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ACUTUMINE AND ACUTUMIDINE, CHLORINE CONTAINING ALKALOIDS WITH A NOVEL SKELETON (2) : CHEMICAL PROOF

M. Tomita, Y. Okamoto, T. Kikuchi and K. Osaki

Faculty of Pharmaceutical Sciences, Kyoto University, Kyoto, Japan

M. Nishikawa and K. Kamiya

Chemical Research Laboratories, Takeda Chemical Industries, Ltd., Osaka, Japan

Y. Sasaki and K. Matoba

Faculty of Pharmaceutical Sciences, Osaka University, Osaka, Japan

K. Goto

Wakabayashi-cho, Setagaya-ku, Tokyo, Japan.

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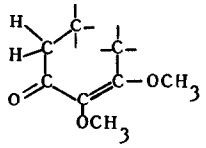
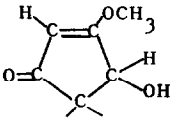
In the preceding paper[1], we reported the structure determination of acutumine (IVa) and acutumidine (IVb), isolated from Sinomenium acutum REHD. et WILS. and Menispermum dauricum DC., by X-ray analysis. In parallel, a series of degradative reactions has also been carried out and the evidences which give chemical support for the structures of these novel type alkaloids are presented in this communication.

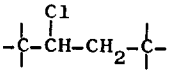
Based on the experimental evidences previously reported[2] and the additional findings, three revised partial structures (I, II and III) are proposed.



I



II



III

As already reported, acutumine has a tetrasubstituted six (or more)-membered α,β-unsaturated ketone system carrying one or two methoxyl groups at α and β position. Hydrogenation of acutumine acetate (IVc) over PtO_2 led to reduction of the double bond of this conj. ketone system and gave a dihydro compound (V), $C_{21}H_{28}NO_7Cl$, m.p. 230-231°. Its NMR spectrum exhibits a pair of AB doublet at 5.45 and 6.60τ (2H, J= 10 cps), which can be ascribed to the newly introduced hydrogens geminal to the methoxyl groups. This observation

indicates the absence of allylic proton in this system. In addition, the NMR spectrum of N,O-dibenzoylacutumidine shows a sharp AB quartet at 7.73τ ($\Delta\delta$= 2.35 ppm, J=17.5 cps) due to the methylene group adjacent to the carbonyl group. These findings are consistently explained by the structure (I).

The partial structure (II) may be proposed from the following evidences: (a) As previously reported, acutumine has a secondary allyl alcohol system and the hydrogen geminal to the hydroxyl group couples only with the vinylic-H. (b) Treatment of acutumine acetate(IVc) with $NaBH_4$ gave a hydroxy compound (VI), whose spectral data suggested that the reduction had occurred at the carbonyl group in the structure I. The compound (VI) was shown to have a positive Cotton effect at 304 mμ in its CD curve, indicating the presence of one more conj. ketone system in acutumine. Therefore, the IR absorption at 1690 cm^{-1} and the UV band at 245 mμ of various acutumine derivatives, which were erroneously assigned to a diene system in the previous communication[2], are now ascribed more likely to a hindered five-membered conj. ketone system. (c) Reduction of acutumine acetate (IVc) with $LiAlH_4$ led to a demethoxy-dihydroxy-ketone (VII), $C_{18}H_{26}NO_5Cl$, m.p. 136-137°, which exhibits a five-membered carbonyl band at 1730 cm^{-1} in the IR spectrum and still shows a positive Cotton effect in the CD curve. (d) The dehydro product (VIII) of acutumine obtained by oxidation with MnO_2 shows IR absorption bands at 1745 and 1695 cm^{-1} which can be attributed to five-membered ene-dione system. The UV and NMR spectra of this product also show the expected change.

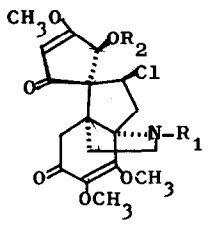
The third partial structure (III) followed mainly from the spectral evidences. The NMR spectra of a series of acutumine derivatives exhibit an one-proton quartet at 4.7-5.5τ region which would best be attributed to the proton on the chlorine-carrying carbon atom. This signal is found to be the X portion of ABX type splitting, the AB portion of which appears in the expected pattern at ca. 7.1-7.4τ region: e.g., the spectrum of O-acetyl acutumidine N-cyanide reveals a sharp quartet (1H, J=8, 11 cps) at 5.57τ and typical two-proton signals of AB portion at 7.12τ. This observation strongly supports the presence of structure (III) in acutumine.

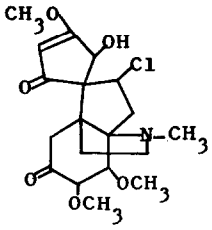
Evidence for the skeletal structure of the alkaloids was advanced as

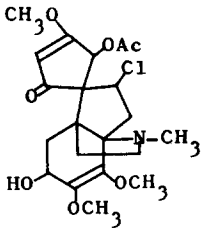
follows. Treatment of acutumine with Zn in boiling Ac_2O afforded a mixture, the neutral fraction of which afforded two aromatic, N-free products.

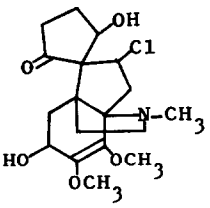
The major product (IXa) shows IR$\nu_{max}^{CHCl_3}$ 1750 cm^{-1} (OAc), 1700 (C=O); NMR ($CDCl_3$) τ : 7.72, 7.85 (6H, 2xOAc), 6.07, 6.11, 6.18 (9H, 3xOCH_3), 4.50 (1H, s., olefinic H), 4.19 (1H, s., C<u>H</u>-OAc), 3.56 (1H, s., aromatic H); UVλ_{max}^{EtOH} mμ 233, 284, 304. These spectral properties are in good agreement with the structure IXa. Mild hydrolysis of this product yielded a phenolic compound, UVλ_{max}^{EtOH} mμ 233, 280, 310; UV$\lambda_{max}^{EtOH-KOH}$ mμ 236, 296, which was subsequently methylated with diazomethane to afford an O-methyl ether (IXb). On acetylation with Ac_2O-Py., it gave an acetate (IXc), IR$\nu_{max}^{CHCl_3}$ 1745 cm^{-1}(OAc), NMR($CDCl_3$) τ : 7.85 (3H, OAc), 6.21, 6.18, 6.10, 6.06 (12H, 4xOCH_3), 4.46 (1H, s., olefinic H), 4.22 (1H, s., C<u>H</u>-OAc), 3.74 (1H, s., aromatic H); UVλ_{max}^{EtOH} mμ 234, 276, 285 (ϵ 12400, 1780, 1590), MS m/e: 362 (M^+). Inspection of NMR spectra of the above degradation products (IXa, IXb, IXc) indicates that the partial structure (II) proposed for acutumine might remain unchanged in these products. The MnO_2 oxydation of the methyl ether (IXb) was also accomplished in a parallel manner with acutumine, whereby obtained an ene-dione compound (XI), m.p.154-156°, IR$\nu_{max}^{CHCl_3}$ 1745 and 1690 cm^{-1}, UVλ_{max}^{EtOH} 263 mμ. When oxidized with $KMnO_4$, IXb gave a product (XII), m.p. 75-77°, $C_{12}H_{14}O_4$, IR$\nu_{max}^{CHCl_3}$ 1695 cm^{-1}, NMR($CDCl_3$) τ : 6.11, 6.05, 6.03 (9H, 3xOCH_3), 2.98 (1H, s., aromatic H), 6.8-7.5 (4H, A_2B_2 pattern); UVλ_{max}^{EtOH} mμ 270, 310 (ϵ 13700, 6310), MS m/e: 222 (M^+). This product was identified as 4,5,6-trimethoxy-1-indanone (XII) by direct comparison with the synthetic sample. From these results, the major product obtained by the Zn-Ac_2O reaction of acutumine should be assigned to the structure IXa.

On the other hand, another degradation product (Xa) was found to contain a chlorine atom. Mild saponification of this product followed by methylation afforded an O-methyl ether (Xb), m.p. 219-221.5°(decomp.), NMR($CDCl_3$) τ : 7.20 (1H, d., J=8 cps, CH-O<u>H</u>), 6.02, 6.20, 6.25 (9H, 3xOCH_3), 5.10 (1H, t., J=9 cps, CH_2-C<u>H</u>(Cl)), 5.08 (1H, d., J= 8 cps, C<u>H</u>-OH; s. on addition of D_2O), 6.5-6.8 (2H, -CH_2-), 4.62 (1H, s., olefinic H), 3.95, 3.67 (2H, 2xd., J= 2 cps, aromatic H); IR$\nu_{max}^{CHCl_3}$ 1700 cm^{-1}, UVλ_{max}^{EtOH} mμ 234, 279, 286 (ϵ 29090, 2630, 2670); MS m/e: 324 (M^+). On reduction with $LiAlH_4$ followed by $KMnO_4$ oxidation, it gave a







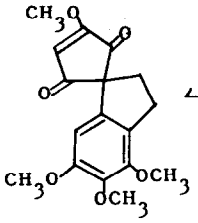


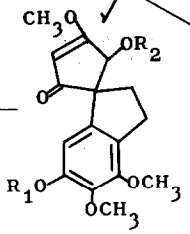
IVa $R_1=CH_3$, $R_2=H$

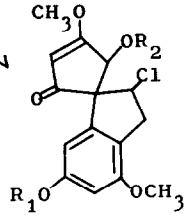
IVb $R_1=R_2=H$

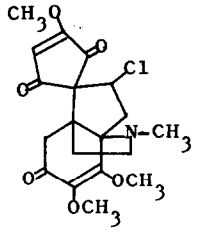
IVc $R_1=CH_3$, $R_2=Ac$

V VI VII









XI

IXa $R_1=R_2=Ac$

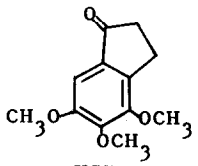
IXb $R_1=CH_3$, $R_2=H$

IXc $R_1=CH_3$, $R_2=Ac$

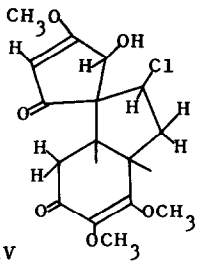
Xa $R_1=R_2=Ac$

Xb $R_1=CH_3$, $R_2=H$

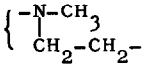
VIII

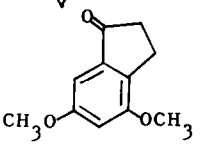


XII

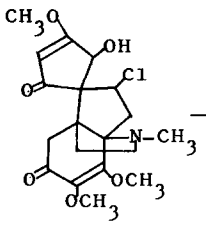


XIV

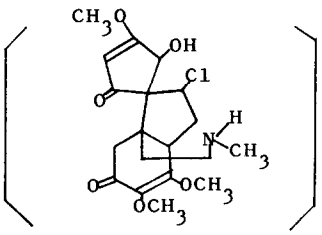




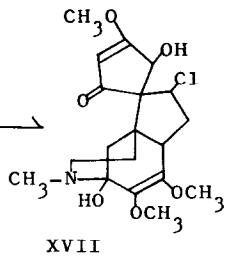
XIII



XV



XVI



XVII

small amount of crystals, $C_{11}H_{12}O_3$ (MS m/e: 192), m.p. 92-96°, IR$\nu_{max}^{CHCl_3}$ 1700 cm^{-1}, NMR($CDCl_3$) τ : 6.18, 6.13 (6H, 2xOCH_3), 3.37, 3.22 (2H, d., J= 2 cps, aromatic H); 6.9-7.5 (4H, A_2B_2 pattern); UVλ_{max}^{EtOH} 262, 324 mμ, which was considered to be 4,6-dimethoxy-1-indanone (XIII) from the spectral data.

In the NMR spectrum of the methyl ether, one-proton triplet at 5.10τ and two-proton signals at 6.5-6.8τ may be regarded as a typical AB_2 type splitting arising from CH(Cl)-CH_2 grouping. The chemical shift value of the latter signals strongly suggests that the methylene group must situate at benzylic position. Therefore, the structure of the methyl ether can be depicted as Xb.

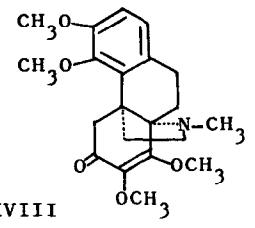
From the foregoing observations, the structure of acutumine may now be expanded to the formula XIV. The remaining moiety (C_3H_7N) was considered to form a $-CH_2-CH_2-N(CH_3)-$ grouping based on NMR study.

The nitrogen end of ethanamine bridge was believed to attach to the allylic position of six-membered conj. ketone system in view of the weak basicity of the alkaloid. A chemical support was provided by the reduction of acutumine with Zn-AcOH, whereupon was obtained a dihydro compound (XVII), $C_{19}H_{26}O_6NCl$, m.p. 168-171°, pKa 6.8 (50% EtOH), IR$\nu_{max}^{CHCl_3}$ cm^{-1} 3400 (OH), 1690 (five-membered conj. ketone), 1610; NMR($CDCl_3$) τ : 7.62 (3H, NCH_3), 6.46, 6.22, 6.10 (9H, 3xOCH_3), 4.70, 5.29 (2H, 2xd., J= 0.8 cps, C<u>H</u>=C-C<u>H</u>-OH), 5.30 (1H, t., J= 9 cps, CH_2-C<u>H</u>(Cl)); UVλ_{max}^{EtOH} 241 mμ (five-membered conj. ketone), MS m/e: 399 (M^+). Acetylation of this product with Ac_2O-Py. afforded a mono acetate which still has one hydroxy group. Although the dihydro compound and its acetate show no characteristic absorption band of six-membered conj. ketone system, they gave an N,O-diacetate upon treatment with Ac_2O-NaOAc, which shows again the absorption band arising from the six-membered conj. ketone system at 270 mμ in the UV spectrum. Consequently, the dihydro compound is most likely a carbinolamine (XVII) formed by cyclization of the normal reduction product (XVI). Further study on this dihydro product is now in progress.

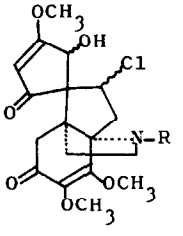
On the basis of the chemical evidences so far presented, the structure of acutumine should be XV, except for stereochemistry.

Our attention was then turned to the absolute configuration around the ethanamine bridge in the alkaloids. The CD curves of acutumine and acutumidine

have a negative Cotton effect near 320 mμ ([θ] -37.2 and -29.8, respectively), which may be attributed to the $n \longrightarrow \pi^*$ transition of six-membered α,β-unsaturated ketone system, since the $NaBH_4$ reduction product (VI) of acutumine acetate shows a weak positive Cotton effect ([θ] + 8.25) at 304 mμ. That is comparable with the Cotton effect ([θ] -23.09 at 320 mμ) of hasubanonine (XVIII)[3] carrying the same structural feature of established absolute configuration.



XVIII



XIXa R= CH_3

XIXb R= H

The structure of acutumine and acutumidine can therefore be represented by the formula XIXa and XIXb, respectively. As to the stereochemistry of the five-membered spiro-ring and of the chlorine atom, chemical indication is not available at present, but the formulas XIXa and XIXb are in accordance with the result obtained from X-ray analysis of acutumine (IVa).

It is pertinent to note here that the established structure of acutumine (IVa) is closely related to the structure of hasubanonine (XVIII)[3] isolated from *Stephania japonica* MIERS, a plant of the same Menispermaceae, and both alkaloids might be biosynthesized through an analogous precursor.

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