Chemical and Photochemical Cyclisations of 1-Alkylidene-1,2,3,4-tetrahydro-2-nicotinoyl- and -isonicotinoyl-β-carbolines: A Regiospecific Synthesis of Naucléfine [1]

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1,2,3,4-Tetrahydro-1-methylene-2-nicotinoyl-β-carboline undergoes oxidative photocyclisation to give the indol-[2',3' : 3,4]pyrido[1,2-*b*][2,7]naphthyridinone alkaloid naucléfine and a ring-E isomer. A similar reaction is observed when the β-carboline is treated with acids, but on treatment with nicotinoyl or benzyl halides cyclisation takes place to give one isomer only. Analogous reactions occur with other 2-substituted 1-alkylidene-1,2,3,4-tetrahydro-β-carbolines. The mechanisms of these processes have been investigated and the ^{1}H n.m.r. spectra of both substrates and products have been analysed.

NAUCLÉFINE (1) is a minor alkaloid of certain plants of the genus *Nauclea* (Rubiaceae).[2a,b] The extracts of one such plant, *N. parva* Merrill, are active against P388 lymphocytic leukaemia in mice.†

The most efficient reported route to naucléfine involves the photocyclisation and subsequent oxidation of 1,2,3,4-tetrahydro-1-methylene-2-nicotinoyl-β-carboline (7) but it is marred by the concomitant formation of isonaucléfine (3), which is only separated from the required alkaloid by careful chromatography.[3]

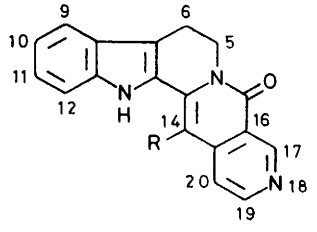
† The crude 95% ethanol extract of the bark shows test control = 138% (dose 100 mg kg^{-1}) against the experimental P388 lymphocytic leukaemia in mice (tests carried out through the courtesy of the National Cancer Institute, Bethesda, Maryland, U.S.A.).

[1] Preliminary report, M. Sainsbury and N. L. Uttley, *J.C.S. Chem. Comm.*, 1977, 319; M. Sainsbury, Chemical Society Perkin Division Symposium, London, March 10th, 1977.

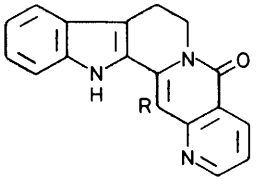
[2] (*a*) F. Hotellier, P. Delareau, and J. L. Pousset, *Phytochem.*, 1975, **14**, 1407; (*b*) M. Sainsbury and B. Webb, *ibid.*, p. 2691.

[3] M. Sainsbury and N. L. Uttley, *J.C.S. Perkin I*, 1976, 2416.

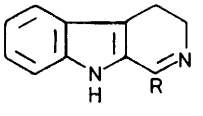
The enamide (7) is prepared from harmalan (5) and nicotinoyl chloride, but we have observed that when a two molar excess of the latter is employed a *single* bright yellow crystalline product is formed. This compound shows i.r. bands at $\nu_{max.}$ 1 665 and 1 640 cm^{-1}, indicating the presence of *two* amide functions, and ^1H n.m.r. signals (see Experimental section) correlate with a tryptamine sub-unit (substituted at position 2 of the heterocycle) and a nicotinoyl group. Additional resonances comprise a 1 H singlet at δ 6.62, a broad 1 H doublet at δ 5.72 coupled to a similar signal at δ 7.01, and a broad 2 H singlet at δ 4.8. On heating the sample to *ca.* 70 °C the last three signals become progressively more sharp. These observations, together with the results of mass spectrometric and elemental analysis, agree with a pentacyclic structure (14) for this product, which is formed presumably by way of the cationic intermediate (11). The temperature dependence of the ^1H n.m.r. spectrum of (14) is due to restricted rotation of the nicotinoyl unit, and it seems likely that the size of this substituent prevents the alternative mode of cyclisation. This conclusion receives support from the fact that when the enamide (7) is treated with perchloric acid, both naucléfine and isonaucléfine are formed, the latter predominating (molar ratio 6 : 1). Here it is assumed that the pyridinium salt (13) is involved and that the initial cyclisation products are rapidly oxidised; indeed, so far all our attempts to isolate such intermediates have failed (see below). Since in the absence of steric effects



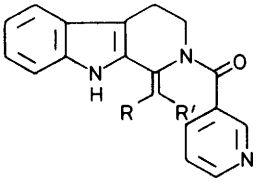
(1) R = H
(2) R = Me



(3) R = H
(4) R = Me

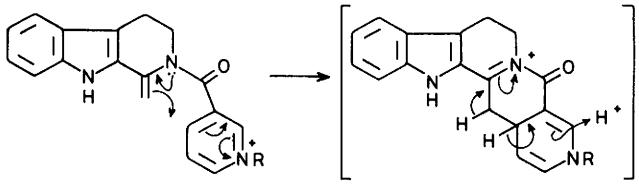


(5) R = Me
(6) R = Et

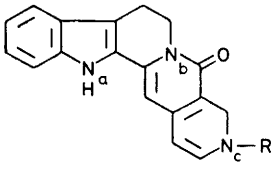


(7) $R^1 = R^2 = H$
(8) $R^1 = H, R^2 = Me$
(9) $R^1 = Me, R^2 = H$
(10) $R^1 = R^2 = Me$

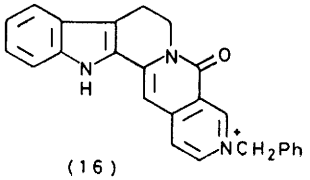
preference for nucleophilic attack at position 2 in pyridinium salts is often observed,[4] the predominance of isonaucléfine over naucléfine is unexceptional Interestingly, Hotellier *et al.*[2a] appear to have observed a chemical, as opposed to a photochemical, ring closure of the enamide (7), but in this case the only product isolated was naucléfine (5% yield). Here a large excess of nicotinoyl chloride was used in the synthesis of the



(11) R = nicotinoyl
(12) R = benzyl
(13) R = H



(14) R = nicotinoyl
(15) R = benzyl



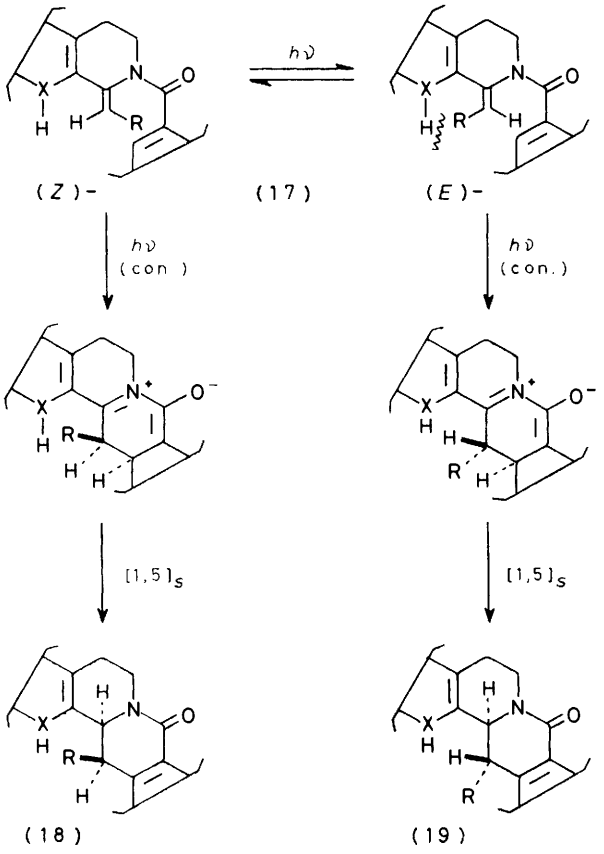
(16)

starting enamide, which was not isolated, but simply eluted in diethyl ether–methanol through a column of alumina. It is possible therefore that the French chemists also observed the same phenomena as ourselves, *i.e.* the participation of the pyridinium salt (11), but in our hands the cyclisation product (14) is unchanged by chromatography over alumina. Alternatively the alumina may function as a Lewis acid and quaternise the pyridine nitrogen atom of the enamide (7), thus stimulating a selective intramolecular nucleophilic attack, again the relative size of the N_b-substituent being important. In contradiction of this proposal, however, we have subjected the enamide to chromatography in the absence of light and failed to observe ring closure, but when light is not excluded some naucléfine *and*, to a lesser extent, some isonaucléfine are formed.

If it were possible to cleave the N_c-nicotinoyl group of the yellow product (14), then oxidation should effect a regiospecific synthesis of naucléfine; direct oxidation might prove even more advantageous since fission of the N_c-substituent would then occur spontaneously. We have been unable to achieve either of these two alternatives under conditions mild enough to avoid extensive decomposition (see Experimental section), but when the enamide (7) was treated with benzyl bromide the only product isolated was the quaternary salt (16); again we assume that the bulky substituent directs cyclisation exclusively to position 4 of the pyridine ring. The ready aerial oxidation of the obligatory dihydro-intermediate (15; or a tautomer) in this sequence is noteworthy, particularly in contrast with the relative

[4] K. Schofield, 'Heteroaromatic Nitrogen Compounds,' Butterworths, London, 1967, pp. 270 *et seq.*; see, however, E. M. Kosower, *J. Amer. Chem. Soc.*, 1956, **78**, 3497; W. von E. Doering and W. E. McEwen, *ibid.*, 1951, **73**, 2104.

stability of the yellow product (14) from the nicotinoyl chloride reaction. In the latter instance, however, the N_c-substituent forms part of an amide system perhaps less able than the amine group of (15) to stabilise a radical centre on an adjacent carbon atom. Conversion of the salt into naucléfine is effected by low pressure hydrogenation in ethanol over platinum followed by dehydrogenation–debenzylation by heating with palladium–charcoal; the yield from the enamide (7) is 65% (other methods, such as heating with sodium acetate in acetic acid–acetic anhydride,[1] are less productive).

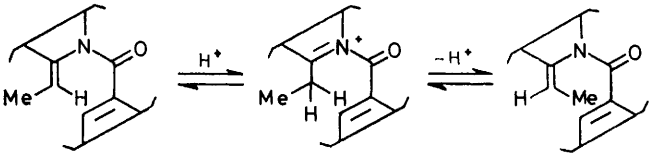


The photocyclisation of enamides of type (17) is an allowed conrotatory process, whereas the subsequent aromatisation of the initial product, if concerted, requires a 'dark' suprafacial 1,5-sigmatropic shift of hydrogen. In the isoquinoline series (X = C), when R = Me, it has been shown [5] that the *E*- and *Z*-isomers arising from the alternative geometries of the double bond are not equally efficient as substrates for photocyclisation. This arises because there is an unsatisfactory steric interaction between the methyl group of the *E*-isomer and the C-8 proton of the isoquinoline ring. Such a constraint does not arise in the other isomer and, by using degassed solvents, the 13-methylberbin-8-one corresponding to (18) is formed, with a *cis*-orientation of hydrogen atoms at C-13 and C-13a, as expected from the concerted stereospecific mechanism shown.

* A similar phenomenon was observed for the mixture of enamides (8) and (9).

From models we conclude that in the case of 2-aroyl-1-ethylidene-1,2,3,4-tetrahydro-β-carbolines (17) (where X is now a nitrogen atom and part of a five- rather than a six-membered ring) the adverse steric effects in the *E*-isomers are much reduced, a conclusion which draws support from the fact that whereas the *E*-isomers are not formed in the isoquinoline series a reaction between 1-ethyl-3,4-dihydro-β-carboline (6) and nicotinoyl chloride gave both *Z*- and *E*-enamides, (8) and (9), respectively. Since it is assumed that the *E*- and *Z*-isomers are photochemically interconverted,[6] the mixture was not separated but was irradiated directly. However, despite careful attention to reagent purity and to control of conditions, we were unable to isolate the expected products corresponding to (18) and (19). Instead only the more highly oxidised derivative (2) was obtained, together with the alternative structure (4) arising through cyclisation of the ethylidene function at the 2-position of the nicotinoyl substituent. Thus even had we been successful in isolating the required intermediates the alternative mode of cyclisation would have led to a complex mixture.

In order to reduce this problem, we next examined the enamides (20) and (21), prepared as a mixture by the action of isonicotinoyl chloride upon 1-ethyl-3,4-dihydro-β-carboline. The ^{1}H n.m.r. spectrum of the mixture at 0 and at 28 °C shows a 3 : 1 preference for the *Z*-form.* (In the *E*-isomer the hydrogen atom attached to the ethylidene function lies in the deshielding zone of the amide carbonyl group, and its resonance occurs at δ 6.2, whereas in the spectrum of the *Z*-isomer the corresponding signal is at δ 5.1.) On heating to 100 °C, however, the spectrum becomes that due to the *Z*-isomer alone, and we assume that there is sufficient water in the solvent [$(CD_3)_2SO$] to allow protonation of the enamide structure as shown with the production of the more stable form, such a change being only rapid at higher temperatures. Here, of course, only one mode of cyclisation is possible but once again we were unable to prevent overoxidation during irradiation of the enamide mixture and the only product isolated was (22).

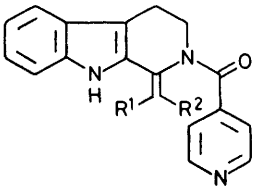


During the preparation of the enamides (20) and (21) we observed that use of an excess of the acid chloride gave a third product, $C_{25}H_{20}N_4O_2$. With a large excess of the acid chloride this became the major product. This result parallels the example leading to the yellow compound (14). However, the new compound is colourless and in the mass spectrometer loses 106 m.u. (corresponding to an isonicotinoyl radical) rather than 107 m.u. as for (14). The i.r. spectrum shows two

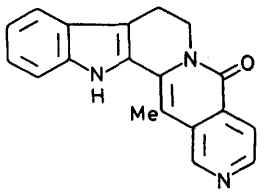
[5] W. E. Stewart and T. H. Siddall, *Chem. Rev.*, 1970, **70** (5), 517, and references cited therein.

[6] G. R. Lenz, *J. Org. Chem.*, 1976, **41**, 2201.

carbonyl bands at 1 665 and 1 695 cm^{-1} and the ^1H n.m.r. signals are commensurate with a tryptamine sub-unit and an isonicotinoyl group. From this and our previous

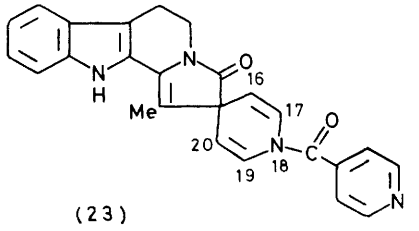


(20) R^1 = H, R^2 = Me
(21) R^1 = Me, R^2 = H



(22)

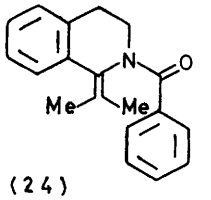
experience we expected this product to be the pentacyclic derivative (23). However, in the ^1H n.m.r. spectrum recorded at 28 °C the signals due to H-16 and H-20 (for numbering see formula) appear as a broad peak at δ *ca.* 4.8 coupled with a similarly broad resonance at δ *ca.* 7.1 due to H-17 and H-19. On heating to



(23)

100 °C these two sets of signals merge into two well defined 2 H doublets (J 8 Hz) at δ 4.8 (H-16 and -20) and 7.1 (H-17 and -19), but on cooling to −30 °C the signals due to H-16 and -20 become two pairs of doublets, δ 4.72 and 5.06 [$J_{17,16(19,20)}$ 8; $J_{16,20}$ 3 Hz] whereas those due to H-17 and -20 are broadened doublets at δ 6.84 and *ca.* 7.2. These observations are consistent with restricted rotation of the 18-isonicotinoyl group, and from the integral ratios of the resonances obtained at low temperature it appears that both rotational isomers are equally populated. The absence of colour in this product is a result of the spiro centre, which prevents the extensive conjugation possible in the analogous yellow compound (14). Similarly, mass spectrometric fission of the substituent at position 18 cannot now occur with concomitant hydrogen loss as was the case for the compound (14).

Surprisingly the two methyl groups of the isopropylidene enamide (24) are insufficiently large to inhibit photocyclisation to the corresponding berbin-8-one (25) and, by using the perdeuteriobenzoyl analogue,



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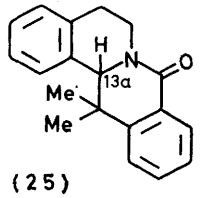
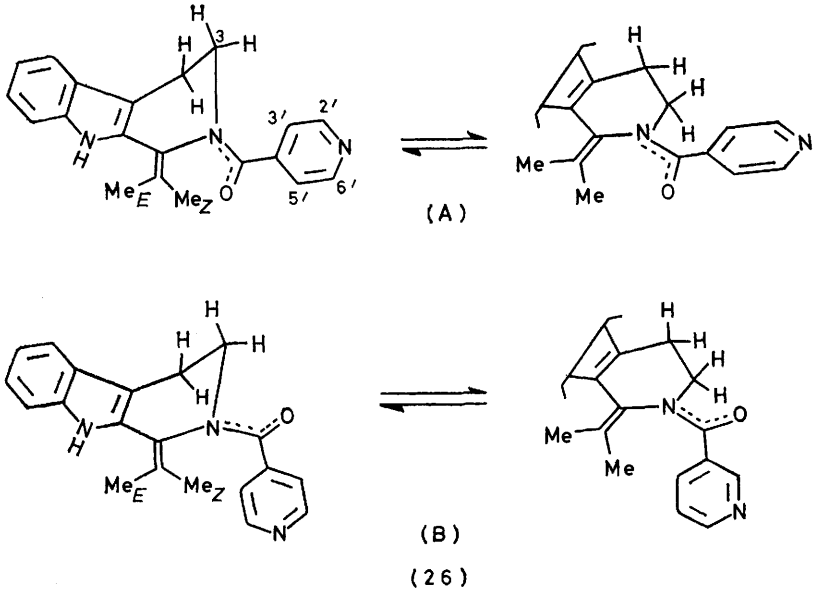


(25)

it was possible to provide direct evidence of a concerted [1,5] shift of hydrogen (deuterium) from the aroyl function to C-13a.[6] Here problems of overoxidation are avoided and so to advance our studies we next prepared the related β-carboline (26), which as a consequence of the partial double bond character of the amide group,[5] we expected to exist in the two 'conformations' (A) and (B). Such isomerisation does occur and at 28 °C the ^1H n.m.r. spectrum exhibits four separate methyl resonances. Two occur at δ 1.95 and 1.90 (integral ratio 2 : 1); these are typical of methyl groups



(A)

(B)

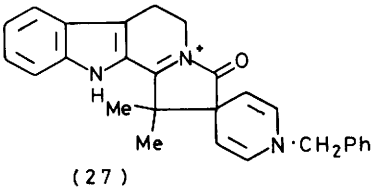
(26)

joined to a double bond and are assigned to Me_E of (A) and (B). The other signals occur at δ 1.46 and 2.26 (integral ratio 2 : 1) and emanate from Me_Z of (B) and (A), respectively, thus indicating a two-fold preference for the arrangement (B). This conclusion is supported by similar signal strength ratios for the resonances due

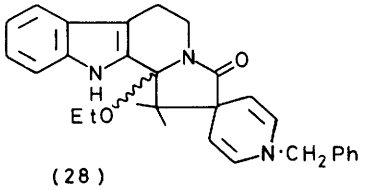
to H-2′, -3′, -5′, and -6′, as well as H-3. Here, however, rapid ring flipping interrelates the axial and equatorial positions as indicated in the formulae. At *ca.* 60 °C only two methyl resonances, of equal intensity, are observed, at δ 1.64 and 2.02; at this temperature the double-bond character of the amide is reduced and proton signals for a ' single ' compound are exhibited.

Although models suggest that sterically the enamide (26) is more disposed to cyclisation than its isoquinoline analogue (24), we find that irradiation causes fission of the N_b-isonicotinoyl substituent of the former, and only harmalan and isonicotinic acid are isolated. Here homolysis is aided by the 1,4-orientation of the pyridine nitrogen atom and the carbonyl group.

In the isomer where the N_b-substituent is a nicotinoyl rather than an isonicotinoyl group this undesired cleavage is less probable, but since two modes of photocyclisation would here be possible, we did not proceed further with this investigation. However, in order to induce a chemical cyclisation we treated the isopropylidene enamide (26) with benzyl bromide. The initial product was a gum but this when eluted in 1 : 99 methanol–diethyl ether through a column of alumina gave a colourless crystalline solid. Spectroscopic analysis indicated the pentacyclic structure (28), which arises from the anticipated iminium salt (27) by attack



(27)



(28)

of the solvent diethyl ether. Since there is equal opportunity for α- or β-approach of the solvent to the salt the pentacycle is formed as a racemic modification and thus the hydrogen atoms of the dihydropyridine ring, the $CH_2{\cdot}CH_2$ unit of the tetrahydrocarboline system, and the ethoxy and benzylic methylene groups are all geometrically non-equivalent.

This complexity is well illustrated in the ^{1}H n.m.r. spectrum (see Experimental section) except for the signals due to the ethoxy and benzylic methylene groups which, presumably owing to rapid rotation, are not differentiated.

In a model of the pentacycle constructed so that the five-membered ring containing the amide function (carbonyl frequency 1 690 cm^{-1}) is planar, or very nearly so, one of the C-14 methyl groups lies within the shielding zone of one of the dihydropyridine double bonds; the other occupies a more open environment. The ^{1}H n.m.r. signals of these methyl groups occur at δ 0.4 and 1.28, respectively.

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 Me_4Si as internal standard (also used as internal reference for ^{13}C n.m.r. spectra).

1-*Ethyl*-3,4-*dihydro*-β-*carboline* (6).—To tryptamine (2 g) in absolute ethanol (70 cm^3) was added propionic anhydride (5 cm^3). The flask was shaken at room temperature for 20 min and the solvent was removed under reduced pressure below 40 °C. The residual oil was partitioned between dichloromethane and water and the excess of propionic acid was removed by addition of sodium carbonate. The dichloromethane layer was separated, dried (Na_2SO_4), and evaporated, affording N_b-propanoyltryptamine as a yellow oil which slowly crystallised (2.3 g, 92%); $\nu_{max.}$ 3 480, 3 250, 3 080, 1 640, 1 590, and 740 cm^{-1}; δ ($CDCl_3$) 8.6 (1 H, s, indole NH), 7.7—7.0 (4 H, m), 6.95 (1 H, d, *J* 2 Hz, 2-H), 5.7 (1 H, s, NH), 3.56 (2 H, t, *J* 7 Hz), 2.93 (2 H, t, *J* 7 Hz), 2.08 (2 H, q, *J* 8 Hz), and 1.08 (3 H, t, *J* 8 Hz). Phosphorus pentaoxide (25 g) was added in portions over ¾ h to a boiling solution of the amide (2 g). The mixture was then heated under reflux for 1 h, and cooled to room temperature. The solution was decanted and the residual dark red solid washed with diethyl ether and added to crushed ice (500 g). After acidification with 2N-hydrochloric acid (20 cm^3), the aqueous solution was extracted again with ether and then made basic with sodium carbonate. The brown precipitate was collected and crystallised from dichloromethane to yield 1-ethyl-3,4-dihydro-β-carboline as a yellow solid (1.4 g, 78%), m.p. 168—170 °C (lit.,[7] 172—173°), $\nu_{max.}$ 3 200—2 800 (N–H), 1 630, 1 610, 1 550, and 750 cm^{-1}; δ ($CDCl_3$) 9.04 (1 H, s, NH), 7.7—7.1 (4 H, m, H-5—8), 3.92 (2 H, t, *J* 8 Hz, H-3), 2.86 (2 H, t, *J* 8 Hz, H-4), 2.7 (2 H, q, *J* 8 Hz), and 1.28 (3 H, t, *J* 8 Hz).

Naucléfine {8,13-*Dihydroindolo*[2′,3′:3,4]*pyrido*[2,1-b]-[2,7]*naphthyridin*-5(7H)-*one*} (1).—The enamide (7) (1.0 g) obtained from nicotinoyl chloride and harmalan was dissolved in dichloromethane (50 cm^3) and treated with benzyl bromide (0.44 cm^3). The solution was set aside in the absence of light for 4 days and then evaporated to give a dark red gum. This was chromatographed on silica; elution with 5 : 95 methanol–diethyl ether slowly afforded the quaternary bromide (16), obtained as dark orange prisms, m.p. >350 °C; $\lambda_{max.}$ 218, 320, and 450 nm; $\nu_{max.}$ 3 200, 1 655, and 1 610 cm^{-1}; δ [$(CD_3)_3SO$] 12.2 (1 H, s, NH), 9.7 (1 H, s, H-17), 8.76 (1 H, d, $J_{19,20}$ 6 Hz, H-19), 7.98 (1 H, d, $J_{19,20}$ 6 Hz, H-20), 7.7—7.0 (10 H, m, H-9, -10, -11, -12, -14, -23, -24, -25, -26, + -27), 5.84 (2 H, s, H-21), 4.44 (2 H, t, $J_{5,6}$ 7 Hz, H-5), and 3.2 (2 H, t, $J_{5,6}$ 7 Hz, H-6). This product (40 mg) was dissolved in absolute ethanol (500 cm^3) and hydrogenated over platinum oxide (100 mg) at 50 lb cm^{-2} during 6 h. After removal of solvent and catalyst the crude product was heated with 10% palladium–charcoal (30 mg) at 250 °C and 0.05 mmHg in a sublimation apparatus. Naucléfine (23 mg) was obtained as the sublimate [overall yield from the enamide (7) 65%] and was identical (m.p., mixed m.p., spectroscopy and t.l.c. in three solvent systems) with naturally occurring naucléfine.[2b]

[7] E. Späth and E. Lederer, *Ber.*, 1930, **63B**, 2102.

Naucléfine (1) *and Isonaucléfine* {8,13-*Dihydroindolo*-[2′,3′:3,4]*pyrido*[1,2-g][1,6]*naphthyridin*-5(7H)-*one*} (3).—The enamide (7) (200 mg) dissolved in chloroform (150 cm³) was heated under reflux with 60% perchloric acid (5 cm³) for 30 min. The mixture was then extracted with water (2 × 100 cm³) and the combined extracts were basified and re-extracted with chloroform to yield, after removal of the solvent, a brown gum. T.l.c. showed naucléfine and isonaucléfine to be present and column chromatography over alumina (elution with methanol–diethyl ether) afforded naucléfine (6 mg) and isonaucléfine (36 mg). Both were fully characterised and subjected to direct comparisons (m.p., mixed m.p., spectroscopy, and t.l.c.) with authentic samples.[2b]

17,18-*Dihydro*-18-*nicotinoylnaucléfine* (14).—Nicotinic acid (4.8 g, 3.26 × 10^{-2} mol) was heated under reflux in a dry nitrogen atmosphere with an excess of freshly distilled thionyl chloride for 3 h. On cooling, the mixture was co-evaporated three times with portions (50 cm³) of dry benzene. To the white solid that remained dry dichloromethane (100 cm³) and triethylamine (20 cm³) were added and the mixture was stirred under dry nitrogen for 1 h. 3,4-Dihydro-1-methyl-β-carboline (2.0 g, 1.09 × 10^{-2} mol) dissolved in dichloromethane (100 cm³) was then added, and the solution was heated under reflux for a further 2 h. After cooling the dichloromethane was removed under reduced pressure to yield a brown gum, which was chromatographed on a column of neutral grade alumina. Elution with methanol–diethyl ether gave 17,18-*dihydro*-18-*nicotinoylnaucléfine* (750 mg) as a bright yellow crystalline solid, m.p. 240 °C (darkens at 235 °C); $\lambda_{max.}$ 220, 267, 300sh, 315, 345, 356sh, 404, and 412 nm; $\nu_{max.}$ 3 170, 1 665, 1 640, 1 625, 1 615, and 1 595 cm^{-1}; *m/e* 394 (M^+, $C_{24}H_{18}N_4O_2$, 10%), 288 (82), 287 (100), 286 (100), 123 (70), and 106 (80); δ_H [$(CD_3)_2SO$] 11.6 (1 H, s, NH), 8.76 (2 H, m, H-23 + -25), 8.00 (1 H, dt, $J_{27.26}$ 8, $J_{27.25}$ 2, $J_{27.23}$ 2 Hz, H-27), 7.58 (1 H, dd, $J_{26.27}$ 8, $J_{26.25}$ 5 Hz, H-26), 7.6—7.1 (4 H, m, H-9, -10, -11, + -12), 7.0 (1 H, d, $J_{19.20}$ 8 Hz, H-19), 6.6 (1 H, s, H-14), 5.72 (1 H, d, $J_{20.19}$ 8 Hz, H-20), 4.8 (2 H, s, H-17), 4.32 (2 H, t, $J_{5.6}$ 7 Hz, H-5), and 3.07 (2 H, t, $J_{6.5}$ 7 Hz, H-6); δ_C [$(CD_3)_2SO$] 166.8 (s, C-21), 158.9 (s, C-16a), 151.4 (d, C-23), 148.6 (d, C-25), 138.1 (s, C-13), 136.9 (s, C-3), 135.8 (d, C-27), 132.4 (d, C-26), 130.0 (s, C-22), 127.6 (s, C-8), 125.2 (s, C-16), 123.8 (d, C-19), 123.6 (d, C-10), 119.6 (d, C-9), 119.4 (d, C-11), 113.1 (s, C-7), 112.2 (s, C-15), 111.78 (d, C-12), 106.06 (d, C-20), 97.4 (d, C-14), 40.1 (t, C-5), 36.7—42.3 (masked by solvent, C-17), and 19.0 (t, C-6) (Found: C, 73.0; H, 4.5; N, 14.0. $C_{24}H_{18}N_4O_2$ requires C, 73.1; H, 4.6; N, 14.2%). The *methiodide*, obtained by treatment with an excess of methyl iodide in acetone solution had m.p. >350 °C, δ [$(CD_3)_2SO$] 11.5 (1 H, s, NH), 9.3 (1 H, s, H-23), 9.14 (1 H, dd, $J_{25.26}$ 5, $J_{25.27}$ 2 Hz, H-25), 8.75 (1 H, dd, $J_{27.26}$ 8, $J_{27.25}$ 2 Hz), 8.26 (1 H, dd, $J_{26.27}$ 8, $J_{26.25}$ 5 Hz, H-26), 7.6—7.0 (4 H, m, H-9, -10, -11, + -12), 7.0 (1 H, d, $J_{19.20}$ 8 Hz, H-19), 6.62 (1 H, s, H-14), 5.72 (1 H, d, $J_{20.19}$ 8 Hz, H-20), 4.8 (2 H, s, H-17), 4.6 (3 H, s, H-28), 4.4 (2 H, t, $J_{5.6}$ 7 Hz, H-5), and 3.08 (2 H, t, $J_{6.5}$ 7 Hz, H-6) (Found: C, 55.8; H, 4.0; N, 10.5. $C_{25}H_{21}IN_4O_2$ requires C, 56.0; H, 3.95; N, 10.45%).

Attempted Degradation of 17,18-*Dihydro*-18-*nicotinoylnaucléfine* (14) *to Naucléfine* (1).—The following conditions were employed, all without success: (i) hydrolysis with dilute (2%) and concentrated (25%) sodium hydroxide in water or aqueous methanol; (ii) hydrolysis with dilute (2%) and concentrated (20%) hydrochloric acid in water or aqueous methanol; (iii) heating with (*a*) palladium–carbon, (*b*) iodine and sodium acetate in ethanol, or (*c*) dichlorodicyanobenzoquinone in various solvents; (iv) extensive u.v. irradiation in methanol.

14-*Methylnaucléfine* (2) *and* 14-*Methylisonaucléfine* {8,13-*Dihydro*-14-*methylindolo*[2′,3′:3,4]*pyrido*[1,2-g][1,6]*naphthyridin*-5(7H)-*one*} (4).—Nicotinic acid (1.0 g, 8.16 × 10^{-3} mol) was heated under reflux in dry nitrogen with an excess of freshly distilled thionyl chloride for 3 h. After cooling, the mixture was co-evaporated three times with portions (30 cm³) of dry benzene. The white solid residue was suspended in dichloromethane (25 cm³) containing triethylamine (5 cm³) and stirred under dry nitrogen for 1 h. 1-Ethyl-3,4-dihydro-β-carboline (0.5 g, 2.72 × 10^{-3} mol) dissolved in dichloromethane (25 cm³) was added, and the solution was heated under reflux for 2 h. After cooling, the solution was washed with water (2 × 100 cm^{-3}), dried (Na_2SO_4), and evaporated to yield a brown oil, which was dissolved in methanol and irradiated for 24 h with a medium-pressure Hanovia lamp. The methanol was then removed and the crude product chromatographed on Merck neutral grade alumina (elution with 3 : 97 methanol–dichloromethane) to afford 14-*methylisonaucléfine* (4) as a yellow solid (30 mg), m.p. 280 °C; $\lambda_{max.}$ 220, 254, 357, and 380 nm; $\nu_{max.}$ 3 420, 1 635, and 1 594 cm^{-1}; δ [$(CD_3)_2SO$] * 8.92 (1 H, dd, $J_{18.19}$ 4, $J_{17.19}$ 1 Hz, 19-H), 8.64 (1 H, dd, $J_{17.18}$ 8, $J_{17.19}$ 1.0 Hz, 17-H), 7.36 (1 H, dd, $J_{19.18}$ 8, $J_{18,17}$ 4 Hz, 18-H), 7.6—7.0 (4 H, m, H-9, -10, -11, + -12), 4.48 (2 H, t, $J_{5.6}$ 7 Hz, 5-H), 3.12 (2 H, t, $J_{5.6}$ 7 Hz, 6-H), and 2.92 (3 H, s, 14-CH_3) (Found: C, 75.6; H, 5.0; N, 14.0. $C_{19}H_{15}N_3O$ requires C, 75.7; H, 5.0; N, 13.95%). Elution with 5 : 95 methanol–dichloromethane gave 14-*methylnaucléfine* (2) as a yellow crystalline solid (70 mg), m.p. 269 °C; $\lambda_{max.}$ 220, 252, 380, and 392 nm; $\nu_{max.}$ 3 425, 1 645, and 1 600 cm^{-1}; δ [$(CD_3)_2SO$] 9.54 (1 H, s, 17-H), 8.7 (1 H, d, $J_{19.20}$ 6 Hz, 19-H), 7.53 (1 H, d, $J_{19.20}$ 6 Hz, 20-H), 7.6—7.0 (4 H, m, H-9, -10, -11, + -12), 4.44 (2 H, t, $J_{5,6}$ 7 Hz, 5-H), 3.1 (2 H, t, $J_{5.6}$ 7 Hz, 6-H), and 2.7 (3 H, s, 14-CH_3) (Found: C, 75.8; H, 5.1; N, 14.0%).

(E)- *and* (Z)-1-*Ethylidene*-3,4-*dihydro*-2-*isonicotinoyl*-β-*carbolines* (20) *and* (21).—The 1-ethylidene-3,4-dihydro-β-carbolines were prepared by the usual procedure from 1-ethyl-3,4-dihydro-β-carboline (1.0 g) and isonicotinic acid (0.7 g). Chromatography on silica and elution with diethyl ether yielded a mixture of *E*- (25%) and *Z*- (75%) isomers, $\lambda_{max.}$ 225, 250, and 315 nm; $\nu_{max.}$ 3 400, 1 630, 1 610, 1 595, 1 570, and 740 cm^{-1}; δ_H (*Z*-isomer) [$(CD_3)_2CO$ at 0 °C] 11.1 (1 H, s, NH), 8.74 (1/3 H, d, *J* 5 Hz, H-2′ + -6′), 8.56 (5/3 H, d, *J* 5 Hz, H-2′ + -6′), 7.6—7.0 (4 H, m, H-5, -6, -7, + -8), 7.44 (1/3 H, d, *J* 5 Hz, H-3′ + -5′), 7.32 (5/3 H, d, *J* 5 Hz, H-3′ + -5′), 5.7 (1 H, m, ½H-5a + ½H-5e), 5.1 (1 H, q, *J* 8 Hz, =C*H*Me), 2.7—3.3 (3 H, m, ½H-3a, ½H-3e, + H_2-4) and 1.3 (3 H, d, *J* 8 Hz, =CH*Me*), δ_H (*E*-isomer) [$(CD_3)_2CO$ at 0 °C] 11.1 (1 H, s, NH), 8.56 (2 H, d, *J* 5 Hz, H-2′ + -6′), 7.6—7.0 (4 H, m, H-5—8), 7.32 (2 H, d, *J* 5 Hz, H-3′ + -5′), 6.2 (1 H, q, *J* 8 Hz, =C*H*Me), 3.8 (1 H, m, ½H-3a + ½H-3e), 2.7—3.2 (3 H, m, ½H-3a, ½H-3e, + H_2-4), and 1.88 (3 H, d, *J* 8 Hz, =CH*Me*).

8,13-*Dihydro*-14-*methylindolo*[2′,3′:3,4]*pyrido*[1,2-b][2,6]-*naphthyridin*-5(7H)-*one* (22).—The enamides (20) and (21) in degassed, dried methanol, were irradiated. After removal of the solvent the crude product was eluted (5 : 95 methanol–dichloromethane) through a neutral alumina

* The numbering system follows that adopted for naucléfine (1).

column to afford yellow *prisms*, m.p. >350 °C; *m/e* 303 (M^+, 100%), 301 (35), 288 (30), and 286 (38); $\lambda_{max.}$ 230, 245sh, 310, and 350 nm; $\nu_{max.}$ 3 280, 1 640, 1 630, and 740 cm^{-1}; δ [$(CD_3)_2SO$ at 28 °C] * 11.1 (1 H, s, NH), 9.3 (1 H, s, H-20), 8.66 (1 H, d, $J_{17,18}$ 5 Hz, H-17), 8.07 (1 H, d, $J_{18,17}$ 5 Hz, H-18), 7.7—7.0 (4 H, m, H-9, -10, -11, + -12), 4.33 (2 H, t, $J_{5,6}$ 6 Hz, H-5), 3.06 (2 H, t, $J_{6,5}$ 6 Hz, H-6), and 2.78 (3 H, s, 14-CH_3) (Found: C, 75.7; H, 4.9; N, 13.9. $C_{19}H_{15}N_3O$ requires C, 75.7; H, 5.0; N, 13.95%).

6,11-*Dihydro*-1′-*isonicotinoyl*-1-*methyl*-5H-*indolizino*-[8,7-b]*indole*-2(3H)-*spiro*-4′(1′H)-*pyridin*-3-*one* (23).—Isonicotinic acid (4.8 g, 3.26 × 10^{-2} mol) was heated under reflux with an excess of thionyl chloride for 3 h. After cooling, the mixture was co-evaporated to dryness three times with portions (50 cm^3) of benzene and the crystalline residue was treated with triethylamine (20 cm^3) in anhydrous dichloromethane (100 cm^3). After stirring under nitrogen for 1 h, this mixture was heated with 1-ethyl-3,4-dihydro-β-carboline (2.0 g, 1.09 × 10^{-2} mol) in dichloromethane (100 cm^3) under reflux for a further 2 h. The solvent was then removed and the residue washed with water (2 × 200 cm^3), dissolved in diethyl ether–methanol, and chromatographed on a column of alumina. Elution with 3 : 97 methanol–diethyl ether gave (23) as *cubes* (1.6 g, 10%), m.p. >350 °C, $\lambda_{max.}$ 208, 230, 322, and 345 nm; $\nu_{max.}$ 3 480, 3 180, 1 695, 1 675, 1 665, 1 624, 950, 760, and 750 cm^{-1}; *m/e* 408 (M^+) and 302 (100%); δ [$(CD_3)_2CO$; −30 °C] 11.08 (1 H, s, NH), 8.9 (2 H, d, *J* 5 Hz, H-2″ + -6″), 7.6—7.4 (4 H, m, H-3″, -5″, -9, + -12), 7.6 [1 H, d, *J* 8 Hz, H-2′ (-6′)], 7.2—7.0 (2 H, m, H-8 + -9), 6.8 [1 H, d, *J* 8 Hz, H-6′ (-2′)], 5.06 [1 H, dd, *J* 8 Hz, $J_{3',5'}$ 3 Hz, H-3′ (-5′)], 4.72 [1 H, dd, *J* 8 Hz, $J_{3',5'}$ 3 Hz, H-5′ (-3′)], 3.72 (2 H, t, *J* 7 Hz, H-5), 3.52 (3 H, s, 1-Me), and 3.04 (2 H, t, *J* 7 Hz, H-6) (Found: C, 73.4; H, 5.0; N, 13.7%; M^+, 408.1580. $C_{25}H_{20}N_4O_2$ requires C, 73.5; H, 4.9; N, 13.1%; *M*, 408.1586); δ [$(CD_3)_2SO$; 100 °C] 10.9 (1 H, s), 8.7 (2 H, d, *J* 4 Hz), 7.6—7.4 (4 H, m), 7.2—7.0 (2 H, m), 7.1 (2 H, d, *J* 8 Hz), 4.8 (2 H, d, *J* 8 Hz), 3.66 (2 H, t, *J* 7 Hz), 3.00 (2 H, t, *J* 7 Hz), and 2.05 (3 H, s). This latter spectrum is closely similar to that observed at +28 °C in the same solvent; however the signals due to H-2′ and -6′ and H-3′ and -5′ are not well resolved.

3,4-*Dihydro*-1-*isopropyl*-β-*carboline* (5; R = Pr^i).—Tryptamine (3 g, 1.87 × 10^{-2} mol) and isobutyric acid (1.65 g, 1.87 × 10^{-2} mol) were mixed and heated at 190 °C for 1 h. The product, a gum, was triturated with diethyl ether to yield a solid (2.8 g), m.p. 145 °C, $\nu_{max.}$ 3 470, 3 250, 3 080, 1 645, 1 590, and 740 cm^{-1}; δ ($CDCl_3$) 9.8 (1 H, s, N_aH), 7.7—7.0 (4 H, m, H-4—7), 7.08 (1 H, d, *J* 2 Hz, H-2), 4.1br (1 H, s, N_bH), 3.53 (2 H, t, *J* 6 Hz), 2.96 (2 H, t, *J* 6 Hz), 2.5 [1 H, m, $CH(CH_3)_2$], 1.15 [3 H, d, *J* 5 Hz, $CH(CH_3)CH_3$], and 1.07 [3 H, d, *J* 5 Hz, $CH(CH_3)CH_3$]. Phosphorus pentaoxide (25 g) was added in portions during 3 h to the above amide (2.0 g) in xylene solution. After heating under reflux for a further 1 h the mixture was cooled and the solution removed by decantation. The residue was washed with diethyl ether before being added to crushed ice (500 g) and acidified with 2N-hydrochloric acid (20 cm^3); the aqueous solution was then extracted with diethyl ether, basified with sodium carbonate solution, and re-extracted with dichloromethane. The organic phase was dried and evaporated to give an oil which crystallised from dichloromethane as prisms (1.3 g, 32%), m.p. 176 °C (lit.,[7] 178—179°); $\nu_{max.}$ 3 200—3 000, 1 620, 1 610, and 750 cm^{-1}; δ ($CDCl_3$) 9.2 (1 H, s, NH), 7.7—7.0 (4 H, m, H-5—8), 3.92 (2 H, t, *J* 7 Hz, H-3), 3.08 [1 H, sept, *J* 8 Hz, $CH(CH_3)_2$], 2.8 (1 H, t, *J* 7 Hz, H-4), and 2.3 [6 H, d, *J* 8 Hz, $CH(CH_3)_2$].

3,4-*Dihydro*-1-*isonicotinoyl*-1-*isopropylidene*-β-*carboline* (26).—This compound was prepared as for the enamide (7),[2b] except that isonicotinic acid (0.7 g) and 3,4-dihydro-1-isopropyl-β-carboline (1.0 g) were used. The product was purified by chromatography on silica; elution with 2 : 98 methanol–diethyl ether gave *cubes* (0.9 g, 60%), m.p. 248 °C, $\lambda_{max.}$ 225, 245, and 312 nm; $\nu_{max.}$ 3 200, 1 660, and 1 640 cm^{-1}, *m/e* 317 (M^+, 6%), 302 (6), 211 (3), 177 (10), 176 (12), 106 (65), and 86 (100); δ [$(CD_3)_2SO$ at +28 °C] 11.10 (2/3 H, s, NH), 11.04 (1/3 H, s, NH), 8.8 (2/3 H, d, *J* 6 Hz, H-2′ + -6′), 8.56 (4/3 H, *J* 6 Hz, H-2′ + -6′), 7.6 (2/3 H, d, *J* 6 Hz, H-3′ + -5′), 7.6—7.4 (2 H, m, H-5 + -8), 7.42 (4/3 H, d, *J* 6 Hz, H-3′ + -4′), 7.3—7.1 (2 H, m, H-6 + -7), 5.0 (1 H, m, 3-H), 3.4—2.7 (3 H, m, 3-H + 4-H_2), 2.26 (1 H, s, 1/3 Me_Z), 1.95 (1 H, s, 1/3 Me_E), 1.9 (2 H, s, 2/3 Me_E), and 1.46 (2 H, s, 2/3 Me), δ [$(CD_3)_2SO$ at +150 °C] 10.28 (1 H, s), 8.57 (2 H, d, *J* 6 Hz), 7.8—7.6 (2 H, m), 7.24 (2 H, d, *J* 6 Hz), 7.2—7.0 (2 H, m), 2.92 (4 H, m), 2.02 (3 H, s), and 1.64 (3 H, s) (Found: C, 75.4; H, 6.0; N, 13.1. $C_{20}H_{19}N_3O$ requires C, 75.7; H, 6.0; N, 13.2%).

Photoreaction of 3,4-*Dihydro*-1-*isonicotinoyl*-1-*isopropylidine*-β-*carboline* (26).—Compound (26) (1.0 g) in methanol (600 cm^3) was irradiated in a Hanovia photochemical reactor for 20 h. The solvent was removed and the residue was chromatographed on silica. Elution with dichloromethane gave some harmalan, but when 10 : 90 methanol–dichloromethane was used, isonicotinic acid (60 mg) was obtained, identified by direct comparison with an authentic specimen (m.p., mixed m.p., spectroscopy, *etc.*).

11b-*Ethoxy*-5,6,11,11b-*hexahydro*-1,1-*dimethyl*-1H-*indolizino*[8,7-b]*indole*-2(3H)-*spiro*-4′(1′H)-*pyridin*-3-*one* (28).—3,4-Dihydro-2-isonicotinoyl-1-isopropylidene-β-carboline (0.45 g) and an equimolar amount of benzyl bromide were heated under reflux in dichloromethane solution for 18 h. The solvent was removed and the residue was chromatographed on alumina. Elution with 1 : 99 methanol–diethyl ether gave a crystalline *solid* (28) (0.095 g, 15%), m.p. 176 °C (from ethanol–water); $\lambda_{max.}$ 230, 276, 284, and 293 nm; $\nu_{max.}$ 3 200, 1 690, 1 604, 740, and 720 cm^{-1}; *m/e* 453 (M^+, 8%), 409 (12), 407 (15), 405 (13), 393 (20), 377 (40), 317 (71), 302 (68), 286 (92), 211 (64), 210 (71), 209 (96), and 195 (100); δ ($CDCl_3$ at 28 °C) 8.06 (1 H, s, NH), 7.6—7.0 (9 H, m, H-7—10 + -2″—6″), 6.26 [1 H, dd, *J* 10 and 2 Hz, H-2′ (-6′)], 6.16 [1 H, dd, *J* 10 and 2 Hz, H-6′ (-2′)], 4.9 [1 H, dd, *J* 10 and 3 Hz, H-3′(-5′)], 4.7 (1 H, dd, *J* 10 and 6 Hz, 5-H_A), 4.30 (2 H, s, CH_2Ph), 4.24 [1 H, dd, *J* 10 and 3 Hz, H-5′(-3′)], 3.48 (2 H, q, *J* 7 Hz, $CH_3{\cdot}CH_2{\cdot}O$), 3.3—3.0 (1 H, m, 5-H_B), 2.9—2.6 (2 H, m, H-6), 1.28 (3 H, s, 1-Me), 1.1 (3 H, t, *J* 7 Hz, $CH_3{\cdot}CH_2{\cdot}O$), and 0.4 (3 H, s, 1-Me) (Found: C, 76.7; H, 6.6; N, 9.3. $C_{29}H_{31}N_3O_2$ requires C, 76.8; H, 6.9; N, 9.3%).

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* Same footnote as on page 2114.