New Derivatives of Tylosin

IV. Dihydro and Tetrahydro Desmycosin Oximes

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We report our experience about oximation of desmycosin derivatives having oxygen at C-13 position in a 12,13-epoxy[1] or 13-hydroxy[2] form. Oximation of the 10,11-dihydro-12,13-epoxy desmycosin dimethylacetal (**1**) gave oxime **2** in a good yield (Fig. 1). The structure of the novel 9-oximino compound was elucidated on the basis of its FAB-MS, ^1H and ^{13}C NMR spectra. Increase of molecular ion for 15 in comparison with that of the parent ketone is in agreement with the replacement of the C-9 keto group with a hydroxyimino one. In the ^1H NMR (DMSO-d_6) spectrum compound **2** showed N–OH absorption exchangeable with D_2O at 10.35 ppm. The ketoxime **2** appeared to be single isomer. Resonance of both α carbons (C-8, C-10) shifted upfield on an oxime formation, with the effect for C-10 being greater than for C-8, suggested an *E*-isomer.[3,4] The other chemical shifts (Table 1) confirmed retention of the epoxy group and were consistent with the assigned structure. Oximation of the 12,13-epoxy derivative (**4**), having C_{10}-C_{11} double bond, gave unexpected epoxyimino compound (**5**). Increased molecular ion for 33 in comparison with that of **4** and disappearance of the enone absorption at 230 nm in the UV spectrum implied addition of hydroxylamine to C_{10}-C_{11} double bond,[5] followed by an internal 9,11 cyclisation. Change of C-10 multiplicity together with strongly upfield shifted C-9, C-10 and C-11 confirmed this presumption. Further evidence was obtained from ^1H NMR spectra. The absence of signal in 10.30 ~ 10.65 ppm region and a new one at 4.18 ppm, exchangeable with D_2O, confirmed the amino group and structure of **5** as depicted on Fig. 1.

Oximation of the 10,13-dihydro-13-hydroxy compound (**6**)[6] gave a mixture of oximes **7** and **8** in a 2:3 ratio both with molecular ion at *m/z* 851 (MH^+) and characteristic N–OH proton absorption, exchangeable with D_2O at 10.49 and 10.35 ppm, respectively. Clearly deshielded H-8 of **7** appears well separated from others protons (3.68 ppm) and upfield shifted resonance of both α carbons (C-8, C-10) with the effect for C-8 being greater than for C-10, suggested *Z*-isomer.[7] Moreover, strong cross peak of 9-NOH/H-20 in the 2D NOESY spectrum of **7**, which is missing for isomeric oxime **8** confirmed predicted assumption. The other chemical shifts in the ^{13}C NMR spectra of **7** and **8** are consistent with proposed *Z*- and *E*-structures, respectively. Oximation of the tetrahydro compound **9** gave isomeric oximes **10** and **11**, with characteristic N–OH absorption exchangeable with D_2O, at 10.31 and 10.14 ppm, respectively. Also, the same were prepared by catalytic hydrogenation of dihydro oximes **7** and **8**, respectively. Increased molecular ion for 2 (*m/z* 853) for both isomers, in comparison with that of the parent dihydro oximes **7** and **8** is in agreement with addition of 1 mol of hydrogen.

Mild acid hydrolysis of the protecting acetal group of **2** gave expected ketoxime **3**. There was no hydrolysis of oxirane ring or internal cyclisation with oximino group.

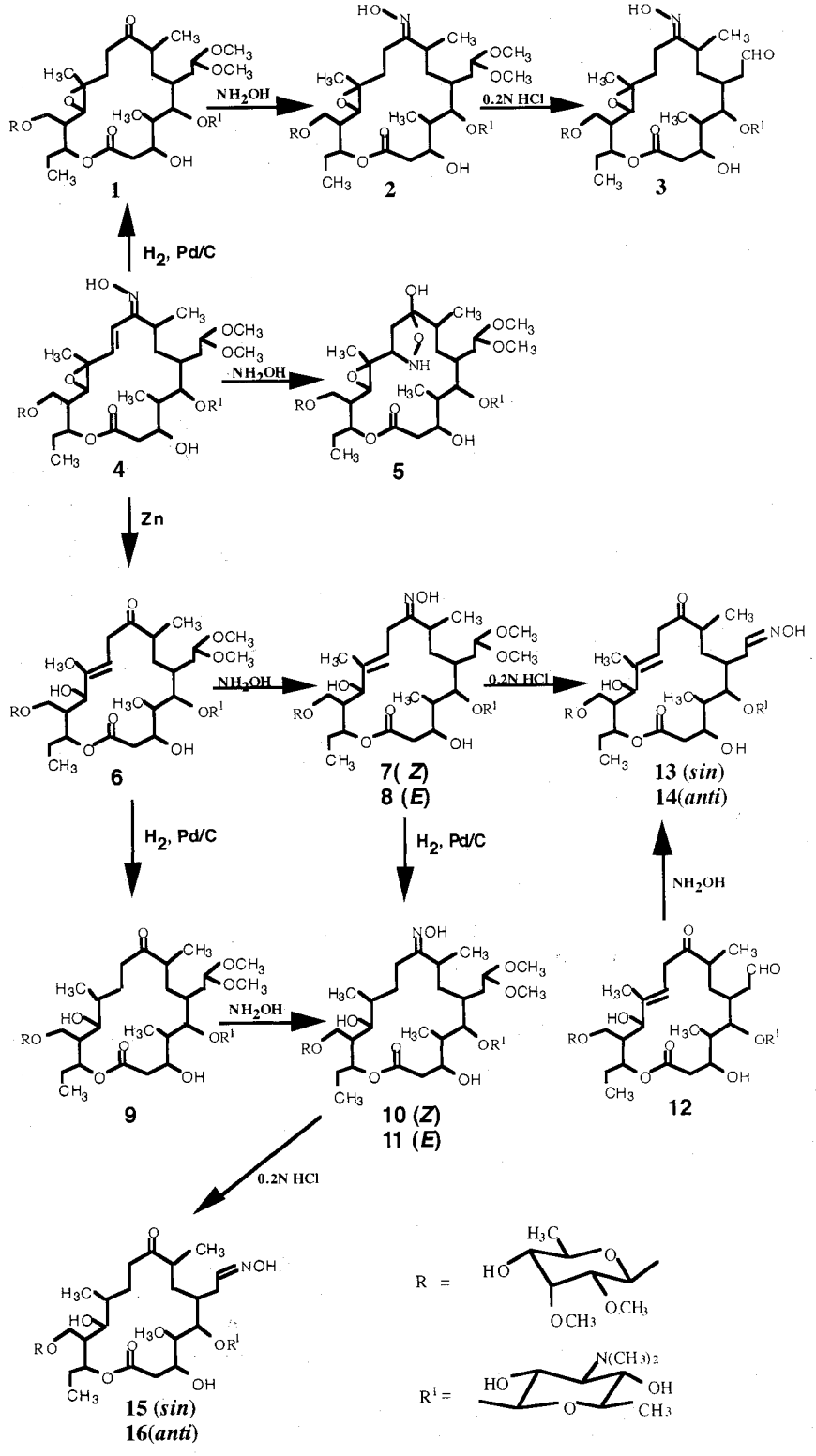
Table 1. The ^{13}C NMR chemical shifts[a] of aglycon[b] of 12,13-epoxy-desmycosin derivatives **1**, **2**, **3** and **5** in comparison with 12,13-epoxy desmycosin (**4**).

C	1	2	3	4	5
1	170.8	173.2	173.3	173.3	170.4
2	40.4	39.9	40.4	39.5	39.7
3	ND	66.9	66.9	70.6	ND
4	39.0	41.5	40.9	40.8	41.2
5	83.0	80.8	80.6	81.8	81.8
6	32.3	ND	ND	33.1	35.7
7	31.7	ND	ND	31.1	29.6
8	42.7	35.0	35.8	45.1	37.0
9	212.2	161.7	161.2	200.3	110.8
10	34.5	20.8	21.2	122.8	41.9
11	28.4	30.3	30.1	151.1	63.3
12	59.7	62.3	62.3	59.5	60.7
13	57.9	61.8	61.7	64.3	54.2
14	41.1	41.1	41.8	43.6	40.5
15	72.5	74.5	74.0	73.8	73.5
16	24.7	23.7	24.2	24.7	25.2
17	9.1	7.8	8.4	9.3	10.4
18	7.9	8.3	8.8	9.2	9.5
19	32.1	31.7	43.3	33.1	31.2
20	103.9	102.1	203.3	102.2	102.9
21	16.8	17.9	18.4	17.9	1.5
22	18.4	15.9	16.5	15.1	18.9
23	66.5	67.5	67.5	67.3	68.2

[a] δ Values in ppm downfield of TMS, spectra were recorded in $CDCl_3$ at 75 MHz as determined from ^1H-^{13}C 2D heteronuclear shift correlated experiments.

[b] There are no significant chemical shifts in sugar moiety of molecule.

Fig. 1. Synthesis of novel dihydro and tetrahydro desmycosin oximes.



Surprisingly, acetal hydrolysis of dihydro compounds **7** and **8**, or tetrahydro compounds **10** and **11** gave the pair of aldoximes **13**, **14** and **15**, **16**, respectively. Downfield chemical shifts of 48 ~ 50 ppm for compounds **13** ~ **16** confirmed C-9 ketone. The new doublets in 151 ~ 152 ppm region and an omission of aldehyde signal in the ^{1}H (~9.6 ppm) and ^{13}C (~203 ppm) NMR spectra are in agreement with hydrolysis of oximino group and an aldoxime formation.[8] The structure the isomeric aldoximes **13** and **14** was confirmed also by

Table 2. The ^{13}C NMR chemical shifts[a] of aglycon[b] of 13-hydroxy desmycosin oximes **7**, **8**, **10**, **11**, **13** and **14** in comparison with ketones **6**, **9** and **12**.

C	6	7	8	9	10	11	12	13	14	15	16
1	173.1	174.2	171.7	173.2	721.5	173.2	172.5	172.9	173.8	173.2	173.0
2	39.3	39.8	40.3	40.1	41.0	40.9	39.5	39.2	39.4	40.1	39.9
3	70.7	66.8	69.2	ND	67.9	ND	70.6	66.2	66.7	ND	ND
4	41.2	41.6	41.5	41.1	41.6	41.4	41.2	41.5	40.5	41.1	41.2
5	80.6	80.9	83.9	173.2	81.5	84.7	80.5	81.6	81.6	84.5	84.4
6	34.3	33.0	35.5	40.1	33.7	35.8	31.7	34.5	34.7	31.7	31.9
7	32.1	33.7	34.5	33.0	30.6	ND	31.8	30.1	30.2	31.8	32.0
8	45.5	27.5	35.6	42.8	28.0	35.6	45.5	45.5	45.9	45.5	45.4
9	211.4	162.0	162.9	215.2	163.8	165.1	211.3	211.8	211.4	211.3	211.5
10	34.0	25.8	25.7	36.2	26.1	25.9	33.9	33.6	34.0	33.9	33.9
11	117.3	120.9	122.0	34.5	24.7	24.3	117.4	118.0	118.2	34.5	34.4
12	139.7	139.1	138.8	38.8	33.7	34.7	139.6	139.9	139.9	38.8	38.7
13	76.5	77.0	75.8	73.3	71.2	71.4	76.6	76.5	76.6	73.3	73.3
14	44.0	44.0	44.5	43.2	42.8	43.2	43.9	44.0	44.1	43.2	43.2
15	74.2	74.5	75.6	75.9	73.5	73.4	74.2	74.3	74.1	75.9	75.6
16	25.0	25.0	25.3	24.5	23.4	24.3	25.1	25.0	25.0	24.5	24.6
17	8.6	8.8	9.8	9.9	8.9	9.4	8.5	8.6	8.5	9.9	9.9
18	9.0	9.6	7.9	7.9	8.4	7.4	9.0	8.8	8.9	7.9	8.0
19	32.1	32.2	31.9	32.7	30.3	31.3	43.7	30.1	26.3	30.2	26.5
20	102.0	103.1	130.0	103.6	102.9	103.2	202.7	151.3	152.0	151.4	152.2
21	18.0	18.6	17.5	17.3	18.1	15.7	18.1	17.9	18.1	17.8	18.0
22	12.5	11.8	11.9	20.1	15.3	15.2	12.4	12.3	12.3	20.1	20.0
23	66.2	66.6	69.2	66.6	66.2	66.5	66.3	66.7	66.3	66.6	66.7

[a] δ Values in ppm downfield of TMS, spectra were recorded in $CDCl_3$ at 75 MHz as determined from ^{1}H-^{13}C 2D heteronuclear shift correlated experiments.

[b] There are no significant chemical shifts in sugar moiety of molecule.

oximation of **12** with one equivalent of hydroxylamine.

In summary, C-9 oximes having free 13-hydroxy group are not stable towards acid hydrolysis. Possible explanation may be in transannular influence of 13-hydroxy group in dihydro (**7**, **8**) as well as tetrahydro (**10**, **11**) oximes, which facilitated initial addition of water to oxime and subsequent elimination of hydroxylamine.

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