云 南 植 物 研 究 1998, 20 (4): 474 ~ 478
Acta Botanica Yunnanica

滇乌碱的结构改造

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摘要 滇乌碱是云南乌头属植物中分布最广、含量最高的一种二萜生物碱成分, 但其毒性高。为了充分利用这一丰富的资源, 我们用滇乌碱为起始物合成了7个衍生物。本文对衍生物合成的方法及合成产物的光谱数据作了报道。

关键词 滇乌碱, 滇乌碱衍生物, 结构修饰
分类号 Q 946

Structural Modification of Yunaconitine

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Abstract Yunaconitine, a diterpenoid alkaloid native to Yunnan in the plants of *Aconitum* species, is the richest in content and the widest in distribution, but its toxicity is high. In order to utilize the rich resource, some structural modification from yunaconitine had been undertaken, and seven derivatives have been got. This paper reports the synthetic ways of these derivatives and their spectra.

Key words Yunaconitine, Derivatives of yunaconitine, Structural modification

Among diterpenoid alkaloids found in the plants of Aconitum species native to Yunnan, China, yunaconitine (**1**) is the richest in content and the widest in distibution (Chen, 1979). But its toxicity is also high [LD_{50} 585μg/kg(i. p. in mouse), LD_{100} 50μg/kg(i.v. in rat)]. In order to utilize the rich resource, some structural modification from yunaconitine had been undertaken.

In the course of transformation of A - ring, we made a plan to synthesize yunaconitinone(**2**) and yunaconitoline(**4**) from yunaconitine.

It has long been known that aconitine, a similar Aconitum diterpenoid alkaloid to yunaconitine, is oxidized by chromic acid to the ketone aconitinone, which very readily loses the elements of methanol and gives rise to an α, β - unsaturated ketone, aconitoline(Majima *et al*, 1936; Jacobs *et al*, 1940). Mayer *et al* (1959), who also prepared aconitoline, claimed that oxidation with chromic acid always gave aconitoline directly.

Our researches have confirmed that the oxidational product of yunaconitine(**1**) with chromic acid

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1997 - 11 - 03 收稿, 1998 - 06 - 22 接受发表

was yunaconitinone(**2**), but **2** could convert to yunaconitoline(**4**) simply by subjecting to silica gel column and eluted with chloroform-ethyl acetate. These conclusions were supported by following evidence.

Yunaconitinone(**2**), cubic crystal (acetone－hexane), exhibited a base peak at 658[(M＋1)$^+$] in FABMS (positive). Its molecular formula was determined as $C_{35}H_{47}O_{11}N$ by combination of FABMS and DEPT spectrum. The ^{1}H NMR showed the signal of 3.58(dd, 4.0, 8.0, 3β－H) in yunaconitine (**1**) disappeared in yunaconitinone(**2**). Meanwhile, the ^{13}C NMR showed also the disappearance of 71.4(C－3, **1**) in yunaconitinone(**2**), and an additional signal of 214.2(C＝O) appeared in 2. The chemical shifts of 42.4(C－2), and 53.4(C－4) in yunacoitinone, which was caused by β－effect and downshifted from 33.5(C－2, **1** and 43.1(C－4,**1**), respectively, also suggested the structure of yunaconitinone as **2**.

Yunaconitoline(**4**), cubic crystal (acetone-hexane), had the base peak at 626[(M＋1)$^+$]. Its molecular formula was determined as $C_{34}H_{43}O_{10}N$ by means of FABMS and DEPT spectrum. The IR spectrum showed bands at 1716 cm^{-1}(ester), 1663 cm^{-1}(carbonyl) and 818 cm^{-1}(double bond). The^{1}H NMR spectrum exhibited an additional double bond signals at 6.42(1H,d,10.3)and 6.22 (1H, d, 10.3), as well as the disappearance of 1α－OCH_3 in 3.09 (s,3H) of **1**. The ^{13}C NMR spectrum showed also a double bond at 146.6(d), 132.1(d), and a carbonyl bond at 200.2(s). These evidence indicated that a six-membered α , β- unsaturated ketone had been formed . So, the structure of yunaconitoline could be **4**.

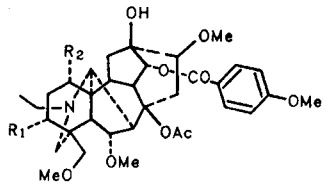
Another ketone compound was also obtained when **1** was converted to **2**. This compound had the similar ^{1}H,^{13}C NMR spectral data to those of **2**, except for the disappearance of ethyl group at N. So, the structure of this ketone compound, named as N－deethylyunaconitinone, was determined as **3**.

Like the similar transformation of **2** to **4**, **3** was also subject to silica gel column and eluted with chloroform－ethyl acetate. But no α , β－ unsaturated ketone compound like **4** formed from **2** was obtained as expected. This result implied that ethyl group at N had the ortho－effect to the process.

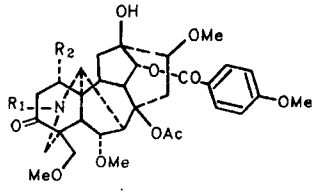
4 was then catalytically hydrogenized by Pt－C, absorbed 1 mol of hydrogen to produce compound **5**.**5** had still the carbonyl bond(^{13}C－NMR: 217. 1) , but the double bond had been saturated. Its structure could be deduced as **5**.

5 was further reduced by sodium borohydride to give a reduced compound **6**. In comparison with **5**, **6** had no carbonyl bond, but an additional carbon substituted by a hydroxyl group appeared [^{13}C NMR: 74.1(d)]. The hydroxyl group was deduced at C－3 position with α－configuration on the basis of stereochemical model and ^{1}H NMR evidence [3.70(dd,8.0,16.0)]. It has been demonstrated that the A－ring hydroxyl and methoxyl groups were removed in these conversion from **1** to **6**.

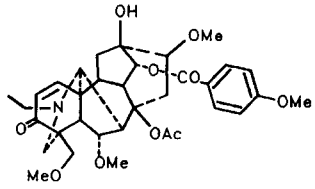
Pyrolysis of yunaconitine (**1**) gave a C_8－C_{15} olefinic compound, pyroyunaconitine(**8**), [^{1}H NMR:5.53(1H,6.3,C－15－H];^{13}C NMR: 147.0(s,C－8),116.5(d, C－15)]. In the routine method, yunaconitine was esterified by acetic anhydride in pyridine to afford a mono acetylized compound, 3－O－acetylyunaconitine(**7**).



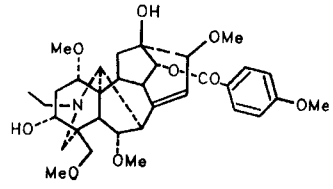
1 R_1=OH, R_2=OMe, Yunaconitine
6 R_1=OH, R_2=H, 1-Demethoxyyunaconitine
7 R_1=OAc, R_2=OMe, 3-O-Acetylyunaconitine



2 R_1=Et, R_2=OMe, Yunaconitinone
3 R_1=H, R_2=OMe, N-Deethylyunaconitinone
5 R_1=Et, R_2=H, 1-Demethoxyyunaconitinone



4 Yunaconitoline



8 Pyroyunaconitine

Experimental

Melting points were uncorrected. ^1H and ^{13}C - NMR were recorded at 400 and 100.16MHz, respectively, using TMS as int. standard. IR were taken for KBr disc. Optical rotations were recorded on SEPA - 300. UV were measured in MeOH. FABMS (Positive) and EIMS were measured with VG Auto Spec - 3000 mass spectrometer.

Yunaconitinone and N - Deethylyunaconitinone

Chromium trioxide(1.01 g) in cold acetone(12 mL) was added to yunaconitine(1.28 g) in cold acetone(20 mL). The reaction mixture was stirred at room temperature for 8 hours. after which the solvent was evaporated under reduced pressure. The dark brown residue was triturated with 10% sodium carbonate, extracted with ether (500 mL).

Dried with anhydrous sodium sulphate, filtered and evaporated to dryness, the ether solution resulted in white powdered yunaconitinone(0. 98 g) which was crystalized in the contact with acetone and n - hexane to consist of colorless cubic crystals, mp. 206.5 ~ 208.5℃, λ_{nm}^{MeOH}: 203(ε,20400), 207.5 (ε,19000), 257.5(ε,22400). ν_{max}^{KBr} cm^{-1}: 1714(C=O). $[\alpha]_D^{21}$ - 36.36°(c,0.11,$CHCl_3$). FABMS (positive): 658 [(M+1)$^+$,64%],598(658 - AcOH,12%). ^{13}C NMR data see Table 1.

The mother liquor, purified by chromatography of silica gel, eluted with chloroform: ethyl acetate 7:3, yielded white powdered N - deethylyunaconitinone(0.17g), mp. 153.0 ~ 155.5℃, ν_{max}^{KBr} cm^{-1}: 1710 - 1719, FABMS(positive):630[(M+1)$^+$,100%]. ^{13}C NMR data see Table 1.

Yunaconitoline

Yunaconitinone(60 mg) was placed on silica gel column. After the alkaloid was eluted with chloroform: ethyl acetate 7:3, yunaconitoline(54 mg) was yielded in powdered form which could be recrystalized from acetone: n - hexane to afford cubic crystals, mp. 225.0 ~ 227.0℃. λ_{max}^{MeOH} nm: 203.5(ε, 21300), 208(ε, 20600), 256(ε, 24500). ν_{max}^{KBr} cm^{-1}: 1663(C=O), 818(C=C). $[\alpha]_D^{24}$ +87.32°(c, 0.355, $CHCl_3$). FABMS(positive): 626[(M+1)$^+$, 100%], 566(626 - AcOH, 58%). ^{1}H NMR: 6.42 (d, 10.3, 1 - H), 6.22(d, 10.3, 2 - H). ^{13}C NMR data see Table 1.

1 - Demethoxyyunaconitinone

Yunaconitoline(178 mg) was dissolved in 75% EtOH, and palladium carbon catalyst (74 mg) was added. The solution was stirred at room temperature under hydrogen atmosphere for 18 hrs, then filtered. The filtrate was evaporated to give white powdered 1 - Demethoxyyunaconitinone(170 mg), mp. 126.0 ~ 129.0℃, FABMS(positive): 628[(M + 1)$^+$, 100%], 568(628 - AcOH, 47%), 469 (17%), 301(88%). ^{13}C NMR data see Table 1.

1 - Demethoxyyunaconitine

Sodium borohydride (900 mg) was added four times in 6 hrs to a solution of 1 - demethoxyyunaconitinone(250 mg) in MeOH(10 mL). The mixture was stirred at room temperature for 10 hrs. The resulting mixture was evaporated to a little volume, poured into water, and extracted with chloroform. The extract was washed three times with water, dried with sodium sulfate, and evaporated under reduced pressure to afford a white powdered 1 - demethoxyyunaconitine (234 mg), mp. 123.0 ~ 126.5℃, FABMS(positive): 630[(M + 1)$^+$, 97%], 570(630 - AcOH, 100%). ^{1}H NMR: 3.70(dd, 8.0, 16.0, 3β - H). ^{13}C NMR data see Table 1.

Pyroyunaconitine

Yunaconitine(100 mg) was heated under reduced pressure(20 mm) during 15 min at 180 ~ 188℃ (air bath). The product was dissolved in chloroform, chromatographed on a short column of silica gel, and eluted with petroleum ether: acetone 7:3. Evaporation of the elutate gives rise to a powdered pyroyunaconitine (54 mg), mp. 135.0 ~ 137.0℃, ν_{max}^{KBr} cm^{-1}: 912(C=C). EIMS(70eV): 599(M$^+$, 0.8%), 568(1.3%), 135(100%). ^{1}H NMR: 5.53(d, 6.3, C - 15 - H). ^{13}C NMR data see Table 1.

3 - O - Acetylyunaconitine

In a routine method, yunaconitine(20 mg), freshly distilled acetic anhydride(6.5 mL) and pyridine (5 mL) was kept at room temperature for 18 hrs. The reaction mixture was acidified with 2% HCl to pH 4, and alkalized with ammonia liquor to pH 9, respectively. The solution was then extracted with chloroform. Evaporation of the extract left the crude product (22 mg) which after recrystalization from acetone: cyclohexane afforded crystaline 3 - O - acetylyunaconitine (19 mg), mp. 168.0 ~ 171.0℃, EIMS (70eV): 701(M+, 17%), 670(57%), 643(57%), 610(62%). ^{1}H NMR: 3.79(d, 11.5). ^{13}C NMR data see Table 1.

Table 1 ^{13}C NMR chemical shifts and assignments*

Carbon	1	2	3	4	5	6	7	8
1	83.1	83.0	84.9	146.6	38.6	29.6	83.4	83.7
2	33.5	42.4	43.5	132.1	25.4	29.1	32.0	33.3
3	71.4	214.2	217.9	200.2	217.1	74.1	71.7	71.9
4	43.1	53.4	56.5	N.R	53.2	43.2	42.5	44.1
5	47.4	44.2	55.0	48.7	48.3	48.9	46.5	48.3
6	82.2	81.1	82.3	82.2	82.9	83.3	81.8	83.1
7	44.7	44.9	44.8	43.8	44.4	44.2	45.3	48.2
8	85.6	85.7	86.6	85.7	85.9	85.7	85.5	147.0
9	48.7	47.8	45.5	49.4	44.1	48.7	49.5	49.8
10	40.8	41.3	40.9	37.4	40.2	40.7	40.6	46.5
11	50.2	50.0	52.0	51.0	45.7	46.1	50.0	51.7
12	35.1	34.5	37.1	38.1	37.4	37.1	35.7	38.2
13	74.6	74.7	76.2	74.8	74.7	74.7	74.9	71.9
14	78.5	78.6	80.3	78.7	78.6	78.7	78.5	78.2
15	39.5	40.4	41.5	40.3	40.5	40.2	39.4	116.5
16	83.5	83.5	83.9	83.8	83.8	83.9	83.8	83.7
17	61.6	61.2	59.5	61.0	65.0	64.1	61.3	N.R
18	76.7	75.8	77.1	71.9	75.5	76.7	71.8	77.9
19	48.7	53.0	46.3	51.4	52.9	48.9	48.9	49.9
N - CH_2	47.4	47.8	—	48.7	48.5	47.2	47.7	48.1
CH_3	13.1	12.6	—	12.9	13.2	13.3	13.7	13.5
1'	55.7	56.0	56.1	—	—	—	56.2	56.3
6'	58.7	58.8	58.6	59.0	59.0	58.9	58.8	58.1
16'	57.7	57.9	56.1	59.0	57.9	57.6	58.1	57.3
18'	59.0	59.0	59.7	59.0	59.1	59.1	58.8	59.3
C = O	169.9	169.8	171.1	170.2	169.8	169.8	169.8	—
CH_3	21.5	21.5	21.7	21.5	21.9	21.6	21.6	—
C = O	166.1	165.8	167.4	165.8	165.8	165.8	166.1	168.2
	122.5	122.5	123.5	122.7	122.5	122.6	122.7	123.1
C_6H_4	131.6	131.6	132.9	131.7	131.7	131.7	131.7	132.0
	113.7	113.8	115.0	113.9	113.9	113.8	113.8	113.5
	163.5	163.6	165.0	163.7	163.6	163.5	163.5	163.4
OCH_3	55.3	55.4	55.0	55.5	55.5	55.4	55.4	55.4

Chemical shifts (δ) in ppm relative to TMS in $CDCl_3$

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