Summary

Methylanhydroitaconitin (III) which was prepared from anhydroitaconitin by treatment with the methylating agent followed by hydrolysis gave 2-methoxy-4-methylbenzaldehyde on ozonolysis. While the ozonolysis of the compound, $C_{14}H_{18}O_5$, which was obtained by alkaline hydrogenation of anhydroitaconitin yielded *cisoid*-dihydrohaematinic acid (XI). From these and other experimental results the structure of the compound, $C_{14}H_{18}O_5$ was established as XII.

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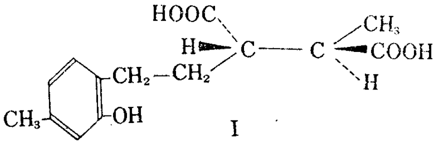
UDC 581.19 : 582.282.12

12. Shoichi Nakajima: Studies on the Structure of Itaconitin. VI.*1 The Structures of Anhydroitaconitin and Its Derivatives.*2

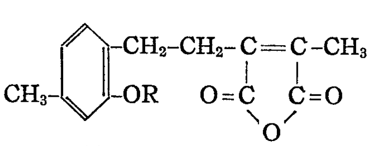
(*Hoshi College of Pharmacy**3)

In previous paper*1 of this series, it was reported that the chemical structure of the alkaline hydrogenation product, $C_{14}H_{18}O_5$, of anhydroitaconitin was established as I. The present paper concerns with the determination of the structures of anhydroitaconitin and all its derivatives so far prepared.



I

Considering from the chemical structure (I) of $C_{14}H_{18}O_5$ acid, dihydroanhydroitaconitin which was yielded by catalytic hydrogenation of anhydroitaconitin under neutral condition[1] could be represented as the structure (II). In neutral solvent, the hydrogenation of anhydroitaconitin took place at the double bond in the side-chain remaining the unsaturated acid anhydride ring unaffected, whereas in alkaline condition, the ring opening of the anhydride moiety caused the hydrogenation at the double bond located between two carboxyl groups and thus two moles of hydrogen was uptaken giving the compound (I).



II: R=H
III: R=COCH3

Favoring the proposed formula (II) of dihydroanhydroitaconitin, its ultraviolet spectral curve (Fig. 1) was almost superimposable with the added spectral curve of *p*-xylenol (UV λ_{max}^{EtOH} mμ (log ε): 216 (3.83), 275 (3.29), 283 (3.26))[2] and 3,4,5,6-tetrahydrophthalic anhydride (UV $\lambda_{max}^{cyclohexane}$ mμ (log ε): 250 (3.55))[3].

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*1 Part V. S. Nakajima: This Bulletin, 13, 64 (1965).

*2 Presented at VIIth Japanese Symposium on the Chemistry of Natural Products (Oct. 1963). Proceedings, p. 144 (in Japanese).

*3 2-Chome, Ebara, Shinagawa-ku, Tokyo (仲嶋正一).

1) Part IV. S. Nakajima, K. Kinoshita, S. Shibata: This Bulletin, 13, 58 (1965).

2) R.A. Friedel, M. Orchin: "Ultraviolet Spectra of Aromatic Compounds," No. 40 (1951), John Wiley & Sons Inc., New York, N.Y.

3) J.E. Baldwin, D.H.R. Barton, J.L. Bloomer, L.M. Jackman, L. Rodriguez-Hahn, J.K. Sutherland: Experientia, 18, 345 (1962).

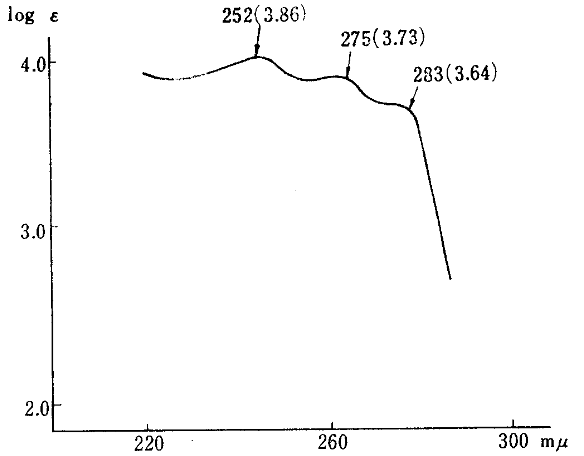


Fig. 1. Ultraviolet Spectrum of Dihydroanhydroitaconitin (in EtOH)

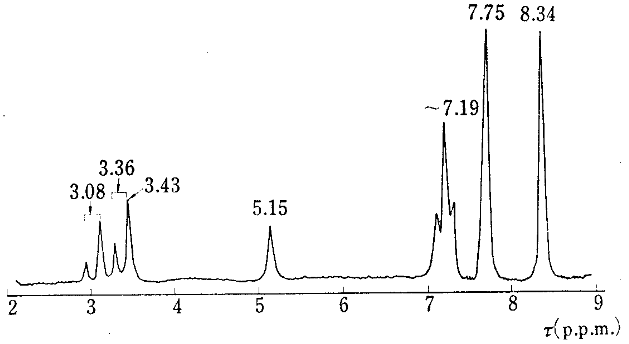


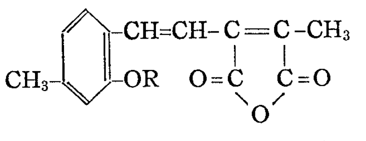
Fig. 2. Nuclear Magnetic Resonance Spectrum of Dihydroanhydroitaconitin, measured in Deuterochloroform at 60 Mc.p.s.

The nuclear magnetic resonance spectral analysis (Fig. 2)[*4] also supported the formula (II). The proton signals of toluene and allyl methyls appeared as singlets at 7.75 and 8.34 τ, respectively. The adjacent methylenes in the side-chain appeared near 7.19 τ as complex signals, probably of A_2B_2 type, the hydroxyl proton at 5.15 τ which was shifted by change of concentration, and two neighbouring protons of the benzene ring as an AB quartet (J=7.5 c.p.s.) centered on 3.08 and 3.36 τ, the latter of which is broadened because of a very weak coupling with another benzene proton appearing at 3.43 τ.

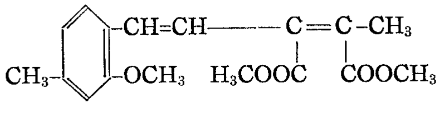
The titration using phenolphthalein as an indicator showed this substance to be monobasic in cold and dibasic in hot[1] solution. This can only be explained by assuming that the five-membered unsaturated acid anhydride reacts as monobasic in cold and as dibasic in hot solution.

Dihydroacetylanhydroitaconitin (III) showed nuclear magnetic resonance signals[*4] at 7.27 τ (A_2B_2), 7.68, 7.70 τ (toluene and acetate methyls), and 8.39 τ (allyl methyl), in resemblance with those of dihydroanhydroitaconitin (II) except the presence of the signal of acetate methyl.

Hence the structure of anhydroitaconitin would be formulated as IV, and the compound, $C_{17}H_{20}O_5$,[*1] which was derived from IV by the action of diazomethane or dimethyl sulfate would be VIII, that can be converted into methylanhydroitaconitin (V)[*1] on hydrolysis.



IV : R=H VI : R=COCH₃
V : R=CH₃ VII : R=COC₂H₅



VIII

Supporting these formulae, the titration of anhydroitaconitin (IV) and acetylanhydroitaconitin (VI) showed both of them to be monobasic in cold[1,4], and IV to be dibasic in hot[1] solution. Acetylanhydroitaconitin revealed three singlets nuclear magnetic resonance signals in the higher field at 7.60, 7.61, and 7.79 τ with the magnitude of

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[*4] The NMR spectrum was measured in $CDCl_3$ at 60 Mc.p.s. using a Varian Associates A-60 apparatus and tetramethylsilane as an internal reference.

4) Part I. K. Kinoshita, S. Nakajima : This Bulletin, **6**, 31 (1958).

three protons each (Fig. 3A) supporting the formula (VI) for this compound. The nuclear magnetic resonance signals of the same compound in the lower field were as shown in Fig. 3B.

The two neighbouring protons in the benzene ring gave AB quartets centered on 7.44 and 7.96 p.p.m. (J=8.0 c.p.s.). The former signals, which are considered to be resulted from the *ortho* proton of the methyl group, are broad and have low intensity probably due to the very weak coupling with another benzene proton appearing at 7.24 p.p.m. as shown in the case of dihydroanhydroitaconitin. Another AB quartet present in this spectrum, centered on 8.08 and 7.30 p.p.m. with a coupling constant of J=16.2 c.p.s. would be the signals of two olefinic protons in the side-chain. This J-value suggests that the two protons exist in the *trans* configuration.

The *trans*-configuration of the olefinic protons in the side-chain would also exist in the corresponding system of IV, V, and VII. This was also verified by the infrared spectra showing the more or less remarkable C-H out-of-plane deformation bands; IV at 982 (Fig. 3 in Part IV1)), V at 980*1, VI at 978,1) and VII at 978 cm^{-1}.1)

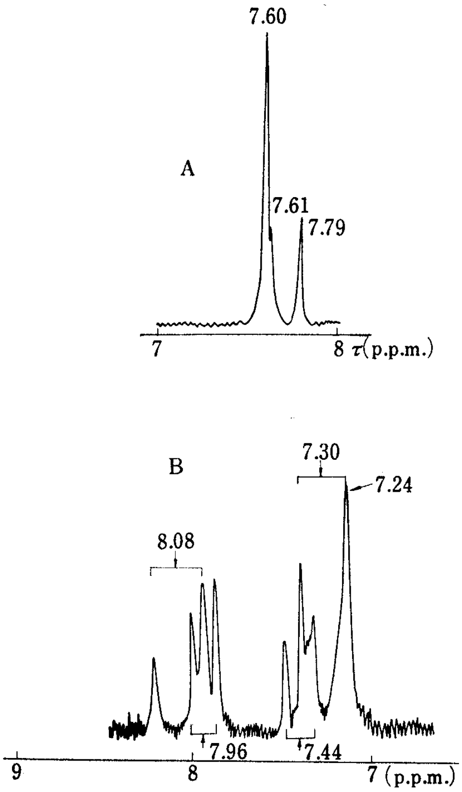
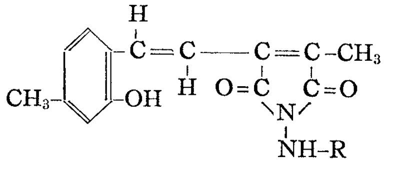


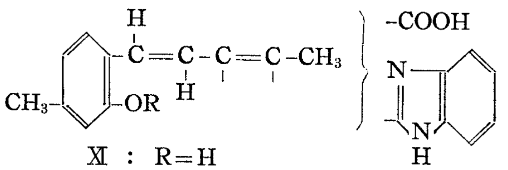
Fig. 3. Nuclear Magnetic Resonance Spectrum of Acetylanhydroitaconitin

A : Higher Field, measured in $CDCl_3$*4
B : Lower Field, measured in Me_2CO*5

As reported in the previous paper, anhydroitaconitin reacted with ketone reagents such as semicarbazide1) or 2,4-dinitrophenylhydrazine.4) The structures of these derivatives can be deduced by analogy with the similar reactions of citraconic5) or dimethylmaleic anhydride.6) Thus the formulae (IX) and (X) are assigned to the structures of the semicarbazide and 2,4-dinitrophenylhydrazide, which are supported by the infrared spectral analyses. The former shows bands at 1726 and 1778 cm^{-1}, and the latter at 1721 and 1768 cm^{-1}, indicating the presence of an α,β-unsaturated five-membered imide grouping in both compounds.



IX : $R=H_2NCO$
X : $R=2,4\text{-}(NO_2)_2C_6H_3$



XI : R=H
XII : $R=CH_3CO$
XIII : $R=CH_3$

The condensation products yielded by the reaction of *o*-phenylenediamine with anhydroitaconitin, acetylanhydroitaconitin and methylanhydroitaconitin would be formulated as XI, XII, and XIII, respectively, by an analogy of the reaction product of *o*-phenylenediamine with phthalic anhydride.7)

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*5 This spectrum was measured at 60 Mc.p.s. using a J. E. O. L. 3H-60 apparatus, and tetramethylsilane as an internal reference.

5) L. Protopopescu, P. Stancovici : Chem. Zentr., **1943**, 268.
6) O. Holst : J. prakt. Chem., (2) **42**, 68 (1890).
7) A. Bistrzycki, J. Risi : Helv. Chim. Acta, **8**, 813 (1925).

Supporting the above formulae, these compounds showed two infrared absorption peaks in their carbonyl region. A strong absorption band between 1695～1705 cm^{-1} indicates the presence of a carboxyl group, and a medium band between 1760～1763 cm^{-1} shows a benzimidazole structure.[*6]

With regard to the infrared spectra of acid anhydrides, an anormalous triplet has been observed in the carbonyl region by Cooke,8) Shibata,9) and Jones, *et al.*10) In the infrared spectra of anhydroitaconitin derivatives, the triplet carbonyl bands observed in the higher frequency range above 1740 cm^{-1} has now been regarded to be resulted from the α,β-unsaturated five-membered acid anhydride grouping present in their molecules. The infrared absorption bands of the acid anhydride system in various derivatives of itaconitin[*7] and anhydroitaconitin are listed in Table I.

TABLE I.

Compounds	State	IR absorption bands (cm^{-1}) in C=O region
Itaconitin[a)]	KBr	1749, 1809, 1855
	$CHCl_3$	1765, 1809, 1855
Hexahydroitaconitin[a)]	cappilary	1766, 1819, 1853
	Nujol	1768, 1821, 1852
	CCl_4	1765, 1814, 1843
	dioxane	1768, 1821, 1852
II	KBr	1760, 1818, 1859
	$CHCl_3$	1764, 1820, 1827
III	KBr	1758, 1819, 1862
IV[a)]	〃	1743, 1808, 1849
	$CHCl_3$	1767, 1813, 1855
	dioxane	1764, 1818, 1857
V	KBr	1753, 1810, 1845
VI	〃	1760, 1808, 1850
	Nujol	1759, 1813, 1861
	dioxane	1766, 1819, 1861
	CS_2	1764, 1810, 1850
VII	KBr	1760, 1813, 1855

a) Spectral curves are shown in respective Figs. 1, 2 and 3 in Part IV.1)

Experimental[*8]

Condensation Reaction of Methylanhydroitaconitin with ***o*-Phenylenediamine**——A solution of methylanhydroitaconitin (V) (2.5 g.) and *o*-phenylenediamine (5.8 g.) in EtOH (50 ml.) was heated at 60° for 10 min. The crude condensation product (3.4 g.) that separated after cooling was purified by crystallization from MeOH. Orange prisms, m.p. 245°. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1} : 978 (*trans* CH=CH), 1395 (CH_3), 1508, 1576, 1627 (phenyl), 1606 (conj. double bond), 1697 (COOH), 1763 (benzimidazole). *Anal.* Calcd. for $C_{21}H_{20}O_3N_2$: C, 72.39; H, 5.79; N, 8.04. Found : C, 72.30; H, 5.05; N, 8.75.

[*6] Benzimidazole itself is known to possess a characteristic medium absorption at 1765 cm^{-1}.

[*7] The presence of the unsaturated five-membered anhydride ring in the structure of itaconitin will be mentioned in Part VII of this series.

[*8] Melting points were uncorrected. Ultraviolet spectra were measured with Cary Model 11 recording spectrophotometer, and infrared spectra with Koken Model DS-301 spectrophotometer.

8) R.G. Cooke : Chem. & Ind. (London), **1955**, 142.

9) S. Shibata : Pharm. Bull. (Tokyo), **5**, 488 (1957).

10) R.N. Jones, C.L. Angell, T. Ito, R.J.D. Smith : Can. J. Chem., **37**, 2019 (1959).

Summary

The structural formula of anhydroitaconitin was established as 2-methyl-3-(*trans*-2-hydroxy-4-methylstyryl)maleic anhydride. The structures of the reaction products of anhydroitaconitin with diazomethane, *o*-phenylenediamine or various ketonic reagents, and acetylanhydroitaconitin, propionylanhydroitaconitin, dihydroanhydroitaconitin, dihydroacetylanhydroitaconitin and all other derivatives hitherto prepared were determined. The ultraviolet, infrared and nuclear magnetic resonance data were provided to support these formulae.

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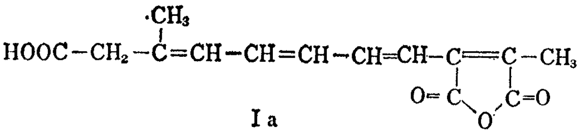
13. **Shoichi Nakajima** : Studies on the Structure of Itaconitin. VII.[*1] The Structures of Itaconitin and Its Derivatives.[*2]

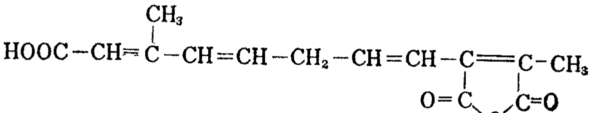
(*Hoshi College of Pharmacy*[*3])

Anhydroitaconitin, the dehydro-product of itaconitin, has been established to possess the structural formula (Ⅲ) as mentioned in Part Ⅵ[*1] of this series of works. The present paper deals with the determination of the structures of itaconitin and its derivatives.

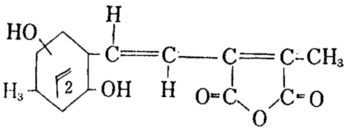
As mentioned in Part Ⅳ[1] of this series, itaconitin which is originally a non-aromatic substance is converted into an aromatic compound, acetylanhydroitaconitin (Ⅱ), on acetylation process, and the latter gives Ⅲ by deacetylation. The easy formation of benzene ring in Ⅱ, or Ⅲ, from itaconitin can only be deduced when one of the structures (Ia), (Ib), and (Ic) is adopted for itaconitin.



Ia



Ib



Ic

Of these formulae, Ic must have an asymmetric carbon atom in the six-membered ring of its molecule. However, itaconitin was found to have no optical activity. Moreover all the attempts for the acetylation without accompanying dehydration and

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[*1] Part Ⅵ. S. Nakajima : This Bulletin, 13, 69 (1965).

[*2] This work was presented at the monthly meeting of the Kanto Branch of Pharmaceutical Society of Japan on Feb., 1964.

[*3] 2-Chome, Ebara, Shinagawa-ku, Tokyo (仲嶋正一).

[1] Part Ⅳ. S. Nakajima, K. Kinoshita, S. Shibata : *Ibid.*, 13, 58 (1965).