HETEROCYCLES, Vol 26, No 5, 1987

STRUCTURE OF PELIRINE AND CHEMICAL CONVERSION OF GARDNERINE TO 11-METHOXY-16-EPIAFFININE

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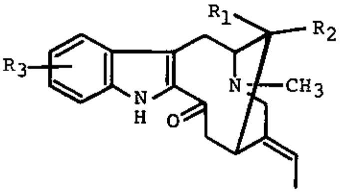
Abstract——The structure of pelirine, isolated from roots of Rauwolfia perakensis was shown to be 10-methoxyepiaffinine by comparison with the spectral data of 11-methoxyepiaffinine which was synthesized from the known alkaloid gardnerine. The proposed structure has been confirmed by X-ray crystallography.

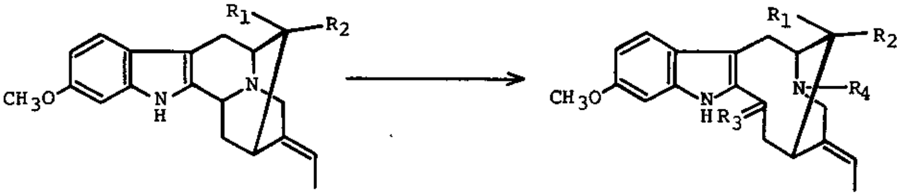
Pelirine was isolated from the roots of Rauwolfia perkensis[1] and was assumed to be one of the methoxy substituted affinine derivatives belonging to be the 2-acyl indole alkaloid.[2,3,4]

The location of the methoxy group on the aromatic ring and the configuration of the hydroxymethyl group on C-16 are still uncertain.



R_1 = CH_2OH, R_2=R_3= H: **1** affinine
R_1=R_3= H, R_2= CH_2OH: **2** 16-epiaffinine
R_1= H, R_2= CH_2OH, R_3=OCH_3 on C-11 **3**
R_1= H, R_2= CH_2OH, R_3= OCH_3 on C-10 **4** pelirine

In this paper we report the partial synthesis of 11-methoxy-16-epiaffinine **3** from gardnerine **5** and that the structure of pelirine was determined to be 10-methoxy-16-epiaffinine **4** from comparison of the spectral data with those of **3** and finally



R_1= CH_2OH, R_2= H: **5**
R_1= CHO, R_2= H: **6**
R_1= H, R_2= CHO: **7**
R_1= H, R_2= CH_2OH: **8**
R_1= H, R_2= CH_2OAc: **9**

R_1= H, R_2= CH_2OAc, R_3= OCH_3,H, R_4= CN: **10**
R_1= H, R_2= CH_2OAc, R_3= O, R_4= CN: **11**
R_1= H, R_2= CH_2OH, R_3= O, R_4= H: **12**

R_1= H, R_2= $CH_2OSi(CH_3)_2$t-Bu, R_3= O, R_4= H: **13**
R_1= H, R_2= $CH_2OSi(CH_3)_2$t-Bu, R_3= O, R_4= CH_3: **14**
R_1= H, R_2= CH_2OH, R_3= O, R_4= CH_3: **3**

5$\longrightarrow$ **6** + **7**: NCS(1.8 eq), Me_2S(1.85 eq) in toluene : DMF (10 : 1), -27° to -20°C, 5 h, and then addition of Et_3N (2 eq). **6**$\longrightarrow$ **7**: aq 0.1N KOH : MeOH (1 : 1), rt, 5 h. **7**$\longrightarrow$ **8**: $NaBH_4$ (excess) in MeOH, rt, 3 h. **8**$\longrightarrow$ **9**: Ac_2O/Py., rt, 7 h. **9**$\longrightarrow$ **10**: BrCN (6 eq), Na_2CO_3(10 eq) in 10% MeOH-$CHCl_3$, rt, 1 h. **10**$\longrightarrow$ **11**: t-BuOCl (1.1 eq) in CH_2Cl_2 with cat. amount of Et_3N, 0°C to rt, 5.5 h; aq N HCl, 1.5 h, rt; **11**$\longrightarrow$ **12**: refluxing in aq N HCl, 5 h. **12**$\longrightarrow$ **13**: $ClSi(CH_3)_2$t-Bu (2 eq), imidazole 2.5 eq in DMF, rt, 4 h. **13**$\longrightarrow$ **14** + **3**: 10%Pd-C/H_2, 37%aq H_2CO in dioxane, rt, 4 h.

by X-ray crystallography.

Gardnerine **5** gave a mixture of gardneral **6** (in 13% yield),[5] 16-epigardneral **7** (in 46% yield)[6] and the starting alkaloid **5** (16%) by the use of NCS-Me_2S oxidation. 16-Epigardnerine **8**[7] was produced easily from 16-epigardneral **7** by $NaBH_4$ reduction. 16-Epigardnerine **8** was also formed from gardnutine[3] in a one pot reaction (in 48% yield). The acetate **9**[8] was smoothly reacted with BrCN and gave rise to a single ring-opened compound **10**[9] in a quantitative yield. t-Butyl hypochlorite reacted with **10** and, without purification, the resulting chloro derivative was hydrolyzed to give a 2-acylindole derivative. After evaporation of the organic solvent used for extraction the hydrolyzed compound was gradually converted to the 2-acylindole derivative **11**[10] in desiccator. After purification by chromatography on SiO_2 column, **11** was obtained in 32% yield as needles. Hydrolysis of **11** with strong acid provided the corresponding secondary amine alcohol **12**[11] in 80% yield. After converting **12** to the silyl ether **13**[12], N-methylation was carried out to provide a mixture of 11-methoxy-16-epiaffinine-O-silylether **14**[13] (in 22% yield) and the desired 11-methoxy-16-epiaffinine **3**[14] (in 48% yield).

		M^+	M^+-H_2O	M^+-CH_2OH	base peak
affinine	1[15]	324		293	152
11-methoxyaffinine[a,16]		354(79)	336(10)	326(56)	152(100)
16-epiaffinine	2[17]	324(1)	306(33)		152(100)
11-methoxy-16-epiaffinine	3[a]	354(3)	336(61)		152(100)
pelirine	4[a]	354(3)	336(88)		152(100)

a) These compounds were measured by use of direct inlet method this time.

Table 1. Mass Spectral Data of Affinine Derivatives.

Affinine **1** and 11-methoxyaffinine[16] whose primary alcohol groups are oriented to the indolic side exhibited strong peaks of M^+ and M^+-CH_2OH besides the base peak at m/z 152.[17] However, 16-epimeric derivatives, **2** and **3**, characteristically revealed a strong peak of M^+-H_2O and a weak peak of M^+ besides the base peak as shown in Table 1. Since pelirine **4** showed the latter tendency, we propose its structure to be 10-methoxy-16-epiaffinine **4**. The ^{13}C-nmr signals of pelirine **4** indicate similar values compared with those of the synthesized model compound **3** except for the signals of aromatic and conjugated carbons as shown in Table 2. ^{1}H-nmr spectra of compounds **3** and **4** also showed excellent similarity with each other except for the aromatic protons.

Finally, in order to confirm the proposed structure of pelirin **4**, X-ray crystallography was used and the deduced structure was proved to be correct.[18] The structure was solved by direct method MULTAN[19] and refined by the full matrix least-squares method to R=0.047.. The ORTEP drawing of **4** is shown in Fig 1.

No	3	4
2	137.8	136.0
3	190.0	200.0
5	57.2	57.1
6	19.5	19.3
7	121.5	119.8
8	123.0	128.7
9	121.5	100.6
10	112.5	154.7
11	160.2	113.2
12	93.6	118.6
13	134.9	132.0
14	43.4	43.5
15	31.7	31.8
16	38.2	38.1
17	67.9	67.9
18	12.1	12.1
19	120.9	120.9
20	135.3	135.2
21	52.8	52.1
N-Me	42.0	42.0
O-Me	55.6	55.9

^{13}C-NMR spectra of 3 and 4. Table 2.

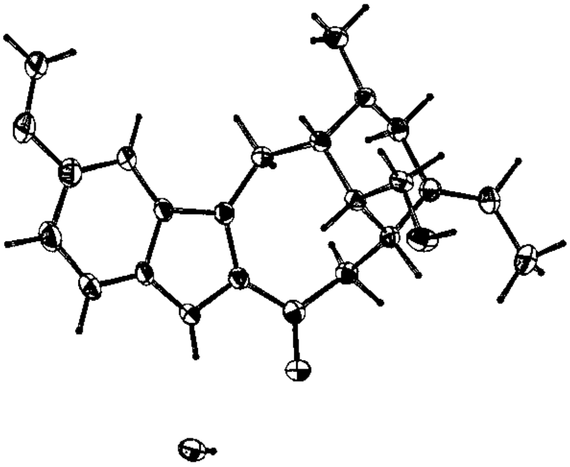


Fig. 1. ORTEP of Pelirine 4

The CD spectrum of **4** showed a curve similar to that of **3** derived from gardnerine **5** having known absolute configuration.[20] Therefore, pelirine **4** has the common indole alkaloid configuration.

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5) mp 278-280°C, $\nu_{C=O}$ 1695cm^{-1}, $\delta(CDCl_3)$ 9.14 (1H,d, J=0.9Hz), Mass m/z(%):322(M^+, 100), 293(M^+-29, 42), 279(24), 212(15), 199(70), 198(50).
6) mp 276-278°C, $\nu_{C=O}$ 1715cm^{-1}, δ 9.64(1H,d, J=0.9Hz).
7) mp 284-287°C, $C_{20}H_{24}N_2O_2$:0.5Me_2CO, $[\alpha]_D^{18}$= -4.3°(MeOH), m/z(%): 324(M^+, 100), 323(M^+-1, 99), 293(40), 199(69), 198(47).
8) mp 234-237°C, $C_{22}H_{26}N_2O_3$, δ_{OCOMe} 1.97(s).
9) amorphous, δ_{C3-OMe} 3.22(s), $\delta_{C11-OMe}$ 3.79(s), δ_{OCOMe} 1.94(s).
10) mp 219-220°C, $C_{23}H_{25}N_3O_4$, m/z(%): 407(M^+, 28), 202(100), 160(64), $\delta_{C11-OMe}$ 3.88(s).
11) amorphous base, λ_{max}^{MeOH} nm: 343, 297, 264, 225.
12) amorphous, δ_{Si-tBu} 0.86(9H, s), $\delta_{C11-OMe}$ 3.87(3H, s).
13) amorphous, δ_{Si-tBu} 0.76(9H, s), 2.47(3H, s, N-Me), 3.84(3H, s, C11-OMe), m/z(%):454(M^+, 19), 397(14), 297(29), 296(100), 295(19).
14) mp 132-135°C, Mass m/z: Calcd for $C_{21}H_{26}N_2O_3$, 354.1942, Found 354.1933, $\nu_{C=O}$ 1620cm^{-1}, λ_{max}^{MeOH} nm(log ε): 342(4.32), 262(3.79), 232(sh, 4.13), 215(sh, 4.34), δ : 9.02(NH, br s), 3.27(C5-H, br dd, J=10, 7Hz), 3.37(C6-H, dd, J=14.3, 7.3), 3.51(C6-H, dd, J=14.3, 10.4), 7.56(C9-H, d, J=8.9), 6.83(C10-H, dd, J=8.9, 2.1), 6.77(C12-H, d, J=2.1), 2.63(C14-H, dd, J=11.9, 7.3), 3.30(C14-H, dd, t.like, J=11.9, 11.8), 3.08(C15-H, br dd, J=11.8, 7.3), 1.97(C16-H, m), 3.59(C17-H, dd, J=10.7, 4.3), 3.66(C17-H, J=10.7, 5.2), 1.70(C18-H_3, dd, J=6.7, 1.8), 5.47(C19-H, br q, J=6.7), 3.01(C21-H, br d, J=13.7), 3.68(C21-H, br d, J=13.7), 2.55(N-Me, s), 3.87(OMe, s).
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18) X-ray data: pale yellow plates, $C_{21}H_{26}O_3N_2:H_2O$, mp 130-131°C. Crystals of **4** belong to monoclinic space group $P2_1$ with cell constant of a= 19.0108(42)Å, b= 7.7596(13)Å, c= 6.8517(19)Å. A total of 2254 unique independent intensities were measured within the range of $3° < 2\theta < 155°$ on a 4-circle diffractometer (Rigaku AFC-5) using Cu Kα radiation (λ = 1.54Å). The structure was solved by the direct method using MULTAN 80 (UNICS III system) and refined anisotropically (isotropically for H) by the least-squares method using the 1789 reflections with $F_o \geqq 3\sigma(F_o)$.
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Received, 9th February, 1987