Syntheses of Dihydro-derivatives of the Benzo[*c*]phenanthridine Alkaloids Avicine and Nitidine by Enamide Photocyclisation †

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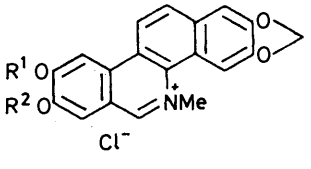
5,6-Dihydro-5-methyl-2,3:8,9-bismethylenedioxybenzo[*c*]phenanthridine (dihydroavicine) (XV) and its 8,9-dimethoxy-analogue (dihydronitidine) (XVII) have been conveniently prepared by a route involving enamide photocyclisation.

NITIDINE (II) is a representative benzo[*c*]phenanthridine alkaloid [1] of those isolated from *Xanthoxylum* species (Rutaceae) and has recently attracted attention because of its potent antileukemic activity.[2] Although various methods for synthesising nitidine have been reported,[3] the literature does not yet contain a convenient and practical preparation.

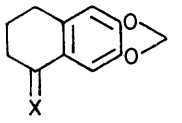
Ninomiya has recently developed the photocyclisation of enamides [4] as a useful tool for the preparation of several condensed aromatic systems including the benzo[*c*]phenanthridine nucleus. We now report an application of this method to the synthesis of dihydro-derivatives of nitidine and the related alkaloid, avicine (I).

Dihydroavicine.—The imine (IV), prepared from the tetralone (III) and methylamine, was readily acylated with 3,4-methylenedioxy- and 2-methoxy-4,5-methylenedioxy-benzoyl chlorides as described previously [4] to afford the enamides (VI) and (V) in good yields. Irradiation of a methanolic 0·02M-solution of the enamide (VI) with a low pressure mercury lamp for 3 h afforded the lactam (XII) as a homogeneous crystalline product in 52% yield. This photoproduct was dehydrogenated by heating with 30% palladium–charcoal in *p*-cymene. However the yield was too low for preparative purposes.

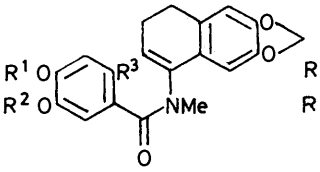
Next we attempted photocyclisation to the didehydrolactam (IX) by employing the enamide (V), which has an additional *ortho*-methoxy-group; regiospecific photocyclisation at the ' root ' of an *ortho*-methoxy-group has been reported as a useful preparative procedure.[5] As expected, nonoxidative photocyclisation of the enamide (V) occurred regiospecifically to afford the didehydro-



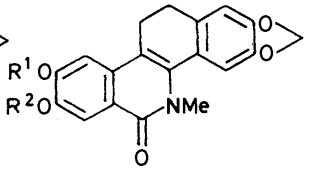
(I) $R^1R^2 = CH_2$
(II) $R^1 = R^2 = Me$



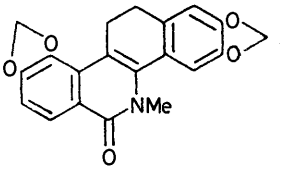
(III) X = O
(IV) X = NMe



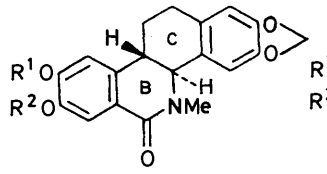
(V) $R^1R^2 = CH_2, R^3 = OMe$
(VI) $R^1R^2 = CH_2, R^3 = H$
(VII) $R^1 = R^2 = Me, R^3 = OMe$
(VIII) $R^1 = R^2 = Me, R^3 = H$



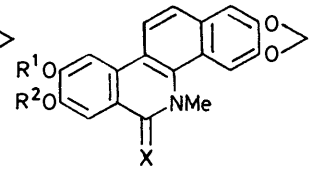
(IX) $R^1R^2 = CH_2$
(X) $R^1 = R^2 = Me$



(XI)



(XII) $R^1R^2 = CH_2$
(XIII) $R^1 = R^2 = Me$



(XIV) $R^1R^2 = CH_2, X = O$
(XV) $R^1R^2 = CH_2, X = H_2$
(XVI) $R^1 = R^2 = Me, X = O$
(XVII) $R^1 = R^2 = Me, X = H_2$

lactam (IX) in 41% yield; the product was homogeneous and had a double bond at the ring junction. In contrast,

† This paper constitutes Part VI of Photocyclisation of Enamides (I. N.) and Part XXIII of Chemical Constituents of Rutaceous Plants (H. I.).

[1] (*a*) R. H. F. Manske in ' The Alkaloids,' ed. R. H. F. Manske, Academic Press, New York and London, 1954, vol. 4, p. 253; R. H. F. Manske, *ibid.*, 1959, vol. 7, p. 430; R. H. F. Manske, *ibid.*, 1968, vol. 10, p. 485; F. Santavy, *ibid.*, 1970, vol. 12, p. 417; (*b*) H. Ishii, H. Ohida, and J. Haginiwa, *Yakugaku Zasshi*, 1972, **92**, 118; (*c*) H. Ishii and T. Komaki, *ibid.*, 1966, **86**, 631.

[2] (*a*) M. E. Wall, M. C. Wani, and H. L. Taylor, 162nd Amer. Chem. Soc. Natl. Meeting, Washington, D.C., 1971, Med. I-34; (*b*) W. M. Messmer, M. Tin-Wa, H. H. S. Fong, C. Bevelle, N. R. Farnsworth, D. J. Abraham, and J. Trojanek, *J. Pharm. Sci.*, 1972, **61**, 1858.

[3] (*a*) S. V. Kessar, G. Singh, and P. Balakrishnan, *Tetrahedron Letters*, 1974, 2269; (*b*) K. Y. Zee-Cheng and C. C. Cheng, *J. Heterocyclic Chem.*, 1973, **10**, 85; (*c*) K. W. Gopinath, J. M. Kohli, M. S. Y. Khan, and A. R. Kidwai, *Indian J. Chem.*, 1963, **1**, 99; (*d*) T. Kametani, K. Kigasawa, M. Hiiragi, and O. Kusama, *J. Heterocyclic Chem.*, 1973, **10**, 31; (*e*) K. Y. Zee-Cheng and C. C. Cheng, *ibid.*, p. 867; (*f*) S. A. Vichkanova and V. V. Adgina, *Antibiotiki*. 1971, **16**, 609; (*g*) J. L. Hartwell, *Cancer Chemotherapy Rep.*, 1960, **7**, 19.

[4] I. Ninomiya, T. Naito, T. Kiguchi, and T. Mori, *J.C.S. Perkin I*, 1973, 1696.

[5] (*a*) I. Ninomiya, T. Kiguchi, and T. Naito, *J.C.S. Chem. Comm.*, 1974, 81; (*b*) Y. Kanaoka and K. Ito, *ibid.*, 1973, 647; (*c*) G. Lenz, *Tetrahedron Letters*, 1973, 1963; (*d*) I. Ninomiya, H. Takasugi, and T. Naito, *Heterocycles*, 1973, **1**, 17; (*e*) R. G. F. Giles and M. V. Sargent, *J.C.S. Chem. Comm.*, 1974, 215; (*f*) Y. Tamura, S. Fukumori, S. Kato, and Y. Kita, *ibid.*, p. 285.

oxidative photocyclisation of the enamide (VI) in the presence of iodine afforded a mixture of two lactams (IX) and (XI) in 25 and 6% yields, respectively. Dehydrogenation of (IX) proceeded smoothly to afford oxyavicine (XIV) in 86% yield. Reduction of (XIV) with lithium aluminium hydride gave dihydroavicine (XV), identical with a sample [1b] derived from natural avicine.

Dihydronitidine.—The imine (IV) was acylated with 3,4-dimethoxy- and 2,4,5-trimethoxy-benzoyl chlorides to afford the corresponding enamides (VIII) and (VII) in good yields. Nonoxidative photocyclisation of these enamides proceeded regiospecifically to afford the corresponding photocyclised lactams (XIII) and (X), each homogeneous, in 53 and 50% yields, respectively. The structures of these products were firmly established by their n.m.r. data and chemical conversions. The lactam (XIII) was shown to have the BC-*trans*-configuration from its n.m.r. spectrum [δ 4·76 (d, *J* 12 Hz, 4b-H)].

As in the avicine synthesis, there were marked differences in the yields of conversions of the lactams (XIII) and (X) into oxynitidine (XVI) by dehydrogenation with 30% palladium–charcoal. Dehydrogenation of (X) proceeded smoothly to give (XVI) in 53% yield but that of (XIII) gave only a 20% yield of (XVI), probably owing to thermal instability of the substrate. Lithium aluminium hydride reduction of (XVI) gave dihydronitidine (XVII) and the structures of (XVI) and (XVII) were unequivocally established by direct comparisons with samples derived from the natural alkaloid.[1c]

EXPERIMENTAL

^{1}H N.m.r. spectra were measured for solutions in deuteriochloroform with tetramethylsilane as internal reference. I.r. spectra were taken for Nujol mulls unless otherwise stated. M.p.s were determined with a hot-stage apparatus. The photochemical reactions were carried out as described in ref. 4.

3,4-*Dihydro*-6,7-*methylenedioxynaphthalen*-1(2H)-*one* (III).—A mixture of 3,4-dihydro-6,7-dihydroxynaphthalen-1(2*H*)-one (20·0 g), prepared according to the procedure of Tamura *et al.*[6a] [m.p. 197—200° (lit.,[6a] 190—191°; lit.,[6b] 195°)], methylene iodide (60·2 g), and anhydrous potassium carbonate (43·6 g) in dimethyl sulphoxide (79 ml) was stirred at 60° in a nitrogen stream for 2 h. The mixture was then diluted with water and extracted with methylene chloride. The combined extracts were washed with aqueous 5% sodium hydroxide and water, dried (K_2CO_3), evaporated, and the residue was distilled [b.p. 154—157° (3 mmHg)] to afford the methylenedioxytetralone (III) (13·9 g, 65·2%), which slowly solidified and afforded prisms, m.p. 74—76° (from benzene–hexane) (lit.,[3d] 71—72°), $\nu_{max.}$ 1665 (CO) and 941 cm^{-1} (OCH_2O).

N-(3,4-*Dihydro*-6,7-*methylenedioxy*-1-*naphthyl*)-N-*methyl*-3,4-*methylenedioxybenzamide* (VI).—Anhydrous methylamine gas was bubbled into a boiling solution of the tetralone (III) (3·8 g) and toluene-*p*-sulphonic acid (small amount) in xylene (70 ml) for 7 h. Water was removed as formed by a Dean–Stark separator. The mixture was evaporated and the residue was dissolved in chloroform (30 ml) and triethylamine (3·8 ml) and cooled in ice. 3,4-Methylenedioxybenzoyl chloride (4·8 g) in chloroform (20 ml) was then added and the mixture was kept at room temperature overnight. The solvent was removed and the residue was extracted with ethyl acetate. The extracts were washed with water, dried (K_2CO_3), and evaporated, and the *product* (VI) was recrystallised from benzene–ether to afford needles (2·86 g, 42·1%), m.p. 169—172°, $\nu_{max.}$ 1640 cm^{-1} (CO), δ 7·76—6·56 (5H, m, aromatic H), 5·96 (2H, s, OCH_2O), 5·91 (2H, s, OCH_2O), 3·47 (1H, t, *J* 5 Hz, C=CH), and 3·21 (3H, s, NMe), *m/e* 351 (M^+) (Found: C, 68·15; H, 4·85; N, 4·05. $C_{20}H_{17}NO_5$ requires C, 68·35; H, 4·9; N, 4·0%).

N-(3,4-*Dihydro*-6,7-*methylenedioxy*-1-*naphthyl*)-N-*methyl*-2-*methoxy*-4,5-*methylenedioxybenzamide* (V).—A similar reaction of the imine (IV), prepared from the tetralone (III) (1·01 g) and methylamine, with 2-methoxy-4,5-methylenedioxybenzoyl chloride afforded the *enamide* (V) (1·13 g, 55·8%) as needles (from benzene–ether), m.p. 178—181°, $\nu_{max.}$ 1647 (CO) and 938 cm^{-1} (OCH_2O), $\lambda_{max.}$ (EtOH) 212 (log ε 4·57) and 311 nm (4·11), δ 6·75, 6·63, 6·58, and 6·35 (each 1H, s, aromatic), 5·91 (2H, s, OCH_2O), 5·85 (2H, s, OCH_2O), 5·65 (1H, t, *J* 5 Hz, C=CH), 3·60 (3H, s, OMe), and 3·24 (3H, s, NMe), *m/e* 381 (M^+) (Found: C, 66·25; H, 5·05; N, 3·55. $C_{21}H_{19}NO_6$ requires C, 66·15; H, 5·0; N, 3·65%).

trans-4b,10b,11,12-*Tetrahydro*-2,3;8,9-*bis*(*methylenedioxy*)-5-*methylbenzo*[c]*phenanthridin*-6(5H)-*one* (XII).—A solution of the enamide (VI) (500 mg) in absolute ether (150 ml) was irradiated with a low-pressure mercury lamp for 7 h (t.l.c. then showed complete disappearance of the starting enamide). Evaporation yielded a crystalline residue which was recrystallised from chloroform to afford pale yellow *crystals* (XII) (262 mg, 52%), m.p. >300°, $\nu_{max.}$ 1635 (CO) and 930 cm^{-1} (OCH_2O), *m/e* 351 (M^+) (Found: N, 3·85. $C_{20}H_{17}NO_5$ requires N, 4·0%).

11,12-*Dihydro*-2,3;8,9-*bis*(*methylenedioxy*)-5-*methylbenzo*[c]*phenanthridin*-6(5H)-*one* (IX).—A solution of the enamide (V) (190 mg) in absolute ether (140 ml) was irradiated similarly for 3 h. The solvent was evaporated off and the residue was chromatographed on alumina with benzene as eluant. The product was recrystallised from ethanol to afford *plates* (72 mg, 41·3%), m.p. 237—241°, $\nu_{max.}$ 1633 (CO) and 929 cm^{-1} (OCH_2O), δ 7·84, 7·02, 6·93, and 6·78 (each 1H, s, aromatic), 6·05 (2H, s, OCH_2O), 5·99 (2H, s, OCH_2O), 3·72 (3H, s, NMe), and 2·68 (4H, s, CH_2CH_2), *m/e* 349 (M^+) (Found: C, 68·6; H, 4·4; N, 4·0. $C_{20}H_{15}NO_5$ requires C, 68·75; H, 4·35; N, 4·0%).

Oxidative Photocyclisation of the Enamide (VI).—A methanolic 0·02M-solution of the enamide (VI) (507 mg) containing iodine (176 mg) was irradiated for 6 h. Evaporation afforded a residue which was dissolved in chloroform. The solution was washed with aqueous sodium thiosulphate and water, dried (Na_2SO_4), and evaporated and the residue was chromatographed on alumina with benzene as eluant. The first fraction afforded the crystalline product, which was recrystallised from methanol to afford needles, m.p. 266—268°, of 11,12-*dihydro*-2,3;9,10-*bis*(*methylenedioxy*)-5-*methylbenzo*[c]*phenanthridin*-6(5H)-*one* (XI) (30 mg, 6%), $\nu_{max.}$ 1610 (CO) and 930 cm^{-1} (OCH_2O), δ 8·12 (1H, d, *J* 8·5 Hz, 7-H), 6·96 (1H, d, *J* 8·5 Hz, 8-H), 6·92 (1H, s, 4-H), 6·77 (1H, s, 1-H), 6·07 (2H, s, OCH_2O), 5·97 (2H, s, OCH_2O), and 3·66 (3H, s, NMe) (Found: C, 68·3; H, 4·2; N, 3·9. $C_{20}H_{15}NO_5$ requires C, 68·75; H, 4·35; N, 4·0%). The second fraction gave 11,12-dihydro-2,3;8,9-bis(methylenedioxy)-5-methylbenzo[*c*]phenanthridin-6(5*H*)-one (IX) (125 mg, 25%) as pale brown crystals, m.p. 252—254° (from methanol),

[6] (*a*) S. Tamura, K. Okuma, and T. Hayashi, *J. Agric. Chem. Soc. Japan*, 1953, **27**, 318; (*b*) T. Momose, H. Oya, Y. Ohkura, and M. Iwasaki, *Chem. and Pharm. Bull.* (*Japan*), 1954, **2**, 119.

identical with the sample obtained from photocyclisation of the enamide (V).

5-Methyl-2,3;8,9-bismethylenedioxybenzo[c]*phenanthridin-6*(5H)*-one* (*Oxyavicine*) (XIV).—A mixture of the didehydrolactam (IX) (152 mg) and 30% palladium–charcoal (30 mg) in *p*-cymene (3 ml) was heated under reflux for 2 h in a nitrogen stream. After cooling, the mixture was treated with chloroform to dissolve the product. The catalyst was filtered off. The filtrate was concentrated under reduced pressure to yield a crystalline residue, which was repeatedly recrystallised from chloroform–ethanol to afford *oxyavicine* (XIV) (130 mg, 86·4%) as plates, m.p. 278—283° [lit.,[7] 257—259° (prisms)], $\nu_{max.}$ 1631 (CO) and 938 cm^{-1} (OCH_2O) (Found: C, 69·2; H, 3·8; N, 3·85. $C_{20}H_{13}NO_5$ requires C, 69·15; H, 3·75; N, 4·05%).

Dihydroavicine (XV).—To a solution of oxyavicine (XIV) (92 mg) in absolute tetrahydrofuran (15 ml), lithium aluminium hydride (70 mg) was added. The resulting mixture was heated under reflux in an argon stream for 2 h, cooled, and treated with dilute hydrochloric acid. The crystalline precipitate was recrystallised from benzene–ether to give *dihydroavicine* (XV) (57 mg, 64·6%) as prisms, m.p. 212—213° (lit.,[1b] 223—224°) (Found: C, 71·95; H, 4·45; N, 4·3. $C_{20}H_{15}NO_4$ requires C, 72·05; H, 4·55; N, 4·2%), identical with natural material.[1b]

N-(3,4-Dihydro-6,7-methylenedioxy-1-naphthyl)-N-methyl-3,4-dimethoxybenzamide (VIII).—Reaction of the imine (IV) [prepared from the tetralone (III) (1·81 g) and methylamine] as before with veratroyl chloride [prepared freshly from veratric acid (3·58 g)] afforded the *enamide* (VIII) as prisms (2·10 g, 60·2%), m.p. 151—153° (from benzene–ether), $\nu_{max.}$ 1634 (CO) and 940 cm^{-1} (OCH_2O), δ 7·15—6·12 (5H, m, aromatic H), 5·97 (2H, s, OCH_2O), 5·47 (1H, t, *J* 5 Hz, C=CH), 3·84 (3H, s, OMe), 3·65 (3H, s, OMe), and 3·20 (3H, s, NMe), *m/e* 367 (M^+) (Found: C, 68·75; H, 5·75; N, 3·8. $C_{21}H_{21}NO_5$ requires C, 68·65; H, 5·85; N, 3·7%).

N-(3,4-Dihydro-6,7-methylenedioxy-1-naphthyl)-N-methyl-2,4,5-trimethoxybenzamide (VII).—Reaction of the imine (IV) [prepared from the tetralone (III) (2·8 g) and methylamine] as before with 2,4,5-trimethoxybenzoyl chloride (3·0 g) afforded the *enamide* (VII) (4,4 g, 60%) as needles, m.p. 143—144° (from ether), $\nu_{max.}$ ($CHCl_3$) 1630 (NCO) and 1618 cm^{-1} (Ar), δ 6·80, 6·70, 6·58, and 6·37 (each 1H, s, aromatic), 5·88 (2H, s, OCH_2O), 5·67 (1H, t, *J* 4 Hz, C=CH), 3·80, 3·61, and 3·60 (each 3H, s, OMe), and 3·24 (3H, s, NMe) (Found: C, 66·6; H, 5·75; N, 3·35. $C_{22}H_{23}NO_6$ requires C, 66·5; H, 5·85; N, 3·5%).

trans-*4b,10b,11,12-Tetrahydro-8,9-dimethoxy-2,3-methylenedioxy-5-methylbenzo*[c]*phenanthridin-6*(5H)*-one* (XIII).—As in the case of (VI), an ethereal solution (70 ml) of the enamide (VIII) (199 mg) was irradiated for 7 h. Evaporation yielded a residue which was chromatographed on silica gel with chloroform as eluant. The eluate was concentrated to give crystals, which were recrystallised repeatedly from ether to afford *needles*, m.p. 221—223° (106 mg, 53·3%), $\nu_{max.}$ 1640 (CO) and 926 cm^{-1} (OCH_2O), δ 7·76, 6·88, 6·84, and 6·74 (each 1H, s, aromatic), 6·04 (2H, s, OCH_2O), 4·76 (1H, d, *J* 12 Hz, 4b-H), 4·02 (6H, s, 2 × OMe), and 3·16 (3H, s, NMe), *m/e* 367 (M^+) (Found: C, 68·7; H, 5·75; N, 3·75. $C_{21}H_{21}NO_5$ requires C, 68·65; H, 5·75; N, 3·8%).

11,12-Dihydro-2,3-methylenedioxy-8,9-dimethoxy-5-methylbenzo[c]*phenanthridin-6*(5H)*-one* (X).—A solution of the enamide (VII) (0·6 g) in absolute ether (120 ml) was irradiated as in the case of (V) for 12 h. The solvent was evaporated off and the residue was chromatographed on alumina with benzene as eluant. The product was recrystallised from benzene–hexane to afford plates, m.p. 242—245° (0·3 g, 50%), $\nu_{max.}$ ($CHCl_3$) 1642 (NCO) and 1608 cm^{-1} (Ar), δ 7·87, 7·00, 6·95, and 6·78 (each 1H, s, aromatic), 5·95 (2H, s, OCH_2O), 3·98 (2H, s, OMe), 3·95 (3H, s, OMe), 3·71 (3H, s, NMe), and 2·71 (4H, s, $CH_2{\cdot}CH_2$) (Found: C, 70·25; H, 5·25; N, 3·35. $C_{21}H_{19}NO_5$ requires C, 69·05; H, 5·25; N, 3·85%).

8,9-Dimethoxy-5-methyl-2,3-methylenedioxybenzo[c]*phenanthridin-6*(5H)*-one* (*Oxynitidine*) (XVI).—(a) *Dehydrogenation of the lactam* (XIII). A solution of the lactam (XIII) (150 mg) in *p*-cymene (5 ml) was heated under reflux in a nitrogen stream in the presence of 30% palladium–charcoal (60 mg) for 10 h. After cooling, chloroform was added to dissolve the product. The catalyst was filtered off and the filtrate was evaporated to afford the product, which was recrystallised from ethanol to give *needles*, m.p. 290—291° (30 mg, 20%), $\nu_{max.}$ 1640 (CO) and 926 cm^{-1} (OCH_2O) (Found: C, 69·4; H, 4·65; N, 4·1. $C_{21}H_{17}NO_5$ requires C, 69·4; H, 4·7; N, 3·85%), identical with authentic oxynitidine obtained from nitidine chloride [1c] (mixed m.p. and i.r. data).

(b) *By dehydrogenation of the didehydrolactam* (X). A mixture of the didehydrolactam (X) (190 mg) and 30% palladium–charcoal (40 mg) in *p*-cymene (5 ml) was heated under reflux for 2 h in a nitrogen stream. After cooling, the mixture was treated with chloroform to dissolve the product. The catalyst was removed and the filtrate was concentrated under reduced pressure. The crystalline residue was repeatedly recrystallised from benzene to afford oxynitidine (XVI) (100 mg, 53%) as needles, m.p. 290—291°, identical with the product obtained in (a).

Dihydronitidine (XVII).—To a solution of oxynitidine (XVI) (20 mg) in absolute tetrahydrofuran (2 ml), lithium aluminium hydride (10 mg) was added. The mixture was heated under reflux in an argon stream for 3·5 h, then cooled and treated with dilute hydrochloric acid. The precipitate was collected, dried *in vacuo* at 120°, and extracted with chloroform. The extracts were evaporated to give *needles*, m.p. 217—221° (12 mg, 60%) (Found: C, 72·3; H, 5·5; N, 4·0. $C_{21}H_{19}NO_4$ requires C, 72·2; H, 5·5; N, 4·0%), identical with natural dihydronitidine.[1c]

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