OXIDATION OF THE 2,16 DOUBLE BOND OF VINCADIFFORMINE

Georgette Hugel, Jean-Yves Laronze, Jacqueline Laronze and Jean Lévy
Faculté de Pharmacie, E.R.A. au C.N.R.S. n° 319, 51, rue Cognacq-Jay
51096 REIMS CEDEX, FRANCE

Abstract - Chemical *vs* photochemical oxidation of the 2,16 double bond of vincadifformine 1 and 3-oxo vincadifformine 2 yielded *inter alia*, respectively the ketoöxindoles 7 and 8. Attempts of partial synthesis of vincatine 15 from these derivatives were unsuccessful. The structure of the LAH reduction product of vincatine is revised to 21. The stereochemical course of an earlier total synthesis of vincadifformine is examined.

In continuation of our studies of the vincadifformine 1a to vincamine 3a oxidative rearrangement [1], a similar transformation of both synthetic (±) 3-oxo vincadifformine 2b [2] and hemisynthetic (-) 3-oxo vincadifformine 2a [3] was attempted. In this paper, optically active substances are given suffix -a and the correspondic racemic substances are given suffix -b. When a reaction is said to have been performed on 3a,b this means that the reaction has been actually performed both on 3a and 3b. Treatment of 2a,b with 1,2 equivalents of MCPBA in benzene (r.t., 30 min.) actually yielded three derivatives : 3-oxo vincamine 5a,b (44%), and 3-oxo 16-epi vincamine 6a,b (11%), the structures of which were determined through examination of their spectral properties, and through reduction ($LiAlH_4$) of 5b and 6b to vincaminol 12b and 16-epi vincaminol 13b respectively.

The third product was the ketodilactam 7a,b (32%), $C_{21}H_{24}O_5N_2$, which displayed a typical oxindole UV spectrum. This last compound was obtained in high yield when 2a,b was oxidised with 2 equivalents MCPBA [4]. Under carefully controlled conditions (0°C, tlc monitoring) oxidation of 2a,b with one equivalent MCPBA again gave the ketodilactam 7a,b (15%) yet accompanied by still a fourth derivative, the hydroxyindolenine 14a,b. The following two experiments assert the intermediacy of 14a,b in the reactions leading from 2a,b to 7a,b on one hand, and 5a,b and 6a,b on the other : upon standing at room temperature, 14a,b was slowly transformed into the indoles 5a,b and 6a,b. Oxidation of 14a,b with an excess of MCPBA prompted its complete transformation to 7a,b.

The scope of these reactions may then be considered as follows : (Chart I)

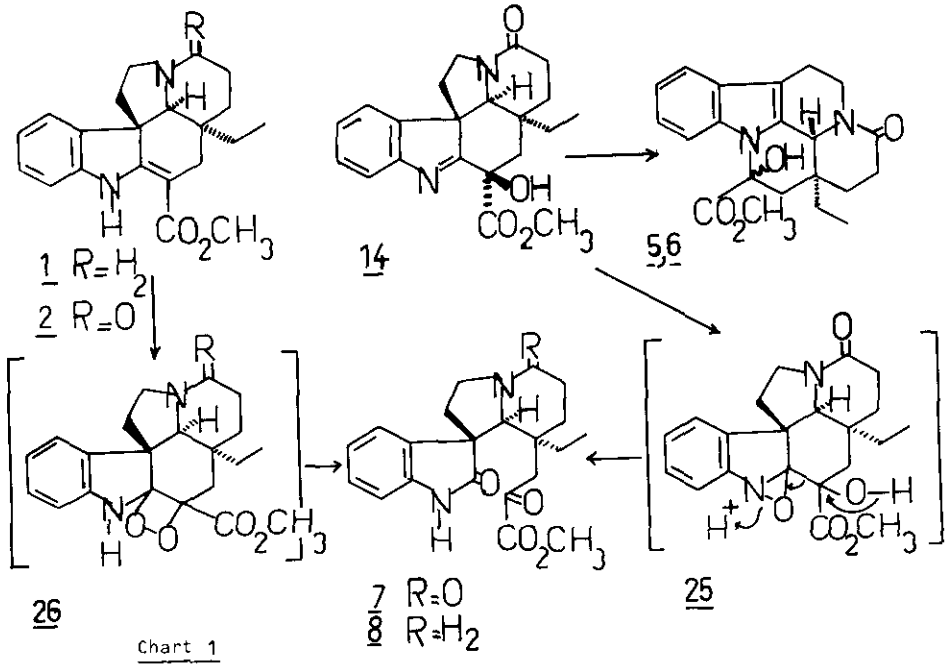


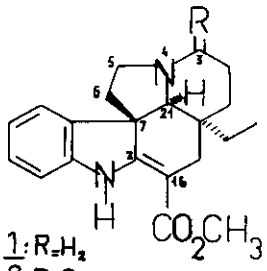
Chart 1

An intermediate hydroxyoxazirane 25 might account for the oxidative cleavage of 14 to 7.

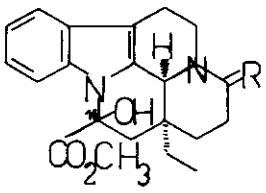
Similar results were obtained photochemically : irradiation of a methanolic solution of 2a in the presence of oxygen and methylene blue afforded 7a in very high yield, along with a small amount of recovered starting material. Such photooxidations of enamines through singlet oxygen via a dioxetane intermediate i.e. 26 are largely precedented [5]. When (-)vincadifformine 1a itself was irradiated under the same conditions, it suffered decomposition to a complex mixture of compounds, from which the ketooxindole 8a could be isolated in only trace amounts. However, (-) vincadifformine hydrochloride could be thus oxidised to 8a (40%), and to a mixture (10%) of vincamine 3a and 16-epi vincamine 4a. It is thought that a partial reduction of an intermediate 16-hydroperoxy indolenine to a 16-hydroxyindolenine accounts for the rearrangement leading to vincamine and its 16-epimer.

Oxidative cleavage - either chemical or photochemical - of the 2,16 double bond of the vincadifformine skeleton, prompted an attempt of partial synthesis of the oxindole alkaloid vincatine 15 [6], in order to determine its absolute configuration - or that of one of its stereoisomers.

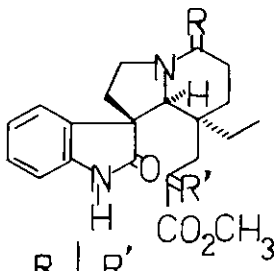
When 8a was treated with KBH_4, even under carefully controlled conditions, the *tetrahydro-derivative* 17a resulted : the keto group and the 4-21 immonium resulting from a CROB's fragmentation were simultaneously reduced. In the case of the non basic ketodilactams 7a,b, KBH_4 reduction afforded the alcohols 9a,b, which were further transformed to the 16-chloro derivatives 10a,b ($SOCl_2$,Py) and then reduced to 11a,b (Zn, AcOH). In order to get the vincatine structure, selective reduction of the



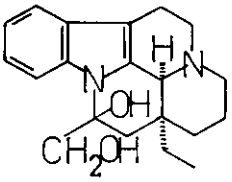
1: R=H_2
2: R=O



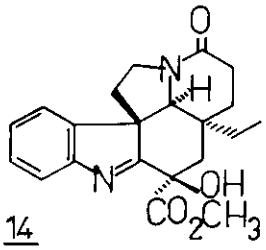
3 : R=H_2 ; 16β-OH
4 : R=H_2 ; 16α-OH
5 : R=O ; 16β-OH
6 : R=O ; 16α-OH



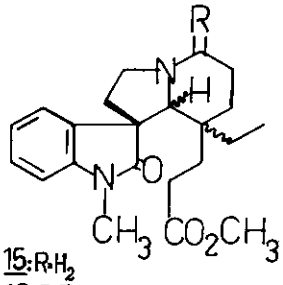
	R	R'
7	O	O
8	H_2	O
9	O	H, OH
10	O	H, Cl
11	O	H_2



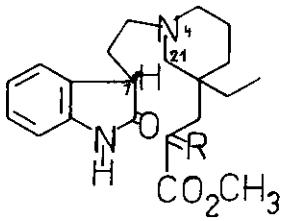
12 : 16β-OH
13 : 16α-OH



14

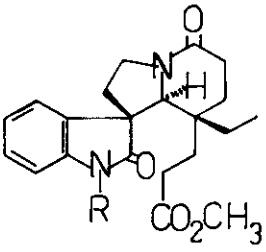


15: R=H_2
16: R=O

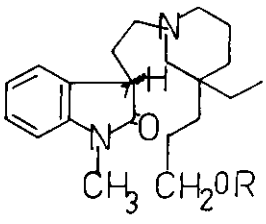


17: R=OH, H
17': R=H, OH

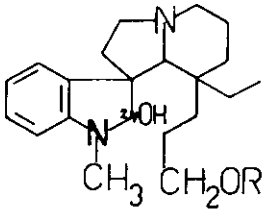
18 : R=H_2



19 : R=H
20 : R=CH_3



21 : R=H
22 : R=$COCH_3$



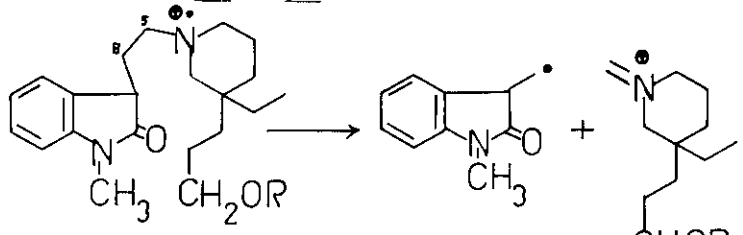
23 : R=H
24 : R=$COCH_3$

a : optically active
b : racemic

3-oxo group in 11a was now necessary. As diborane is known to react more readily with tertiary than with secondary amides, 11a was treated with this reagent in THF. This time again, reduction of the fragmentation immonium species ocurred, and a mixture of starting material and tricyclic oxindoles 18a resulted from the reaction.

These, and other results from these laboratories [7] prompted us to reinvestigate the structure of the $LiAlH_4$ reduction product of vincatine 15a [6], shown to be identical (except for rotation) with the $LiAlH_4$ reduction product of one stereoisomer of the dilactam 16b [8]. This work has been performed on the more easily available stereoisomer of the dilactam 16b : i.e. the dilactame 20b. This compound, obtained through alkylation of 19b (*vide infra*) (MeI,NaH) was nearly quantitatively reduced to a more polar product, the monoacetyl derivative of which was prepared. On the basis of their spectral properties, structures 21b and 22b are to be respectively ascribed to these last two products, in place of the isomeric structures 23b and 24b suggested by MEISEL and DÖPKE [6].

Actually both products exhibit oxindole UV spectra ; on its IR spectrum compound 22b shows two bands at 1700 and 1730 cm^{-1}. Their ^1H NMR spectra (splitting of signals) and their behaviour on tlc are strongly indicative of an equilibrium mixture of the two C(7) epimers. Moreover the base peak of their mass spectra, i.e. m/z 184 ($C_{11}H_{22}NO$, H.R.) for 21b and m/z 226 for 22b are best interpreted by the highly favoured cleavage of the 5-6 double bond, rather than by the complex process formerly designed to account for structures 23b and 23b.



21 : R=H

22 : R=COCH3

m/z 184

m/z 226

Finally, compound 23b would probably suffer in acidic medium a rearrangement to the corresponding β-carboline, which is actually not the case and still confirms the structure. This result discouraged us to attempt the same work on the optically active isomer 11a, of known configuration.

Our approach to the total synthesis of vincadifformine will now be recalled [2] : condensation of 2-hydroxytryptamine (Chart 2) with dimethyl 4-formyl 4-ethyl pimelate yielded 4 (?) stereoisomers, which could only be separated into two products A and B. Product B, the more polar, could be induced to cyclise to a stereoisomer 27b of 3-oxo vincadifformine, *via* the corresponding iminoether The stereoisomer 27b slowly epimerized to 3-oxo vincadifformine 2b in basic medium.

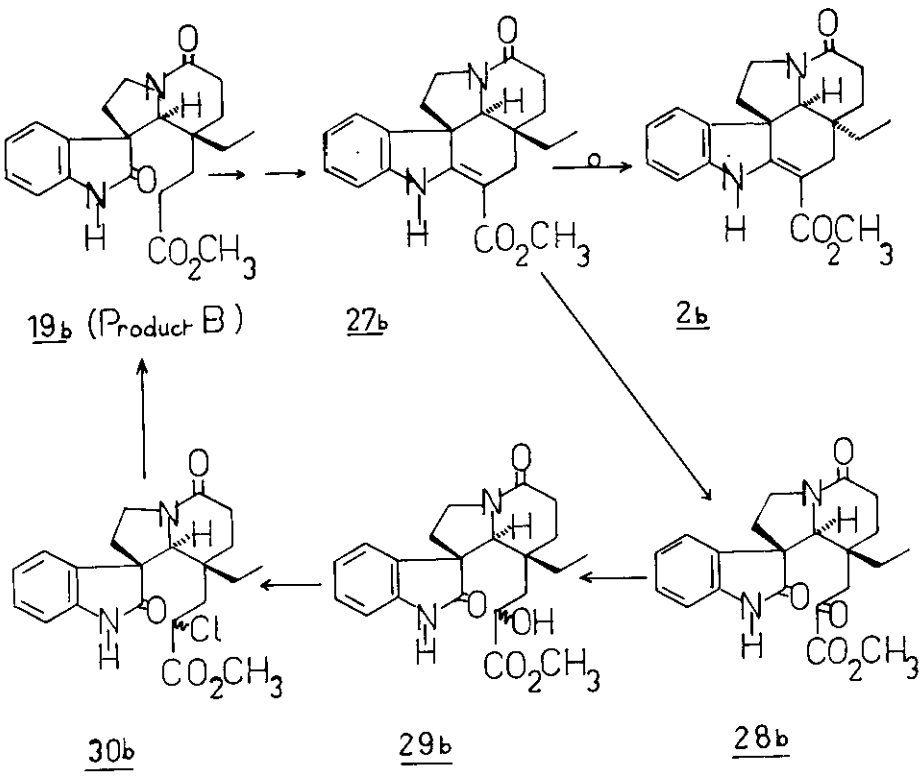


Chart 2

On the contrary, product A, the less polar did not suffer the 2,16 cyclisation under similar conditions.

Examination of the molecular models shows the depicted configuration to be the more probable for the stereoisomer 27b. Now, oxindole 11b, obtained through degradation of 3-oxo vincadifformine 2b was definitively different from the constituents of product A. It had the same Rf as product B, but its NMR spectrum was strikingly different. Then, oxindole 11b might only be a very minor constituent of product B.

Degradation of the stereoisomer 27b was performed along the same lines as that of 2b, i.e. 27b → 28b → 29b → 30b. Hydrogenolysis of the chlorine of 30b yielded a compound 19b whose Rf, IR and NMR spectra were identical to those of product B. This shows 19b to be the major - if not unique - component of product B.

Although the configuration of 27b remains hypothetical, these results allow a better understanding of the stereochemical course of the synthesis of 2b.

EXPERIMENTAL

NMR spectra were recorded in $CDCl_3$ with TMS as the internal standard on a Perkin-Elmer R12b. IR spectra were taken on a Beckman Acculab 4. Optical rotations were measured on a Perkin-Elmer modele 241 polarimeter. Mass spectra were obtained from a JEOL JMA-2000 m.p. were measured on a Reichert microscope and corrected and UV were measured on a Varian series 634.

MCPBA oxidation of 3-oxo vincadifformine 2a,b : 3-oxo vincamine 5a,b, 16-epi 3-oxo vincamine 6a,b and compound 7a,b

A soln of 2a,b (173 mg, 0.5 mmol) and MCPBA (103 mg, 0.6 mmol) in benzene (50 ml) was stirred at r.t. for 30 min. The soln was washed with 5 % aqueous bicarbonate and the benzene was evaporated. TLC showed the presence or three products 5a,b, 6a,b and 7a,b (increasing polarity) 5a,b (77 mg, 44%) m.p. 214° (5b) 220° (5a) (MeOH), $(\alpha)_D^{25}$ -88° (c=0.8, $CHCl_3$). UV : λ_{max}^{nm} (logε) 226(4.52), 274 (3.93), 282 (3.91)and 290 (3.75). IR (KBr) ν_{max} (cm^{-1}) 1740 and 1725. NMR : δ_H ppm : 4.95 (1H,q) ; 4.4 (1H,s) ; 3.9 (3H,s) ; 0.98 (3H,t). MS m/z : 368 (10%, $C_{21}H_{24}O_4N_2$= $M^{+\cdot}$), 350 (100%), 321 (80%), 279 (40%).

6a,b (19 mg, 11%) m.p. 210° (6b), 218° (6a) (MeOH). $(\alpha)_D^{25}$ -81° (c=0.3, $CHCl_3$). UV : λ_{max}^{nm} (logε) 224 (4.52), 274 (3.95), 281 (3.93) and 290 (3.75). IR (KBr) : ν_{max} (cm^{-1}) 1750 and 1620. NMR δ_H ppm : 4.9 (1H,m) ; 4.3 (1H,s) ; 3.65 (3H,s) ; 0.95 (3H,t) MS m/z : 368 (20%,$C_{21}H_{24}O_4N_2$= $M^{+\cdot}$), 350 (10%), 321 (20%), 279 (100%).

7a,b (60 mg, 32%) m.p. 228-230° (7a and 7b) (MeOH). $(\alpha)_D^{25}$ -111° (c=1, MeOH). UV : λ_{max}^{nm} (logε) 216 (4.49), 248 (3.94) and 280 (3.34). IR (KBr) ν_{max} (cm^{-1}) : 1720-1700 and 1625. NMR δ_H ppm : 9.8 (1H,m) ; 4.11 (1H,s) ; 3.68 (3H,s) ; 3.15 (2H,s) ; 0.53 (3H,t). MS m/z : 384 (100%, $C_{21}H_{24}O_5N_2$=$M^{+\cdot}$), 366 (10%), 337 (10%), 187 (50%), 159 (60%).

16-hydroxyindolenin 14a

A soln of 4a (173 mg) and MCPBA (104 mg) in benzene (50 ml) was stirred at 0° until appearance of 14a (TLC monitoring : more polar product, brownred coloured on ceric sulfate reagent exposure). After work up 14a (130 mg, 68%) and 70 (30 mg, 25%) were isolated by TLC.

14a m.p. 214-215° (CH_2Cl_2/ether). $(\alpha)_D^{25}$ -163° (c=0.7, MeOH). UV : λ_{max}^{nm} : 227 and 275. IR ($CHCl_3$) ν_{max} (cm^{-1}) 3280, 1725 and 1615. NMR δ_H ppm : 4.5 (1H,m) ; 3.95 (3H,s) ; 3.80 (1H,s) ; 0.70 (3H,t). MS m/z : 368 (10%, $C_{21}H_{24}O_4N_2$=$M^{+\cdot}$), 367 (80%), 309 (100%), 171 (10%), 170 (15%).

Oxidation of indolenin 14a : compound 7a

A soln of 14a (10 mg) and MCPBA (20 mg, excess) in benzene (5 ml) was stirred for 1 h. at r.t. After work up 7a (8 mg) was isolated.

Photooxidation of 3-oxovincadifformine 2a,b : compound 7a,b

A soln of 4 (48 mg) in methanol (15 ml) was irradiated during 1 h. in the presence of methylene

blue (with a conventional H.P. Hanovia equipment). After distillation and column chromatography (SiO_2) 39 mg (80%) of 7a,b were isolated together with 3 mg of starting material.

Photooxidation of vincadifformine 1a : compound 8a vincamine 3a and 16-epivincamine 4a

The hydrochloride prepared from 200 mg of vincadifformine 1a, was irradiated in methanol (20ml) during 4 h. as above. Methanol was evaporated *in vacuo* and the residue diluted with $NaHCO_3$aq and extracted with CH_2Cl_2. The organic layer was washed several times with $NaHSO_3$aq dried and evaporated. TLC of the residue gave four compounds of increasing polarity : starting material 1a (35 mg), the compound 8a (90 mg, 40%) and the known vincamines 3a (10 mg) and 4a (2 mg).

Compound 8a : $(\alpha)_D^{25}$ -167 (c=0.5, MeOH). UV λ_{max}^{nm} (log ε) 216 (4.15), 253 (3.94), 277sh. (3.32). IR ($CHCl_3$) ν_{max} (cm^{-1}) : 3300, 1710 and 1700. NMR δ_H ppm 8.73 (1H,m) ; 5.22 (1H,s) ; 3.8 (3H,s) 0.7 (3H,m). MS m/z : 370 (60%, $C_{21}H_{26}O_4N_2$=$M^{+\cdot}$), 283 (50%), 159 (15%), 124 (100%).

Preparation of compound 11a,b :

Alcohols 9a,b : A mixture of 7a,b (45 mg) and KBH_4 (7 mg) was stirred in MeOH (5 ml) at 0° during 1 h. After usual work up the residue was submitted to a preparative TLC and more polar compounds 9a,b (41 mg, 90%) were isolated (2 spots on TLC).

9a,b : UV λ_{max}^{nm} 216, 250 and 281. IR ($CHCl_3$) ν_{max} (cm^{-1}) : 1740, 1710, 1620. NMR δ_H ppm 9.9 (1H,m) ; 3.61 (3H,s) ; 2.84 and 2.92 (1H,s) ; 0.6 (3H,m). MS m/z:386 (70%, $C_{21}H_{26}O_5N_2$=$M^{+\cdot}$), 228 (75%), 187 (25%), 182 (100%), 159 (85%).

16-chlorocompounds 10a,b

A soln of 9a,b (65 mg) and 0,5 ml of $SOCl_2$ in pyridine (1 ml) was stirred for 3 h. at 75° under nitrogen. The mixture was diluted with H_2O, extracted with $CHCl_3$. The chloroformic layer was dried, evaporated to give, without further purification compounds 10a,b (63 mg, 92%) (same Rf than 9a,b) as a mixture of two products.

10a,b : UV λ_{max}^{nm} : 217, 252, 283. IR ($CHCl_3$) ν_{max} (cm^{-1}) : 3200, 1740, 1710 and 1620. NMR δ_H ppm : 8.9 (1H,m) ; 4.1 (2H,m) ; 3.65 and 3.62 (3H,s) ; 0.6 (3H,m). MS m/z : 406 (3%, $C_{21}H_{25}O_4N_2{}^{37}Cl$=$M^{+\cdot}$), 404 (10%, $C_{21}H_{25}O_4N_2{}^{35}Cl$), 310 (40%), 159 (70%), 109 (100%).

Compound 11a,b

A mixture of zinc dust (600 mg) and acetic acid (10 ml) was heated under reflux until evolution of hydrogen started. Then a soln of 10a,b (41 mg) in 6 ml of AcOH was added, and the reflux was continuted for 1 h. After cooling, the mixture was filtered, added with $NaHCO_3$aq and extracted with $CHCl_3$. Evaporation of the $CHCl_3$ gave, without purification 11a,b (36 mg, 95%).

Compound 11a,b : m.p.245-250° (MeOH), $(\alpha)_D^{25}$ -97° (c=0.3, MeOH). UV λ_{max}^{nm} 218, 253, 283. IR ($CHCl_3$) ν_{max} (cm^{-1}) 3180, 1735, 1710, 1620. NMR δ_H ppm : 8.77 (1H,s) ; 4.13 (2H,m) ; 3.60 (3H,s) ; 0.63 (3H,m). MS m/z : 370 (100%, $C_{21}H_{26}O_4N_2$=$M^{+\cdot}$), 187 (20%), 159 (60%).

Reduction of 8a : compound 17a and 17'a

The hydrochloride prepared from 35 mg of 8a in methanol (10 ml) and CH_2Cl_2 (5 ml) was treated with KBH_4 (30 mg) during 1 h à 20°. After work up a mixture of 2 isomers (25 mg) was separed by TLC.

17a (less polar) $[\alpha]_D^{25}$ -9° (c=1, MeOH). UV λ_{max}^{nm} (log ε) 216 (3.85), 250 (3.80), 282 (3.10). IR ($CHCl_3$) ν_{max} (cm^{-1}) : 3300, 1700, 1620. NMR δ_H ppm : 3.71 (3H,s) ; 0.80 (3H,t). MS m/z:374 (5%, $C_{21}H_{30}O_4N_2$=$M^{+\cdot}$), 315 (5%), 286 (20%), 272 (10%), 229 (50%), 228 (100%), 160 (50%), 159 (50%), 144 (30%), 140 (40%), 130 (45%).

17'a (more polar) : $[\alpha]_D^{25}$ -2° (c=1, MeOH). UV λ_{max}^{nm} (log ε) : 215 (3.97), 250 (3.78), 280 (3.08). IR ($CHCl_3$) ν_{max} (cm^{-1}) : 3280, 1710, 1620. NMR δ_H ppm : 3.70 (3H,s), 0.80 (3H,t). MS m/z : 374 ($C_{21}H_{30}O_4N_2$=$M^{+\cdot}$). Same fragmentation and ion abundance as 17a.

Reduction of 11b : compound 18b

A mixture of 11b (185 mg, 0.5 mmol) and 1M borane-THF complex (0.5ml) in anhydrous THF (2 ml) was kept 3 h. at 25°. After acidic work up 92 mg of the starting material 11b was recovered. Alkalinisation of the mother liquors and extraction with $CHCl_3$, yielded after purification, 18b (40 mg, 42% of transformed 11b).

Compound 18b : UV λ_{max}^{nm} 214, 250, 285. IR ($CHCl_3$) ν_{max} (cm^{-1}) : 3200, 1740, 1715 and 1700. NMR δ_H ppm : 8.07 (1H,m) ; 3.72 and 3.68 (3H,s) ; 0.85 (3H,m). MS m/z:358 (25%, $C_{21}H_{30}O_3N_2$=$M^{+\cdot}$), 225 (10%), 212 (100%), 160 (10%), 146 (15%).

Compound 16b

A mixture of 11b (92 mg) and a 55% NaH dispersion (45 mg) was stirred for 10 min in dry DMF (8 ml) at 0°. Excess of MeI (0.5 ml) was added and the mixture was stirred for 15 min at 0°, then 2 h at 45° and diluted with water (100 ml). After extraction with $CHCl_3$ and crystallization 85 mg (89%) of 16b were obtained.

16b :m.p.209° (MeOH). UV λ_{max}^{nm} 218, 258, 280. IR (KBr) ν_{max} (cm^{-1}) 1735, 1700, 1630. NMR δ_H ppm 3.53 (3H,s) ; 3.22 (3H,s) ; 0.72 (3H,m). MS m/z : 384 (100%, $C_{22}H_{28}O_4N_2$=$M^{+\cdot}$), 253 (10%), 297 (10%), 225 (10%), 196 (15%), 173 (30%), 160 (5%), 139 (5%).

Reduction of 16b : 21b

A mixture of 16b (30 mg) and $LiAlH_4$ (30 mg) in anhydrous THF (25 ml) was refluxed for 4 h. The usual work up gave after TLC 23 mg (85%) of 21b.

21b : UV λ_{max}^{nm} (neutral medium) : 220, 252, 291 ; ($HClO_4$) : 220, 253, 281. IR ν_{max} (cm^{-1}) : 3300, 1700. NMR δ_H ppm : 3.59 (3H,s) ; 0.70 (3H,m). MS m/z : 344 (15%, $C_{21}H_{32}O_2N_2$=$M^{+\cdot}$), 198 (39%), 184 (100%), 182 (31%), 173 (33%), 159 (30%).

Acetylation of 21b : 22b

A soln of 21b (35 mg) and Ac_2O (2 drops) in pyridin (1 ml) was kept 20 h at r.t. After extraction, a less polar product 22b (35 mg) was isolated.

22b : UV λ_{max}^{nm} 214, 252, 280. IR ν_{max} (cm^{-1}) : 1730 and 1700. NMR δ_H ppm : 3.19 (3H,s) ; 2.01 (3H,s) ; 0.70 (3H,m). MS m/z : 386 (24%, $C_{23}H_{34}O_3N_2$=$M^{+\cdot}$), 240 (35%), 226 (100%), 174 (15%), 160 (10%), 159 (5%), 147 (15%), 146 (15%).

MCPBA oxidation of compound 19b : oxindole 28b :

In the same way(*vide supra* 2a,b → 5a,b), the action of MCPBA (50 mg) upon 19b (85 mg) yielded 28b (41 mg : 46%).

28b : m.p. 246°(MeOH). UV λ_{max}^{nm} (log ε) : 215 (4.49), 255 (3.93) and 285 (3.24). IR (film) ν_{max} (cm^{-1}) : 1730, 1710 and 1625. NMR δ_H ppm : 9.35 (1H,s) ; 4.75 (1H,s) ; 3.68 (3H,s) ; 0.72 (3H,t). MS m/z : 384 (100%, $C_{21}H_{24}O_5N_2$=$M^{+\cdot}$), 367 (10%), 282 (10%), 267 (10%), 239 (10%), 210 (10%), 187 (30%), 159 (40%), 138 (40%), 130 (10%).

KBH_4 reduction of compound 28b : alcohols 29b

The action of KBH_4 (11 mg)(*vide supra* 7a,b → 9a,b) and 28b (105 mg) in MeOH (8 ml) gave 29b (93 mg, 88%), as a mixture of two stereoisomers.

29b (mixture) : UV λ_{max}^{nm} : 215, 252 and 280. IR (film) ν_{max} (cm^{-1}) : 3220, 1730-1700, and 1620. NMR δ_H ppm : 9.51 (1H,s) ; 4.78 (1H,s) ; 3.60 (3H,s) ; 3.07 (2H,s) ; 0.71(3H,t). MS m/z 386 (80%, $C_{21}H_{26}O_5N_2$=$M^{+\cdot}$), 368 (20%), 228 (50%), 182 (60%), 159 (100%).

16-chloro compounds 30b

A mixture of $SOCl_2$ (30 drops) and 29b (65 mg) in pyridine(2 ml) yielded (*vide supra* 9a,b → 10a,b) 30b (50 mg, 70%) as a mixture of 2 stereoisomers.

30b : UV λ_{max}^{nm} : 217, 252 and 281. IR (film) ν_{max} (cm^{-1}) : 1735, 1705 and 1620. NMR δ_H ppm : 9.45 (1H,s) ; 3.62 and 3.72 (3H,s) ; 0.78 (3H,t). MS m/z : 406 (2%, $C_{21}H_{25}O_4N_2{}^{37}Cl$=$M^{+\cdot}$), 404 (6%, $C_{21}H_{25}O_4N_2{}^{35}Cl$=$M^{+\cdot}$), 368 (25%), 310 (30%), 267 (100%) 159 (70%).

Oxindole 19b

A mixture of 30b (41 mg), zinc dust (600 mg) in 10 ml AcOH gave, after work up (*vide supra* 10a,b → 11a,b) compound 19b (39 mg, 95%)

19b : m.p.256° (MeOH). UV λ_{max}^{nm} : 218, 253 and 283. IR (film) ν_{max} (cm^{-1}) : 1730-1700 and 1620. NMR δ_H ppm : 9.1 (1H,s) ; 4.10 (1H,s) ; 3.53 (3H,s) ; 0.73 (3H,t). MS m/z : 370 (100%, $C_{21}H_{26}O_4N_2$=$M^{+\cdot}$), 339 (10%), 196 (15%), 159 (40%).

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