Summary

Methylandrotaconitin (III) which was prepared from anhydrotaconitin 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_{16}O_{6}, which was obtained by alkaline hydrogenation of anhydrotaconitin yielded cisoid–dihydrohaematicin acid (XI). From these and other experimental results the structure of the compound, C_{14}H_{16}O_{6} was established as XI.

(Received July 27, 1964)


(Hoski 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_{16}O_{6}, of anhydrotaconitin was established as I. The present paper concerns with the determination of the structures of anhydrotaconitin and all its derivatives so far prepared.

Considering from the chemical structure (I) of C_{14}H_{16}O_{6} acid, dihydroanhydrotaconitin which was yielded by catalytic hydrogenation of anhydrotaconitin under neutral condition*1 could be represented as the structure (II). In neutral solvent, the hydrogenation of anhydrotaconitin 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).

Favoring the proposed formula (II) of dihydroanhydrotaconitin, its ultraviolet spectral curve (Fig. 1) was almost superimposable with the added spectral curve of p-xyleneol (UV \( \lambda_{max} \) m\( \mu \) (log \( e \)) : 216 (3.83), 275 (3.29), 283 (3.26)\(^{2}\) and 3,4,5,6-tetrahydrophthalic anhydride (UV \( \lambda_{max} \) cyclohexane m\( \mu \) (log \( e \)) : 250 (3.55)\(^{3}\)).

*1 Part V. S. Nakajima: This Bulletin, 13, 64 (1965).
*3 2-Chome, Ebara, Shinagawa-ku, Tokyo (仲崎正一).
The nuclear magnetic resonance spectral analysis (Fig. 2) also supported the formula (II). The proton signals of toluene and allyl methyls appeared as singlets at 7.75 and 8.34 \( \tau \), respectively. The adjacent methylenes in the side-chain appeared near 7.19 \( \tau \) as complex signals, probably of \( \text{A}_2\text{B}_2 \) type, the hydroxyl proton at 5.15 \( \tau \) which was shifted by change of concentration, and two neighbouring protons of the benzene ring as an \( \text{AB} \) quartet (\( J=7.5 \text{c.p.s.} \)) centered on 3.08 and 3.36 \( \tau \), the latter of which is broadened because of a very weak coupling with another benzene proton appearing at 3.43 \( \tau \).

The titration using phenolphthalein as an indicator showed this substance to be monobasic in cold and dibasic in hot 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.

Dihydroacetylhydroitoacinitin (III) showed nuclear magnetic resonance signals at 7.27 \( \tau \) (\( \text{A}_2\text{B}_2 \)), 7.68, 7.70 \( \tau \) (toluene and acetate methyls), and 8.39 \( \tau \) (allyl methyl), in resemblance with those of dihydroanhydroitoacinitin (II) except the presence of the signal of acetate methyl.

Hence the structure of anhydroitoacinitin would be formulated as IV, and the compound, \( \text{C}_7\text{H}_8\text{O}_6 \), which was derived from \( \text{V} \) by the action of diazomethane or dimethyl sulfate would be VIII, that can be converted into methylanditoacinitin (V) on hydrolysis.

Supporting these formulae, the titration of anhydroitoacinitin (\( \text{V} \)) and acetylhydroitoacinitin (\( \text{VI} \)) showed both of them to be monobasic in cold\(^4\), and \( \text{V} \) to be dibasic in hot solution. Acetylhydroitoacinitin revealed three singlets nuclear magnetic resonance signals in the higher field at 7.60, 7.61, and 7.79 \( \tau \) 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.

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 W. 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 980,2 at 978,1 and W at 978 cm⁻¹.1

As reported in the previous paper, anhydroitaconitin reacted with ketone reagents such as semicarbazide7 or 2,4-dinitrophenylhydrazine.9 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.

\[ \text{CH}_3 \quad \text{H} \quad \text{C}=\text{C} \quad \text{C}=\text{C} \quad \text{C}=\text{C} \quad \text{C}=\text{H} \]

K : R = H₂NCO
X : R = 2,4-(NO₂)₂C₆H₅

\[ \text{CH}_3 \quad \text{H} \quad \text{C}=\text{C} \quad \text{C}=\text{C} \quad \text{C}=\text{C} \quad \text{C}=\text{H} \]

XI : R = H
XII : R = CH₃CO
XIII : R = CH₃

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

With regard to the infrared spectra of acid anhydrides, an anomalous triplet has been observed in the carbonyl region by Cooke, Shibata, and Jones, et al. 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 and anhydroitaconitin are listed in Table I.

**Table I.**

<table>
<thead>
<tr>
<th>Compounds</th>
<th>State</th>
<th>IR absorption bands (cm⁻¹) in C=O region</th>
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</thead>
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<tr>
<td>Itaconitin</td>
<td>KBr</td>
<td>1749, 1809, 1855</td>
</tr>
<tr>
<td>CHCl₃</td>
<td></td>
<td>1765, 1809, 1855</td>
</tr>
<tr>
<td>Hexahydroitaconitin</td>
<td>capillary</td>
<td>1766, 1819, 1853</td>
</tr>
<tr>
<td>Nujol</td>
<td></td>
<td>1768, 1821, 1852</td>
</tr>
<tr>
<td>CCl₄</td>
<td></td>
<td>1765, 1814, 1843</td>
</tr>
<tr>
<td>Dioxane</td>
<td></td>
<td>1768, 1821, 1852</td>
</tr>
<tr>
<td>II</td>
<td>KBr</td>
<td>1760, 1818, 1859</td>
</tr>
<tr>
<td>CHCl₃</td>
<td></td>
<td>1764, 1820, 1827</td>
</tr>
<tr>
<td>III</td>
<td>KBr</td>
<td>1758, 1819, 1862</td>
</tr>
<tr>
<td>IV</td>
<td>n</td>
<td>1743, 1808, 1849</td>
</tr>
<tr>
<td>CHCl₃</td>
<td></td>
<td>1767, 1813, 1855</td>
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<tr>
<td>Dioxane</td>
<td></td>
<td>1764, 1818, 1857</td>
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<tr>
<td>V</td>
<td>KBr</td>
<td>1753, 1810, 1845</td>
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<tr>
<td>VI</td>
<td>n</td>
<td>1760, 1808, 1850</td>
</tr>
<tr>
<td>Nujol</td>
<td></td>
<td>1759, 1813, 1861</td>
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<tr>
<td>Dioxane</td>
<td></td>
<td>1766, 1819, 1861</td>
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<tr>
<td>CS₂</td>
<td></td>
<td>1764, 1810, 1850</td>
</tr>
<tr>
<td>VII</td>
<td>KBr</td>
<td>1760, 1813, 1855</td>
</tr>
</tbody>
</table>

* Spectral curves are shown in respective Figs. 1, 2 and 3 in Part V, D.

**Experimental**

Condensation Reaction of Methylhydroitaconitin with o-Phenylenediamine — A solution of methylhydroitaconitin (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 νₜₚₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑᵉᵦₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑᵉᵦₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑᵉᵦₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑᵉᵦₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑᵉᵦₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑ showcircumstances. Ultraviolet spectra were measured with Cary Model 11 recording spectrophotometer, and infrared spectra with KoKen Model DS-301 spectrophotometer.

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.

(Received July 27, 1964)

13. Shoichi Nakajima: Studies on the Structure of Itaconitin. VII. The Structures of Itaconitin and Its Derivatives. (Hoshi College of Pharmacy)

Anhydroitaconitin, the dehydro-product of itaconitin, has been established to possess the structural formula (III) as mentioned in Part VI 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 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.

\[ \text{HOOC-CH=CH=CH=CH=CH=C=C-CH_3} \]
\[ \text{CH_3} \]

\[ \text{HOOC-CH=CH=CH=CH=CH=C=C-CH_3} \]
\[ \text{CH_3} \]

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 V. 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 (仲崎正一).

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