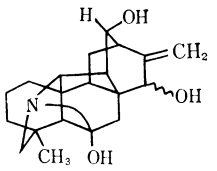
Communications to the Editor

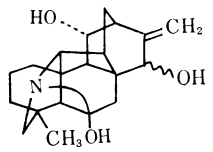
UDC 547.94.02:582.675.1

The Structure of Pseudokobusine

In the structural study of an aconite alkaloid, pseudokobusine, $C_{20}H_{27}O_3N$, m.p. 271° (decomp.) from aconite roots*1 collected in Hokkaido, the writer has previously reported[1] the characterization of three hydroxyl groups and the result of the selenium dehydrogenation reaction of pseudokobusine. In the present communication, he wishes to describe evidences which point out the structure of pseudokobusine to be either (Ia) or (Ib).



(Ia)



(Ib)

Chart 1.

When pseudokobusine (I) was acetylated with acetic anhydride in pyridine, a mixture of basic and neutral acetates was obtained as a viscous syrup, from which the neutral acetate was isolated and hydrolyzed with 1% methanolic potassium hydroxide to N-acetyl-seco-pseudokobusine (II), m.p. 230~231°(from MeOH-Me_2CO), $[\alpha]_D^{23.5}$ −81.4°(MeOH), (*Anal.* Calcd. for $C_{22}H_{29}O_4N$: C, 71.13; H, 7.87; N, 3.77. Found : C, 70.78; H, 7.32; N, 3.62) in 48% yield from pseudokobusine. N-acetyl nature of this neutral acetylation product was shown by its infrared absorption band at 1596 cm^{-1} and nuclear magnetic resonance peak*2 at 7.87 τ as a singlet and the simultaneous formation of a ketone group in a six-membered ring was suggested by an infrared band at 1700 cm^{-1} and by a weak ultraviolet absorption maximum at 299 mμ (ε 33). The ketone group of (II) was inert to the carbonyl reagents, yet sodium borohydride in boiling aqueous methanol reduced it to a hydroxyl group, affording (III), m.p. 230~231°(decomp.), ν_{max}^{KBr} 1600 cm^{-1} (*Anal.* Calcd. for $C_{22}H_{31}O_4N$: C, 70.75; H, 8.37. Found : C, 70.98; H, 8.01). The double bond of pseudokobusine (I) remained unchanged during the N-acetylation process because (II) still exhibited two signals on the exo-cyclic methylene type of double bond at 4.72 τ and 4.92 τ in its nuclear magnetic resonance spectrum. An N-acetyl ketone structure of (II) was strongly supported by the fact that pseudokobusine was recovered when (II) was treated with 20% potassium hydroxide in aqueous triethylene glycol at 170±10°.[2]

Pseudokobusine (I) was subjected to the cyanogen bromide degradation. A neutral compound (IV), m.p. 223°(from MeOH-Me_2CO), ν_{max}^{KBr} 2218, 1697 cm^{-1}, (*Anal.* Calcd. for $C_{21}H_{26}O_3N_2$: C, 71.16; H, 7.39; N, 7.90. Found : C, 70.86; H, 7.11; N, 7.74), which possessed no bromine atom in its structure, was obtained in 31% yield and again the formation of a ketone function in a six-membered ring was noticed in its infrared absorption spectrum besides the expected N-cyano band, so that the degradation reaction was considered to proceed in the same course as the above N-acetylation and the pro-

*1 The plant is assumed to be *Aconitum yesoensis* NAKAI.

*2 N. M. R. spectra were measured in $CHCl_3$ by Varian DP 60 spectrometer operated at 60 Mc.

1) M. Natsume : This Bulletin, 8, 374 (1960).

2) cf. Cycloneosamandione was reported to react in the same way. C. Schöpf, O. W. Müller : Ann., **633**, 127 (1960).

duct (IV) was designated as N-cyano-seco-pseudokobusine. Absolutely analogous to the above, hydrolysis of the N-cyano bond of (IV) with the strong alkali regenerated pseudokobusine (I).

Pseudokobusine methiodide (V) was dissolved in diluted ammonium hydroxide and the solution was extracted with a large amount of chloroform. An unstable tertiary base (VI), m.p. 158~161°, $\nu_{max}^{CHCl_3}$ 1675 cm^{-1}, was obtained and characterized after being converted to the fairly stable dihydro derivative (VII) and the rearrangement product (VIII) of the allyl alcoholic part. Details concerning with this subject will be reported elsewhere.[3] In the infrared absorption spectrum of the tertiary base (VI), the band of a carbonyl group was observed at the longer wave length than the ketones in above cases. The carbonyl group formed here was completely inactive to the ketone reagents, sodium borohydride and to the modified Wolff-Kishner reduction by Barton,[4] but the treatment of (VI) with 10% hydriodic acid gave rise to form pseudokobusine methiodide (V) at room temperature. This ready transformation to the quaternary salt together with the carbonyl infrared band at the longer wave length suggested that the carbonyl group was the same ketone function, which appeared in the N-acetyl or N-cyano ketone compounds (II, IV) and it had been trans-annularly interacted[5] from the tertiary nitrogen atom in this case.

All these facts have pointed out that pseudokobusine (I) has a masked amino ketone group $\overset{|}{N}-\overset{|}{C}-OH$, which is generally stable to oxidations and reductions, but behaves as

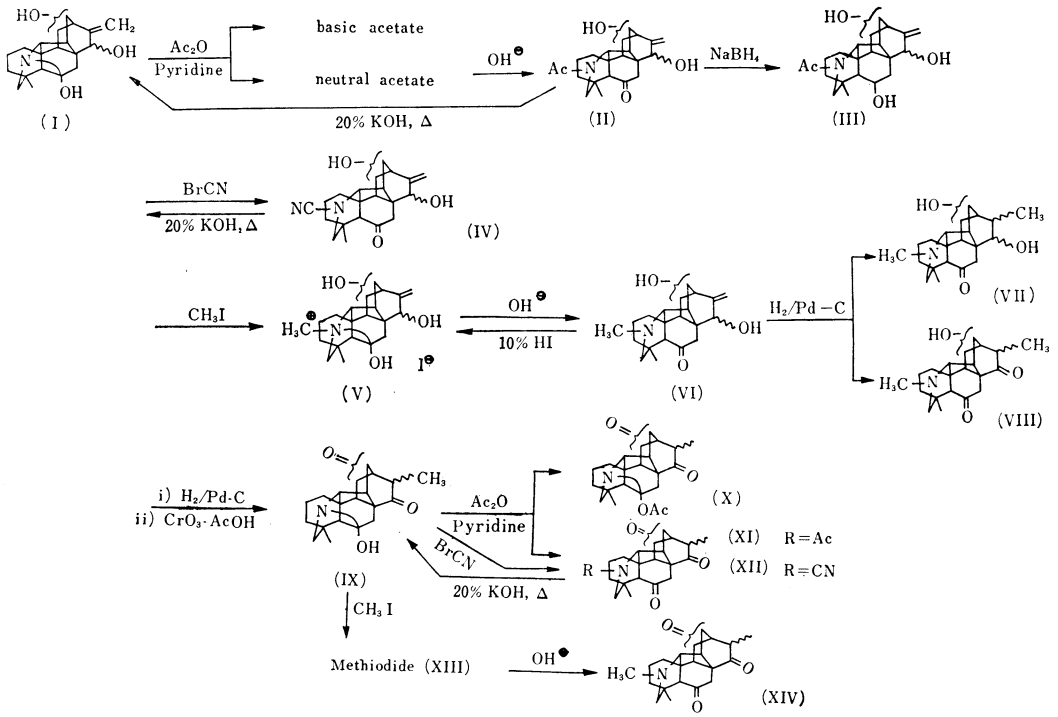


Chart 2.

3) T. Okamoto, M. Natsume, H. Zenda : This Bulletin in preparation.
4) D.H.R. Barton, D.A.J. Ives, B.R. Thomas : J. Chem. Soc., **1955**, 2056.
5) N.J. Leonard, M. Oki, *et al.* : J. Am. Chem. Soc., **76**, 3463 (1954); **77**, 6234, 6237, 6239, 6241, 6245, (1955); N.J. Leonard, D.F. Morrow, M.T. Rogers : *Ibid.*, **79**, 5476 (1957); F.A.L. Anet, A.S. Bailey, R. Robinson : Chem. & Ind. (London), **1953**, 944.

its tautomeric form $HN-C=O$ in cases of the above three reactions. In order to make sure that the tertiary hydroxyl group of (I) is really taking a rôle in the masked amino ketone group, ketodihydropseudokobusinone (IX)[1] or its methiodide was subjected to acetylation, cyanogen bromide degradation and alkaline treatment. Corresponding N-acet or N-cyano triketone compounds (XI, XII) was obtained as syrups, accompanied with the formation of the crystalline O-acetate (X) which had been reported[1] previously in the case of acetylation, and their structures (XI, XII) were assumed from characteristic infrared band of N-acetyl or N-cyano group at 1632 or 2221 cm^{-1}. Ketodihydropseudokobusinone (IX) was recovered when the N-acetyl triketone (XI) was hydrolyzed with 20% potassium hydroxide at the elevated temperature. N-Methyl triketone compound (XIV), m.p. 207~210°, ν_{max}^{Nujol} 1714, 1708, 1683 cm^{-1} (*Anal.* Calcd. for $C_{21}H_{27}O_3N$: C, 73.87; H, 7.97. Found : C, 73.94; H, 8.25) was obtained from ketodihydropseudokobusinone methiodide (XIII), m.p. 252~254° (decomp.) (*Anal.* Calcd. for $C_{20}H_{25}O_3N \cdot CH_3I \cdot H_2O$: C, 51.78; H, 6.21. Found : C, 51.97; H, 6,11) by the alkaline treatment. The newly formed ketone absorbed at the longer wave length (1683 cm^{-1}) and no hydroxyl group was detected in its infrared region.

The study of nuclear magnetic resonance of pseudokobusine derivatives provided a knowledge about the relationship between the angular C-methyl group and this tertiary hydroxyl group of the masked amino ketone system. The nuclear magnetic resonance signal*[2] of angular methyl protons of ketodihydropseudokobusinone (IX) was observed at 8.64 τ as a singlet, whereas that of its O-acetate (X) at 8.94 τ. Thus the angular methyl protons of (IX) was under a certain influence of the hydroxyl group and their resonance signal appeared at the lower field than usual. When the free hydroxyl was acetylated, the chemical shift of the methyl protons resumed to a normal value in the case of (X). The angular methyl protons of pseudokobusine methochloride, m.p. 273~275° (decomp.) (*Anal.* Calcd. for $C_{20}H_{27}O_3N \cdot CH_3Cl \cdot \frac{1}{2}H_2O$: C, 64.85; H, 8.03; N, 3.63. Found : C, 64.47; H, 8.00; N, 3.85) showed the same chemical shift at 3.22 p.p.m.*[3] from DHO as those of (IX)-methochloride, m.p. >290° (*Anal.* Calcd. for $C_{20}H_{25}O_3N \cdot CH_3Cl \cdot H_2O$: C, 63.70; H, 7.64; N, 3.54. Found : C, 63.14; H, 7.43; N, 3.26) and this signal was at the lower field than that (3.48 p.p.m.) of methochloride of kobusine, m.p. 302~305° (decomp.) (*Anal.* Calcd. for $C_{20}H_{27}O_2N \cdot CH_3Cl$: C, 69.31; H, 8.31; N, 3.85. Found : C, 69.34; H, 8.23; N, 3.89), which has been confirmed to possess no tertiary hydroxyl group,[6,7] and it would be estimated that the methyl protons of pseudokobusine were suffered from the down-field shift by approximately 0.26 p.p.m. due to the tertiary hydroxyl group. Model study of this nuclear magnetic resonance phenomenon was carried out[8] using steroid derivatives with hydroxyl substituents and it has been reported that the methyl proton signals were shifted to down-field by 0.180~0.247 p.p.m. with a hydroxyl group at the 1,3-diaxial relationship versus 18 or 19 C-methyl group and these signals which had been affected were shifted upward from their down-field positions, when the hydroxyl group was acetylated. This fact supports the spacially close position of the tertiary hydroxyl group to the angular methyl in the structure of pseudokobusine (I).

Out of three hydroxyl groups of pseudokobusine, the tertiary hydroxy was thus proved to form a masked amino ketone with the tertiary nitrogen atom and one of two secondary hydroxyls has been shown[1] in the allyl alcoholic function. The location of the remaining hydroxyl is to be determined in chemical reactions with relation to the allyl alcoholic grouping. N-acetyl-seco-pseudokobusine (II) was oxidized with osmium

*3 Varian DP 60 spectrometer at 60 Mc. in D_2O solution.

6) T. Okamoto : This Bulletin, **7**, 44 (1959).

7) T. Okamoto, M. Natsume, H. Zenda, S. Kamata : *Ibid.*, **10**, 883 (1962).

8) Y. Kawazoe, *et al.* : *Ibid.*, **10**, 338 (1962).

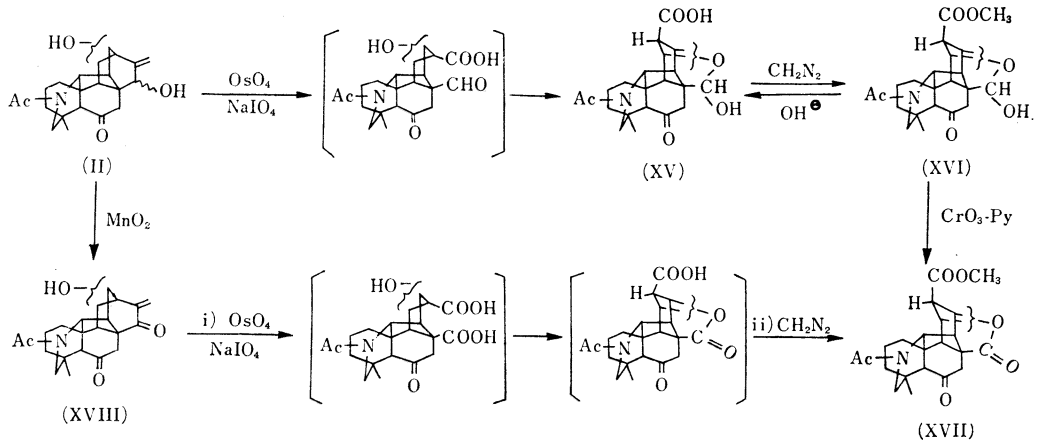


Chart 3.

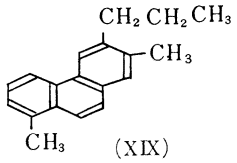
tetroxide-sodium metaperiodate[9] to yield a monocarboxylic acid (XV), m.p. 277~278° (decomp.), ν_{max}^{KBr} ~1720, 1605 cm^{-1} (*Anal.* Calcd. for $C_{21}H_{27}O_6N$: C, 64.76; H, 6.99. Found : C, 64.02; H, 6.70). Its methyl ester (XVI), m.p. 238~240° (decomp.), ν_{max}^{KBr} 1736 (ester), 1696 (ketone), 1621 (N-Ac) cm^{-1} (*Anal.* Calcd. for $C_{22}H_{29}O_6N$: C, 65.49; H, 7.25. Found : C, 65.41, 65.17; H, 7.32, 7.63) was obtained by treatment with diazomethane and the ester (XVI) was converted back to the carboxylic acid (XV) by mild alkaline saponification at room temperature. The ester (XVI) still possessed a hydroxyl group, so that it was oxidized with chromium trioxide-pyridine complex. A crystalline compound (XVII), m.p. 216~217°, ν_{max}^{KBr} 1778, 1728 (ester), 1699 (ketone), 1630 (N-Ac) cm^{-1} (*Anal.* Calcd. for $C_{22}H_{27}O_6N \cdot \frac{1}{2}H_2O$: C, 64.44; H, 6.87. Found : C, 64.90; H, 6.60) was obtained, whose infrared absorption spectrum revealed the formation of a new carbonyl band at the shorter wave length contrary to the expectation obtaining a ketone function in a six-membered ring. The new carbonyl group formed here was determined to be a lactone group from the following experiment.

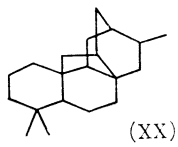
The allyl alcoholic function of N-acetyl-seco-pseudokobusine (II) was converted to an α,β-unsaturated ketone system by oxidation with manganese dioxide,[10] and resulting N-acetyl-seco-pseudokobusinone (XVIII), m.p. 301~302° (decomp.), ν_{max}^{Nujol} 3420 (OH), 1699 (isolate ketone), 1692 (conjugated ketone), 1630 (N-Ac and double bond) cm^{-1}, λ_{max}^{EtOH} 225~228 mμ (ε 9680) (*Anal.* Calcd. for $C_{22}H_{27}O_4N$: C, 71.52; H, 7.37; N, 3.79. Found : C, 71.20; H, 7.28; N, 3.79) was subjected to the osmium tetroxideperiodate oxidation, followed by esterification with diazomethane. The product obtained here, m.p. 216~217°, was identified as (XVII), meaning that the functional group of infrared band at 1778 cm^{-1} in (XVII) was a γ-lactone. This fact, in other words, provides an evidence for the location of the hydroxyl group in question and it is limited to be at δ-position with respect to the carbon atom having the allyl alcoholic hydroxyl in the structure of pseudokobusine (I).

Selenium dehydrogenation of pseudokobusine (I) was reported[1] to give 1,7-dimethyl-6-propylphenanthrene (XIX) and this result suggested the carbon skeleton of pseudokobusine would be (XX) analogous to the domestic aconite alkaloids, ignavine[11] and hypognavine.[12] Considering the fact that pseudokobusine has the masked amino ketone

9) R. Pappo, D.S. Allen, R.U. Lemieux, W.S. Johnson : J. Org. Chem., **21**, 478 (1956).
10) S. Attenburrow, F.F.B. Cameron, J.H. Chapman, R.M. Evans, B.A. Hems, A.B.A. Jansen, T. Walker : J. Chem. Soc., **1952**, 1094.
11) E. Ochiai, T. Okamoto : This Bulletin, **7**, 550, 556 (1959).
12) S. Sakai : *Ibid.*, **7**, 50, 55 (1959).

goup $\overset{|}{N}-\overset{|}{C}-OH$, whose hydroxyl group is spacially close to the angular methyl group and the alkaloid has also the allyl alcoholic group with one more hydroxyl group as illustrated in a partial structure (XXI), the structure of pseudokobusine is represented either by (Ia) or (Ib).


(XIX)


(XX)

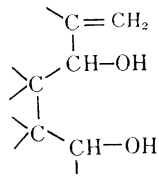

(XXI)

Chart 4.

The author expresses his deep gratitude to Prof. Emeritus E. Ochiai and Prof. T. Okamoto for their helpful suggestions and he is also indebted to Mr. Y. Kawazoe for his nuclear magnetic resonance measurement and discussions. Thanks are due to Dr. K. Nukada, Goverment Chemical Industrial Research Institute, Tokyo and Mr. N. Hayakawa, Japan Institute for Atomic Energy for the use of nuclear magnetic resonance spectrometers and the members of the Analysis Center of this Faculty for elementary analyses and spectral measurements.

Faculty of Pharmaceutical Sciences,
University of Tokyo,
Hongo, Tokyo.

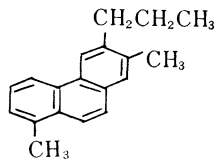
Mitsutaka Natsume (夏目充隆)

June 8, 1962

UDC 547.94.02:582.675.1

Structural Correlation of Kobusine to Pseudokobusine

In the previous paper[1] concerning the structural study of an aconite alkaloid, kobusine,*1 $C_{20}H_{27}O_2N$, it was reported that all oxygen functions of kobusine are secondary hydroxyl groups which are located on six-membered rings and one of the two hydroxyl groups consists of an allyl alcoholic grouping of the type $H_2C=\overset{|}{C}-\overset{|}{C}-OH$. Selenium dehydrogenation reaction of kobusine was carried out[2] and 1,7-dimethyl-6-propylphenanthrene (I) was isolated from the neutral portion of the degradation mixture. On


(I)

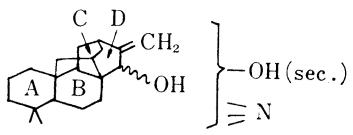

(II)

Chart 1.

*1 Kobusine is obtained from aconite roots in Hokkaido, which is assumed to be *Aconitum yesoensis* Nakai.

1) T. Okamoto : This Bulletin, **7**, 44 (1959).
2) M. Natsume : *Ibid.*, **7**, 539 (1959).