AROMATIC SUBSTITUTION EFFECTS IN THE ASPIDOSPERMANE-EBURNANE REARRANGEMENT OF INDOLE ALKALOIDS

Guy Lewin, Yves Rolland and Jacques Poisson [x]

Centre d'Etudes Pharmaceutiques, C.N.R.S., E.R.A. 317, 92290 Châtenay-Malabry France

Abstract - The influence of substitutions in aromatic part of indole alkaloids with aspidosperma skeleton on their rearrangement into products with eburnane-type structure is studied. Results are applied to vincamine derivatives.

The transformation of indole alkaloids of "Aspidosperma" type into derivatives with eburnane framework was predicted by Wenkert [1] according to a biosynthetic hypothesis, and performed in vitro by Le Men and coll. [2,3]

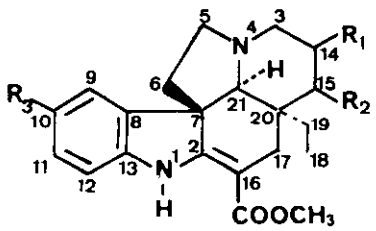
So, in a first time, (-)tabersonine (1a) is oxidized by a peroxyacid in benzene into hydroxy *indolenine-N-4-oxide* (2a) ; *in a second time* (2a) gives, in reducing and acidic medium (AcOH + Triphenylphosphine), a mixture of 14,15-dehydro vincamine (3a) and 16-epi-14,15-dehydro vincamine (4a)[3]. In the same conditions vincadifformine (1b) provides a mixture of vincamine (3b) and 16-epi-vincamine (4b) [(+)]. Identical transformation can be effected in a single step by protecting N-4 center from oxidation with useful mineral acids or organic carboxylic acids, even weak, in a polar solvent (alcohol, water or their mixtures)[4].

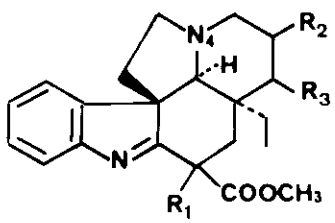
The preparation of derivatives of vincamine (3b) by hemisynthesis, let to study the action of some electrophilic reagents on products (1a) and (1b), and the influence of substitutions obtained on the aspidospermane-eburnane rearrangement.

I - Chlorinated derivatives [5]

Tabersonine (1a) with an admixture of 1 equivalent of hydrochloric acid in methanol and 1 mole of m-chloro-perbenzoic acid (m-CPBA) at room temperature provides a mixture of 16-epi-14,15-dehydro vincamine (4a) and 14,15-dehydro vincamine (3a) by oxidative rearrangement (reaction 1).

(+) Vincamine itself is used in medicine as a brain oxygenating drug, especially in Europe.





1a R_1 and R_2 olefinic bond; R_3 = H

1b R_1 = R_2 = H ; R_3 = H

1c R_1 = R_2 = H ; R_3 = Br

1d R_1 = R_2 = H ; R_3 = NO_2

1e R_1 = R_2 = H ; R_3 = NH_2

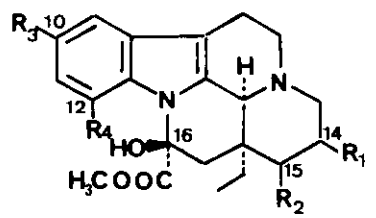
1f R_1 = R_2 = H ; R_3 = NHAc

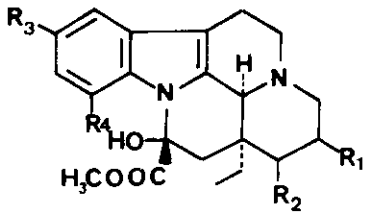
2a R_1 = OH ; R_2 and R_3 olefinic bond ; bond $N_4 \longrightarrow O$

2b R_1 = Br ; R_2 = R_3 = H

2c R_1 = Cl ; R_2 = R_3 = H

2d R_1 = Cl ; R_2 = R_3 = H ; bond $N_4 \longrightarrow O$





3a	R_1 and R_2 olefinic bond ; R_3 = R_4 = H	4a
3b	R_1 = R_2 = R_3 = R_4 = H	4b
3c	R_1 and R_2 olefinic bond ; R_3 = Cl R_4 = H	4c
3d	R_1 and R_2 olefinic bond ; R_3 = R_4 = Cl	4d
3e	R_1 = R_2 = H ; R_3 = Br R_4 = H	4e
3f	R_1 = R_2 = H ; R_3 = NHAc R_4 = H	4f

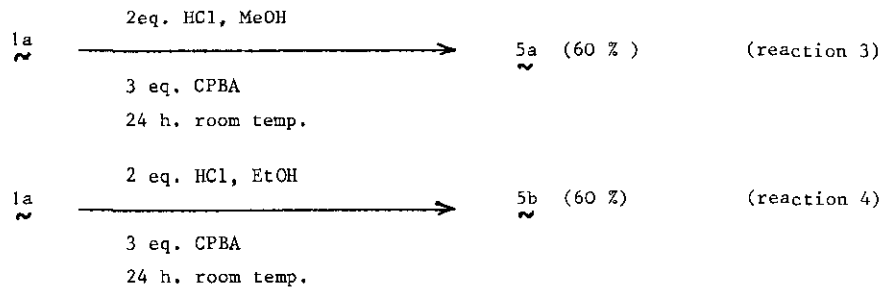
1a —(HCl 1 eq, MeOH ; m-CPBA 1 eq. ; 24h room temp.)→ 3a (30 %) + 4a (60 %) (reaction 1)

If oxidative reaction is carried out with 2 moles of m-CPBA, the main product isolated is 16-epi-14,15-dehydro-10-chloro vincamine (4c) [mp = 196-198° C ; $[\alpha]_D$ = + 91,5° ($CHCl_3$) ; UV $\lambda^{max.}_{EtOH}$ (log ε) 232 (4,41) ; 282 (3,76) ; 289 (3,75) ; 300 (3,58) ; MS m/e 386 ($M^{\cdot +}$)] with a little 14,15-dehydro-10-chloro vincamine (3c) [mp = 194° C ; $[\alpha]_D$ = + 160° (MeOH)] (reaction 2)

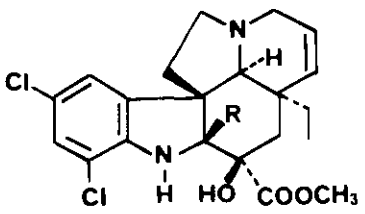
1a —(HCl 1 eq., MeOH ; m-CPBA 2 eq. ; 24 h. room temp.)→ 3a (25 %) + 4a (55 %) (reaction 2)

In this case, electrophilic substitution by Cl^+ generated in situ and oxidative rearrangement are simultaneous and formation of "16-epi" derivatives is predominant (+).

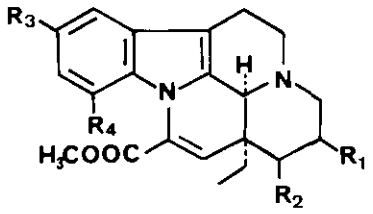
If reaction is performed with 2 equivalents of HCl and 3 moles of peroxyacid, the product is not an eburnane derivative but has the structure of dichloro compound with "Aspidosperma" skeleton. Compared with tabersonine (1a), this derivative incorporated 2 chlorine, 1 oxygen and 1 molecule of methanol. His structure (5a), proved by physical methods, was confirmed by X-ray cristallography [7] [mp = 204-206° C ; $[\alpha]_D$ = + 113°5 ($CHCl_3$) ; UV $\lambda^{max.}_{EtOH}$ (log ε) 254 (3,81), 317 (3,36) ; MS m/e 452 ($M^{\cdot+}$)] (reaction 3). Homolog (5b) afforded when reaction is carried out in ethanol [mp = 218-220° $[\alpha]_D$ = + 132°5 ($CHCl_3$) ; UV $\lambda^{max.}_{EtOH}$ (log ε) 254 (4,00), 317 (3,50) ; MS m/e 466 ($M^{\cdot+}$)] (reaction4)



Equivalent results are obtained on vincadifformine 1b but with very low yields.



5a R = OMe
5b R = OEt



9a R_1 and R_2 = olefinic bond ; $R_3 = R_4 = Cl$
9b $R_1 = R_2 = H$; $R_3 = NO_2$; $R_4 = H$

It is allowed to think that substitution of nucleophile on C-2 (MeO^- in 5a, EtO^- in 5b) is obtained after oxidation, with electronic assistance of two chlorine present on aromatic ring, at the expense of rearrangement into eburnane skeleton. However this rearrangement is possible by simple heating in trifluoracetic acid (TFA) : products 5a and 5b provide the 10,12-dichloro-14,15-dehydro apovincamine (9a) [mp = 194-197° C ; $[\alpha]_D$ = 131° ($CHCl_3$) ; UV $\lambda^{max.}_{EtOH}$ (log ε) 241 (4,48), 279 (4,11), 316 (3,85), 327 (3,97) ; MS m/e 402 ($M^{\cdot+}$)] . A similar result is observed by heating

(+) Sakai has mentionned the preparation of 16-chloro-1,2-dehydro-2,16-dehydro-tabersonine-N4-oxide by action of a peroxyacid on tabersonine hydrochloride [6].

in DMSO at 160°C with simultaneous occurence of 10,12-dichloro-14,15-dehydro vincamine (3d) and his 16-epimer (4d). By further heating of this mixture of isomers in TFA, 10,12-dichloro-14,15-dehydro apovincamine is recovered.

II - Brominated derivatives

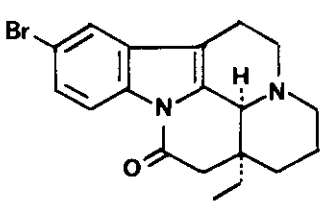
In the preparation of bromoderivatives, halogenation and rearrangement are distinct steps. By action of N-bromosuccinimide (NBS) in strong acids, vincadifformine (1b) is substituted on C-10 ; 1b dissolved in TFA and reacting with 1 equivalent of NBS at room temperature affords 10-bromo-vincadifformine (1c) in quantitative yield [$[\alpha]_D$ = - 580° ($CHCl_3$) ; UV $\lambda^{max.}_{MeOH}$ (log ε) 310 (4,24), 330 (4,22), MS m/e 418-416 ($M^{\cdot +}$)].

Under these conditions, the bromination on C-10 can be explained either by a direct electrophilic substitution, or by formation of an unstable 16-bromo-indolenine (2b) intermediate, by analogy with rearrangement of 3-bromo-indolenines into 5-or 6-bromo indoles[8] . The second mechanism is the most likely, for vincadifformine (1b) gives 16-chloro indolenine (2c), in the same conditions with N-chlorosuccinimide. With excess of NBS no dibrominated is produced. Similar results are obtained with tabersonine 1a.

10-bromovincadifformine (1c), with 1 mole of peroxyacid and 1 equivalent of $HClO_4$ in methanol, during one week at room temperature, affords a mixture of 10-bromo vincamine (3e) [mp = 205°C ; $[\alpha]_D$ = + 55° ($CHCl_3$) ; UV $\lambda^{max.}_{MeOH}$ (log ε) 233 (4,53), 285 (3,88), 290 (3,89), 300 (3,76). MS m/e 432, 434 ($M^{\cdot +}$)] and 16-epi-10-bromo vincamine (4e) [mp = 185-186°C, $[\alpha]_D$ = + 7° ($CHCl_3$)] (reaction 5).

$$1c \xrightarrow[\text{MeOH}]{\begin{array}{l}HClO_4\ ,\ 1\ eq.\\ \text{MeOH}\\ \text{m-CPBA, 1 eq.}\\ \text{room temp. 1 week}\end{array}} 3e\ (50\ \%) + 4e\ (25\ \%) \qquad \text{(reaction 5)}$$

By heating in benzene with t-BuOK, the product 3e is converted into 10-bromovincamone (6) : the position of bromine is inferred by the NMR ^1H signal of H-12 at δ 8,25 ppm (J_{HH} = 8 Hz), shielded by the proximity of carbonyl group.



6

III - Nitro- and amino- derivatives

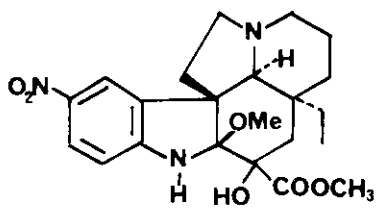
The nitration of vincadifformine (1b) was performed by HNO_3 in CF_3COOH : with 1 equivalent of HNO_3 during 2 hours, the reaction product is a mixture of 16-nitro-1,2-dehydro-2,16-dihydro vincadifformine (7a) [mp = 143-154°C , $[\alpha]_D$ = - 300° ($CHCl_3$) ; UV $\lambda^{max.}_{EtOH}$ (log ε) 283 (3,77) ; MS m/e 383 ($M^{\cdot+}$)] and 10-nitro vincadifformine (1d) [$[\alpha]_D$ = - 810° ($CHCl_3$) ; UV $\lambda^{max.}_{CH_3OH}$ (log ε) 263 (3,87), 289 (3,79), 390 (4,28) ; MS m/e 383 ($M^{\cdot+}$)] (reaction 6).

Traces of 12-nitrovincadifformine are also present (identification by MS and NMR ^1H).

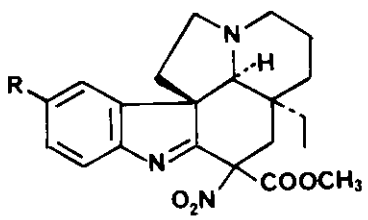
1b $\xrightarrow[CF_3COOH]{HNO_3 \text{ , 1 eq.}}$ 7a (15 %) + 1d (70 %) (reaction 6)

2 h, room temp.

With 2 equivalents of HNO_3 , the 10,16-dinitro-1,2-dehydro-2,16-dihydrovincadifformine (7b) is produced in quantitative yield. [mp = 165-167°C ; $[\alpha]_D$ = - 354° ($CHCl_3$) ; UV $\lambda^{max.}_{EtOH}$ (log ε) 300 (4,06) ; MS m/e 428 ($M^{\cdot+}$)] . Here, two reactions of aromatic nitration and oxidation on C-16 occurs simultaneously.



8



7a R = H

7b R = NO_2

10-nitrovincadifformine (1d), in conditions of oxidative rearrangement ($HClO_4$ 1 eq., m-CPBA 1 eq., MeOH, 24 h at room temperature) does not give eburnane derivative, but product 8 related to 5a [$[\alpha]_D$ = + 114° ($CHCl_3$) ; UV $\lambda^{max.}_{EtOH}$ (log ε) 230 (3,74), 245 (3,65), 258 (3,60), 372 (4,13), MS m/e 431 ($M^{\cdot+}$) ; NMR spectra near to these of 5a] . Like chlorinated derivatives 5, upon heating in TFA product 8 is converted into 10-nitro apovincamine (9b) (yield : 65 %) [mp = 167-168°C ; UV $\lambda^{max.}_{EtOH}$ (log ε) 262 (4,23), 292 (4,24), 330 (4,02), MS m/e 381 ($M^{\cdot+}$)].

On the other hand, 10-acetamido vincadifformine (1f), obtained by catalytic hydrogenation of 10-nitro vincadifformine (1d) and acetylation mainly gives by oxidative rearrangement (24 hours) 10-acetamido vincamine (3f) [$[\alpha]_D$ = + 29° ($CHCl_3$) ; UV $\lambda^{max.}_{EtOH}$ (log ε) 246 (4,10) ; MS m/e 411 ($M^{\cdot+}$)].

Discussion :

From comprehensive view of these results, it appears clearly that electronic lessening of indole nucleus of vincadifformine or tabersonine is unfair to the oxidative rearrangement into the vincamine derivatives. Thus :

- a bromine substituent on C-10 in vincadifformine (1b) slows down much the reaction (1 week instead of 24 h)
- dichlorotabersonine or nitro vincadifformine are not rearranged and give with alcohols addition products on hydroxy-indolenines, respectively 5a, 5b and 8.

The latter, heated in TFA, are transformed respectively into 10,12-dichloro-14,15-dehydro apovincamine (9a) and 10-nitroapovincamine (9b), by removing of substituent in C-2 and regeneration of an indoleninium ion immediately rearranged. More, it is shown that acidity of the medium can be important to the aspidospermane-eburnane rearrangement and must increase with electron-with-drawing substituents.

On the other hand, the coupling of aromatic substitution with rearrangement in this serie is interesting because of preparation facilities of 10-substituted vincamine derivatives. Inversely, direct electrophilic substitution on indole nucleus of vincamine guide the group on C-9 or C-11[9].

Aknowledgements :

We wish thank Omnium Chimique (Louvain-La-Neuve, Belgium), especially MM. J. Renard, J. Mannart and P. Sarlet, for collaboration and supply of raw material.

References :

1. E. Wenkert and B. Wickberg, J. Amer. Chem. Soc., 1965, 87, 1580.
2. G. Hugel, J. Levy and J. Le Men, C.R. Acad. Sc. (C), 1972, 274, 1350.
3. G. Hugel, B. Gourdier, J. Levy and J. LeMen, Tetrahedron, 1980, 36, 511.
4. Omnium Chimique, German Patent 2 652 165 (CA, 87, 102510e, 1977).
5. This transformation was described in sealed orders registered with No 01898 at Société Chimique de France (G. Lewin, Y. Rolland and J. Poisson, 1977 April 20th).
6. N. Aimi, Y. Asasa, S. Tsuge, T. Kohmoto, K. Mogi and S. Sakai, Heterocycles, 1976, 5, 267.
7. J. Lamotte, L. Dupont and O. Dideberg ; G. Lewin, Acta Cryst., 1980, B 36, 196.
8. T. Hino and M. Nakagawa, Heterocycles, 1977, 6, 1680.
9. Omnium Chimique, French Patent 2 320 302 (CA, 88, 23235m, 1978) ; Synthelabo, European Patent 1940 (CA, 92, 59073d, 1980) ; Sandoz, Swiss Patents 611 622 ; 611 623 (CA, 91, 108129s, 108130k, 1979).

Received, 21st July, 1980