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INTER- AND INTRAMOLECULAR ADDITION OF ESTER ANIONS TO NICOTINIUM SALTS

A FACILE APPROACH TO NAUCLEFINE AND ELLIPTICINE DERIVATIVES

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Abstract—Reaction of ester anions (**3a–c**) with 1-(2′-indolyl-ethyl)nicotinium chloride (**2a**) and 1-(1′-methyl-2′-indolylethyl)-nicotinium chloride (**2b**) leads to 2,7-naphthyridine-1,3-diones **5a–c**. Acid catalyzed cyclization of the latter yield pentacyclic napthyridocarboline derivatives **1a–c**. In an analogous reaction sequence, addition of the anion of 2-carboethoxy-1,3-dithiacyclopentane (**11**) to 1-benzyl-3-[N-2′(indolylethyl)]-carbamoylpyridinium bromide results in the corresponding naphthyridindione derivative **13** which, via subsequent desulfurization (Raney-Ni) and cyclization gives the alkaloid nauclefine (**10**). An approach to the pyridocarbazole system, involving the intramolecular addition of ester aniion of 1-benzyl-3-[1′-methyl-2′-(1″-ethoxycarbonylethyl)-3′-indolyl] carbonylpyridinium bromide to the 4-position of the pyridinium moiety of the molecule, has been developed. The reaction has been employed for the synthesis of olivacine and diverse ellipticine derivatives.

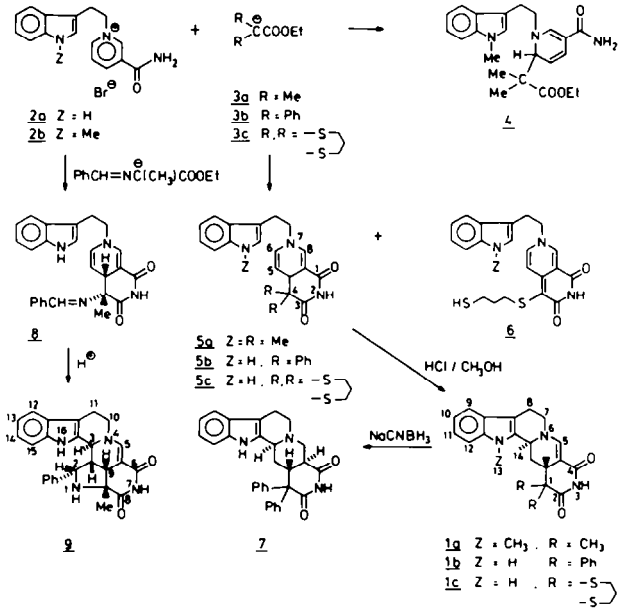
Addition of nucleophiles to pyridinium salts carrying electronegative substituents at the 3-position leads to stable 1,4-dihydropyridine derivatives. Reaction of ester anions with nicotinamide salts proceeds via kinetically controlled C(4)- and C(6)-addition;[1] however, the C(4)- adduct undergoes a subsequent intramolecular nucleophilic attack of the ester function by the amide N-atom.

The overall reaction leads to the construction of a 4-substituted 2,7-naphthyridine derivative, in one practical step. The generality of this sequence of events has led to the development of a convenient synthesis of the spirocyclopentano-naphthyridine alkaloid sesbanine.[2] We now present the application of the basic principle of the aforementioned approach to the synthesis of nauclefine and ellipticine derivatives.

Synthesis of naphthyridocarboline derivatives and nauclefine

The synthesis of naphthyridocarbolines is of considerable interest in view of the biological properties of alkaloids of Nauclea parva.[3] The known alkaloid nauclefine (**10**, Scheme B) incorporates a naphthyridocarboline skeleton. Our strategy for the synthesis of naphtyridocarbolines (**1**, Scheme A), visualized the addition of ester anions to 3 - carbamoyl - 1 - [2 - (2 - indolyl) - ethyl]pyridinium salts (**2a,b**) and subsequent cyclization of the indolylnaphthyridine derivatives (**5**, Scheme A).[4]

Reaction of anion **3a** with salt **2b**, according to the procedure described earlier,[2] led to a mixture of the C(6) adduct **4** (34%) and the naphthyridine derivative **5a** (17%). The latter obviously resulted from a pri-



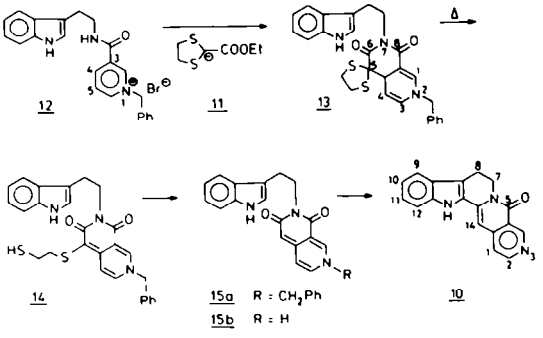
Scheme A.

mary addition product of **3a** to the C(4)-position of pyridinium salt **2b**. In contrast to these results, addition of anion **3b** to the salt **2a** led to **5b** as the only isolable product. The difference between the reactions of the two anions is consistent with the known pattern of reaction of nucleophiles with nicotinamide salts; which kinetically favour attack at C(6), while C(4)-adducts are the thermodynamically stable products.[1,2] Initially formed C(6)-adducts of **3b** would be expected to dissociate to the starting ions, in view of the stabilization of the negative charge in anion **3b**.

Furthermore, C(4)-adducts are transformed to stable 2,7-naphthyridin-1,3-diones via a nucleophilic attack of the ester group, by the amide moiety. Reaction of anion **3c** and **2a** leads, in an analogous manner, to indolylnaphthyridine **5c**. Under the reaction conditions **5c** is partly converted into **6** via a simple thiol-elimination. The reaction **5c**→**6** can be completed by refluxing the former in methanol. **5a–c** Can be conveniently cyclized to **1a–c**, respectively, as single isomers, by treatment with acid. Protonation of **6** under the same conditions produces a stable 2,7-naphthyridinium ion which does not give rise to a cyclized product. Reduction of **1b** by $NaCNBH_3$ results in the saturation of the remaining double bond in the naphthyridine moiety, to give **7**. The relative stereochemistry of the C(4a), C(13b) and C(14a) centres of **7** could be deduced from its 500 MHz-NMR-spectrum, via decoupling experiments. The details of the structure elucidation will be published elsewhere.

The anion derived from the benzylidene derivative of alanine ethyl ester adds to salt **2a** to form the anticipated naphthyridinedione **8**[2b] which undergoes an acid catalyzed double cyclization to **9**. The process is presumably triggered by protonation of the benzylidene N followed by nucleophilic attack of the dihydropyridine. The thereupon generated electrophile (C=N̄ group) is quenched by the indole moiety. Whether the two cyclization steps are concerted or otherwise, cannot be discussed without specific information on this point. The relative stereochemistry of the various centres in **9** has been established by differential Nuclear Overhauser Spectroscopy (Experimental). The *cis*-geometry of the Me group and the H in **8** is assigned on the basis of the structure of **9**.

Several synthesis of the alkaloid nauclefine (**10**, Scheme B) have been reported in the last years.[5] The use of demethoxyharmaline for the synthesis of nauclefine[5b,d] suffers from the practical disadvantage of employing an expensive, though commercially available, starting material. Based on the experience gained in this laboratory, an approach utilizing the reaction of ester anion **11** with the N-benzylpyridinium salt **12** (derived from tryptamine, nicotinyl chloride and benzyl bromide (Experimental), was investigated. This reaction proceeded in the expected fashion and the product **13** was obtained in good yield. Upon heating **13**, thiol **14** was formed, which could be converted to **15b**, via the corresponding benzyl derivative (**15a**), in two reductive steps. Spectral data (IR and NMR) of **15b** attested to the dihydropyridine tautomeric structure. Treatment of **15b** with HBr/AcOH gave crystalline nauclefine (m.p. 282–284°) whose spectra were in agreement with those reported in the lit.[3,5] The sequence of reactions described in Scheme B constitutes a very convenient synthesis of nauclefine and its derivatives, especially those in which modifications are introduced by appropriate choice of the ester anion.



Scheme B.

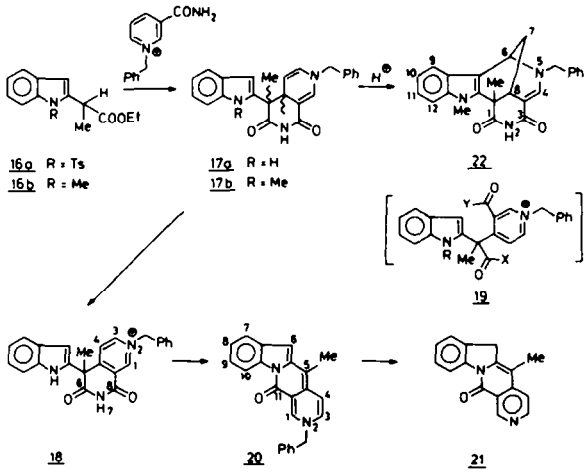
Ellipticine and olivacine derivatives

The reported anti-tumour activity of ellipticine,[6] combined with its remarkably low bone-marrow toxicity has stimulated a great deal of interest in its chemical synthesis[7] and its mechanism of action.[6a,8] A practical synthesis of ellipticine, which can be conveniently extended to its analogues and derivatives is of great value, especially in view of the different toxicities and the very poor solubility characteristics of simple ellipticine–derivatives.

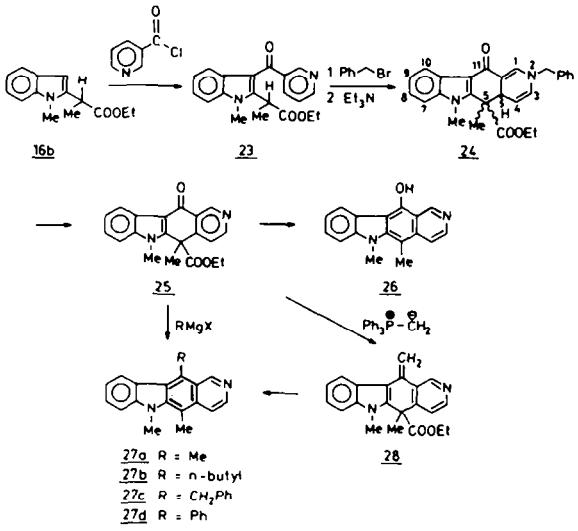
Our first attempt to prepare the pyridocarbazole skeleton of ellipticine, employing the now familiar reaction of ester anions with pyridinium salts, is discussed in terms of the reactions described in Scheme C. The 2-(2-indolyl)propionate derivatives (**16a,b**) were prepared by modification of known procedures.[9] Addition of anions prepared from **16a,b** to N-benzyl-3-carbamoylpyridinium bromide led to formation of **17a,b** as mixtures of isomers (**17a**: 60%, **17b**: 70%).

The further strategy for the synthesis of ellipticine required the conversion of **17a,b**-via hydrolysis- to an intermediate of type **19**, which could be subsequently cyclized and alkylated. Hydrolysis of **18**, under a variety of conditions, failed to show clean synthetically useful reactions. Alcoholysis with K_2CO_3 (DMSO–ROH) yielded the tetracyclic product **20**, presumably formed through ring-opening of the cyclic imide, followed by decarboxylation and ring-closure involving the indole nitrogen. Structure **20** is assigned on the basis of its spectroanalytical data and its transformation to the pyridine derivative **21**. Reaction of **18b** with acid resulted in an interesting cyclization to a product to which structure **22** has been assigned (vide experimental). Formation of **22**, whose skeleton is related to that of the alkaloids uleïne[10] and dasycarpidone[11] is formed as a result of C(3)-protonation of the dihydropyridine ring, followed by nucleophilic attack via C(3), of the indole system.

In view of the aforementioned results, we envisaged that an *intramolecular* addition of the ester anion to pyridinium salts, employing an appropriate synthon—such as **23** (Scheme D)—ought to lead to the desired pyridocarbazole intermediate. Pre-



Scheme C.



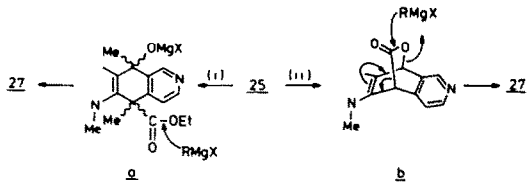
Scheme D.

liminary results on the formation of such an intermediate and its conversion to ellipticine and olivacine derivatives have been communicated.[12] We now present details of this study and the synthesis of a series of new ellipticine derivatives using the now readily accessible pyridocarbazole intermediate (**24** Scheme D).

Indolylester **16b** was acylated with nicotinoyl chloride, at the 3-position to yield pyridyl ketone **23**. The pyridine nitrogen was quarternized by reaction with benzyl bromide and the resulting salt treated with triethyl amine to give smoothly the tetracyclic pyridocarbazole derivative **24**.

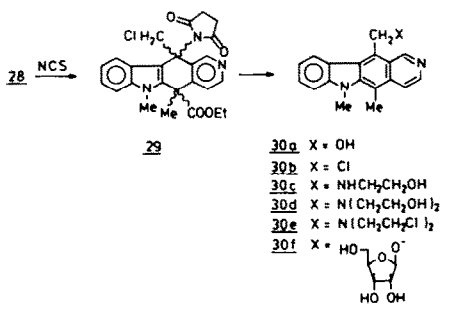
Oxidation and debenzylation of **24** (N-benzylacridinium bromide, followed by hydrogenolysis) proved very effective in converting it to the corresponding pyridine derivative **25**. Hydrolysis of **25** proceeded in the expected manner to yield compound **26**.

Conversion of **24** to ellipticine derivatives required alkylation of the C(11)–CO function. Reaction of **25** with an excess of MeMgBr gave, in one practical step, the desired 6-methyl-ellipticine **27a**. Analogous reactions with n-BuMgBr, $PhCH_2MgBr$ and PhMgBr yielded ellipticine derivatives **27b–27d**, respectively. Methylellipticine **27a** can also be prepared via the sequence **25**→**26**→**27a**. Reaction of **25** with methylenetriphenylphosphorane provided the exocyclic methylene derivative **26**, which underwent a facile hydrolytic decarboxylation. The mechanism of conversion of **25** and **27a–d**, upon reaction with Grignard reagents, deserves some comment. Two pathways for this transformation need to be considered. In one of these (i), the Grignard adduct **a** undergoes reaction with a further equivalent of the Grignard reagent, involving attack of the ester carbonyl, and leading to expulsion of ^-OMgX with concomitant aromatization. This reaction pathway is very likely to be followed in the reaction with methylmagnesium iodide. The product **27a** in this case can be observed prior to hydrolysis. For the cis stereo-isomers a second pathway (ii) could be envisaged in which lactone **b** is formed, via intramolecular attack of the ester by the initially generated alkoxide ion. The lactone (**b**) can then open by reaction with a second molecule of RMgX, forming RCOOMgX and **27**. At

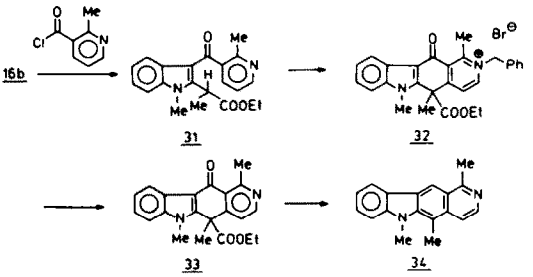


present, however, there is no independent evidence for formation of the lactone systems during the reaction. Complete aromatization was obtained, when the products of the Grignard reaction were heated with KOH/glycol. The methylene product **28** proved to be a valuable intermediate for diverse functionalized ellipticine derivatives. Reaction with N-chlorosuccinimide yielded a mixture of two diastereomeric adducts, corresponding to structure **29**. Without separation, the mixture was subjected to hydrolytic decarboxylation, whereupon the hydroxymethyl derivative **30a** was obtained. Decarboxylation results in an anion which aromatizes by expulsion of the succinimide ion. Treatment of **30a** with thionyl chloride yields the corresponding chloride **30b** (Scheme E). Both **30a** and **30b** are synthetically useful intermediates, since they can serve as nucleophilic and electrophilic reagents, respectively. Thus, **30b** reacted with $H_2NCH_2CH_2OH$ and $HN(CH_2CH_2OH)_2$ to give readily the derivatives **30c** and **30d**, respectively. Compound **30d** was converted to **30e** (hydrochloride) by treatment with thionyl chloride. It is noteworthy that **30e** incorporates the structural elements of both, ellipticine and a nitrogen mustard[13] and is in principle capable of forming cross-links in DNA after intercalation. In order to increase the solubility of the ellipticine system, it was considered of interest to link it to a saccharide moiety. Reaction of **30a** with 2,3,5 tribenzoylribofuranosyl acetate, in the presence of $SnCl_4$,[14] yielded the expected acetal which was deprotected to riboside **30f**.

The facile synthesis of the pyridocarbazole system **25** (Scheme D), prompted us to apply the sequence of reactions to the preparation of 6-methyl olivacine **34** (Scheme F). Reaction of ester **16b** with 2-methylnicotinoyl chloride (Scheme F) gave the ketone **31** in fair yield. Cyclization of **31** to the pyridocarbazole system **32** was achieved in two steps, involving N-benzylation followed by treatment with base (Et_3N). Oxidative debenzylation, once again utilizing two steps, provided the keto ester **33**. Reduction of the latter product with Redal yielded, finally, 6-methylolivacine, whose spectral data were in complete agreement with the assigned structure. It should



Scheme E.



Scheme F.

be mentioned that, in analogy to the reaction of Grignard reagents with ketone **25**, the reduction of **34** by Redal can also be proceeded by one of the two mechanisms, discussed earlier.

Further exploitation of the reaction of ester anions with nicotinium salts, with the aim of synthesizing polycyclic heterocycles is being undertaken in our laboratory.

EXPERIMENTAL

All m.ps are uncorrected. IR spectra were recorded on a Perkin–Elmer 257 spectrometer. The absorptions are given in cm^{-1}. PMR spectra were run on a Varian Associates Model A-60-D and XL-100 or Bruker WM 250 instruments, using TMS as an internal standard. Unless stated otherwise, IR and PMR spectra are taken in $CHCl_3$ and $CDCl_3$ respectively. Nuclear Overhauser Difference experiments were carried out (Bruker WM 250) by flushing the sample with dry N_2 for 15 min and using the micro programmes for nOe difference spectroscopy in the ASPECT 2000 NMR software manual by Bruker, part 4.7B).[15] Decoupling power was 14L or 16L. Mass-spectra were obtained with a Varian Mat-711 spectrometer.

Addition of the anion of ethyl isobutyrate **3a** to N-(2-(N-methylindol - 3′yl)ethyl) - 3 - carbamoyl pyridinium chloride **2b**

Ethyl isobutyrate (1.5 mmol) was added to 1.5 mmol lithium diisopropylamide in 3 ml THF at −76°, followed by 0.5 mmol **2b**. After 1.5 hr of reaction at 0°, water was added and the mixture was extracted with EtOAc. Drying the EtOAc soln and chromatography over a short silica column (eluents: EtOAc) yielded 0.065 g **4** (17%) and 0.03 g **5a** (8%).

Compound **4**: oil. IR: 3520, 3410 (NH_2). 1715 (C=O), 1650 (C=O), 1630. PMR: δ 1.05–1.3 (m. 9H, $3CH_3$), 3.0 (t, 2H, CH_2C), 3.4 (t, 2H, CH_2–N), 3.70 (s, 3H, N–CH_3), 4.08 (q, 2H, CH_2–O), 4.51 (d × d, 1H, H-6, J = 1, J = 5), 4.91 (d × d, 1H, H-5, J = 10), 5.40 (broad, 2H, NH_2), 6.40 (d × d, 1H, H-4, J = 1, J = 10), 6.78 (s, 1H, indole H-2), 7.1–7.6 (multiplet, 5H, aromatic protons).

Compound **5a**: m.p. 144–148° (methanol). IR: 3380 (N–H), 1705, 1685 (N–C=O), 1650, 1575. PMR: δ 1.21 (s, 6H, $2CH_3$), 3.01 (t, 2H, CH_2–C, J = 7), 3.48 (t, 2H, CH_2–N, J = 7), 3.70 (m, 1H, H-4a), 3.75 (s, 3H, N–CH_3), 4.56 (d × d, 1H, H-5, J = 2.5, J = 8), 5.82 (d × d × d, 1H, H-6, J = 2, J = 2.5, J = 8), 6.86 (s, 1H, indole H-2), 7.1–7.6 (m, 5H, aromatic protons), 7.75 (broad, 1H, N–H).

Addition of the anion of ethyl diphenylacetate **3b** *to N-(2-(indol - 3′ - yl)ethyl)3 - carbamoyl pyridinium chloride* **2a**[16]

To a suspension of 4 mmol NaH in DMSO was added 2 mmol ethyl diphenyl acetate at room temp. After the evolution of H_2 had ceased, 1 mmol of salt **2a**[16] was added and the mixture was stirred during 2 hr. Addition of water and extraction with EtOAc afforded **5b** (yield 49%). **5b**: m.p. 190–195° (MeOH). IR: 3480 (indole N–H), 3370 (imide N–H), 1705, 1690 (N–C=O), 1655, 1575. PMR: (d_6-DMSO):

δ 2.87 (t, 2H, CH_2–C, J = 8), 3.54 (t, 2H, CH_2–N, J = 8), 4.31 (d × d, 1H, H-5, J = 2.5, J = 8), 4.82 (m, 1H, H-4a), 6.07 (d × d × d, 1H–H_6, J = 2, J = 2.5, J = 8), 6.85–7.7 (m, 16H, aromatic protons), 10.46 and 10.85 (N–H).

Addition of the anion of 2 - *carbethoxy* - 1,3 - *dithiane* **3c** *to* N - (2 - (*indol* - 3′ - *yl*) - 3 - *carbamoylpyridinium chloride* **2a**

To a soln of 1.1 mmol 2-carbethoxy - 1,3 - dithiane in 5 ml THF, 3.3 mmol NaH was added. After the addition of 1 mmol **2a**[16] the mixture was stirred at room temp. during 1 hr. Addition of water and extraction with EtOAc produced a mixture of **6** and the corresponding dithiane **5c**. Heating the residue in MeOH produced **6** as the sole product. **6**: m.p. 200–206°. IR (KBr) 3320, (indole N–H), 2800 (imide N–H), 1675, 1590 (C–O), 1500. PMR (d_6-DMSO): δ 1.70 (q, 2H, C–CH_2–C), 2.5–2.75 (m, 4H, CH_2S), 3.23 (t, 2H, CH_2-indole, J = 7), 4.36 (t, 2H, CH_2–N, J = 7), 7.0–7.75 (m, 7H, aromatic protons), 8.35 (d, 1H, H-8, J = 1.5), 10.32 and 10.94 (N–H). **5c**: instable oil (yield *ca* 50%), used without purification in the next step.

Cyclization of **5a–c**

A suspension of 1 mmol **5a–c** was refluxed in 10 ml 1% HCl/MeOH until the yellow colour faded away (approx. 5 min). After cooling the soln **1a–c** was obtained as white crystals (yield, approx. 90%). **1a**: m.p.: 271–276°. IR: 3380 (N–H), 1700, 1675 (C–O), 1600. PMR: δ 1.30 (s, 3H, CH_3), 1.65 (s, 3H, CH_3), 3.75 (s, 3H, N–CH_3), 4.74 (m, 1H, H–13a), 7.1–7.5 (m, 4H, aromatic protons), 7.70 (d, 1H, H-5, J = 1.5).

Compound **1b**: m.p.: 314–316°. IR: 3460 (indole–N–H), 3370 (imide N–H), 1700, 1675 (N–C = O), 1600. PMR: δ 4.18 (m, 1H, H-13a), 6.9–7.4 (m, 14H, aromatic protons), 7.62 (d, 1H, H-5, H = 1.5), 9.01 (s, 1H, N–H). **1c**: m.p. 235° (dec). IR (KBr): 3300–3100 (N–H), 1685, 1655 (C=O), 1575. PMR (d_6-DMSO): δ 4.90 (m, 1H, H-13a), 6.9–7.4 (m, 4H, aromatic protons), 7.75 (d, 1H, H-5, J = 1.5), 10.2 (s, 1H, N–H), 11.2 (s, 1H, N–H). MS (FD): 411 (M^+). **1b**. Found: N, 9.12, $C_{30}H_{25}N_3O_2$ requires: N, 9.14.

Reduction of **1b** to **7**

A suspension of 0.5 mmol **1b** and 1 mmol sodiumcyanoborohydride in a mixture of 5 ml THF, 1 ml AcOH and 1 ml MeOH was heated at 45° during 4 hr. Addition of water, K_2CO_3 and extraction with EtOAc followed by crystallization from MeOH yielded **7** as white crystals (75%). **7**: m.p.: 271–273°. IR: 3460 (indole N–H), 3360 (imide N–H), 1720, 1700 (C–O). PMR: (500 MHz): δ 1.95 (d × d × d, 1H, H-14α, J = 15, J = 15, J = 5), 2.19 (d × d × d, 1H, H-14β, J = 15, J = 2, J = 1), 2.51 (d × d × d, 1H, H-4a, J = 4.5, J = 7.5, J = 7.5), 2.59 (d × d, 1H, H-8, J = 15, J = 4), 2.75 (d × d × d, 1H, H-14α, J = 15, J = 15, J = 2), 2.87 (d × d, 1H, H-5α, J = 11.5), 3.11 (m, 1H, H-8), 3.24 (d × d × d, 1H, H-7, 4.46 (m, 1H, H-13), 7.2–7.5 (m, 14H, aromatic protons), 7.65 (s, 1H, N–H), 8.22 (s, 1H, N–H). **7**. Found: N, 8.96, $C_{30}H_{27}N_3O_2$ requires: N, 9.10.

Synthesis of **9**

To a suspension of 2.2 mmol NaH in 5 ml dry THF was successively added 1 mmol N-benzylidene alanine ethyl ester and 1 mmol of **2a**. After stirring the mixture at room temp. for 1 hr, addition of water and extraction with EtOAc afforded **8**. A soln of **8** in MeOH/AcOH 10 : 1 was refluxed until the yellow colour faded (10 min) Column chromatography (silica–EtOAc/petrolcum ether 1 : 1) afforded **9** as white crystals (40%, for the two steps). **9**: m.p.: 305–310°. IR: 3460 (indole–N–H), 3370 (imide N–H), 1700, 1675 (C=O), 1600. PMR: δ 1.60 (s, 3H, CH_3), 2.05 (broad, 1H, H-1), 2.65 (d × d, 1H, H-9, J = 2, J = 7), 3.52 (d × d, 1H, H-2a, J = 7, J = 9), 4.38 (s, 1H, H-3), 4.70 (d, 1H, H-2, J = 9), 2.5–3.3 (m, 4H, CH_2–CH_2), 6.9–7.3 (m, 10H, aromatic protons), 7.45, 8.20 (2s, 2H, N–H). Irradiating the methyl signal and measuring the nOe difference spectra gave signals for H-2, H-2a and H-9. MS (FD): 424 (M^+).

Pyridinium salt **12**

To a suspension of 10 mmol 2 - (indol - 3 - yl) - ethylamine and 15 mmol pyridine - 3 - carboxychloride - HCl in 50 ml acetonitrile was added, at room temp., 35 mmol Et_3N, over a period of 10 min. After 1 hr at room temp. the mixture was refluxed for 5 min. The solvent was evaporated, the residue taken up in EtOAc and extracted with water and K_2CO_3 aq. After drying and pumping off the solvent the residue was dissolved in 25 ml acetonitrile and refluxed for 15 min with 10 mmol benzyl bromide. The oil which separated was dissolved by the addition of some MeOH. Upon cooling the clear soln, salt **12** crystallized in 76% yield. **12**: m.p.: 138–140°. IR (KBr): 3200–3500 (N–H), 1660 (C–O), 1620. PMR (d_6-DMSO): δ 3.06 (1, 2H, J = 7, CH_2–C), 3.65 (m, 2H, CH_2–N), 6.02 (s, 2H, $CH_2Ø$), 6.9–7.7 (m, 10H, aromatic protons), 8.33 (d × d, 1H, J = 8, J = 7, H-5), 9.06 (d × d, 1H, J = 8, J = 1.5, H-6), 9.40 (d × d, 1H, J = 1.5, J = 7, H-4), 9.44 (broad 1H, NH–CO), 9.77 (s, 1H, H-2), 10.9 (broad, NH-indole).

Addition of the anion of **11** to pyridinium salt **12**

A soln of 3 mmol **12** in 75 ml hot EtOH was cooled to 10°, after which successively **11** (4.5 mmol) and 9 mmol NaOEt in EtOH was added. After stirring 1 hr at 10° and 1 hr at room temp. the solvent was evaporated and the residue taken up in water and extracted with EtOAc. After drying and evaporating the solvent the residue was covered with xylene and refluxed for 30 min. Evaporating the solvent produced **14** which was directly used in the next step. Chromatography (silica, EtOAc) yielded pure **14** as a yellow solid. **14**: m.p. 190–193°. IR (KBr): 3240 (N–H), 2540 (S–H), 1665, 1625 (C=O), 1580, 1520. PMR (d_6-DMSO): δ 2.5–2.9 (m, 4H, –S–CH_2–CH_2–S), 2.8–3.1 (m, 2H, CH_2–C), 4.1–4.4 (m, 2H, CH_2–N), 5.36 (s, 2H, $CH_2Ø$), 6.9–7.9 (m, 11H, aromatic protons), 8.75 (d, 1H, J = 2, H-2), 10.8 (broad, 1H, N–H).

Removal of the ethylene di-thiol group from **14**

The product of the preceding reaction was dissolved in THF and excess. Raney Ni was added. Refluxing the soln for 10 min, filtering and evaporating the solvent, produced **15a** as a yellow oil. The crude product was crystallized from $CHCl_3$ yielding 0.515 g **15a** (34%) as yellow crystals containing $CHCl_3$. **15a**: m.p. 105–110° (loss of $CHCl_3$)): IR: 3470 (N–H), 1675, 1600–1620 (C–O). PMR (CD_3OD): δ 3.0 (m, 2H, CH_2-indole), 4.25 (m, 2H, CH_2–N), 5.20 (s, 2H, $CH_2Ø$), 5.55 (s, 1H, H-5), 6.8 (d, 1H, J = 6, H-4), 7.1 (s, 1H, indole–H–2′), 7.32 (d, 1H, J = 6, H-3), 7.3–7.5 (m, 10H, aromatic protons), 7.75 (d, 1H, indole, J = 8), 7.85 (s, 1H, $CHCl_3$), 8.55 (s, H-2).

Debenzylation of **15a**

N-benzyl derivative **15a** (0.5 g) was dissolved in 10 ml EtOAc/MeOH 1 : 1 containing 0.5% HCl. After addition of 0.2 g 10% Pd–C the mixture was reduced at room temp. and 1 atm at H_2 during 5 hr. The catalyst was filtered off and the filtrate concentrated *in vacuo*. By trituration with MeOH **15b** was obtained in 60% yield (0.31 g). **15b**: m.p.: 260–265°. IR (KBr): 3200–3400 (NH), 1720, 1660 (C=O), PMR (d_6-DMSO): δ 2.9 (t, 2H, CH_2C), 4.15 (t, 2H, CH_2N), 5.45 (s, 1H, H-5), 6.85 (d, 1H, J = 6, H-4), 6.95–7.2 (m, 2H, H-5′, H-6′), 7.22 (s, 1H, H-2′), 7.40 (d, 1H, J = 6, H-3), 7.55 (d, 1H, J = 5, H-4′), 7.75 (d, 1H, J = 6, H-7′), 8.43 (s, 1H, H-1′), 10.8 (s, 1H, N–H).

8,13 - *Dihydro-indolo*[2′,3′:3,4]*pyrido*[1,2-b][2,7]*naphtyridin* - 5(7H) *on* (*Nauclefine*) **10**

Dihydropyridine **15b** (0.04 g) was heated at 40° in 1 ml 40% HBr–AcOH during 1 hr. After concentrating *in vacuo*, the residue was treated with Na_2CO_3 in water and extracted with EtOAc. Chromatography over a short column (silica–EtOAc) and triturating with MeOH afforded **10** in 70% yield. **10**: m.p.: 282–284° (lit.[5a] m.p. 285–290°). IR

(KBr): 3200–3500 (N–H), 1650 (C=O), 1600. PMR (d_6–DMSO): δ 3.2 (t, 2H, J = 7, CH_2–C), 4.42 (t, 2H, J = 7, CH_2–N), 7.05 (s, 1H, H-14), 7.1 (t, 1H, H = 6, H-10), 7.3 (t, 1H, J = 6, H-11), 7.48 (d, 1H, J = 6, H-9), 7.55 (d, 1H, J = 5, H-1), 7.65 (d, 1H, H-12), 8.65 (broad, 1H, H-2), 9.38 (broad, 1H, H-4), 11.85 (s, 1H, N–H). UV (ethanol): 393, 374, 355 (sh), 290.

N-Tosyl-2-carbethoxycarbonyl-indole

To a soln of 0.1 mol N-tosylindole in 200 ml THF, at −76°, was added dropwise 0.105 mol n-BuLi. After 10 min the resulting suspension was slowly warmed to 0° and added to a soln of 0.4 mol ethyl oxalate in 150 ml THF under mechanical stirring. After 20 min the soln was neutralized with 0.1 mol AcOH and after evaporation of the solvents the residue was chromatographed over a short column (silica–EtOAc/petroleum ether 1 : 10). Recrystallization from petroleum ether/EtOAc afforded 21.8 g (58%) N-tosyl-2-carbethoxy carbonyl-indole: m.p.: 91–92°. IR: 1735, 1690 (C=O). PMR: δ 1.40 (t, 3H, CH_3), 2.27 (s, 3H, tosyl-CH_3), 4.42 (q, 2H, OCH_2), 7.05 (s, 1H, H-3), 7.1–7.8 (m, 7H, aromatic protons), 8.0 (m, 1H, H-7).

Ethyl 2-(N-tosylindol-2-yl) acrylate

To a soln of 12 mmol methylidene phosphorane in 50 ml THF at 0° was added 11.3 mmol solid N-tosyl-2-carbethoxycarbonylindole in portions. When the characteristic colour of phosphorane had disappeared the mixture was stirred at room temp. for 2 hr. Chromatography over a short column (silica: EtOAc/petroleum ether 1 : 3) and recrystallization from EtOH afforded the product in 56% yield, m.p.: 103–105°. IR: 1720 (C=O), 1620 (C=C). PMR: δ 1.28 (t, 3H, CH_3), 2.22 (s, 3H, tosyl CH_3), 4.25 (q, 2H, OCH_2), 5.76 (d, 1H, J = 1.5, vinylproton), 6.45 (d, 1H, J = 1.5, vinylproton), 6.52 (s, 1H, H-3), 6.9–7.6 (m, 7H, aromatic protons), 8.0 (m, 1H, H-7).

Ethyl 2-(N-tosyl-indol-2-yl)-propionate **16a**

To an ethanolic soln of ethyl 2 - (N - tosyl - indol - 2 - yl) - propionate (6.5 mmol) was added 100 mg 10% Pd–C and the mixture reduced at room temp. under atmospheric pressure. Filtration and crystallization from EtOH yielded 3 mmol (45%) **16a**. The mother liquor contained the isomeric ethyl 2 - (N - tosyl - 3 - hydro - indol - 2 - yl) methacrylate. By dissolving in THF and treatment with NaOEt during 3 hr at room temp., the isomer was converted into **16a**, total yield: 72%. **16a**: m.p. 94–96°. IR: 1730 (C=O). PMR: δ 1.18 (t, 3H, CH_3), 1.54 (d, 3H, CH_3), 2.27 (s, 3H, CH_3), 4.16 (q, 2H, OCH_2), 4.55 (q, 1H, C–H), 6.55 (s, 1H, H-3), 6.9–7.7 (m, 7H, aromatic protons), 8.0 (m, 1H, H-7).

Ethyl 2-hydroxy-2-(N-methyl-indol-2'-yl)-propionate

To a soln of 0.1 mol N-methylindole in THF at 0° was added 0.11 mol n-BuLi. After cooling to −50° 0.13 mol ethyl pyruvate was added dropwise and the mixture was stirred for 1 hr. AcOH was added till neutrality and after addition of water the mixture was extracted with ether. Recrystallization from EtOAc/petroleum ether afforded 63% of the product, m.p.: 53–54°. IR: 3530 (N–H), 1730 (C=O), 1460. PMR: δ 1.14 (t, 3H, CH_3), 1.87 (s, 3H, C–CH_3), 3.62 (s, 3H, N–CH_3), 3.68 (s, 1H, OH), 4.20 (q, 2H, OCH_2), 6.47 (s, 1H, H-3'), 7.0–7.7 (m, 4H, aromatic protons).

Ethyl 2-(N-methyl-indol-2'-yl)-propionate **16b**

A mixture of 25 mmol ethyl 2 - hydroxy - 2 - (N - methyl - indol - 2 - yl)propionate and 8 ml $POCl_3$ in 75 ml pyridine was stirred at room temp. during 1 hr and at 75° during 1.5 hr. After cooling, the mixture was poured upon ice and extracted with ether. Drying and evaporating of solvent produced crude ethyl 2 - (N - methyl - indol - 2 - yl) acrylate, which was dissolved in EtOH and stirred with 0.5 g $NaBH_4$ during 2 hr. Addition of water, extraction with ether and distillation afforded **16b** as a colourless oil, yield 58% (two steps). **16b**: b.p. 125–130°/0.01 mm. IR: 1730 (C=O), 1475. PMR: δ 1.18 (t, 3H, CH_3), 1.60 (d, 3H, CH_3), 3.62 (s, 3H, N–CH_3), 3.88 (q, 1H, H-2), 4.10 (q, 2H, OCH_2), 6.37 (s, 1H, H-3'), 7.0–7.7 (m, 4H, aromatic protons).

Addition of the anion of **16a** *to N-benzyl -3 - carbamoylpyridinium bromide, followed by oxidation to* **18**

To a cooled (−20°) suspension of 25 mmol NaOEt in THF was added 5 mmol **16a** and after 10 min 7 mmol N - benzyl - 3 - carbamoylpyridinium bromide. The mixture was stirred at room temp. for 5 hr. Neutralization (AcOH) and chromatography over a short column (silica–EtOAc/petroleum ether 1 : 1, followed by pure EtOAc) afforded 3 mmol (60%) of the instable dihydropyridine as a 1 : 1 mixture of stereo-isomers (according to NMR). The mixture was taken up in acetonitrile and stirred during 1 hr with 3 mmol N - benzylacridinium bromide. The product **18** could be filtered off, yield 95%. **18**: m.p. 203–204° (dec). IR(KBr): 1725, 1705 (C=O), 1640. PMR (d_6-DMSO): δ 2.16 (s, 3H, CH_3), 6.10 (s, 2H, CH_2Ph), 6.57 (s, 1H, H-3'), 6.9–7.8 (m, 9H, aromatic protons), 8.08 (d, 1H, J = 7, H-4), 9.37 (d, 1H, J = 7, H-3), 10.0 (s, 1H, H-1), 11.16 and 12.30 (2s, N–H).

Addition of the anion of **16b** *to N-benzyl - 3 - carbamoyl pyridinium bromide*

To a suspension of 40 mmol NaOEt in 80 ml THF was added 10 mmol **16b** at room temp. After cooling to 0° 15 mmol N - benzyl - 3 - carbamoyl pyridinium bromide was added and the mixture was stirred at room temp. during 2 hr. Addition of water and extraction with EtOAc, afforded a mixture (70%) from which one isomer crystallized (2.16 mmol, 22%).

Compound **17b**: m.p. 185–190°. IR: 3380 (N–H), 1705, 1690 (C=O), 1655, 1580. PMR: δ 1.71 (s, 3H, CH_3), 3.80 (s, 3H, N–CH_3), 4.16 (broad, 1H, H-4a), 4.45 (s, 2H, CH_2Ph), 4.91 (d × d, 1H, J = 3, J = 8, H-4), 5.94 (d × d × d, 1H, J = 2, J = 2, J = 8, H-3), 6.91 (s, 1H, H-3'), 7.0–7.5 (m, 10H, aromatic protons + H-1). **17b**. Mass spectrum: m/e = 398.1869 (calc. for $C_{25}H_{23}N_3O_2$: 398.1868).

2-Benzyl - 5 - methyl indolo[1,2,-b][2,7]*naphtyridin - 1 - (2H) - one* **20**

A soln of 0.5 g **18**, 2 g K_2CO_3 and 0.1 ml 2-ethoxyethanol in DMSO was heated at 80° during 2 hr. Addition of water, extraction with CH_2Cl_2 and evaporating the solvent afforded crude **20**. Trituration with EtOH and filtration yielded 0.3 g (82%) of **20** as brownish crystals. **20**: m.p. 217–219°. IR: 1670 (C=O), 1630, 1600, 1575 and 1545. PMR: δ 2.15 (s, 3H, CH_3), 4.80 (s, 2H, CH_2Ph), 6.4–6.6 (m + s, 3H, H-3, H-4, H-6), 7.2–7.4 (m, 7H, H-9, H-10, Ph), 7.60 (d, 1H, J = 6, H-7), 8.18 (s, 1H, H-1), 8.78 (d, 1H, J = 6, H-10). Mass (electron-impact): m/s = 338 ($M^{\oplus}$), 247 ($M-CH_2Ph$).

5 - *Methyl - indolo*[1,2-b][2,7] - *naphtyridin* - 11 (6H) - *one* **21**

N-benzyl derivative **20** (0.3 g), dissolved in 5 ml EtOH containing slight excess of conc. HCl was shaken with 0.1 g 10% Pd–C under H_2 at atmospheric pressure. After 3 hr, filtering the catalyst concentrating, and treating the residue with $NaHCO_3$ aq and EtOAc afforded **21** in 70% yield. **21**: m.p.: 180–182°. IR: 1665 (C=O), 1640, 1600. PMR: δ 2.38 (s, 3H, CH_3), 4.25 (s, 2H, H-6), 7.3–7.5 (m, 4H, H-4, H-7, H-8, H-9), 8.75 (d, 1H, J = 9, H-10), 8.77 (d, 1H, J = 6, H-3), 9.75 (s, 1H, H-1).

Acid cyclization of **17b** *to* **22**

A suspension of **17b** (0.1 g) in 3 ml EtOAc was refluxed with a catalytic amount of *p*-toluenesulphonic acid until a clear soln resulted (approx 10 min). Cooling the soln afforded **22** as colorless crystals (78%). **22**: m.p. 225–227°. IR: 3380 (N–H), 1680 (C=O), 1600. PMR: δ 1.63 (s, 3H, CH_3), 2.05, 2.30 (AB-system with extra coupling, 2H,

J = 13, J = 5, J = 2, H-7), 2.88 (d, 1H, J = 5, H-8), 3.88 (s, 3H, N–CH_3), 4.45, 4.62 (AB system, 2H, J = 16, CH_2Ph), 4.62 (broad, 1H, H-6), 7.1–7.6 (multiplet, 10H, aromatic protons + H-4), 8.0 (broad, 1H, N–H). Irradiating, the Me-signal and measuring the nOe-difference spectra gave strong signals for one of the protons H-7, H-8 and N–CH_3.

Reaction of **16b** *with nicotinoyl chloride*

A mixture of 10 mmol **16b** and 20 mmol nicotinoyl chloride (HCl-salt) in 15 ml sulfolane was stirred at 120° during 30 min. The resulting purple soln was diluted with water, neutralized with solid $NaHCO_3$ and extracted with EtOAc. Evaporating the solvent and chromatography over a short column (silica, EtOAc/petroleum ether 1 : 3 followed by 3 : 1) afforded **23** as a 1 : 1 mixture with sulfolane (yield 55%). **23**: oil. IR: 1725 (C=O), 1620, 1590. PMR: δ 1.13, (t, 3H, CH_3), 1.60 (d, 3H, J = 7, CH_3), 3.70 (s, 3H, N–CH_3), 4.11 (q, 2H, OCH_2), 4.77 (q, 1H, J = 7, C–H), 7.0–7.6 (m, 5H, aromatic protons + pyridine, H-5), 8.12 (d × d × d, 1H, J = 2, J = 2, J = 8, H-4), 8.80 (d × d, 1H, J = 2, J = 8, H-6), 8.99 (d, 1H, J = 2, H-2).

2 - *Benzyl* - 5 - *carbethoxy* - 5,6 - *dimethyl* 4a,5 - *dihydro* - *pyrido*[4,3,b]*carbazol*(5-H) - 11 - *one* **24**

A soln of **23** (contaminated with sulfolane) and excess benzyl bromide in $CHCl_3$ was kept overnight at room temp. The pyridinium-salt was absorbed on silica and the solvent evaporated. Sulfolane and excess benzyl bromide were removed by washing with EtOAc. For the cyclization to **24**, the salt-containing silica was suspended in EtOAc and stirred at room temp. with excess Et_3N. Filtering, washing the silica with EtOAc and evaporating the solvent yielded **24** as a 1 : 1 mixture of isomers. (81% over two steps). **24**: oil. IR: 1720, 1680 (C=O), 1570. PMR: δ 1.55, 1.71 (2s, 3H, C(5)–CH_3), 3.50, 3.65 (2s, 3H, N–CH_3), 4.30 (s, 2H, N–CH_2), 4.4–4.9 (2d × d, 1H, J = 2.5, J = 8, H-4a), 5.92 (m, 1H, H-3), 7–7.5 (m, 9H, aromatic protons + H-1), 8.40 (m, 1H, H-7).

N-Benzyl derivative of 5 - *carbethoxy*,5,6 - *dimethyl* - *pyrido*-[4.3-b]*carbazol* - (5H) - 11 - *one* **25**

The mixture of isomers **24** was dissolved in acetonitrile and stirred for 1 hr at room temp. with 1 equiv N-benzyl acridinium bromide. Addition of EtOAc gave 90% of **25** as yellow crystals.

Compound **25**: m.p. 178–180° (EtOH) IR: 1740, 1665 (C=O), 1620, PMR (d_6-DMSO: δ 1.08 (t, 3H, CH_3), 2.10 (s, 3H, C(5)–CH_3), 3.90 (s, 3H, N–CH_3), 4.23 (m, 2H, OCH_2), 6.10 (AB-system, 2H, J = 13, CH_2Ph), 7.50 (m, 5H, aromatic protons), 7.65 (m, 2H, H-8 + H-9), 7.85 (d, 1H, J = 8, H-10), 8.33 (d, 1H, J = 7, H-7), 8.45 (d, 1H, J = 7, H-4), 9.40 (d, 1H, J = 7, H-3), 9.92 (s, 1H, H-1).

5 - *Carbethoxy*,5,6 - *dimethyl* - *pyrido* - [4,3-b]*carbazol*(5H)-11 - *one* **25**

A suspension of the N-benzyl-derivative of **25** (1 g), 1.0 g $NaHCO_3$ and 0.15 g 10% Pd–C in 50 ml EtOH was shaken under 1 atm H_2 pressure during 5 hr. Catalyst and solvent were removed and the residue was dissolved in EtOAc, filtrated and diluted with petrolum ether. The product was obtained as yellow crystals in 80% yield, **25**: m.p. 134–135°.

IR: 1735, 1645 (C=O), 1585. PMR: δ 1.05 (t, 3H, J = 7, CH_3), 1.98 (s, 3H, CH_3), 3.82 (s, 3H, N–CH_3), 4.17 (q, 2H, OCH_2), 7.3–7.5 (m, 4H, aromatic protons), 8.53 (m, 1H, H-10), 8.29 (d, 1H, J = 6, H-3), 9.61 (s, 1H, H-1). **25**. Found: N, 8.27, $C_{20}H_{15}N_2O_3$ requires: N, 8.38.

11 - *Hydroxy* - 5,6 - *dimethyl* - *pyrido* - [4,3-b]*carbazole* **26**

A soln of **25** in EtOH was refluxed with 2.5 equiv NaOEt during 30 min. After cooling, addition of AcOH produced **26** as a red ppt (50%). The product is highly insoluble in most organic solvents but can be crystallized from DMF, **26** m.p.: 220–225°. IR (KBr): 1640, 1605, 1540 and 1460 cm^{-1}. PMR (d_6-DMSO): δ 2.93 (s, 3H, CH_3), 4.20 (s, 3H, N–CH_3), 7.26 and 7.47 (2t, 2H, J = 8, H-8 + H-9), 7.59 (d, 1H, J = 8, H-7), 7.86 (d, 1H, J = 7, H-4), 8.13 (d, 1H, J = 8, H-10), 8.48 (d, 1H, J = 7, H-3), 9.45 (s, 1H, H-1), UV (C_2H_5OH): 294, 323, 400, 470 nm. MS (FD): 262 (M^+).

Reaction of Grignard reagents with **25**

To a soln of 0.2 mmol **25** in THF were added *ca* 5 equiv. of the Grignard reagents. After 3 hr at 20° and 5 min reflux the solvent was evaporated. The residue was heated at 160° during 15 min in a mixture of 50% KOH aq in ethylene glycol. The product was isolated by extraction with EtOAc and subsequent recrystillization.

6-*Methylellipticine* **27a**

From MeMgI **27a**: (40%) m.p. 211–212° (water/EtOH). IR: 1595, 1470, PMR: δ 3.00 (s, 3H, C(5)–CH_3), 3.14 (s, 3H, C(11)–CH_3), 4.08 (s, 3H, N–CH_3), 7.30, 7.58 (2t, 2H, J = 8, H-8 + H-9), 7.38 (d, J = 8, H-7), 7.86 (d, 1H, J = 7, H-4), 8.32 (d, 1H, J = 8, H-10), 8.46 (d, 1H, J = 7, H-3), 9.64 (s, 1H, H-1). Mass spectrum: *m/e* = 260.1307 (Calc. for $C_{18}H_6N_2$: 260.1301). Found: C, 82.9; H, 6.3; N, 10.7; $C_{18}H_6N_2$ requires: C, 83.04; H, 6.19; N, 10.76.

11-*n-Butyl*-5,6-*dimethylpyrido*-[4,3-b]*carbazole* **27b**

From n-butylmagnesium bromide. **27b**: (25%). m.p. 143–144° (EtOAc/petroleum ether). IR: 1595, 1470. PMR: δ 1.05 (t, 3H, CH_3), 1.65 (sextet, 2H, CH_2), 1.90 (quintet, 2H, CH_2), 3.04 (s, 3H, C(5)–CH_3), 3.68 (t, 2H, C–(11)–CH_2), 4.10 (s, 3H, N–CH_3), 7.28, 7.55 (2t, 2H, J = 8, H-8 + H-9), 7.40(d, 2H, J = 8, H-7), 7.90 (broad, 1H, H-4), 8.24 (d, 1H, J = 8, H-10), 8.50 (broad, 1H, H-3), 9.68 (broad, 1H, H-1). Mass spectrum: *m/e* = 302.1762 (Calc. for $C_{21}H_{22}N_2$: 302.1741).

11-*Benzyl*-5,6-*dimethylpyrido*-[4,3-b]*carbazole* **27c**

From benzyl magnesium bromide. **27c**: (40%) m.p. 226–229°. IR: 1595, 1470, 1390. PMR: δ 3.12 (s, 3H, C–CH_3), 4.18 (s, 3H, N–CH_3), 5.13 (s, 2H, CH_2Ph), 7.13, 7.52 (2t, 2H, J = 8, H-8 + H-9), 7.16 (s, 5H, Ph), 7.41 (d, 1H, H-7), 7.92 (d, 1H, H-4), 8.11 (d, 1H, J = 8, H-10), 8.48 (broad, 1H, H-3), 9.55 (broad, 1H, H-1), Mass spectrum: *m/e* = 336.1624 (Calc. for $C_{24}H_{20}N_2$: 336.1622).

11-*Phenyl*-5,6-*dimethylpyrido*-[4,3-b]*carbazole* **27d**

From phenylmagnesium bromide. **27d**: (44%): m.p. 254–256° (EtOAc). IR: 1590, 1470, 1390. PMR: δ 3.15 (s, 3H, C–CH_3), 4.16 (s, 3H, N–CH_3), 6.78 (d, 1H, J = 8, H-10), 6.91 (t, 1H, J = 8, H-9), 7.38 (d, 1H, J = 8, H-7), 7.45 (m, 3H, H-8 + 2H–Ph), 7.62 (m, 3H, Ph), 7.95 (broad, 1H, H-4), 8.49 (broad, 1H, H-3), 9.02 (broad, 1H, H-1). Mass spectrum: *m/e*: 322.1499 (Calc. for $C_{23}H_{18}N_2$: 322.1528).

5-*Carbethoxy*-5,6-*dimethyl*-11-*methylene* *pyrido*[4,3-b]*carbazole* **28**

To 7 mmol methyl triphenylphosphonium iodide in THF at −10° was slowly added 7 mmol n-BuLi followed by 3 mmol **25**. The mixture was stirred at 0–10° during 3 hr. Chromatography over a short column (silica–EtOAc/petroleum ether 1 : 1) yielded **28** as an oil (approx 65%), which polymerizes and oxidizes upon standing and consequently was used immediately in the next step. **28**: unstable oil. IR: 1725 (C=O), 1625 (C→C), 1590. PMR: δ 1.08 (t, 3H, CH_3), 1.90 (s, 3H, C(5)–CH_3), 3.67 (s, 3H, N–CH_3), 4.12 (m, OCH_2), 5.98, 6.02 (2s, 2H, C=CH_2), 7.3–7.5 (m, 4H, H-4, H-7, H-8, H-9), 8.08 (d, 1H, J = 8, H-10), 8.53 (d, 1H, J = 6, H-3), 9.32 (s, 1H, H-1).

Reaction of **28** *with N-chlorosuccinimide*

The product of the preceding reaction was dissolved in 20 ml CH_2Cl_2. After addition of 2.2 mmol N-chlorosuccinimide, the mixture was stirred at room temp. (1 hr). The solvent was evaporated and the residue was taken up in EtOH. Cooling produced **29** as white crystals (58% over two steps; 3 : 2; mixture of isomers). **29** m.p. 190–200°. IR:

1720, 1705 (C=O), 1600. PMR: δ 1.03 (t, 3H, CH_3), 2.08 (s, 3H, CH_3), 2.64 (s, 4H, CH_2CH_2), 3.73 (s, 3H, N–CH_3), 4.20 (m, 2H, OCH_2), 4.96, 5.20 (AB-system, 2H, J = 11, CH_2Cl), 7.0 7.7 (m, 5H, aromatic protons), 8.58 (d, 1H, J + 5, H-3), 8.77 (broad, 1H, H-1). Separate signals occurring from the minor isomer: 1.16 (t, 3H, CH_3), 2.01 (s, 3H, CH_3), 4.92, 5.19 (AB-system, 2H, J = 11, CH_2Cl).

11-*Hydroxymethyl*-5,6-*dimethyl pyrido*[4,3-b]*carbazole* **30a**

To a soln of 1.5 g KOH in 3 ml water and 10 ml ethylene glycol was added 0.8 g **29**. Upon heating at 160–170° the soln turned yellow and after 10 min the product crystallized. Cooling and addition of water afforded 0.36 g of **30a** as yellow needles (77%). **30a**: m.p. 251–253°. IR: 3200 (OH), 1600, 1590, 1470. PMR: δ 3.06 (s, 3H, C–CH_3), 4.13 (s, 3H, N–CH_3), 5.53 (s, 3H, CH_2OH), 7.35, 7.62 (2m, 2H, H-8, H-9), 7.62 (m, 1H, H-7), 8.03 (d, 1H, J = 6, H-4), 8.46 (d, 1H, J = 8, H-10), 8.48 (d, 1H, J = 6, H-3), 9.77 (s, 1H, H-1). **30a**. Found: N, 9.90, $C_{18}H_{16}N_2O$ requires: N, 10.13.

11-*Chloromethyl*-5,6-*dimethylpyrido*[4.3-b]*carbazole* **30b**

A suspension of **30a** in $SOCl_2$ was stirred at room temp. during 2 hr. After removing excess of reagent *in vacuo* at room temp. the remaining yellow solid was used immediately in the substitution reactions.

11-(2-*Hydroxyethylamino*)5,6-*dimethyl pyrido*[4,3-b]*carbazole* **30c**

Chloride **30b** obtained from 0.25 mmol **30a** was heated at 100° in 1 ml 2-aminoethanol until the starting material dissolved (15 min). Cooling and addition of water afforded **30c** in 70% yield. **30c**: yellow crystals. m.p.: 167–171° (EtOH-ether). IR: 3600–3400 (OH–NH), 1600, 1470. PMR: δ 3.05 (s, 3H, CH_3), 3.1 (broad, 2H, CH_2N), 3.82 (broad, 2H, CH_2O), 4.11 (s, 3H, N–CH_3), 5.05 (s, 2H, C-(11)–CH_2), 7.38, 7.60 (2t, 2H, H-8, H-9), 7.45 (d, 1H, H-7), 7.92 (d, 1H, J = 6, H-4), 8.37 (d, 1H, J = 8, H-10), 8.46 (d, 1H, J = 6, H-3), 9.90 (s, 1H, H-1). **30a** Found: N, 9.90, $C_{18}H_{16}N_2O$ requires: N, 10.13.

11-(*Bis*-2-*hydroxyethyl*)*amino*-5,6-*dimethylpyrido*[4,3-b]*carbazole* **30d**

Chloride **30b** (obtained from 0.25 mmol **30a**) was refluxed in acetonitrile with 1.5 mmol bis(2-hydroxylethyl) amine (30 min). After cooling, addition of water, extraction with $CHCl_3$ and recrystalizing the residue from MeOH afforded 0.15 mmol of **30d** (60%). **30d**: m.p. 190–193°. IR: 3500–3000 (OH), 1590, 1470. PMR: δ 2.90 (t, 4H, J = 7, CH_2N), 3.07 (s, 3H, CH_3), 3.55 (t, 4H, J = 7, CH_2O), 4.15 (s, 3H, N–CH_3), 4.87 (s, 2H, CH_2N), 7.30, 7.58 (2t, 2H, J = 8, H-8, H-9), 7.40 (d, 1H, J = 8, H-7), 7.90 (d, 1H, J = 6, H-4), 8.40 (d, 1H, J = 6, H-3), 8.48 (d, 1H, J = 8, H-10), 9.92 (s, 1H, H-1).

11-(*Bis*-2-*chloroethyl*)*amino*-5,6-*dimethylpyrido*[4,3-b]*carbazole* **30e**

A soln of 0.25 mmol **30d** in $SOCl_2$ was kept at room temp. during 20 hr. The crystals of **30e** (as its hydrochloride salt) were collected and washed with ether, yield 60%. **30e** (HCl): IR (KBr): 3500–2200 (ammonium-salts), 1635, 1575. PMR (CD_3OD): 3.12 (t, 4H, J = 7, CH_2N), 3.23 (s, 3H, CH_3), 3.65 (t, 4H, CH_2Cl), 4.35 (s, 3H, N–CH_3), 5.15 (s, 2H, CH_2N), 7.44, 7.75 (2m, 2H, H-8, H-9), 7.75 (m, 1H, H-7), 8.37 (d, 1H, J = 7, H-4), 8.56 (d, 1H, J = 7, H-3), 8.65 (d, 1H, J = 8, H-10), 10.40 (s, 1H, H-1). MS (FD) 399.401 (M^+).

11-(β-*D*-*Ribofuranos*-1′-*yl*)-5,6-*dimethylpyrido*[4,3-b]*carbazole* **30f**

To a suspension of 0.2 mmol **30a** and 0.5 mmol 2,3,5-tribenzoyl-ribofuranosyl acetate in 2 ml acetonitrile were added two drops $SnCl_4$. The mixture was stirred at room temp. during 2 hr. The yellow soln was poured into 10 ml $CHCl_3$ containing 1 ml Et_3N. The product was purified by chromatography over a short column (silica, EtOAc/petroleum ether 1 : 1). The tribenzoate of **30f** was dissolved in 1 ml dry THF. The soln was diluted with 1 ml MeOH and a catalytic amount of NaOMe was added. The mixture was stirred overnight at room temp. and the crystals collected (0.17 mmol, 86%). **30f**: m.p. 243–245°. IR (KBr): 3500–3000 (OH), 1600, 1475). PMR (d_6-DMSO), 3.10 (s, 3H, C–CH_3), **30f**. Mass spectrum: m/e = 408, 1675 (calc. for $C_{23}H_{24}N_2O_5$: 408.1680). 3.5–3.7 (m, 3H, H-4′), H-5′), 3.9 (m, 2H, H-2′, H-3′), 4.18 (s, 3H, N–CH_3), 5.09 (s, 1H, H-1′), 5.18 (AB-system, 2H, C-(11)–CH_2), 7.28 (t, 1H, H-8 or H-9), 7.63 (m, 2H, H-7, H-8 or H-9), 8.66 (d, 1H, H-4), 8.48 (d, 2H, H-3, H-10), 9.80 (s, 1H, H-1).

Reaction of **16b** *with 2-methylnicotinoyl chloride*

A soln of 10 mmol **16b** and 11 mmol 2-methylnicotinoyl chloride (HCl-salt) in 15 ml sulfolane was stirred at 160–170° during 20 min. The resulting soln was diluted with water, neutralized with solid $NaHCO_3$ and extracted with EtOAc. **31** was obtained as a mixture with sulfolane in about 30% yield. **31** oil. IR: 1730, 1620 (C=O), 1580. PMR: δ 1.25 (t, 3H, CH_3), 1.66 (d, 3H, J = 7, CH_3), 2.55 (s, 3H, CH_3), 3.76 (s, 3H, N–CH_3), 4.25 (q, 2H, OCH_2), 5.05 (q, 1H, Me–C–H), 6.5–7.5 (m, 15H, aromatic protons), 7.70 (d × d, 1H, J = 1.5, J = 7, H-4), 8.66 (d × d, 1H, J = 1, J = 5, H-6).

Cyclization to **32**

The mixture of **31** and sulfolane was heated at 110° with excess benzyl bromide during 30 min. After cooling the mixture was dissolved in $CHCl_3$ absorbed on silica and washed with EtOAc. The salt-containing silica was suspended in EtOAc and stirred with an excess Et_3N during 1 hr. The product of the cyclization was, without further purification, dissolved in acetonitrile and stirred with 3.5 mmol N-benzyl acridinium bromide. Upon addition of EtOAc 1.8 mmol **32** was obtained as yellow crystals (18%, based upon **16b**), **32**: m.p.: 174–177°. IR: 1740, 1655 (C=O), 1615. PMR: δ 1.16 (t, 3H, CH_3), 2.10 (s, 3H, C(5)–CH_3), 3.50 (s, 3H, C(1)–CH_3), 3.86 (s, 3H, N–CH_3), 4.28 (q, 2H, OCH_2), 6.23 (s, 2H, CH_2Ph), 7.3–7.5 (m, 8H, aromatic protons), 8.22 (d, 1H, J = 7, H-4), 8.41 (m, 1H, H-10), 9.98 (d, 1H, J = 7, H-3).

5-*Carbethoxy*-1,5,6-*trimethyl*-*pyrido*[4,3-b]*carbazol*-(5H)-11-*one* **33**

A soln of 0.85 g **32** in 10 ml EtOH was hydrogenated with 0.15 g (10%) Pd–C and 1.0 g $NaHCO_3$ during 3 hr at atmospheric pressure. Catalyst and solvent were removed and the residue was dissolved in hot EtOAc. Filtration and cooling yielded 81% **33** as yellow crystals. **33**: m.p.: 162–164°. IR: 1730, 1640 (C=O), 1570. PMR: δ 1.06 (t, 3H, CH_3), 1.95 (s, 3H, C(5)–CH_3), 3.22 (s, 3H, C–(1)–CH_3), 3.78 (s, 3H, N–CH_3), 4.17 (q, 2H, OCH_2), 7.35 (d, 1H, J = 6, H-4), 7.40 (m, 3H, aromatic protons), 8.45 (m, 1H, H-10), 8.63 (d, 1H, J = 6, H-3). **33**. Found: N, 7.77, $C_{21}H_{17}N_2O_3$ requires: N, 8.04.

1,5,6-*Trimethylpyrido*[4,3-b]*carbazole* (*olivacine*) **34**

To a soln of **33** (0.3 mmol) in THF was added 0.6 mmol sodium bis-methoxy-ethyleneoxy aluminiumhydride (Redal) (dissolved in toluene) in portions, over a period of 2 hr. The product was purified by chromatography over a short column (silica–EtOAc), yield 57%. **34**: m.p. 228–229°. (EtOAc). IR: 1625, 1600. PMR: δ 2.81 (s, 3H, C–(1)–CH_3), 2.98 (s, 3H, C–(5)–CH_3), 3.86 (s, 3H, N–CH_3), 7.15–7.35 (m, 2H, H-8 + H-9), 7.49 (d, 1H, J = 8, H-7), 7.63 (d, 1H, J = 6.5, H-4), 8.06 (d, 1H, J = 8, H-10), 8.32 (d, 1H, J = 6.5, H-3), 8.39 (s, 1H, H-11). MS: Found 260.1302. Calc. for $C_{18}H_{16}N_2$: 260.1301. Found: C, 82.7, H, 6.2; N, 10.6; $C_{18}H_{16}N_2$ requires: C, 83.04; H, 6.19; N, 10.76.

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