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Oxidation of indolines to nitrones and new rearrangement in *seco*-curane type indoline alkaloids

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Abstract—At room temperature 3-chloroperoxybenzoic acid oxidizes the deacetylated strychnobrasiline to the corresponding nitrone. Two unexpected rearrangements are observed when the reaction is performed at 40°C. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

In connection with our interest in the chemistry of the Nb–C21 *seco*-curane alkaloids and in order to develop an hemisynthesis of N_b–C3 *seco*-curane alkaloids as malagashanine **2**[1] from strychnobrasiline **1**, we recently reported an unusual rearrangement in the lithium aluminium hydride reduction of **1**.[2] Herein, we describe the reaction of compound **3** (obtained by treatment of strychnobrasiline with HCl)[2] with MCPBA to the corresponding nitrone **4** in quantitative yield. An unexpected Baeyer–Villiger type rearrangement is observed when the reaction is continued at 40°C. The structure determination of the new compounds are mainly supported by the ^{15}N and ^{13}C NMR data.

2. Results and discussion

2.1. Action of MCPBA at room temperature

In the first experiment, **3** dissolved in CH_2Cl_2 and treated with excess of MCPBA for 5 min at room temperature afforded in 90% yield the nitrone **4**, the structure of which was determined as follows. Compared to **3**, the raw formula attributed from mass spectrum data ($C_{20}H_{22}N_2O_3$) corresponded to one oxygen more and two hydrogen atoms less. From the ^1H NMR spectrum it clearly appeared that the N–CH_3 and the C20, C21 double bond did not react with MCPBA and the structural characterization of the strychnobrasiline skeleton was easily achieved through the concerted analysis of COSY, NOESY and HMBC data (Fig. 1).

From the ^1H NMR spectrum, one main observation was the deshielding of the signals attributed to the aromatic protons suggesting, according to the raw formula, the substitution of the indolic NH by oxygen. The disappearance of the indolic proton and of the doublet corresponding to H-2 was in agreement with the loss of two hydrogen atoms compared to **3**. Lastly the presence of the N_a, C-2 double bond implied into the nitrone function was substantiated by the observation in the ^{13}C spectrum of a quaternary carbon peak at δ 150.2 ppm attributed to C-2.

There remains a lack of information regarding ^{13}C and ^{15}N NMR data of nitrones. So we compared the C-2 and N_a chemical shifts measured, respectively, for **4** and 1,2-didehydroaspidospermidine **5**.[3] As previously described by Yavari and Roberts,[4] the replacement of the lone pair of electrons on the nitrogen atom of the imino ring by a bond to another atom leads to an upfield shift of the ^{13}C and ^{15}N resonances. Data obtained for **4** and **5** showed that after N-oxidation the magnitude of ^{13}C-shielding for C-2 and C-13 are -42.2 and -9.9 ppm, respectively, and ^{15}N-shielding for N_a about -21 ppm (Table 1).

Oxidation of secondary amines as isoquinoline alkaloid with hydrogen peroxide at room temperature is described to give nitrone, only in the presence of sodium tungstate catalyst.[5] It is worthy of note that in the case of strychnobrasiline, probably due to the high reactivity of the indolinic nitrogen,[2] nitrone was easily obtained at room temperature without metal complex catalyst.

Keywords: alkaloid; Baeyer–Villiger reaction; indoline; nitrone; ^{15}N NMR.

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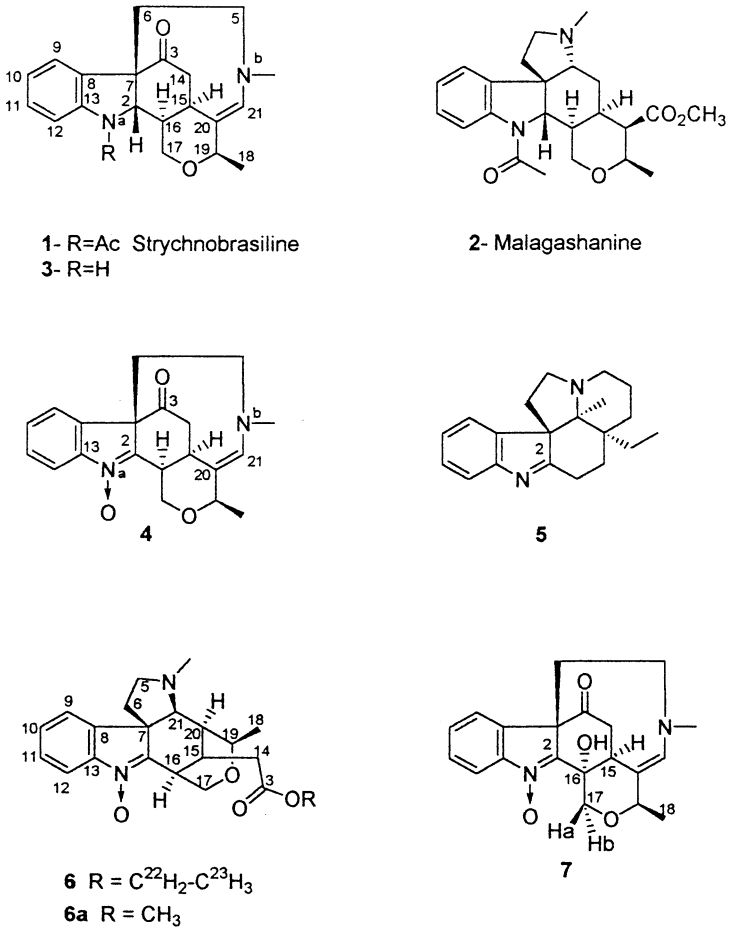

Figure 1. Structures of strychnobrasiline, malagashanine and new compounds.

2.2. Action of MCPBA at 40°C

To progress in the N_b reactivity knowledge, further experiments were performed at 40°C. Compound **3** was dissolved in chloroform and treated with MCPBA at reflux for 5 h. After washing with sodium hydrogenocarbonate, **6** was isolated as main product. On the basis of mass spectral data, the raw formula $C_{22}H_{28}N_2O_4$ was attributed. From NMR experiments, the main differences observed compared to the spectra of the starting material **3** were the disappearance of the proton H-21 at 5.50 ppm and of the C-3 carbonyl at 191.5 ppm, due, respectively, to the reduction of the C-20, C-21 double bond and to the rearrangement of the N_b, C-21 *seco*curane skeleton. In other way, the CH_3 doublet at 1.50 ppm (J=6.8 Hz) sustained the presence of the tetrahydropyranic ring and, surprisingly, the mass spectrum peak at m/z 339 ($M-OC_2H_5$) and the carbonyl at 171.3 ppm in ^{13}C spectrum the presence of an ester group. Last the chemical shifts measured in the ^{15}N and ^{13}C spectra for N_a and C-2 and C-13, respectively, compared to the values obtained for the nitrone **4** (Table 1), clearly showed the presence of the nitrone moiety. Structure elucidation of **6** and total signals assignment were achieved on the basis of 2D NMR experiments: H-19, H-20, H-21 sequence was defined from COSY and HMBC correlations were consistent with the five membered ring resulting from the C-3, C-7 bond scission and the C-21, C-7 bond formation (Fig. 2). Relative configurations were attributed on the basis of Noe's observed between H-19 and H-20; H-20 and H-21; H-20 and H-15; H-15 and H-16 (Fig. 3). Furthermore, Noe's between H-15

Table 1. Chemical shifts (δ ppm) reported from ^{15}N and ^{13}C NMR spectra

Compound	N_a	N_b	C-2	C-13
3	68.9	46.3	59.4	148.6
4	286.0	48.3	150.2	144.8
6	283.0	25.6	153.4	144.3
5	307.0	62.0	192.4	154.7
7			152.4	144.0

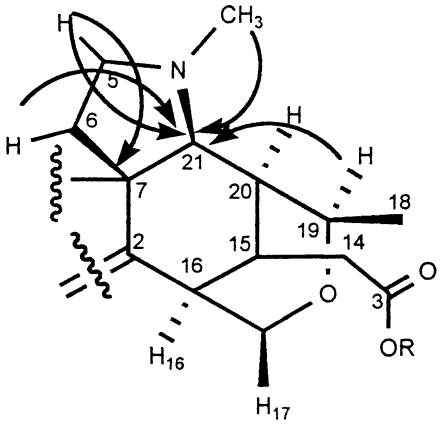

Figure 2. Substructure of **6** as revealed by selected HMBC correlations.

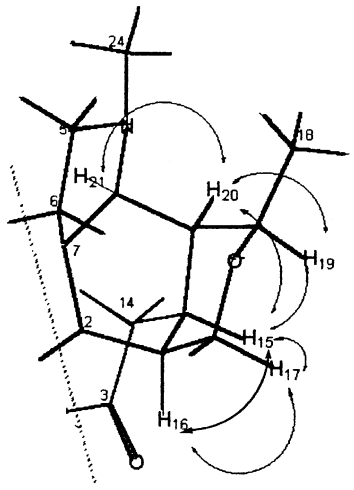

Figure 3. Substructure of **6** as revealed by significant NOE correlations.

and protons H-17 and H-19 defined the chair conformation of the tetrahydropyrane ring and the axial position of H-15 in C and D ring.

To explain the substitution of C-3 by ethoxy radical we made the hypothesis that it came from the medium, knowing that chloroform contains traces of ethanol. This hypothesis was confirmed when the reaction was performed in the presence of methanol yielding the methoxy analog, **6a**.

When **3** was treated with MCPBA in anhydrous chloroform or dichloromethane at reflux, only the hydroxy nitrone **7** could be isolated. The raw formula $C_{20}H_{22}N_2O_4$, attributed from the mass spectrum corresponded to two oxygens more than the starting material **3**. Furthermore the peaks observed in the mass spectrum at *m*/*z*=337 and 339, corresponding to M−18 and M−16, suggested the presence of an hydroxyl group. The ^{1}H spectrum was consistent with the strychnobrasiline skeleton: the CH_3-18 and N–CH_3 groups appeared respectively as doublet at δ 1.36 ppm and singlet at δ 2.26 ppm; the singlet at δ 5.53 ppm, attributed to H-21, defined the C-20, C-21 double bond. The main differences observed were the AB system attributed to the two H-17 protons at δ 4.37 ppm and 3.99 ppm and the disappearance of the H-16 multiplet. These data were consistent with the presence of a quaternary carbon at C-16 (δ 75.1 ppm) linked to an hydroxyl group, the proton of which appeared as a broad singlet at δ 6.90 ppm. This assignment was sustained by the correlations observed by HMBC between the OH proton and C-2, C-15 and C-16. The nitrone moiety was confirmed by the signals at δ 152.4 (C-2) and δ 144.2 (C-13) unambiguously attributed according to the previous ^{15}N and ^{13}C NMR data (see Table 1). Configuration OH-16α was attributed on the basis of Noe observed between OH and H-17a, H-17b and H-15.

To explain the formation of **6**, we made the hypothesis that the treatment of **3** with MCPBA gave the intermediate lactone **4a** (Fig. 4), after 'insertion' of oxygen according to a Baeyer–Villiger rearrangement mechanism. As described in the case of unsymmetrical cyclic ketones, the tertiary alkyl preferentially migrates to give the intermediate unstable lactone **4a** which might be in equilibrium with the corresponding opened form. This latter intermediate, trapped as an ester gives **6** after loss of the C-7 hydroxyl and C-21, C-7 bond formation. Consequently, in absence of alcohol, the postulated lactone intermediate cannot be isolated and the reaction only leads to the formation of the compound **7**.

3. Conclusion

We showed that the indolinic amino group of *seco*-curane type alkaloid, can be oxidized to nitrone upon treatment with 3-chloroperoxybenzoic acid at room temperature. To our knowledge, this reaction has never been described in indoline (dihydroindole) alkaloids. When the reaction was performed at 40°C, a new rearrangement of Nb, C3-*seco*-curane was observed: the main resulting derivative **6** having a nitrone functionality and Nb, C21-*seco*curane skeleton. We suggested a Baeyer–Villiger type mechanism to explain the formation of **6** which constitutes a new analog to malagashanine, an antimalarial alkaloid previously isolated from *Strychnos myrtoïdes*.[6] Estimation of the antimalarial activities of the new synthetized compounds will contribute to the structure–activity relationship determination of Strychnos alkaloids, and to progress in our program on their antimalarial properties.

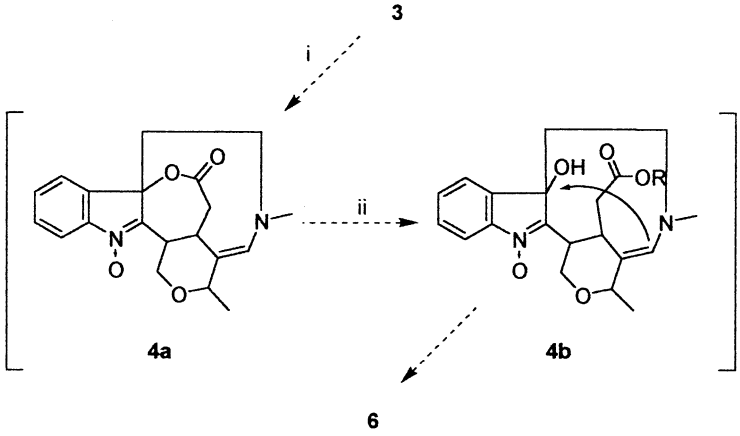

Figure 4. Hypothetical intermediates in the formation of **6** from strychnobrasiline; (i) MCPBA, $CHCl_3$; (ii) ROH.

4. Experimental

4.1. General

Commercial reagents were used as received. 3-Chloroperoxybenzoic acid (70%) was from Fluka and dichloromethane stabilized with amylene from Aldrich. Thin layer chromatography (TLC) were performed on plates of silica gel precoated with Kieselgel 60 F_{254}; column chromatography was carried out on 200–400 mesh silica gel 60 (Merck). ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 400.13 and 100.61 MHz, respectively, on a Bruker AMX-400 spectrometer at 300 K with a Bruker Gradient Unit (BGU) and an inverse gradient triple-resonance probe-head with a self-shielded gradient coil. The ^1H and ^{13}C chemical shifts are expressed in ppm relative to TMS, coupling constant (J) are given in Hz. ^{15}N chemical shifts are referenced to liquid NH_3. UV was recorded on a Kontron spectrometer and high-resolution mass spectra on a Jeol MS700 apparatus.

4.1.1. Compound 4. Deacetylated strychnobrasiline (100 mg, 0.3 mM), **3**, dissolved in 5 ml of chloroform were treated with 200 mg (2.6 equiv.) of MCPBA. After 5 min at room temperature the mixture was washed with $NaHCO_3$ 10% and the organic phase evaporated to dryness. Compound **4** (92 mg, 0.27 mM) was isolated as yellow oil and directly used for spectral determinations. MS calcd for $C_{20}H_{23}N_2O_3$ [M+1]: 339.165, found: 339.170; UV λ_{max} (log ε): 242 (3.96), 290 (3.84) nm; ^1H NMR $CDCl_3$: δ=7.73 (1H, d, J=7.0 Hz, H-9), 7.61 (1H, d, J=7.0 Hz, H-12), 7.40 (2H, m, H-10, H-11), 5.48 (1H, s, H-21), 4.36 (1H, dd, J=12.0, 2.2 Hz, H-17a), 4.16 (1H, dd, J=12.0, 5.5 Hz, H-17b), 4.10 (1H, q, J=6.3 Hz, H-19), 3.64 (1H, m, H-16), 3.06 (1H, m, H-15), 2.94 (2H, m, H-14a, H-5a), 2.70 (1H, dd, J=14.2, 3.9 Hz, H-6a), 2.37 (1H, dd, J=11.5, 3.7 Hz, H-5b), 2.25 (3H, s, N–CH_3), 2.04 (1H, dd, J=16.7, 4.3 Hz, H-14b), 1.90 (1H, dd, J=14.2, 3.2 Hz, H-6b), 1.36 (3H, d, J=6.3 Hz, CH_3-18); ^{13}C NMR $CDCl_3$: δ=193.7 (C-3), 150.2 (C-2), 144.8 (C-13), 140.2 (C-20), 139.1 (C-8), 130.7 (C-21), 129.2 (C-11), 128.0 (C-10), 124.0 (C-9), 114.1 (C-12), 75.9 (C-19), 65.9 (C-17), 58.9 (C-7), 50.2 (C-5), 43.0 (C-14), 42.6 (C-16), 41.3 (N–CH_3), 37.1 (C-15), 35.9 (C-6), 16.9 (C-18).

4.1.2. Compound 6. Compound **3** (100 mg, 0.3 mM) dissolved in 4 ml of chloroform or dichloromethane containing 5% of ethanol was treated with 200 mg (2.6 equiv.) of MCPBA at 40°C for 4.5 h. The mixture was then washed with 10% $NaHCO_3$ and the organic phase evaporated to dryness. The residue was chromatographed on silica gel. Elution with CH_2Cl_2/MeOH: 93/7 afforded 53 mg (0.14 mM) of **6** as a gum: $[\alpha]_D^{20}$=+14° ($CHCl_3$, c=0.5); UV λ_{max} (log ε): 241 (3.80), 292 (3.70) nm; MS(EI): M+=384 (53), 367 (8), 339 (4), 227 (13), 156 (20), 128 (15), 105 (32), 43 (100); HRCIMS calcd for $C_{22}H_{29}O_4N_2$: 385.2128, found: 385.2126; ^1H NMR $CDCl_3$: δ=7.76 (1H, br d, J=7.5 Hz, H-12), 7.44 (1H, ddd, J=7.5, 7.5, 1.0 Hz, H-11), 7.38 (1H, ddd, J=7.5, 7.5, 1.0 Hz, H-10), 7.33 (1H, br d, J=7.32 Hz, H-9), 4.17 (1H, br d, J=11.3 Hz, H-17a), 4.01 (2H, q, J=7.1 Hz, H-22), 3.95 (1H, dd, J=11.4, 2.3 Hz, H-17b), 3.77 (1H, br q, J=7.0 Hz, H-19), 3.70 (1H, m, H-16), 3.58 (1H, m, H-6a), 3.33 (1H, d, J=6.7 Hz, H-21), 3.31 (1H, m, H-5a), 3.10 (1H, m, H-5b), 2.61 (1H, m, H-15), 2.58 (3H, s, N–CH_3), 1.98 (1H, dd, J=16.0, 5.8 Hz, H-14a), 1.93 (1H, m, H-20), 1.53 (1H, dd, J=16.0, 9.7 Hz, H-14b), 1.50 (1H, d, J=6.8 Hz, CH_3-18), 1.37 (1H, m, H-6b), 1.13 (3H, t, J=7.1 Hz, CH_3-23); ^{13}C NMR $CDCl_3$: δ=171.3 (C-3), 153.4 (C-2), 144.3 (C-13), 144.0 (C-8), 128.6 (C-10), 128.1 (C-11), 121.7 (C-9), 115.3 (C-12), 79.5 (C-19), 70.0 (C-21), 69.4 (C-17), 60.6 (C-22), 57.0 (C-7), 53.9 (C-5), 45.1 (C-15), 40.6 (C-20), 40.1 (N–CH_3), 36.7 (C-16), 35.3 (C-14), 33.3 (C-6), 20.7 (C-18), 14.1 (C-23).

In the presence of MeOH and following the same experimental conditions, the reaction gave the methyl ester **6a**; HRCIMS: calcd for $C_{21}H_{27}O_4N_2$ (M+1): 371.1972, found: 371.1973; calc for m/z=$C_{21}H_{27}O_3N_2$[(M+1)−O]: 355.2023, found: 355.2017.

4.1.3. Compound 7. Compound **3** (100 mg, 0.3 equiv.) was dissolved in 4 ml of anhydrous $CHCl_3$ or stabilized dichloromethane and 200 mg (2.6 equiv.) of MCPBA added. The reaction was refluxed for 5 h, washed with $NaHCO_3$ 10% and the organic solvent removed. The residue was chromatographed on silica gel. Elution with CH_2Cl_2/MeOH: 97/3 afforded 22 mg (0.06 mM) of **7** as a gum; HRCIMS: calcd for $C_{20}H_{23}O_4N_2$ 355.1658, found 355.1659; UV λ_{max} (log ε): 242 (3.84), 292 (3.73) nm; ^1H NMR $CDCl_3$: δ=7.78 (1H, ddd, J=7.4, 1.7, 0.5 Hz, H-9), 7.63 (1H, ddd, J=7.7, 1.7, 0.5 Hz, H-12), 7.46 (2H, m, H-10, H-11), 6.90 (1H, s, OH), 5.53 (1H, s, H-21), 4.37 (1H, dd, J=12.2 Hz, H-17a), 4.28 (1H, q, J=6.2 Hz, H-19), 3.99 (1H, d, J=12.2 Hz, H-17b), 2.98 (1H, dd, J=15.7, 4.1 Hz, H-5a), 2.80 (1H, dd, J=7.3, 2.6 Hz, H-14a), 2.62 (2H, m, H6a, H14b), 2.38 (1H, dd, J=11.5, 4.3 Hz, H-5b), 2.26 (3H, s, N–CH_3), 1.96 (1H, ddd, J=14.6, 4.0 Hz, 1.2, H-6b), 1.36 (3H, d, J=6.3 Hz, CH_3-18); ^{13}C NMR $CDCl_3$: δ=193.0 (C-3), 152.4 (C-2), 144.0 (C-13), 139.2 (C-8), 138.1 (C-20), 132.1 (C-21), 130.0 (C-10), 128.3 (C-11), 124.3 (C-9), 114.2 (C-12), 75.5 (C-19), 75.1 (C-16), 71.9 (C-17), 58.8 (C-7), 49.8 (C-5), 43.9 (C-15), 41.2 (N–CH_3), 38.8 (C-14), 36.2 (C-6), 16.9 (C-18).

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