NOVEL CONFORMATIONAL EFFECTS OF THE N-BENZYLOXYCARBONYL-CIS-3a-ARYL-OCTAHYDROINDOLE NUCLEUS. FORMAL TOTAL SYNTHESIS OF RACEMIC ELWESINE AND EPIELWESINE.[1]

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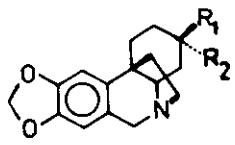
Abstract - The formal total synthesis of racemic elwesine (I) and epielwesine (II) is described. The preferred ground-state conformation of the cis-3a-aryl-octahydroindole precursors is shown to be dependant on the substituent on nitrogen.

As a continuation of our studies on the utilization of the Arylacetonitrile Route[2] for the preparation of Sceletium (Aizoaceae) alkaloids, we now wish to report a formal total synthesis of racemic elwesine (I) and epielwesine (II), two alkaloids belonging to the 5,10b-ethanophenanthridine family of the Amaryllidaceae.[3,4]



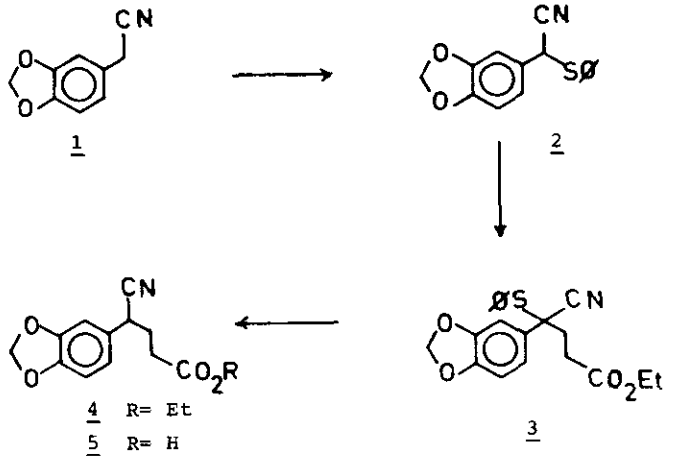
I R= H R_1= OH

II R= OH R_1= H

Our synthetic strategy (Scheme I) is based on a new method of construction of the relevant cis-3a-aryl-octahydroindol-6-one nucleus, which is known[4b] to be a useful synthetic precursor for the ethanophenanthridine alkaloids via the Pictet-Spengler cyclization.

Therefore, our initial aim was to obtain sufficient amounts of the 4-carbethoxy-2-(3,4-methylenedioxyphenyl)butyronitrile 4. Since it is known[5] that under basic catalysis (ie. Triton B) nitrile 1[6] readily adds 2 moles of ethyl acrylate and the direct method using equimolar amounts of a strong base (ie. lithium diisopropylamide, LDA) in aprotic media[7] gave but moderate yields of the desired mate-

rial, we decided instead to use the α-sulfenylated intermediate 2,[8] mp 81-82°(Et_2O-Hex), prepared in 88% yield by treatment of 3,4-methylenedioxyphenylacetonitrile[6] 1 with a slight excess diphenyl disulfide and powdered KOH in dry tetrahydrofuran (THF).[9] Addition of ethyl acrylate proceeded readily in the presence of catalytic amounts of Triton B (THF, rt, 20 min) to afford the sulfenylated cyano ester 3 as a colorless viscous oil in 96% yield. Furthermore, desulfurization of this material using Urushibara's nickel in hot acetone[2b] provided 4, again in 96% yield, showing the expected benzylic methine as a one-proton triplet (J=7 Hz) at 3.89 ppm. In this manner, cyano ester 4 can be routinely prepared in 80-85% overall yield without having to isolate any intermediates.



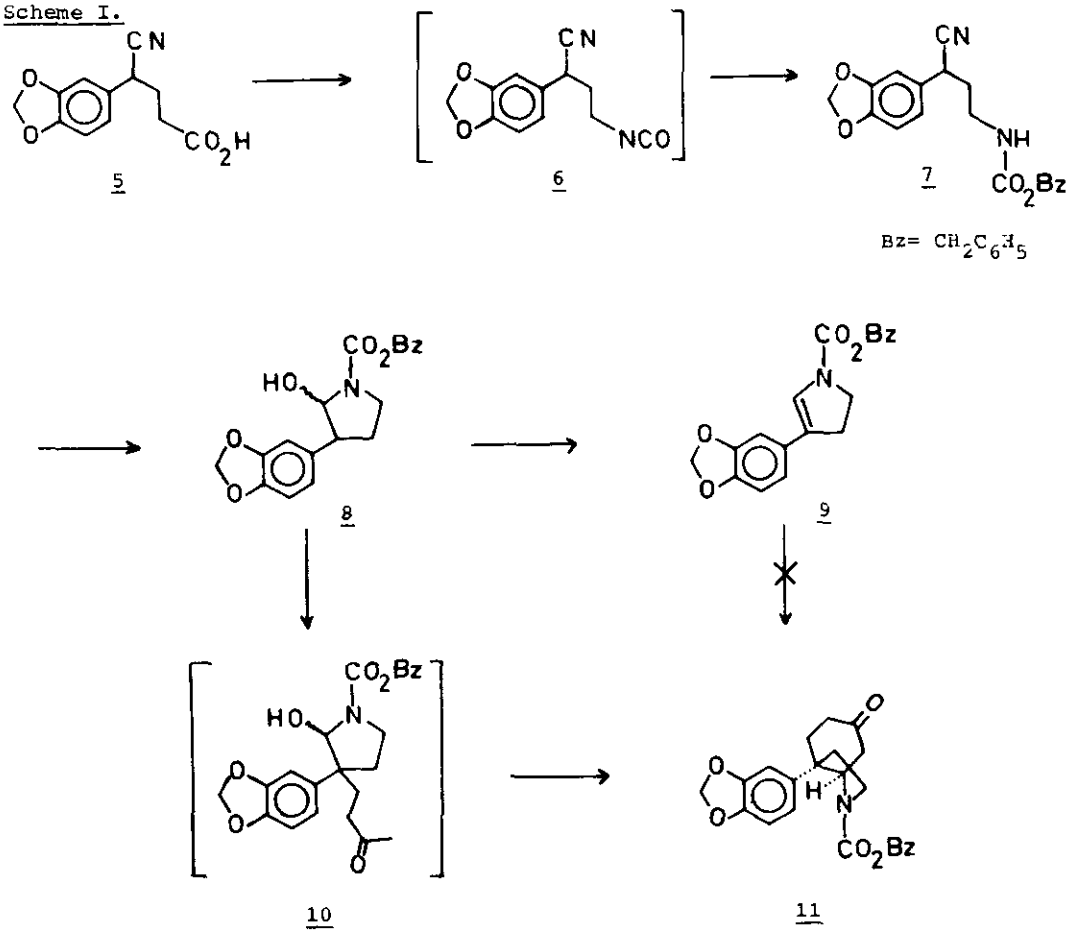
Acid 5 was obtained next, in nearly quantitive yield, by base treatment (2N NaOH, MeOH, rt, 2.5 h) of the latter compound and was then submitted to a modified Curtius rearrangement.[10] The resulting (crude) isocyanate 6, ν max 2260 cm^{-1}, was immediately treated with excess benzyl alcohol (toluene, reflux, 1 h) to furnish urethane 7, as a viscous oil, in 87% yield. Diisobutylaluminum hydride (DIBAL) reduction[11] (toluene, -75°→25°, 1 h) followed by stirring with 10% (v/v) aqueous hydrochloric acid (rt, 40 min) produced the oily N-benzyloxycarbonyl-2-hydroxy-3-(3,4-methylenedioxyphenyl)-pyrrolidine 8 in 48% overall yield (Scheme I).

In an attempt to obtain the desired octahydroindol-6-one nucleus directly, pyrrolidine 8 was reacted with a slight excess methyl vinyl ketone (MVK) in the presence of a catalytic amount of conc HCl[12] (acetonitrile, reflux, 12 h). The only product isolated from this reaction (90%) was the endocyclic enamide 9, mp 135-137° (Et_2O-Hex), arising from a straightforward acid-catalyzed dehydration. Because of

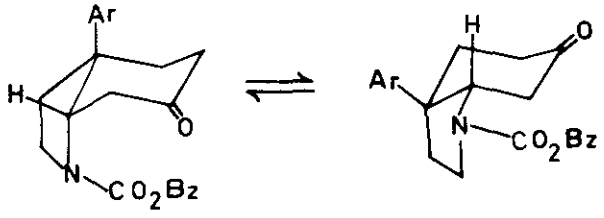
the electron-withdrawing ability of the N-benzyloxycarbonyl grouping compound 9 shows now a drastically reduced nucleophilicity at the β-carbon, as compared to similar systems having an N-alkyl (ie. methyl or benzyl) substituent, thus precluding its use and that of related compounds in the classical endocyclic enamine-type annelation.[12]

However, taking into account its hemiamidal nature, intermediate 8 reacted with MVK under basic catalysis (THF, Triton B, 0°, 30 min) and the resulting (crude) adduct 10 immediately heated with 20% (v/v) methanolic hydrochloric acid to afford in 46% overall yield the desired (oily) N-benzyloxycarbonyl-cis-3a-(3,4-methylenedioxyphenyl)-octahydroindol-6-one 11.

Scheme I.



Double resonance (nmdr) experiments allowed us to assign the one-proton triplet (J_{app} = 7 Hz) at 4.63 ppm to the conformationally diagnostic C_{7a}-H, whilst the two-proton doublet at 2.88 ppm corresponds to the C-7 methylene (Table). This is a rather surprising result, since it has been previously shown[4b,13] that the cis-3a-aryl-octahydroindole systems and its N-alkyl derivatives prefer a ground-state conformation where the bulky 3a-aryl substituent adopts an axial orientation. As a consequence, the equatorially-oriented C_{7a}-H bisects the C-7 methylene and thus appears as a triplet (J_{app}= 3.2-3.5 Hz). Even in those compounds derived from the cis-3a-aryl-octahydroindol-2,6-dione[14] the same ground-state conformation is maintained, with the relevant C-7a methine appearing again as a triplet (J_{app} = 4.0-4.5 Hz). Furthermore, the possibility of ketone 11 having a trans-fused arrangement can be readily ruled out by comparison with the reported nmr data for trans-mesembranone.[14a] Therefore, 11 must exist as a conformationally mobile system where the observed coupling constant for the C_{7a}-H (J_{app} = 7 Hz) is in reality an average value for conformers 11a and 11b.



11a 11b

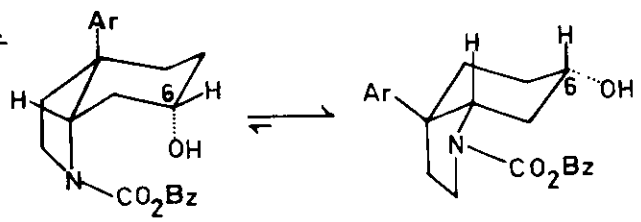
Ar= 3,4-methylenedioxyphenyl

To proceed with our scheme of synthesis (vide supra), ketone 11 was next reduced with DIBAL[11] (THF, -70°, 1 h) and the epimeric alcohols 12 and 13 (relative ratio= 3.5:1) were isolated in 95% yield after purification by preparative layer chromatography on silica gel. It is well-known[4b,13] that hydride reduction of similar systems having N-alkyl substitution yields predominantly the axial alcohol (observed axial: equatorial alcohol ratio= 2.33-3.0:1) as evidenced by the characteristic W 1/2 values[15] (W 1/2= 8-11 Hz for the major product and 18-21 Hz for the minor one) shown by the corresponding C-6 methine proton. Moreover, the infrared (ir) spectra of both epimers are also very indicative of the stereochemical nature of the C-6 substituent; thus the main product (axial) shows a strong intramole-

cular hydrogen bond (ν max= 3380-3325 cm^{-1}) whilst the minor isomer (equatorial) shows both a free-hydroxyl absorption and a weak intermolecular interaction (ν max= 3600 and 3500 cm^{-1}) that dissapears upon dilution. In our particular case, the observed absorption maxima (neat) for both isomers (ν max= 3420-3410 cm^{-1}) are indicative of intermolecular hydrogen bonding since they shift to higher frequencies on dilution (c= 0.025 M).[4b]

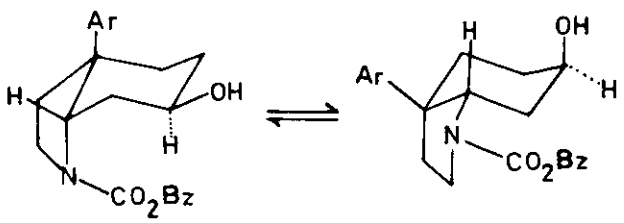
On the other hand, whereas the major product 12 shows a broad multiplet centered at δ 3.83 ppm (W 1/2= 20 Hz) for the C_6-H and a dd (J= 6.5 and 11 Hz) at 4.33 ppm for the C_{7a}-H, its isomer 13 shows a multiplet at 4.00 (W 1/2= 10.5 Hz) and a dd (J= 7.3 and 7.5 Hz) at 4.47 ppm for the same protons (Table). Clearly enough these data do not correlate at all with previous cases having N-alkyl substitution unless one considers that the effect of the N-benzyloxycarbonyl grouping is to alter or even revert the original ground-state conformational equilibria[4b,13] to those shown in Scheme II.

Scheme II.



12a 12b

Ar= 3,4-methylenedioxyphenyl



13a 13b

We have thus shown that the nature of the N-substituent is indeed a determining factor in the conformational equilibrium of the cis-3a-aryl-octahydroindole system. Although the magnitude of this effect differs for isomers 12 and 13, it is obvious that a combination of the steric and/or electronic factors of this particular substituent, chosen for synthetic purposes, is responsible for the observed changes.[16]

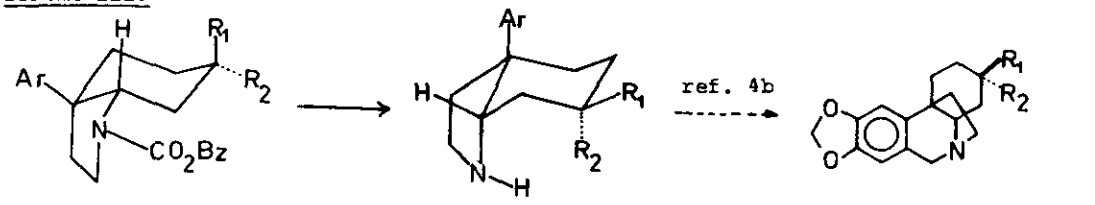
TABLE. Selected nmr for compounds 11-13.[a]

Compound	C-6 hydrogen δ	C-6 hydrogen W 1/2, Hz	C-7a hydrogen δ	C-7a hydrogen J_{app} or J, Hz (mult.)
11	--	--	4.63	7.0 (t)
12	3.83	20.0	4.33	6.5, 11.0 (dd)
13	4.00	10.5	4.47	7,3, 7.5 (dd)

[a] 90-MHz Varian EM-390. Spectra were run in $CDCl_3$ using TMS as internal standard. Chemical shifts are reported in ppm.

Finally, when alcohol 12 was submitted to a Pd-catalyzed hydrogenolysis (10% Pd-C, MeOH, 60 psig, 3 h) in order to remove the protecting group, amino alcohol 14, mp 177-179° (benzene-Et_2O), after sublimation at 95°/0.1 mm (lit[4b] mp 179-180°), mp (hydrochloride salt) 245-247° (MeOH-Et_2O) (lit[4b] mp 246-251.5°) was produced in nearly quantitive yield. Similarly, the minor isomer 13 afforded the known[4b,16] amino alcohol 15, mp 152-154° (lit[4b] mp 154-156.5°), after sublimation at 87-90°/0.1 mm. It is worth mentioning that both products proved spectroscopically identical (nmr, ir) to the samples prepared earlier by Stevens.[4b,16] This also demonstrates that upon removal of the protecting group in question the molecules revert back to the originally preferred ground-state conformation, namely the one having an axial 3a-aryl moiety (Scheme III).

Scheme III.



12 R_1= H , R_2= OH — 14 R_1= H , R_2= OH — II R_1= OH , R_2= H

13 R_1= OH, R_2= H — 15 R_1= OH, R_2= H — I R_1= H , R_2= OH

Ar= 3,4-methylenedioxyphenyl

In order to complete our synthetic task, all that is needed is to introduce a one-carbon unit between the nitrogen atom and the aromatic ring. Since this

transformation has already been performed[4b] on both isomers 14 and 15, via a Pictet-Spengler cyclization, our synthesis of the latter compounds constitutes in fact a formal total synthesis of epielwesine (II) and elwesine (I), respectively.[17]

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16. We thank Professor R. V. Stevens (U. of California at Los Angeles for valuable suggestions regarding the preferred ground-state conformation of alcohols 12 and 13 and for kindly providing us with authentic comparison spectra (ir and pmr) of aminoalcohols 14 and 15.

17. All new compounds were adequately characterized by spectral methods (ir, pmr and ms) and, when possible, gave satisfactory high resolution mass spectral and/or combustion analytical data.

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