Photocyclisation of Enamides. Part X.[1] Total Syntheses of the Yohimbine Skeleton: Demethoxycarbonyldihydrogambirtannine, Angustidine, Nauclétine, (±)-Angustoline, and Related Compounds [2]

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N-Acylation of the pyrido[3,4-*b*]indole derivative harmalan (I) occurred smoothly to afford the enamides (II) and (Va—c), which underwent ready photocyclisation to give the yohimbine-type compounds (III), angustidine (VIa), nauclétine (VIb), (VId), (VIIa, b, d, and e), and (±)-angustoline (VIc) (after reduction).

PREVIOUS papers [3,4] have described the photocyclisation of enamides derived from 1-alkyl-3,4-dihydroisoquinolines to afford various protoberberine alkaloids. We now report examples of the ready photocyclisation of *N*-aroyl-1,2,3,4-tetrahydro-1-methylenepyrido[3,4-*b*]indoles to yohimbine-type derivatives. The potential of this route to the yohimbine alkaloids is demonstrated by total syntheses of demethoxycarbonyldihydrogambirtannine (IV),[2a] angustidine [2a] (VIa), (±)-angustoline [2b] (VIc), and nauclétine (VIb).[2b]

Synthesis of Demethoxycarbonyldihydrogambirtannine (IV).[2a]—Harmalan (4,9-dihydro-1-methyl-3*H*-pyrido-[3,4-*b*]indole) (I) is known [5] to undergo ready *N*-acylation to afford *N*-acyl-1,2,3,4-tetrahydro-1-methylenepyrido-[3,4-*b*]indoles. Treatment of harmalan (I) with benzoyl chloride indeed afforded the *N*-benzoyl derivative (II) in 85% yield, which showed $\nu_{max.}$ 1 640 cm^{-1} (C=C–N–CO) and was unstable to acid and to ether. Irradiation of a methanolic solution of the enamide (II) with a low-

[1] Part IX, I. Ninomiya, T. Kiguchi, S. Yamauchi, and T. Naito, preceding paper.

[2] Preliminary communications (*a*) I. Ninomiya, H. Takasugi, and T. Naito, *J.C.S. Chem. Comm.*, 1973, 732; (*b*) I. Ninomiya, and T. Naito, *Heterocycles*, 1974, **2**, 607.

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

[4] I. Ninomiya, T. Naito, and H. Takasugi, *J.C.S. Perkin I*, 1975, 1791.

[5] H. Nishikawa, W. H. Perkin, jun., and R. Robertson, *J. Chem. Soc.*, 1924, 657.

pressure mercury lamp at room temperature for 8 h yielded the lactam (III) as the sole product in 37% yield, which exhibited i.r. absorption at 3 250 (NH) and 1 650 cm^{-1} for a six-membered lactam carbonyl group, and n.m.r. signals at δ 8.30 and 7.87—6.93 for H-14 and eight aromatic protons (but no olefinic proton signal). Reduction of the lactam (III) with lithium aluminium hydride followed by sodium borohydride afforded demethoxycarbonyldihydrogambirtannine [6] (IV).

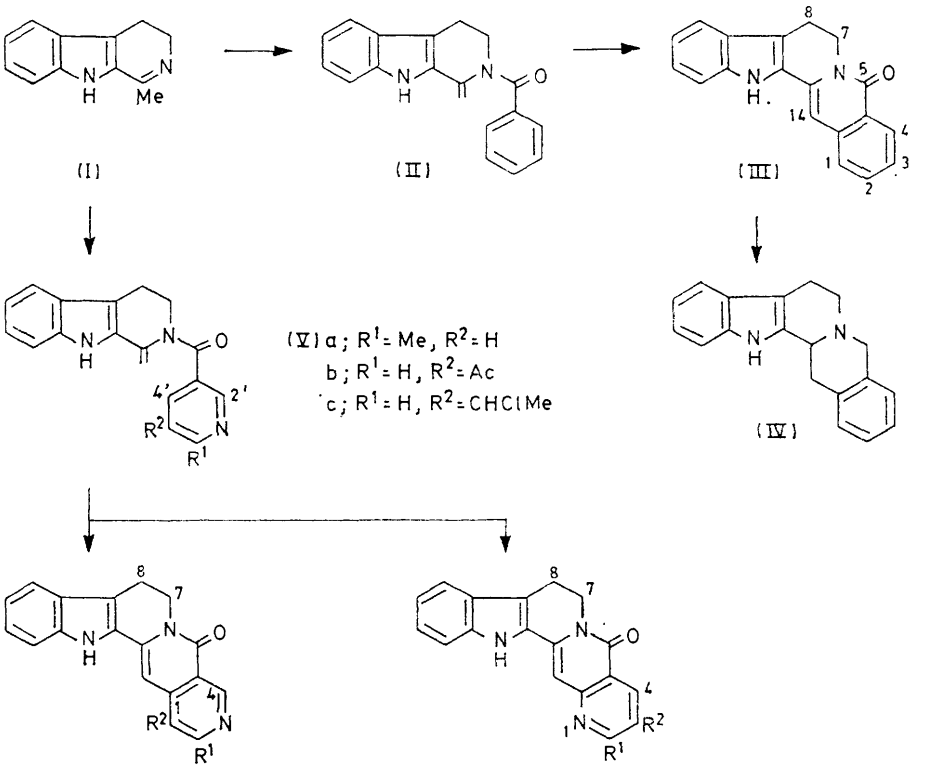
Total Syntheses of Angustidine [2a] (VIa), *Nauclétine* [2b] (VIb), *and* (±)-*Angustoline* [2b] (VIc).—In 1973, Cheung and his co-workers isolated [7] three new Corynanthé alkaloids, angustoline (VIc), angustine (VIe), and angustidine (VIa) from *Strychnos angustiflora* Benth., a medicinal plant indigenous to South China. By applying enamide photocyclisation, we have completed syntheses of angustidine (VIa) and angustoline (VIc).

The enamides (Va and b) were prepared by reactions of harmalan (I) with 6-methyl- and 5-acetyl-nicotinoyl chloride, respectively (the latter was obtained by treatment of sodium 5-acetylnicotinate with oxalyl chloride). Irradiation of the enamides (Va and b) afforded two types of the photocyclisation products (VIa and b) and (VIIa and b), respectively, which were separated by chromatography on alumina. The structures were established from spectral data, especially the n.m.r. signals of the two aromatic protons on the pyridine ring. The photoproduct (VIa) was identical with angustidine (m.p.s and i.r. and n.m.r. spectra).

Reduction of the photoproducts (VIb) and (VIIb) with sodium borohydride afforded the corresponding alcohols (VIc) and (VIIc), respectively; the former (VIc) was identical with natural angustoline in i.r., n.m.r., and mass spectra.

Since angustoline (VIc) had been converted [7a] into angustine [8] (VIe) and dihydroangustine [9] (VIf), the above synthesis completed formal syntheses of all three alkaloids.

Photocyclisation of the enamide (Vc), obtained from harmalan (I) and 5-(1-chloroethyl)nicotinoyl chloride,



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[7] (*a*) T. Y. Au, H. T. Cheung, and S. Sternhell, *J.C.S. Perkin I*, 1973, 13; (*b*) J. D. Phillipson, S. R. Hemingway, N. G. Bisset, P. J. Houghton, and E. J. Shellard, *Phytochemistry*, 1974, **13**, 973.

[8] T. Kametani, M. Takeshita, M. Ihara, and K. Fukumoto, *Heterocycles*, 1975, **3**, 627.

[9] Synthesised independently by two groups: R. T. Brown, A. A. Charalambides, and H. T. Cheung, *Tetrahedron Letters*, 1973, 4837; A. Shafiee and E. Winterfeldt, *Chem. Ber.*, 1974, **107**, 966; *Synthesis*, 1974, 185.

afforded three photocyclisation products (VId), (VIId), and (VIIe), which were separated by chromatography on alumina. Compound (VId) is (±)-angustoline methyl ether. These three photoproducts appear to be formed either by hydrogenolysis or by substitution of the chloride by the solvent during irradiation.

Recently, French chemists [10] have isolated two alkaloids, naucléfine and nauclétine, of which the latter has the same structure as the photocyclisation product (VIb).

EXPERIMENTAL

^{1}H N.m.r. spectra were measured with a Varian A 60D instrument for solutions in deuteriochloroform unless otherwise stated (tetramethylsilane as internal reference). M.p.s were determined with a Kofler-type hot-stage apparatus. The photochemical reactions were carried out as described in Part I.[11]

2-*Benzoyl*-2,3,4,9-*tetrahydro*-1-*methylene*-1H-*pyrido*[3,4-b]-*indole* (II).—To a solution of harmalan (I) (1.2 g) and triethylamine (800 mg) in anhydrous benzene (60 ml), benzoyl chloride (920 mg) was added dropwise with stirring. After refluxing for 2 h, the mixture was cooled and filtered to remove triethylamine hydrochloride. Evaporation left a residue, which was chromatographed on alumina with chloroform as eluant to give the enamide (II), as a yellow oil (1.6 g, 85%), $\nu_{max.}$ ($CHCl_3$) 3 500 (NH) and 1 640 (CO) cm^{-1}, which was unstable to moisture and was therefore used without purification.

8,13-*Dihydrobenzo*[g]*indolo*[2,3-a]*quinolizin*-5(7H)-*one* (III).—A methanolic solution (0.03M) of the enamide (II) (1.4 g) was irradiated for 8 h. Evaporation afforded a residue which was chromatographed on alumina. Elution with chloroform gave a solid which was recrystallised from ethanol to afford yellow needles (III) (265 mg, 37%), m.p. 299—300° (lit.,[12] 299°), $\nu_{max.}$ (Nujol) 3 250 (NH), 1 650 (CO), 1 620, 1 600, and 1 585 cm^{-1},δ [$(CD_3)_2SO$] 8.30 (1 H, d-like, *J* 7.5 Hz, 4-H), 7.87—6.93 (8 H, m, H-14 and aromatic H), 4.43 (2 H, t, *J* 6.5 Hz, 7-H_2), and 3.10 (2 H, t, *J* 6.5 Hz, 8-H_2).

Demethoxycarbonyldihydrogambirtannine (IV).—To a suspension of the lactam (III) (175 mg) in anhydrous tetrahydrofuran (60 ml), lithium aluminium hydride (120 mg) was added in small portions with cooling. The mixture was refluxed for 2 h, then cooled. The excess of hydride was decomposed with ethyl acetate. Evaporation left a residue, which was extracted with ether–tetrahydrofuran to give an unstable enamine. To a solution of the residue in methanol (30 ml), sodium borohydride (150 mg) was added and the mixture was refluxed for 2 h. After evaporation, water was added to decompose the complex, and the resulting aqueous layer was extracted with chloroform. The combined extracts were washed with water, dried, and evaporated to give a solid, which was recrystallised from methanol–water to give pale yellow prisms (IV) (87 mg, 52%), m.p. 191—193° (lit.,[6,12] 192—194°), identical (i.r. spectrum) with an authentic sample.[13]

Preparation of the Enamides (Va—c).—(a) 2,3,4,9-*Tetrahydro*-2-(6-*methylnicotinoyl*)-1-*methylene*-1H-*pyrido*-[3,4-b]*indole* (Va). By the procedure given for (II), acylation of (I) with 6-methylnicotinoyl chloride, prepared [14] from 5-ethyl-2-methylpyridine, in anhydrous benzene–chloroform, afforded an oil. Chromatography on alumina with chloroform as eluant afforded a yellow oil (Va) (46%) $\nu_{max.}$ ($CHCl_3$) 3 500 (NH) and 1 640 (CO) cm^{-1}, δ 9.75br (1 H, s, NH), 8.55 (1 H, d, *J* 2 Hz, 2′-H), 7.83 (1 H, dd, *J* 8 and 2 Hz, 4′-H), 7.70—6.95 (5 H, m, 5′- and aromatic H), 5.08 and 4.34 (2 H, each d, *J* 1.5 Hz, H_2C=C), 4.26 (2 H, t, *J* 6 Hz, 3-H_2), 3.01 (2 H, t, *J* 6 Hz, 4-H_2), and 2.57 (3 H, s, Me) (Found: M^+, 303.1374. $C_{19}H_{17}N_3O$ requires *M*, 303.1372).

(b) *The enamide* (Vb). To a suspension of sodium 5-acetylnicotinate (374 mg), prepared according to the procedure of Lukeš *et al.*,[15] in anhydrous benzene (3 ml), oxalyl chloride (384 mg) was added and the mixture was refluxed for 1 h, then evaporated. The residue was dissolved in anhydrous benzene (10 ml) and used for acylation of harmalan (I) (331 mg) to give the *enamide* (Vb) as a yellow solid (500 mg, 76%), $\nu_{max.}$ ($CHCl_3$), 3 520 (NH), 1 695 (Ac), and 1 640 cm^{-1} (C=CNCO), δ 9.92br (1 H, NH), 9.07 and 8.78 (2 H, each d, *J* 2 Hz, 6′- and 2′-H), 8.33 (1 H, t, *J* 2 Hz, 4′-H), 7.65—6.85 (4 H, m, aromatic H), 5.33 and 4.33 (2 H, each d, *J* 2 Hz, H_2C=C), 4.25 (2 H, t, *J* 5.5 Hz, 3-H_2), 3.02 (2 H, t, *J* 5.5 Hz, 4-H_2), and 2.53 (3 H, s, COMe) (Found: M^+, 331.1315. $C_{20}H_{17}N_3O_2$ requires *M*, 331.1321).

(c) *The enamide* (Vc). Reduction of ethyl 5-acetylnicotinate [15] with sodium borohydride, followed by hydrolysis of the ester, afforded 5-(1-hydroxyethyl)nicotinic acid (58%). Acylation of harmalan (I) (200 mg) with the acid chloride hydrochloride, prepared from the carboxylic acid in the presence of triethylamine (2 ml) in anhydrous chloroform–benzene (3 : 2; 50 ml), afforded the *enamide* (Vc) (500 mg) as an orange oil, $\nu_{max.}$ 3 525 (NH) and 1 640 (CO) cm^{-1}, δ 9.00br (1 H, s, NH), 8.66 and 8.61 (2 H, each d, *J* 2 Hz, 6′- and 2′-H), 7.96 (1 H, t, *J* 2 Hz, 4′-H), 7.75—6.90 (4 H, m, aromatic H), 5.12 and 4.39 (2 H, each d, *J* 2 Hz, H_2C=C), 5.09 (1 H, q, *J* 7 Hz, CHCl), 4.27 (2 H, t, *J* 6 Hz, 3-H_2), 3.03 (2 H, t, *J* 6 Hz, 4-H_2), and 1.82 (3 H, d, *J* 7 Hz, CH*Me*) [Found: M^+ − HCl 315.1366. $C_{20}H_{17}N_3O$ (*M* − HCl) requires 315.1372].

Irradiation of the Enamide (Va).—By the procedure given for (III), a 0.02M-solution of the enamide (Va) (400 mg) in methanol (60 ml) was irradiated for 8 h. The solvent was removed and the residue was chromatographed on alumina with chloroform as eluant to give a solid, which was recrystallised from chloroform to afford yellow crystals (VIa) (82 mg, 21%), m.p. >300° (lit.,[7a] 309—311°), identical with natural angustidine, $\nu_{max.}$ (Nujol) 3 350—3 150 (NH), 1 650 (CO), 1 620, 1 600, and 1 580 cm^{-1}, δ [100 MHz; $(CD_3)_2SO$] 11.73 (1 H, s, NH), 9.21 (1 H, s, 4-H), 7.70—7.03 (4 H, m, aromatic H), 7.30 (1 H, s, 1-H), 6.91 (1 H, s, 14-H), 4.37 (2 H, t, *J* 6.5 Hz, 7-H_2), 3.09 (2 H, t, *J* 6.5 Hz, 8-H_2), and 2.55 (3 H, s, Me) (Found: M^+, 301.1203. $C_{19}H_{15}N_3O$ requires *M*, 301.1215). Chromatography of the residue from the mother liquor on silica gel afforded 8,13-*dihydro*-2-*methylindolo*[2′,3′:3,4]*pyrido*[1,2-g][1,6]*naphthyridin*-5(7H)-*one* (VIIa) (52 mg, 13%), as yellow crystals, m.p. >300°, $\nu_{max.}$ (Nujol) 3 310 (NH), 1 645 (CO), 1 618, 1 595, and 1 580 cm^{-1}, δ [$(CD_3)_2SO$] 11.70br (1 H, NH), 8.38 (1 H, d, *J* 8 Hz, 4-H), 7.71—6.94 (6 H, m, H-14, H-3, and

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[14] P. L. A. Plattner, W. Keller, and A. Boller, *Helv. Chim. Acta*, 1954, **37**, 1379.
[15] R. Lukeš and P. Vaculík, *Chem. listy*, 1957, **51**, 1510.

aromatic H), 4.40 (2 H, t, *J* 6.5 Hz, 7-H_2), 3.12 (2 H, t, *J* 6.5 Hz, 8-H_2), and 2.60 (3 H, s, Me) (Found: M^+, 301.1207. $C_{19}H_{15}N_3O$ requires *M*, 301.1215).

Irradiation of the Enamide (Vb).—As in the case of (III), a methanolic solution (90 ml) of the enamide (Vb) (600 mg) was irradiated for 5 h. (Crystals appeared on the surface of the quartz vessel.) Evaporation yielded a residue which was triturated and recrystallised from chloroform–methanol to give pale yellow crystals, m.p. >300°, of 3-*acetyl*-8,13-*dihydroindolo*[2′,3′:3,4]*pyrido*[1,2-g][1,6]*naphthyridin*-5(7-H)-*one* (VIIb) (50 mg, 8%), $\nu_{max.}$ (Nujol) 3 300br (NH), 1 685 (Ac), 1 640 (NCO), 1 605, 1 590, and 745 cm^{-1} (Found: M^+, 329.1169. $C_{20}H_{15}N_3O_2$ requires *M*, 329.1164). Chromatography of the residue obtained from the mother liquor on alumina with chloroform–benzene (1 : 1) as eluant gave a solid, which was recrystallised from methanol–chloroform to yield pale yellow crystals, m.p. >300°, of 1-*acetyl*-8,13-*dihydroindolo*[2′,3′:3,4]*pyrido*[1,2-b][2,7]*naphthyridin*-5(7H)-*one* [10] (VIb) (180 mg, 30%), $\nu_{max.}$ (Nujol) 3 400—3 100 (NH), 1 670 (Ac), 1 645 (NCO), 1 590, 1 100, 830, 805, and 750 cm^{-1} (Found: M^+, 329.1163. $C_{20}H_{15}N_3O_2$ requires *M*, 329.1164).

Irradiation of the Enamide (Vc).—As in the case of (III), a methanolic solution (65 ml) of the enamide (Vc) (500 mg) was irradiated for 5.5 h. The solvent was evaporated off and the residue was chromatographed on alumina with chloroform–benzene (1 : 9) as eluant. The first fraction afforded the crystalline product, which was recrystallised from methanol–chloroform to afford pale yellow needles, m.p. >300°, of 3-*ethyl*-8,13-*dihydroindolo*[2′,3′:3,4]*pyrido*-[1,2-g][1,6]*naphthyridin*-5(7H)-*one* (VIId) (25 mg), $\nu_{max.}$ ($CHCl_3$) 3 300 (NH), 1 640 (CO), 1 595, 820, 740, and 730 cm^{-1}, δ [$(CD_3)_2SO$] 11.78br (1 H, s, NH), 8.85 (1 H, d, *J* 2 Hz, 4-H), 8.39 (1 H, d, *J* 2 Hz, 2-H), 4.43 (2 H, t, *J* 6.5 Hz, 7-H_2), 3.12 (2 H, t, *J* 6.5 Hz, 8-H_2), 2.78 (2 H, q, *J* 7.5 Hz, CH_2Me), and 1.28 (3 H, t, *J* 7.5 Hz, CH_2*Me*), *m/e* 315 (M^+), $\lambda_{max.}$ (EtOH) 217, 248, 267 (sh), 260, and 279 nm. The second fraction gave 8,13-*dihydro*-3-(1-*methoxyethyl*)*indolo*-[2′,3′:3,4]*pyrido*[1,2-g][1,6]*naphthyridin*-5(7H)-*one* (VIIe) (5 mg) as pale yellow crystals (from methanol–chloroform), m.p. 266—269°, $\nu_{max.}$ (Nujol) 3 300—3 060 (NH), 1 645 (CO), 1 620, 1 610, 1 105, 820, and 740 cm^{-1}, *m/e* 345 (M^+). The last fraction gave 8,13-*dihydro*-1-(1-*methoxyethyl*)*indolo*-[2′,3′:3,4]*pyrido*[1,2-b][2,7]*naphthyridin*-5(7H)-*one* (VId) (25 mg) as pale yellow crystals (from methanol–chloroform), m.p. 220—223°, $\nu_{max.}$ (Nujol) 3 300—3 050 (NH), 1 655 (CO), 1 620, 1 610, 1 110, and 740 cm^{-1}, δ [$(CD_3)_2SO$] 9.35 (1 H, s, 4-H), 8.70 (1 H, s, 2-H), 7.27 (1 H, s, 14-H), 4.93 (1 H, q, *J* 6 Hz, C*H*-OMe), 4.42 (2 H, t, *J* 6 Hz, 7-H_2), 3.13 (2 H, t, *J* 6 Hz, 8-H_2), and 1.58 (3 H, d, *J* 6 Hz, CH*Me*), *m/e* 345 (M^+), $\lambda_{max.}$ (EtOH) 218, 252, 290, 301, 376, and 396 nm.

(±)-*Angustoline* (VIc).—To a solution of the lactam (VIb) (35 mg) in methanol (50 ml), an excess of sodium borohydride was added and the mixture was stirred at room temperature for 1 h, then evaporated. Water was added and the yellow solids which separated were filtered off, washed with water, and dried. Recrystallisation from methanol–chloroform afforded pale yellow crystals (VIc) (28 mg, 80%), m.p. 292—294° (lit.,[7a] 310—314°), identical (n.m.r. and mass spectra) with natural angustoline, $\nu_{max.}$ (Nujol) 3 500—3 100 (OH and NH), 1 640 (CO), 1 605, 1 590, 805, and 745 cm^{-1}, δ [$(CD_3)_2SO$] 11.98br (1 H, s, NH), 9.45 (1 H, s, 4-H), 8.98 (1 H, s, 2-H), 7.27 (1 H, s, 14-H), 5.48br (1 H, OH), 5.40br (1 H, C*H*OH), 4.43 (2 H, t, *J* 6.5 Hz, 7-H_2), 3.13 (2 H, t, *J* 6.5 Hz, 8-H_2), and 1.55 (3 H, d, *J* 6 Hz, Me), *m/e* 331 (M^+) (Found: M^+, 331.1324. $C_{20}H_{17}N_3O_2$ requires *M*, 331.1321).

8,13-*Dihydro*-3-(1-*hydroxyethyl*)*indolo*[2′,3′:3,4]*pyrido*[1,2-g][1,6]*naphthyridin*-5(7H)-*one* (VIIc).—By the procedure given for (VIc), reduction of the lactam (VIIb) with sodium borohydride afforded a yellow solid, which was recrystallised from methanol to give the *alcohol* (VIIc) (80%) as pale yellow crystals, m.p. >300°, $\nu_{max.}$ (Nujol) 3 500—3 100 (OH and NH), 1 640 (CO), 1 605, 1 595, 840, 825, and 735 cm^{-1}, δ [$(CD_3)_2SO$] 11.73br (1 H, s, NH), 8.90 (1 H, d, *J* 2 Hz, 4-H), 8.50 (1 H, d, *J* 2 Hz, 2-H), 7.23 (1 H, s, 14-H), 5.55 (1 H, d-like, *J* 4 Hz, OH), 4.97 (1 H, m, C*H*OH), 4.45 (2 H, t, *J* 6.5 Hz, 7-H_2), 3.13 (2 H, t, *J* 6.5 Hz, 8-H_2), and 1.48 (3 H, d, *J* 6 Hz, Me) (Found: M^+, 331.1323. $C_{20}H_{17}N_3O_2$ requires *M*, 331.1321).

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