bα,10bα,11α,12β)-12-*Acetoxy*-4b,5,6,10b,11,12-*hexa-hydro*-2,3-*dimethoxy*-5-*methylbenzo*[c]*phenanthridin*-11-*ol* (10d).—To a stirred solution of the glycol (10a) (200 mg) in chloroform (20 ml) was added acetic anhydride (0.5 ml) at room temperature. The mixture was kept at room temperature for 15 h, chloroform was then added and the chloroform layer was washed in turn with saturated aqueous sodium hydrogen carbonate and water, dried, and evaporated to give a brown oil. Purification by p.l.c. on silica gel afforded the *acetate* (10d) as a yellow oil (200 mg, 90%), $\nu_{max.}$ 3 600 (OH) and 1 720 cm^{-1} (OAc); δ_H 6.67 (2 H, s, 1- and 4-H), 5.93 (1 H, d, *J* 7 Hz, 12-H), 4.55 (1 H, dd, *J* 10 and 7 Hz, 11-H), 4.03 and 3.57 (each 1 H, ABq, *J* 16 Hz, 6-H), 3.89 (6 H, s, 2 × OMe), 3.47 (1 H, d, *J* 4 Hz, 4b-H) 2.98 (1 H, dd, *J* 10 and 4 Hz, 10b-H), 2.23 (3 H, s, NMe), and 2.10 (3 H, s, Ac) (Found: C, 65.95; H, 6.25; N, 3.45. $C_{22}H_{25}NO_5 \cdot H_2O$ requires C, 65.8; H, 6.8; N, 3.5%) [Found: (M^+ − AcOH), 323.152. $C_{22}H_{25}NO_5$ − AcOH requires *m*/*z* 323.152].

(4bα,10bα,11β)-4b,5,6,10b,11,12-*Hexahydro*-2,3,12-*trimethoxy*-5-*methylbenzo*[c]*phenanthridin*-11-*ol* (10f).—To an ice-cooled solution of the acetate (10d) (200 mg) in methylene dichloride (10 ml) and triethylamine (100 mg), was added, dropwise, mesyl chloride (80 mg). The reaction mixture was kept at room temperature for 1 h and then, upon dilution with methylene dichloride, was washed in turn with saturated aqueous sodium hydrogen carbonate and water, dried, and evaporated to give the mesyl ester (10e) as a yellow oil, $\nu_{max.}$ 1 730 (OAc), and 1 360 and 1 170 cm^{-1} (OMs). Without purification, the diester (10e) was refluxed in 5% methanolic potassium hydroxide for 1 h. After evaporation of methanol, the resulting residue was treated with chloroform and water. The combined chloroform layers were washed with water, dried, and evaporated to give a solid. Purification by p.l.c. on silica gel afforded the *title compound* (10f) (125 mg, 67%) as crystals, m.p. 156—158 °C; $\nu_{max.}$ 3 200 cm^{-1} (OH); δ_H 6.93 and 6.70 (each 1 H, s, together 1- and 4-H), 4.43—4.20 (2 H, m, 11- and 12-H), 3.97, 3.90, and 3.67 (each 3 H, s, OMe) 3.33 (1 H, m, $w_{\frac{1}{2}}$ 4.5 Hz, 10b-H), and 2.27 (3 H, s, NMe) (Found: C, 70.8; H, 7.0; N, 4.15. $C_{21}H_{25}NO_4$ requires C, 70.95; H, 7.1; N, 3.95%); *m*/*z* 355 (M^+).

Hydrogenolysis of the Glycol Monomethyl Ether (10f).—By the procedure given for (10a), hydrogenolysis of the ether (10f) (120 mg) over 40% palladium–charcoal and purification of the crude product by p.l.c. on silica gel afforded (4bα,10bα,11β)-4b,5,6,10b,11,12-hexahydro-2,3-dimethoxy-5-methylbenzo[*c*]-phenanthridin-11-ol (10g) (19 mg, 17%) as crystals, m.p. 201.5—202 °C (from diethyl ether); $\nu_{max.}$ 3 200 cm^{-1} (OH); δ_H 6.73 and 6.70 (each 1 H, s, together 1- and 4-H), 4.34 (1 H, m, $w_{\frac{1}{2}}$ 6 Hz, 11-H), 4.04 and 3.67 (each 1 H, ABq, *J* 15 Hz, 6-H), 3.89 and 3.91 (each 3 H, s, OMe), 3.64 (1 H, dd, *J* 3 and 1.5 Hz, 4b-H), 3.21 (2 H, m, 12-H_2), 3.04 (1 H, t, *J* 3 Hz, 10b-H), and 2.29 (3 H, s, NMe) (Found: M^+, 325.166. $C_{20}H_{33}NO_3$ requires *M*, 325.168); (4bα,10bα,11β,12α)-4b,5,-6,10b,11,12-*hexahydro*-2,3-*dimethoxy*-5-*methylbenzo*[c]*phenan-thridine*-11,12-*diol* (10h) (44 mg, 38%) as crystals, m.p. 209—211 °C (from diethyl ether); $\nu_{max.}$ 3 600 cm^{-1} (OH); δ_H 6.99 and 6.69 (each 1 H, s, together 1- and 4-H), 4.79 (1 H, d, *J* 2 Hz, 12-H), 4.07 (1 H, m $w_{\frac{1}{2}}$ 5 Hz, 11-H), 4.04 and 3.64 (each 1 H, ABq, *J* 15 Hz, 6-H), 3.56 (1H, m, $w_{\frac{1}{2}}$ 4 Hz, 4b-H), 3.31 (1 H, t-like, *J* 2 Hz, 10b-H), 3.89 and 3.91 (each 3 H, s, OMe), and 2.29 (3 H, s, NMe) (Found: C, 69.1; H, 6.7; N, 4.2. $C_{20}H_{23}NO_4 \cdot 1/3H_2O$ requires C, 69.15; H ,6.85; N, 4.05%); and (4bα,10bα,11β,12β)-4b,5,6,10b,11,12-hexahydro-2,3-dimethoxy-5-methylbenzo[*c*]phenanthridine-11,12-diol (10i) (10 mg, 8%) as crystals, m.p. 195—196 °C (from diethyl ether); $\nu_{max.}$ 3 600 cm^{-1} (OH); δ_H 6.67 (2 H, s, 1- and 4-H), 4.72 (1 H, d, *J* 4.5 Hz, 12-H), 4.27 (1 H, m, $w_{\frac{1}{2}}$ 6 Hz, 11-H), 4.04 and 3.71 (each 1 H, ABq, *J* 15 Hz, 6-H), 3.97 and 3.92 (each 3 H, s, OMe), 3.62 (1 H, m, $w_{\frac{1}{2}}$ 5 Hz, 4b-H), 3.13 (1 H, t-like, *J* 2.5 Hz, 10b-H), and 2.27 (3 H, s, NMe) (Found: M^+, 341.163. $C_{20}H_{23}NO_4$ requires *M*, 341.163).

References

1 Part 17, I. Ninomiya, O. Yamamoto, and T. Naito, *J. Chem. Soc., Perkin Trans. 1*, 1980, 212.
2 I. Ninomiya, O. Yamamoto, and T. Naito, *Heterocycles*, 1977, **7**, 131.
3 M. Shamma, 'The Isoquinoline Alkaloids,' Academic Press, New York, 1972, p. 315; M. Shamma and J. L. Moniot, 'The Isoquinoline Alkaloids Research, 1972—1977,' Plenum Press, New York, 1978, p. 271.
4 W. Oppolzer and K. Keller, *J. Am. Chem. Soc.*, 1971, **93**, 3836; W. Oppolzer, *Heterocycles*, 1980, **14**, 1617.
5 M. Cushman, T.-C. Choong, J. T. Valko, and M. P. Koleck, *Tetrahedron Lett.*, 1980, **21**, 3845; *J. Org. Chem.*, 1980, **45**, 5067.
6 M. Onda, K. Yuasa, and J. Okada, *Chem. Pharm. Bull.*, 1974, **22**, 2365; M. Onda, H. Yamaguchi, and Y. Harigaya, *ibid.*, 1980, **28**, 866.
7 I. Ninomiya, O. Yamamoto, T. Kiguchi, and T. Naito, *J. Chem. Soc., Perkin Trans. 1*, 1980, 203.
8 M. Cushman and Y. P. Gupta, *Heterocycles*, 1982, **19**, 1431, M. Cushman, A. Abbaspour, and Y. P. Gupta, *ibid.*, p. 1587.
9 I. Ninomiya and T. Naito, *Heterocycles*, 1981, **15**, 1433.
10 J. Slavik, L. Slavikova, and J. Brabenec, *Coll. Czech. Chem. Commun.*, 1965, **30**, 3697; J. Slavik and L. Slavikova, *ibid.*, 1977, **42**, 2686.
11 K. Isobe, J. Taga, and Y. Tsuda, *Heterocycles*, 1978, **9**, 625.
12 R. A. Sheldon and J. K. Kochi, 'Organic Reactions,' ed. W. G. Dauben, Wiley, New York, 1972, vol. 19, pp. 279—421.
13 I. Ninomiya, T. Naito, T. Kiguchi, and T. Mori, *J. Chem. Soc., Perkin Trans. 1*, 1973, 1696.
14 T. Matsuura and K. Omura, *Synthesis*, 1974, 173; M. Nakagawa, *J. Synthetic Org. Chem. (Jpn.)*, 1973, **31**, 375.
15 Y. Harigaya, S. Takamatsu, H. Yamaguchi, T. Kusano, and M. Onda, *Chem. Pharm. Bull*, 1980, **28**, 2029; M. Onda, Y. Harigaya, and T. Suzuki, *ibid.*, 1977, **25**, 2935.
16 K. B. Wiberg, 'Oxidation in Organic Chemistry,' Part A, Academic Press, New York, 1965, p. 326.
17 E. Seoane, *An. R. Soc. Esp. Fis. Quim. Ser. B*, 1965, **61**, 755.

Received 9*th February* 1983; *Paper* 3/204