APPROACHES TO THE TOTAL SYNTHESIS OF THE MONTANINE (AMARYLLIDACEAE) ALKALOIDS. PREPARATION OF ISOMERIC 3-ARYLOCTAHYDROINDOLES

Ignacio H. Sánchez,* María Isabel Larraza, Irma Rojas, Francisco Kuri Breña, and Humberto J. Flores
Instituto de Química, Universidad Nacional Autónoma de México,
Circuito Exterior, Ciudad Universitaria, Coyoacán 04510, México, D. F.
Krzysztof Jankowski
Département de Chimie, Université de Moncton,
Moncton, N. B., Canada E1A 3E9

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 species[1] characterized by having a 5,11-methanomorfanthridine 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]

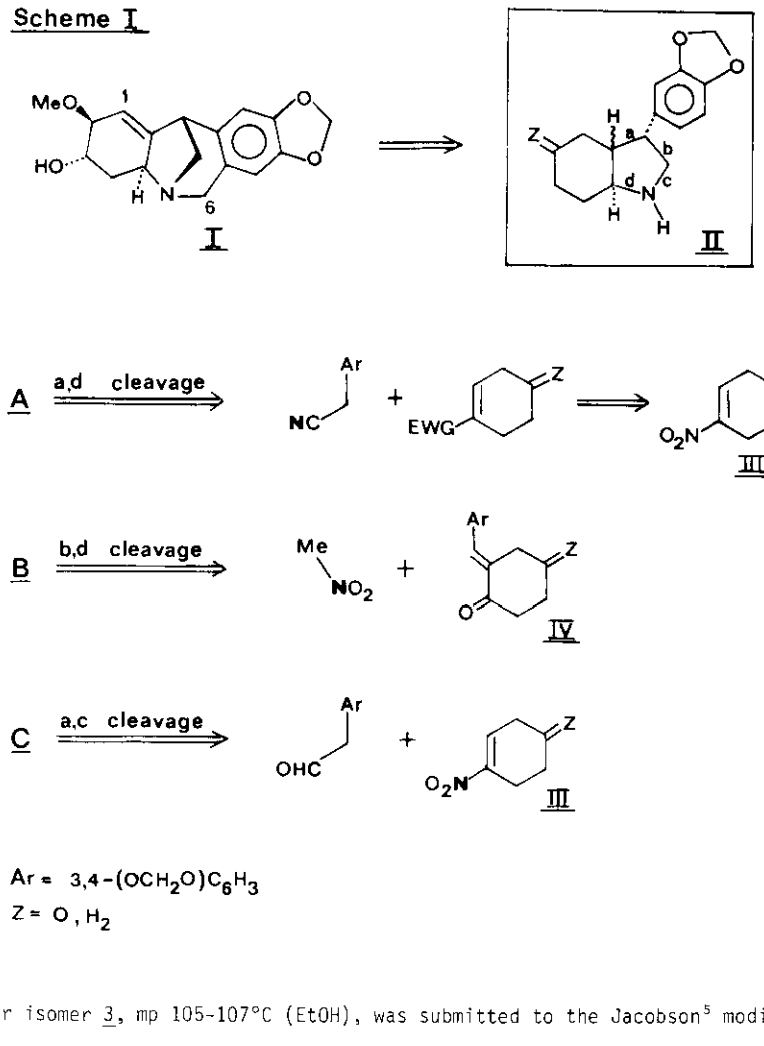
As continuation of our synthetic program dealing with alkaloids from Amaryllidaceae,[3] we now report the first approaches to the total synthesis of the montanine compounds.

An antithetic analysis (Scheme I) 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 3α-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-nitrocyclohexene[4] (2) (^{n}BuLi/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}BuLi/THF/-20°C) furnished instead a 1:1 mixture of the corresponding cis- and trans- addition products in 51% overall yield.

Scheme I

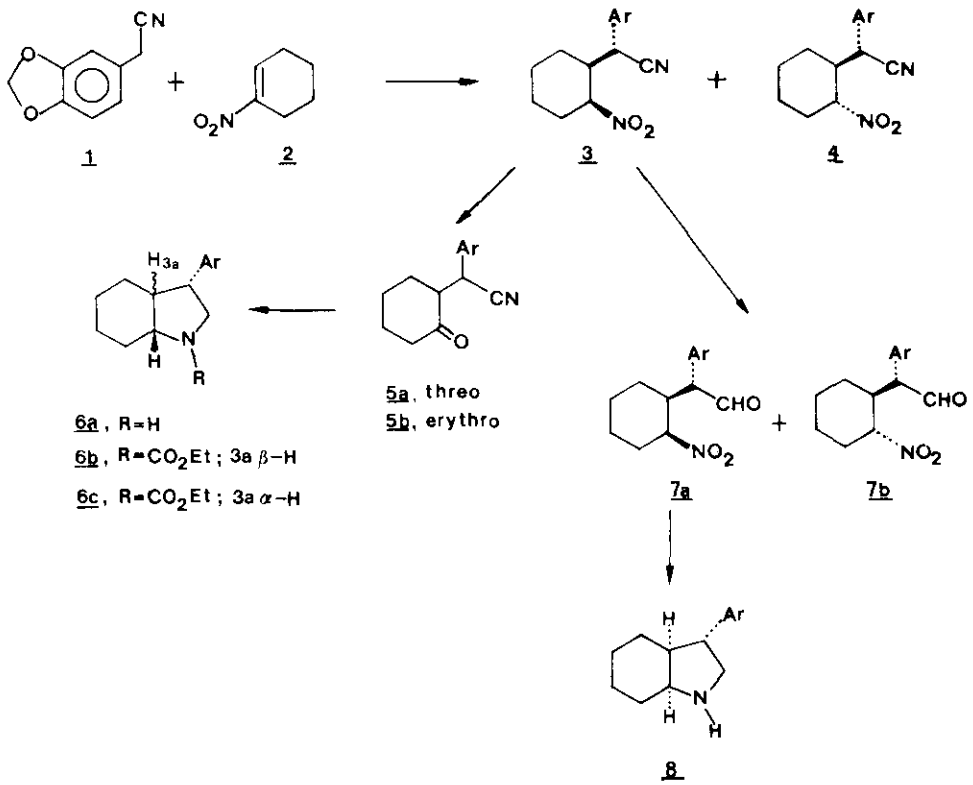


Ar = 3,4-$(OCH_2O)C_6H_3$
Z = O, H_2

When the major isomer 3, mp 105-107°C (EtOH), was submitted to the Jacobson[5] modification of the Nef reaction, a 79% yield of a 1:1 (^{1}H-NMR) mixture of the threo - 5a and erythro - 5b isomers[6] 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] ^{i}PrOH, 50 psi, 45-55°C, 48 h) afforded the oily octahydroindole 6a (R=H) in 52% yield. Reaction of the latter with ethyl chloroformate (CH_2Cl_2, Et_3N, 0°C) provided the protected cis- (6b)

and trans- octahydroindoles (6c),[8] as a 1:1 mixture (^{1}H-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



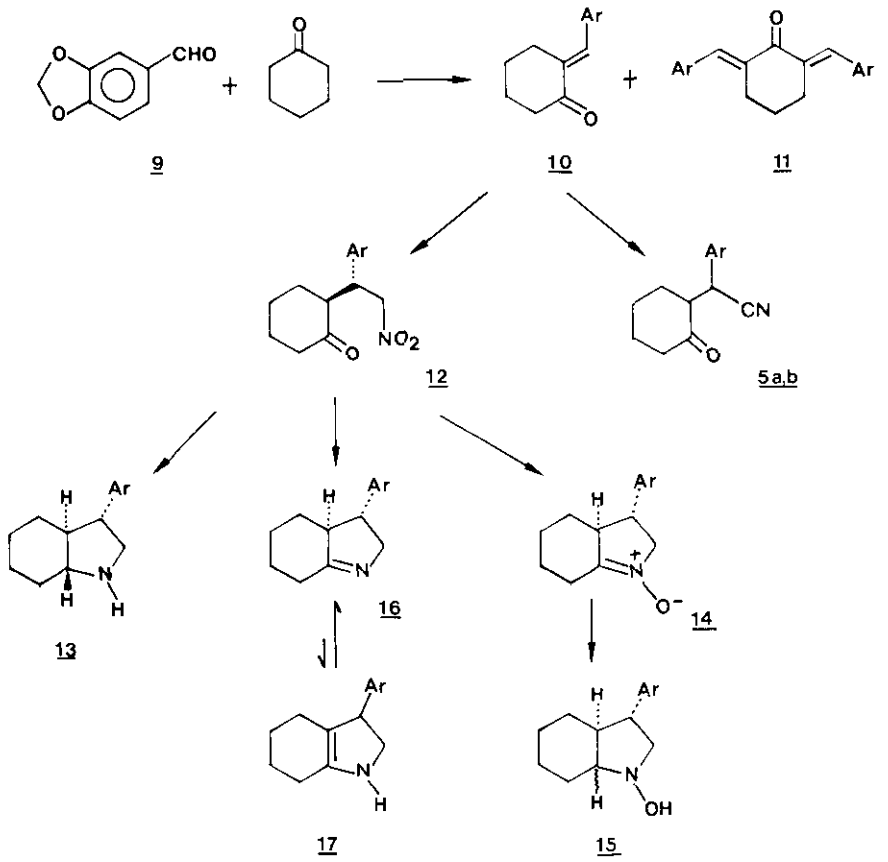
Ar = 3,4-(OCH_2O) C_6H_3

On the other hand, route C was also developed as depicted in Scheme II. Isomer 3 was reduced with ^{i}Bu_2AlH (THF, 0°C; 81%) to yield a 1:1 mixture (^{1}H-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 octahydroindole[8] 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 piperonylidenecyclohexanone (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 conditions[11] (C_6H_6, 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



Ar = 3,4-(OCH_2O)C_6H_3

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 diasteroisomer,[13] mp 162-163°C (EtOH). Reductive cyclization, as before, afforded the oily trans-fused octa-

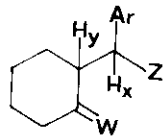


Table 1. Selected ^{1}H-NMR Data for Relevant Compounds.[a]

Compound	Formula	Type	Z	W	Chemical Shift, ppm Hx	Others		mp, °C
3	$C_{15}H_{16}O_4N_2$	cis	CN	NO_2,H_w	3.85, d J=11 Hz	H_w:5.12, b $W_{\frac{1}{2}}$=8.8 Hz		105-107
4	$C_{15}H_{16}O_4N_2$	trans	CN	NO_2,H_w	3.90, d J=4 Hz	H_w:4.60, td J=11, 4 Hz		oil
5a	$C_{15}H_{15}O_3N$	threo	CN	O	4.45, d J=5 Hz			130-131
5b	$C_{15}H_{15}O_3N$	erythro	CN	O	4.05, d J=7.5 Hz			oil
7a	$C_{15}H_{17}O_5N$	cis	CHO	NO_2,H_w	3.61, dd J=10, 1.2 Hz	H_w:5.10, b $W_{\frac{1}{2}}$=7.5 Hz	CHO:9.57, d J=1.2 Hz	oil
7b	$C_{15}H_{17}O_5N$	trans	CHO	NO_2,H_w	3.90, dd J=10, 2 Hz	H_w:4.20, b $W_{\frac{1}{2}}$=7.5 Hz	CHO:9.57, d J=2 Hz	92-93
12	$C_{15}H_{17}O_5N$	threo	CH_2NO_2	O	3.65, td[12] Ja,x=Jx,y= 10 Hz Jb,x=5 Hz		CH_aNO_2:4.52, dd[12] Ja,b=13 Hz Ja,x=10 Hz CH_bNO_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 ^{1}H-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 ^{3}J 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 Zn[14] (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 borohydride[15] treatment (EtOH-H_2O, rt, 3 h) gave the cyclic hydroxylamine 15 in 66% yield. Finally, reduction under Chandrasekaran's conditions[16] ($TiCl_4$, 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.

ACKNOWLEDGEMENT

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8. Complete stereochemical assignments were performed using high field (360 MHz) ^{1}H- and ^{13}C NMR techniques, including 2D-HETCOR, HOMOCOSY and NOE experiments and will be the subject of a future paper.

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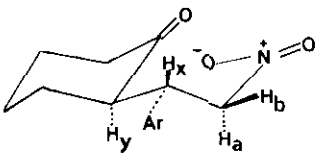
13. The conformation shown below follows from the observed coupling constants: $J_{a,x} = J_{x,y} = 10$ Hz, $J_{b,x} \approx 5$ Hz, and $J_{a,b} = 13$ Hz. The strong electrostatic interaction between the cyclohexanone carbonyl and the side chain nitro group is causing such conformation to prevail. Similar interactions are seen for like compounds in the monocyclic nitro derivatives of the series (see Table I).



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