ACID-CATALYSED RED-OX REARRANGEMENT OF A HEMIKETAL [1]

Jean Le Men[+], Monique Zèches and Françoise Sigaut
E.R.A./C.N.R.S. n°319 - Faculté de Pharmacie, 51 rue Cognacq-Jay
51096 REIMS CEDEX, FRANCE

Abstract - Hemiketals 5a,b generated from the indole alkaloids ajmalicine 1a and tetraphylline 1b, yielded the isomeric hemiketals 7a,b upon acidic treatment. Ajmalicine 1a was converted in low yield to dihydrocorynantheol 10a through 7a.

Saponification and decarboxylation of ajmalicine 1a (Table 1) is known to generate hemiketal 5a [2], a reaction later used [3] for introducing various functionalities on carbon atoms 17 and 19 in heteroyohimbine alkaloids. This project was undertaken in view of the partial synthesis of cinchophylline analogs [4,5,6].

Refluxing 1a [7] in 0.93M methanolic KOH yielded ajmalicine acid 2a (15%; mp 182°C ; $(\alpha)_D$+8°, pyridine) [8] and the methoxy derivative 3a (40% ; mp 225°C ; $(\alpha)_D$-36°, pyridine) resulting [9] from Michael addition prior to saponification. Schielding of the α-site by the 19-methyl group and eventual epimerization of the carboxyl group account for the configuration of C-16 and C-17 in 3a. Methyl *p*-tolyltriazene [10] esterified 2a back to 1a, and 3a to 4a, an acidic treatment of which regenerated 1a. *Similarly 3a yielded 2a upon CF_3CO_2H treatment.* These transformations show that the basic conditions did not affect the oxidation level of C-17 and C-19 in 2a and 3a.

When refluxed for 4 h in 2N HCl, 2a gave the known hemiketal 5a (15% ; mp 266-267°C ; $(\alpha)_D$-131°, pyridine) along with the unexpected isomer 7a (30% ; mp 236°C ; $(\alpha)_D$-86°, pyridine), which was obtained as the sole reaction product upon prolonged (12 hours) heating of 2a, 3a or 5a in the same reagent. Less surprising was the quantitative transformation of 5a to 7a in refluxing 0.93M methanolic KOH. Acetylation of 5a gave the 17-O-acetate 6a (90% ; mp 135°C ; $(\alpha)_D$-52°, $CHCl_3$), while acetylation of 7a gave the methylketone 8a (90% ; mp 85°C ; $(\alpha)_D$-19.5°, $CHCl_3$). The tetraphylline derivatives [6] 2b (mp 230-232°C ; $(\alpha)_D$-26°, H_2O), 5b (mp 212-214°C ; $(\alpha)_D$-142°, pyridine), 6b (mp 186-188°C ; $(\alpha)_D$-53°, $CHCl_3$), 7b (mp 140-142°C ; $(\alpha)_D$-135°, pyridine) and 8b (mp 90-92°C ; $(\alpha)_D$-26°, $CHCl_3$) were obtained under similar conditions : however saponification was performed in ethanolic KOH, and the unstable 3b could not be fully characterized.

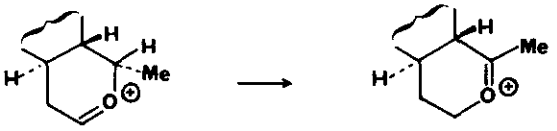
That no skeletal rearrangement had occurred during the transformation of 5b to 7b was further proved by their common KBH_4 reduction product, diol 11b : $(\alpha)_D$-6.5°, $CHCl_3$ (diacetate 12b : $(\alpha)_D$-18°,

$CHCl_3$). However reduction of 7b was not stereoselective, as the epimeric diol 13b (diacetate 14b) was simultaneously obtained : 12b / 14b : 68%/17%.

Both hemiketalic systems 5 and 7 allowed access to tetracyclic derivatives related to corynantheane : thus 5b (refluxed for 2 h with NH_2OH, CH_3COONa, MeOH, H_2O) was derived to oxime 15b (80% ; mp 134-136°C ; $(\alpha)_D$-53°, pyridine) and thence to nitrile 16b ($(CF_3CO)_2O$, $CHCl_3$, Δ40° for 2 h ; 89% ; $(\alpha)_D$-34.5°, $CHCl_3$), the 19-O-mesylate of which yielded the vinyl (9%) and ethylidene (9%) compounds 17b and 18b with DBU (DMSO, Δ75°C for 5 h).

Ketone 8a yielded (tosylhydrazine, EtOH, refluxed for 5 h ; 85%) tosylhydrazone 9a, which gave dihydrocorynantheol 10a (12% ; mp 183°C ; $(\alpha)_D$-19°, $CHCl_3$) upon $LiAlH_4$ reduction (THF, refluxed for 18 h).

The basic red-ox rearrangement of 5a,b to 7a,b is probably related to an internal crossed-Cannizzaro reaction similar to that proposed earlier [11] for the conversion of pretazettine to tazettine. In acidic medium, it is suggested that oxonium 19a,b evolves to 20a,b due to steric decompression of the 19-methyl group and to the related carbocation being more substitued. Although hydride shifts have been evoked in the acid-catalyzed epimerization of the 27-Me in ketalic steroidal sapogenins [12] a 4-center prototropic mechanism may also be suggested in the present case.



19a,b 20a,b

Table 1

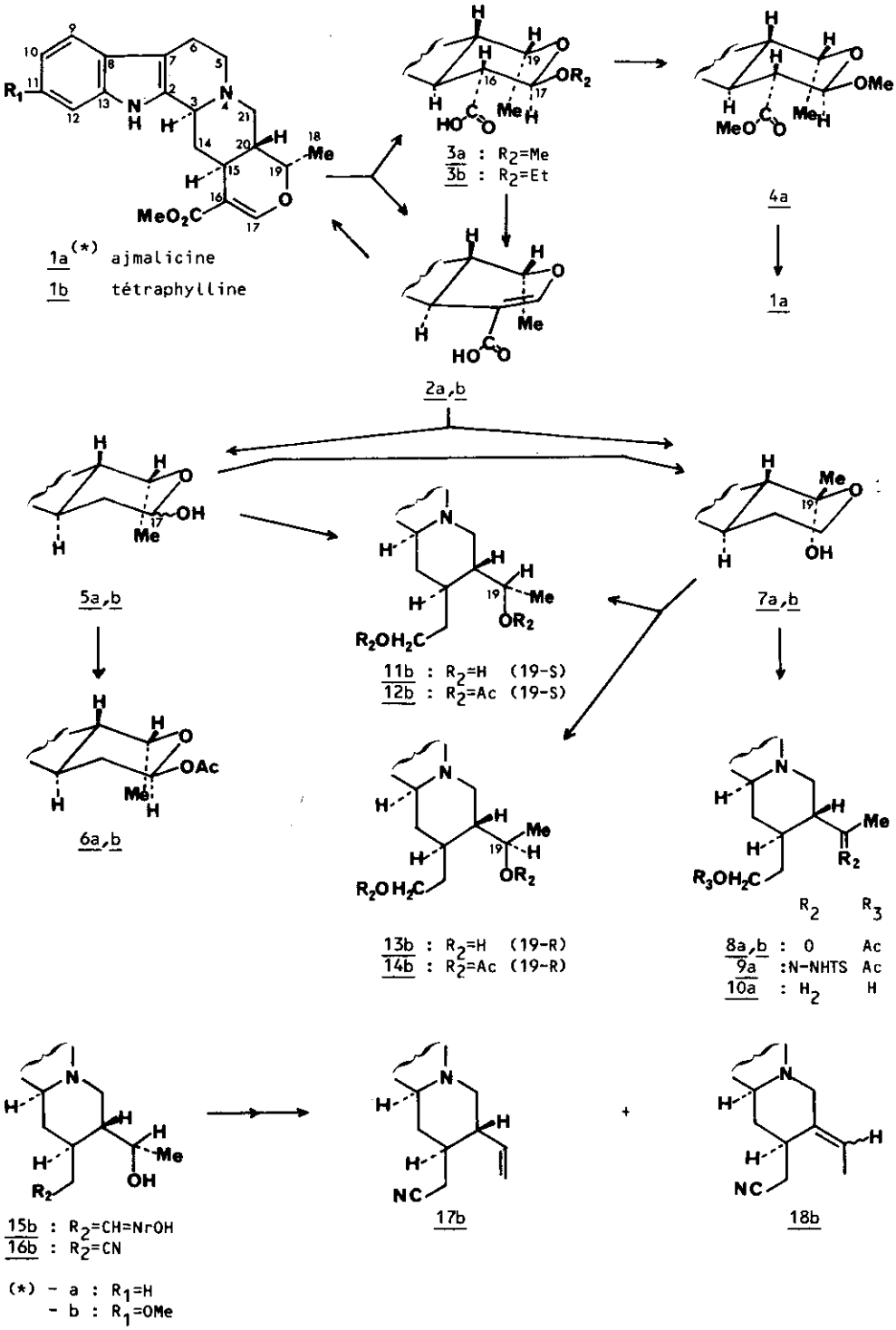

1a (*) ajmalicine
1b tétraphylline
3a : R2=Me
3b : R2=Et
4a
2a,b
5a,b
6a,b
7a,b
11b : R2=H (19-S)
12b : R2=Ac (19-S)
13b : R2=H (19-R)
14b : R2=Ac (19-R)
8a,b : O Ac
9a :N-NHTS Ac
10a : H2 H
15b : R2=CH=NrOH
16b : R2=CN
17b
18b
(*) - a : R1=H
- b : R1=OMe

Table 2 : 60MHz proton nmr shifts of new compounds

2a*	CH_3-18 : d(J=6) 1.12 ; H-19 : dq(J_1=2,J_2=6) 4.4 ; H-17 : s, 7.8 ; COOH : s, 11.6
2b**	CH_3-18 : d(J=6) 1.5 ; H-19 : m, 4.5 ; H-17 : s, 7.53 ; COOH : s, 11.5
3a*	CH_3-18 : d(J=6)1.3 ; H-19 dq(J_1=7,J_2=6)4.3 ; H-17 : d(J=8)5.2 ; COOH : s,12.25 ; OCH_3:s,3.5
5a***	CH_3-18 : d(J=6) 1.28 ; OH-17 : s, 1.66 ; H-19 : dq, 4.2
5b*	CH_3-18 : d(J=7) 1.2 ; H-19 : m, 4.3 ; H-17 : m, 5.4
6a	CH_3-18 : d(J=6) 1.2 ; CH_3CO :s, 2.05 ; H-19 : m, 4.20 ; H-17 : dd(J_1=8,J_2=3) 5.8
6b*	CH_3-18 : d(J=7) 1.2 ; CH_3CO- : s, 2 ; H-19 : m, 4.25 ; H-17 : d(J=8) 6.15
7a***	CH_3-18 : s, 1.42 ; OH-19 : s, 1.78
7b*	CH_3-18 : s, 1.65 ; OH-19 : s, 4.9
8a	CH_3-18 : s, 2.08 ; CH_3CO : s, 2.22 ; CH_2-17 : t, 4.15
8b*	CH_3-18 : s, 1.95 ; CH_3CO : s, 2.2 ; CH_2-17 : t, 4.05
10a***	CH_3-18 : t(J=6) 0.86 ; OH-17 : s, 1.73
12b***	CH_3-18 : d(J=7)1.27 ; CH_3CO-19 and -17 : s, 2.07 ; CH_2-17 : m, 4.18 ; H-19 : q, 5.3
14b***	CH_3-18 : d(J=7)1.2 ; CH_3CO -19 and -17 : s, 2.03 ; CH_2-17 : m, 4.16 ; H-19 : dq, 5.25
15b*	CH_3-18 : d(J=7)1.37 ; H-19 : q, 4.4 ; H-17 : s, 7.7 ; OH oximes : s, 13 and 12.4
16b***	CH_3-18 : d(J=7) 1.18
17b***	CH_2-18 and CH-19 : m (3H), 4.7 to 5.8
18b***	CH_3-18 : d(J=7) 1.75 ; H-19 : q(J=7) 5.21

Chemical shifts are recorded in ppm downfield from TMS.

The spectra were taken in * pyridine -d_5, ** DMSO -d_6 or *** $CDCl_3$.

Table 3 : ^{13}C Chemical Shifts*

Carbon	1a[13]	2a	3a	6b	7b	Carbon	1a	2a	3a	6b	7b
C(2)	134.0	137.4	136.0	135.0	135.5	C(15)	30.1	32.0	35.6	31.8	33.8
C(3)	59.8	60.9	60.3	60.5	60.6	C(16)	106.5	112.0	55.5	37.2	33.1
C(5)**	52.7	53.4	53.5	53.7	53.8	C(17)	154.5	150.8	98.7	89.6	60.0
C(6)	21.3	22.6	22.5	22.7	22.6	C(18)	14.5	15.0	14.5	14.2	27.7
C(7)	106.1	107.3	107.8	107.5	107.5	C(19)	73.3	73.2	71.4	72.6	95.8
C(8)	126.6	128.1	128.0	122.8	122.8	C(20)	40.2	42.1	42.4	43.4	49.8
C(9)	117.3	117.9	118.3	118.9	118.8	C(21)**	56.2	57.3	57.0	57.1	57.0
C(10)	118.4	118.8	119.2	108.9	108.7	$-OCH_3$(11)	-	-	-	55.6	55.5
C(11)	120.5	120.8	121.1	156	156.3	$-\overset{O}{\overset{\|}{C}}-OCH_3$	-	-	-	169.0	-
C(12)	110.6	112.1	111.5	95.8	95.8	$CH_3-\overset{O}{\overset{\|}{C}}-O$	-	-	-	21.1	-
C(13)	135.9	137.1	136.0	138.2	138.2	COOH	-	174.9	174.8	-	-
C(14)	32.1	34.3	35.3	37.4	37.3	$-OCH_3$(17)	-	-	55.9	-	-

* *Chemical shifts are recorded in ppm* downfield from TMS. The spectra of compounds 2a, 3a, 6b, 7b were taken in pyridine $-d_5$ solution.

** Assignements can be interchanged.

ACKNOWLEDGEMENTS- The authors gratefully acknowledge the help of Professor Jean Lévy in the preparation of this communication and thank Professor Mrs L.Le Men-Olivier for her constant interest and encouragements.

REFERENCES AND NOTES

1 . Part of this work was presented at International Symposium on Alkaloids, London, 18-20 april, 1979.

2 . (a) E.Wenkert and N.V.Bringi, J.Am.Chem.Soc., 1958, 80, 3484.

(b) E.Wenkert and N.V.Bringi, J.Am.Chem.Soc., 1959, 81, 1474.

3 . Siphar S.A., Brevet Suisse, 1975, n°8846/75.

4 . M.Zèches, F.Sigaut, L.Le Men-Olivier, J.Lévy and J.Le Men, Bull.Soc.Chim.France, 1981, 75.

5 . M.Zèches, B.Richard, P.Thépenier, L.Le Men-Olivier and J.Le Men, Phytochemistry, 1980, 19,2451.

6 . M.Zèches-Hanrot, Thèse Doctorat d'Etat ès Sc.Pharm., 1979, Reims.

7 . F.Sigaut-Titeux, Thèse Doctorat d'Etat ès Sc.Pharm., 1981, Reims.

8 . Satisfactory spectral data were obtained for all new compounds. Their molecular ions (SM) are correct except for 3a (highest peak at m/z 156) 3b (highest peak at m/z 324) and 6b (highest peak at m/z 324). Their ^{1}H and ^{13}C nmr spectra are reported on Tables 2 and 3.

9 . A similar behaviour of corynantheine was reported earlier :

(a) A.L.Djakoure, Thèse Doctorat ès Sc.Physiques, 1973, Paris.

(b) A.L.Djakoure, F.X.Jarreau and R.Goutarel, Tetrahedron, 1975, 31, 2247.

10 . E.H.White, A.A.Baum and D.E.Eitel, Org.Synth., 1968, 48, 102.

11 . W.C.Wildman and D.T.Bailey, J.Am.Chem.Soc., 1969, 91, 150 and references cited therein.

12 . R.B.Woodward, F.Sondheimer and Y.Mazur, J.Am.Chem.Soc., 1958, 20, 6693.

13 . E.Wenkert, C.J.Chang, H.P.S.Chawla, D.W.Cochran, E.W.Hagaman, J.C.King, K.Orito, J.Am.Chem.Soc., 1976, 98, 3645.

Received, 31st May, 1982