Synthesis of the Indolo[2',3':3,4]pyrido[1,2-*b*][2,7]naphthyridinone Alkaloid Nauclefine and its Ring-E Isomers

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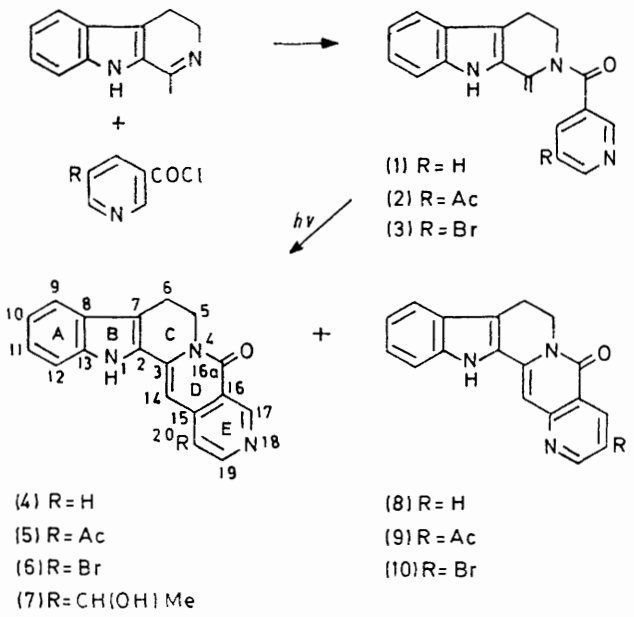
Nauclefine has been reported to be the only product from the photocyclisation of the enamide derived from harmalan and nicotinoyl chloride. Re-investigation has shown, however, that two compounds are formed: the alkaloid and an isomer in which cyclisation to the 2-position of the pyridyl unit has occurred. These components have been separated and the remaining ring-E isomers have been synthesized. ^{1}H and ^{13}C n.m.r. data for these structures are analysed.

THE alkaloid nauclefine (parvine †) (4) has been synthesised by the route outline in the Scheme.[1,2] However,



SCHEME

because of the two possible modes of photocyclisation of the enamide (1)[3] it was surprising that nauclefine appeared to be the sole product of this reaction. When the photolysis was repeated, t.l.c. (alumina) showed only one spot, identical in behaviour with the natural product (R_F 0.75 in acetone; 0.62 in methanol), and a similar correlation of mass, i.r., and u.v. spectra was apparent. The ^{1}H n.m.r. spectrum had been recorded previously for a recrystallised sample of the photolysis product,[2] but this time when the spectrum of the crude material was determined, the presence of a minor component (10—12%) was revealed. This conclusion was supported by ^{13}C n.m.r. data (see later).

The isomers were separated by column chromatography with dichloromethane–methanol mixtures (which also allows the recognition of two components on t.l.c.), affording pure nauclefine and isonauclefine (8). ^{1}H N.m.r. assignments for ring E in each of the two compounds are summarized in Table 1. Chemical shifts and coupling constants for solutions in $(CD_3)_2SO$ agree well with values calculated for model systems,[4] but in trifluoroacetic acid solution the signals for H-17 and -19 in nauclefine appear as a doublet and a triplet, respectively.

This effect has been noted previously in isoquinolines [5] and is presumably due to *N*-protonation. The signals of isonauclefine in trifluoroacetic acid solution do not show this increased multiplicity; interestingly, nauclefine readily forms a methiodide whereas its isomer does not. The H-17 resonance of nauclefine is only slightly changed in trifluoroacetic acid solution, with respect to its position in $(CD_3)_2SO$ (+0.24 p.p.m.), but the H-17 signal in isonauclefine undergoes a considerable downfield shift (+0.72 p.p.m.) and the H-19 resonance is actually moved upfield (−0.12 p.p.m.). These results suggest that quaternization of the ring-E nitrogen atom in isonauclefine is not favoured, possibly because of steric interaction with the *peri* H-14, and thus in trifluoroacetic acid solution protonation of the oxygen atom of the amide carbonyl group may occur preferentially.

Au *et al.*[6] note that angustoline is a strong base which is protonated even by acetic acid. For example, dropwise addition of acetic acid to a methanolic solution of the alkaloid causes a progressive, and ultimately complete, shift of the longest wavelength absorption band in the electronic spectrum from 395 to 439 nm. These workers propose that the conjugate acid, formed by protonation of the ring-E nitrogen atom, is stabilized through resonance with the indolic nitrogen atom. Such stabilization is possible with both the similarly formed conjugate acids of nauclefine and isonauclefine but, significantly, whereas the electronic spectrum of the former is slowly changed by dropwise addition of acetic acid ($\lambda_{max.}$ 391 to 448 nm) that of isonauclefine is not. Only in 75% acetic acid in methanol does an absorption band start to appear at 445 nm, and even in glacial acetic acid this band does not replace the absorption maxima of the free base at 362 and 380 nm,‡ and

† The use of this name should be discontinued since Pousset's study [1] has precedence over ours.[2]

‡ The electronic spectrum of bromoisonauclefine is not affected by the addition of acetic acid.

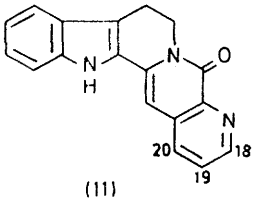
[1] F. Hotellier, P. Delareau, and J. L. Pousset, *Phytochemistry*, 1975, **14**, 1407.
[2] M. Sainsbury and B. Webb, *Phytochemistry*, 1975, **14**, 2691.
[3] (*a*) I. Ninomiya, H. Takasugi, and T. Naito, *J.C.S. Chem. Comm.*, 1973, 732; (*b*) I. Ninomiya and T. Naito, *Heterocycles*, 1974, **2**, 607.
[4] (*a*) S. Castellano, C. Sun, and R. Kostelnik, *J. Chem. Phys.*, 1967, **46**, 327; (*b*) T. Tokuhiro, N. K. Wilson, and G. Fraenkel, *J. Amer. Chem. Soc.*, 1968, **90**, 3622.
[5] D. G. Lugton, Ph.D. Thesis, Bath, 1969.
[6] T. Y. Au, H. T. Cheung, and S. Sternhell, *J.C.S. Perkin I*, 1973, 13.

extinction coefficient measurements indicate that *ca.* 70% of the unprotonated form is present in this solvent.

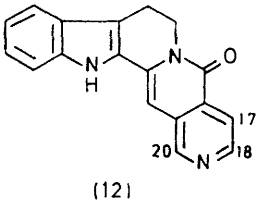
Cyclisation involving the γ-carbon atom of the pyridyl group and the exocyclic methylene group in the enamide precursor (1) is favoured electronically, but Ninomiya [3a] noted in the synthesis of angustoline that the enamide (2), in which the pyridine unit bears a relatively bulky 3-substituent, affords the isomers (5) and (9) in a molar ratio of 4 : 1.

In an attempt to increase the yield of isonauclefine the bromoenamide (3) was irradiated; it was hoped that after separation of the products the bromo-substituent in (10) might be removed by hydrogenolysis. However, although the isomers (6) and (10) were obtained in a molar ratio of 2.4 : 1 and were separated by column chromatography, all attempts failed to remove the bromine atom in either.

In order to assist in the interpretation of the ^1H and ^{13}C n.m.r. spectra of nauclefine and isonauclefine, the isomers (11) and (12) were prepared, by photocyclisation

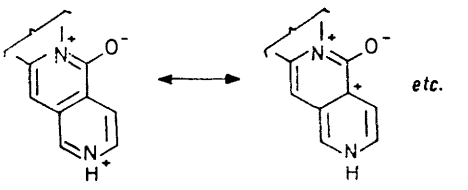


(11)



(12)

of the enamides derived from harmalan with picolinoyl and isonicotinoyl chloride, respectively. The electronic absorption spectra of (11) and (12) are little changed by the addition of acetic acid. Here, however, the adverse resonance effects implicit in the *N*-protonated forms might be expected to destabilize them; see, for example, part structure (13). In line with this conclusion, (11) does not form a methiodide even under forcing conditions, but perversely the 19-aza-isomer (12) is readily converted into its methiodide salt. In the first case, however, the

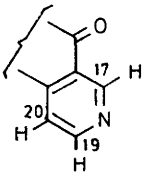


(13)

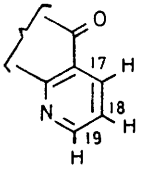
carbonyl group at C-16a imposes an additional steric constraint to quaternary salt formation.

TABLE 1

Chemical shifts (δ values; MeSi standard) and coupling constants (*J*/Hz) for ring-E protons of nauclefine (A) and isonauclefine (B) in $(CD_3)_2SO$ and in $CF_3{\cdot}CO_2H$



(A)



(B)

	(A)			(B)	
	$(CD_3)_2SO$	$CF_3{\cdot}CO_2H$		$(CD_3)_2SO$	$CF_3{\cdot}CO_2H$
H-17	9.32br (s)	9.56 (d, *J* 6)	H-17	8.54 (dd, $J_{17.18}$ 8, $J_{17.19}$ 2)	9.26 (d, *J* 6)
H-19	8.66br (d)	8.36 (t, *J* 6)	H-18	*ca.* 7.4	7.70 (t, *J* 6)
H-20	*ca.* 7.6	7.83 (d, *J* 6)	H-19	8.90 (dd, $J_{18.19}$ 5, $J_{17.19}$ 2)	8.78 (d, *J* 6)

Provisional ^{13}C n.m.r. assignments for nauclefine and its ring-E isomers are summarized in Table 2. These allocations are based upon chemical shift values expected for specific types of carbon atom,[4b,7,8] and off-resonance ^1H decoupling studies.

TABLE 2

Provisional ^{13}C n.m.r. assignments (δ values; $MeSi_4$ standard) for nauclefine and its ring-E isomers

Carbon no.	Structures (4) †	(8) †	(11) ‡	(12) §
3	136.93	135.70	§	134.14
5	39.96	39.96	45.29	39.50
6	19.10	19.11	20.72	19.04
7	114.51	113.60	114.06	113.02
8	127.38	127.64	127.38	127.77
9	119.71	119.32	120.49	119.19
10	124.26	123.94	123.42	123.74
11	119.51	119.52	121.73	119.58
12	111.78	111.72	110.91	111.65
13	138.36	138.17	138.16	138.10
14	96.83	100.28	§	96.12
15	121.35	152.79	126.37	128.61
16	125.23	120.10	141.87	130.82
16a	160.85	161.50	§	160.20
17	150.77	135.50		125.30
18		121.01	147.5	145.25
19	150.32	154.81	131.21	
20	118.73		143.30	149.22

† $(CD_3)_2SO$ as solvent. ‡ $CF_3{\cdot}CO_2H$ as solvent. § Masked by solvent absorption.

[7] H. L. Retcofsky and R. A. Friedel, *J. Phys. Chem.*, 1968, **72**, 290.

[8] E. Wenkert, J. S. Bindra, Ching-Jer Chang, D. W. Cochran, and F. M. Schell, *Accounts Chem. Res.*, 1974, **7**, 46.

EXPERIMENTAL

U.v. spectra were recorded for solutions in methanol; i.r spectral data refer to Nujol mulls; ^{1}H n.m.r. spectra were recorded at 100 MHz with tetramethylsilane (TMS) as internal standard. TMS was also used as internal reference for ^{13}C n.m.r. spectra. Column chromatography was conducted with Merck neutral grade alumina.

Nauclefine (4) *and Isonauclefine* (8).—The enamide (1) (400 mg), prepared from nicotinoyl chloride and harmalan,[1,2] in methanol (800 cm^3), was irradiated in a Hanovia reactor with ' soft ' u.v. light. After 20 h the solvent was removed and the brown amorphous residue subjected to spectroscopic and chromatographic analysis; δ[$(CD_3)_2SO$] 9.32br (s) and 8.9 (q) (integral ratio 1 : 0.09), and 8.66br (s) and 8.54 (q) (integral ratio 1 : 0.09). Column chromatography and elution with 3% methanol in dichloromethane gave *isonauclefine* {8,13-*dihydroindolo*[2′,3′:3,4]*pyrido*[1,2-g]-[1,6]*naphthyridin*-5(7H)-*one*} (8), m.p. >350 °C, *m/e* 287 (M^+, 100%), 286 (85), 272 (12), and 258 (13), $\lambda_{max.}$ 362 and 380 nm, $\nu_{max.}$ 3 240, 1 650, 1 606, and 1 593 cm^{-1}, δ[$(CD_3)_2SO$] 11.76 (1 H, s, NH), 8.90 (1 H, dd, *J* 5 and 2 Hz, 19-H), 8.54 (1 H, dd, *J* 8 and 2 Hz, 17-H), 7.7—7.0 (5 H, m), 4.4 (2 H, t, *J* 7 Hz, 5-H_2), and 3.12 (2 H, t, *J* 7 Hz, 6-H_2) (Found: C, 75.2; H, 4.5; N, 14.2. $C_{18}H_{13}N_3O$ requires C, 75.2; H, 4.6; N, 14.6%).

Elution with 5% methanol in dichloromethane afforded nauclefine, identical (m.p. and mixed m.p. 298—299 °C) with the natural alkaloid (lit.,[2] m.p. 293—294 °C); methiodide, m.p. 330 °C (lit.,[2] 330 °C), *m/e* 287 (M^+, 100%), 286 (80), 272 (12), and 258 (13%), $\lambda_{max.}$ 372 and 391 nm, $\nu_{max.}$ 3 180, 1 650, 1 615, and 1 597 cm^{-1} (Found: C, 75.2; H, 4.4; N, 14.3%).

2-(5-*Bromonicotinoyl*)-1,2,3,4-*tetrahydro*-1-*methylene*-β-*carboline* (3).—*Compound* (3), from harmalan and 5-bromonicotinoyl chloride, had m.p. 158 °C; $\nu_{max.}$ 3 330, 1 650, 1620, and 1 580 cm^{-1}, $\delta_H(CDCl_3)$ 8.93 (1 H, s, NH), 8.66 (1 H, dd, *J* 2.2 and 0.3 Hz), 8.51 (1 H, dd, *J* 2 and 0.3 Hz), 7.98 (1 H, dd, *J* 2.2 and 2 Hz), 5.03 (1 H, d, *J* 2.2 Hz), 4.32 (1 H, d, *J* 2.2 Hz), 4.2 (2 H, t, *J* 6 Hz), and 3.0 (2 H, t, *J* 6 Hz), δ_C [$(CD_3)_2SO$] 136.2 (C-3), 44.65 (C-5), 22.96 (C-6), 113.67 (C-7), 128.68 (C-8), 119.26 (C-9), 124.20 (C-10), 120.36 (C-11), 111.33 (C-12), 138.3 (C-13), 103.33 (C-14), 137.45 (C-15), 126.7 (C-16), 166.18 (C-16a), 151.75 (C-17), 146.81 (C-19), and 133.4 (C-20) (Found C, 58.6; H, 3.7; N, 11.2. $C_{18}H_{14}BrN_3O$ requires C, 58.7; H, 3.8; N, 11.4%).

20-*Bromonauclefine* (6) *and* 18-*Bromoisonauclefine* (10).—The enamide (3) (0.8 g) was irradiated in the usual way and the product chromatographed. Elution with dichloromethane gave 18-*bromoisonauclefine* (50 mg), m.p. >350 °C, *m/e* 367, 365 (M^+, 68%), 364 (40%), 257 (14), 215 (21), and 125 (100), $\lambda_{max.}$ 260, 360, and 380 nm, $\nu_{max.}$ 3 200, 1 640, 1 600, and 1 580 cm^{-1}, δ [$(CD_3)_2SO$] 11.3 (1 H, s, NH), 8.88 (1 H, d, *J* 2.5 Hz, 17-H), 8.58 (1 H, d, *J* 2.5 Hz, 20-H), 7.7—7.0 (4 H, m), 7.18 (1 H, s, 14-H), 4.4 (2 H, t, *J* 7 Hz, 5-H_2), and 3.1 (2 H, t, *J* 7 Hz, 6-H_2) (Found: C, 59.2; H, 3.5; N, 4.1. $C_{18}H_{12}BrN_3O$ requires C, 59.0; H, 3.3; N, 4.4%). With 1% methanol in dichloromethane, 20-*bromonauclefine* (6) 120 mg), m.p. >350°, was obtained, *m/e* 367, 365 (68%), 364 (40), 257 (14), 215 (21), and 125 (100), $\lambda_{max.}$ 240, 254, 295, 306, 373, and 403 nm, $\nu_{max.}$ 3 200br, 1 660, 1 635, and 1 600 cm^{-1}, δ [$(CD_3)_2SO$] 12.0 (1 H, s, NH), 9.23 (1 H, s, 17-H), 8.84 (1 H, s, 20-H), 7.7—7.0 (4 H, m), 7.12 (1 H, s, 14-H), 4.38 (2 H, t, *J* 7 Hz, 5-H_2), and 3.17 (2 H, t, *J* 7 Hz, 6-H_2) (Found: C, 59.3; H, 3.3; N, 4.1%).

Nauclefine Ring-E *Isomers* (11) *and* (12).—The *isomer* (11) {8,13-*dihydroindolo*[2′,3′:3,4]*pyrido*[2,1-g][1,7]*naphthyridin*-5(7H)-*one*} was obtained by irradiation of the enamide from picolinoyl chloride and harmalan (this enamide was not purified, but used directly); it had m.p. 250—251 °C (decomp.) (from methanol), *m/e* 287 (M^+, 100%), 286 (85), 272 (12), 258 (13); $\lambda_{max.}$ 354 and 375sh nm, $\nu_{max.}$ 3 210, 1 650, 1 620, 1 605, and 1 595 cm^{-1}, δ [$(CD_3)_2SO$] 11.76 (1 H, s, NH), 8.76br (1 H, s, 18-H), 8.08 (1 H, d, *J* 8 Hz, 20-H), 7.66 (1 H, m, 19-H), 7.6—7.0 (4 H, m), 7.04 (1 H, s, 14-H), 4.44 (2 H, t, *J* 7 Hz, 5-H_2), and 3.12 (2 H, t, *J* 7 Hz, 6-H_2) (Found: C, 75.2; H, 4.5; N, 14.3. $C_{18}H_{13}N_3O$ requires C, 75.2; H, 4.6; N, 14.6%). The *isomer* (12) {8,13-*dihydroindolo*-[2′,3′ : 3,4]*pyrido*-[1,2-b][2,6]*naphthyridin*-5(7H)-*one*} was prepared in similar manner from the enamide from isonicotinoyl chloride and harmalan {the *enamide* had m.p. 206 °C, δ [$(CD_3)_2SO$] 11.2 (1 H, s), 8.6 (2 H, dd, *J* 4.25 and 1.5 Hz), 7.7—6.9 (4 H, m), 7.32 (2 H, dd, *J* 4.25 and 1.5 Hz), 5.36br (1 H, s, *J* <1 Hz), 4.54br (1 H, s, *J* <1 Hz), 4.06 (2 H, t, *J* 6 Hz), 2.92 (2 H, t, *J* 6 Hz) (Found: C, 74.7; H, 5.55; N, 13.9. $C_{18}H_{15}N_3O$ requires C, 74.7; H, 5.2; N, 14.0%)}. After removal of the solvent used in the irradiation experiment, the crude isomer (12) was purified by elution (4% methanol in dichloromethane) through a silica column to afford yellow prisms, m.p. >350 °C, *m/e* 287 (M^+, 100%), 286 (63), 272 (12), and 258 (13); $\lambda_{max.}$ 353 and 390sh nm, δ [$(CD_3)_2SO$] 11.6 (1 H, s, NH), 9.02 (1 H, s, 20-H), 8.58 (1 H, d, *J* 5 Hz, 17-H), 8.02 (1 H, d, *J* 5 Hz, 18-H), 7.7—7.0 (4 H, m), 7.14 (1 H, s, 14-H), 4.4 (2 H, d, *J* 7 Hz, 5-H_2), and 3.08 (2 H, t, *J* 7 Hz, 6-H_2) (Found: C, 75.1; H, 4.6; N, 14.5%); methiodide, m.p. >350 °C, δ [$(CD_3)_2SO$] 11.98 (1 H, s, NH), 9.68 (1 H, s, 20-H), 8.67 (1 H, d, *J* 6 Hz, 17-H), 8.53 (1 H, d, *J* 6 Hz, 18-H), 7.7—7.0 (4 H, m), 7.16 (1 H, s, 14-H), 4.44 (2 H, t, *J* 6 Hz, 5-H_2), and 3.16 (2 H, t, *J* 6 Hz, 6-H_2).

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