# Photocyclisation of Enamides. Part VIII.[1] Synthesis of 13-Methylberbines; Total Synthesis of (±)-Cavidine [2]

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Photocyclisation of 2-aroyl-1-ethylidene-1,2,3,4-tetrahydroisoquinolines, which exist in two geometric forms, provides a useful route to various 13-methylberbines, as exemplified by the first total synthesis of (±)-cavidine.

13-METHYLBERBINE constitutes the skeleton of many protoberberine alkaloids [3] such as corydaline and cavidine. As an extension of our work [1] on photocyclisation of enamides prepared from 1-alkyl-3,4-dihydroisoquinolines, we now report that the enamides from 1-ethyl-3,4-dihydroisoquinoline undergo stereospecific photocyclisation to form 13-methylberbin-8-ones. This reaction is applied in the first total synthesis of (±)-cavidine.[2] The n.m.r. spectra of the starting enamides, particularly nuclear Overhauser effect (n.O.e.) measurements, provide a new means of assigning their geometric configurations.

*Geometric Isomerism of Enamides.*—Theoretically, there exist two geometric isomers [(B) and (C)] of the enamides from 1-ethyl-3,4-dihydroisoquinoline (A). The configuration of this type of enamide has hitherto been determined either from their u.v. spectra as in the case of the 2-acyl-1-benzylideneisoquinolines,[4,5] or from their

[1] Part VII, I. Ninomiya, T. Naito, and H. Takasugi, *J.C.S. Perkin I*, 1975, 1720.

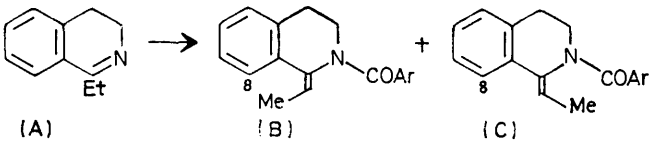
[2] Preliminary communication, I. Ninomiya, H. Takasugi, and T. Naito, *Heterocycles*, 1973, **1**, 17.

[3] M. Shamma, 'The Isoquinoline Alkaloids,' Academic Press, New York, 1972, p. 269.

[4] I. Baxter and G. A. Swan, *J. Chem. Soc.*, 1965, 4014.

[5] N. C. Yang, G. R. Lenz, and A. Shani, *Tetrahedron Letters*, 1966, 2941.

n.m.r. spectra as for the 2-ethoxycarbonyl derivatives.[6] However, it is difficult to determine the configuration of the enamides (B) and (C) by these methods.

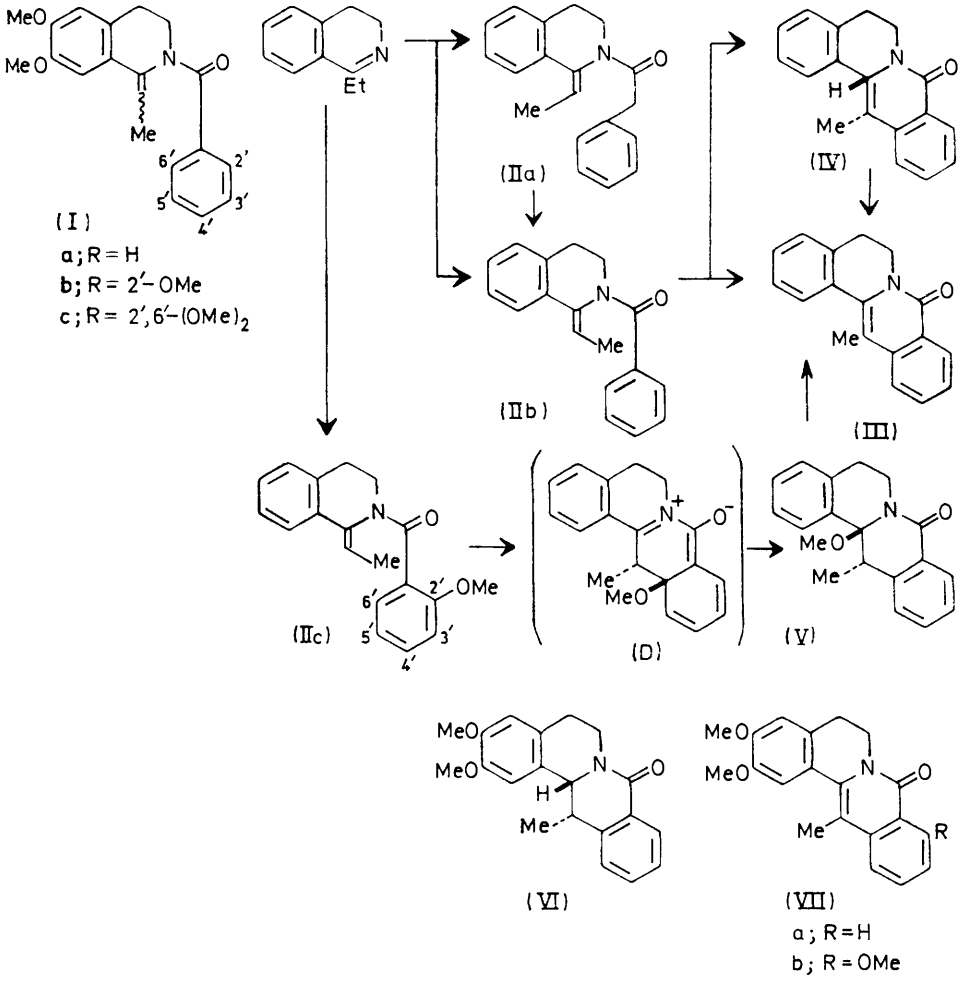



Dreiding models of the enamides (B) and (C) clearly showed that an olefinic proton in (C) or a vinylic methyl group in (B) is very close to the 8-proton, and therefore a large n.O.e. would be expected. Anticipating that the bulkiness of the *N*-aroyl group would affect the ratio of the products (B) and (C), we prepared three enamides (Ia—c) having *N*-benzoyl- (Ia), 2′-methoxybenzoyl- (Ib), and 2′,6′-dimethoxybenzoyl- (Ic) groups; however the products were homogeneous as indicated by t.l.c. and n.m.r. (Table 2).

The n.O.e. data in Table 2 clearly show that the enamides (Ia and b) exist in the *Z*-form, and (Ic) exists in the *E*-form. In addition, the olefinic proton signals of (Ia and b) appear at lower field than that of (Ic). These results agree with those for the enamides from 1-methyl-3,4-dihydroisoquinoline, in that an olefinic proton *trans* with respect to an *N*-aroyl group resonates at lower field than a *cis*-proton.

Next we determined the configurations of other enamides (IIa—c) by comparison of chemical shifts of olefinic and vinylic methyl protons, since in these cases, n.O.e. data cannot be obtained owing to overlap of the 8-proton signal with those of the other aromatic protons.

The n.m.r. spectra of the enamides (Ib) and (IIc) each showed two sets of signals for olefinic and vinylic methyl protons at room temperature. However at 110 °C, the n.m.r. spectrum showed that the enamide (Ib) was present in only one conformation. This can be explained on the basis of hindered rotation around the N–CO bond at the lower temperature. In most cases only one




[6] (*a*) M. P. Cava, S. C. Havlicek, A. Lindert, and R. J. Spangler, *Tetrahedron Letters*, 1966, 2937; (*b*) N. C. Yang, A. Shani, and G. R. Lenz, *J. Amer. Chem. Soc.*, 1966, **88**, 5369; (*c*) M. P. Cava and S. C. Havlicek, *Tetrahedron Letters*, 1967, 2625; (*d*) M. P. Cava, M. J. Mitchell, S. C. Havlicek, A. Lindert, and R. J. Spangler, *J. Org. Chem.*, 1970, **35**, 175; (*e*) G. Y. Moltrasio, R. M. Sotelo, and D. Giacopello, *J.C.S. Perkin I*, 1973, 349.

enamide isomer was isolated, the exception being that of the enamides (IIa and b).

*Photocyclisation of the Enamides* (I) *and* (II).—1-Ethyl-3,4-dihydroisoquinoline was readily benzoylated as described previously [4] to afford a mixture of two isomeric enamides (IIa and b) in 50% yield. However, this mixture was readily isomerised to the more stable isomer (IIb) during chromatography, though the less stable isomer (IIa) could be isolated by careful recrystallisation of the crude mixture.

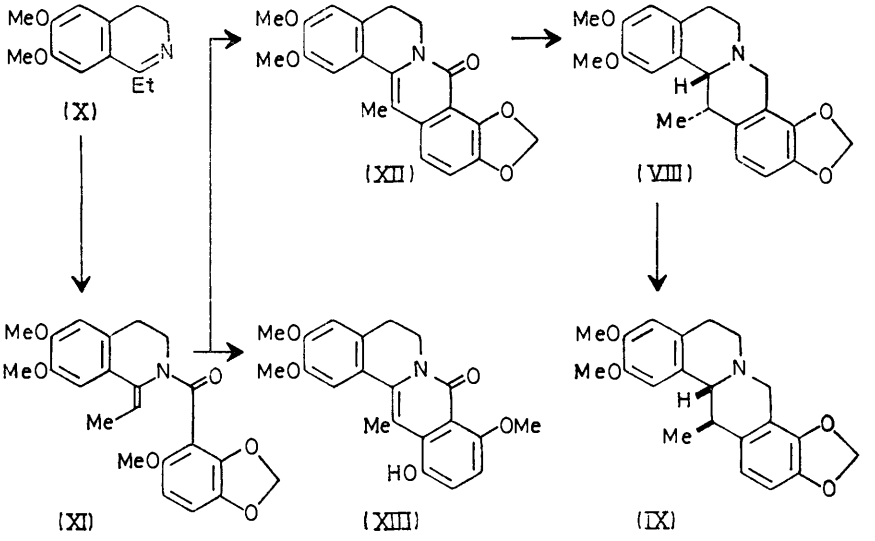
Irradiation of a methanolic solution of the stable enamide (IIb) for 7.5 h afforded two products, (III) and (IV), in 4 and 30% yield, respectively, which were separated by chromatography and identified from their n.m.r. spectra. In particular, the fact that the 13-proton signal in (IV) appeared at δ 3.25 as a quartet of doublets with $J$ 7 and 3.5 Hz confirmed the stereospecificity of photocyclisation of this type of enamide. On the other hand, photocyclisation of the less stable enamide (IIa) gave a mixture of the same photoproducts, (III) and (IV), which suggested that complete isomerisation occurred during the photocyclisation. When the lactam (IV) was kept in air at room temperature, complete conversion into the didehydrolactam (III) occurred during several months.[7]

When an ethereal solution of the *ortho*-methoxyenamide (IIc), prepared from 2-methoxybenzoyl chloride, was irradiated, the isolated product was the 13a-methoxy-lactam (V), which was homogeneous according to both t.l.c. and n.m.r. spectroscopy. The spectrum showed the presence of eight aromatic protons, suggesting that there was no methoxy-group on the benzene ring, and a quartet due to the 13-proton, indicating the lack of a neighbouring proton. Thus the methoxy-group had migrated to the 13a-position stereospecifically. This structural assignment for (V) confirmed the proposed mechanism [8] for the photocyclisation of this type of enamide, *i.e.* an electrocyclic reaction [(IIc) ⟶ (D)], followed by a thermal [1,5] sigmatropic shift of a methoxy-group [(D) ⟶ (V)]. The migrated methoxy-group in (V) was susceptible to elimination to afford the didehydrolactam (III) when kept at room temperature in solution or heated in the presence of acid. Data for the photocyclisation of the enamides (Ia—c) are summarised in the Experimental section.

*Total Synthesis of* (±)-*Cavidine.*—In 1964, Taguchi and his co-workers isolated two protoberberine alkaloids, base II (VIII) and its stereoisomer, thalictrifoline (IX), from a Corydalis plant.[9] Base II was later identified, and designated cavidine by Manske.[10]

From 1-ethyl-3,4-dihydro-6,7-dimethoxyisoquinoline (X), (±)-cavidine was readily synthesised by a route analogous to that reported in the preceding paper.[1] Acylation of the 3,4-dihydroisoquinoline (X) with 6-methoxy-2,3-methylenedioxybenzoyl chloride [11] afforded the enamide (XI) in 77% yield, which showed the n.m.r. signals for an olefinic proton at δ 5.41 as a quartet and for a vinylic methyl group at 1.69 as a doublet. The *E*-configuration was assumed as a result of comparison with the data in Tables 2 and 4.

Irradiation of the enamide (XI) in methanol afforded two photoproducts, (XII) and (XIII), in 41 and 29% yield, respectively. These structures were deduced from spectral data. Reduction of the major photoproduct (XII) with lithium aluminium hydride followed by sodium borohydride afforded the tertiary amine (VIII), m.p. 194—195°, in 37% yield from (XII), which showed distinct Bohlmann bands in the i.r. spectrum at 2 800—2 750 $cm^{-1}$ and n.m.r. peaks for the 13a-proton ($W_{\frac{1}{2}}$ 6 Hz) and the 13-methyl protons at δ 0.93, which suggested that (VIII) had a BC-*trans*-ring




[7] G. R. Lenz, *J. Org. Chem.*, 1974, **39**, 2846.
[8] I. Ninomiya, T. Kiguchi, and T. Naito, *J.C.S. Chem. Comm.*, 1974, 81.
[9] H. Taguchi and I. Imaseki, *Yakugaku Zasshi*, 1964, **84**, 955.
[10] C. K. Yu, D. B. MacLean, R. G. A. Rodrigo, and R. H. F. Manske, *Canad. J. Chem.*, 1970, **48**, 3673.

junction and two protons at positions 13 and 13a in the *cis*-configuration. The tertiary amine (VIII) was identical with a sample of natural base II, m.p. 190—191°. Since base II has been converted into thalictrifoline,[9] this synthesis formally completed the first total synthesis of thalictrifoline.

## EXPERIMENTAL

$^1$H N.m.r. spectra, including n.O.e. measurement, were obtained for solutions in deuteriochloroform with Varian A-60D and HA-100 instruments (tetramethylsilane as internal reference). M.p.s were determined with a hot-stage apparatus. The photochemical reactions were carried out as described in the preceding paper.[1]

*General Procedure for Preparing the Enamides* (Ia—c) *and* (IIa—c).—To a solution of the 1-ethyl-3,4-dihydroisoquinoline (0.01 mol) and triethylamine (0.012 mol) in anhydrous benzene (150 ml), a solution of an appropriate aroyl chloride (0.01 mol) in anhydrous benzene (50 ml) was added with stirring. After refluxing for 2 h, the mixture was cooled and filtered to remove triethylamine hydrochloride. Evaporation of the filtrate left a residue, which was purified either by chromatography or recrystallisation to give the pure enamide (Tables 1 and 2).

TABLE 1

Enamides (I) and (II)

| Compound | Yield (%) | M.p. (°C) (solvent) | Formula | Analysis (%) [a] C | H | N |
|---|---|---|---|---|---|---|
| (Ia) | 80 | 179—180 (PhH–$Et_2O$) | $C_{20}H_{21}NO_3$ | 74.4 (74.3 | 6.5 6.55 | 4.5 4.35) |
| (Ib) | 77 | 158—159 (PhH–$C_6H_{14}$) | $C_{21}H_{23}NO_4$ | 71.25 (71.35 | 6.55 6.55 | 4.25 3.95) |
| (Ic) | 61 | 161—162 (PhH–$Et_2O$) | $C_{22}H_{25}NO_5$ | 69.2 (68.9 | 6.7 6.55 | 3.75 3.65) |
| (IIa) | 5 | 135.5—136.5 ($Et_2O$) | $C_{18}H_{17}NO$ | 82.15 (82.1 | 6.45 6.5 | 5.35 5.3) |
| (IIb) | 45 | 75—76 ($Et_2O$–$C_6H_{14}$) | $C_{18}H_{17}NO$ | 82.05 (82.1 | 6.5 6.5 | 5.3 5.3) |
| (IIc) | 84 | 125—125.5 (PhH–$Et_2O$) | $C_{19}H_{19}NO_2$ | 77.55 (77.8 | 6.4 6.55 | 4.8 4.75) |

[a] Required values in parentheses.

TABLE 2

Spectral data for compounds (I) and (II)

| Compound | $\nu_{max.}$ ($CHCl_3$)/ $cm^{-1}$ | δ |
|---|---|---|
| (Ia) | 1 625 (NCO) | 6.98 (1 H, s, 8-H), 6.68 (1 H, s, 5-H), 5.73br (1 H, q, olefinic H; 15% intensity increase upon irradiation at 6.98), 5.30—4.70vbr (1 H, 3-H), 3.88 (6 H, s, OMe × 2), and 1.38br (3 H, d, *J* 7 Hz, C=CMe) |
| (Ib) | 1 630 (NCO) | At room temp: 6.85 (1 H, s, 8-H), 6.20 (1/3 H) and 5.63 (2/3 H) (each q, *J* 7 Hz, olefinic), 5.15 (2/3 H, m, 3-H), 3.88 (4 H), 3.85 (3 H), and 3.30 (2 H) (each s, OMe × 3), 1.90 (1 H) and 1.41 (2 H) (each d, *J* 7 Hz, C=CMe) At 110 °C: 6.88 (1 H, s, 8-H), 5.65 (1 H, olefinic; 15% intensity increase upon irradiation at 6.88), and 1.52 (d, 3-H, *J* 7 Hz, C=CMe) |
| (Ic) | 1 625 (NCO) | 6.73 (1 H, s, 8-H), 5.45 (1 H, q, *J* 7.5 Hz, olefinic), 4.03 (2 H, t, *J* 6.5 Hz, 3-$H_2$), 3.88 and 3.82 (6 H, each s, OMe × 2), 3.53 (6 H, s, OMe × 2), 2.92 (2 H, t, *J* 6.5 Hz, 4-$H_2$), and 1.64 (3 H, d, *J* 7.5 Hz, C=CMe; 5% intensity increase upon irradiation at 6.73) |
| (IIa) | 1 630 (NCO) | 5.22 (1 H, q, *J* 7.5 Hz, olefinic), 4.00 (2 H, t, *J* 7 Hz, 3-$H_2$), 2.98 (2 H, t, *J* 7 Hz, 4-$H_2$), and 1.62 (3 H, d, *J* 7.5 Hz, C=CMe) |
| (IIb) | 1 630 (NCO) | 5.81br (1 H, q, *J* 7 Hz, olefinic), 5.00vbr (1 H, 3-H), and 1.36br (3 H, d, *J* 7 Hz, C=CMe) |
| (IIc) | 1 630 (NCO) | 6.35 (1/4 H) and 5.75 (3/4 H) (each q, *J* 7 Hz, olefinic), 5.10 (3/4 H, m, 3-H), 3.85 (3/4 H), and 3.15 (9/4 H) (each s, OMe), and 1.88 (3/4 H) and 1.40 (9/4 H) (each d, *J* 7 Hz, C=CMe) |

*General Procedure for Photocyclisation of the Enamides* (Ia—c) and (IIa—c).—A 0.02M-solution of the enamide [(Ia—c) or (IIa—c)] in methanol [ether was employed only in the case of (IIa)] was irradiated for several hours, generally until the starting enamide disappeared (t.l.c.). The solvent was removed and the residue purified either by recrystallisation or by chromatography on silica gel to afford the photocyclised lactams (Tables 3 and 4).

TABLE 3

Photocyclisation products

| Compound | Yield (%) | M.p. (°C) (solvent) | Formula | Analysis (%) [a] C | H | N |
|---|---|---|---|---|---|---|
| (III) | 4 | 121—122 ($Et_2O$) | $C_{18}H_{15}NO$ | 83.05 (82.75 | 5.8 5.8 | 5.45 5.35) |
| (IV) | 30 | 127—128 ($Et_2O$) | $C_{18}H_{17}NO$ | 82.1 (82.1 | 6.55 6.5 | 5.25 5.3) |
| (V) | 25 | 133—135 ($Et_2O$) | $C_{19}H_{19}NO_3$ | | [b] | |
| (VI) | 37 | Oil | $C_{20}H_{21}NO_3$ | $M^+$ 323.153 [c] (323.152) | | |
| (VIIa) | 9 from (Ia) 35 from (Ib) | 163.5—165 ($Et_2O$–$C_6H_{14}$) | $C_{20}H_{19}NO_3$ | 74.7 (74.75 | 5.85 5.95 | 4.35 4.35) |
| (VIIb) | 34 | 157—158.5 (PhH–n–$C_6H_{14}$) | $C_{21}H_{21}NO_4$ | 71.8 (71.8 | 6.25 6.0 | 3.65 4.0) |

[a] Required values in parentheses. [b] Owing to instability, elemental analysis could not be carried out. [c] High resolution mass spectral analysis (JEOL-JMS-01SG instrument).

TABLE 4

Spectral data for photocyclisation products

| Compound | $\nu_{max.}$ ($CHCl_3$)/ $cm^{-1}$ | δ |
|---|---|---|
| (III) | 1 630 (NCO), 1 603, 1 580 | 8.57 (1 H, m, 9-H), 4.30 (2 H, t-like, 6-$H_2$), 2.93 (2 H, t-like, 5-$H_2$), and 2.59 (3 H, s, 13-Me) |
| (IV) | 1 640 (NCO) | 8.16 (1 H, m, 9-H), 5.11 (1 H, d, *J* 3.5 Hz, 13a-H), 5.20—4.75 (1 H, m, 6*eq*-H), 3.25 (1 H, qd, *J* 7 and 3.5 Hz, 13-H), and 0.82 (3 H, d, *J* 7 Hz, 13-Me) |
| (V) | 1 635 (NCO), 1 065 (C–O) | 8.18 (1 H, m, 9-H), 5.40—4.85 (1 H, m, 6*eq*-H), 3.31 (1 H, q, *J* 7 Hz, 13-H), 3.00 (3 H, s, OMe), and 0.78 (3 H, d, *J* 7 Hz, 13-Me) |
| (VI) | 1 635 (NCO) | 8.17 (1 H, m, 9-H), 6.70 (2 H, s, 1- and 4-H), 5.15—4.90 (2 H, m, 13a- and 6*eq*-H), 3.88 (6 H, s, OMe × 2), 3.20 (1 H, m, 13-H), and 0.85 (3 H, d, *J* 7 Hz, 13-Me) |
| (VIIa) | 1 635 (NCO) | 8.53 (1 H, m, 9-H), 7.17 (1 H, s, 1-H), 6.82 (1 H, s, 4-H), 4.28 (2 H, t-like, 6-$H_2$), 3.95 and 3.91 (6 H, each s, OMe × 2), 2.86 (2 H, t-like, 5-$H_2$), and 2.62 (3 H, s, C=CMe) |
| VIIb) | 1 645 (NCO) | 7.61 (1 H, t, *J* 8 Hz, 11-H), 7.30 (1 H, dd, *J* 8 and 2 Hz, 12-H), 7.13 (1 H, s, 1-H), 6.92 (1 H, dd, *J* 8 and 2 Hz, 10-H), 6.79 (1 H, s, 4-H), 4.25 (2 H, t, *J* 6.5 Hz, 6-$H_2$), 4.00, 3.93, and 3.88 (9 H, each s, OMe × 3), 2.83 (2 H, t, *J* 6.5 Hz, 5-$H_2$), and 2.55 (3 H, s, 13-Me) |

1-*Ethylidene*-1,2,3,4-*tetrahydro*-2-(6-*methoxy*-2,3-*methylenedioxybenzoyl*)-6,7-*dimethoxyisoquinoline* (XI).—To a solution of 1-ethyl-3,4-dihydro-6,7-dimethoxyisoquinoline (X) (4.4 g) in anhydrous benzene (150 ml) and triethylamine (3 g), a solution of 6-methoxy-2,3-methylenedioxybenzoyl chloride [11] (4.3 g) in anhydrous benzene (50 ml) was added dropwise, and the mixture was refluxed for 1.5 h. After cooling, the precipitated salt was filtered off. The filtrate was evaporated under reduced pressure to give a viscous paste, which was triturated with ether to afford a solid. Recrystallisation from benzene–ether afforded the *enamide* (XI) (6.1 g, 77 %), as needles, m.p. 165—167°, $\nu_{max.}$ ($CHCl_3$) 1 625 $cm^{-1}$ (NCO), δ 6.80 (1 H, s, 8-H), 6.73 (1 H, s, 5-H), 6.77 and 6.21 (2 H, ABq, *J* 8.5 Hz, 3'- and 4'-H), 5.95—5.75 (2 H, m, $OCH_2O$), 5.41 (1 H, q, *J* 7 Hz, olefinic), 3.87, 3.83, and 3.47 (9 H, each s, OMe × 3), and 1.69 (3 H, d, *J* 7 Hz, C=CMe) (Found: C, 66.1; H, 5.8; N, 3.5. $C_{22}H_{23}NO_6$ requires C, 66.5; H, 5.85; N, 3.5%).

*Photocyclisation of the Enamide* (XI).—By the general procedure, the enamide (XI) (2.38 g) in methanol (300 ml) was irradiated for 9 h. Chromatography on alumina with chloroform as eluant separated two products. Chloroform initially eluted 13,13a-*didehydro*-2,3-*dimethoxy*-13-*methyl*-9,10-*methylenedioxyberbin*-8-*one* (XII) (889 mg, 41%), m.p. 243—245° (from chloroform–methanol), $\nu_{max.}$ ($CHCl_3$) 1 640 (NCO) $cm^{-1}$, δ 7.20 (2 H), 7.10 (1 H), and 6.79 (1 H) (each s, aromatic), 6.21 (2 H, s, $OCH_2O$), 4.21 (2 H, t-like, 6-$H_2$), 3.93 and 3.90 (6 H, each s, OMe × 2), 2.83 (2 H, t-like, 5-$H_2$), and 2.53 (3H, s, 13-Me) (Found: C, 68.95; H, 5.15;

[11] F. P. Doyle, K. Hardy, J. H. C. Nayler, M. J. Soulal, E. R. Stove, and H. R. J. Waddington, *J. Chem. Soc.*, 1962, 1453.

N, 3.85. $C_{21}H_{19}NO_5$ requires C, 69.05; H, 5.25; N, 3.85 %). Chloroform containing 2% methanol then eluted *13,13a-didehydro-12-hydroxy-2,3,9-trimethoxy-13-methylberbin-8-one* (XIII) (638 mg, 29%), m.p. 225—226° (decomp.) (from ethyl acetate–methanol), $\nu_{max.}$ (Nujol) 3 200 (OH) and 1 635 (NCO) $cm^{-1}$, δ 9.41br (1 H, OH), 7.21 (1 H, s, 1-H), 7.10 and 6.87 (2 H, ABq, *J* 8 Hz, 10- and 11-H), 6.97 (1 H, s, 4-H), 3.83, 3.79, and 3.75 (9 H, each s, OMe × 3), and 2.68 (3 H, s, 13-Me) (Found: $M^+$, 367.142. $C_{21}H_{21}NO_5$ requires *M*, 367.142)

(±)-*Cavidine* (VIII).—To a solution of the foregoing lactam (XII) (365 mg) in anhydrous tetrahydrofuran (70 ml), lithium aluminium hydride (190 mg) was added in portions and the mixture was stirred under reflux for 2 h. After cooling, the excess of reagent was decomposed with water. The mixture was evaporated to dryness and the residue was extracted with ether–tetrahydrofuran. The extracts were evaporated to give a solid which was dissolved in methanol (40 ml). Sodium borohydride (200 mg) was added and the mixture was refluxed for 1.5 h, then evaporated. The residue was dissolved in 10% hydrochloric acid, neutralised with potassium carbonate, and extracted with chloroform. The extracts were washed with water, dried, and evaporated and the residue was recrystallised from methanol to afford the amine (VIII) (130 mg, 37%), m.p. 194—195°, was identical with natural base II [9]; $\nu_{max.}$ ($CHCl_3$) 2 800—2 750 $cm^{-1}$ (Bohlmann bands), δ 6.68 (3 H) and 6.60 (1 H) (each s, aromatic H), 5.92 (2 H, s-like, $OCH_2O$), 4.07 and 3.50 (2 H, ABq, *J* 15.5 Hz, 8-$H_2$), 3.85 (6 H, s, OMe × 2), 3.73br (1 H, s, $W_{\frac{1}{2}}$ 6 Hz, 13a-H), and 0.93 (3 H, d, *J* 7 Hz, 13-Me) (Found: C, 70.8; H, 6.3; N, 4.05. $C_{21}H_{23}NO_4$ requires, C, 71.35; H, 6.55; N, 4.0%).

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