REACTIONS OF 16-NITROINDOLENINES OF THE VINCADIFFORMINE TYPE

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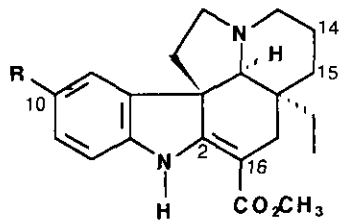
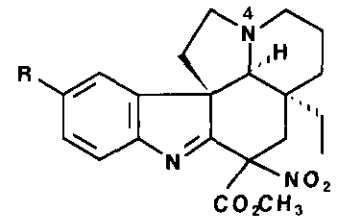
Abstract- The reactivity of 16-nitroindolenine **(4)**, a byproduct of the aromatic nitration of vincadifformine **(1)**, has been studied. In TFA **4** yielded 10-nitrovincadifformine **(3)** whereas acid hydrolytic treatment led to the tetracyclic oxindole structure **(8)** by cleavage of the 2-16 bond. Reduction of **4** ($SnCl_2$ or hydrogenolysis) allowed recovery of **1** in good yield.

In two previous papers, [1,2] we have described the synthesis of 16-nitroindolenines from vincadifformine **(1)** and its 10-bromo derivative **(2)**: thus in an organic acid medium [acetic acid-trifluoroacetic acid (TFA) (9:1), 4 h, room temperature], vincadifformine **(1)**, when treated with 1 eq. 52.5% HNO_3, yielded a mixture of 10-nitrovincadifformine **(3)** and 16-nitroindolenine **(4)** (7:3) whereas, when treated with 5 eq. 52.5% HNO_3, it was converted to the 10,16-dinitroindolenine **(6)**. Under the same conditions 10-bromovincadifformine **(2)**, when treated with 1 eq. 52.5% HNO_3, gave the 10-bromo-16-nitroindolenine **(5)**.



1 R = H ; **2** R = Br ; **3** R = NO_2
7 R = NO_2; 2,16-dihydro



4 R = H ; **5** R = Br ; **6** R = NO_2
11 N-4 oxide of **5**

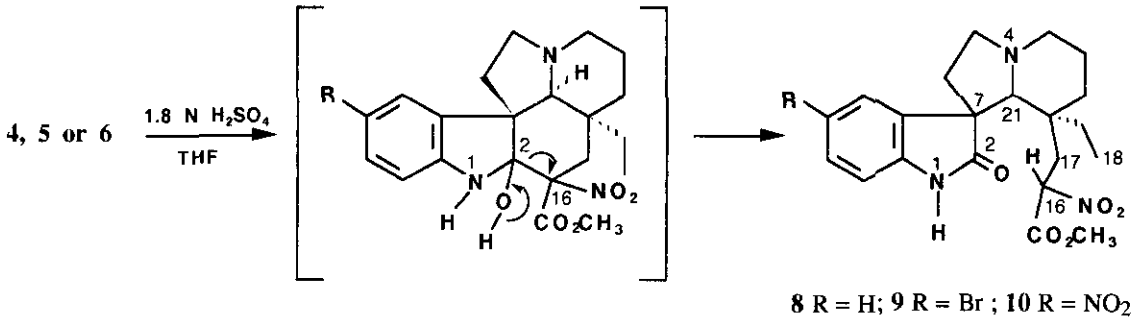
Recent pharmacological studies on 2,16-dihydro-10-nitrovincadifformine (**7**) and its analogues have demonstrated the antihypoxic properties of these compounds which could be useful for the prevention or the treatment of some brain injuries.[3] The first step in the synthesis of such compounds is nitration at C-10; therefore we decided to study in detail the chemical behaviour of the 16-nitroindolenines, byproducts of the reaction.

1) Migration 16→10 of the nitro group

16-Nitroindolenine (**4**) was quantitatively transformed into 10-nitrovincadifformine (**3**) when treated with TFA (1 h, room temperature), pure enough for further reactions directly and without chromatography.[4] Under the same conditions, the 10-substituted nitroindolenines (**5**) and (**6**) led to very complex unidentified mixtures.

2) Cleavage of the 2-16 bond

Substitution of TFA by a hydrolytic acid medium [THF-1.8 N H_2SO_4 (1:3), 15 h room temperature or 45 min reflux] entirely changed the course of the reaction: under these experimental conditions **4**, **5** and **6** generate the oxindoles (**8**), (**9**) and (**10**), respectively, in excellent yield (>85%) by cleavage of the 2-16 bond (Scheme 1).

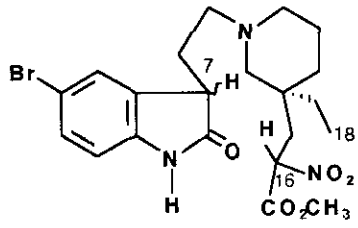


8 R = H; **9** R = Br ; **10** R = NO_2

Scheme 1

The structure of these oxindoles (homogeneous in tlc with several solvent systems) has been established by spectral analysis [CIms: peaks M+1 at m/z 402 (**8**), 480-482 (**9**) and 447 (**10**); ir ($CHCl_3$): bands at 3100 (NH), 1735 (CO_2CH_3) and 1705 (lactam) cm^{-1}; uv typical oxindole chromophore (λ max nm 216, 250, 281 (**8**); 219, 259, 293 (**9**)]. However an ^1H nmr study of compound (**9**) ($CDCl_3$, 500 MHz) revealed a mixture of four diastereoisomers with significant signals for N1-H (7.90, 8.20, 8.25, 8.32 ppm), CO_2CH_3 (3.68, 3.75, 3.79, 3.82), C18-H_3 (0.58, 0.60, 0.76, 0.80), C16-H and C17-H_2 (4.90 and 1.60, 2.80; 4.95 and 1.60, 2.70; 5.40 and 1.95, 2.30; 5.60 and 2.45) and C21-H (2.90). This composition was confirmed by analytical hplc and can be explained by the presence of the well-known four interconvertible stereoisomers on C-7 and C-21 resulting from the Grob's fragmentation previously described in this class.[5-8] In order to prevent this fragmentation, we tried quaternization of the N-4 as the methiodide or as the N-oxide. Whereas N-4 methylation was unsuccessful,[9] the

N4-oxide (**11**) could be obtained from **5**. However **11** was unreactive in hydrolytic acid medium (no reaction when refluxed for 2 h). According to modelization study on **5** and **11**, the nitro group, nearer the C-2 in **11** (cause of the N-oxide function), could hinder the hydration of the indolenine. Finally, the reaction of **9** with KBH_4 (MeOH, 15 h, room temperature) was resulted in cleavage of the 7-21 bond and gave as principal products a mixture of two isomers (**12**). [uv spectrum identical with **9**; Elms: peaks at m/z 481-483 (M^+), 257 (100%); ^1H nmr ($CDCl_3$): splitting of signals at δ (ppm) 0.60-0.75 (t, J = 7.5 Hz, 3H-18), 3.80-3.90 (s, 3H, CO_2CH_3), 8.10-8.30 (s, 1H, NH); other main characteristic signals at δ 3.60 (m, 1H-7) and 5.20 (m, 1H-16) ppm]. The preparation of two isomeric compounds (**12**) from the mixture (**9**) can be explained by the loss of asymmetry at C-21 and the equilibrium at C-7 during this sort of reduction as previously described by Lévy *et al.*[5]



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The cleavage of the 2-16 bond was closely dependent on the electron-withdrawing 16-nitro group. To date, such cleavage of the 2-16 bond with production of tetracyclic oxindoles from vincadifformine (or analogues with the same anilinoacrylate ester chromophore) has only been described by chemical or photochemical oxidation.[5,7]

3) Reduction of 16-nitroindolenine (**4**): recovery of vincadifformine (**1**)

With the two reductive tested methods (1st method: $SnCl_2$ in acetic acid or ethanol; 2nd method: H_2, PtO_2 in acetic acid), **4** reverted to vincadifformine (**1**) in good yield. Thus formation of 16-nitroindolenines of alkaloids with the *Aspidosperma* skeleton could be an interesting strategy for protecting the anilinoacrylate ester chromophore, which is easily recovered by reduction.

EXPERIMENTAL

Uv spectra were acquired on a Unicam SP 1800 and ir spectra on a Perkin-Elmer 457 spectrophotometer. Elms and CIms were determined with a Nermag R10-10C and HRms with a Varian MAT 311. Nmr spectra were obtained on a Bruker AMX-500 (500.13 MHz for ^1H).

Reaction of 4 with CF_3COOH:

Compound (**4**) (38 mg, 0.1 mmol) was dissolved in 5 ml of trifluoroacetic acid and the reaction was left at room

temperature for 1 h. The mixture was poured into iced water, neutralized with aqueous 2N NaOH and extracted with CH_2Cl_2. The organic layer was washed, dried over Na_2SO_4, filtered and evaporated. Purification by tlc on silica gel (CH_2Cl_2-MeOH, 99:1) provided **3** (27 mg, 80%).

Reaction of 5 with aqueous sulfuric acid:

Compound **(5)** (92 mg, 0.2 mmol) was dissolved in 5 ml of THF, then 15 ml of 1.8N H_2SO_4 were added and the solution was stirred for 45 min under nitrogen at 120°C. The reaction mixture was diluted with H_2O, and aqueous 1N NaOH was added until pH 5 was reached and the layer was extracted with CH_2Cl_2. After standard work-up, the residue was purified by tlc on silica gel (CH_2Cl_2-MeOH, 98:2) and provided **9** as amorphous compound (82 mg, 85%). Analysis of **9** by hplc (Lichrosorb^R SI 60, 5 µ; *n*-heptane-EtOH-$HClO_4$ 650:350:0.35; detection at 205 nm) exhibited four peaks in the ratio 38:17:15:30. Ms, uv, ir and ^1H nmr: see text; Anal. Calcd for $C_{21}H_{26}N_3O_5Br$: C 52.51, H 5.46, N 8.75. Found: C 52.75, H 5.27, N 8.83.

Oxidation of 5 by *m*-chloroperbenzoic acid:

Compound **(5)** (46 mg, 0.1 mmol) was dissolved in 10 ml of CH_2Cl_2, *m*-CPBA (41 mg, 0.12 mmol) was added and the solution was left at room temperature for 3 h. The mixture was washed with 5% $NaHCO_3$ aqueous solution and after standard work-up the residue was purified by tlc on silica gel (CH_2Cl_2-MeOH, 92.5:7.5) and yielded **11** (34 mg, 71%). Amorphous; EIms m/z (% rel. int.) 477-479 (M^+) (1), 124 (100); uv (EtOH) λ_{max} nm (log ε) 233 (4.24), 293 (4.01); ir (CH_2Cl_2) 1755, 1550 cm^{-1}.

Reduction of 9 by KBH_4:

Compound **(9)** (24 mg, 0.25 mmol) was dissolved in 5 ml of MeOH, then KBH_4 (20 mg, 0.37 mmol) was added and the solution was left at room temperature overnight. Standard work-up provided a dry residue (10 mg). Purification by tlc on silica gel (CH_2Cl_2-MeOH, 97:3) yielded **12** (7 mg, 30%). Ms, uv, ir and ^1H nmr: see text; HRms Calcd for $C_{21}H_{28}N_3O_5Br$: 481.1213. Found: 481.1229.

Reduction of 4 by $SnCl_2.2\ H_2O$:

To a solution of **4** (19 mg, 0.05 mmol) in 5 ml of AcOH-H_2O (3:1), a solution of $SnCl_2.2\ H_2O$ (45 mg, 0.2 mmol) in the same solvent (5 ml) was added, and the mixture was left at room temperature overnight. Standard work-up (extraction at pH 4) provided **1** (13 mg, 80%). When EtOH was used instead of AcOH-H_2O, **1** was recovered after heating 1 h with reflux.

Hydrogenolysis of 4:

A solution of **4** (38 mg, 0.1 mmol) in 5 ml of AcOH was hydrogenated under 1 atm pressure of hydrogen with PtO_2 catalysis (4 mg) at room temperature until the end of absorption. The catalyst was separated and the filtrate diluted with water, aqueous 2N NaOH was added until pH 6 was reached and the mixture was extracted with CH_2Cl_2. Dry residue (29 mg, 85%) was identified to **1**.

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