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SYNTHETIC AND STRUCTURAL STUDIES IN THE GONIOMITINE ALKALOID SERIES : A NEW REDUCTIVE CYCLIZATION REACTION IN THE INDOLE FIELD

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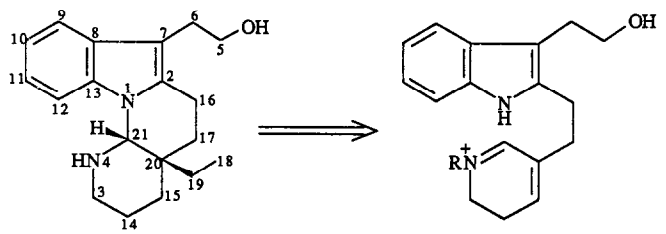
Abstract *A synthetic approach towards the indole alkaloid goniomitine 1 has been studied via a route inspired by a biogenetic hypothesis. The key step of this reaction sequence is a reductive cyclization which involves the intramolecular attack of an indole nitrogen on a piperideinium ion under basic conditions.*

In a recent publication,[1] we described the structure determination of the indole alkaloid, goniomitine 1, isolated from the root bark of Gonioma malagasy. The proposed structure for 1 was inferred from its spectral data and a plausible biogenesis from the alkaloid vincadifformine. In order to ascertain unambiguously the unprecedented structure 1 for the new alkaloid, it was necessary to synthesize either the natural product itself or a closely related analog.



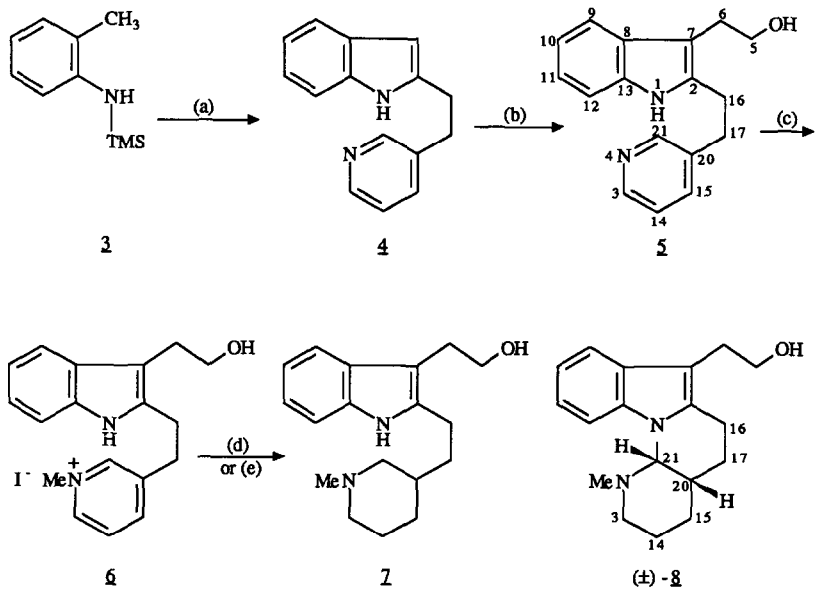
goniomitine 1 2

Scheme 1

The most simple way to create the aminal type function between N-1 and C-21[2] is suggested by the biogenetic hypothesis[1], i.e., a nucleophilic attack of N-1 on the Δ^1 piperideinium ion of 2 (Scheme 1). Most of the synthetic attempts to prepare such reactive intermediates have involved the use of pyridines or piperidines.[3] Prompted by previous results,[3] we investigated a strategy involving the transformation of the pyridinium salt 6 (Scheme 2) into the corresponding dihydropyridinium salt 2 which we expected to cyclize. The resultant Δ^3 piperideine would have been convenient for further introduction of an ethyl chain. Unfortunately, this scheme failed when a modified Polonovski reaction was used in an attempt to generate the conjugated iminium salt 2 (R = CH_3). Therefore, rather than embark upon the developement of an entirely new route, we investigated the feasibility of a reaction we had discovered for the formation of the Aspidosperma alkaloid nucleus.[4] Hydrogenation of α-(3-pyridylmethyl)-indole-2-acetamide in methanolic hydrogen chloride over platinum produced an intermediate pyridinium ion

which in turn reacted with the indole system in an intramolecular Mannich reaction.[4] This procedure was extended to pyridinium salts for the eburnamonine alkaloid synthesis.[5]

With this aim in mind we have prepared the suitable compound 4 from N-trimethylsilyl-o-toluidine 3 according to a recent method.[6] The dianion of 3 was condensed with methyl 3-(3-pyridyl)propanoate to afford the C-2 substituted indole 4[7] in 55% yield. The Grignard derivative of 4 reacted with ethylene oxide to give compound 5.[8] (33% yield and recovered starting material 4 43% i.e., 57% transformation). Compound 5 yielded the pyridinium salt 6 (97%, mp 155°Cfrom MeOH-Et_2O) on treatment with methyl iodide in CH_2Cl_2.



(a)[6] i : 2.2 equiv n-BuLi/n-hexane, reflux 6h; ii : methyl 3-(3-pyridyl)propanoate/THF, -78°C → 15°C; (b)[6] 10 equiv MeMgI, 10 equiv ethylene oxide/Et_2O, 1h then reflux, 2h; (c) MeI/CH_2Cl_2, reflux 2h; (d) H_2, PtO_2/MeOH, 3h; (e) H_2, PtO_2, NaOMe/MeOH, 3h.

Scheme 2

The problem associated with indoles' reactivity must be considered since it was felt that under the original acid conditions, indole β-protonation would occur leading to an indolenine unable to form an aminal function. To circumvent this problem inherent in indole reactivity, the hydrogenation reaction of 6 was performed in methanol in the presence of sodium methoxide over platinum. These new conditions produced two compounds 7[9] (36%) and 8[10] (23%). In contrast, hydrogenation of 6 in neutral conditions gave only 7 (91%).

The spectral characteristics of the tetracyclic compound 8 were in agreement with its assigned structure. The most striking features are the deshielding of the C-21 proton (δ 4.43) at ^1H NMR and of the C-21 carbon (δ 73.4) at ^{13}C NMR as observed for goniomitine 1.[1] The C/D-cis ring junction of 8 was determined from the coupling constant

between C-21 and C-20 protons (J = 3Hz). The use of 1D difference NOE and NOESY NMR technique on 8 shows that it adopts the conformation as depicted in figure 1. The comparison of the ^{13}C NMR spectra of 1 and the synthetic compounds 7 and 8 (Table 1) supports the previously proposed structure 1 for the natural product.[1]

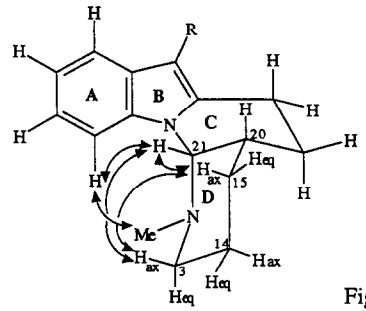


Figure 1

Table 1 ^{13}C NMR chemical shift values (δ) (50MHz, $CDCl_3$)

Carbon N°	Compound 7[a)]	Compound 8[a)]	Goniomitine 1[1]
2	135.6	134.5	132.7
3	55.9	55.9	45.4
5	62.6	62.7	62.6
6	28.0	27.8	27.8
7	107.3	106.1	106.8
8	128.6	128.5	129.3
9	118.0	117.7	118.1
10	119.1	119.4	120.8[b)]
11	121.0	120.3	119.9[b)]
12	110.5	109.8	108.7
13	136.7	137.2	135.5
14	24.4	20.5	18.5
15	29.9	29.6	21.0[b)]
16	23.5	20.2	33.8[b)]
17	34.3	21.3	21.9
18	-	-	7.1
19	-	-	28.7
20	35.5	34.7	35.3
21	61.3 (CH_2)	73.4 (CH)	71.1 (CH)
N-Me	46.1	43.3	-

a) These assignments were determined from 2D (^{13}C-^{1}H) spectrum.
b) The previous assignments require revision.

In conclusion, the achievement of the synthesis of (±)-20-desethyl-N_b-methyl-goniomitine 8 represents an interesting example of a new reductive cyclization reaction in the indole field. Intramolecular nucleophilic attack of the indole nitrogen occurs on the pyridinium salt itself prior to hydrogenation since, in contrast to previous conditions[4,5], the basic medium does not allow further protonation of an intermediate dihydropyridine system. It is also noteworthy that only 1,2 substitution takes place although 1,4 substitution cannot be excluded a priori.[11]

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7 - 4 : mp 139°C (CH_2Cl_2-Et_2O). MS m/z : 222 (M^+). IR ($CHCl_3$) cm^{-1} : 3450 (NH). NMR (400 MHz, $CDCl_3$) δH : 3.06 (m, 4H, 16- and 17-H_2), 6.28 (br.s, 1H, 7-H), 7.09 (td, J = 8 and 1.5Hz, 1H, 10-H), 7.14 (td, J = 8 and 1.5Hz, 1H, 11-H), 7.22 (dd, J = 8 and 5 Hz, 1H, 14-H), 7.30 (dd, J = 8 and 1.5Hz, 1H, 12-H), 7.47 (dt, J = 8 and 2Hz, 1H, 15-H), 7.54 (dd, J = 8 and 1.5Hz, 1H, 9-H), 8.26 (br, 1H, NH), 8.49 (dd, J = 5 and 2Hz, 1H, 3-H), 8.51 (d, J = 2Hz, 1H, 21-H). (50MHz) δC : 29.4 (C-16), 32.5 (C-17), 99.5 (C-7), 110.5 (C-12), 119.2 (C-10), 119.6 (C-9), 120.8 (C-11), 123.5 (C-14), 128.6 (C-8), 136.1 (C-2), 136.3 (C-15), 137.0 (C-13), 138.1 (C-20), 146.9 (C-3), 149.1 (C-21).
$C_{15}H_{14}N_2$ calculated C, 81.05 ; H, 6.35 ; N, 12.60%. Found C, 80.94 ; H, 6.37 ; N, 12.76%.

8 - 5 : mp 134°C (CH_2Cl_2-n-hexane). MS m/z : 266 (M^+). IR ($CHCl_3$) cm^{-1} : 3550-3100 (br, OH), 3450 (NH). NMR (400 MHz, $CDCl_3$) δH : 2.86 (t, J = 7Hz, 2H, 6-H_2), 2.95 (t, J = 7Hz, 2H, 17-H_2), 3.03 (t, J = 7Hz, 2H, 16-H_2), 3.75 (t, J = 7Hz, 2H, 5-H_2), 7.10 (br t, J = 8Hz, 1H, 10-H) ; 7.15 (br t, J = 8Hz, 1H, 11-H), 7.19 (dd, J = 8 and 5 Hz, 1H, 14-H), 7.29 (br d, J = 8Hz, 1H, 12-H), 7.40 (br d, J = 8Hz, 1H, 15-H), 7.54 (br d, J = 8Hz, 1H, 9-H), 8.14 (br, 1H, NH), 8.39 (br s, 1H, 21-H), 8.46 (br d, J = 5Hz, 1H, 3-H). (50MHz) δC : 27.9, 28.1 (C-6, C-16), 33.7 (C-17), 62.9 (C-5), 108.6 (C-7), 110.7 (C-12), 118.5 (C-9), 119.7 (C-10), 121.8 (C-11), 123.5 (C-14), 128.7 (C-8), 135.1 (C-2), 136.1 (C-15), 136.4 (C-13), 147.9 (C-3), 149.9 (C-21).
$C_{17}H_{18}N_2O$ calculated C, 76.66 ; H, 6.81 ; N, 10.51%. Found C, 76.43, H, 6.88 ; N, 10.67%.

9 - 7 : viscous oil. MS m/z : 286 (M^+). IR ($CHCl_3$) cm^{-1} : 3440 (NH), 3550-3050 (br, OH). NMR (200MHz, $CDCl_3$) δH : 0.92 (m, 1H, 15-Heq), 1.63 (m, 7H, 14- and 17-H_2, 15-Hax, 20-H and 21-Hax), 2.03 (br t, J = 10Hz, 1H, 3-Hax), 2.28 (s, 3H, NMe), 2.76 (m, 4H, 3-Heq, 21-Heq and 16-H_2), 2.96 (t, J = 7Hz, 2H, 6-H_2), 3.83 (t, J = 7Hz, 2H, 5-H_2), 7.07 (m, 2H, 10- and 11-H), 7.30 (br d, J = 8Hz, 1H, 12-H), 7.50 (br d, J = 8Hz, 1H, 9-H), 9.33 (br, 1H, NH). ^{13}C NMR (see Table 1).

10 - 8 : viscous oil. MS m/z : 284 (M^+). IR ($CHCl_3$) cm^{-1} : 3570-3150 (br, OH), NMR (400MHz, $CDCl_3$) δH : 1.54 (br d, J = 13Hz, 1H, 14-Heq), 1.68 (m, 1H, 17-Hax), 1.82 (m, 2H, 15-H_2), 1.94 (m, 1H, 14-Hax), 2.00 (m, 1H, 20-H), 2.07 (s, 3H, NMe), 2.35 (td, J = 12 and 3Hz, 1H, 3-Hax), 2.47 (m, 1H, 17-Heq), 2.84-3.02 (m, 2H, 3-Heq and 16-Hax), 3.00 (t, J = 7Hz, 2H, 6-H_2), 3.17 (dq, J = 17 and 2 Hz, 1H, 16-Heq), 3.81 (t, J = 7 Hz, 2H, 5-H_2), 4.43 (d, J = 3Hz, 1H, 21-H), 7.10 (t, J = 8Hz, 1H, 10-H), 7.15 (t, J = 8Hz, 1H, 11-H), 7.44 (d, J = 8Hz, 1H, 12-H), 7.55 (d, J = 8Hz, 1H, 9-H). ^{13}C NMR (see Table 1).

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