PENTACYCLIC INDOLE ALKALOIDS : A SHORT SYNTHESIS OF (±)-N(a)-BENZYL-20-DESETHYLASPIDOSPERMIDINE

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Abstract - The synthesis of (±)-N(a)-benzyl-20-desethylaspidospermidine in 8 steps and 25 % overall yield from cyclohexanedione is described.

The considerable biological importance of aspidosperma alkaloids due mainly to their presence in active compounds (e.g., vincamine and antitumor dimeric indole alkaloids)[1, 2] has stimulated much work on their synthesis[3]. We would like to report the synthesis of the title compound[4], a pentacyclic alkaloid which is an interesting target because of its unique ring system, which is the basic skeleton of indole pentacyclic alkaloids. Our explored approach[4] to 20-desethylaspidospermidine (alkaloid numbering[5]) has focused on use of the A-B-C tricyclic hexahydrocarbazol-4-one as a key intermediate and further building of D and E rings with the crucial problem of the control of the relative stereochemistry of C/D and D/E rings which present four asymetric centers.

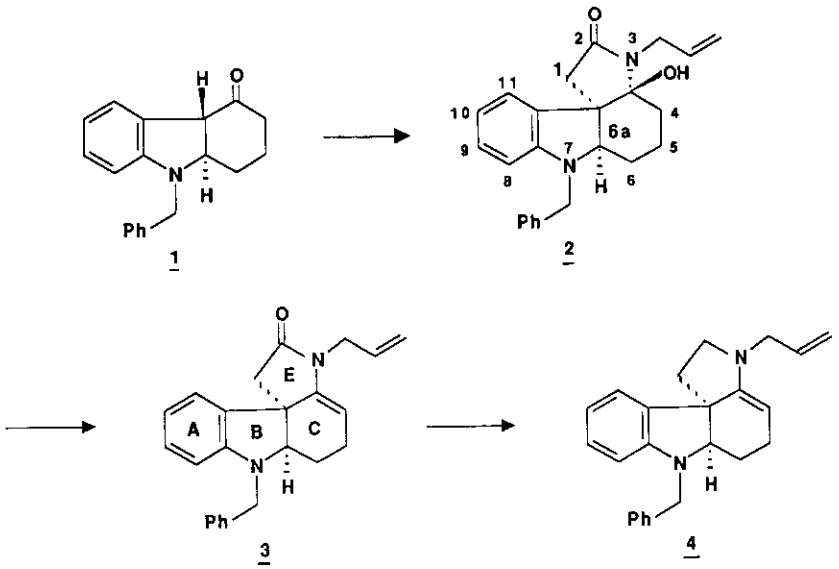
Synthesis of 1 was achieved according to published methods [4]; its thermodynamic enolate was alkylated with N-allyliodoacetamide (prepared from N-allylchloroacetamide [6] by halogen exchange) and the spontaneous cyclization of the intermediate so obtained gave a single hydroxyamide 2 in excellent yield (95 %). This reaction exhibits the remarkable position of the nitrogen atom of the amide group with regard to the carbonyl group on C-4 of the hexahydrocarbazolone.

Structure 2 was especially determined by spectroscopic data ; as shown in literature for similar compounds[4,7] the relative stereochemistry of rings B/C and C/E is *cis* : the alkylation of 1 was known to produce a B/C *cis* ring junction[4] and thermodynamic considerations led to postulating a *cis* C/E ring junction. Further treatment of 2 in dehydrating conditions (CH_2Cl_2 continuously dried on molecular sieves in a Soxhlet apparatus, camphorsulfonic acid) led to enamide 3 in nearly quantitative yield. The reduction of this enamide 3, performed in usual conditions[8] ($LiAlH_4$, THF), gave enamine 4 (yield : 92 %) as an unstable compound which was directly used after a rapid purification on alumina pad (see Scheme 1).

This readily accessible tetracyclic enamine constitutes a key intermediate for further synthesis of pentacyclic indole alkaloids. Four of the five rings were built with the required stereochemistry established during the alkylation step and the two nitrogen atoms were differently protected allowing the selective deprotection of N_b with transition metals without deprotecting the N_a benzyl group.

Our strategy to reach the synthesis of the title compound involved the condensation of a Michael acceptor such as methyl acrylate, with the enamine 4 followed by the deprotection of N_b nitrogen atom and the intramolecular cyclization of amino-ester 7 thus formed ; this cyclization would create the D ring.

Scheme 1



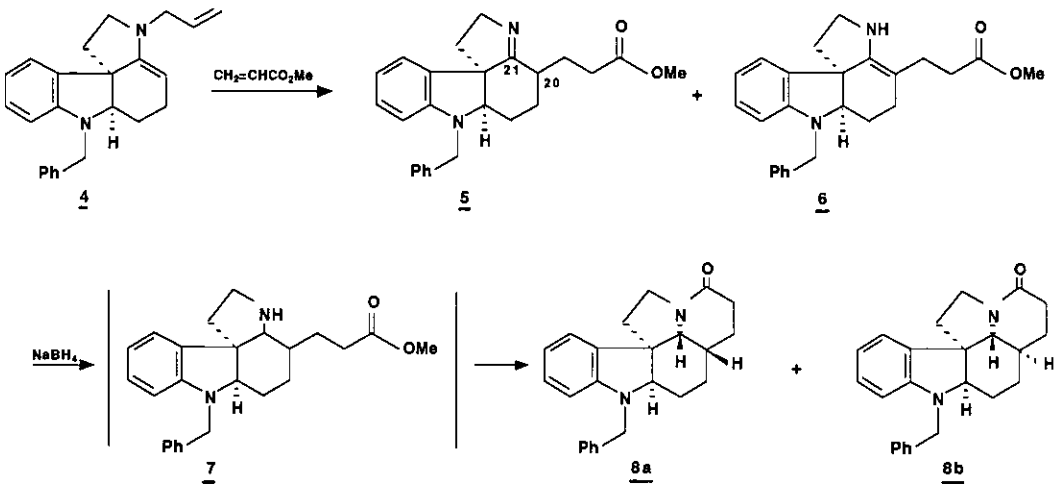
In fact, the reaction between **4** and methyl acrylate (MeOH, Δ) directly led to imine **5** (in 40 % yield after chromatographic purification) with some proportions of the tautomeric enamine **6**, as shown by ^{1}H and ^{13}C nmr spectra. Imine **5** can be isolated after chromatographic purification and its structure was deduced from the disappearance of the characteristic peaks of the allylic hydrogen in ^{1}H-nmr spectrum and from the observation of imine and ester functions in the ir and ^{13}C nmr spectra (ir : 1640 and 1745 cm^{-1} and ^{13}C nmr C-3a at δ 179.4).

The reduction of the imine function ($NaBH_4$, EtOH) was followed by the spontaneous intramolecular cyclization of the non-isolated amino-ester **7** and the amide **8** was obtained in 75 % yield as a diastereoisomeric mixture of **8a** and **8b** in a 70/30 ratio determined in ^{13}C nmr by time shared decoupling without NOE. The structures of these compounds were attributed on the basis of ir spectrum (lactam band at 1640 cm^{-1}) and the ^{1}H and ^{13}C-nmr spectra (two carbon C-3 at δ 168.2 and 169.1). Unfortunately these compounds could not be separated. Nevertheless the stereochemistry of **8a** and **8b** was determined by correlation with the three known diastereoisomers[4] of the N_a-benzyl-20-desethylaspidospermidine **9** (Scheme 2). The reduction of the **8a** and **8b** mixture with $LiAlH_4$ led to compounds **9a** and **9b** (90 % yield) in a 75/25 ratio (Scheme 3). Chromatographic separation of **9a**, **9b** mixture was performed and the most abondant isomer unambiguously issued from **8a** was identical to an authentical sample of N_a-benzyl-20-desethylaspidospermidine **9a**[4]. It will be noted that **8** can be prepared from **4**, in one pot, in 53 % yield, as described in experimental part.

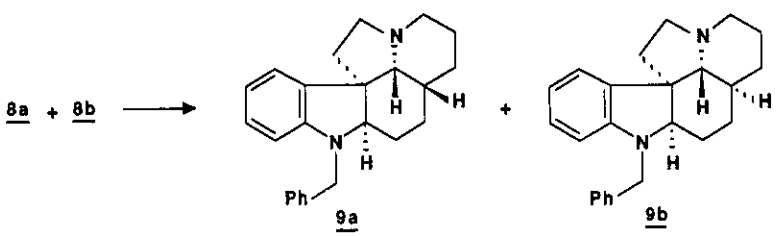
The reduction of the imine **5** proceeded by its β face (the β terminology was used for the upper face referred to the absolute configuration of aspidospermidine) and gave a *cis* C/E ring junction, stereochemistry of natural alkaloids. The formation of two diastereoisomeric lactams with a *cis* C/D ring junction came from the two possible stereochemistries of the lateral chain of compound **5**.

In conclusion, the tetracyclic enamine **4**, easily obtained from cyclohexanedione, constitutes a key intermediate in the synthesis of (±)-N_a-benzyl-20-desethylaspidospermidine **9a**. Michael condensation of

Scheme 2



Scheme 3



an acrylate with the enamine 4 followed by reduction of the amide so obtained has been shown to be an efficient method for building D and E rings of pentacyclic indole alkaloids.

EXPERIMENTAL

All melting points were obtained on a Reichert micro-hotstage apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 377 spectrophotometer. The ^{1}H-nmr spectra were recorded on Jeol C60H and Brucker MSL-300H spectrometers. Chemical shifts were recorded in ppm downfield from an internal standard (tetramethylsilane). The following abbreviations were used : s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. The ^{13}C nmr spectra were determined on a Jeol FX60 (15.08 MHz) instrument. Mass spectra were measured on a Varian CH5 spectrometer. Chromatographic separations were made using a silica gel (Merck silica gel, 0.040-O.063 mm, 230-400 mesh ATSM) or an aluminium oxide (Merck, O.O63-0.200 mm, 70-230 mesh ATSM) in the specified solvent system. Thin-layer chromatography (tlc) was carried out with precoated silica gel plates (Kiesel 60 F-254, Merck).

2-Oxo-3-allyl-3a-hydroxy-7-benzyl-2,3,3a,4,5,6,6a,7-octahydro-1*H*-pyrrolo[2,3-d]-carbazole (2)

A solution of hexahydrocarbazol-4-one 1 (620 mg, 2.2 mmol) in anhydrous THF (80 ml) was added drop to drop, under argon, to a KH suspension (35 % in oil, 280 mg, 2.42 mmol) in anhydrous THF (10 ml) and stirred at room temperature for 5 min. The resultant medium was added to a solution of N-(iodoacetyl)-allylamine (500 mg, 2.2 mmol) in THF (20 ml). The mixture was stirred for an additionnal 10 min at room temperature ; then water was carefully added and the majority of THF was distilled. The aqueous phase was extracted with CH_2Cl_2 ; the organic layer was dried over magnesium sulfate and concentrated. The crude product gave after chromatographic separation by elution with ethyl acetate-hexane (5:5) 2 (780 mg, 95%) as crystals. mp 129-130 °C. Ir (CCl_4) cm^{-1} ν : 3545, 1700. ^{1}H-Nmr ($CDCl_3$) δ : 1.00-2.40 (m, 6H, H-4, H-5, H-6) ; 2.45 (s, exchangeable with D_2O, OH) ; 2.70 (s, 2H, H-1) ; 3.80-4.00 (m, 2H, CH_2-CH = CH_2) ; 4.25 (q, 2H, J_{AB} = 15 Hz, Δν = 23 Hz, N_a CH_2 Ph) ; 5.00-6.20 (m, 3H, CH = CH_2) ; 6.40-7.60 (m, 9H, aromatic H). ^{13}C-Nmr ($CDCl_3$) δ : 17.2 (C-5) ; 23.9 (C-6) ; 34.7 (C-4) ; 41.2 (C-1) ; 41.7 (C-11b) ; 51.2 (C-12) ; 52.6 (C-15) ; 68.4 (C-6a) ; 91.4 (C-3a) ; 109.2 (C-8) ; 117.8 (C-14) ; 119.3 (C-11) ; 124.4 (C-9) ; 128.4 (C-10) ; 130.2 (C-11a) ; 135.1 (C-13) ; 138.9 (C-15) ; 153.6 (C-7a) ; 172.1 (C-2). Ms m/z (%) : 374 (10), 275 (13), 247 (10), 220 (6), 149 (14), 128 (8), 98 (16), 91 (100), 65 (14), 41 (21). Mol. Wt. (high resolution ms) calcd for $C_{24}H_{26}N_2O_2$: 374.1988 ; found : 374.1991.

2-Oxo-3-allyl-7-benzyl-2,3,5,6,6a,7-hexahydro-1*H*-pyrrolo[2,3-d]carbazole (3)

(±)-10-Camphorsulfonic acid (0.010 g) was added to a solution of amido-alcohol 2 (1 g, 2.7 mmol) in CH_2Cl_2 (120 ml) and the resultant solution was refluxed in the presence of molecular sieves (4 Å) for 24 h. After cooling the reaction mixture was neutralized with anhydrous K_2CO_3. After filtration and evaporation the crude mixture was purified by crystallization from ether to give 3 as white crystals (940 mg, 96 %). mp 112-113°C. Ir ($CHCl_3$) cm^{-1} ν : 1730, 1680. ^{1}H-Nmr ($CDCl_3$) δ : 1.20-2.30 (m, 4H, H-5, H-6) ; 2.60 (s, 2H, H-1) ; 3.60 (m, 3H, H-6a and CH_2-CH =C) ; 4.35 (q, 2H, J_{AB} = 15 Hz, Δν = 21 Hz, CH_2Ph) ;

5.00-6.10 (m, 4H, H-4 and C<u>H</u> = C<u>H</u>$_2$) ; 6.20-7.60 (m, 9H, aromatic H). ^{13}C-Nmr ($CDCl_3$) δ : 19.7 (C-5) ; 27.4 (C-6) ; 42.6 (C-1) ; 47.6 (C-11b) ; 48.6 (C-12) ; 50.7 (C-15) ; 67.7 (C-6a) ; 101.9 (C-4) ; 107.0 5C-8) ; 118.0 (C-14) ; 118.3 (C-11) ; 121.9 (C-9) ; 128.1 (C-10) ; 132.1 (C-11a) ; 135.2 (C-13) ; 139.1 (C-16) ; 143.2 (C-3a) ; 151.0 (C-7a) ; 172.8 (C-2). Ms m/z (%) : 356 (38), 265 (46), 237 (4), 224 (4), 183 (13), 174 (11), 146 (8), 130 (10), 91 (100), 65 (8), 41 (24). Mol. Wt. (high resolution ms) calcd for $C_{24}H_{24}N_2O$: 356.1883 ; found : 356.1888.

3-Allyl-7-benzyl-2,3,5,6,6a,7-hexahydro-1*H*-pyrrolo[2,3-d]carbazole (4)

A solution of enamide **3** (900 mg, 2.6 mmol) in THF (50 ml) was added to a suspension of $LiAlH_4$ (295 mg, 7.8 mmol) in THF (100 ml). The mixture was refluxed for 24 h, cooled and then water (2 ml) was added. After filtration the inorganic salts were washed with CH_2Cl_2 ; the organic layers were combined, dried over $MgSO_4$ and evaporated. A quick filtration on neutral alumina pad and elution with ethyl acetate gave the enamine **4** (820 mg, 92 %) as an unstable oily compound.

7-Benzyl-4-methoxycarbonylethyl-2,4,5,6,6a,7-hexahydro-1*H*-pyrrolo[2,3-d]carbazole (5)

Freshly distilled methyl acrylate (0.44 ml, 5.1 mmol) was added to a solution of enamine **4** (700 mg, 2.05 mmol) in MeOH (50 ml). The resultant mixture was refluxed for 12 h ; then the majority of solvent was evaporated and the crude product was quickly purified by chromatography on silica gel. Elution with ethyl acetate-hexane (6:4) gave imine **5** (318 mg, 40 %) as an oil. Other fractions gave **5** contaminated by enamine **6**.

Compound 5 : ir (CCl_4) cm^{-1} ν : 1745, 1640. ^{1}H-Nmr ($CDCl_3$) δ : 0.90-1.00 (m, 1H, H-6) ; 1.20-1.40 (m, 1H, H-6) ; 1.60-2.00 (m, 4H) ; 2.10-2.30 (m, 3H) ; 2.40-2.50 (m, 2H, H-1) ; 3.30-3.40 (m, 1H) ; 3.55 (s, 3H, CH_3) ; 3.60-3.70 (m, 1H, H-6a) ; 3.80-3.90 (m, 1H, H-4) ; 4.30 (q, 2H, J_{AB} = 17 Hz, Δν = 83 Hz, N-C<u>H</u>$_2$Ph), 6.30 (d, J = 7.5 Hz, 1H, H-8) ; 6.55 (t, J = 7.8 Hz, 1H, H-10) ; 6.65 (d, J = 7.5 Hz, 1H, H-9) ; 7.00 (t, J = 7.9 Hz, 1H, H-11) ; 7.15-7.40 (m, 5H, other aromatic H). ^{13}C-Nmr ($CDCl_3$) δ : 23.5 (C'-6) ; 25.0 (C'-5) ; 25.6 (C-6) ; 26.5 (C-5) ; 27.9 (C-12) ; 28.9 (C'-12) ; 31.9 (C-13) ; 38.8 (C-4) ; 39.7 (C'-4) ; 40.6 (C-1) ; 43.3 (C'-1) ; 48.9 (CH_2Ph) ; 49.2 ($C'H_3$) ; 51.4 (CH_3- : 57.3 (C'-2) ; 57.5 (C-2) ; 62.0 (C'-11b) ; 62.2 (C-11b) ; 71.6 (C'-6a) ; 72.6 (C-6a) ; 106.6 (C'-8) ; 107.6 (C-8) ; 117.3 (C'-11) ; 117.8 (C-11) ; 122.1 (C-9) ; 122.5 (C'-9) ; 127.2 (C-10) ; 127.5 (aromatic C) ; 128.5 (C'-10) ; 132.5 (C'-11a) ; 149.1 (C-7a) ; 149.2 (C'-7a) ; 174.0 (CO_2Me) ; 179.4 (C-3a and C'-3a). Ms m/z (%) : 388 (15), 340 (2) , 234 (30), 156 (100), 142 (20), 122 (15), 105 (20), 91 (70), 84 (87), 77 (20), 71 (18), 57 (52), 49 (87), 41 (57), 29 (25). Mol. Wt. (high resolution ms) calcd for $C_{25}H_{28}N_2O_2$: 388.2150 ; found : 388.2139.

N(a)-Benzyl-3-oxo-20-desethylaspidospermidine : (8a and 8b)

To a solution of **5** (500 mg, 1.29 mmol) in EtOH (70 ml) was added $NaBH_4$ (735 mg, 19.35 mmol) ; the mixture was stirred for 8 hours. The solvent was evaporated and the residue extracted with CH_2Cl_2. After usual treatment the organic layers were dried over $MgSO_4$ and evaporated. The crude product was purified on

silica gel and eluted with ethyl acetate-hexane (8:2) to give **8a** and **8b** as an inseparable mixture (347 mg, 75 %).

One pot synthesis of 8a and 8b from 4

To a solution of enamine **4** (800 mg ; 2.34 mmol) in absolute methanol (35 ml) was added drop to drop methyl acrylate (0.5 ml ; 5.8 mmol) ; the resulting mixture was refluxed for 12 h. After cooling, the solvent was evaporated and the residue was dissolved in ethanol (130 ml) ; $NaBH_4$ (1,17 g, 30.9 mmol) was then added and the mixture was stirred for 8 h to give after evaporation, extraction and purification **8a** + **8b** (444 mg, 53 %). Ir (CCl_4) cm^{-1} ν : 2940, 2860, 1640, ^{1}H-Nmr ($CDCl_3$, 300 MHz) δ : 1.00-1.20 (m, 3H) ; 1.40-1.60 (m, 1H) ; 1.60-2.00 (m, 5H) ; 2.90-3.10 (m, 1H) ; 3.30-3.65 (m, 3H) ; 4.20 (q, 2H, J = 16 Hz, Δν = 98 Hz) ; 6.30 (d, J = 7.3 Hz, 1H, H-12) ; 6.65 (t, J = 7.7 Hz, 1H, H-10) ; 6.95 (t, J = 7.7 Hz, 1H, H-11) ; 7.10-7.35 (m, 6H, aromatic H and H-9). ^{13}C-Nmr ($CDCl_3$) δ : 20.2, 20.4, 24.6, 26.2, 26.3, 27.6, 29.1, 31.1, 32.5, 33.4, 34.8, 36.5, 43.0, 43.8, 48.8, 49.2, 53.9, 61.4, 65.2, 66.3, 66.8, 107.5, 108.7, 118.0, 118.4, 121.9, 123.8, 130.9, 131.9, 138.2, 138.4, 150.5, 168.2, 169.1. Ms m/z (%) : 359(22), 358(86), 234(19), 233(100), 221(5), 220(24), 92(8), 91(95). Mol. Wt. (high resolution ms) calcd for $C_{24}H_{26}N_2O$: 358.2045 ; found : 358.2064.

(±) *N(a)-Benzyl-20-desethylaspidospermidine* (9a) and (9b)

The mixture of amides **8a** and **8b** (400 mg, 1.12 mmol) in anhydrous THF (20 ml) was treated with $LiAlH_4$ (80 mg, 2 mmol) and refluxed for 1 h. After evaporation, extraction with CH_2Cl_2 and concentration the organic residue was purified on silica gel and eluted with $CHCl_3$-EtOH (95:5) to give **9a** (309 mg, 62 %) and **9b** (77 mg, 20 %) identified to authentical samples[4].

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REFERENCES

1. P.L. Feldman and H. Rapoport, J. Am. Chem. Soc., 1987, **109**, 1603 and references cited therein.
2. a) P. Magnus, M.Ladlow, and J. Elliott, J. Am. Chem. Soc., 1987, **109**, 7929.
   b) P. Magnus, M. Ladlow, J. Elliott, and C.S. Kim, J. Chem. Soc., Chem. Commun., 1989, 518.
3. a) K. Cardwell, B. Hewitt, M. Ladlow, and P. Magnus, J. Am. Chem. Soc., 1988, **110**, 2242.
   b) A.I. Meyers and D. Berney, J. Org. Chem., 1989, **54**, 4673 and references cited therein.
4. J.-C. Gramain, H.-P. Husson, and Y. Troin, J. Org. Chem., 1985, **50**, 5517.
5. J. Le Men and W.I. Taylor, Experientia, 1965, **21**, 508.
6. P.C. Hamm and A.J. Speziale, J. Agr. Food Chem., 1957, **5**, 30.
7. J.-C. Gramain, H.-P. Husson, and Y. Troin, Tetrahedron Lett., 1985, **26**, 2323.
8. M. Langlois, C. Guillonneau, J. Meingan, and J. Maillard, Tetrahedron, 1971, **27**, 5641.

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