[Chem. Pharm. Bull. 19(4) 770—791 (1971)]

UDC 547.94.02.05 : 581.192 : 582.675.4

# Studies on the Alkaloids of Menispermaceous Plants. CCLIX.[1] Alkaloids of *Menispermum dauricum* DC. (*Suppl.* 7).[1] Structures of Acutumine and Acutumidine,[2] Chlorine-Containing Alkaloids with a Novel Skeleton

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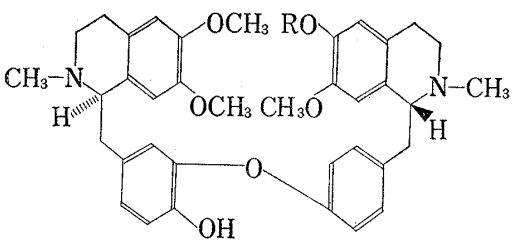
(Received October 24, 1970)

Structures of acutumine (XXXVIIa) and acutumidine (XXXVIIb), isolated from *Menispermum dauricum* DC. and *Sinomenium acutum* Rehd. et Wils. (Menispermaceae), were investigated. On the basis of a series of degradative and spectroscopic evidences, their structures including absolute stereochemistry are assigned to the formula XXXVIIa and XXXVIIb, respectively, which are in good agreement with the result obtained from the X-ray analyses of acutumine and acetylacutumine. Apparently, these alkaloids represent a new class of alkaloids with a novel skeleton and also provide rare examples of chlorine-containing alkaloids.

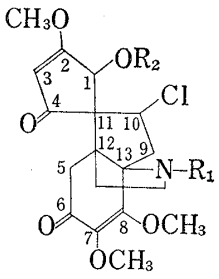
Acutumine was first isolated from *Sinomenium acutum* Rehd. et Wils. (Menispermaceae, Japanese name: Oh-tsuzurafuji) by K. Goto and H. Sudzuki,[4] who proposed an empirical formula either $C_{20}H_{27}O_8N$ or $C_{21}H_{27}O_8N$ for this alkaloid and suggested the presence of a ketone, a carboxyl, an N-methyl, and three methoxyl groups. Ever since no further investigation on the structure of this alkaloid had been made and its structure has long been unknown.

In the course of our recent investigation on the tertiary base fraction from *Menispermum dauricum* DC. (Japanese name: Kohmori-kazura), a Menispermaceous plant, small amounts of two crystalline alkaloids were newly isolated together with two biscoclaurine-type alkaloids,[5] dauricine(Ia)[6] and daurinoline(Ib).[7] One of them was proved to be identical with acutumine by direct comparison of infrared(IR) spectra and mixed melting point determination with an authentic sample, and the other was found to be the N-nor base of acutumine, for which we proposed the name acutumidine. Both were also isolated from *Sinomenium acutum* Rehd. et Wils. In this paper we wish to present full details of structure elucidation of these alkaloids. As will be clear in the sequel, they represent a new class of alkaloids with a novel skeleton and also provide very rare examples of chlorine-containing alkaloid.[8] For the con-

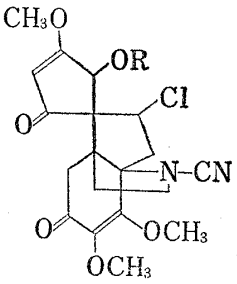
1) Part CCLVIII: M. Tomita, Y. Okamoto, Y. Nagai, S. Tanaka, and T. Hayata, *Yakugaku Zasshi*, **90**, 1182 (1970).
2) Preliminary communications of this work appeared in *Tetrahedron Letters*, **1967**, 2421, 2425.
3) Location: *a*) *Misasagi, Yamashina, Higashiyama-ku, Kyoto*; *b*) *Shimoadachi-cho, Sakyo-ku, Kyoto*; *c*) *4, Nishinocho, Juso, Higashiyodogawa-ku, Osaka*; *d*) *6-5, Toneyama, Toyonaka-city, Osaka.*
4) K. Goto and H. Sudzuki, *Bull. Chem. Soc. Japan*, **4**, 220 (1929).
5) Another dauricine-type alkaloid, dauricoline, has been isolated from the same plant. See M. Tomita, Y. Okamoto, Y. Nagai, K. Kitayama, and H. Yanagawa, *Yakugaku Zasshi*, **90**, 1178 (1970).
6) "Celebration Publication for the Retirement of Professor Masao Tomita, 1926—1967," Hirokawa Publishing Co., Tokyo, Japan, 1967, p. 85.
7) Ref. 6), p. 86.
8) It should be noted that recently Gordon-Gray reported the isolation of a chlorine-containing alkaloid, chlorodeoxysceleratine, from a *Senecio* species. This alkaloid has been shown to be the diester of retronecine with scleratinic acid, a diacid carrying a chlorine atom. See C. G. Gordon-Gray, *J. Chem. Soc.* (*C*), **1967**, 781.



Ia : R=$CH_3$
Ib : R=H



IIa : $R_1$=$CH_3$, $R_2$=H
IIb : $R_1$=$R_2$=H
IIc : $R_1$=$CH_3$, $R_2$=Ac
IId : $R_1$=$CH_3$, $R_2$=$COC_6H_5$
IIe : $R_1$=$R_2$=Ac
IIf : $R_1$=$R_2$=$COC_6H_5$



IIIa : R=H
IIIb : R=Ac

Chart 1

venience, we will at the outset give the correct plane structures and present later the relevant evidences and their stereochemistry.

The isolation scheme of acutumine(IIa) and acutumidine(IIb) from the plant materials and their approximate yields were given in Chart 2, taking, for instance, the case of *M. dauricum*. It should be noted herewith that the separation of the crystalline mixture obtained from the chloroform extract into acutumine and acutumidine was effectively achieved by taking advantage of the remarkable difference of solubility in acetonitrile, while the usual chromatographic technique was inpractical because of the insolubility of both alkaloids in ordinary organic solvents.

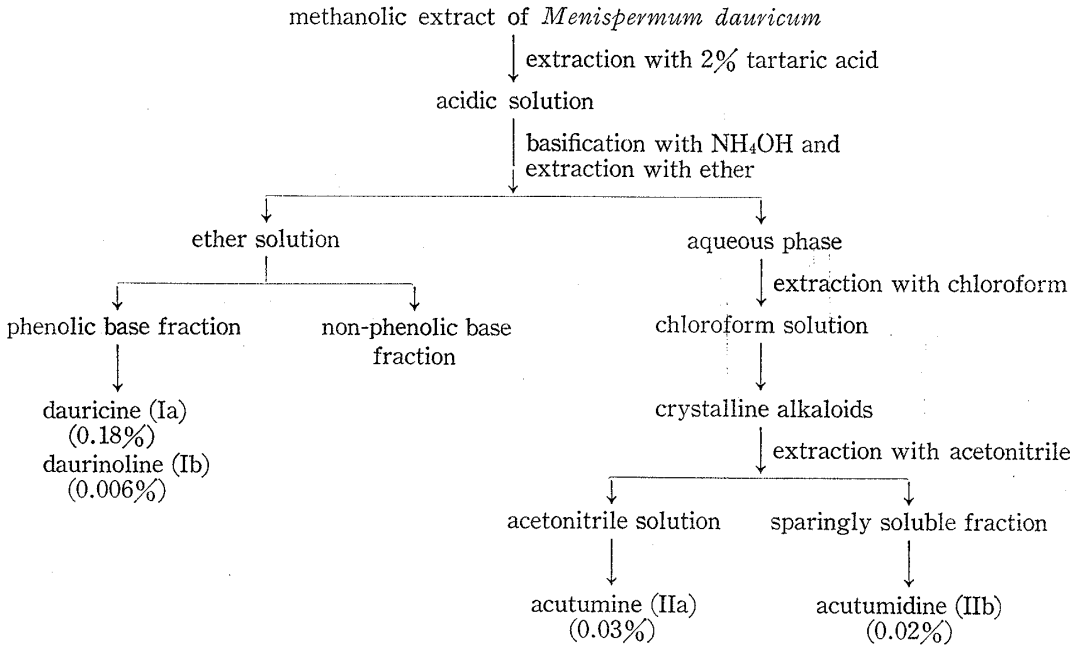



Chart 2. Scheme of Isolation and Yields of Alkaloids

Acutumine (IIa), mp 238—240° (decomp.), $[\alpha]_D$ −206° (pyridine), is a very weak base ($pK_a$ 5.3 in 50% ethanol) and it is moderately stable in acidic medium, but considerably unstable in alkaline medium. It gave a positive reaction to the Beilstein's halogen test and, in addition, the presence of a chlorine atom in the molecule was suggested by its mass spectrum,[9] in which

9) Mass spectra were taken on a Hitachi Mass Spectrometer Model RMU-6D equipped with a direct inlet system (Model MG-150).

appeared the molecular ion peak at *m/e* 397 and the characteristic isotope peak at *m/e* 399 with a relative intensity of 3:1. The combustion values were also in good agreement with the formula $C_{19}H_{24}O_6NCl$. It is now evident that the molecular formula of acutumine(IIa) should be revised to $C_{19}H_{24}O_6NCl$.

In the nuclear magnetic resonance(NMR) spectrum(pyridine-$d_5$)[10] (Fig. 1), acutumine (IIa $\tau$) showed signals for an N-methyl group (7.60 $\tau$, 3H) and three methoxyl groups (6.28, 6.21, 5.96$\tau$) along with significant signals at 4.99, 4.82 and 4.41 $\tau$ for each one proton which could be attributed to C<u>H</u>-OH, =C<u>H</u>, and C<u>H</u>-Cl hydrogens, respectively. The presence of a secondary hydroxyl group was also indicated by the fact that the NMR spectrum in dimethylsulfoxide-$d_6$ demonstrated an one-proton doublet at 3.86 $\tau$ ($J$=6 cps) which disappeared on addition of deuterium oxide.[11] The ultraviolet (UV) spectrum[12] ($\lambda$ max 240, 270 m$\mu$) (Fig. 2) indicated the existence of conjugated carbonyl or diene chromophores. As shown in Fig. 3, the IR spectrum[13] (Nujol) of acutumine exhibited strong absorption bands in the carbonyl region, two of which at 1670 and 1690 $cm^{-1}$ suggested the presence of two carbonyl groups. The strong absorptions near 1600 $cm^{-1}$ might be ascribed to enol ether grouping, since a possibility of amide grouping could be excluded from the consideration of the basicity of acutumine. On treatment with hydroxylamine and sodium acetate in methanol, acutumine(IIa) afforded a mono-oxime, mp 213°, $C_{19}H_{25}O_6N_2Cl$, which still showed the IR absorption band at 1680 $cm^{-1}$, but no longer the band at 1670 $cm^{-1}$. From the foregoing observations it is clear that the alkaloid(IIa) has a conjugated carbonyl, a secondary hydroxyl, and three methoxyl groups. The remaining oxygen atom is presumably involved in an unreactive, hindered carbonyl group corresponding to the IR band at 1690 $cm^{-1}$.

Acutumidine(IIb), mp 239—241° (decomp.), p$K_a$ 6.6 (50% ethanol), $[\alpha]_D$ −212° (pyridine), has a molecular formula $C_{18}H_{22}O_6NCl$ and displayed the UV and IR spectra(Fig. 2, 4) very simi-

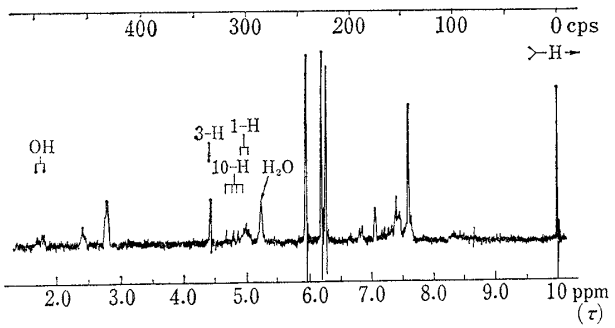



Fig. 1. NMR Spectrum of Acutumine (IIa) (in Pyridine-$d_5$)

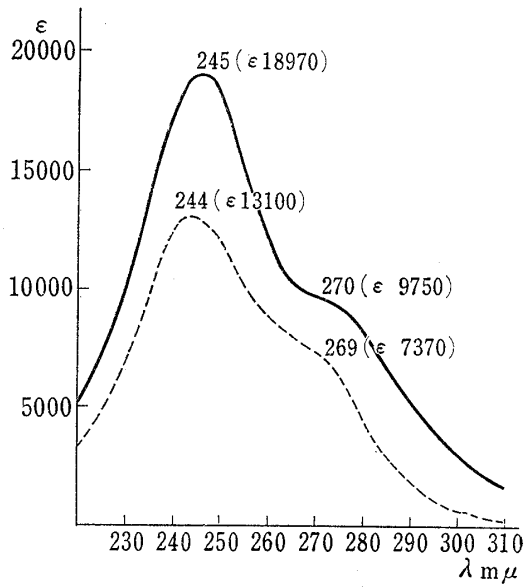



Fig. 2. UV Spectra of Acutumine (IIa) and Acutumidine (IIb)

——: acutumine ------: acutumidine

10) Unless otherwise specified, the NMR spectra were taken in $CDCl_3$ using tetramethylsilane as the internal reference and chemical shifts are recorded in $\tau$ value. Singlet signals whose top are splitted just a little or which have scanty shoulder are described in term of broad singlet (br. s.).

11) O.L. Chapman and R.W. King, *J. Am. Chem. Soc.*, **86**, 1256 (1964).

12) UV spectra were measured in ethanol solutions.

13) IR spectra were measured in chloroform solution unless otherwise specified.

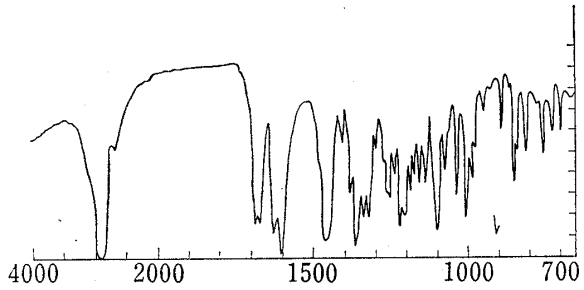



Fig. 3. IR Spectrum (Nujol) of Acutumine (IIa)

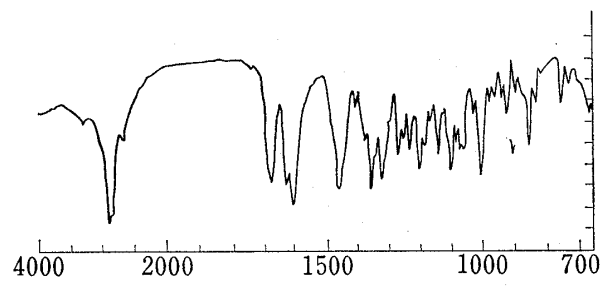
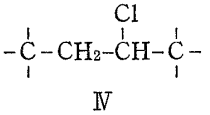



Fig. 4. IR Spectrum (Nujol) of Acutumidine (IIb)

lar to those of acutumine(IIa). On acetylation and benzoylation, it gave a crystalline N, O-diacetate(IIe), mp 216—220°(decomp.), and an oily N,O-dibenzoate(IIf), respectively. The interrelationship between acutumine(IIa) and acutumidine(IIb) was established by the conversion of the latter to the former by the N-methylation with formalin and formic acid.

Acetylation of acutumine with acetic anhydride–pyridine afforded acetylacutumine(IIc), mp 162—164°, $C_{21}H_{26}O_7NCl$, p$K_a$ 4.6. The IR spectrum of this compound showed new bands at 1750 and 1220 $cm^{-1}$ due to an acetoxyl group and the NMR spectrum(Fig. 5) revealed an acetyl methyl signal at 7.64 $\tau$ along with a pair of doublets ($J$=0.8 cps) at 4.58 and 4.01 $\tau$ corresponding each to one proton, which were found to be mutually coupling in allylic relation by the spin decoupling experiments. The lower-field doublet at 4.01 $\tau$ was considered to arise from the hydrogen geminal to the acetoxyl group, since the corresponding signal appeared at 4.99 $\tau$ in the NMR spectrum (pyridine-$d_5$) of acutumine, whereas the higher-field one at 4.58 $\tau$ was reasonably assigned to an olefinic proton. Another important signal observed was the one-proton quartet ($J$=7.5, 11 cps) at 5.5 $\tau$ which would be attributed to the proton on the chlorine-carrying carbon atom in view of the chemical shift value[14]; this signal occurred in 4.7—5.5 $\tau$ region in the NMR spectra of a series of acutumine derivatives. Furthermore, this signal was shown to be the X-portion of an ABX type splitting[15] from the decoupling experiments, the AB portion of which being obscured by other signals near 7.4 $\tau$. This ABX pattern was more clearly demonstrated in the spectrum in benzene-$d_6$ solution: *i.e.*, the X-portion appeared at 5.42 $\tau$ (quartet) and the AB portion was observed as a triplet (B part) at 6.90 $\tau$ and a quartet (A part) at 7.53 $\tau$ with the coupling constants $J_{AB}$=12.5, $J_{AX}$=7.0, and $J_{BX}$=12.5 cps. The large value of the above AB coupling constant could be ascribed only to the geminal coupling of a methylene group and therefore indicated the presence of a grouping $-CH_2-CH(Cl)-\overset{|}{C}-$ in the molecule. Besides, the NMR spectrum of O-acetyl-N-cyano-acutumi-




IV

Chart 3

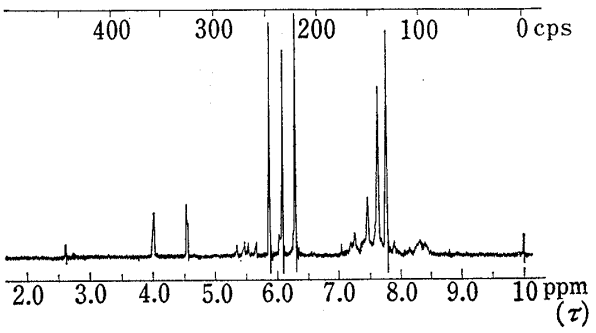



Fig. 5. NMR Spectrum of Acetylacutumine (IIc)

14) L.M. Jackmen, "Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, London, 1959, p. 54.
15) K.B. Wiberg and B.J. Nist, "The Interpretation of NMR Spectra," W.A. Benjamin, Inc., New York, 1962, p. 11, 21; J.D. Roberts, "An Introduction to the Analysis of Spin–Spin Splitting in High-Resolution NMR Spectra," W.A. Benjamin, Inc., New York, 1962, p. 71.

dine(IIIb), obtained by the treatment of acutumidine(IIb) with BrCN followed by acetylation, revealed a sharp quartet (1H, $J$=8, 11 cps) at 5.57 $\tau$ and typical two proton signals of AB portion at 7.12 $\tau$, which indicated that the carbon atom adjacent to the methylene is quarternary. These spectral evidences strongly suggest the presence of the partial stracture(IV) in acutumine.

Acetylacutumine(IIc) was then reduced with sodium borohydride to give three products, V, VIa, and VIb, which could be separated by silica gel chromatography and recrystallization.

Acetylacutuminol(V), an oily product, was shown to retain the acetoxyl group by the IR spectrum(1745 $cm^{-1}$), while the carbonyl band at 1670 $cm^{-1}$ in the IR spectrum and the 270 m$\mu$ band in the UV spectrum disappeared. The formation of a new hydroxyl group was indicated by its IR band at 3500 $cm^{-1}$, and by the NMR signal at 5.3—5.8 $\tau$ (1H, >C<u>H</u>-OH). The oxidation of V with activated manganese dioxide regenerated acetylacutumine(IIc), confirming that the carbonyl group just reduced is an $\alpha,\beta$-unsaturated ketone. Considering the UV

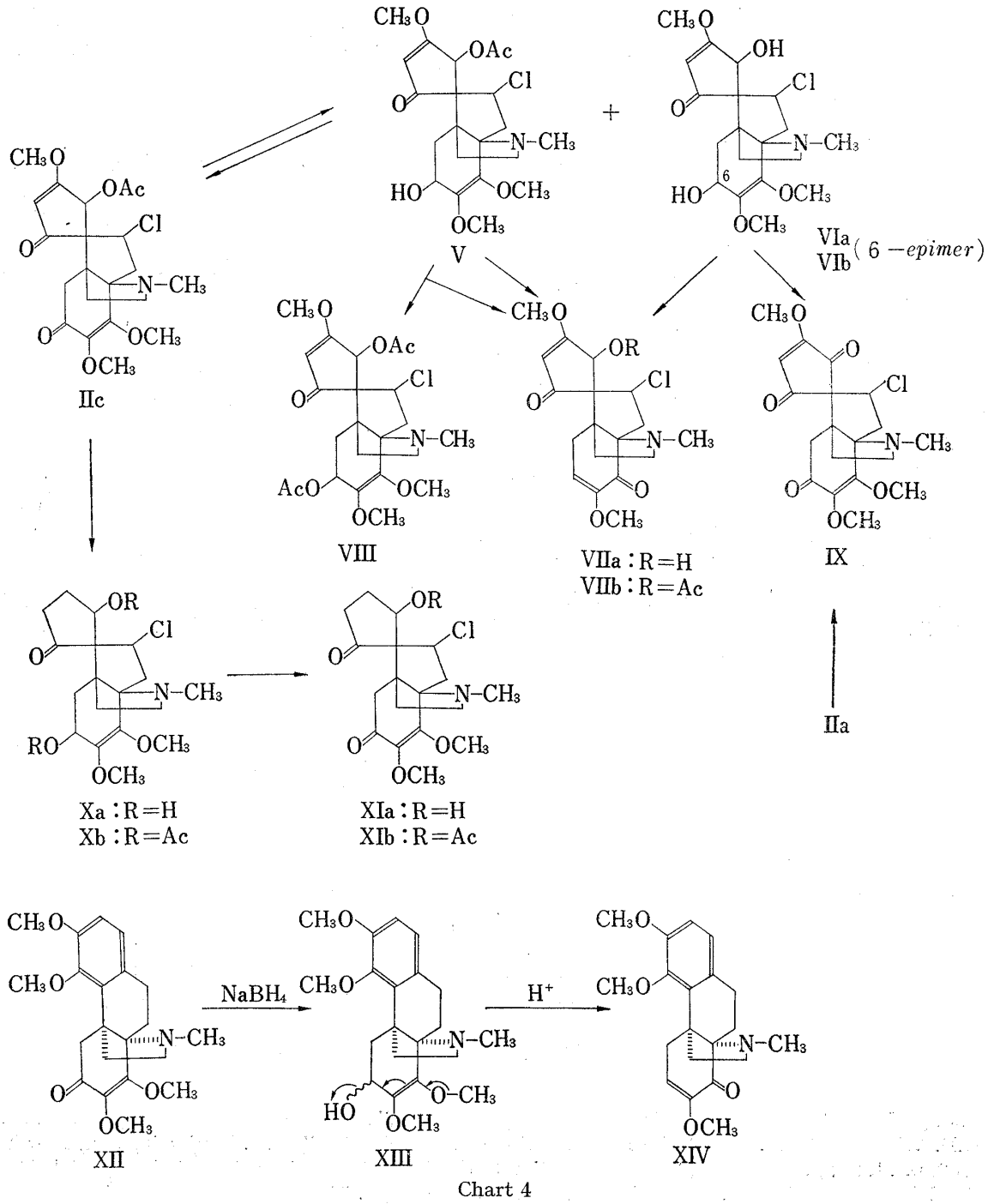



Chart 4

absorption (270 mμ), this is presumably a tetra-substituted α, β-unsaturated ketone having one or two methoxyl groups in the α- or β-position.[16]

Other reduction products, acutuminol-A(VIa), mp 168—171°, and acutuminol-B(VIb), mp 190—193°, showed neither acetoxyl nor carbonyl band at 1670 $cm^{-1}$ in their IR spectra, indicating that the hydrolysis of acetoxyl group occurred in addition to the reduction of carbonyl group. They have the same molecular formula $C_{19}H_{26}O_6NCl$ and gave the very similar spectral data each other(see experimental part). They afforded the same product(IX) on oxidation with manganese dioxide. Also the treatment of VIa and VIb with hydrobromic acid gave the same diketo compound(VIIa)(discussion on these compounds will be given later). It follows that the compounds VIa and VIb should be epimers concerning the hydroxyl group produced newly by reduction of the conjugated ketone group.

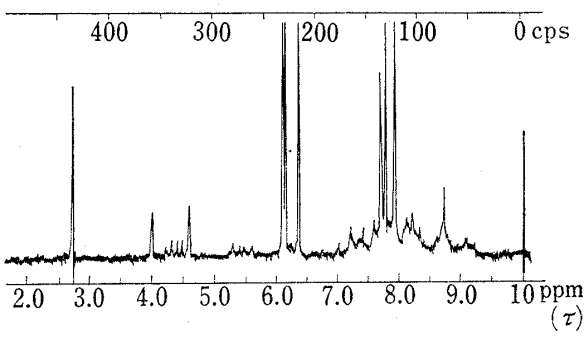



Fig. 6. NMR Spectrum of Acutuminol Diacetate (VIII)

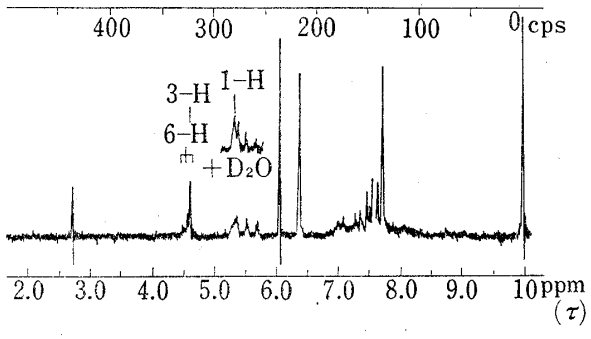



Fig. 7. NMR Spectrum of Diketo Compound (VIIa)

Acetylation of acetylacutuminol(V) with acetic anhydride-pyridine afforded a diacetate (VIII), mp 149—152°, together with a small amount of oily keto-acetate (VIIb). The NMR spectrum(Fig. 6) of the former(VIII) showed a clean one proton quartet due to a C<u>H</u>-OAc hydrogen at 4.37 τ ($J$=5, 10.5 cps), suggesting the presence of a methylene group adjacent to the carbonyl group of the α, β-unsaturated ketone system described above. Though the NMR signal arisng from this active methylene group in acetylacutumine (IIc) appeared as a broad singlet[17] at 7.46 τ, the corresponding signal in the NMR spectrum (benzene-$d_6$) of N,O-dibenzoylacutumidine (IIf) occurred as a sharp AB quartet at 7.73 τ ($\Delta\delta$ =0.30 ppm, $J$=17.5 cps). This requires that the other side of the methylene group is a quarternary carbon atom.[18] The compound VIII was shown to have a positive Cotton effect ([θ]=+8,250) at 304 mμ in its Circular diehroism (CD) curve (methanol), proving the presence of one more conjugated ketone system in acutumine, which is unaffected by sodium borohydride reaction.

On the other hand, keto-acetate(VIIb) revealed a new absorption band at 275 mμ in addition to the 239 mμ band in the UV spectrum and a very strong carbonyl band near 1680 $cm^{-1}$ in the IR spectrum. In the NMR spectrum it showed signals associated with one acetoxyl and two methoxyl groups and a new signal assignable to an olefinic proton near 4.55 τ. These data suggest that the keto-acetate(VIIb) may be a product formed by the elimination of one equivalent of methanol. This was proved by the following evidences:

Mild treatment of acetylacutuminol(V) with hydrobromic acid–methanol(1:4) at room temperature gave a diketo-compound(VIIa), mp 196—199°(decomp.), $C_{18}H_{22}O_5NCl$. This compound(VIIa) was also obtained by the same reaction of a acutuminol-A(VIa) and acutu-

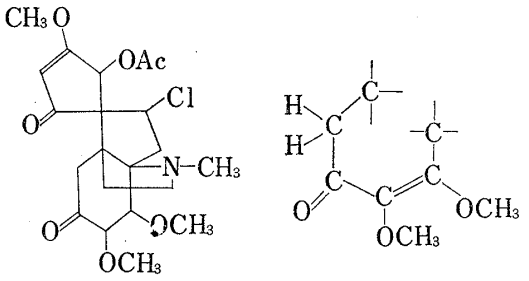
16) A.I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," Pergamon Press, London, 1964, p. 59.

17) In the 100 MC NMR spectrum in benzene-$d_6$, this signal appears as a pair of doublets centered at 7.28 and 7.90 τ ($J$=16 cps).

18) Ref. 14), p. 57; T. Takahashi, *Tetrahedron Letters*, **1964**, 565.

minol-B(VIb) as described before. Acetylation of this product gave rise to a monoacetate which was identified with the above mentioned keto-acetate(VIIb). The IR spectrum of the diketo-compound(VIIa) revealed an intense absorption band at 1690 $cm^{-1}$ attributable to the overlapping of two conjugated carbonyls. As shown in Fig. 7, its NMR spectrum exhibited only two methoxyl signals at 6.39 and 6.07 $\tau$, indicating that the demethylation occurred by the acid treatment. In addition, the appearance of one proton triplet($J$=5 cps) at 4.58 $\tau$ suggests the formation of a new double bond in VIIa, which is supposed to consist of a conjugated ketone system. In the UV spectrum it showed a shoulder at 274 m$\mu$ ($\varepsilon$: 4080) besides a 243 m$\mu$ band, which is compatible with the formation of a conjugated ketone having one methoxyl group.[16] This reaction is now reasonably interpreted by assuming the acid-catalysed elimination of hydroxyl group from the allyl alcohol system -$CH_2$-CH(OH)-C=C($OCH_3$) -accompanied by the concerted double bond migration and the demethylation of a methoxyl group, giving a partial structure -$CH_2$-CH=C-C=O. A chemical precedent has reported by Tomita, *et al.*[19] who found that hasubanonine(XII) gave a conjugated ketone(XIV) upon sodium borohydride reduction followed by acid treatment(Chart 4).

Additional information was provided by the catalytic hydrogenation of acetylacutumine (IIc) over platinum oxide which led to a dihydro compound(XV), $C_{21}H_{28}O_7NCl$, mp 230—231°. In its IR spectrum the carbonyl band at 1670 $cm^{-1}$ shifted to 1720 $cm^{-1}$(six(or more)-membered ketone) and the UV absorption at 270 m$\mu$ disappeared, confirming that only the reduction of double bond of the unhindered conjugated ketone system took place. Its NMR spectrum exhibited a pair of AB doublets at 5.46 and 6.60 $\tau$ (2H, $J$=10 cps), which could be ascribed to the newly introduced hydrogens geminal to the methoxyl groups. Furthermore this observation is suggestive of the absence of any proton on the neighboring carbon atom.




XV XVI

Chart 5

On the basis of the foregoing results, acutumine is now presumed to have a partial structure XVI.

We then focussed our attention on the partial structure around the secondary alcohol and hindered carbonyl functions. Attempts of oxidation on acutumine(IIa) with chromic acid and of dehydration with thionyl chloride or phosphorous oxychloride led to intractable mixtures. Mesylation of IIa and subsequent metal hydride reduction led also to a fruitless result. Eventually, oxidation of acutumine(IIa) with manganese dioxide proceeded smoothly to give oily acutuminone (IX), which could not be induced to crystallize, but its homogenity was confirmed by thin-layer chromatography(TLC). As mentioned before, this compound (IX) was also obtained by treatment of acutuminol-A(VIa) and acutuminol-B(VIb) with the same reagent. In its IR spectrum new carbonyl bands appeared at 1745 and 1695 $cm^{-1}$, and the UV absorption maximum shifted from 240 m$\mu$ to 265 m$\mu$. These spectral changes are compatible with the formation of an ene-dione system.[20] The NMR spectrum of IX was characterized by the disappearance of the doublet of C<u>H</u>-OH hydrogen and the remarkable down-field shift of the olefinic proton signal(3.62 $\tau$) which now appeared as a sharp singlet. It is now clear that the hydroxyl group in acutumine is an allylic one, and moreover, this may be involved in the partial structure XVII in view of the long range coupling constant($J$=0.8

19) M. Tomita, T. Ibuka, Y. Inubushi, Y. Watanabe, and M. Matsui, *Chem. Pharm. Bull.* (Tokyo), **13**, 538 (1965).
20) Ref. 16), p. 61.

cps) between the olefinic and CH-OH hydrogens as well as the IR absorption at 1690 $cm^{-1}$ and the UV band at 245 m$\mu$ in acutumine.

Reduction of acetylacutumine(IIc) with lithium aluminium hydride was then attempted. The reaction led to a demethoxy-keto-diol(Xa), mp 136—137°, $C_{18}H_{26}O_5NCl$, which exhibited no characteristic UV absorption band and no IR band due to any conjugated carbonyl and acetoxyl group, instead, a saturated five-membered carbonyl band appeared at 1730 $cm^{-1}$. Acetylation of this product with acetic anhydride-pyridine afforded a diacetate(Xb), mp 138—142° (decomp.), $C_{22}H_{30}O_7NCl$, which still showed a positive Cotton effect ($[\theta]=+4{,}900$) at 311 m$\mu$ in its CD curve (in methanol). The NMR spectrum of this diacetate demonstrated two acetyl methyl signals at 7.92, 7.81 $\tau$ and two one-proton signals at 4.83—4.23 $\tau$ associated with hydrogens geminal to the acetoxyl groups. Besides, in the NMR spectra of both Xa and Xb one of methoxyl signals and the olefinic proton signal arising from the allyl alcohol system disappeared.

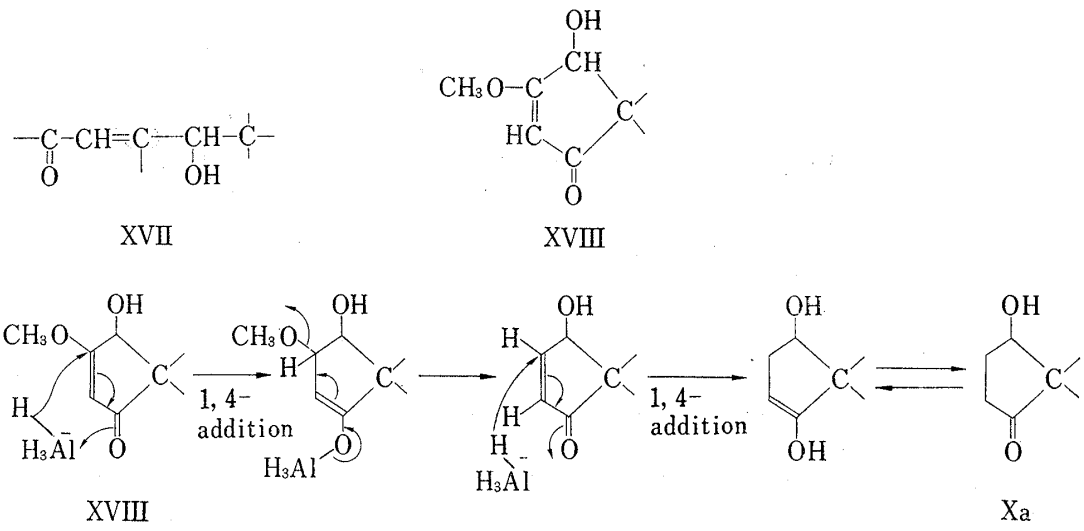


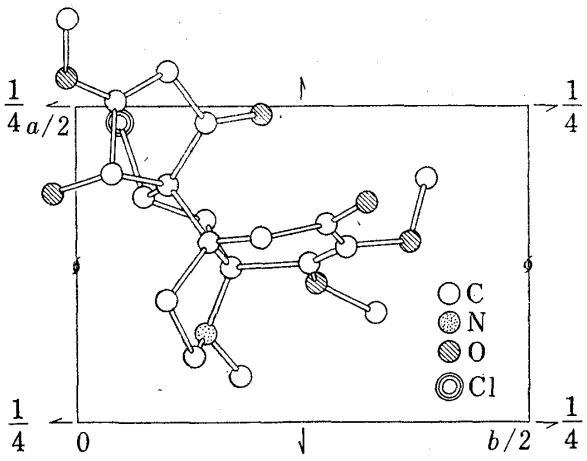

Chart 6

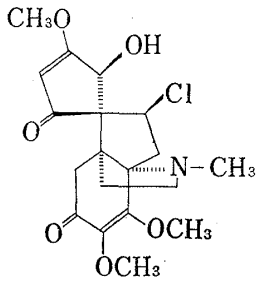
Oxidation of Xa with activated manganese dioxide gave a monohydroxy product(XIa), mp 166—169°, $C_{18}H_{24}O_5NCl$, whose spectral data clearly indicated the regeneration of the $\alpha$, $\beta$-unsaturated ketone system(XVI): namely, IR absorptions at 1670 $cm^{-1}$ (Conj. C=O), 1600 $cm^{-1}$ (enolic C=C) and UV absorption at 269 m$\mu$ ($\varepsilon$ 9935). This product has still one hydroxyl group as evidenced by the NMR signal at 5.7—5.35 $\tau$ (1H, broad triplet, $J=8$ cps, CH-OH), and gave an oily monoacetate(XIb) whose NMR spectrum showed a broad triplet at 4.85—4.45 $\tau$ ($J=8$ cps) due to the CH-OAc hydrogen. From these facts it is evident that coupled with demethoxylation, the saturation of the double bond in the structure XVII has taken place upon the lithium aluminium hydride reduction, yielding a saturated five-membered keto-alcohol. It is worth mentioning here that the carbon atom adjoining to the carbinol carbon in XIa has now two hydrogen atoms from the above NMR data. Thus the eliminated methoxyl group is considered most likely to have been located at the $\beta$-position of five-membered conjugated ketone in the structure XVII. This reaction process is consistently explained by a mechanism as shown in Chart 6, because such a $\beta$-methoxy-enone, a vinylogue of methyl ester, is expected to undergo readily elimination of the methoxyl group. Thus, the partial structure XVII is now expanded to XVIII.

21) M. Nishikawa, K. Kamiya, M. Tomita, Y. Okamoto, T. Kikuchi, K. Osaki, Y. Tomiie, I. Nitta, and K. Goto, *J. Chem. Soc.* (B), **1968**, 652.

To make a summary of the foregoing findings, we can conclude that acutumine is a tertiary base containing one N-methyl, one hydroxyl, three methoxyls, and two conjugated ketones, and should have the partial structures IV, XVI and XVIII. Since no other double bond is present in acutumine, it must have a tetracyclic structure, considering its molecular formula $C_{19}H_{24}O_6NCl$.

At this stage of investigation, X-ray analyses of acutumine and its acetate were successfully performed and the results have been fully discussed in a separate report.[21] The complete structure of acutumine can be represented by the formula XIX and Fig. 8.




XIX

Fig. 8

In parallel, we also carried out a series of degradative reactions which led to the chemical proof for the structures of these novel type alkaloids.

Initially, several attempts to clarify the gross structure of acutumine by conventional methods such as dehydrogenation reaction, Hofmann degradation or von Braun reaction were unsuccessful and attempted reductive removal of oxygen functions by the usual thioketal or tosylhydrazone method and by chromous chloride reduction was again unsatisfactory. However, a clue for the skeletal structure of the alkaloids was eventually provided as follows.

Treatment of acutumine (IIa) with zinc powder in boiling acetic anhydride afforded a complex mixture, the neutral fraction of which afforded two aromatic N-free products, XXa and XXIa, on silica gel chromatography. The major product (XXa), tentatively designated as acetylphenol-A, showed the IR absorptions at 1750 (OAc), 1700 (C=O), and 1615 $cm^{-1}$ and the UV absorptions at 233, 275 (sh) and 304 (sh) m$\mu$, suggestive of an aromatic ring. The NMR spectrum exhibited two acetyl methyls at 7.72, 7.85 $\tau$, three methoxyl groups at 6.07, 6.11, 6.18 $\tau$, two broad singlets due to the C<u>H</u>=C–C<u>H</u> (OAc) grouping at 4.50, 4.19 $\tau$, and one proton singlet attributable to an aromatic proton at 3.56 $\tau$, but no longer the quartet signal due to the proton on the chlorine-carrying carbon atom.

Mild hydrolysis of this product (XXa) yielded a phenolic compound (XXb) (UV $\lambda_{max}^{EtOH}$ m$\mu$: 233, 280, 310; UV $\lambda_{max}^{EtOH\text{-}KOH}$ m$\mu$: 236,296) which was subsequently methylated with diazomethane to afford an O-methyl ether (XXc), mp 74—77°. This compound has the molecular formula $C_{16}H_{18}O_6$ as indicated by its molecular ion peak at *m/e* 320 in the mass spectrum and showed the four methoxyl signals (6.08, 6.11, 6.19, and 6.23 $\tau$) in the NMR spectrum (Fig. 9). On acetylation, it gave a monoacetate (XXd), which showed an acetoxyl band at 1745 $cm^{-1}$ in the IR spectrum and signals for an acetyl methyl at 7.85 $\tau$, olefinic proton at 4.46 $\tau$ (1H, s), and IH singlet at 4.22$\tau$ (C<u>H</u>–OAc) in the NMR spectrum.

Inspection of NMR spectra of the above degradation products (XXa, XXc, XXd) led us to conclude that on the zinc–acetic anhydride reaction the aromatization at the partial structure XVI took place with concomitant elimination of the ring containing a nitrogen

atom. The partial structure XVIII proposed for acutumine might remain unchanged in these products. The manganese dioxide oxidation of the methyl ether (XXc) was then accomplished in a parallel manner with acutumine, whereby obtained an ene-dione compound (XXII), mp 161—162°, $C_{17}H_{18}O_6$. As expected, it revealed the IR bands at 1745 and 1695 $cm^{-1}$ and the broad UV absorption at 263 mμ (ε 12200).[22]

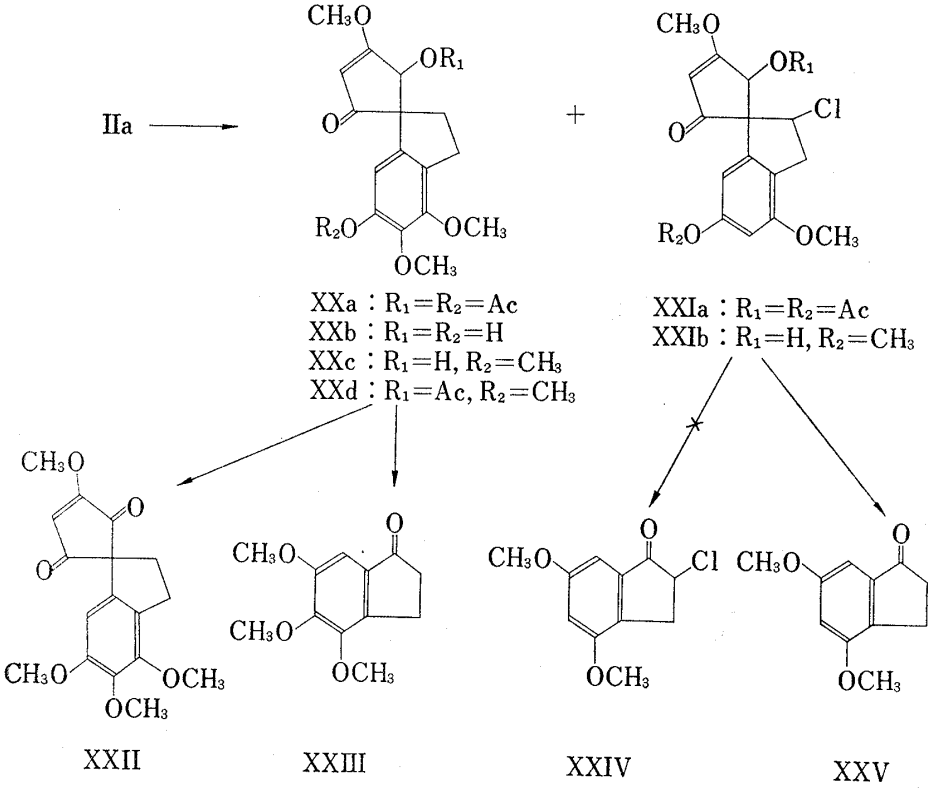



Chart 7

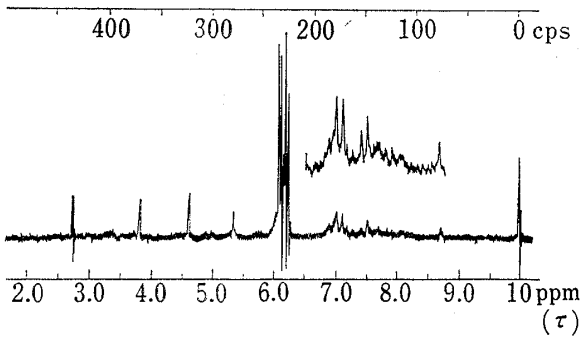



Fig. 9. NMR Spectrum of Phenol-A O-Methyl Ether (XXc)

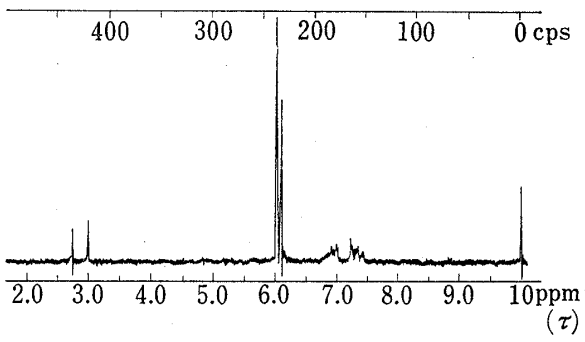



Fig. 10. NMR Spectrum of 4,5,6-Trimethoxy-1-indanone (XXIII)

When oxidized with potassium permanganate, the methyl ether (XXc) gave a ketone (XXIII), mp 75—77°, which was analyzed for $C_{12}H_{14}O_4$ and showed a IR band at 1700 $cm^{-1}$ and UV absorptions at 270 and 313 mμ. In the NMR spectrum (Fig. 10), it revealed signals for an aromatic proton, three methoxyls, and $A_2B_2$ type signals (6.8—7.5 τ,4H).

22) The UV peak ascribed to the benzene ring appears to be overlapping with this band.

From these spectral data and the view that the aromatic ring may be derived from the partial structure XVI, the ketone was believed to be 4,5,6-trimethoxy-1-indanone (XXIII).[23] The identity wes established by the direct comparison with a synthetic sample (XXIII) obtained by the acid catalyzed cyclization of $\beta$-(2,3,4-trimethoxyphenyl) propionic acid (XXIX)[24] which was prepared in three-step transformation from trimethylpyrogallol (XXVI) (Chart 8).

Therefore, acetylphenol-A should be assigned to the structure XXa.

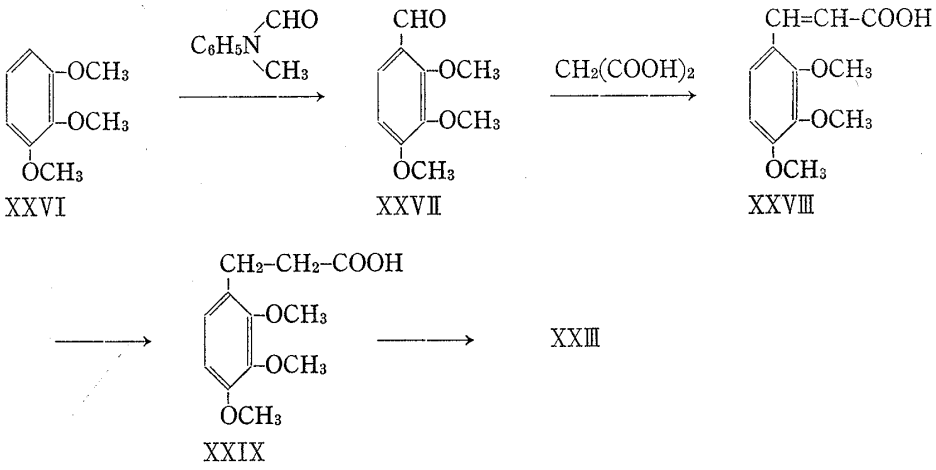



Chart 8

On the other hand, the minor product (acetylphenol-B:XXIa) of the zinc-acetic anhydride reaction of acutumine was found to contain a chlorine atom. Although this product could not be isolated in homogeneous state, after the mild hydrolysis followed by methylation it gave a pure O-methyl ether (XXIb), mp 219—221.5° (decomp.), $C_{16}H_{17}O_5Cl$. It showed the close similarity to phenol-A O-methyl ether (XXc) in the UV and IR spectra, but, distinct differences were noticed in the NMR spectrum (Fig. 11) which revealed three singlets for three methoxyl groups and a pair of doublets ($J$=2 cps) at 3.95 and 3.67 $\tau$ due to the mutually *meta*-coupling aromatic protons along with other characteristic signals arising from the partial structure IV and XVIII.

An attempt of direct oxidation of this methyl ether (XXIb) with potassium permanganate failed to give a indanone derivative (XXIV). However, on reduction with lithium aluminium hydride[25] and subsequent permaganate oxidation, it gave a small amount of crystalline compound, $C_{11}H_{12}O_3$, mp 92—96°, showing an IR absorption at 1700 $cm^{-1}$ (C=O) and UV absorptions at 262, 324 m$\mu$. In the NMR spectrum there appeared two methoxyl signals and two *meta*-coupling aromatic proton signals at 3.37 and 3.22 $\tau$. This product must be 4,6 dimethoxy-1-indanone (XXV) from these spectral data.

It should be noted that one proton triplet at 5.10 $\tau$ and two proton signals at 6.5—6.8 $\tau$ in the NMR spectrum of the above mentioned methyl ether (XXIb) may be regarded as a typical $AB_2$ type splitting[15] arising from CH(Cl)-$CH_2$ grouping. The chemical shift of the latter singals requires that the methylene group is located at benzylic position. Therefore, the structure of the methyl ether can be depicted as XXIb.

23) R.D. Hawarth and J.M. McLachlan, *J. Chem. Soc.*, **1952**, 1583. An alternative possibility, 5,6,7-trimethoxy-1-indanone, is untenable since it was reported to have mp 111.5—113.5° (see J. Koo, *J. Am. Chem. Soc.*, **75**, 1891 (1953)).

24) J.W. Cook, W. Graham, A. Cohen, R.W. Lapsley, and C.A. Lawrence, *J. Chem. Soc.*, **1944**, 322.

25) This reduction was carried out in order to remove the chlorine atom. However, this chlorine resisted considerably the reduction and could only be partially removed.

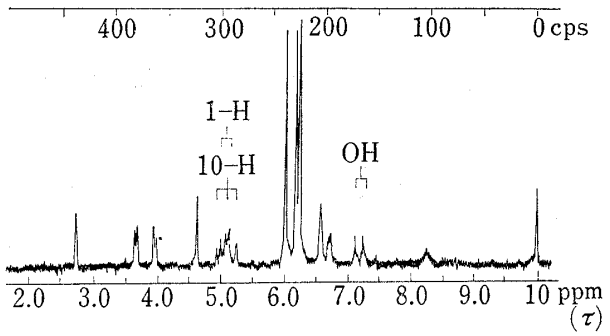
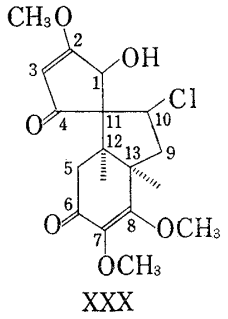



Fig. 11. NMR Spectrum of Phenol-B O-Methyl Ether (XXIb)



XXX

Chart 9

Summarizing the foregoing observations, the structure of acutumine may now be expanded to the formula XXX. The remaining moiety ($C_3H_7N$) is considered to form a ethanamine bridge $-\overset{|}{C}-CH_2-CH_2-N(CH_3)-\overset{|}{C}-$ based on the NMR study of N–cyano–O–acetylacutumidine (IIIb), which exhibited the $A_2X_2$ type signals arising from the two methylene groups at 6.32—6.67 $\tau$ (2H) and 8.05—8.40 $\tau$ (2H).

The nitrogen end of ethanamine bridge may be linked to the allylic position ($C_{13}$) of six–membered conjugated ketone system in view of the weak basicity ($pK_a$ 5.3)[26] of the alkaloid. A chemical support was provided by the reduction of acutumine with zinc powder in acetic acid, whereupon was obtained a dihydro product (XXXIIa or XXXIIb), mp 168—171°, $C_{19}H_{26}O_6NCl$, $pK_a$ 6.8 (50% ethenol). Since the IR spectrum of this product showed no characteristic band of the six–membered conjugated carbonyl, but the absorption bands at 3400 $cm^{-1}$ (OH) and 1690 $cm^{-1}$ (five–membered Conj. C=O) and the UV spectrum only one absorption at 241 m$\mu$, it is evident that the chemical change occurred only at the six–membered conjugated ketone system. This procedure may be rationalized in term of the expected reduc-

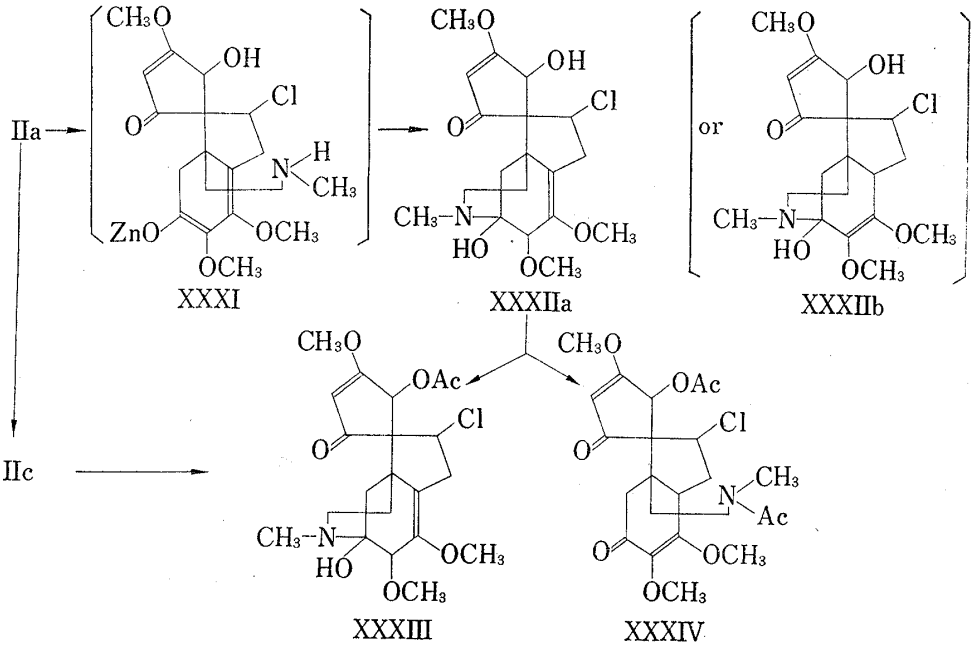



Chart 10

26) The lower $pK_a$ value of acutumine than the general value of α-aminoketone vinilogues might be ascribed to the steric inhibition of solvation. See D.F. Morrow, M.E. Brokke, G.W. Moersch, M.E. Butler, G.F. Klein, W.A. Neuklis, and E.C.Y. Huang, *J. Org. Chem.*, **30**, 212 (1965).

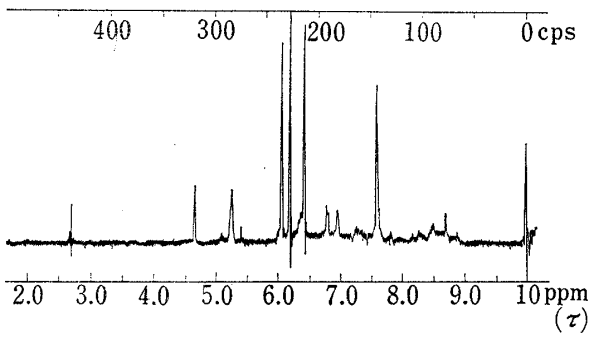



Fig. 12. NMR Spectrum of Carbinolamine Compound (XXXIIa)

tive cleavage of $C_{13}$-N linkage (XXXI) followed by recryclization to give a carbinolamine (XXXIIa or XXXIIb).

The formula XXXIIa is more likely proposed for this product from the following NMR spectral evidences (Fig. 12): (a) the low chemical shift values (6.80, 6.94 $\tau$) of the methylene protons of CH(Cl)–$C\underline{H}_2$ grouping correspond to that of allylic position, (b) one proton signal attributable to a $C\underline{H}$–$OCH_3$ hydrogen appears near 6.37 $\tau$ and more clearly at 6.02 $\tau$ (singlet) in the spectrum in pyridine.

Acetylation of this product with acetic anhydride-pyridine or acetic anhydride-sodium acetate afforded a monoacetate (XXXIII) and an N,O-diacetate (XXXIV). The former (XXXIII) was found to be identical with the acetylcarbionolamine (XXXIII) produced by the zinc–acetic acid reaction of acetylacutumine (IIc). The latter (XXXIV) was obtained as a homogeneous oil in 6—30% yield from the neutral fraction. In the IR spectrum it showed a broad carbonyl absorption at 1660—1610 $cm^{-1}$ together with other characteristic bands and in the UV spectrum strong absorptions at 242 and 272 m$\mu$, indicating the formation of a six-membered conjugated carbonyl group.

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

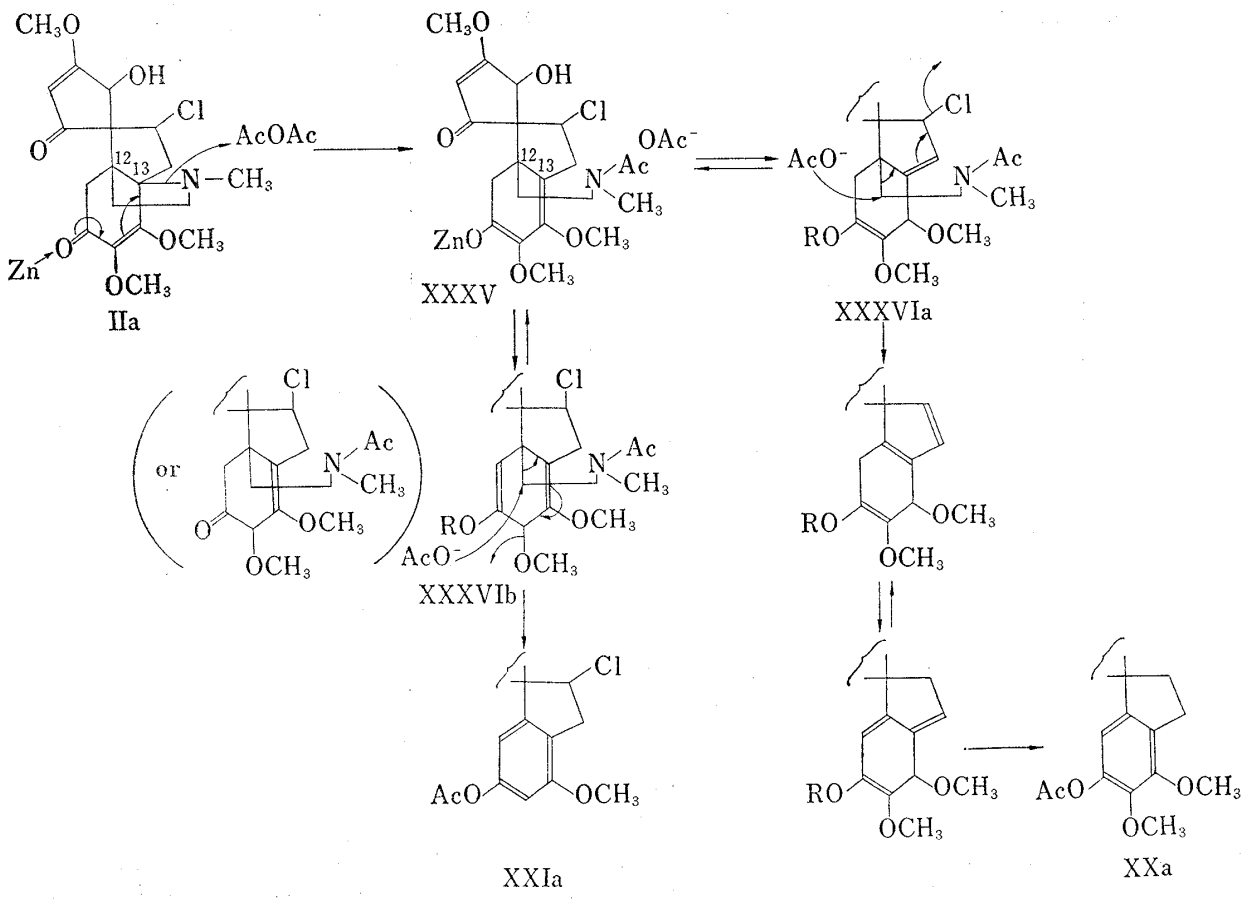
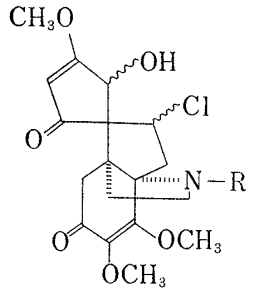



Chart 11

The mechanism for aromatization of acutumine (IIa) with zinc in acetic anhydride may be visualized as shown in Chart 11. Reductive cleavage of the $C_{13}$-N bond would give XXXV which may be in equilibration with XXXVIa and XXXVIb. Further reaction of the latter two with acetate anion would give XXa and XXIa, respectively.

Our attention was then turned to the absolute configuration around the ethanamine bridge in the alkaloids. The CD curves of acutumine and acutumidine (in methanol) had a negative Cotton effect near 320 m$\mu$ ([$\theta$] $-37200$ and $-29800$, respectively), which may be attributed to the $n\rightarrow\pi^*$ transition of six-membered $\alpha,\beta$-unsaturated ketone system, since the sodium borohydride reduction product (VIII) showed a weak positive Cotton effect ([$\theta$]$+8250$) at 304 m$\mu$. That is comparable with the Cotton effect ([$\theta$] $-23090$ at 320 m$\mu$) of hasubanonine (XII)[19] carrying the same structural feature of established absolute configuration.

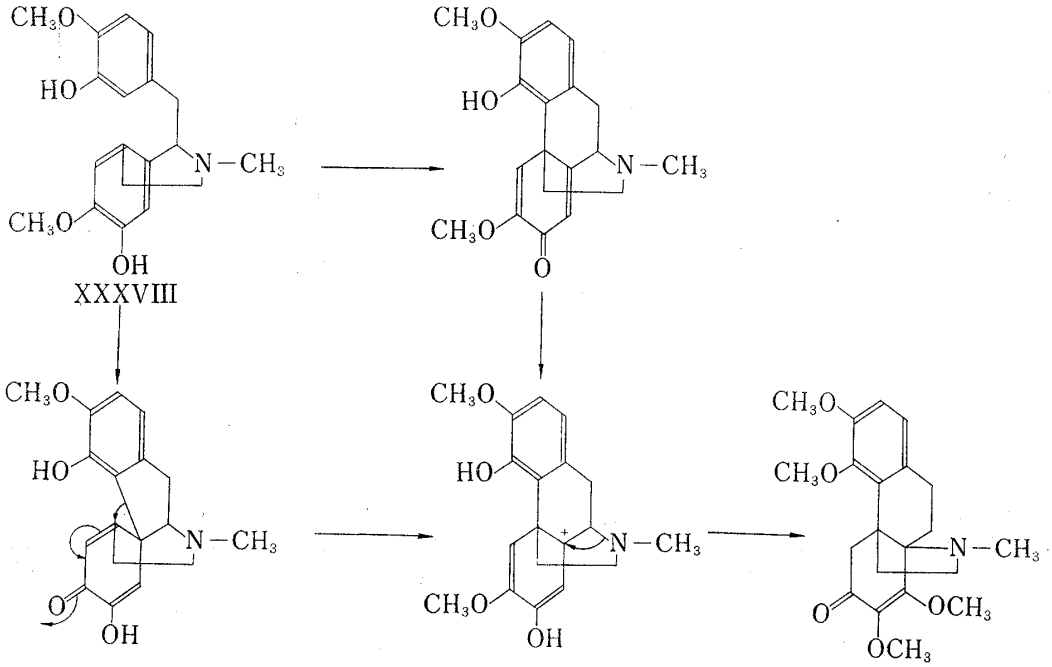
The structure of acutumine and acutumidine can therefore be represented by the formula XXXVIIa and XXXVIIb, respectively. As to the stereochemistry of the five-membered spiro-ring and of the chlorine atom, chemical indication is not available at present, but the formulas XXXVIIa and XXXVIIb are in accordance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



XXXVIIa : R=$CH_3$
XXXVIIb : R=H

Chart 12

We now briefly comment on the biogenesis of these unique alkaloids. The established structure of acutumine is closely related to the structure of hasubanonine (XII) isolated from *Stephania japonica* Miers, a plant of the same Menispermaceae, and both alkaloids might be biosynthesized through analogous precursors. It was proposed by Tomita and his co-workers[27] that hasubanonine type alkaloids would be biosynthesized by 1,2-shift of the nitrogen atom from a sinomenine type intermediate[28] produced by phenol oxidation of a precursor



XXXVIII

XII

Chart 13

27) Ref. 6), p. 81.
28) The biogenesis of sinomenine has been studied by Barton, *et al.* See D.H.R. Barton, Mrs. A.J. Kirby, and G.W. Kirby, *Chem. Commun.* (London), **1965**, 52.

(XXXVIII) as shown in Chart 13. Since skeletal carbons of acutumine (IIa) are one carbon less than those of hasubanonine (XII), one carbon atom must be removed at some stage in the biosynthetic pathway. Another important point is the incorporation of a chlorine atom.[29] These are problems of particular interest.

Recently, Barton, *et al.*[30] suggested the compound (XXXIX) as a suitable precursor for acutumine and advanced a biogenetic scheme which is reproduced in Chart 14. Phenol coupling of XXXIX would furnish a bis-dienone intermediate (XXXX). Further oxidation to a epoxide (XXXXI), followed by Favorskii–type rearrangement and decarboxylation, would then produce the A-ring. The 1,2-shift of the nitrogen atom in XXXX accompanied by the hydride shift would form a carbonium ion (XXXXII) to which a chloride anion might be introduced, giving the acutumine type alkaloid. Apparently this hypothesis is very suggestive and useful for the experimental works which remain to be done.

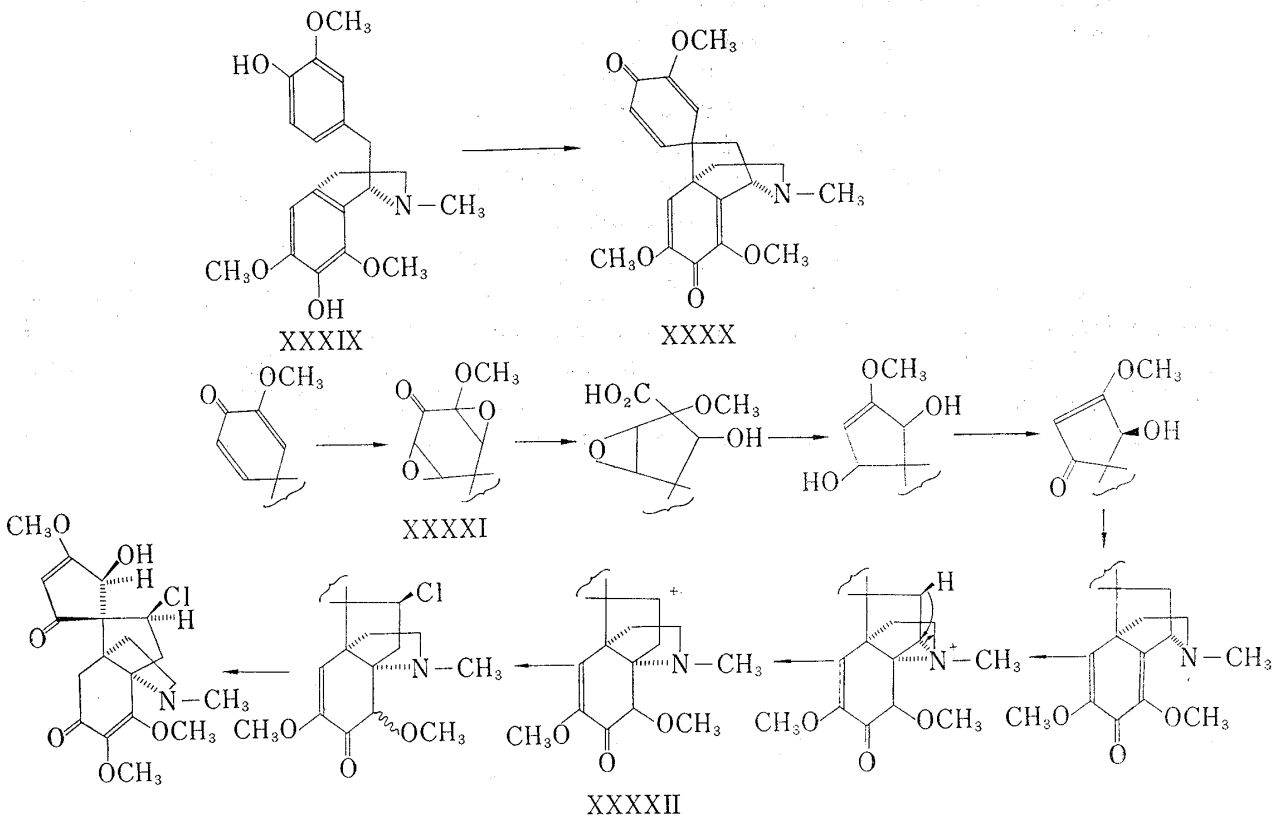



Chart 14

## Experimental[31]

**Isolation of Alkaloids from *Menispermum dauricum* DC.**——A finely-cut dried rhizome (8.5 kg) of *M. dauricum* collected at Hanase, Kyoto, at the end of June, 1964, was extracted three times with boiling MeOH. The combined extracts were evaporated under reduced pressure and the residue (3 kg) was dissolved in 2%

29) Experimental examples of incorporation of halide anion were reported in steroid field, see S.L. Neidleman, *Tetrahedron Letters*, **1966**, 5337.

30) D.H.R. Barton, A.J. Kirby, and G.W. Kirby, *J. Chem. Soc.* (*C*), **1968**, 929.

31) All melting points were measured on Yanagimoto Micro Melting Point Apparatus and are uncorrected. The conditions of TLC were as follows: *a*) Aluminum oxide G (acc. to Stahl), solvent: chloroform; *b*) Aluminum oxide G, chloroform–ethyl acetate (5 : 1); *c*) Aluminum oxide G, chloroform–acetone (1 : 1); *d*) Silica gel G (acc. to Stahl), solvent: chloroform–acetone (5 : 1) or chloroform–acetone (1 : 1); in every case a solution of potassium permanganate in dil. $H_2SO_4$ was employed as the detection reagent.

aq. tartaric acid and the insoluble part was removed by filtration. The acidic solution (*ca.* 7 liter) was made alkaline by addition of conc. $NH_4OH$ and extracted exhaustively with ether (6 times) and then with chloroform (4 times). From the ether extracts crude non-phenolic bases (500 mg) and crude phenolic bases (60 g) were obtained by the usual working up. From the phenolic base fraction 15 g of dauricine chloroform adduct (Ia), mp 100—103°, and 0.5 g of daurinoline (Ib), pale yellow oil, were isolated. On the other hand, the chloroform extracts were combined, dried ($K_2CO_3$), and concentrated *in vacuo*. To the residue was added acetone and left standing for a few days at room temperature to give a crystalline precipitate (5 g), which showed mainly 2 spots on TLC[31c,d] in the approximate ratio of 5:3 (corresponding to acutumine and acutumidine, respectively). This was dissolved again in 3% aq. HCl and then basified cautiously with 10% $NH_4OH$ under cooling in an ice–water bath. The precipitated crystals were collected by filtration, washed with $H_2O$ and acetone, and dried. This substance was then extracted repeatedly with refluxing acetonitrile until the insoluble part showed single spot on TLC. The insoluble part was further purified by reprecipitation using 3% aq. HCl and 10% $NH_4OH$, affording 1.5 g of acutumidine (IIb) which melted at 239—241° (decomp.). On the other hand, the combined acetonitrile solution was concentrated *in vacuo* and the residue was recrystallized from chloroform–methanol (1:1) to afford 2.5 g of acutumine (IIa) as colorless needles, mp 238—240° (decomp.).

**Isolation of Acutumine (IIa) and Acutumidine (IIb) from *Sinomenium acutum* RHED. et WILS.**——A plant material (80 kg) (on the market), collected at Kochi district in May of 1965, was extracted with MeOH and the extract (9.5 kg) was treated with 2% aq. tartaric acid as in the case of *Menispermum dauricum* DC. The acidic solution (*ca.* 30 liter) was basified with conc. $NH_4OH$ and extracted thoroughly with ether (20 times)[32] and then with chloroform (15 times). Treatment of the chloroform extracts gave pale yellow needles (21 g), which were recrystallized from chloroform–MeOH (1:1) to afford 20 g of pure acutumine (IIa).

Another plant material (80 kg) (on the market), collected at Takamatsu district in May of 1966, was worked up in the same manner as above, and 38 g of crude crystals was obtained. Recrystallizations from chloroform–MeOH (1:1) gave acutumine (30 g) and a mixture (5 g) of acutumine and acutumidine (*ca.* 5:1).

**Isolation of Acutumine (IIa) and Acutumidine (IIb) from the Alkaline Aqueous Solution remaining after Extraction of Sinomenine from *Sinomenium acutum***——An alkaline solution after extraction of sinomenine (1000 liter, kindly provided by Shionogi & Co., Ltd.) was extracted with a large amount of chloroform. The chloroform extract was filtered with cotton, evaporated under reduced pressure, and the residue was diluted with acetone and left standing to give a crystalline substance (40 g) which was collected by filtration. The mother liquor was evaporated to dryness under reduced pressure. The residue was chromatographed over silica gel (5 kg) and eluted with chloroform and acetone. The eluate with acetone gave an additional crop of crystalline substance (10 g). The crude crystals thus obtained were a mixture of acutumine (IIa) and acutumidine (IIb) (*ca.* 5:1), and the isolation of each compound was achieved in the same manner as described above.

**Properties of Acutumine (IIa)**——Colorless needles, mp 238—240° (decomp.), p$K_a$ 5.3 (50% EtOH). $[\alpha]_D^{15}$ −206° (c=0.69, pyridine). *Anal.* Calcd. for $C_{19}H_{24}O_6NCl$: C, 57.36; H, 6.08; N, 3.51. Found; C, 57.66; H, 5.91; N, 3.42. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 1690, 1670 (5- and 6-membered conj. ketone), 1625, 1605 (enolic C=C). UV $\lambda_{max}^{EtOH}$ m$\mu$ ($\varepsilon$): 245 (18, 970) (5-membered conj. keton), 270 (9750) (6-membered conj. keton). NMR (pyridine-$d_5$) $\tau$: 7.60 (3H, $NCH_3$), 6.28, 6.21, 5.96 (9H, 3×$OCH_3$), 4.99 (1H, d, $J$=5 cps, C<u>H</u>–OH; br. s, on addition of $D_2O$), 4.82 (1H, q, $J$=7.5, 11 cps, $CH_2$–C<u>H</u>(Cl)), 4.41 (1H, br. s, olefinic H), 1.75 (1H, d, $J$=5 cps, C<u>H</u>–OH (disappeared on addition of $D_2O$)); NMR (DMSO-$d_6$) $\tau$: 3.86 (1H, d, $J$=6 cps, HC–O<u>H</u>). Mass Spectrum *m/e*: 397 ($M^+$), 362 (M–Cl), 209 (base peak), 194, 181, 166, 150. Hydrobromide: Recrystallization from MeOH afforded colorless needles, mp 238—241° (decomp.). *Anal.* Calcd. for $C_{19}H_{24}O_6NCl\cdot HBr$: C, 47.67; H, 5.26. Found: C, 47.60; H, 4.96. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3300 (OH), 2450 (>$N^+$-H), 1675 (conj. C=O), 1630, 1600 (enolic C=C). Mass Spectrum *m/e*: 397 (M−HBr), 362 (M−HBr−35), 209 (base peak), 194, 181, 166, 150.

Mono-oxime: Colorless prisms, mp 213° (decomp.) (from EtOH). $[\alpha]_D^{35}$ −81.8° (*c*=0.55, MeOH). *Anal.* Calcd. for $C_{19}H_{25}O_6N_2Cl$: C, 55.28, H, 6.10; N, 6.78. Found: C, 55.09; H, 6.35; N, 6.85. UV $\lambda_{max}^{EtOH}$ m$\mu$ ($\varepsilon$): 244 (23800), 268 (11300). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3200 (OH), 1690 (conj. C=O), 1640, 1600 (enolic C=C). NMR (pyridine) $\tau$: 7.54 (3H, $NCH_3$), 6.24 6.13, 5.98 (9H, 3×$OCH_3$), near 5.1 (2H), 4.7 (1H, q, $J$=7, 11 cps), 4.4 (1H, br. s). Mass Spectrum *m/e*: 412 ($M^+$), 396, 377 (M–Cl), 361, 303, 244 (base peak), 208, 193.

**Properties of Acutumidine (IIb)**——Colorless needles, mp 239—241° (decomp.), p$K_a$ 6.6 (50% EtOH). $[\alpha]_D^{19}$-212.5° (*c*=0.16, pyridine). *Anal.* Calcd. for $C_{18}H_{22}O_6NCl$: C, 56.33; H, 5.78; N, 3.65. Found: C, 56.13; H, 5.73; N, 3.52. UV $\lambda_{max}^{EtOH}$ m$\mu$ ($\varepsilon$): 244 (13100), 269 (7370). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 1680, 1670 (5- and 6-membered conj. C=O), 1630, 1600 (enolic C=C). NMR (DMSO-$d_6$) $\tau$: 6.46, 6.13, 6.03 (9H, 3×$OCH_3$), 5.20—5.70 (2H), 4.60 (1H, br. s, olefinic H), 3.87 (1H, d, $J$=7 cps, –C<u>H</u>–OH). Mass Spectrum *m/e*: 383 ($M^+$), 348 (M–Cl), 195 (base peak), 167, 152.

**Acetylacutumine (IIc)**——A suspension of acutumine (IIa) (100 mg) in $Ac_2O$ (2 ml) and pyridine (0.1 ml) was allowed to stand at room temperature for 2 days. After decomposition of excess $Ac_2O$ by addition of

32) Sinomenine should be removed as thoroughly as possibly by exhaustive extraction with ether in order to simplify the isolation and purification of acutumine.

$H_2O$, the reaction mixture was basified with conc. $NH_4OH$ and extracted with ether. The ether extract was washed with $H_2O$, dried ($K_2CO_3$), and evaporated to dryness *in vacuo*. Crystallization from ether–hexane gave acetylacutumine (IIc) (90 mg) as colorless needles, mp 162—164°. p$K_a$ 4.6 (50% EtOH), $[\alpha]_D^{30}$ −94° ($c$= 0.38, $CHCl_3$). CD (MeOH) $[\theta]^{25}$ (m$\mu$): +60300 (266), −37200 (318). *Anal.* Calcd. for $C_{21}H_{26}O_7NCl$: C, 57.34; H, 5.92; O, 25.48; N, 3.19; Cl, 8.08. Found: C, 57.05; H, 6.51; O, 25.45; N, 3.06; Cl, 9.64. UV $\lambda_{max}^{EtOH}$ m$\mu$ ($\varepsilon$): 243 (18900) (5-membered conj. C=O), 270 (9200) (6-membered. conj. C=O). IR $\nu_{max}^{CHCl_3}$ cm$^{-1}$: 1750, 1220 ($OCOCH_3$). NMR $\tau$: 7.78 (3H, $-OCOCH_3$), 7.64 (3H, $NCH_3$), 6.30, 6.09, 5.89 (9H, 3×$OCH_3$), 5.5 (1H, q, $J$=7.5, 11 cps, $-C\underline{H}$(Cl)), 4.58 (1H, d, $J$=0.8 cps, olefinic H), 4.01 (1H, d, $J$=0.8 cps, C$\underline{H}$–OAc). Mass Spectrum *m/e*: 439 ($M^+$), 404 (M–Cl), 209 (base peak), 194, 181, 166, 150.

**Benzoylacutumine (IId)**——To a cooled suspension of acutumine (IIa) (50 mg) in absolute pyridine (1 ml) was added $C_6H_5COCl$ (0.5 ml) under stirring and the mixture kept at room temperature overnight. The dark brown reaction mixture was diluted with $H_2O$, basified with $NH_4OH$, and extracted with ether. The etherial extract was washed with $H_2O$ and dried ($K_2CO_3$). Removal of the solvent gave an oil, which was chromatographed over alumina (0.6×7 cm) and eluted with benzene to give benzoylacutumine (IId) (40 mg). Recrystallizations from ether gave colorless prisms, mp 239—241° (decomp.), $[\alpha]_D^{24}$ −226° ($c$=1.43, MeOH–chloroform (1:1)). *Anal.* Calcd. for $C_{26}H_{28}O_7NCl$: C, 62.22; H, 5.62; N, 2.79. Found: C, 61.96; H, 5.51; N, 2.53. UV $\lambda_{max}^{EtOH}$ m$\mu$ ($\varepsilon$): 240 (33960), 270 (sh) (10630), 282 (sh) (7900). IR $\nu_{max}^{CHCl_3}$ cm$^{-1}$: 1725 ($-OCOC_6H_5$). NMR $\tau$: 7.68 (3H, $NCH_3$), 6.30, 6.12, 5.90 (9H, 3×$OCH_3$), 5.38 (1H, q, $J$=7.5, 11 cps, C$\underline{H}$(Cl)), 4.51 (1H, br. s, olefinic H), 3.75 (1H, br. s, C$\underline{H}$–$OCOC_6H_5$), 1.75—2.65 (5H, $-COC_6\underline{H}_5$).

**N,O-Diacetylacutumidine (IIe)**——A mixture of acutumidine (IIb) (50 mg), $Ac_2O$ (1 ml), and pyridine (3 drops) was allowed to stand at room temperature for 4 days. The reaction mixture was diluted with $H_2O$, basified with $NH_4OH$, and extracted with chloroform. The combined extracts were washed with $H_2O$, dried ($K_2CO_3$), and evaporated to dryness *in vacuo*. The residue was chromatographed in chloroform over silica gel (0.6 × 6 cm) and the crystallization of the eluate from chloroform–ether gave N,O-diacetylacutumidine (IIe) (40 mg) as colorless needles, mp 216—220° (decomp.). $[\alpha]_D^{16}$ −189.3° ($c$=0.56, $CHCl_3$). *Anal.* Calcd. for $C_{22}H_{26}O_8NCl$: C, 56.47; H, 5.60; N, 2.99. Found: C, 56.73; H, 5.80; N, 2.76. UV $\lambda_{max}^{EtOH}$ m$\mu$ ($\varepsilon$) 241 (19400), 273 (9920). IR $\nu_{max}^{CHCl_3}$ cm$^{-1}$: 1750 (OAc), 1700 (5-membered conj. C=O), 1658 (6-membered conj. C=O, N–Ac), 1612. NMR $\tau$: 7.83 (3H, N–Ac), 7.78 (3H, OAc), 7.57 (2H, C$\underline{H}_2$–CO), 6.31, 6.10, 5.88 (9H, 3× $OCH_3$), 5.57 (1H, q, $J$=8, 11 cps; $-CH_2C\underline{H}$ (Cl)), 4.53, 4.02 (2H, 2× d, $J$=0.8 cps, $-C\underline{H}$=C–C$\underline{H}$–OAc). Mass Spectrum *m/e*: 467 ($M^+$) (base peak), 452, 432, 424, 237, 209, 195, 180, 152. CD (MeOH) $[\theta^{25}]$ (m$\mu$): +43,800 (266), −29,800 (322).

**N,O-Dibenzoylacutumidine (IIf)**——To a ice-cooled, stirred suspension of acutumidine (IIb) (50 mg) in pyridine (1 ml) was added $C_6H_5COCl$ (0.5 ml) and the mixture was stirred for 15 hr at room temperature. The excess reagent was decomposed by the addition of $H_2O$ and the mixture was basified with $NH_4OH$, extracted with ether. The etherial extract was washed with $H_2O$, dried ($K_2CO_3$), and evaporated to leave a yellow oil, which was chromatographed over alumina (0.6 × 7 cm) and eluted with benzene and with chloroform. From the fractions eluted with chloroform was obtained 30 mg of N,O-dibenzoylacutumidine (IIf) as a pale yellow oil which showed a single spot on TLC[31b]: UV $\lambda_{max}^{EtOH}$ m$\mu$: 238, 272, 283 (sh). IR $\nu_{max}^{CHCl_3}$ cm$^{-1}$: 1720 ($O-COC_6H_5$), 1700 (C=O), 1630–1670 (conj. C=O, $NCOC_6H_5$), 1610. NMR (benzene-$d_6$) $\tau$: 7.73 (2H, $\Delta\delta$=0.30, AB quartet, $J$=17.5 cps, active methylene), 7.10, 6.21, 6.08 (9H, 3× $OCH_3$), 5.08—5.66 (2H), 4.82 (1H, br. s, olefinic H), 3.68 (1H, br. s, C$\underline{H}$–$OCOC_6H_5$), 2.53—3.04 (10H, aromatic H). NMR $\tau$: 7.51 (2H, br. s, $-C\underline{H}_2$-CO–), 6.22, 6.10, 5.87 (9H, 3× $OCH_3$), 5.2—5.8 (2H), 4.46 (1H, br. s, olefinic H), 3.74 (1H, br. s, C$\underline{H}$–$OCOC_6H_5$).

**N-Methylation of Acutumidine (IIb)** ——A mixture of acutumidine (IIb) (50 mg), 37% HCHO (0.5 ml), and 98—100% HCOOH (0.5 ml) was heated on water bath for 2 hr. The cooled reaction mixture was basified with $NH_4OH$, extracted with chloroform, dried ($K_2CO_3$), and evaporated. Recrystallization of the residue from MeOH–chloroform gave 28 mg of colorless needles, mp 236—238° (decomp.), which were identified with acutumine (IIa) by mixed melting point determination and IR comparison (in Nujol).

**Reduction of Acetylacutumine(IIc) with Sodium Borohydride**——To an ice-cooled solution of acetylacutumine (200 mg) in MeOH (5 ml) was added $NaBH_4$ (200 mg) under vigorous stirring and the reaction was monitored by TLC. When the spot of the starting material on TLC was practically disappeared (about 2 hr),[33] the reaction was discontinued by addition of $H_2O$ (2 ml) and chloroform (100 ml). The mixture was shaken well and the inorganic precipitate was removed by filtration, washed thoroughly with chloroform. After drying over $Na_2SO_4$, the combined filtrates were evaporated *in vacuo* to give a pale yellow oil (180 mg), which was chromatographed on a silica gel column (0.8×9.5 cm). Elution with chloroform yielded first a small amount of the unreacted acetylacutumine (IIc) and then acetylacutuminol (V) (80 mg), pale yellow oil. Subsequent elution with acetone gave a crystalline mixture (60 mg), which was fractionally recrystallized from chloroform–MeOH to give 12 mg of acutuminol-A (VIa) and 25 mg of acutuminol-B (VIb).

33) The reduction must be stopped at the point that only a minute amount of the starting material (IIc) can be still detected on TLC, because the longer reaction time lowers markedly the yield of acetylacutuminol (V).

Acetylacutuminol (V): Pale yellow oil. UV $\lambda_{max}^{EtOH}$ mμ: 238. IR $\nu_{max}^{CHCl_3}$ cm$^{-1}$: 3500 (OH), 1745 (OAc), 1700 (C=O), 1620 (enol ether). NMR τ: 7.78 (3H, OAc), 7.71 (3H, $NCH_3$), 6.25, 6.18, 6.12 (9H, 3× $OCH_3$), 5.47 (1H, q, $J$=7.5, 11 cps), 5.3—5.8 (1H, m, C<u>H</u>-OH), 4.61 (1H, br. s, olefinic H), 4.00 (1H, br. s, C<u>H</u>-OAc).

Acutuminol-A (VIa): Needles, mp 168—171° ($CHCl_3$-MeOH). UV $\lambda_{max}^{EtOH}$ mμ (ε): 239 (17900). IR $\nu_{max}^{Nujol}$ cm$^{-1}$: 3500 (OH), 1690 (C=O), 1650 (C=C), 1615, 1605. NMR τ: 7.70 (3H, $NCH_3$), 6.32, 6.09, 5.96 (9H, 3× $OCH_3$), 5.3—5.8 (2-3H), 4.66 (1H, br. s, olefinic H). Mass Spectrum *m/e*: 399 ($M^+$) ($C_{19}H_{26}O_6NCl$), 381, 364 (M−Cl), 346, 345, 330, 304, 211, 193 (base peak), 179, 178, 151, 150, 136, 120.

Acutuminol-B (VIb): Needles, mp 190—193° ($CHCl_3$-MeOH). UV $\lambda_{max}^{EtOH}$ mμ (ε): 240 (16140). IR $\nu_{max}^{Nujol}$ cm$^{-1}$: 3500 (OH), 1690 (C=O), 1640 (C=C), 1610, 1600. NMR (pyridine-$d_5$) τ: 7.58 (3H, $NCH_3$), 6.30, 6.22, 6.18 (9H, 3× $OCH_3$), 4.40—5.50 (3-4H), 4.48 (1H, br. s, olefinic H). Mass Spectrum *m/e*: 399 ($M^+$) ($C_{19}H_{26}O_6NCl$), 381, 364 (M−Cl), 346, 345, 330, 304 (base peak), 211, 193, 178, 152, 151, 150, 136, 120.

**Oxidation of Acetylacutuminol (V) with Activated Manganese Dioxide**——Acetylacutuminol (V) (90 mg) was stirred with freshly prepared $MnO_2$ (1.1 g) in chloroform at room temperature for 10 hr. The mixture was filtered and the oxide residue was washed well with chloroform. Evaporation of the combined filtrates gave a brown oil (60 mg) which was chromatographed over silica gel (0.8×7 cm) from chloroform. Recrystallizations of the eluate from ether–hexane gave 52 mg of acetylacutumine (IIc), needles, mp 161—162°. Identity was established by mixed fusion and IR comparison (in $CHCl_3$).

**Acetylation of Acetylacutuminol (V)**——A mixture of 50 mg of V in $Ac_2O$ (1 ml) and pyridine (0.1 ml) was kept standing for 2 days at room temperature. After decomposition of excess $Ac_2O$ by addition of $H_2O$, the mixture was basified with conc. $NH_4OH$, extracted with ether, washed with $H_2O$, dried ($K_2CO_3$) and evaporated. The residue was chromatographed on a silica gel column (0.5×10 cm). Elution with chloroform gave the diacetate (VIII) (30 mg), which was recrystallized from ether–hexane to afford needles, mp 149—152°. $[\alpha]_D^{30}$ −111.9° ($c$=0.51, $CHCl_3$). *Anal.* Calcd. for $C_{23}H_{30}O_8NCl$: C, 57.09; H, 6.25. Found: C, 56.80; H, 6.27. UV $\lambda_{max}^{EtOH}$ mμ (ε): 238 (19500). IR $\nu_{max}^{CHCl_3}$ cm$^{-1}$: 1735 (OAc), 1700 (C=O), 1650 (C=C), 1620 (enol ether). NMR τ: 7.95, 7.80 (6H, 2× OAc), 6.38, 6.17, 6.13 (9H, 3× $OCH_3$), 5.46 (1H, q, $J$=7, 11 cps, C<u>H</u>-Cl), 4.61, 4.00 (2H, 2× d, $J$=0.8 cps, -C<u>H</u>=C-C<u>H</u>-OAc), 4.37 (1H, q, $J$=5, 10.5 cps, C<u>H</u>-OAc). CD (MeOH) $[\theta]^{25}$ (mμ): +8250 (304). Mass Spectrum *m/e*: 483 ($M^+$), 448 (M−Cl), 423, 388, 374, 346, 253, 193 (base peak), 179, 178, 151, 150, 136, 120.

Subsequent elution of the column with acetone gave a keto acetate (VIIb), faint yellow oil, 5 mg. UV $\lambda_{max}^{EtOH}$ mμ: 239, 275 (sh). IR $\nu_{max}^{CHCl_3}$ cm$^{-1}$: 1745 (OAc), 1695 (C=O), 1650, 1615. NMR τ: 7.78 (3H, OAc), 7.75 (3H, $NCH_3$), 6.39, 6.12 (6H, 2× $OCH_3$), 5.7 (1H, t, $J$=10 cps, C<u>H</u>-Cl), 4.55 (2H, two olefinic protons), 3.97 (1H, br. s, C<u>H</u>-OAc).

**Treatment of Acetylacutuminol (V) with Hydrobromic Acid**——Acetylacutuminol (V) (30 mg) was dissolved in a mixture of conc. HBr and MeOH (1:1) (1.5 ml) and allowed to stand for 24 hr at room temperature. After dilution with $H_2O$, the mixture was basified with $NH_4OH$ under ice-cooling, extracted with chloroform, dried ($K_2CO_3$), and evaporated to leave a faint brown oil (15 mg), which was purified by silica gel chromatography (0.5 × 5 cm). Elution with acetone gave a crystalline substance, which was recrystallized from acetone–ether to afford a diketo compound (VIIa) as colorless needles, mp 196—199° (decomp.). *Anal.* Calcd. for $C_{18}H_{22}O_5NCl$: C, 58.77; H, 6.03. Found: C, 58.68; H, 6.22. UV $\lambda_{max}^{EtOH}$ mμ (ε): 243 (20920), 274 (sh) (4080). IR $\nu_{max}^{CHCl_3}$ cm$^{-1}$: 3550, 3350 (0H), 1690 (conj. C=O), 1650, 1612. NMR τ: 7.73 (3H, $NCH_3$), 6.39, 6.09 (6H, 2×$OCH_3$), 5.1—5.7 (2H, C<u>H</u>-Cl, C<u>H</u>-OH), 4.60 (1H, br. s, olefinic H), 4.58 (1H, t, $J$=5 cps, olefinic H). Mass Spectrum *m/e*: 367 ($M^+$), 352, 332 (M−Cl), 324, 304, 179, 151, 136, 120.

**Acetylation of Diketo Compound (VIIa)**——Treatment of VIIa (17 mg) with $Ac_2O$ (1 ml) and pyridine (5 drops) for 2 days at room temperature yielded the mono-acetate (VIIb), which was purified by silica gel chromatography. Elution with acetone gave 16 mg of VIIb, colorless oil, which revealed a single spot on TLC[31b]. This product was identified with VIIb, obtained by acetylation of acetylacutuminol (V), by IR comparison.

**Treatment of Acutuminol-A (VIa) and -B (VIb) with Hydrobromic Acid**——Mixed crystals of VIa and VIb (35 mg), obtained by reduction of IIc with $NaBH_4$, were dissolved in conc. HBr–MeOH (1:4) (1 ml) and kept for 2 days at room temperature. The reaction mixture was basified with $NH_4OH$ under ice-cooling and extracted with chloroform, dried ($K_2CO_3$), and evaporated to dryness. The residue was recrystallized from acetone–ether to give the diketo compound (VIIa) (20 mg) as colorless needles, mp 196—199° (decomp.), which was identified with VIIa obtained by treatment of acetylacutuminol (V) with the same reagent.

**Oxidation of Acutuminol-A (VIa) and -B (VIb) with Activated Manganese Dioxide**——A mixture of 30 mg of mixed crystals of VIa and VIb (mp 172—179°) and 480 mg of activated $MnO_2$ was stirred in chloroform (5 ml) for 6 hr at room temperature. Usual work-up and silica gel chromatography (0.5×5cm) from chloroform gave 25 mg of a pale brown oil, which was identified with acutuminone (IX) by IR comparison.

**Hydrogenation of Acetylacutumine (IIc)** Acetylacutumine (IIc) (100 mg) was hydrogenated over $PtO_2$ (15 mg) in MeOH for 9 hr. Filtering the catalyst off and evaporation of the solvent under reduced pressure gave an oily residue (90 mg), which was chromatographed on neutral alumina (0.8×4 cm). Elution with benzene–hexane (1:1) and recrystallization from ether gave dihydroacetylacutumine (XV), colorless needles (21 mg), mp 230—231°. $[\alpha]_D^{33}$ −80.9° ($c$=0.21, $CHCl_3$). UV $\lambda_{max}^{EtOH}$ mμ (ε): 242 (18470). IR $\nu_{max}^{CHCl_3}$

$cm^{-1}$: 1755 (OAc), 1720 (C=O), 1700 (conj. C=O), 1620. NMR $\tau$: 7.75 (3H, OAc), 7.49 (3H, $NCH_3$), 6.12, 6.21, 6.44 (9H, $3\times OCH_3$), 5.46, 6.60 (2H, $2\times$d, $J=10$ cps, C<u>H</u> ($OCH_3$)-C<u>H</u> ($OCH_3$)), 5.2—5.7 (1H, m), 4.63 (1H, br. s, olefinic H), 4.08 (1H, br. s, C<u>H</u>-OAc). Mass Spectrum *m/e*: 441 ($M^+$, $C_{21}H_{28}O_7NCl$), 410, 375, 374 (base peak), 314, 290, 230, 179, 151, 136, 120.

**Oxidation of Acutumine (IIa) with Activated Manganese Dioxide**——Acutumine (IIa) (34 mg) was stirred with activated $MnO_2$ (590 mg) in chloroform (5 ml) for 9.5 hr at room temperature. After $MnO_2$ was filtered off, the filtrate was evaporated to dryness and the residue was chromatographed in chloroform over silica gel ($0.6\times 6$ cm). Elution with chloroform gave 22 mg of acutuminone (IX), a faint yellow oil, which showed a single spot on TLC[31b,d]. $[\alpha]_D^{33}$ $-25.3°$ ($c=0.75$, $CHCl_3$). UV $\lambda_{max}^{EtOH}$: 265 m$\mu$. IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1745, 1695 (5-membered ene-dione system), 1670 (6-membered conj. C=O), 1615. NMR $\tau$: 7.62 (3H, $NCH_3$), 6.31, 6.01, 5.90 (9H, $3\times OCH_3$), 5.36 (1H, q, $J=8$, 11 cps; C<u>H</u> (Cl)), 3.62 (1H, s, olefinic H). Mass Spectrum *m/e*: 395 ($M^+$), 360 (M–Cl), 332, 209 (base peak), 194, 181, 166, 150. Subsequent elution with acetone gave 8 mg of a by-product,[34] pale yellow oil. UV $\lambda_{max}^{EtOH}$ m$\mu$: 254, 320; UV $\lambda_{max}^{EtOH-KOH}$ m$\mu$: 281, 403, 450 (sh). IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1745, 1710, 1690, 1660, 1610, 1570. NMR $\tau$: 7.62 (3H, $NCH_3$), 6.22, 5.99, 5.73 (9H, $3\times OCH_3$), 5.43 (1H, q, $J=8$, 11 cps, C<u>H</u> (Cl)), 3.69 (1H, s, olefinic H). Mass Spectrum *m/e*: 409 ($M^+$), 381, 374 (M–Cl), 310, 195 (base peak), 180, 164.

**Reduction of Acetylacutumine (IIc) with Lithium Aluminium Hydride**——$LiAlH_4$ (50 mg) was added portionwise with swirling to a solution of acetylacutumine (IIc) (100 mg) in dioxane–ether (1:10) (10 ml) and the swirling continued for 4 hr at room temperature. After destroying the excess reagent by addition of $H_2O$ and $NH_4Cl$, the reaction mixture was filtered and the residue was washed with chloroform several times. The combined filtrates were dried over anhyd. $Na_2SO_4$ and evaporated to give a viscous oil (90 mg), which was chromatographed on a silica gel column ($0.8\times 7$ cm) and eluted with chloroform and chloroform–MeOH (100:1). The eluate with chloroform–MeOH (100:1) was recrystallized from benzene to give 60 mg of demethoxy-keto-diol (Xa), colorless needles, mp 136—137°. $[\alpha]_D^{30.5}$ $+53.9°$ ($c=0.31$, $CHCl_3$). *Anal.* Calcd. for $C_{18}H_{26}O_5NCl$: C, 58.14; H, 7.05. Found: C, 57.85; H, 6.97. The UV spectrum showed no characteristic absorption band. IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 3500: 3350 (OH), 1730 (5-membered C=O), 1660 (C=C). NMR $\tau$: 7.69 (3H, $NCH_3$), 6.24, 6.19 (6H, $2\times OCH_3$), 5.75—5.0 (3H, m, C<u>H</u>-Cl, -C<u>H</u>-OH).

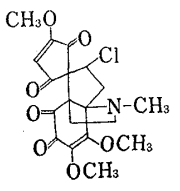
**Acetylation of Demethoxy-keto-diol (Xa)**——Treatment of demethoxy-keto-diol (Xa) (50 mg) with $Ac_2O$ (1 ml) and pyridine (0.1 ml) at room temperature overnight yielded the diacetate (Xb), which was purified by alumina chromatography ($0.5\times 6.4$ cm). Elution with benzene and recrystallizations from ether–hexane afforded colorless needles, mp 138—142° (decomp.) (40 mg). $[\alpha]_D^{32}$ $+10.0°$ ($c=0.6$, $CHCl_3$). CD (MeOH) $[\theta]^{25}$ (m$\mu$): $+4940$ (311). *Anal.* Calcd. for $C_{22}H_{30}O_7NCl$: C, 57.94; H, 6.63; N, 3.07. Found: C, 58.02, H, 6.73, N, 2.25. UV: no characteristic peak. IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1730, 1655. NMR $\tau$: 7.92, 7.81 (6H, $2\times$OAc), 7.74 (3H, $NCH_3$), 6.40, 6.18 (6H, $2\times OCH_3$), 5.30 (1H, q, $J=7.5$, 11 cps; C<u>H</u>-Cl), 4.83—4.23 (2H, m, $2\times$C<u>H</u>-OAc). Mass Spectrum *m/e*: 455 ($M^+$), 420 (M–Cl), 396, 360, 294, 284, 193 (base peak), 178, 161, 150.

**Oxidation of Demethoxy-keto-diol (Xa) with Activated Manganese Dioxide**——To a solution of Xa (80 mg) in 5 ml of chloroform was added activated $MnO_2$(850 mg) and stirred for 9 hr at room temperature. Usual working up gave a monohydroxy compound (XIa) which was recrystallized from chloroform–ether to give colorless needles (60 mg), mp 166—169°. $[\alpha]_D^{29}$ $-31.4°$ ($c=0.51$, $CHCl_3$). *Anal.* Calcd. for $C_{18}H_{24}O_5NCl$: C, 58.45; H, 6.54; N, 3.79. Found: C, 58.77; H, 6.70; N, 3.45. UV $\lambda_{max}^{EtOH}$ m$\mu$ ($\varepsilon$): 269 (9935). IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1730 (5-membered C=O), 1670 (6-membered conj. C=O), 1600 (enol ether). NMR $\tau$: 7.12 (3H, $NCH_3$), 6.29, 5.89 (6H, $2\times OCH_3$), 5.7—5.35 (1H, br. t, C<u>H</u>-OH), 5.24 (1H, t, $J=9$ cps, C<u>H</u>-Cl). Mass Spectrum *m/e*: 369 ($M^+$), 334 (M–Cl), 306, 209 (base peak), 194, 181, 166, 150.

**Acetylation of Monohydroxy Compound (XIa)**——A mixture of XIa (38 mg), $Ac_2O$ (1 ml), and pyridine (3 drops) was allowed to stand for 2 days at room temperature. The reaction mixture was worked up in the usual way and the product was chromatographed over silica gel ($0.5\times 6$ cm) in chloroform. Monoacetate (XIb) was obtained as a colorless oil (30 mg) which showed a single spot on TLC.[31b] IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1730 (OAc, 5-membered C=O), 1665 (6-membered conj. C=O), 1600. NMR $\tau$: 7.82 (3H, OAc), 7.64 (3H, $NCH_3$), 6.30, 5.90 (6H, $2\times OCH_3$), 5.32 (1H, q, $J=8$, 11 cps; C<u>H</u>-Cl), 4.85—4.45 (1H, br. t, C<u>H</u>-OAc).

**Von Braun Reaction of Acutumidine (IIb)**——To a suspension of acutumidine (IIb) (100 mg) in absolute benzene was added 300 mg of BrCN and heated under reflux in an oil bath for 6 hr with stirring. After evaporation of the solvent under reduced pressure, residual BrCN was removed completely by several evaporations with benzene. The residue was chromatographed over silica gel ($0.7\times 8$ cm) and developed with chloroform. Subsequent elution with chloroform–acetone followed by recrystallization from acetone gave

34) The structure of this compound might be XXXXIII. However, further investigation could not be carried out because of its scant amount.



XXXXIII

40 mg of N-cyano-acutumidine (IIIa), colorless needles, mp 259—261° (decomp.). $[\alpha]_D^{34}$ −82.6° ($c$=0.23, $CHCl_3$–MeOH). *Anal.* Calcd. for $C_{19}H_{21}O_6N_2Cl$: C, 55.82; H, 5.18. Found: C, 56.05; H, 5.24. UV $\lambda_{max}^{EtOH}$ mμ (ε): 244 (20000), 266 (12700). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3500 (OH), 2210 (N-CN), 1690 (5-membered conj. C=O), 1670 (6-membered conj. C=O), 1630, 1610. NMR (pyridine-$d_5$)τ: 8.02—8.40 (1H, m), 7.1—7.42 (3H), 6.7—6.95 (2H, $C\underline{H}_2CH$–(Cl)), 6.38, 6.10, 5.82 (9H, 3×$OCH_3$), 4.72—5.15 (3-4H), 4.47 (1H, br. s, olefinic H). Mass Spectrum *m/e*: 408 ($M^+$), 373, 372, 233, 220, 191, 175, 155, 113.

**Acetylation of N-Cyano-acutumidine (IIIa)**——A 20 mg sample of IIIa was treated with $Ac_2O$ (1 ml) pyridine (5 drops) at room temperature for 2 days. Working up of the mixture in the usual manner and recrystallization from acetone gave N-cyano-O-acetylacutumidine (IIIb) (18 mg) which melted over 270°. $[\alpha]_D^{35.5}$ −126.6° ($c$=0.15, $CHCl_3$). *Anal.* Calcd. for $C_{21}H_{23}O_6N_2Cl\cdot{}^1/_3H_2O$: C, 55.21; H, 5.18. Found: C, 55.24; H, 5.36. UV $\nu_{max}^{EtOH}$ mμ (ε): 243 (20400), 266 (12400). IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 2220 (N-CN), 1750 (OAc), 1700 (5-membered conj. C=O), 1670 (6-membered conj. C=O), 1620. NMR τ: 8.05—8.40 (2H), 7.75 (3H, OAc), 6.98—7.25 (2H, $C\underline{H}_2$-CH (Cl) ), 6.32—6.67 (2H), 6.23, 6.09, 5.82 (9H, 3×$OCH_3$), 5.57 (1H, q, $J$=8, 11 cps; $CH_2$-C<u>H</u>-Cl), 4.52, 4.04 (2H, 2×br.s, -C<u>H</u>=C-C<u>H</u>-OAc). Mass Spectrum *m/e*: 450 ($M^+$) (base peak), 355, 233, 220, 195, 157, 136, 113.

**Treatment of Acutumine (IIa) with Zinc in Acetic Anhydride**——To a suspension of acutumine (IIa) (1.2g) in $Ac_2O$ (20 ml) was added Zn powder (2g)[35] and heated under reflux for 6 hr in an oil bath with stirring (bath temperature was kept at 150—160°). After filtration of the cooled mixture, $Ac_2O$ was decomposed by addition of ice–water and acidic solution was extracted thoroughly with ether (10 times). The etherial extract was washed successively with $H_2O$, 10% aq. $K_2CO_3$, and $H_2O$. After drying ($Na_2SO_4$), removal of the solvent gave a mixture of neutral products, brownish red oil (720 mg). The acidic aqueous layer was made alkaline with $NH_4OH$ and extracted with chloroform, dried ($K_2CO_3$), and evaporated to afford a basic fraction, brown oil (120 mg). The above neutral fraction was chromatographed over silica gel (1.2×11 cm) from chloroform. Initial fraction (490 mg, eluted with 50 ml of chloroform) was again chromatographed over silica gel (0.8×10 cm) to give a mixture of acetylphenol-A (XXa) and acetylphenol-B (XXIa) (340 mg). Futher purification of a 50 mg portion of this mixture by alumina chromatography gave pure acetylphenol-A (XXa), a colorless oil which revealed a single spot on TLC[31b] (major product). IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1750 (OAc), 1700(5-membered conj. C=O), 1615. UV $\lambda_{max}^{EtOH}$ mμ: 233, 275 (sh), 304(sh). NMR τ: 7.72, 7.85 (6H, 2×OAc), 6.07, 6.11, 6.18 (9H, 3×$OCH_3$), 4.50, 4.19 (2H, 2×br. s, H<u>C</u>=C-C<u>H</u>-OAc), 3.56 (1H, s, aromatic H). However, acetylphenol-B(XXIa), a minor product, could not be obtained in homogeneous state by this chromatography.

**Hydrolysis of Acetylphenol-A(XXa) followed by O-Methylation**——To a solution of acetylphenol-A(XXa) (100 mg) in MeOH (3 ml) was added $NaHCO_3$ (106 mg) and $H_2O$ (5 drops) and the mixture was gently boiled for 5 minutes on a water bath. After evaporation of the solvent *in vacuo*, the residue was dissolved in chloroform, dried over anhyd. $Na_2SO_4$, and filtered. Evaporation of the solvent gave a crude product (XXb) (76 mg) which was used for the subsequent methylation without further purification. An etherial solution of diazomethane (prepared from 5 g of nitrosomethylurea) was added to a solution of XXb in MeOH (10 ml), and the solution was allowed to stand overnight at room temperature. Usual working up gave a crude O-methyl ether which was chromatographed on a silica gel column (0.8×9 cm) from chloroform to afford a semicrystalline (XXc) substance (60 mg), showing a nearly single spot on TLC.[31b] Further purification by distillation in high vacuum ($4\times10^{-4}$—$6\times10^{-4}$ mmHg, at 150—200°) gave phenol-A O-methyl ether (XXc), colorless oil, which solidified slowly, mp 74—77°. $[\alpha]_D^{33}$ −85.8° (c=0.68, $CHCl_3$). UV $\lambda_{max}^{EtOH}$ mμ (ε): 232 (23020), 275 (3290), 285 (2690), 306 (1060). IR $\gamma_{max}^{CHCl_3}$ $cm^{-1}$: 3550, 3380 (OH), 1690, 1608. NMRτ: 6.08, 6.11, 6.19, 6.23 (12H, 4×$OCH_3$), 5.35 (1H, d, J=5.0 cps; singlet at the presence of $D_2O$, -C<u>H</u>-OH), 4.61 (1H, s, olefinic H), 3.81 (1H,s, aromatic H). Mass Spectrum *m/e*: 320 ($M^+$, $C_{17}H_{20}O_6$) (base peak), 305, 288, 274, 243, 229.

**Hydrolysis of the Mixture of Acetylphenol-A and-B followed by Methylation**——The mixture of acetylphenol-A(XXa) and -B (XXIa) described above (290 mg) was dissolved in MeOH (10 ml) and to this solution were added $NaHCO_3$ (200 mg)and $H_2O$(1.5 ml), then heated on a water bath for 7 minutes. The reaction mixture was worked up in the same manner as above and the crude hydrolysis product was treated with diazomethane without further purificaton. Usual treatment gave a residue (250 mg) which was chromatographed over silica gel (1.0×12 cm). Careful elution with chloroform gave first an unidentified substance, yellow oil, and next 6 mg of phenol-B O-methyl ether (XXIb) which was recrystallized from acetone–ether to give colorless needles, mp 219—221.5° (decomp.). $[\alpha]_D^{17}$ −360° ($c$=0.5, MeOH). *Anal.* Calcd. for $C_{16}H_{17}O_5Cl$: C, 59.19; H, 5.28. Found: C, 59.29; H, 5.20. IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1700 (C=O). UV $\lambda_{max}^{EtOH}$ mμ (ε): 234 (29090), 279 (2630), 286 (2670). NMRτ: 7.20 (1H, d, $J$=8 cps, CH-O<u>H</u>), 6.02, 6.20, 6.25, (9H, 3×$OCH_3$) 5.10 (1H, t, $J$=9 cps, $CH_2$-C<u>H</u> (Cl), 508 (1H, d, $J$=8cps, 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, 2×d, $J$=2 cps, aromatic H). Mass Spectrum *m/e*: 324 ($M^+$), 288 (M-HCl, base peak) 243, 229, 175, 145. Further elution of the column with chloroform and with acetone gave 100 mg of phenol-A O-methyl ether (XXc).

**Acetylation of Phenol-A O-Methyl Ether** (XXc)——A mixture of XXc (20 mg), $Ac_2O$ (2 ml) and pyridine (0.1 ml) was allowed to stand at room temperature overnight. The excess $Ac_2O$ was decomposed

35) Zn powder was prepared by washing twice with dil. HCl, then with distilled water three times, and drying over $P_2O_5$ at 100° *in vacuo*.

with $H_2O$, basified with $NH_4OH$, and extracted with ether. The product thus obtained was chromatographed over alumina (0.5×12.5 cm). Fractions eluted with benzene and benzene–ether were combined and evaporated to give a monoacetate (XXd) as a colorless oil (15 mg). IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1745 (OAc), 1700 (C=O). UV $\lambda_{max}^{EtOH}$ $m\mu$ ($\varepsilon$) : 234 (12400), 276 (1780), 285 (1590). NMR $\tau$: 7.85 (3H, OAc), 6.21, 6.18, 6.10, 6.06 (12H, 4×$OCH_3$), 4.46 (1H, s, olefinic H), 4.22 (1H, s, CH–OAc), 3.74 (1H, s, aromatic H). Mass Spectrum *m/e*: 362 ($M^+$, $C_{19}H_{22}O_7$) (base peak), 332, 320, 303, 245, 229.

**Oxidation of Phenol-A O-Methyl Ether (XXc) with Activated Manganese Dioxide**——Activated $MnO_2$ (1g) was added to a solution of the methyl ether (XXc) (100 mg) in chloroform (10 ml) and stirred for 12 hr at room temperature. $MnO_2$ was filtered off and the filtrate was evaporated to dryness. Chromatography of the residue on a silica gel column (0.6×7.5 cm) in chloroform and recrystallization from acetone–ether afforded a product (XXII), pale yellow needles, mp 161—162° (60 mg). $[\alpha]_D^{34.5}$ +1.6° ($c$=0.6, $CHCl_3$). *Anal.* Calcd. for $C_{17}H_{18}O_6$: C, 64.14; H, 5.71. Found: C, 64.20; H, 5.59. UV $\lambda_{max}^{EtOH}$ $m\mu$ ($\varepsilon$): 225 (11300), 263 (12200). IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1745, 1690 (5-membered ene-dione system). NMR $\tau$: 6.25, 6.17, 6.07, 5.94 (12H, 4×$OCH_3$), 3.88 (1H, s, olefinic H), 3.54 (1H, s, aromatic H). Mass Spectrum *m/e*: 318 ($M^+$, $C_{17}H_{18}O_6$) (base peak), 303, 219, 191, 161, 159.

**Permanganate Oxidation of Phenol -A O-Methyl Ether (XXc)**——To a solution of 90 mg of XXc in acetone (freshly distilled with $KMnO_4$) was addd dropwise 5% aq. $KMnO_4$ (10 ml) with stirring and then refluxed on a water bath (bath temperature at 60—70°) for 4 hr. After removal of the generated $MnO_2$ by filtration, the filtrate was evaporated under reduced pressure and extracted with AcOEt. The combined AcOEt extracts were dried ($Na_2SO_4$) and evaporated under reduced pressure to give an oily residue (32 mg), which was chromatographed over sillica gel (0.5×6.5 cm). Elution with chloroform yielded a crystalline compound (XXIII) (20 mg) which was recrystallized from ether–hexane, giving colorless needles, mp 75—77°. *Anal.* Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.79; H, 6.43. UV $\lambda_{max}^{EtOH}$ $m\mu$ ($\varepsilon$): 270 (13700), 310 (6310). IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1700 (C=O). NMR $\tau$: 6.11, 6.05, 6.03 (9H, 3×$OCH_3$), 6.8—7.5 (4H, $A_2B_2$ pattern), 2.98 (1H, s, aromatic H). Mass Spectrum *m/e*: 222 ($M^+$, base peak), 207, 192, 179, 164, 149, 137. 121.

**Synthesis of 4,5,6-Trimethoxy-1-indanone (XXIII)**——i) 2,3,4-Trimethoxy-benzaldehyde (XXVII): A mixture of N-methylformanilide (13.5 g) and phosphorous oxychloride (15.3 g) was stirred at room temperature in a flask protected from moisture by a drying tube. In about 15 minutes the mixture solidified. To this mixture was added trimethylpyrogallol (16.8 g) with shaking and then stirred for 6 hr. The reaction mixture was poured into ice water and allowed to stand overnight. The product was then taken up in ether (3 times) and the etherial solution was shaken well with a saturated aq. $NaHSO_3$ (40 g) in a separatory funnel. The aquoes layer containing the aldehyde-bisulfite adduct was separated and to this solution was added excess $Na_2CO_3$ in small portions and heated at 60° for 3 hr. After cooling, the separated oily material was extracted with ether, dried ($K_2CO_3$), and evaporated to give the aldehyde (XXVII) (11.5 g), mp 30—32°.

ii) 2,3,4-Trimethoxy-cinnamic Acid: In a flask were placed 10.4 g of malonic acid, 8.3 g of 2,3,4-trimethoxy-benzaldehyde (XXVII), and 20 ml of pyridine and warmed on a water bath. To this mixture was added piperidine (0.75 ml), a reflux condencer and a thermometer being fitted to the flask and the mixture heated in an oil bath. Internal temperature was gradually raised to 80° and maintained for 1 hr, then finally heated under reflux for additional 3 hr. After cooling, the reaction mixture was poured into 200 ml of cold water. The mixture was acidified by addition of conc. HCl with stirring to separate white crystals which were collected by suction, washed with cold water several times. The crude acid was dissolved in 2.6% aq. NaOH, filtered, and the filtrate was acidified with HCl to give 9.3 g of 2,3,4-trimethoxy-cinnamic acid (XXVIII), colorless needles, mp 174—176°.

iii) $\beta$-(2,3,4-Trimethoxyphenyl) propionic Acid (XXIX): To a solution of XXVIII (45 g) in 90% EtOH was added 4.5 g of Na-Hg (2.8%) and heated for 2 hr on a water bath with stirring. Occasionally, basicity of the reaction mixture was weakened by addition of glacial acetic acid. Hg was removed by decantation and the solvent was evaporated to the half volume under reduced pressure. The solution was acidified with conc. HCl and cooled with a freezing mixture to precipitate crystals (XXIX), which were collected by filtration. Colorless needles (3.5 g), mp 68—70°.

iv) 4,5,6-Trimethoxy-1-indanone (XXIII): A mixture of XXIX (1.4 g)and PPA (2 g) was heated for 2 hr on a water bath (bath temperature at 70—80°). After cooling and dilution with $H_2O$, the mixture was extracted with ether, washed with $H_2O$, dried over anhyd. $Na_2SO_4$, and evaporated to leave a yellowish red oil, which was chromatographed on a silica gel column (1.0×16 cm). Elution with chloroform and recrystallization from ether–hexene gave 4,5,6-trimethoxy-1-indanone (XXIII), colorless needles, mp 75—77° (400 mg). *Anal.* Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.72; H, 6.36.

**Reduction of Phenol-B O-Methyl Ether (XXIb) with Lithium Aluminium Hydride followed by Oxidation with $KMnO_4$**——The compoumd (XXIb) (54 mg) was reduced with lithium aluminium hydride (80 mg) in THF (2 ml) for 2 hr at room temperature. After decomposition of the excess reagent with $H_2O$ and $NH_4$-Cl, the mixture was diluted with chloroform (100 ml), dried ($Na_2SO_4$), filtered, and evaporated to dryness. The residue thus obtained was dissolved in acetone and to this solution was added 5% solution of $KMnO_4$ in acetone–water (3:2) (20 ml) and gently refluxed with stirrimg for 1 hr (bath temperature: 60—70°). The excess $KMnO_4$ was decomposed by addition of EtOH and the inorganic precipitate was filtered off. The filtrate was evaporated to dryness *in vacuo* and the residue was then extracted with chloroform, dried

($Na_2SO_4$), and again evaporated. Chromatography of the residue over silica gel (0.5×6 cm) from chloroform gave a keto compound (XXV), which was purified by sublimation in high vacuum ($6\times10^{-4}$ mmHg, at 50—75°) to afford colorless needles (8 mg), mp 92—96°. UV $\lambda_{max}^{EtOH}$ mμ: 262, 324. IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1700(C=O). NMR τ: 6.18, 6.13 (6H, 2×$OCH_3$), 6.9—7.5 (4H, $A_2B_2$ pattern), 3.37, 3.22 (2H, 2×d, $J$=2 cps, aromatic H), Mass Spectrum *m/e*: 192 ($M^+$, $C_{11}H_{12}O_3$) (base peak), 149, 121.

**Reduction of Acutumine (IIa) with Zinc-Acetic Acid**——A solution of acutumine (IIa) (170 mg) in glacial acetic acid (10 ml) was stirred with Zn powder (400 mg) at room temperature for 20 hr. After removal of Zn powder by filtration, the reaction mixture was diluted with $H_2O$, basified with $NH_4OH$, and extracted with ether and then with chloroform. The combined chloroform extracts were dried ($K_2CO_3$) and evaporated to give a pale yellow residue (160 mg). Recrystallization from acetone–ether afforded a carbinolamine (XXXIIa) (100 mg) as colorless needles, mp 168—171°. $[\alpha]_D^{32}$ −170.4° (c=0.88, MeOH). *Anal.* Calcd. for $C_{19}H_{26}O_6NCl$: C, 57.07; H, 6.55; N, 3.50. Found: C, 56.90; H, 6.52; N, 3.34. p$K_a$ 6.8 (50% EtOH). UV $\lambda_{max}^{EtOH}$ mμ (ε): 240 (17700). IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 3400 (OH), 1690 (5-membered conj. C=O), 1610. NMR τ: 7.62 (3H, $NCH_3$), 6.80, 6.94 (2H, C<u>H</u>$_2$–CHCl), 6.46, 6.22, 6.10 (9H, 3×$OCH_3$), 6.37 (1H, C<u>H</u>–$OCH_3$), 4.70, 5.29 (2H, 2×d, $J$=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); NMR (pyridine) τ: 7.41 (3H, $NCH_3$), 6.33, 6.30, 6.18 (9H, 3×$OCH_3$), 6.18 (1H, C<u>H</u>–$OCH_3$), 4.55—4.95 (3H), 4.51 (1H, s, olefinic H). Mass Spectrum *m/e*: 399 ($M^+$), 384, 362, 348, 332, 316, 304, 300, 115 (base peak).

**Reduction of Acetylacutumine (IIc) with Zinc-Acetic Acid**——A solution of acetylacutumine (IIc) (250 mg) in glacial acetic acid (20 ml) was stirred with Zn powder (555 mg) for 23 hr at room temperature. Ether extracts and chloroform extracts, obtained in the same manner as above, were each dried ($K_2CO_3$) and evaporated to leave 150 mg of a faint yellow oil and 80 mg of a brownish red oil, respectively. The oily residue obtained from the etherial extract was chromatographed over silica gel (0.8×6.7 cm). Elution with chloroform gave 120 mg of monoacetylcarbinolamine (XXXIII) as a colorless oil which showed a single spot on TLC.[31b] UV $\lambda_{max}^{EtOH}$ mμ: 238. IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 3400 (OH), 1765 (OAc), 1700 (5-membered conj. C=O), 1615. NMR τ: 7.82 (3H, OAc), 7.62 (3H, $NCH_3$), 5.55 (1H, t, $J$=9.5 cps, C<u>H</u>–Cl), 4.65, 3.93 (2H, 2×d, $J$=0.8 cps, C<u>H</u>=C–C<u>H</u>–OAc). Mass Spectrum *m/e*: 441 ($M^+$, $C_{21}H_{28}O_7NCl$), 332, 314, 272, 133, 119 (base peak), 115. Subsequent elution with acetone gave the carbinolamine (XXXIIa) (5 mg). The crude product obtained from the chloroform extract was also chromatographed over silica gel to give the carbinolamine (XXXIIa) (45 mg).

**Acetylation of Carbinolamine (XXXIIa) with Acetic Anhydride-pyridine**——A mixture of carbinolamine (XXXIIa) (100 mg), $Ac_2O$ (2 ml) and pyridine (5 drops) was allowed to stand at room temperature for 2 days. After decomposition of the excess $Ac_2O$ by addition of $H_2O$, the acidic mixture was extracted with ether and then with chloroform. The etherial extract was washed successively with $H_2O$, 10% aq. $K_2CO_3$, and $H_2O$ and dried ($Na_2SO_4$). Removal of solvent gave a oily residue which behaved on TLC[31a-d] as a homogeneous material, but on NMR examination as a mixture. Attempts of separation resulted in failure because of its unstable nature. The chloroform extract was dried ($Na_2SO_4$) and evaporated to afford a brownish red oil (10 mg). Chromatography of the latter over silica gel (0.5×5 cm) from chloroform and acetone gave 6 mg of N,O-diacetate (XXXIV) as a colorless oil, TLC: single spot. UV $\lambda_{max}^{EtOH}$ mμ: 242 (5-membered conj. C=O), 272 (6-membered conj. C=O). IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1750 (OAc), 1700 (C=O), 1660—1610 (6-membered conj. C=O, N–Ac, enolic C=C). NMR τ: 7.95, 7.81 (6H, NAc and OAc), 7.06 (3H, N(Ac)C<u>H</u>$_3$), 6.32, 6.11, 5.95 (9H, 3×$OCH_3$), 5.53 (1H, q, $J$=7, 10 cps, C<u>H</u>–(Cl)), 4.6, 3.70 (2H, 2×d, $J$=0.8 cps, C<u>H</u>=C–C<u>H</u>–OAc). On the other hand, the acidic aqueous layer was basified with $NH_4OH$ and extracted with chloroform. After drying ($Na_2SO_4$), evaporation of the solvent left a basic product (8 mg), which was chromatographed over silica gel (0.5×3 cm) to afford acetylcarbinolamine (XXXIII) (6 mg). Identity was established by IR comparison.

**Acetylation of XXXIIa with Acetic Anhydride-sodium Acetate**——A solution of XXXIIa (50 mg) and anhyd. AcONa (100 mg) in $Ac_2O$ (5 ml) was heated under reflux in an oil bath for 2 hr. The excess $Ac_2O$ was decomposed with $H_2O$ and the acidic solution was extracted with ether and with chloroform, each extract was treated in the usual manner. The residue (20 mg) obtained from the chloroform extract was chromatographed over silica gel (0.6×6.5 cm) and eluted with acetone to afford N, O-diacetate (XXXIV) (15 mg) as a colorless oil. On the other hand, working up of the acidic aqueous layer as usual gave a basic oily product (10 mg). Purification of this fraction through silica gel chromatography (0.5×3.3 cm) furnished acetylcarbinolamine (XXXIII) (6 mg).

**Acknowledgement** The authors wish to thank Dr. H. Tanaka of Shionogi & Co., Ltd. for preparing the methanol extracts of plants, and for a gift of aqueous solution remaining after extraction of sinomenine from *Sinomenium acutum*, Dr. Y. Asahi of Takeda Chemical Industries, Ltd. for CD measurements, Dr. K. Tohri of Shionogi & Co., Ltd. for the measurement of 100 MC NMR spectrum, Mr. S. Matsumoto of Osaka University for p$K_a$ determinations. They also thank Dr. T. Shingu and Miss M. Okawa for NMR measurements, Mr. A. Kato, Dr. T. Ibuka, and Mr. M. Kitano for taking mass spectra, Mr. M. Yamamoto for IR determinations and ORD measurements, and Dr. K. Konobu and Miss Y. Mano and collaborators for microanalyses.