

APPROACHES TO THE TOTAL SYNTHESIS OF THE MONTANINE (AMARYLLIDACEAE) ALKALOIDS.

PREPARATION OF ISOMERIC 3-ARYLOCTAHYDROINDOLES

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Abstract - The preparation of various isomeric 3-aryloctahydroindoles, potential synthons for the total synthesis of the montanine-like Amaryllidaceae alkaloids, is described.

The montanine alkaloids comprise a small number of bases isolated from Amaryllidaceae species¹ characterized by having a 5,11-methanomorphanthridine skeleton. Although an enormous synthetic effort has been directed towards other members of the series, e.g., lycoramines, galanthamines, and 5,10b-ethanophenanthridines,² there are but a few structure elucidation studies regarding the montanine bases.¹

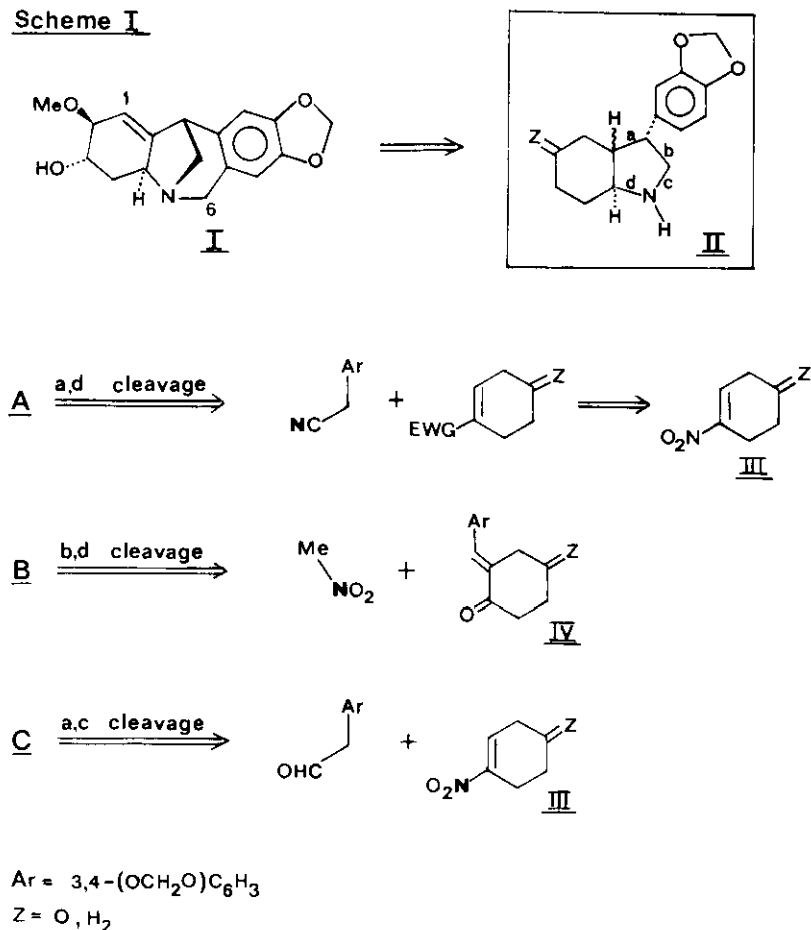
As continuation of our synthetic program dealing with alkaloids from Amaryllidaceae,³ we now report the first approaches to the total synthesis of the montanine compounds.

An antithetic analysis (Scheme 1) of montanine (I) itself provides in principle, after removal of the benzylic carbon atom at position 6 and simplification of the oxygenation pattern, three main routes for the construction of the key 3 α -aryloctahydroindole nucleus II. Routes A and C have a common intermediate, namely, the functionalized 1-nitrocyclohexene derivative III,⁴ whereas route B utilizes the arylidenecyclohexanone precursor IV.

Along the lines of strategy A ($Z=H_2$), we proceeded to react 3,4-(methylenedioxy)phenylacetonitrile (1) with 1-nitrocyclohexene⁴ (2) (ⁿBuLi/THF/-50°C) to furnish a 65% yield of a 27:1 mixture of the

cis- and trans- addition products 3 and 4, respectively (Scheme II). In fact, the major isomer 3 is the result of a kinetically controlled addition reaction. Moreover, the stereoselectivity of this transformation is both temperature and substrate dependent since reaction of N,N-diethyl 3,4-(methylenedioxy)phenylacetamide with 1-nitrocyclohexene under similar conditions ($n\text{BuLi/THF}/-20^\circ\text{C}$) furnished instead a 1:1 mixture of the corresponding cis- and trans- addition products in 51% overall yield.

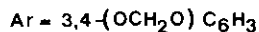
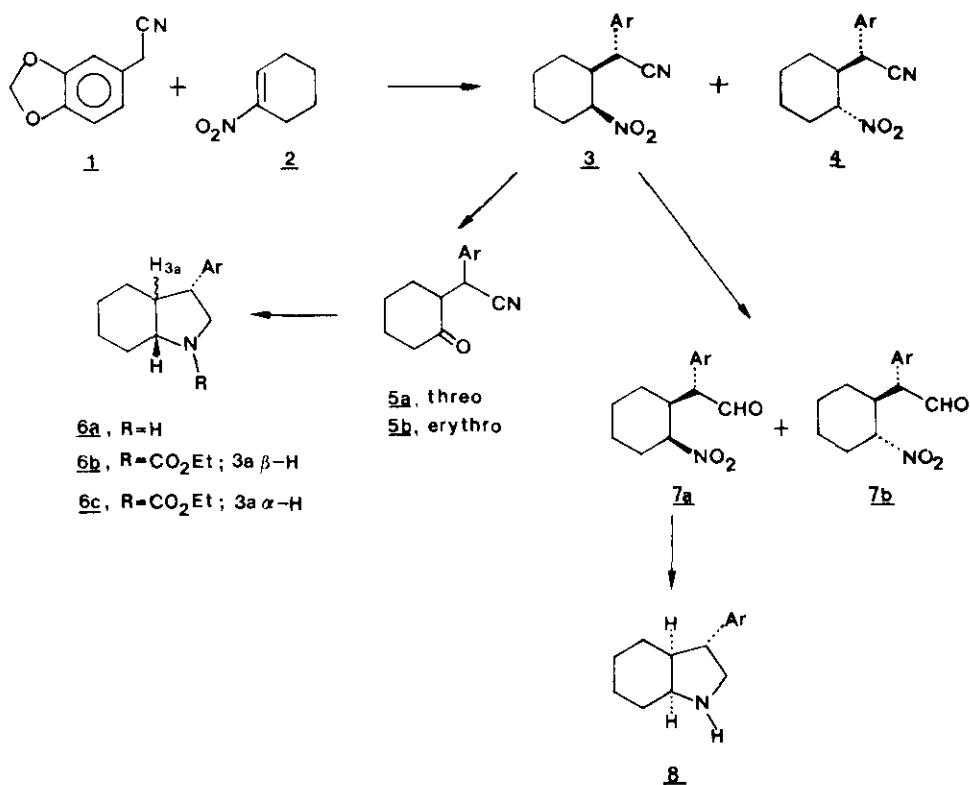
Scheme I



When the major isomer 3, mp 105-107°C (EtOH), was submitted to the Jacobson⁵ modification of the Nef reaction, a 79% yield of a 1:1 (¹H-NMR) mixture of the threo - 5a and erythro - 5b isomers⁶ was realized (see Table I). Whereas the threo isomer proved to be crystals, mp 130-131°C (EtOH), the erythro one remained as an oil. Subsequent reductive cyclization of this mixture (Urushibara's nickel,⁷ ¹PrOH, 50 psi, 45-55°C, 48 h) afforded the oily octahydroindole 6a (R=H) in 52% yield. Reaction of the latter with ethyl chloroformate (CH₂Cl₂, Et₃N, 0°C) provided the protected cis- (6b)

and *trans*-octahydroindoles (**6c**),⁸ as a 1:1 mixture (¹H-NMR) separable by crystallization. Isomer **6b** showed to be crystals, mp 113-115°C (EtOH), while the other remained as an oil.⁹

Scheme II

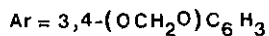
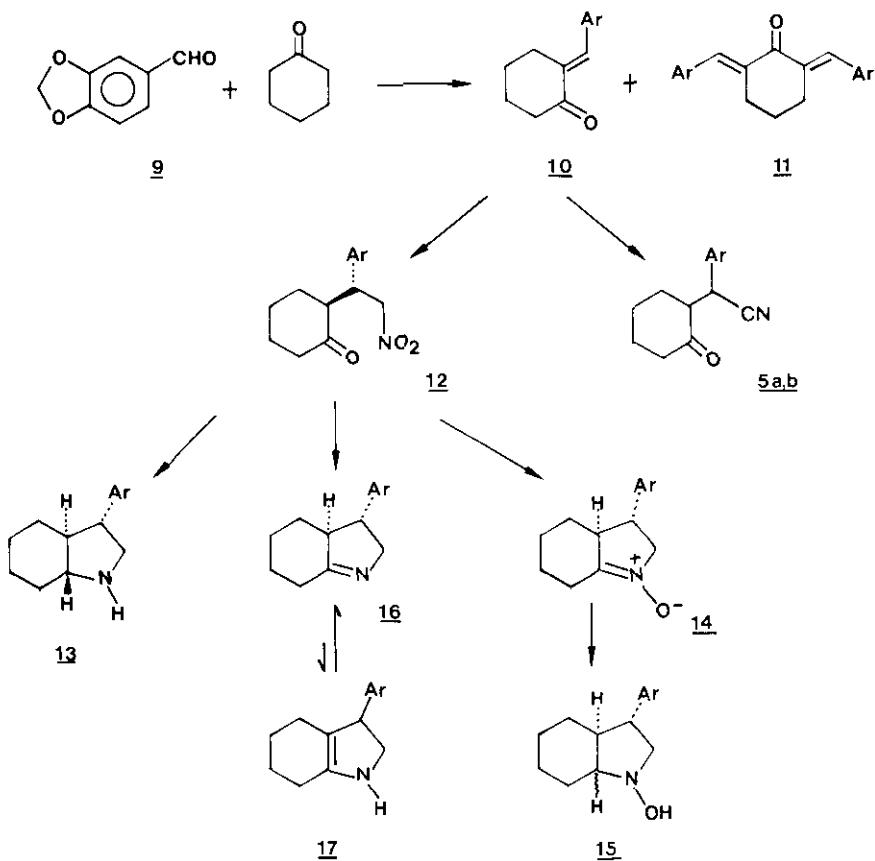


On the other hand, route **C** was also developed as depicted in Scheme II. Isomer **3** was reduced with ⁱBu₂AlH (THF, 0°C; 81%) to yield a 1:1 mixture (¹H-NMR) of the oily *cis*- (**7a**) and the crystalline mp 92-93°C (EtOH), *trans*- nitroaldehyde **7b** after careful work-up. When submitted to the reductive cyclization conditions described above, **7a** provided the *cis*- fused octahydroindole⁸ **8** bearing the desired 3α-aryl substituent in 57% yield. However, the *trans*-isomer **7b** furnished only non-cyclic and/or polymeric materials under the same conditions.

Moreover, route **B** (Scheme III) was also appraised as follows. Piperonal (**9**) was allowed to react with cyclohexanone under controlled conditions (NaOH catalysis) to give piperonylidencyclohexanone (**10**), mp 87-88°C (lit.¹⁰ mp 88-89°C) in 92% yield, together with a small amount of the bis-pipero-

nylidene derivative 11, mp 188-189°C (EtOAc). Further reaction of 10 with potassium cyanide under Liotta's conditions¹¹ (C₆H₆, acetone cyanohydrin, 18-crown-6, reflux, 6 h) provided ketone 5 (see Scheme II) in 61% yield as the readily separable 67:33 mixture of the same threo-5a and erythro-5b isomers, respectively (*vide supra*), thus providing an alternate, amenable for scale-up route to such versatile intermediates.

Scheme III



Furthermore, when enone 10 was allowed to react with nitromethane using a "supported" tetrabutylammonium fluoride catalyst,¹² ketone 12 was obtained in 92% yield as the single threo diastereoisomer,¹³ mp 162-163°C (EtOH). Reductive cyclization, as before, afforded the oily trans-fused octa-

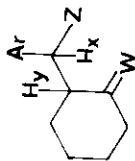


Table 1. Selected ¹H-NMR Data for Relevant Compounds. ^a

| Compound | Formula | Type | Z | W | Hx | Chemical Shift, ppm | Others | mp, °C |
|-----------|---|---------|---------------------------------|----------------------------------|---|--|---|---------|
| <u>3</u> | C ₁₅ H ₁₆ O ₄ N ₂ | cis | CN | NO ₂ , H _w | 3.85, d J=11 Hz | H _w : 5.12, b W ₂ =8.8 Hz | | 105-107 |
| <u>4</u> | C ₁₅ H ₁₆ O ₄ N ₂ | trans | CN | NO ₂ , H _w | 3.90, d J=4 Hz | H _w : 4.60, td J=11, 4 Hz | | oil |
| <u>5a</u> | C ₁₅ H ₁₅ O ₃ N | threo | CN | 0 | 4.45, d J=5 Hz | | | 130-131 |
| <u>5b</u> | C ₁₅ H ₁₅ O ₃ N | erythro | CN | 0 | 4.05, d J=7.5 Hz | | | oil |
| <u>7a</u> | C ₁₅ H ₁₇ O ₃ N | cis | CHO | NO ₂ , H _w | 3.61, dd J=10, 1.2 Hz | H _w : 5.10, b W ₂ =7.5 Hz | CHO: 9.57, d J=1.2 Hz | oil |
| <u>7b</u> | C ₁₅ H ₁₇ O ₃ N | trans | CHO | NO ₂ , H _w | 3.90, dd J=10, 2 Hz | H _w : 4.20, b W ₂ =7.5 Hz | CHO: 9.57, d J=2 Hz | 92-93 |
| <u>12</u> | C ₁₅ H ₁₇ O ₃ N | threo | CH ₂ NO ₂ | 0 | 3.65, td ¹² 10 Hz Jb, x=5 Hz | | CH ₂ NO ₂ : 4.52, dd ¹² Ja, b=13 Hz Ja, x=10 Hz CH ₂ NO ₂ : 4.90, dd ¹² Ja, b=13 Hz Jb, x=5 Hz | 162-163 |

a) All values refer to internal tetramethylsilane (TMS). Multiplicity: s=singlet; d=doublet; t=triplet; b=broad. Ar=3,4-methylenedioxyphenyl.

hydroindole ⁸ 13 in 68% yield. See Table I for a collection of selected ¹H-NMR data for relevant compounds. A careful analysis of the data shown there suggests that for those compounds having large coupling constants $J = 10-11$ Hz (ie., entries 3, 7a, 7b and 12), a fix in conformation, caused by electrostatic interactions amongst the various functional groups must prevail. However, trans product 4 shows a coupling constant of only 4 Hz. Molecular models show that indeed in this case the cyano group can not interact adequately with the nearby nitro function and thus the observed constant should correspond to the average ³J value for this particular non-rigid system. Considering the importance and availability of ketone 12, several other reduction reactions were evaluated as well. Thus, reaction with activated Zn¹⁴ (1:9 v/v aqueous HOAc, rt, 0.5 h) furnished nitrone 14 (ν_{max} 1615 cm⁻¹), mp 142-144°C (EtOAc-EtOH), in 72% yield, which upon potassium borohydride¹⁵ treatment (EtOH-H₂O, rt, 3 h) gave the cyclic hydroxylamine 15 in 66% yield. Finally, reduction under Chandrasekaran's conditions¹⁶ (TiCl₄, Mg amalgam, THF, rt, 1.5 h) produced imine 16 together with a small amount of enamine 17.

In conclusion, we have devised several easy to implement synthetic entries into the 3-aryloctahydroindole system. The utilization of such intermediates in the total synthesis of the montanine-like alkaloids is now in progress and will be reported elsewhere.

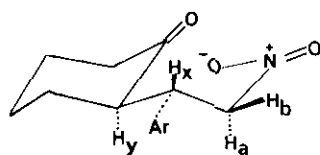
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