SYNTHESIS OF N₄-BOC-5β-CYANO-DEFORMYL-E-GEISSOSCHIZINE: A POTENTIAL SYNTHON IN THE PREPARATION OF SARPAGAN AND AJMALAN RING SYSTEMS

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Abstract - The paper describes a short, synthetic route to N₄-BOC-5β-cyano-deformyl-E-geissoschizine (8), a prototype of potential synthons in the preparation of sarpagan and ajmalan ring systems.

INTRODUCTION

In the course of efforts to find feasible synthetic approaches to sarpagin ajmalin-type indole alkaloids,¹,² it became evident to us that an easy method that would permit a regioselective formation of Δ⁴₀⁻iminium ions (or their equivalents) from appropriate indolo[2,3-a]quinolizidine (1) derivatives was a prerequisite for a successful accomplishment of our goal.
We have previously shown\textsuperscript{3} that the formation of particular indolo[2,3-\textit{a}]quinolizidine iminium ions by the modified Polonovski reaction\textsuperscript{4,8} strongly depends on whether the intermediate indolo[2,3-\textit{a}]quinolizidine N\textsubscript{5}-oxide is \textit{cis} (2) or \textit{trans} (3). Thermodynamically the most stable iminium ion will be formed as the main product when stereoelectronic requirements for E2-type \textit{trans}-dialylic elimination are fulfilled. As a consequence, \textit{cis}-N\textsubscript{5}-oxides should be more favourable than \textit{trans}-N\textsubscript{5}-oxides to the formation of \(\Delta^{5\text{60}}\)-iminium ions. Recently we developed a procedure that permits the oxidation of indolo[2,3-\textit{a}]quinolizidines to \textit{cis}- or \textit{trans}-N\textsubscript{5}-oxides to be directed at will.\textsuperscript{9}

Thus, the time appeared ripe for a more detailed study of the preparation of indolo[2,3-\textit{a}]quinolizidine \(\Delta^{5\text{60}}\)-iminium ions (4) (IUPAC numbering\textsuperscript{10}) (or their equivalents), in particular from indolo[2,3-\textit{a}]quinolizidine derivative possessing an \(\textit{E}\)-ethylidene side-chain at C-3 (compound 5), as do many of the indole alkaloids. Significantly, the C-3 \(\textit{E}\)-ethylidene side-chain (in biogenetic numbering,\textsuperscript{10} C-20 \(\textit{E}\)-ethylidene side-chain) usually strongly favours the \(\Delta^{4\text{65}}\)-iminium ion (6) (IUPAC numbering) (in biogenetic numbering, \(\Delta^{4\text{60}}\)-iminium ion) formation (Scheme 1).

\begin{center}
\textbf{Scheme 1.} Formation of indolo[2,3-\textit{a}]quinolizidine \(\Delta^{5\text{60}}\)-iminium ion (4) and indolo[2,3-\textit{a}]quinolizidine \(\Delta^{4\text{65}}\)-iminium ion (6).
\end{center}

In the present paper we describe the transformation of deformyl-\textit{E}-geissoschizine (7) (an indolo[2,3-\textit{a}]-quinolizidine derivative possessing an \(\textit{E}\)-ethylidene side chain at C-3; IUPAC numbering) to N\textsubscript{5}-Boc-5\(\beta\)-cyano-deformyl-\textit{E}-geissoschizine (8), which is the synthetic equivalent of N\textsubscript{5}-Boc-deformyl-\textit{E}-geissoschizine \(\Delta^{4\text{65}}\)-iminium ion (9) (biogenetic numbering) (Scheme 2).
RESULTS AND DISCUSSION

Oxidation of our earlier described \( \text{N,}-\text{Boc-deformyl-E-geissoschizine (10)} \) with \( \text{m-chloroperbenzoic acid (m-CPBA)} \) led exclusively to \( \text{N,}-\text{Boc-deformyl-E-geissoschizine cis-N, -oxide (11)} \) (Scheme 3).

We have shown earlier\(^{1,9,11}\) that, when the substitution pattern permits, \( \text{N,}-\text{Boc protected indolo[2,3-a]quinolizidine cis-N, -oxides exist predominantly in conformation b (for definition of conformation b, see Ref. 11). This should favour the successful preparation of \( \Delta^{(6)} \)-iminium ions (in biogenetic numbering, \( \Delta^{(6)} \)-iminium ions) (Scheme 4).} \)

Treatment of the cis-N_5-oxide (11) with trifluoroacetic anhydride (TFAA) (modified Polonovski reaction) at -17°C and KCN (cyano trapping^12,13) yielded N_5-Boc-5β-cyano-deformyl-E-geissoschizine (8) in 30% yield. Small amounts of other compounds, among them N_5-Boc-deformyl-E-geissoschizine (10), N_5-Boc-21α-cyano-deformyl-Z-geissoschizine (12), and N_5-Boc-6-trifluoroacetyl-5,6-didehydro-deformyl-E-geissoschizine (13), were isolated (Scheme 5).

Scheme 5. Formation of compounds (8), (10), (12), and (13).
The formation of compound (12) (Z-ethylidene side-chain) can be explained by a Z-favoured E/Z side-chain equilibrium between the intermediate iminium ions (Scheme 6).

Scheme 6. E/Z side-chain equilibrium between the intermediate iminium ions.

The $^{13}$C-Nmr data for compounds (8), (11), (12), and (13) are given Figure 1. Comparison of the measured chemical shifts, taking into account the conformational considerations relevant for indolo[2,3-a]quinolizidines in general, provides clear evidence of the stereostructures depicted in the formulae.

Figure 1. The $^{13}$C-nmr data for compounds (8), (11), (12), and (13).
The stereochemistry of compound (8) (predominantly in conformation $\phi^*$) at C-5 was confirmed by the coupling constants of H-5: 5.5 Hz and 2.5 Hz. This indicated equatorial orientation for H-5 (H-5α) and as a consequence axial orientation for the C-5 cyano-group.

CONCLUSIONS

The present results confirm that, in iminium ion formation (modified Polonovski reaction) and cyano-trapping, $N_\alpha$-Boc-deformyl-$E$-geissoschizine cis-$N_\alpha$-oxide (11) yields $N_\alpha$-Boc-5β-cyano-deformyl-$E$-geissoschizine (8), which is the synthetic equivalent of $N_\alpha$-Boc-deformyl-$E$-geissoschizine $\Delta^{495}$-iminium ion (9).

The results would be useful in the preparation of compounds possessing the sarpagan or ajmalan ring system. Further studies are in progress.

EXPERIMENTAL

$\text{Ir}$ spectra were recorded with a Perkin-Elmer 700 spectrophotometer in CHCl$_3$. $\text{Ir}$ absorption bands are given in reciprocal centimetres (cm$^{-1}$). $^1\text{H}$- and $^{13}\text{C}$-nmr spectra were measured in CDCl$_3$ either with a Varian Gemini-200 spectrometer working at 199.975 MHz ($^1\text{H}$-Nmr) and 50.289 MHz ($^{13}\text{C}$-Nmr) or a Varian Unity-400 NMR spectrometer working at 399.952 MHz ($^1\text{H}$-Nmr) and 100.577 MHz ($^{13}\text{C}$-Nmr). Chemical shifts are given in ppm by reference to TMS ($^1\text{H}$-Nmr; $\delta_\text{H}=0.0$ ppm) and CDCl$_3$ ($^{13}\text{C}$-Nmr; $\delta_\text{C}=77.0$ ppm). Abbreviations s, d, t, q, m, and br are used to designate singlet, doublet, triplet, quartet, multiplet, and broad, respectively. For the $^{13}\text{C}$-nmr data, see Figure 1. Mass spectrometry (Elms and HRms) was done on a Jeol DX 303/DA 5000 instrument.
Preparation of N-Boc-deformyl-E-geissoschizine cis-N₅-oxide (11):
A solution of N-Boc-deformyl-E-geissoschizine (10) (114 mg, 0.27 mmol) and m-chloroperbenzoic acid (m-CPBA) (60 mg, 1.3 equiv.) in dry CH₂Cl₂ (5 ml) was stirred at room temperature for 3 h (Ar atm). Normal work-up and purification by column chromatography (alumina, CH₂Cl₂/MeOH:98/2) yielded compound (11).

Compound (11): Y. 83 mg (70%). Amorphous material. Ir: 1725 br (2 x C=O). 'H-Nmr: 1.68 [9H, s, -C(CH₃)₃], 1.80 (3H, d, J=7 Hz, =CHCH₃), 3.68 (3H, s, -OCH₃), 4.03 (1H, d, J=13 Hz, H-21α), 4.15 (1H, d, J=13 Hz, H-21β), 4.85 (1H, br d, J=12 Hz, H-3), 5.89 (1H, q, J=7 Hz, =CECH₂), 7.23-7.29 (2H, m, H-10, H-11), 7.44 (1H, d, J=8 Hz, H-9), 8.04 (1H, d, J=8 Hz, H-12). Ms: 440 (M⁺), 383, 340, 323, 295, 170, 169, 156 (100%). HRms found: 440.2304. Calcd for CₓHₓNₓOₓ: 440.2311.

Preparation of N-Boc-5₆-cyano-deformyl-E-geissoschizine (8):
The cis-N₅-oxide (11) (80 mg, 0.18 mmol) was dissolved in dry CH₂Cl₂ (6 ml) and the mixture was cooled to -17°C with an icesalt bath. Trifluoroacetic anhydride (TFAA) (0.07 ml, 2.5 equiv.) was added with a syringe during 5 min and stirring was continued for 2 h, with the temperature kept at -1°C with an icesalt bath. During one further hour the temperature of the reaction mixture was allowed to rise to -5°C, whereafter the bath was taken away. The temperature of the reaction mixture was allowed to rise to 20°C, KCN (36 mg, 3 equiv.) in H₂O (2 ml) was added, and the pH of the aqueous layer was adjusted to pH 5 by addition of solid NaOAc. The mixture was stirred for 45 min, basified to pH 10 with 10% Na₂CO₃, and extracted with CH₂Cl₂. Normal work-up and purification by flash chromatography (silica, CH₂Cl₂) followed by plc (silica, CH₂Cl₂/MeOH:98/2) gave compound (8) together with compounds (10), (12), and (13).

Compound (8): Y. 24 mg (30%). Amorphous material. Ir: 2350 m (CN), 1730 br (2 x C=O). 'H-Nmr: 1.66 [9H, s, -C(CH₃)₃], 1.68 (3H, d, J=7 Hz, =CHCH₃), 3.64 (3H, s, -OCH₃), 4.04 (1H, dd, J₁=5.5 Hz, J₂=2.5 Hz, H-5α), 4.16 (1H, br d, J=10 Hz, H-3), 5.52 (1H, q, J=7 Hz, =CHCH₃), 7.20-7.34 (2H, m, H-10, H-11), 7.42 (1H, d, J=8 Hz, H-9), 8.08 (1H, d, J=8 Hz, H-12). Ms: 449 (M⁺), 422, 392 (100%), 366, 348, 321, 293, 212, 169, 168. HRms found: 449.2289. Calcd for CₓHₓNₓOₓ: 449.2315.

Compound (10): Y. 8 mg (10%). Amorphous material. For the analytical data, see Ref. 11.

Compound (12): Y. 10 mg (12%). Amorphous material. Ir: 2300 m (CN), 1725 br (2 x C=O). 'H-Nmr: 1.66 [9H, s, -C(CH₃)₃], 1.72 (3H, d, J=7 Hz, =CHCH₃), 3.70 (3H, s, -OCH₃), 4.68 (1H, br d, J=10 Hz, H-3), 4.91 (1H, s, H-21β), 5.44 (1H, q, J=7 Hz, =CHCH₃), 7.20-7.30 (2H, m, H-10, H-11), 7.39 (1H, d, J=8 Hz, H-9), 8.11 (1H, d, J=8 Hz, H-12). Ms: 449 (M⁺), 422, 392, 366, 293 (100%). HRms found: 449.2302. Calcd for CₓHₓNₓOₓ: 449.2315.

Compound (13): Y. 7 mg (8%). Amorphous material. Ir: 1730 br (3 x C=O). 'H-Nmr: 1.68 [9H, s, -C(CH₃)₃], 1.74 (3H, d, J=7 Hz, =CHCH₃), 3.66 (3H, s, -OCH₃), 4.23 (1H, d, J=15 Hz, H-21α), 4.32
(1H, d, J=15 Hz, H-21β), 5.49 (1H, dd, J1=11 Hz, J2=4 Hz, H-3), 5.63 (1H, q, J=7 Hz, =CH2CH3), 7.22-7.30 (2H, m, H-10, H-11), 7.58 (1H, s, H-5), 8.09 (1H, d, J=8 Hz, H-12), 8.46 (1H, d, J=8 Hz, H-9). Ms: 518 (M+), 462, 418, 417, 343, 264 (100%), 195, 167. HRms found: 518.1999. Calcd for C27H29F4N3O5: 518.2028.

REFERENCES AND NOTES

10. Two numbering systems are used: the IUPAC numbering system for compounds whose names are based on the word "indolo[2,3-a]quinolizidine", and the biogenetic numbering system of Le Men and Taylor\textsuperscript{16} for compounds whose names are based on the word "geissoschizine".

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