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SKELETAL REARRANGEMENT OF MIYACONITINE

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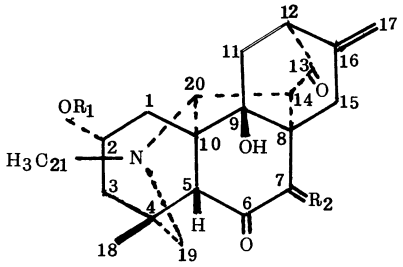
Alkaline hydrolysis of miyaconitine (I) or miyaconitinone (II) has been found to give skeletal rearrangement products, miyaconine (IV) and apomiyaconine (V).

In previous papers,[1,2] structure determination of miyaconitine (I) and miyaconitinone (II), major alkaloids of aconitum miyabei Nakai, were described. We wish to report here skeletal rearrangement of I.

I	R_1= $COCH_3$	R_2= 
II	R_1= $COCH_3$	R_2= O
III	R_1= H	R_2= O



While hydrolysis of II with 0.1N sulfuric acid gave an alkamine, miyaconinone (III), which on acetylation was reconverted into II as described in the previous paper,[1] treatment of I with 1N methanolic potassium hydroxide for 1 hr afforded miyaconine[3] (IV) $C_{21}H_{25}O_5N$, M^+371.423, m.p.278-278.5°; λ_{max}^{EtOH} 300 nm (ε233); ν_{max}^{KBr} 3160 cm^{-1} (broad OH), 1780 (γ-lactone), 1721 (carbonyl), 1653, 900 (>C=CH_2); $\delta_{TMS}^{CDCl_3}$ 1.15 (3H. s. ≡C-CH_3), 2.45 (3H. s. >N-CH_3), 5.03 (2H. br. s. >C=CH_2), 7.67 [1H. d. J=10 Hz. OH (hydrogen bond)], which on acetylation with acetyl chloride gave diacetylmiyaconine, $C_{25}H_{29}O_7N$, m.p. 151-154°; ν_{max}^{KBr} no (OH), 1808, 1764, 1742 (-COO-), 1719 (>C=O); $\delta_{TMS}^{CDCl_3}$ 1.05 (3H. s. ≡C-CH_3), 4.92 (1H. m. ≡C<u>H</u>-$OCOCH_3$), 2.04,

2.23 (each 3H. s. $OCOCH_3$), 2.45 (3H. s. $>N-CH_3$), 5.03 (2H. m. $>C=CH_2$). Also IV was obtained by treatment of III with 5% hydrochloric acid under reflux for 2 hr, and given by a mild oxidation of I with an alkaline solution of triphenyltetrazolium chloride (TTC) at room temperature.

Reaction of IV with 1N methanolic potassium hydroxide under reflux for 2 hr afforded, apomiyaconine (V), $C_{20}H_{25}O_4N$, M^+ 343.411, m.p. 259.5-260°, ν_{max}^{KBr} 3620, 3500, 3300 (broad OH), 1742, 1725 (>C=O), 3080, 1650, 905 ($>C=CH_2$); $\delta_{TMS}^{CDCl_3}$ 1.22 (3H. s. $\equiv C-CH_3$), 2.38 (3H. s. $>N-CH_3$), 5.05 (2H. d. $>C=CH_2$ J=10 Hz), 7.75 [1H. d. J=12 Hz. OH (hydrogen bond)]. The mass spectrum reveals that a considerable decrease in molecular weight took place in the course of the reaction from IV to V. Accordingly loss of one carbon atom during the reaction was reasonably assumed, and then confirmed by ^{13}C NMR spectroscopy. The ^{13}C NMR signals of IV and V were assigned by use of ^1H off-resonance decoupling techniques and by comparison of their chemical shifts with those of diterpenoids including gibberelins[4] as shown in the Table. It is noteworthy that only oxidative decarboxylation of benzylic-acid type compounds with lead tetraacetate has been reported.[5]

Acetylation of V with acetic anhydride in the presence of a catalytic amount of p-toluensulfonic acid on a steam bath for 1 hr gave diacetylapomiyaconine, $C_{24}H_{29}O_6N$, m.p. 176-177°; ν_{max}^{KBr} no (OH), 1735, 1715 (>C=O), 1650, 907 ($>C=CH_2$); $\delta_{TMS}^{CDCl_3}$ 1.12 (3H. s. $\equiv C-CH_3$), 2.01, 2.06 (each 3H. s. $OCOCH_3$), 2.40 (3H. s. $>N-CH_3$), 4.93 (1H. m. $>C\underline{H}-OCOCH_3$), 5.10 (2H. m. $>C=CH_2$).

From the above chemical and spectral data, structures of IV and V, and the reaction sequence are reasonably drawn as shown in the Scheme.

Transannular carbonyl absorptions observed in the IR spectra of I, II, and III show that lone-pair electrons of the nitrogen atom in the azabicyclo[3.3.1]-nonane ring system tend toward the B ring site.[1] On the other hand, in ^1H NMR, the respective proton signals at δ7.67 and 7.75 in IV and V disappear by treatment with deuterium oxide as similarly observed for the CHO signal in a formate and a formamide. These facts suggest that the nitrogen lone-pair electrons form the hydrogen bonds with 2α-hydroxyl function in the A ring. From an examination of ^{13}C NMR spectra (see Δδ values in the table) together with Dreiding models, it was concluded that the hydrogen atom at C-5 should still have the β-configuration in IV and V.

Table. ^{13}C NMR Data[a]

No.	δ_C miyaconine		δ_C apomiyaconine		$\Delta\delta$ (in ppm)
C-1	35.79	t.	33.67	t.	-2.12
2	64.43	d.	64.85	d.	+0.42
3	50.41	t.	47.50	t.	-2.91
4	36.22	s.	34.82	s.	-1.40
5	47.93	d.	54.96	d.	+7.03
6	85.60	s.	211.49[b]	s.	
7	178.79[c]	s.			
8	56.48	s.	61.52	s.	+5.04
9	84.57	s.	79.60	s.	-4.97
10	50.78	s.	49.14	s.	-1.64
11	26.33	t.	33.30	t.	+6.97
12	43.80	d.	46.59	d.	+2.79
13	208.22	s.	208.28	s.	+0.06
14	53.63	d.	54.96	d.	+1.33
15	26.33	t.	22.75	t.	-3.58
16	138.26	s.	140.63	s.	+2.37
17	113.39	t.	113.33	t.	-0.06
18	25.29	q.	25.42	q.	+0.13
19	54.66	t.	56.06	t.	+1.40
20	64.00	d.	64.31	d.	+0.31
21	41.63	q.	41.37	q.	-0.31

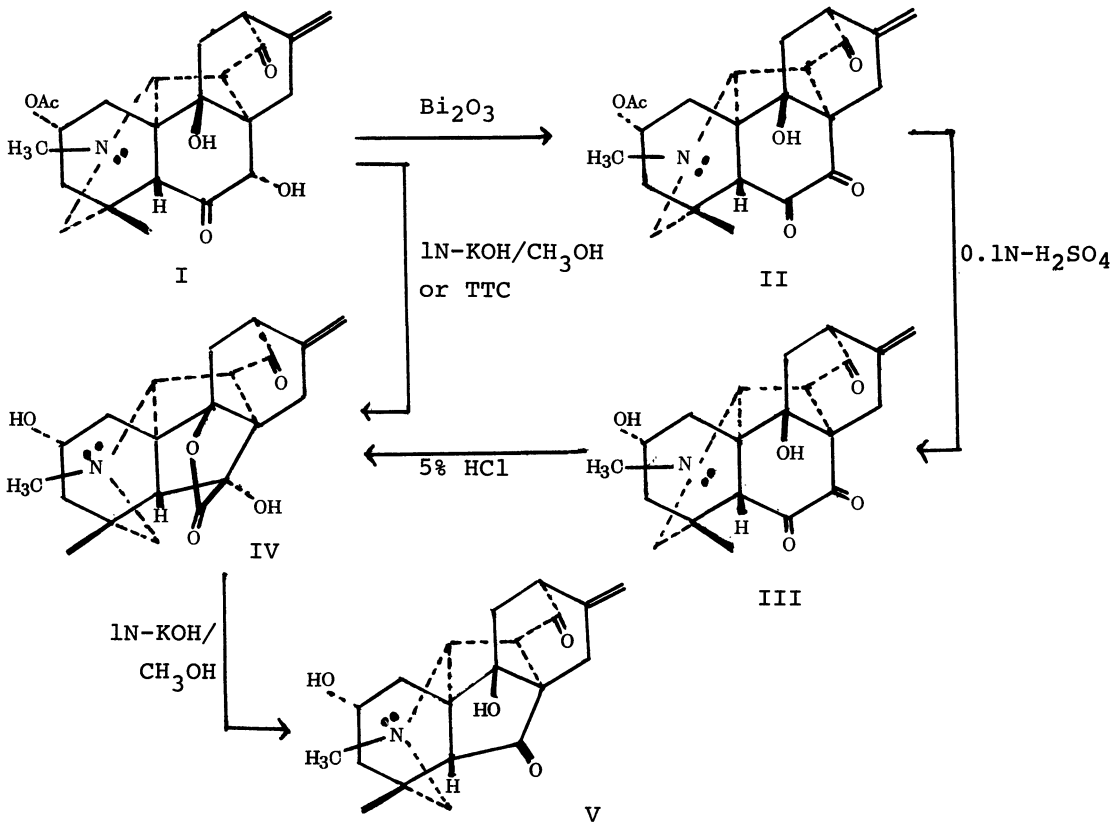
a The ^{13}C FT NMR spectra were taken with a JEOL PFT 100 Spectrometer equipped with EC 100 at 25.15 MHz in $CDCl_3$ containing TMS as an internal reference (δ_C 0). Estimated errors for δ_C were about ±0.06 ppm. Multiplicities indicated are those obtained by off-resonance decoupling techniques.

b Five membered ring carbonyl.

c γ-lactone carbonyl.

The reported anthracene formation[6] in dehydrogenation of II is rationalized in terms of the rearrangement, and this rearrangement also provides as explanation for the formation of IV as an artifact in the course of purification of I and II through chromatography.[7]

The detailed chemistry of miyaconitine will be presented in the near future.



Scheme

References

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