

REACTIONS OF 16-NITROINDOLENINES OF THE VINCADIIFORMINE TYPE

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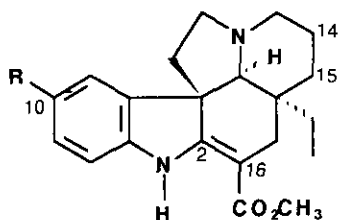
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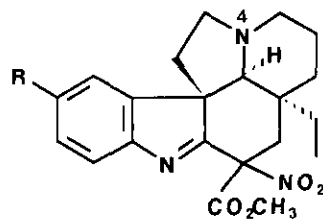
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Abstract- The reactivity of 16-nitroindolenine (**4**), a byproduct of the aromatic nitration of vincadifformine (**1**), has been studied. In TFA **4** yielded 10-nitrovincadifformine (**3**) whereas acid hydrolytic treatment led to the tetracyclic oxindole structure (**8**) by cleavage of the 2-16 bond. Reduction of **4** (SnCl₂ 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% HNO₃, yielded a mixture of 10-nitrovincadifformine (**3**) and 16-nitroindolenine (**4**) (7:3) whereas, when treated with 5 eq. 52.5% HNO₃, it was converted to the 10,16-dinitroindolenine (**6**). Under the same conditions 10-bromovincadifformine (**2**), when treated with 1 eq. 52.5% HNO₃, gave the 10-bromo-16-nitroindolenine (**5**).



1 R = H ; **2** R = Br ; **3** R = NO₂
7 R = NO₂; 2,16-dihydro



4 R = H ; **5** R = Br ; **6** R = NO₂
11 N-4 oxide of **5**

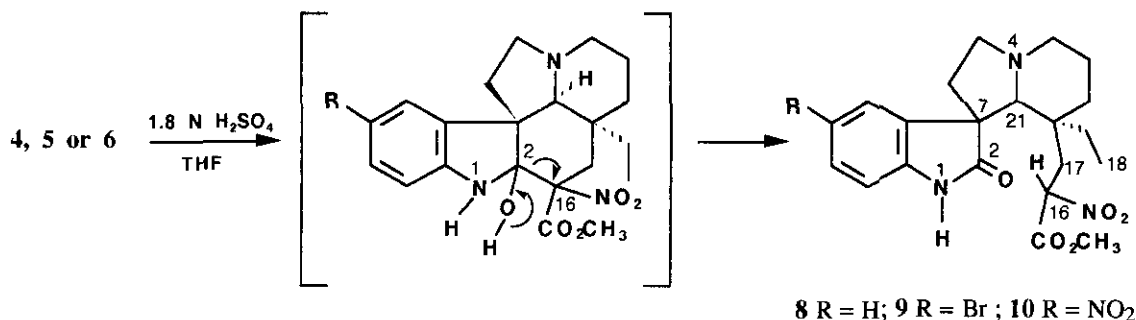
Recent pharmacological studies on 2,16-dihydro-10-nitrovincadifformine (**7**) and its analogues have demonstrated the antihypoxic properties of these compounds which could be useful for the prevention or the treatment of some brain injuries.³ The first step in the synthesis of such compounds is nitration 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

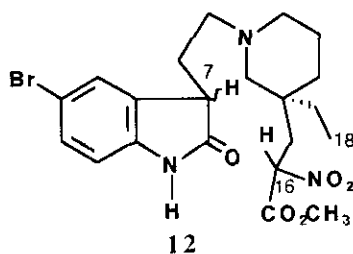
Substitution of TFA by a hydrolytic acid medium [THF-1.8 N H₂SO₄ (1:3), 15 h room temperature or 45 min reflux] entirely changed the course of the reaction: under these experimental conditions **4**, **5** and **6** generate the oxindoles (**8**), (**9**) and (**10**), respectively, in excellent yield (>85%) by cleavage of the 2-16 bond (Scheme 1).



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 (CHCl₃): bands at 3100 (NH), 1735 (CO₂CH₃) 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**) (CDCl₃, 500 MHz) revealed a mixture of four diastereoisomers with significant signals for N1-H (7.90, 8.20, 8.25, 8.32 ppm), CO₂CH₃ (3.68, 3.75, 3.79, 3.82), C18-H₃ (0.58, 0.60, 0.76, 0.80), C16-H and C17-H₂ (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; EIMS: 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



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. Eims 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 $\text{C}_{21}\text{H}_{26}\text{N}_3\text{O}_5\text{Br}$: 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 $\text{C}_{21}\text{H}_{28}\text{N}_3\text{O}_5\text{Br}$: 481.1213. Found: 481.1229.

Reduction of **4** by $\text{SnCl}_2 \cdot 2 \text{H}_2\text{O}$:

To a solution of **4** (19 mg, 0.05 mmol) in 5 ml of AcOH- H_2O (3:1), a solution of $\text{SnCl}_2 \cdot 2 \text{H}_2\text{O}$ (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 PtO₂ 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 CH₂Cl₂. Dry residue (29 mg, 85%) was identified to **1**.

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