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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12. Shoichi Nakajima : Studies on the Structure of
Itaconitin. VI.*¹ The Structures of Anhydro-
itaconitin 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.

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 condition¹⁾ 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 $\lambda_{\max}^{\text{EtOH}}$ m μ (log ϵ) : 216 (3.83), 275 (3.29), 283 (3.26))²⁾ and 3,4,5,6-tetrahydrophthalic anhydride (UV $\lambda_{\max}^{\text{cyclohexane}}$ m μ (log ϵ) : 250 (3.55))³⁾.

*¹ Part V. S. Nakajima : This Bulletin, 13, 64 (1965).*² Presented at VIII 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. 2. Nuclear Magnetic Resonance Spectrum of Dihydroanhydroitacotin, measured in Deuteriochloroform at 60 Mc.p.s.

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

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

three protons each (Fig. 3A) supporting the formula (V) 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 N, V, and VII. This was also verified by the infrared spectra showing the more or less remarkable C-H out-of-plane deformation bands; N at 982 (Fig. 3 in Part N¹⁾), V at 980*¹, VI at 978,¹⁾ and VII at 978 cm⁻¹.¹⁾

As reported in the previous paper, anhydro-itaconitin 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 (K) 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.

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⁾

Fig. 3. Nuclear Magnetic Resonance Spectrum of Acetylanhydroitaconitin

A : Higher Field, measured in CDCl_3 *4

B: Lower Field, measured in $\text{Me}_2\text{CO}^{\ast 5}$

*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 anomalous 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)}	capillary	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 methyl-anhydroitaconitin (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 $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 978 (*trans* CH=CH), 1395 (CH_3), 1508, 1576, 1627 (phenyl), 1606 (conj. double bond), 1697 (COOH), 1763 (benzimidazole). *Anal.* Calcd. for $\text{C}_{21}\text{H}_{20}\text{O}_3\text{N}_2$: 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.

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

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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 IV¹⁾ 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.

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

*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).