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ON THE STRUCTURE OF MIYACONITINE

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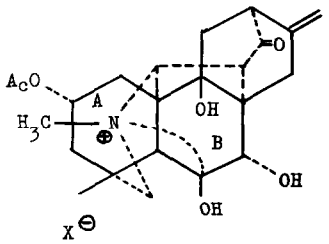
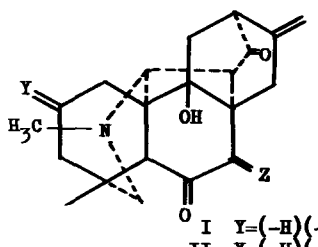
Miyaconitine (I) and miyaconitinone (II), the major alkaloids from Aconitum miyabei Nakai, have been studied in our laboratories (1-4). On the basis of the chemical and spectral data found in continuing investigations as well as the biogenetical consideration, we have arrived at a conclusion that formulas I and II are most valid for these alkaloids. An independent X-ray crystallographic analysis of miyaconitine hydrobromide dihydrate has established its three-dimensional structure including the absolute configuration which correspond to Ia', as will be described in the accompanying paper by H. Shimanouchi, Y. Sasada and T. Takeda(5).



Ia X = ClO_4
Ia' X = Br



I Y=(-H)(—OAc) Z=(-H)(—OH)
II Y=(-H)(—OAc) Z=O
IV Y=(-H)(—OH) Z=O
V Y=O Z=O

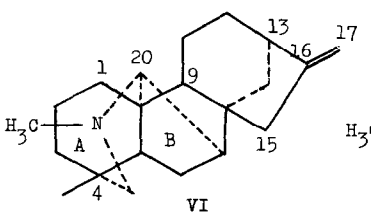
The high resolution mass spectra of I and II (M^+ 415.20 and 413.19) established the respective molecular formulas $C_{23}H_{29}O_6N$ and $C_{23}H_{27}O_6N$ (cf. refs. 1 and 4). Both alkaloids form the corresponding perchlorates (Ia and IIa) (1), resist acetylation (AcCl or Ac_2O in pyridine) (1) and have been correlated by conversion of I into II by oxidation (CrO_3 or Bi_2O_3 in AcOH) (1,4). This corelation has been demonstrated by the color reaction not only for aldehyde or α-ketol reagents (4) but also for an α-diketone reagent: II was positive to o-dinitrobenzene

test (6) but negative in the absence of formalin, while I was positive under the latter conditions.

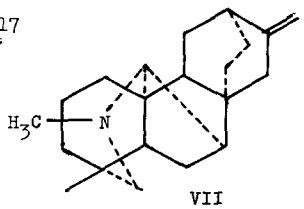
Alkaloid I on hydrogenation (Pt in EtOH) formed its dihydro derivative (III) $C_{23}H_{31}O_6N$ (M^+ 417.49; Found; C, 65.82; H, 7.57; N, 3.22%), m.p. 168-170°C. Hydrolysis of II with acid proceeded smoothly without skeletal rearrangement to give miyaconinone (IV) $C_{21}H_{25}O_5N$ (1,4), which on acetylation (only AcCl) was reconverted into II. Further oxidation of IV (CrO_3 in H_2SO_4 or MnO_2 in $CHCl_3$) afforded its dehydro derivative (V) $C_{21}H_{23}O_5N$ (Found; C, 67.93; H, 6.61; N, 3.75%), m.p. 273-274°C. Compounds II, IV and V consumed only 1 mole of periodic acid, although the rate varied depending on the solvent acidity (cf. ref. 4).

These chemical reactions and the UV (EtOH), IR (KBr) and NMR spectra ($CDCl_3$) (7) indicate that I contains the following structural units: a tertiary methyl group [I, τ 8.45 (3H, s); II, τ 8.62 (3H, s); V, τ 8.48 (3H, s)]; a terminal methylene group (I, τ 5.05 (2H, br d), ν_{max} 1648 and 877 cm^{-1} (4); II, τ 5.03 (2H, br d), ν_{max} 1648 and 883 cm^{-1} (4); III, no distinct absorption maximum near 880 cm^{-1}; IV, ν_{max} (Nujol) 1655 and 882 cm^{-1}; V, τ 4.90 (2H, br d), ν_{max} 1645 and 887 cm^{-1}]; an acetoxyl group (AcO-CH) [I, τ 7.96 (3H, s) and 4.81 (1H, br W_H = 10 c/s), ν_{max} 1730 and 1250 cm^{-1}; IV, no absorption maximum near 1730 cm^{-1}; V, no sharp signals at τ 7.6 - 8.4]; an N-methyl group (I, τ 7.60 (3H, s); II, τ 7.72 (3H, s); V, τ 7.74 (3H, s)]; a secondary and a tertiary hydroxyl groups (I, τ 6.03 (1H, s), ν_{max} 3470 cm^{-1} (4); III, ν_{max} 3620 and 3460 cm^{-1}; IV, ν_{max} 3450 and 3370 cm^{-1}; V, no signal near τ 6.0; ν_{max} 3460 cm^{-1}]; two carbonyl groups [I, ν_{max} ca. 1715 (sh) (cf. ref. 4) and 1678 cm^{-1} (4); Ia, ν_{max} 1701 cm^{-1}; II, ν_{max} 1715 (br, two C=O) and 1676 cm^{-1} (4); IIa, ν_{max} 1712 (br, two C=O); III, ν_{max} 1706 and 1673 cm^{-1}; IV, ν_{max} 1724, 1717 and 1678 cm^{-1} (cf. ref. 4); V, ν_{max} 1724 - 1692 cm^{-1} (br, four C=O)]. Hence the molecular formulas of both alkaloids are extended as shown in the following:

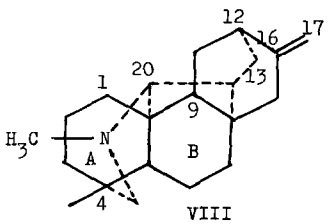
$C_{20}H_{21}(OH)_2(=O)_2(OCOCH_3)(NCH_3)$ for I and $C_{20}H_{20}(OH)(=O)_3(OCOCH_3)(NCH_3)$ for II. Therefore, these compounds involve a $C_{20}H_{29}N$ unit as a fundamental base. On the basis of this fundamental formula as well as the biogenetical consideration, the following three structures, one being of kaurenoid type and the other of atisirenoid, would be proposed as possible formulas for the $C_{20}H_{29}N$ base(8).



VI



VII

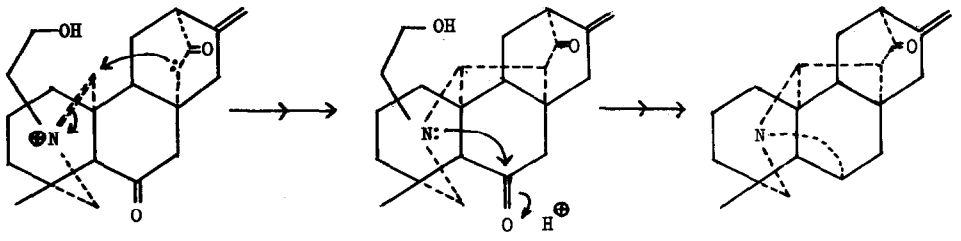


VIII

The carbonyl absorption maxima at remarkably low frequencies (1678 and 1676 cm^{-1}) in the IR spectra of I and II disappeared on formation of the respective perchlorates Ia and IIa. In addition, the absorption [λ_{max} ca. 423 mμ (log ε ca. 1.6)] characteristic for an α-diketone moiety in the UV spectrum of II also disappeared on the same transformation. On the other hand, I and Ia exhibited carbonyl absorptions with increased intensity [λ_{max} 288 mμ (log ε 2.6) and 295 (2.6), respectively], while III that with normal intensity [λ_{max} 290 mμ (log ε 1.6)]. These facts are explicable well if one of the two carbonyl groups in I, composing an α-ketol grouping with the secondary hydroxyl group, is located at the position (B or A ring) where the formation of a N^+-C(OH) bond is possible, and another at the β-position to the double bond. Furthermore, the UV and IR spectra changed extraordinarily on passing from IV to V[λ_{max} 294 mμ (log ε 2.6) to λ_{infl} 286 mμ (log ε 3.0) and 342 (2.1) and ν_{max} 1678 to 1692 cm^{-1}]. This strongly suggests that the newly formed C=O group in V, formed by transformation of the acetoxyl group in I, would be situated closely (A or B ring) to the nitrogen atom. Finally, the color reaction (NN'-dimethylaminobenzaldehyde test, V positive and IV negative) and the NMR spectrum of v (four proton multiplet, τ 7.09 and W_H 25 c/s) indicated that at least an active methylene group would exist adjacently to the new C=O group of V in question. This finding implies that the acetoxyl and α-ketol groups are located in the A and B rings, respectively, and hence formula VIII is preferable to those VI and VII as the fundamental skeleton of I. In view of the periodic acid oxidation data the β,γ-unsaturated carbonyl and tertiary hydroxyl groups must be disposed at C_{13} and C_9, respectively. Thus the alkaloids are most favorably represented by (planar) formulas I and II. The absolute configuration of I has been determined by the X-ray analysis of the hydrobromide (Ia'), and the transformation of I to Ia' is interpretable well in terms of the trans-annular effect.

It is to be noted that these alkaloids I and II are regarded as biogenetic intermediates

in the transformation from atisine skeleton ($C_{20}H_{31}N$ base) to hetisine ($C_{20}H_{27}N$ base) in Aconitum alkaloids, as shown in the following scheme.



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References

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2) S. Kakimoto, Bull. Chem. Soc. Japan 32, 349 (1959).

3) H. Suginome and S. Kakimoto, Ibid. 32, 352 (1959).

4) S. Kakimoto, N. Katsui and Y. Ichinohe, Ibid. 32, 1153 (1959).

5) H. Shimanouchi, Y. Sasada and T. Takeda, the following paper.

6) F. Feigl and C. C. Neto, Anal. Chem. 28, 377 (1956).

7) Abbreviations; s, singlet; d, doublet; br, broad; sh, shoulder; infl, inflexion.

8) E.g. S. W. Pelletier, Quarterly Reviews 21, 525 (1967).