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THERMAL REARRANGEMENTS OF SOME INDOLE ALKALOID DERIVATIVES

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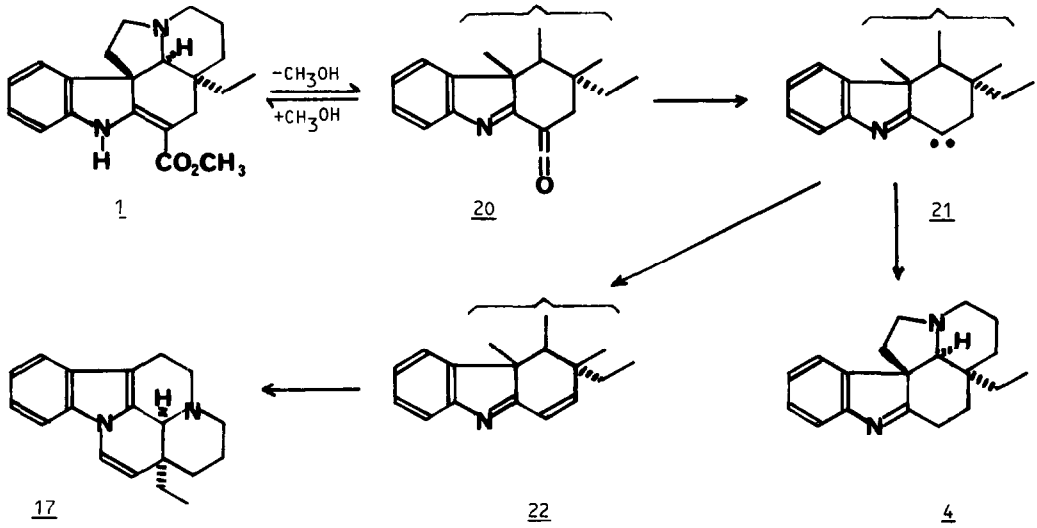
Abstract - Under both static and flow thermolysis conditions, several compounds with an "*aspidosperma*" framework rearranged to "*vinca*" derivatives. Thus (-)1,2-dehydroaspidospermidine (4) rearranged to (-)aspidospermidine and compound 17 on pyrolysis (200°C) while flow thermolysis (580°C) gave vincane (14). Compound 6 rearranged to vincamine (13a) and 16-epi vincamine (13b) under either condition ; increasing the temperature resulted in formation of apovincamine (19) (pyrolysis) or vincamone (16) (flow thermolysis).

Numerous indolc alkaloids easily suffer skeletal rearrangements, some of which occur in biosynthetic pathways. Whilst acid or base-catalysed rearrangements have been intensively investigated, less attention has been devoted to the thermal rearrangements of such compounds[1], although several synthetic indoles and pyrroles have been subjected to thermal treatment[2a,b]. In continuation of our studies of the "*aspidosperma*" to "*vinca*" rearrangement, we now report on the thermal behaviour of some vincadifformine (1) derivatives (Table 1), both under static and flow thermolysis conditions.

PYROLYSIS CONDITIONS (tables 1 and 2)

Compounds were pyrolyzed in an evacuated and sealed tube, without any solvent. Time and temperature conditions are indicated on table 2. Vincadifformine (1) itself (*exp.1*) was relatively stable (60% recovery), except for loss of



Scheme 1

the methoxycarbonyl group (→ 4) and partial racemization, presumably through the intermediacy of 7[3]. Only small amounts of rearranged "*vinca*" derivatives were formed : compound 17, previously obtained[4] through acidic treatment of 3, or of the isomeric ketone 10[5] and apovincamine (19).

Formation of 17 may take place *via* the well known mechanism of thermolysis of enamino esters (6) (scheme 1) : iminoketene 20 gives iminocarbene 21, a precursor of 22 which further rearranges to 17, and a possible precursor of 4.

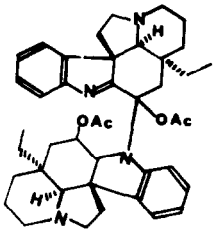
Apovincamine (19) could result from a dimerization process (see *exp.3*).

Acetoxy indolenine 2[4] (*exp.2*) rearranged to 8[4] upon migration of the acetyl group, and to the "*vinca*" derivative 17.

(-)1,2-dehydroaspidospermidine (4) yielded an equimolecular amount of aspidospermidine 9 and (-)eburnamenine (17) (*exp.3*). As 4 and 17 have been isolated from natural sources, these amazing results constitute the easiest *in vitro* "*aspidosperma*" to "*vinca*" rearrangements. It must be pointed out that 9 is one oxidation level below, and 17 one oxidation level above the starting material, i.e.(-)1,2-dehydroaspidospermidine (4). That 17 does not result from an intermolecular oxido-reductive process between 4 and a primitively formed vincane (14) (a compound with the same oxidation level as 4) is concluded from *exp.4*, where 14 was completely recovered after heating with 4.

The results of *experiment 3* suggest the formation on the glass surface of a dimeric intermediate[7] such a 23, which could generate 24 and 25 either through successive 1,5 sigmatropic shifts or through ionic mechanisms (scheme 2).

Species 25 would suffer thermolysis to 9 + 17. Significantly, no such rearrangement took place when 4 was submitted to flow thermolysis (*vide infra*) i.e. under conditions unfavorable for a dimerization process.



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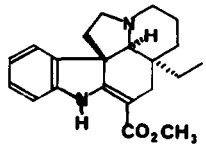
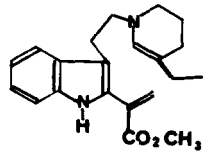
Pyrolysis of acetoxy indolenine 5[8] (*exp.5*) was difficult and caused decomposition and tar production to a large extent. It yielded derivatives 4, 8 and 18, which all had lost the CO_2Me group and formally derive from 2. The structure of 18 was deduced from its mass spectrum, and from its $LiAlH_4$ reduction to vincanol (15) and vincane (14). The simultaneous formation of 4 and 18 could involve an intermediate such as 26, the formation of which necessitates a reductive process on the glass surface (see *exp.2*).

TABLE 1



1 : (-)-vincadifformine



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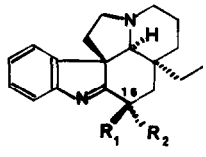
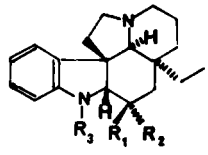
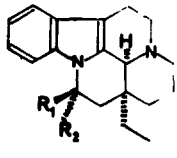


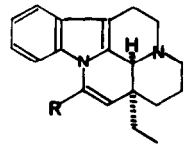


	R_1	R_2
2	$OCOCH_3$	H
3	OH	H
4	H	H
5	$OCOCH_3$	CO_2CH_3
6	OH	CO_2CH_3

	R_1	R_2	R_3
8	= O		$COCH_3$
9	H,H		H
10	= O		H
11	OH,CO_2CH_3		CH_3
12	= O		CH_3



	R_1	R_2
13a	OH	CO_2CH_3
13b	CO_2CH_3	OH
14	H	H
15	H	OH
16	= O	

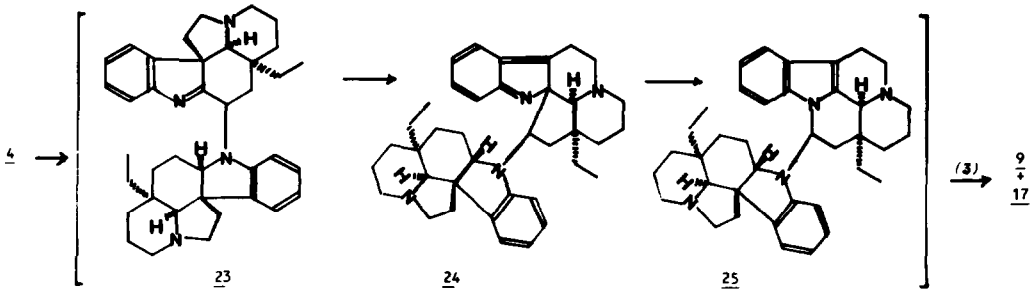


	R
17	H
18	$OCOCH_3$
19	CO_2CH_3

TABLE 2

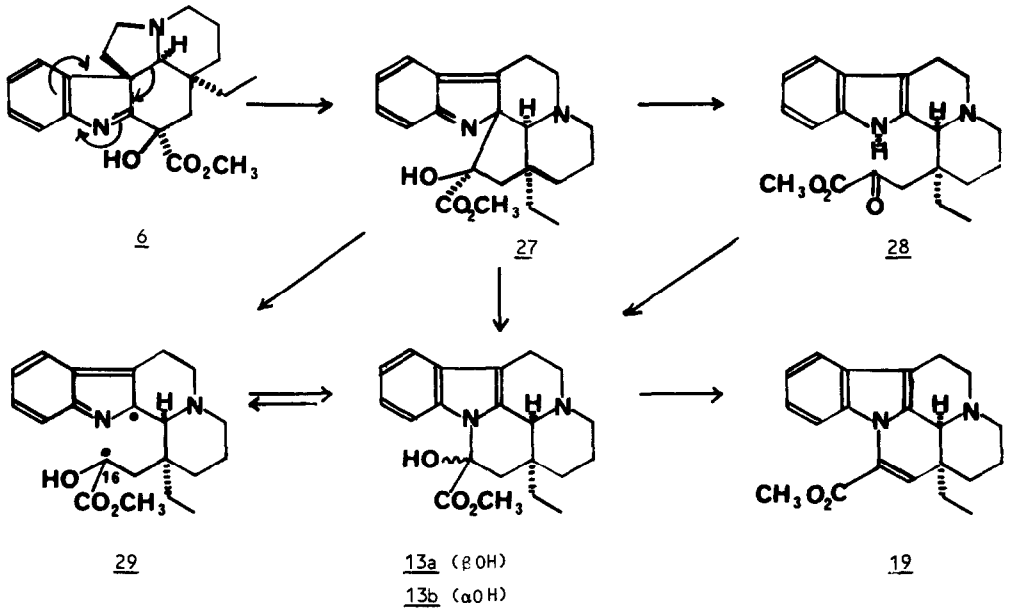
Pyrolysis (evacuated sealed tube)

Exp. nr.	Starting compound	Temperature (°C)	time (mn)	isolated derivatives (%)	
				Recovery	other products
1	1, $(\alpha)_D$ = -590° (MeOH)	210	150	1(60%) $(\alpha)_D$=-486°	4(15%) ; 17(4%) ; 19(1%)
2	2	200	60	2(35%)	8(40%) ; 17(14%)
3	4	200	30-120	4(60%)	9(15%) ; 17(15%)
4	4(85%) + 14(15%)	200	30	4(62%) 14(15%)	9 (4%) ; 17 (8%)
5	5	280	30	5(2%)	8(30%) ; 4(10%) ; 18(14%)
6a	6	150	15	-	13a(60%) ; 13b(35%)
6b	6	200	15	-	13a(45%) ; 13b(3%) ; 19(40%)
6c	6	250	15	6(2%)	13a(15%) ; 13b(3%) ; 19 (60%)
6d	6	280	15	-	19 (80%)
7a	13a	250	15	13a(96%)	13b (traces)
7b	13a	290	15	13a(86%)	13b(2%) ; 19(5%)
8a	13b	200	15	13b(4%)	13a(8%) ; 19(75%)
8b	13b	250	15	13b(1%)	13a(7%) ; 19(83%)



Scheme 2

With compound 6, the results of *exp. 6a* (150°) were comparable with those of the acid catalyzed rearrangement[8]. The thermodynamically more stable vincamine (13a) (60%) predominated over 16-epivincamine (13b)[9]. At higher temperatures (*exp. 6b-6d*) 13a and 13b gradually gave place to apovincamine (19). Dehydration is probably catalysed by the glass surface. However, in that range of temperatures, vincamine (13a) itself (*exp. 7a,b*) was remarkably stable and only sparingly gave apovincamine (19), while 16-epivincamine (13b) (16-OH axial) (*exp. 8a,b*) was prone to dehydration. Accordingly, the high yield of apovincamine (19) isolated in *exp. 6d* cannot result from the dehydration of vincamine (13a). It might reflect (scheme 3) the increased formation of 16-epivincamine (13b) at higher temperatures, eventually through the radical mechanism depicted on the scheme. Formation of biradical 29 might be favored by the captodative effect of the substituents on C-16.

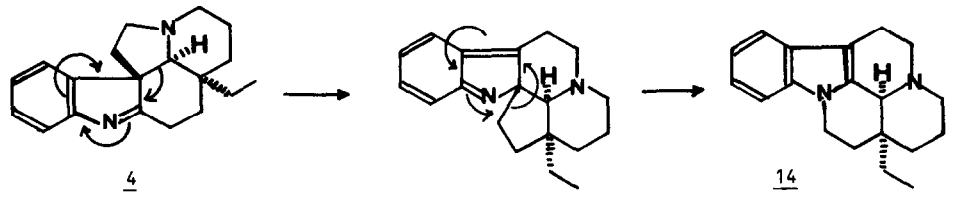


Scheme 3

FLOW THERMOLYSIS CONDITIONS (Table 3)

Flow thermolysis was performed in the apparatus described by CHUCHE et al[10].

In striking contrast with the pyrolysis *experiment 3*, under flow thermolysis conditions, (-)1,2-dehydroaspidospermidine (4) (*exp. 9*) yielded vincane (14), a compound with the same oxidation level as the starting material. A rather high temperature (580°C) had to be reached in order to bring about the transformation. The reaction is now intramolecular, and two successive 1,5 sigmatropic shifts may account for the rearrangement (scheme 4).



Scheme 4

The stability of vincamine (13a) was tested in *experiments 10a-c*. Some dehydration to apovincamine (19) occured, but the main derivative was vincamone (16), (yield increasing with temperature) along with some 16-epi vincamine (13b). Similarly 16-epi vincamine (13b) (*exp.11a,b*) yielded vincamone (16). As the thermal cleavage of such hydroxy esters seemed not to have been previously observed, two more model compounds were submitted to flow thermolysis. Compound 11[11] (*exp.12*) with the same functionality on C-16 also gave rise to a carbonyl derivative in good yield, i.e. ketone 12[4].

At 450°C, (+)methylmandelate cleanly yielded benzaldehyde[12] (47%).

In each case, the reaction results in the formal loss of methylformate. However, the ^1H NMR spectrum of the reaction mixture from methylmandelate showed the signal for methanol (2.85 ppm), and not for methylformate.

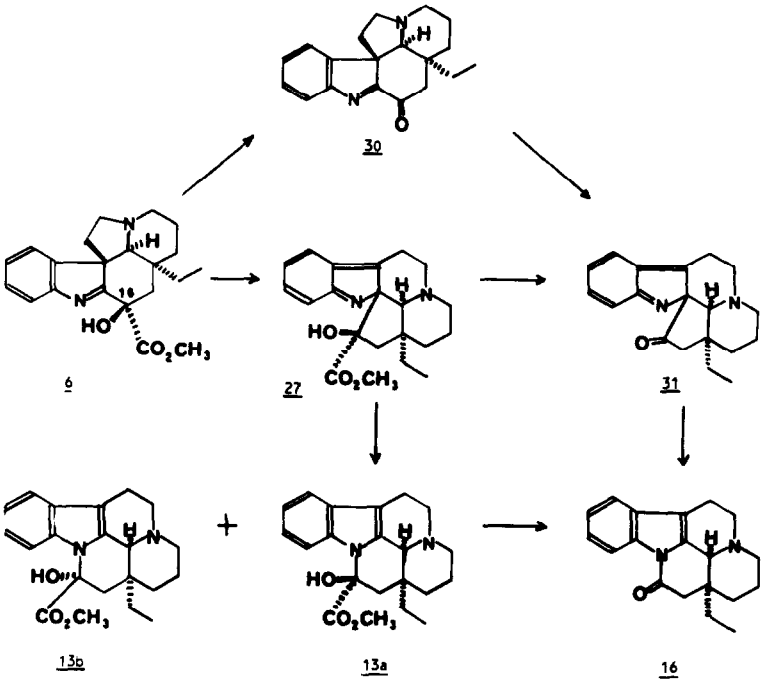
Flow thermolysis of methylformate itself (450°) actually gave rise to methanol (23%, NMR). Hence, evolution of methanol from the gem-hydroxy, methoxycarbonyl compounds studied may originate from a direct fragmentation, or from a secondary decomposition of initially formed methylformate. The results fully parallel earlier reports on the thermal treatment of α-hydroxy acids, which were shown either to dehydrate or to decompose to a carbonyl compound + CO + H_2O[13].

In *experiments 13a-d*, compound 6 was submitted to flow thermolysis in the 300-450° range of temperature. Vincamine (13a), 16-epivincamine (13b) and vincamone (16) resulted, and the yield of vincamone (16) increased with temperature. Despite the results of *exp.10a-b*, which suggest that 16 arises from 13a,b, intermediates 30 and 31 may also account for this rearrangement (scheme 5).

TABLE 3

Flow thermolysis

Exp. nr.	Starting compound	Température (°C)	isolated derivatives (%)	
			Recovery	other products
9	4	580°	4 (66%)	14(6%)
10a	13a	350°	13a (43%)	16(24%) 13b(2%) 19(2%)
10b	13a	400°	13a (20%)	16(40%) 13b(7%) 19(traces)
10c	13a	450°	13a (10%)	16(60%) 13b(2%) 19(traces)
11a	13b	350°	13b (35%)	16(40%) 13a(8%) 19(5%)
11b	13b	400°	13b (29%)	16(47%) 13a(9%) 19(10%)
12	11	400°	11 (7%)	12 (70%)
13a	6	300°	6 (traces)	16(9%) 13a(53%) 13b(18%)
13b	6	350°		16(26%) 13a(45%) 13b(8%)
13c	6	400°		16(40%) 13a(20%) 13b(7%)
13d	6	450°		16(70%) 13a(5%)



Scheme 5

CONCLUSION

This set of experiments shows that the "*aspidosperma*" (viz 2-6 ; 8-12) to "*vinca*" (viz 13-19) rearrangement is a thermodynamically highly favored process.

Under pyrolysis conditions on a glass surface, some ionic mechanisms are probably involved ; the course of the reactions is complicated by dehydration processes, and by the probable intervention of dimeric species.

Under flow thermolysis conditions, the rearrangement is best interpreted in terms of two 1,5 sigmatropic shifts, and by the cleavage of a gem-hydroxy, methoxycarbonyl function to a carbonyl group.

ACKNOWLEDGEMENT : We gratefully acknowledge the help of Prof.J.CHUCHE (University of Reims) and his collaborators for helpful discussions and disposition of their flow thermolysis equipment.

EXPERIMENTAL SECTION :

Melting points were taken on a Reichert Microscopeand are uncorrected. Specific rotations were measured on an electronic polarimeter Perkin-Elmer Model 241. I.R. spectra were measured on a Beckmann Acculab 4 spectrophotometer, U.V. spectra were measured on a Varian 634 spectrophotometer.

NMR spectra were measured on a Perkin-Elmer R12B spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were taken with a AEI, MS50 spectrometer. Separations were performed on t.l.c. with Kieselgel 60 PF_{254} Merck, using MeOH : CH_2Cl_2 mixtures as eluents.

1) Pyrolysis : general conditions (14)

Samples (50-300 mg) were introduced in a Pyrex glass tube, which was evacuated (0.01 torr.) and sealed. The tube was heated under the conditions specified in experiments 1-8. After cooling, the tube was opened, the compounds were dissolved in chloroform or methylene chloride and separated by t.l.c. Their respective yields are listed on Table 2. The compounds were identified by comparaison of their Rf, I.R., U.V., N.M.R. and mass spectra with those of known compounds. New compounds are described here under.

Experiment 5 : compound 5 → 5 + 8 + 4 + 18

Thermolysis of compound 5 (100 mg) at 280° during 30 mn gave compound 5 (2 mg, 2%), (-)1,2-dehydroaspidospermidine (4) (7 mg, 10%), compound 8 (30 mg, 30%) and compound 18 (8 mg, 14%).

Compound 18 : $(\alpha)_D$-131° (c=0.5, MeOH) ; I.R. (film) : 1645 cm^{-1} ; U.V. (MeOH) : 226(5.56), 260(5.56), 293(5.01), 301(5.03), 312(4.99) ; M.S. m/e 336 $M^{+\cdot}$.

Reduction of 16-acetoxy, 16-dehydrovincane (18) → 14 + 15

Compound 18 (10 mg) was reduced with an excess of $LiAlH_4$ (10 mg) in refluxing THF (3 ml) during 1 hour. After extraction and t.l.c. separation, vincane (14) (4 mg, 50%) and vincanol (15) (3 mg, 30%) were obtained.

2) Flow thermolysis : general conditions (14)

The flow thermolysis system was that described by M.MANISSE and J.CHUCHE[10]. The sample was dissolved in toluene (0.2 to 4%) and passed dropwise through a Pyrex column heated in an oven. Effluent was condensed at the bottom of the column in a Dewar vessel filled with liquid nitrogen. The whole system was maintained at a pressure of 20 Torr. Isolation of the products was effected after evaporation of the solvent by t.l.c., in most cases.

16-hydroxy 1-methyl 2,16-dihydrovincadifformine (11)

Compound 11 was prepared from vincadifformine (1) as described for 16-hydroxy 1-methyl 2,16-dihydrotabersonine from tabersonine[11]. m.p. 124-128 (hexane, CH_2Cl_2) $(\alpha)_D$+30° (c=0.1, MeOH) ; I.R. (KBr) : 1730, 3400 cm^{-1} ; U.V. (MeOH) : 207, 248, 298 ; N.M.R. : 0.5(t, 3H,CH_2CH_3), 2.62(s,3H), 3.82(s,3H) ; M.S. m/e 370 $M^{+\cdot}$

Compound 12[4] : $(\alpha)_D$-13° (c=0.3, MeOH) ; I.R. (film) : 1720 cm^{-1} ; U.V. (MeOH) : 215(4.27), 253(3.91), 300(3.45) ; M.S. m/e 310 $M^{+\cdot}$.

(+)-methylmandelate, preparation and flow thermolysis

(+)-mandelic acid was refluxed with methanol during 24 hours in the presence of BF_3 etherate to give (+)-methylmandelate : m.p. 53-58° (hexane) ; $(\alpha)_D$+160° (c=1, MeOH) ; N.M.R. : 3.40(s,1H,OH), 3.79(s,3H,CH_3), 5.22(s,1H,CH), 7.43(s,5H) ; M.S. m/e 166 $M^{+\cdot}$.

Methylmandelate (200 mg) was dissolved in toluene (10 ml) and submitted to flow thermolysis at 450°. The organic layer was washed three times with a solution of sodium hydrogenosulfate. Evaporation of the toluene layer gave 60 mg (30%) of methylmandelate. The aqueous layer was basified with a K_2CO_3 solution and extracted with CH_2Cl_2. Careful evaporation of methylene chloride left 49 mg (40%) of benzaldehyde characterised as its semicarbazone (m.p. 215-222 (MeOH)) which was compared with an authentic sample.

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