First Total Synthesis of (±)-Melinonine-E

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The alkaloid melinonine-E has been synthesised for the first time, the key steps being the elaboration of the 2-azabicyclo[3.3.1]nonane nucleus by a radical cyclisation, the epimerisation of the cyano group to an axial position, and the closure of the *C* ring by Bischler–Napieralski cyclisation.

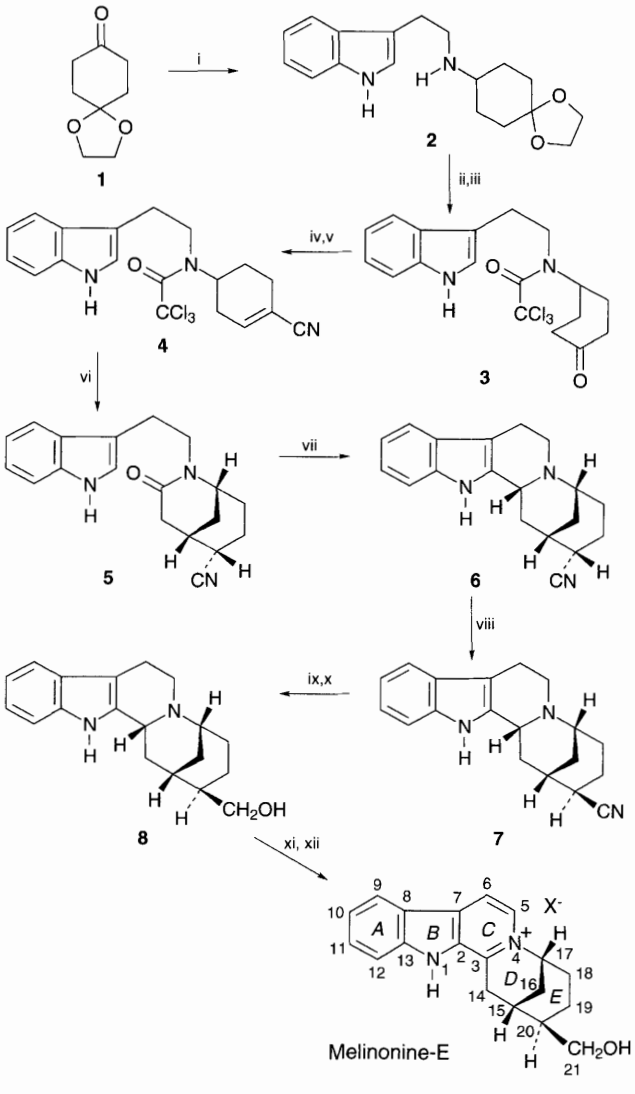
Melinonine-E is a quaternary indole alkaloid isolated from *Strychnos melinoniana*, reported for the first time in 1957, whose structural elucidation was not carried out until 1984.[1] Biogenetically, it seems to be derived from antirhine (Vallesiachotaman type) by closure of the *E* ring [bond formed C(17)-C(18)][2] and aromatisation of the *C* ring. The pentacyclic ring system of melinonine-E, consisting of a β-carbolinium moiety fused to a 2-azabicyclo[3.3.1]nonane (morphan) nucleus, is unprecedented among natural or synthetic products.[3]

We report here the first total synthesis of melinonine-E. The strategy we have developed for assembling the pentacyclic ring system of the alkaloid involves the construction of an appropriately substituted and functionalised 2-azabicyclo[3.3.1]nonane (rings *D* and *E*) and the final closure of the *C* ring by a Bischler–Napieralski cyclisation. The required 2-azabicyclo[3.3.1]nonane **5** was formed from trichloroacetamide **4** in a process involving the closure of the piperidine ring by attack of an α-(carbamoyl)methyl radical upon the α,β-unsaturated nitrile moiety.

The starting material for our synthesis was the protected cyclohexanone **2**,† which was prepared by reductive amination of 1,4-cyclohexanedione monoethylene acetal **1** with tryptamine in the presence of sodium triacetoxyborohydride[4] (89%). After trichloroacetylation and further chemoselective hydrolysis, ketone **3** was obtained in good yield.

For the purpose of the one-carbon homologation (C-21), ketone **3** was converted to an *O*-silylcyanohydrin[5] and then to the α,β-unsaturated nitrile **4** by treatment with $POCl_3$ at benzene reflux temperature[6] (62% overall yield). Compound **4** was treated with tributyltin hydride (1.1 equiv.) and 0.1 equiv. of AIBN in refluxing benzene (0.12 mol dm^{-3}) over 16 h. Under these conditions, the expected cyclisation to the 2-azabicyclo[3.3.1]nonane ring system took place (63% yield) to give a mixture of **5** (minor amounts) and its C-14[2] chloro- and dichloro-substituted derivatives. As was expected, an additional treatment of the crude mixture with Bu_3SnH (2.2 equiv.) brought about the hydrogenolysis of the C–Cl bonds to provide (38% for the two steps) the nitrile **5** as a single stereoisomer. When the cyclisation was conducted in the presence of an excess of Bu_3SnH (3.2 equiv.), the cyclised product **5** was directly obtained in 46% yield. From the synthetic standpoint, however, the best results in this radical cyclisation were achieved when tris(trimethylsilyl)silane (3.5 equiv.),[7] which is a poorer hydrogen donor, was used as the radical mediator. Under these conditions, after an additional treatment with Bu_3SnH–AIBN, the required azabicyclo **5** was isolated in 70% yield. The relative configuration at C-20 in compound **5** (equatorial cyano group) was deduced from the multiplicity (qd, J = 13.5 and 4 Hz) of H-7ax (assigned from the 2D NMR spectra), which indicates the axial disposition for the proton at C-6. This configuration is the expected one taking into account that hydrogen abstraction by radicals in cyclic systems occurs from the most accessible face.[8] The above cyclisation not only provides a new synthetic entry to the 2-azabicyclo[3.3.1]nonane ring system[9] but also constitutes one of the scarce examples of synthetically useful 6-exo-trig cyclisations from 3-aza-6-heptenyl radicals.[10]

Cyclisation to the desired pentacyclic system was achieved by the Bischler–Napieralski reaction. Thus, treatment of lactam **5** with phosphoryl chloride, followed by $NaBH_4$ reduction, stereoselectively led to the pentacyclic amine **6**, which showed spectroscopic data in agreement with both a 3-Hβ relative configuration and a *trans C/D* ring conformation for the quinolizidine system[11] (δ 22.8 for C-6 and δ 4.0, dm, J = 11.8 Hz for H-3).



Scheme 1 *Reagents and conditions*: i, tryptamine, $NaBH(OAc)_3$, AcOH, 1,2-dichloroethane, 72 h, 87% ; ii, Cl_3CCOCl, CH_2Cl_2, py, 48 h, 89%; iii, 3 mol dm^{-3} HCl, THF, 65 °C, 5 h, 85%; iv, Me_3SiCN, ZnI_2 (cat), CH_2Cl_2, 65 °C, 2 h; v, $POCl_3$, benzene, py, reflux 5 h, 62% from **3**; vi, $(SiMe_3)_3SiH$ (3.5 equiv), benzene, AIBN (0.3 equiv.), 16 h, then Bu_3SnH (1 equiv.), AIBN (0.3 equiv.), 7 h, 70%; vii, $POCl_3$, benzene, reflux, 75 min, then $NaBH_4$, MeOH, 90 min, 75%; viii, LDA (3.3 equiv), THF, −78 °C, 2 h, then 0.5 mol dm^{-3} HCl, −78 °C; ix, DIBAL-H, toluene, −20 °C, 1 h, then 5% H_2SO_4, −20 °C, 2 h, 79%; x, NaBH4, MeOH, room temp., 3 h, 83%; xi, Pd, maleic acid, H_2O, 16 h, then $NaClO_4.H_2O$, 63%; xii, IRA-400, quantitative

At this point three operations were required to complete the synthesis: epimerisation of the C-20 equatorial cyano group to an axial position, adjustment of the functionalisation at C-21 and aromatisation of the β-carboline unit.

The epimerisation at C-20 was partially accomplished by deprotonation of nitrile **6** with LDA, followed by quenching of the resulting stabilised anion with diluted hydrochloric acid at −78 °C.[12] A mixture of pentacyclic nitriles **6** and **7** (2:3), the latter with the natural relative stereochemistry at C-20, was obtained. It is worth mentioning that the major epimer **7** arises from the equatorial protonation of the exocyclic α-cyano carbanion to leave an axial cyano substituent.[13] Both isomers were separated by column chromatography and the unwanted minor epimer, **6**, was recyclable. The relative configuration at C-20 in nitriles **6** and **7** was established from their ^{13}C NMR data by considering the existence or absence of γ-effects upon C-14, C-16 or C-18.[14]

DIBAL-H reduction of nitrile **7**, followed by hydrolysis of the intermediate imine, afforded the corresponding aldehyde without appreciable epimerisation. This aldehyde was immediately reduced ($NaBH_4$) to the alcohol **8**. Finally, treatment of **8** with palladium black and maleic acid[15] in boiling water for 24 h caused the dehydrogenation of the *C* ring to give melinonine-E in 63% yield. The ^1H and ^{13}C NMR data of our synthetic (±)-melinonine-E chloride matched those reported in the literature for the natural product.[1b] The R_F values of the corresponding picrates were also coincident.

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Footnote

† Satisfactory analytical and spectral data were obtained for all new compounds.

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