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SYNTHESIS OF POLYNUCLEAR HETEROCYCLES VIA THE REACTION OF α-ESTER CARBANIONS WITH QUATERNIZED NICOTINAMIDE SALTS. A FACILE STEREOSELECTIVE SYNTHESIS OF SESBANINE[1]

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Abstract—α-Ester carbanions add to N-benzylnicotinamide salts to give C-4 and C-6 substituted primary products. The C-4 substituted dihydronicotinamides undergo a further reaction involving nucleophilic attack of the amide nitrogen on the carbonyl group of the ester. The resulting cyclization products can be oxidized and debenzylated to 1,2-dioxo-1,2,3,4-tetrahydro-2,7-naphthyridine derivatives. The sequence of reactions has been utilized in the synthesis of several polynuclear heterocycles and in the stereoselective synthesis of the alkaloid sesbanine.

In 1979 Powell and coworkers reported on the antileukemic properties of an extract of the seeds of *Sesbania Drummondii*.[2] The active principle was named sesbanine and its structure was shown to be **1** (Scheme 1) by X-Ray crystallography. The unusual spirocyclic 2,7-naphthyridine structure of sesbanine, together with its reported cytostatic activity, stimulated interest in our and other laboratories[3] in the development of a synthetic scheme for the preparation of this interesting compound on a practical scale. Recently, however, Powell and Smith[4] have reported that cytostatic activities on P-388 lymphocytic leukemia *in vivo* and KB-cells *in vitro*, found in the extracts of Sesbania seeds, were not due to sesbanine. Since the structures of the active principles are not as yet known, it remains uncertain whether or not these are related to the spirocyclic [2,7]-naphthyridine skeleton.

We now report the details of an approach to sesbanine which is of general application to this class of compounds. Preliminary results on the subject have been communicated earlier.[1] In the scheme which has been developed the principal steps consist of (a) the addition of a suitably functionalized anion **2** to N-benzyl-3-carbamoylpyridinium bromide **3**, and, (b) under conditions of the reaction, the cyclization of the intermediate adduct **4**, to the imide system **5**.[5]

It should be emphasized that this approach leads to formation of the tricyclic skeleton of the alkaloid in one practical step (Scheme 1). For purposes of the discussion we shall consider the chemistry of these steps in detail.

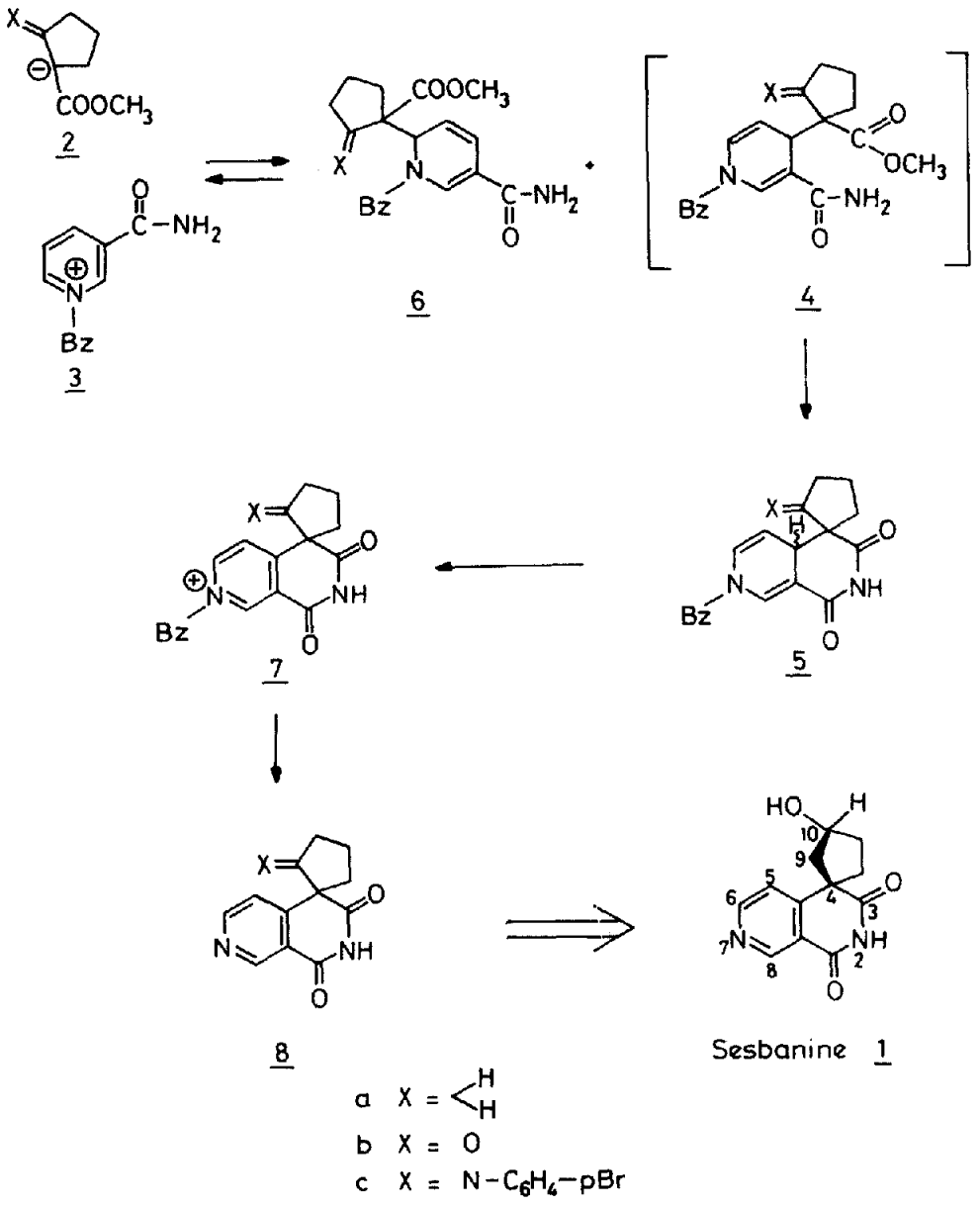
Nucleophilic addition to pyridinium salts

The addition of nucleophiles to pyridinium salts, leading to dihydropyridines, has been the subject of a variety of theoretical[6] and experimental[7,8] studies. According to frontier orbital considerations,[6] addition at C-4 or C-6 can be expected, depending on the hardness of the nucleophile. However, even when the 1,4-dihydropyridine is thermodynamically favoured, addition at C-6, under kinetic control, cannot be excluded. If the nucleophile itself is sufficiently stable, rapid addition and elimination reactions lead to an equilibrium in which ultimately the thermodynamically more stable 1,4-dihydropyridine becomes the major product.[8b] This isomerization was shown by Damji and Fyfe[7] to occur, for instance, in the reaction of 3-cyanopyridinium methiodide with methoxide as the nucleophile. In our study, equilibria between **4** and **6** are to be expected, when the reaction is carried out with relatively stable carbanions, such as **2b,c**.

In intermediates of type **4**, subsequent attack of the carbamoyl group on the ester carbonyl leading to formation of the cyclic imides **5b,c**, will, independent of the original composition of the mixture, drive the reaction to completion.[5] With less stable anions, such as **2a**, production of a mixture of **4a** and **6a** would be anticipated. When the reaction of N-benzyl-3-carbamoyl pyridinium bromide **3** with **2a** was carried out, formation of an isomeric mixture was indeed observed. Thus the anion of **2a**, obtained by treatment with lithium diisopropylamide (THF, −76°), reacted with **3**, at −30°, to give a yellow crystalline product (m.p. 174–178°, 51%) whose spectral data were in agreement with structure **5a**. From the mother liquor 25% of the 1,6-dihydropyridine **6a** could be isolated as a colourless oil. On the other hand, as expected, the reaction of **3**, with the more stable anion **2c**, led to the imide **5c** as the sole product, in 97% yield.

In the case of 2-carbethoxycyclopentanone **2b**, the presence of the keto function provided an alternate course for the reaction. While the addition of the preformed potassium salt of **2b** to **3**, took place as expected, this was followed by the attack of the carbamoyl function on the keto group, with the formation of a tricyclic system **9** as a mixture of isomers (67%) from which one isomer could be crystallized. The latter product was oxidized and debenzylated to **10** via a sequence of reactions, to be described later (*vide infra*). The ring junction in **10** was assigned the *cis* configuration in view of the observed magnetic non-equivalence of the ester-methylene group. This difference in chemical shift of the two protons was considerably increased by converting the hydroxyl group into the corresponding TMS ether.

Hydroxylactam **10** was readily dehydrated to the cyclic enamide **11**, whose structure was conclusively established by its synthesis via a sequence of reactions, shown in Scheme 3.

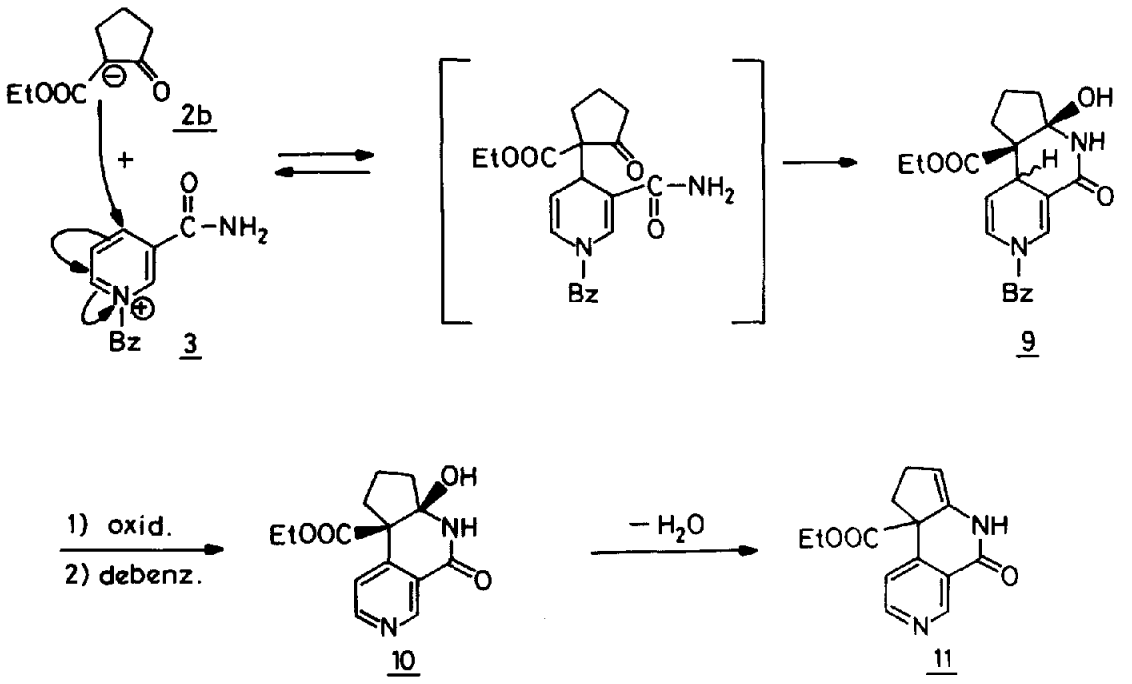


Scheme 1.

Reaction of nicotinamide and 2-carbethoxycyclopentanone, under acidic conditions, afforded enamide **12**, which was converted into the white crystalline salt **13** by treatment with benzyl bromide. Cyclization of salt **13**, to **14**, was achieved by reaction with 1,5-diazabicyclo[4,3,0]nonene-5[9] at room temperature. Oxidation of the dihydropyridine derivative **14**, followed by debenzylation of the resulting salt **15**, yielded tricyclic enamide ester **11**, which was identical to the product obtained in Scheme 2.

That, by addition of carbanions to quaternized nicotinamide **3**, interesting polyheterocyclic compounds can be obtained with facility, is further exemplified by the reaction described in Scheme 4. Reaction of anion **16**, obtained from the ethyl ester of N-benzylidene alanine[10] produced the expected 2,7-naphthyridine system **17** in good yield. The *cis* relation of the proton at C-4a and the methyl group at C-4 was established via nuclear Overhauser difference spectroscopy. Upon irradiating the methyl group at $\delta = 1.47$ protons at $\delta = 4.88$ and $\delta = 4.03$ showed a large increase in intensity of the signal (see expt.). When **17** was treated with acetic acid in methanol, further cyclization to **18** was affected. The stereochemistry of **18** was also clarified by studying nuclear Overhauser Effects. Proton signals of H_9 (at $\delta = 2.88$, d×d, J = 6, J = 2), H-2a (at $\delta = 3.17$, d×d×d, J = 9, J = 7, J = 1.6), and H-2 (at $\delta = 4.75$, d, J = 9) all showed considerable increase in intensity upon irradiating the methyl signal at $\delta = 1.58$.

The *trans* relation of the phenyl and the methoxy

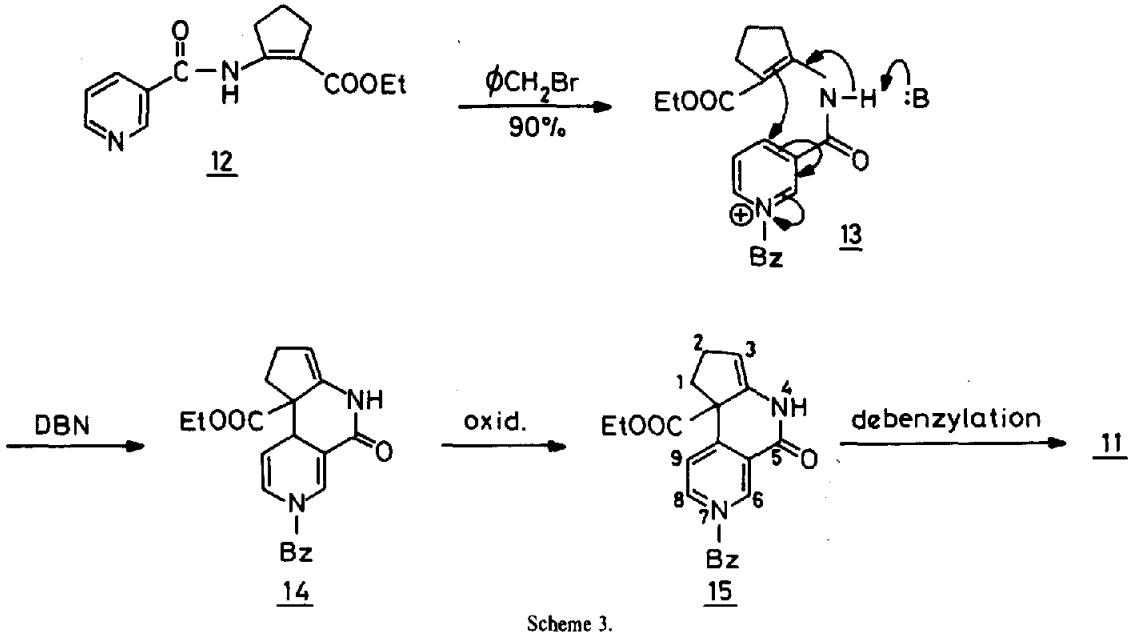


Scheme 2.

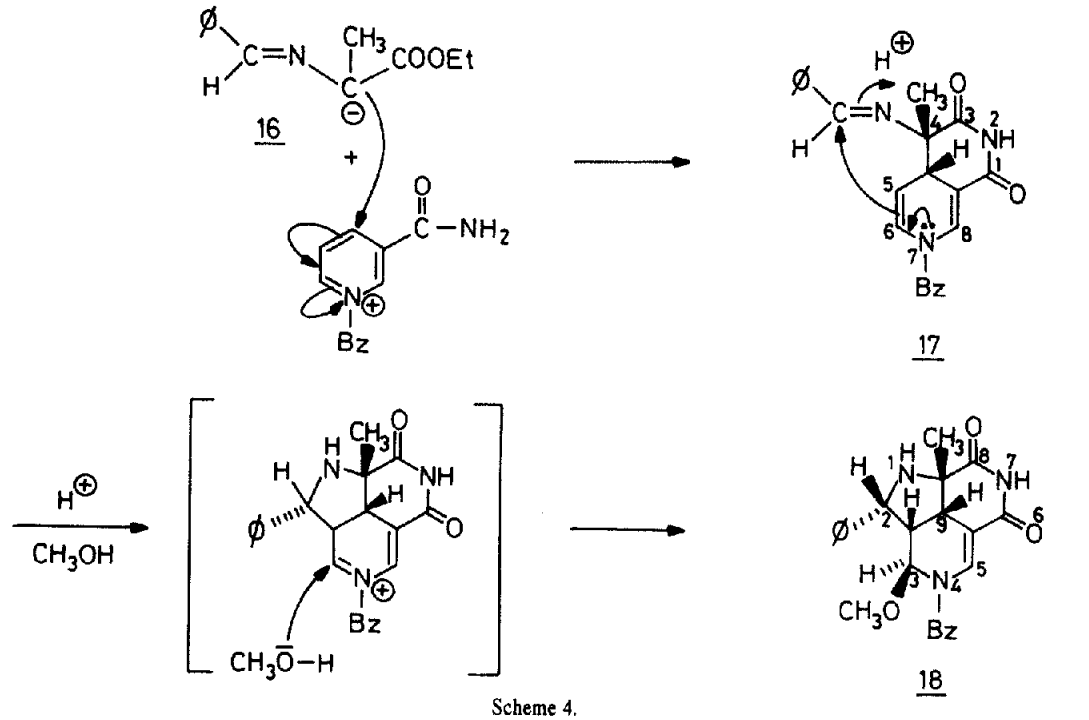
groups was deduced from the chemical shift of proton H-3. The signal at $\delta = 4.0$ for this proton suggests strong shielding by an aromatic system.

Oxidation and debenzylation of the addition products

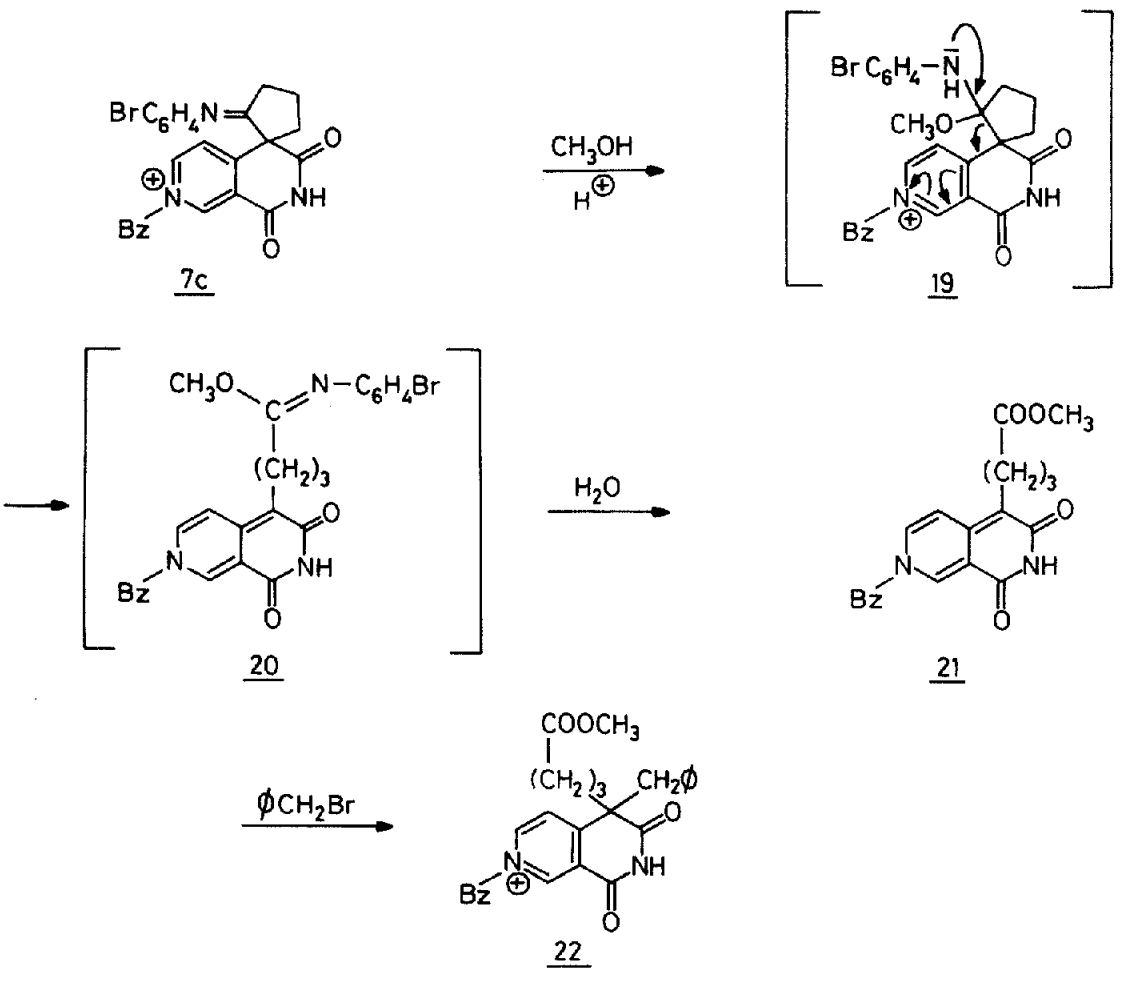
The products obtained in the reactions of carbanions with pyridinium salts consist of dihydropyridines. Although the stability of these systems is dependent on the nature of the substituents, they are, nevertheless, more or less reactive hydride donors, which can be oxidized by potent hydride acceptors, such as N-benzyl- or N-carbethoxymethylene quinolinium salts. In our hands the latter systems proved to be the most suitable oxidizing reagents for dihydropyridines, such as **5a,c**, **9**, **14**. The reactions were clean and rapid, at room temperature. Recently[11] excellent results on dehydrogenation of dihydropyridines have been obtained with N-benzyl-acridinium bromide, which is a still more reactive hydride acceptor. The pyridinium salts obtained in these reactions are usually stable compounds which can be



Scheme 3.



Scheme 4.



Scheme 5.

further handled conveniently. Treatment of **7c** with methanol/HCl (reflux) however, resulted in ring opening and hydrolysis, according to the sequence of reactions described in Scheme 5. The end product **21** reacted with benzyl bromide to give **22** as a thick oil. Pyridinium salts **7a,c**, **15** and that derived from **9** were debenzylated by hydrogenolysis over palladium, to give **8a,c**, **10** and **11**, respectively. Good results were also obtained by debenzylation with triphenylphosphine in DMF.

Synthesis of sesbanine and 10-*epi-sesbanine*

Based upon the chemistry developed thus far, a convenient route to sesbanine (**1**) would utilize two synthons, namely **23** and N-benzyl-3-carbamoylpyridinium bromide (**3**) (Scheme 6).

The sequence for the preparation of the cyclopentyl ester **23** was carried out according to the literature procedure.[12] The beta keto-ester obtained, was converted into the acetal **23** by standard procedures.

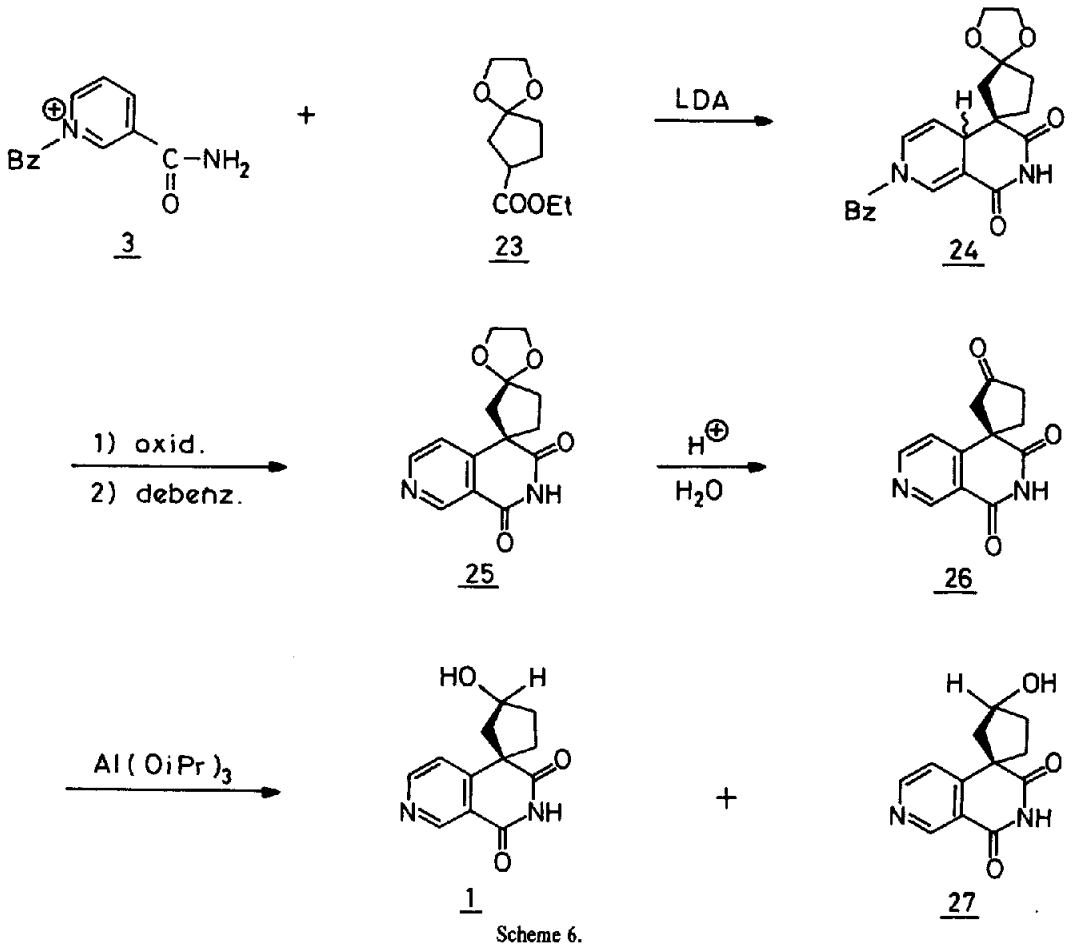
Addition of the anion of **23** (LDA/THF, −76°) to **3** gave the 2,7-naphthyridine derivative **24**, along with the C-6 addition product. Chromatography yielded **24** as a mixture of stereoisomers. Oxidation of this mixture was carried out with N-benzylquinolinium bromide and the subsequent removal of the benzyl group could be most conveniently achieved by heating the pyridinium salt at 230°C/0.01 mm, for a short time. During this treatment the product **25** sublimes and is thereby obtained in a purified state (78%, m.p. 224–225°, from methanol).

Deprotection of **25** by refluxing in aqueous methanol/HCl produced sesbanone **26** in 85% yield.

The last step in the synthesis of sesbanine consists of reduction of the ketone function in **26**. Attempts to achieve this by reaction with sodium borohydride, even at −15°, resulted in additional reduction of one of the imide carbonyl groups. The keto group could, however, be smoothly reduced by using the Meerwein–Ponndorf Verley reduction procedure.[13] When **26** was refluxed with 5 equivalents of aluminium-isopropoxide in isopropanol (4 h), a mixture of sesbanine **1** and epi-sesbanine **27** was obtained. Chromatography over silica yielded the pure compounds in a 6:1 ratio. The stereoselectivity observed in the reduction is most likely the result of steric hindrance to the attack of the alcoholate reagent by the peri proton of the naphthyridine system.

For the reduction to proceed, it is essential that the hydride ion in the complex approaches the carbonyl carbon atom at an angle of approximately 105°.[14] As can be anticipated, such a mechanism would require a fairly rigid transition state.

While, in principle, both faces of the carbonyl of the cyclopentanone moiety can be attacked, inspection of models strongly suggests that the transition state in which the hydride approaches from the side (of the



Scheme 6.

cyclopentanone ring) remote from the peri hydrogen, is highly favoured.

The scope of the annelation reaction, involving the addition of ester anions to nicotinamide salts, and its application to the synthesis of polyheterocycles and alkaloids is being actively pursued in this 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 samples with dry nitrogen 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.

Addition of nucleophiles to N-benzyl-3-carbamoyl pyridinium bromide **3**

(a) *Reaction with ethyl cyclopentanecarboxylate.* To a freshly prepared solution of 6.2 mmol Lithium diisopropylamide in 15 ml of dry THF at −76° was added 6.2 mmol ethyl cyclopentanecarboxylate **2a** under a nitrogen atmosphere. After ten minutes 3 mmol **3** was added and the mixture was slowly warmed to −30°/−20°C. The mixture was kept at this temperature during four hours, after which 3 mmol acetic acid was added. Shaking with water and chloroform and evaporating the chloroform after drying, produced an oily residue. This was triturated with ethyl acetate upon which **5a** was obtained as yellow crystals in 51% yield. Chromatography of the mother liquor (silica, ethyl-acetate/methanol 20:1) produced 25% of **6a** as a colourless oil. **5a**: m.p. 174–178°. IR(KBr): 3200 (N–H), 1700, 1670 (C=O), 1660, 1580. PMR (DMSO-d_6): 1.5–1.8 (m, CH_2CH_2), 2.0–2.5 (m, CH_2), 3.7–3.8 (m, H-4a), 4.45 (s, CH_2Ph), 4.58 (d × d, H-5, J = 2, J = 8), 6.14 (d × d × d, H-6, J = 1, 5, J = 2, J = 8), 7.22 (d, H-8, J = 1.5), 7.31 (s, Ph), 10.1 (broad, N–H). MS (70 eV): 308 (M^+). **6a**: Oil, IR: 3530, 3240 (NH_2), 1710 (C=O ester), 1650 (C=O, amide); PMR: 1.20 (t, 3H, CH_3), 1.3–2.4 (m, 4 × CH_2), 4.08 (q, 2H, $COOCH_2$), 4.47 (d × d, 1H, H-6, J = 1, J = 5), 4.95 (d × d, 1H, H-5, J = 10, J = 5), 5.55 (broad signal, 2H, NH_2), 6.37 (d × d, 1H, H-4, J = 1, J = 10), 7–7.4 (m, 6H, phenyl + H-2).

(b) *Reaction with ethyl 2-(p-bromophenylamino)cyclopent-1-enecarboxylate* **2c**. To a suspension of 80 mmol sodium hydride in dry THF at −20° was added, portionwise, 80 mmol of **2c** under N_2. When the evolution of hydrogen had ceased, the solution was cooled to −40° and 40 mmol of **3** was added. After 4 h stirring at room temperature, 40 mmol of acetic acid was added. The reaction mixture was adsorbed on silica (± 100 g) and after evaporating the solvents the silica was transferred to a glass-filter and eluted with ethyl-acetate/petroleum ether 1:3, to remove the excess of **2c**. The product **5c** was obtained by eluting with ethyl acetate/petroleum ether 1:1 as a yellow amorphous compound in 97% yield. **5c**: IR: 3400 (N–H), 1705 (C=O), 1685 (C=O), 1660. PMR: 1.5–3.0 (m, $CH_2CH_2CH_2$), 4.38 (s, CH_2Ph), 4.56 (d × d, H-5, J = 2.5, J = 8), 4.64–4.70 (m, H-4a), 5.90 (d × d × d, H-6, J = 2, J + 2.5, J = 8), 6.62 (d, J = 9, 2ArH), 7.1–7.5 (m, Ph + 2ArH), 8.25 (broad, N–H).

(c) *Reaction with ethyl 2-oxo-cyclopentanecarboxylate* **2b**. To a solution of 1 mmol **2b** (potassium salt)[16] in 2 ml ethylacetate under a nitrogen atmosphere was added 1 mmol **3** and the mixture stirred at room temperature during 2 h. The potassium bromide was removed by filtration and the filtrate kept at −20° during one night. Tricyclic product **9** was obtained as yellow crystals (67%; one isomer). **9**: IR: 3400 (N–H), 3300 (broad, O–H), 1720 (C=O, ester), 1680 (C=O, lactam), 1630, 1580; PMR: 1.23 (t, CH_3), 1.5–2.5 (m, 3 × CH_2), 4.17 (q, $COOCH_2$), 4.47 (d × d, H-4, J = 2, J = 8), 4.30 (s, $PhCH_2$), 4.5–5.5 (broad, OH), 5.76 (d × d × d, H-5, J = 6, J = 2, J = 2), 6.36 (s, N–H), 7.25 (m, Ph + H-7). According to chromatographic data, the mother liquor contained both **9** and its C_{3b}-epimer. In order to improve the yield of **10**, in the following experiments the dihydropyridines **9** were not isolated but the mixture was oxidized and debenzylated to **10**.

Coupling of **2b** *and* **3**, *followed by oxidation and debenzylation to* **10**

A solution of 2.97 g (10 mmol) **3** and 1.94 g (10 mmol) **2b** (potassium salt) in 15 ml acetonitrile was stirred at room temperature during 2 h. After filtering off the potassium bromide 3 g N-carbethoxymethylquinolinium bromide was added and the mixture kept at room temperature during 1 h. Cooling to 4° afforded 2.7 g (60%) **10** as its N-benzyl salt (m.p. 168–170°).

To a solution of 2.7 g of the N-benzyl derivative, dissolved in 40 ml of ethanol was added 1 g $Pd/BaSO_4$ and 0.6 g sodium bicarbonate. The mixture was reduced at 2.5 atm. during 2 h whereupon **10** crystallized. Upon addition of chloroform and warming, the product dissolved again. Filtering, evaporation of solvents and recrystallising the residue from ethanol afforded **10** in 62% yield (1.01 g).

10 m.p. 198–201°. IR(KBr): 3200 (broad, N–H + O–H), 1720 (C=O ester), 1670 (C=O, amide). PMR(DMSO-d_6): 1.15 (t, CH_3), 1.5–3.0 (m, $CH_2CH_2CH_2$), 4.15 (2q, $COOCH_2$, $\Delta\delta$ = 2 Hz), 6.43 (s, O–H), 7.32 (d, H-4, J = 5.5), 8.62 (s, N–H), 8.67 (d, H-5, J = 5.5), 9.07 (s, H-7).

10 was converted into its TMS derivative by adding 55 mg to a suspension of 10 mg NaH and 1 ml THF, at room temperature. After 15 min 25 μl trimethylsilyl chloride was added and the reaction mixture was stirred for 30 min. Preparative tlc afforded the trimethylsilyl ether as a solid. M.p. 156–158°. IR: 3400 (N–H), 1725 (C=O, ester), 1630, 1550. PMR: 0.09 (s, $(CH_3)_3$), 1.26 (t, CH_3), 1.5–3.0 (m, $(CH_2)_3$), 4.21 (2q, $COOCH_2$, $\Delta\delta$ = 9 Hz), 7.13 (d, H-4, J = 5), 7.92 (s, broad, N–H), 8.68 (d, H-5, J = 5), 9.31 (s, H-7).

Dehydration of **10**

A solution of 1 mmol **10** was refluxed in 3 ml acetic acid during 3 h. The solvent was evaporated and the residue recrystallized from ethanol, yield 82%.

11 m.p. 147–149°. IR: 3420 (N–H), 1720 (C=O, ester), 1670 (C=O, lactam). PMR: 1.12 (t, CH_3), 2.0–2.9 (m, C–$2H_2$), 3.1 (m, C–$3H_2$), 4.07 (q, $COOCH_2$), 5.39 (t, H-1, J = 2), 7.27 (d, H-4, J = 5), 8.76 (d, H-5, J = 5), 9.25 (s, H-7), 9.51 (s, N–H).

N-(Carbethoxycyclopent-1-ene)nicotinamide **12**

A mixture of 12.2 g nicotinamide, 40 g ethyl 2-oxo-cyclopentanecarboxylate **2b** and 1.0 g p-toluenesulphonic acid was heated at 120° during 3 days under a slow stream of dry N_2 to remove the water produced. The reaction mixture was purified by column chromatography (silica, ethyl acetate/petroleum ether) and the product **12** recrystallized from ethanol, yield 13.4 g (52%), m.p. 96.5–97°. IR: 3300 (N–H), 1690, 1655 (C=O). PMR: 1.31 (t, CH_3), 1.95 (m, CH_2), 2.55 (m, CH_2), 3.30 (m, CH_2), 4.24 (q, $COOCH_2$), 7.39 (d × d, H-5, J = 4.5, J = 8), 8.19 (d × d × d, H-6, J = 8, J = 1.5, J = 2), 8.76 (d × d, H-4, J = 4.5, J = 1.5), 9.18 (d, H-2, J = 2), 11.4 (s, broad, N–H).

Quaternization of **12**

A soln of 0.52 g **12** and 0.26 ml benzyl bromide in 5 ml acetonitrile was refluxed during 1 h. Upon cooling the quaternary salt **13** crystallized in 86% yield (0.74 g), m.p. 196–202°. IR(KBr): 1690, 1660, 1630. PMR: 1.28 (t, CH_3), 1.8–2.1 (m, CH_2), 2.55 (m, CH_2), 3.2 (m, CH_2), 4.24 (q, $COOCH_2$), 6.12 (s, $PhCH_2$), 7.4–7.8 (Ph), 8.47 (d × d, H-5, J = 6, J = 8), 8.94 (d × d, H-6, J = 8, J = 2), 9.56 (d, H-4, J = 6, J = 8), 9.75 (broad s, H-6), 11.15 (s, N–H).

7 - *Benzyl* - 9b - *carbethoxy* - 1,2,4,5,9a,9b - *hexahydrocyclopenta*[c][2.7]*naphthyridine* - 5 - *one* **14**

To a suspension of 3.8 g of **13** in 10 ml acetonitrile was added at room temperature 1.1 ml 1,5-diazabicyclo[4,3,0]non-5-ene in 5 ml of acetonitrile. When all the solid material had dissolved the dark reaction mixture was cooled in ice. After 2 h at 0° the precipitate was collected. Yield 1.6 g (52%) of light yellow material. **14**: m.p. 158–166°. IR: 3420 (N–H), 1715 (C=O, ester), 1680 (C=O, lactam), 1665, PMR: 1.11 (t, CH_3), 1.5–2.8 (m, CH_2–

CH_2), 3.73 (broad s, H-3b), 4.08 (2 q, $COOCH_2$, $\Delta\delta = 4$ Hz), 4.28 (s, $PhCH_2$), 4.70 (d × d, H-4, J = 2, J = 8), 4.90 (t, H-1, J = 2.5), 5.69 (d × d × d, H-5, J = 8, J = 2, J = 2), 7.1–7.35 (m, Ph + H-7), 8.6 (s, N–H).

Oxidation of **14**

A soln of 0.35 g of **14** and 0.3 g N-carbethoxymethylene quinolinium bromide in 3 ml acetonitrile was stirred at room temperature during 2 h. The precipitate of pure **15** was collected, yield 0.39 g (91%), m.p. 157–160°. IR(KBr): 3400 (N–H), 1720 (C=O), 1680 (C=O), PMR (CD_3OD): 1.23 (t, CH_3), 2.1–3.2 (m, CH_2–CH_2), 4.09 (q, $COOCH_2$), 5.51 (t, H-1, J = 2), 5.98 (s, $PhCH_2$), 7.4–7.6 (m, Ph), 8.19 (d, H-4, J = 6.5), 9.23 (d × d, H-5, J = 6.5, J = 1.5), 9.46 (d, H-7, J = 1.5).

Debenzylation of **15**

A solution of 0.3 g of **15** in ethanol, containing three equivalents of sodium bicarbonate was reduced in the presence of a catalytic amount of $Pd/BaSO_4$ at a hydrogen pressure of 3 atm. The reaction mixture was purified by chromatography (silica, ethyl acetate) and produced **11** in 71% yield, identical with the compound previously obtained according to spectral and chromatographic data.

Reaction of **3** *with N-benzylidenealanine ethyl ester* **16**[10]

To a suspension of 0.22 mol. sodium hydride in 250 ml of dry THF was added 0.1 mol **16**, followed by 0.1 mol **3** in small portions. After the addition the mixture was stirred during 1 h and the excess sodium hydride decomposed with methanol. After the addition of 200 ml of water, the product was extracted with ethyl acetate. Drying and cooling the organic phase produced **17** in 48% yield as a yellow crystalline compound, m.p. 196–198°. IR: 3380 (N–H), 1710, 1690 (C=O), 1660 (C=N). PMR: 1.47 (s, CH_3), 4.03 (broad, H-4a), 4.38 (s, $PhCH_2$), 4.88 (d × d, H-4, J = 3, J = 8), 5.90 (d × d × d, H-3), 7.20 (s, Ph), 7.2–7.5 (m, 3 H, PhC=N), 7.45 (d, H-1, J = 2), 7.75 (m, 2 H, PhC=N), 8.23 (s, HC=N), 9.05 (broad, N–H). NOE difference spectrum: on irradiating the methyl group at 1.47, the protons at 4.03 and 4.88 showed clear signals.

4 - *Benzyl* - 3 - *methoxy* - 8a - *methyl* - 2 - *phenyl* - 1,2,2a,3,4,6,7,8,9,9a - *decahydropyrrolo*[2,3,4 - d.e]*naphthyridin* - 6,8 - *dione* **18**

A solution of 1.0 g of **17** in 25 ml methanol, containing 1 ml water and 0.2 ml acetic acid was refluxed until the yellow colour had disappeared (5 min). Upon cooling **18** crystallized in 76% yield, m.p. 213–215°C. IR: 3380 (N–H), 1705, 1680 (C=O), 1605, PMR: 1.58 (s, CH_3), 2.04 (N–H), 2.88 (d × d, H-9, J = 6, J = 2), 3.12 (s, OCH_3), 3.17 (d × d × d, H-2a, J = 2, J = 7, J = 9), 3.35 (AB-system CH_2Ph, J = 15), 4.01 (d, H-3, J = 2), 4.75 (broad d, H-2, J = 9), 6.94 (m, Ph), 7.13 (d, H-5, J = 2), 7.2–7.4 (m, Ph), 7.95 (broad s, N–H).

Irradiating the methyl signal and measuring the NOE difference spectra gave strong signals for H-2, H-2a and H-9.

Oxidation of **5a** *and* **5c**

A solution of the dihydropyridines **5a** or **5c** and N-carbethoxymethylenequinolinium bromide (slight excess) in acetonitrile was stirred overnight at room temperature. The precipitate was collected. Yield of oxidized product: ~80%; **7a**: m.p. 220–230°. IR(KBr): 3580 (N–H), 1720, 1700 (C=O). PMR (DMSO-d_6): 1.5–2.5 (m, 4 × CH_2), 7.56 (d, H-5, J = 5.5), 8.75 (d, H-6, J = 5.5), 9.08 (s, H-8), 11.35 (N–H). **7c**: m.p. 215–218°. IR(KBr): 3400 (N–H), 1720, 1705 (C=O). PMR(DMSO-d_6): 2.0–3.0 (m, 3 × CH_2), 6.04 (s, $PhCH_2$), 6.8–7.7 (m, Ph), 8.02 (d, H-5, J = 7), 9.2 (d × d, H-6, J = 2, J = 7), 9.63 (d, H-8, J = 2).

7 - *Benzyl* - 4 - *methoxycarbonylpropyl* - 1,2,3,7 - *tetrahydro*[2,7]*naphthyridin* - 1,3 - *dione* **21**

1 Mmol naphthyridinium salt **6c** was refluxed during 3 h in 5 ml methanol, containing one drop of conc. HCl. The mixture was neutralized with $NaHCO_3$ solution and extracted with chloroform. The product **21** was recrystallized from ethyl acetate and isolated in 61% as yellow crystals. The mother liquor contained p-bromoaniline. **21**: m.p. 228–231°. IR: 3400 (N–H), 1730 ($COOCH_3$), 1695, 1650 (C=O), PMR: 1.4–2.0 (m, CH_2), 2.1–2.7 (m, 2 × CH_2), 3.60 (s, $COOCH_3$), 4.95 (s, CH_2Ph), 6.82 (d.AB system, H-5 + H-6, J = 8, J = 1.5), 8.20 (d, H-8, J = 1.5), 9.15 (s, N–H).

Reaction of **21** *with benzyl bromide*

Naphthyridinium-salt **22** was obtained by heating **21** with excess benzyl bromide at 100° during 1 h. Addition of ethyl acetate afforded **22** as an oil, IR: 3600–3300 (–N–H, $N^{\oplus}$), 1725, 1700 (C=O), PMR (CD_3OD): 2.0–3.0 (m, 3 × CH_2), 3.60 (s, CH_2Ph), 5.98 (s, CH_2Ph), 6.5–6.75 (m, 2H, Phα), 6.7–7.15 (m, 3 H, Ph), 7.5 (5 H, Ph), 8.62 (d, H-5, J = 7), 9.35 (d × d, H-6, J = 1.5, J = 7), 9.45 (d, H-2, J = 1.5).

Addition of the anion of **23** *to N-benzyl-3-carbamoylpyridinium bromide* **3**

To a solution of 100 mmol lithium diisopropylamide in 300 ml tetrahydrofuran at −76° was added 100 mmol **23**. After 10 min 50 mmol **3** was added and the mixture was stirred at −40° during 5 h and then neutralized with 50 mmol acetic acid. Silica was added, the solvents were evaporated and the silica was percolated in a short column. Petroleum ether–ethylacetate 3:1 provided the excess of **23**. Elution with petroleum ether–ethylacetate 1:1 afforded addition product **24** as a dark oil (50%), IR: 3400 (N–H), 1705, 1690 (C=O), PMR: 1.7–3.0 (m, 3 × CH_2), 3.8–3.95 (m, OCH_2CH_2O), 4.33 (s, $PhCH_2$), 4.75 (d × d, H-5, J = 8, J = 2), 5.90 (d × d × d, H-6, J = 1.5, J = 2, J = 8), 7.25 (m, H-8 + Ph), 7.85 (s, broad, N–H).

Oxidation of **24**

To a solution of 15 g **24** in 75 ml acetonitrile was added 9 g N-benzylquinolinium bromide and the mixture was stirred during two days. The dark red mixture was filtered and the crystals of **25** (N-benzyl derivative) washed with acetonitrile, ethylacetate and ether, yield 7.5 g (67%). **25** (N-benzyl derivative) m.p. 220–225° (dec). IR(KBr): 2800 (N–H), 1720, 1705 (C=O). PMR(DMSO-d_6 + CD_3OD): 2.0–3.1 (m, 3 × CH_2), 4.0 (m, OCH_2CH_2O), 5.97 (s, CH_2Ph), 7.3–7.6 (m, Ph), 8.48 (d, H-5, J = 7), 9.24 (d × d, H-6, J = 7, J = 1.5), 9.60 (d, H-8, J = 1.5).

Debenzylation to protected sesbanone **25**

In a sublimation apparatus 1 g benzyl derivative **25** was heated at 230° at a pressure of 0.01 mm Hg during 1 h. **25** sublimed in 78% yield (0.48 g), m.p. 224–225°. IR(KBr): 2820 (N–H), 1700 (C=O). PMR(DMSO-d_6): 1.9–3.0 (m, 3 × CH_2), 3.96 (m, OCH_2CH_2O), 7.67 (d, H-5, J = 5.5), 8.81 (d, H-6, J = 5.5), 9.06 (s, H-8), 11.45 (broad s, N–H). Analysis: C: 61.3, H: 5.3, N: 10.1%. $C_{14}H_{14}N_2O_4$ requires C: 61.31, H: 5.15, N: 10.21%.

Hydrolysis to sesbanone **26**

Ketal **25** (1 mmol) was refluxed during 45 min in a mixture of 4 ml methanol, 1 ml water and 0.2 ml conc. HCl. The warm solution was neutralized with 0.28 ml triethylamine, upon which sesbanone **26** crystallized, yield 85%, m.p. 278–280°. IR(KBr): 2800–2400 (N–H), 1740, 1710, 1700 (C=O). PMR(DMSO-d_6): 2.3–2.6 (m, CH_2–CH_2), 2.7–2.9 (m, CH_2–C=O), 7.71 (d, H-5, J = 5.5), 7.83 (d, H-6, J = 5.5), 9.10 (s, H-8), 11.6 (broad s, N–H). Found: C, 62.2; H, 4.5; N, 11.9. $C_{12}H_{10}N_2O_3$ requires C, 62.61; H, 4.38; N, 12.17%.

Reduction of **26** *to sesbanine* **1** *and epi-sesbanine* **27**

Sesbanone **26** (1 mmol) was refluxed in 10 ml dry isopropanol containing 5 eq. aluminium tri-isopropoxide. The reaction mixture was treated with silica, the solvents were evaporated and the silica percolated with ethyl acetate–methanol 10:1 in a short column. The filtrate contained a mixture of **1** and **27**. Recrystallization from methanol did not lead to pure products. The isomers were separated by preparative TLC, yielding 50% of **1** and 6% of **27**. **1**: m.p. 240–242°. IR(KBr): 2850–2500 (N–H) 1710, 1690 (C=O). PMR(DMSO-d_6): 1.7–2.4 (m, 5 cyclopentaneprotons). 2.65 (d × d, H-q, J = 5, J = 14), 4.50 (m, H-10), 5.10 (broad, O–H). 7.87 (d, H-5, J = 6), 8.80 (d, H-6, J = 6), 9.04 (s, H-8), 10.7 (broad, N–H). MS (70 eV): $M^+ = 232$. **27**: m.p. 235–237°. IR (KBr): 2850–2500 (N–H), 1710, 1690 (C=O). PMR(DMSO-d_6): 1.7–2.4 (m, 5

cyclopentaneprotons). 2.65 (d × d, H-q, J = 5, J = 14), 4.50 (m, H-10), 7.45 (d, H-5, J = 6), 8.74 (d, H-6, J = 6), 9.05 (s, H-8).

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