Indian Journal of Chemistry
Vol. 37B, April 1998, pp.422 - 424

Note

Chemical constituents of *Clausena lansium*: Part III — Structure of Lansamide-3 and 4[†]

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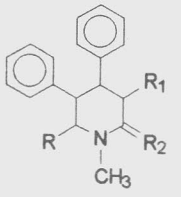
Received 24 May 1996; accepted 9 October 1997

Three novel cyclic amides Lansamide-2, Lansamide-3 and Lansamide-4 have been isolated from the leaves of *Clausena lansium*. These amides are found to have marked spasmolytic activity in isolated guinea pig ileum. The structure of two of them have been discussed here and the structure of Lansamide-2 has been published separately.

Our continued interest in the chemistry of new compounds from *Clausena* species[1-6] and specially *Clausena lansium*[6-11] (fam. Rutaceae) prompted us to investigate new chemical constituents of *C.lansium* (Lour.) Skeels (Syn. *C. wampi* Olive) in detail. Four novel cyclic amides have been isolated by Chinese workers from the leaves[9,10] of this plant. The ethanolic extract of the leaves showed marked spasmolytic activity in isolated quinea pig ileum; which was found to be concentrated in the hexane and benzene fractions in our bioassay results. Column chromatography together with preparative layer chromatography of these t wo fractions led to the isolation of three cyclic amides (Lansamide-2,3 and 4). The chemical structure of 2 has been established X-ray crystallography[11]. The structure elucidation of Lansamaide-3 and Lansamide-4 has been discussed in this communication.

Based on elemental analysis and EIMS Lansamide-3 **1** was found to have the molecular formula $C_{18}H_{19}NO_3$; it gave a molecular ion peak at m/z 297. The IR spectrum of the compound suggested the presence of hydroxyl groups (3390 and 3320 cm^{-1}), an amide carbonyl group (1686 cm^{-1}) and mono-substituted benzene ring (1650, 1450, 1405, 730 and 700 cm^{-1}). The aromatic nature was also supported by the UV spectrum in MeOH (λ_{max} at 253, 260, 265 and 270 nm).



1	R, R_1 = OH	R_2 = O
2	R, R_1 = $OCOCH_3$	R_2 = O
3	R, R_1 = OH	R_2 = CH_2
4	R = OCH_3, R_1 = OH	R_2 = O
5	R = OCH_3, R_1 = $OCOCH_3$	R_2 = O

Figure 1

Lansamide-3 formed a diacetate **2**, and on LAH reduction gave a product which had 14 mu less than Lansamide-3 **1** showing the reduction of the lactam carbonyl to a methylene function (see structure **3**).

On the basis of the above observation and ^1H NMR (Table I) and ^{13}C NMR (Table II) data, EI and CI-MS spectra, Lansamide-3 was identified as 3,6-dihydroxy-1-methyl-4,5-diphenyl-2-piperidone **1**. Lansamide-3 was expected to be a racemate, since neither the parent compound nor its derivatives exhibited optical rotation. Its structure was confirmed by X-ray studies.

Lansamide-4 **4** was found to have the molecular formula $C_{19}H_{21}NO_3$ based on elemental analysis and

Table I — ^{1}HNMR chemical shifts δ-=scale, DMSO-d_6 or $CDCl_3$, TMS standard, 400 Mhz) of Lansamide-3 and Lansamide-4

Proton No.	Lansamide-3†	Lansamide-4‡
N-CH_3	3.20(3*H*,s)	3.20(3*H*,s)
H-3	4.80(1H,d,*J*=5Hz)	4.60(1H,d,*J*=5Hz)
H-4	3.70(1H,dd,*J*=10Hz)	3.85(1H,dd,*J*=5,10Hz
H-5	4.31(1H,dd,*J*=5,10Hz	4.36(1H,dd,*J*=5,10Hz
H-6	3.82(1H,d,*J*=10Hz)	4.80(1H,d,*J*=10Hz)
OH/OCH_3 at 3- and 6-position	4.95 to 5.24(2H,m)	3.52(3H,s,OCH_3 at C-6)
Ar-H	6.7 to 7.46(2H,m) 7.12 to 7.30 (8H,m)	6.87 (2H,m) 6.93 to 7.20(8H,m)

† Spectrum was taken in DMSO-d_6.
‡ Spectrum was taken in $CDCl_3$

[†] CDRI Communicatrion No..4340

Table II — ^{13}C NMR chemical shifts (δ-scale) of lansamide-3 and lansamide-4 (DMSO-d_6 or $CDCl_3$, TMS standard, 100 Mhz)

Carbon No	Lansamide-3†	Lansamide-4‡
C-1	30.15(d)	33.68 (q)
C-2	174.01 (s)	173.43 (s)
C-3	68.58 (d)	66.83 (d)
C-4	49.28 (d)	48.68 (d)
C-5	65.06 (d)	44.10 (d)
C-6	71.85 (d)	93.59 (d)
C-6-OCH_3	–	57.00 (q)
C-1′	136.18 (s)	136.12 (s)
C-1″	140.76 (s)	
Ar-C (1OC, m)	126.14 to 128.55 (m, 1OC)	126.94 to 128.98 (m, 1OC)

† Spectrum was taken in DMSO-d_6.
‡ Spectrum was taken in $CDCl_3$.

a molecular ion peak at m/z 311 in its EIMS. The IR spectrum suggested the presence of hydroxyl group (3350 cm^{-1}), an amide carbonyl (1640 cm^{-1}) and the aromatic ring (1610, 1480, 1460, 1450, 740 and 710 cm^{-1}). The aromatic nature was also supported by the UV absorption at 265, 258, 255 and 245 nm). Lansamide-4 gave the monoacetate **5** with acetic anhydride and pyridine. On the basis of these observations and from ^1H NMR (Table I) and ^{13}C NMR (Table II) data and EIMS of **5**, the structure 3-hydroxy-6-methoxy-1-methyl-4,5-diphenyl-2-piperidone **4** was proposed. Lansamide--4 also lacked optical activity. The structure of this compound was similar tol that of Lansamide-3 except the presence of one methoxyl group at C-6 position instead of hydroxyl group. Therefore Lansamide-4 is the methoxyl derivative of Lansamide-3.

Experimental Section

General. The plant material was collected from HRI, Saharanpur, India in April 1976 and a herbarium specimen has been deposited in the Botany Division of the Institute.

All mps are uncorrected. NMR spectra were recorded either at 100 Mhz or 400 Mhz (WM-400) with TMS as internal reference. Column chromatography was carried out on silica gel (60-120 mesh).

Extraction and isolation of Lansamides. Powdered leaves (2.5 kg) were extracted with 95% ethanol and the residue, thus obtained, was fractionated into hexane, benzene, ethyl acetate and *n*-butanol soluble fractions. The Lansamaide-2 to 4 were isolated from both hexane and benzene fractions by column chromatography over silica gel and eluting with 2 to 5% MeOH-$CHCl_3$ mixtures, and then by preparative layer chromatography in the same solvent.

Lansamide-3 1. White needles, mp 236-37°C. Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.55; H, 6.43; N, 4.72. Found: C, 72.45; H, 6.50; N, 4.63%; EIMS: m/z 297 (M^+, 4.0%), 279 (70), 268 (100), 250(88), 234(15), 220(65), 190(100), 162(65), 144(12), 134(80), 117,(100), 105(42), 91(75), 77(50) and 60(75).

Lansamide-3 acetate 2. White cubes, mp 164-65°C. Anal. Calcd for $C_{22}H_{23}NO_5$: C, 69.29; H, 6.04; N, 3.67. Found: C, 69.10; H, 6.08; N, 3.62%; IR(KBr): 1740, 1720, 1680 and 1225cm^{-1}; EIMS: m/z 381 (M^+, 33%), 339(2), 321(5), 279(5), 261(20), 231(40), 171(100), 144(35), 91(25), and 77(25).

LAH reduction of Lansamide-3. Lansamide-3 (50 mg) was dissolved in THF (10 mL) and to this solution LAH (100 mg) was added. The reaction mixture was stirred at room temperature for 4 hr and then refluxed for 5 hr. It was worked-up as usual and the product recrystallized from....., yield 35 mg, mp 208-10°C; MS: m/z 283 (M^+).

Lansamide-4 4. White needles, mp 187-88°C. Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.31; H, 6.75; N, 4.50. Found: C, 73.4.; H, 6.68; N, 4.28%; EIMS: m/z 311 (M^+, 8%), 279 (43), 250 (65), 222(14), 131(90), 91(28), and .74(100).

Lansamide-4 acetate 5. White needles, mp 169-70°C. Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.38; H, 6.51; N, 3.96. Found: C, 71.2.; H, 6.46; N, 4.02%; IR(KBr): 1725 cm^{-1} (OAc); EIMS: m/z 353 (M^+), 321(28%),and .279(100).

Acknowledgement

We wish to thank the Director, Central Drug Research Institute, Lucknow for providing necessary research facilities.

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