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Studies on the Structure of Itaconitin. VIII.[1] Synthesis of Methylanhydroitaconitin[2]

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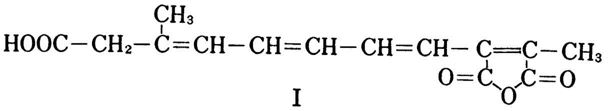
Methylanhydroitaconitin was synthesized from 4-(2-methoxy-4-methylphenyl)-3-butenoic acid, which was derived from 2-methoxy-4-methylbenzaldehyde by heating with sodium succinate and acetic anhydride. The difference of temperature in the latter reaction caused the formation of 1,4-bis(2-methoxy-4-methylphenyl)-1,3-butadiene. Methylstyrylmaleic anhydride was also prepared.

It was reported in the preceding paper[1] that the molecular structure of itaconitin, a yellow coloring matter of *Aspergillus itaconicus* Kinoshita, was determined as I. The syntheses of 3-methylnonanedioic acid,[4] which is the oxydation product of ozonized hexahydroitaconitin, and of *cisoid*-dihydrohaematinic acid,[5] which is the compound derived from dihydroanhydroitaconitin by alkaline hydrogenation followed by ozone degradation, were the synthetic proof for this structure.



$$\mathrm{HOOC{-}CH_2{-}\overset{\displaystyle CH_3}{\overset{|}{C}}{=}CH{-}CH{=}CH{-}CH{=}CH{-}\underset{O=C\diagdown_{O}\diagup C=O}{C{=\!=}C}{-}CH_3}$$

I

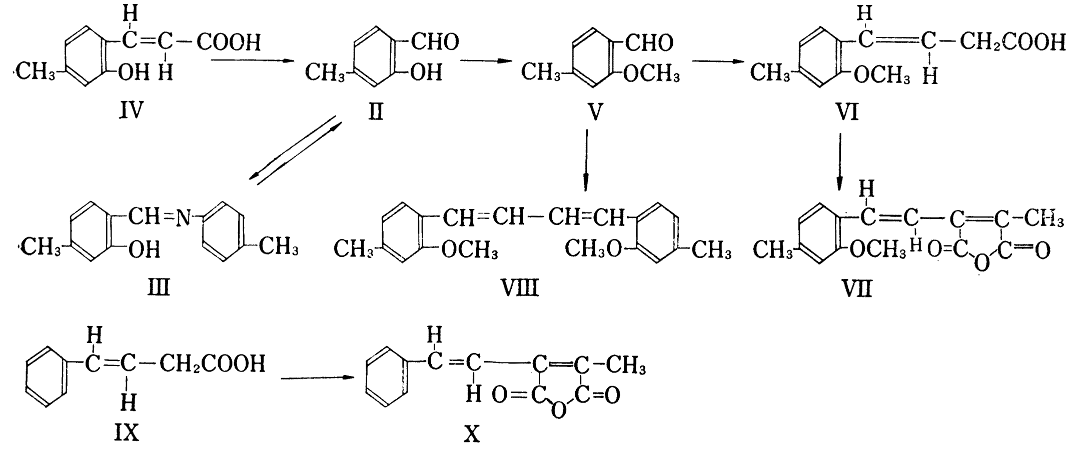


Chart 1

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[1] Part VII: S. Nakajima, *Chem. Pharm. Bull.* (Tokyo), 13, 73 (1965).

[2] A part of this work was presented at the 86th Annual Meeting of the Pharmaceutical Society of Japan, Tokushima, on 29th, Oct., 1965.

[3] Location: *2-Chome, Ebara, Shinagawa-ku, Tokyo.*

[4] This compound was erroneously reported in Part VII of this series as 2-methylnonanedioic acid. The authors want to correct it.

[5] S. Nakajima, *Chem. Pharm. Bull.* (Tokyo), 13, 64 (1965).

The present authors report in this paper the synthesis of methylanhydroitaconitin (VII), together with methylstyrylmaleic anhydride (X) for further strong synthetic support for this structural determination of itaconitin and related compounds. As reported in Part I[6] and V[5] of this series, methylanhydroitaconitin (VII) is the compound derived from itaconitin (I) by a characteristic phenol-forming cyclization[7] by the action of acetic anhydride, followed by deacetylation and methylation.

First of all, the authors attempted synthesis of methylstyrylmaleic anhydride (X) as a model compound of methylanhydroitaconitin (VII). 4-Phenyl-3-butenoic acid (IX) was prepared by the procedure of Fittig, *et al.*,[8] and was treated with sodium pyruvate and acetic anhydride to give a compound with a molecular formula $C_{13}H_{10}O_3$, melting at 152°. Viewed from the fact this compound has three distinct carbonyl peaks of anhydride, which is a typical phenomenon at itaconitin and the related compounds, at 1759, 1807, and 1853 cm^{-1} in its infrared (IR) spectrum, the structure of this compound can be determined as methylstyrylmaleic anhydride (X). In addition, the presence of strong (IR) peak at 968 cm^{-1} indicated that this compound (X) had a double of *trans*-configuration as in the cases of various itaconitin derivatives, whose configuration at the corresponding double bond had been difinitely decided by nuclear magnetic resonance (NMR) specrtoscopy.[9]

2-Hydroxy-4-methylbenzaldehyde (II) used as the starting material for the synthesis of methylanhydroitaconitin (VII) was prepared either by Tiemann–Reimer reaction[10] from *m*-cresol or by ozone degradation of 2-hydroxy-4-methyl-*trans*-cinnamic acid (IV). In the former reaction, separation of 2-hydroxy-4-methylbenzaldehyde from a mixture of various low-melting isomeric aldehydes was accomplished by deriving it to the Schiff base (III). The 2-hydroxy-4-methylbenzaldehyde (II) was derived into 2-methoxy-4-methylbenzaldehyde (V) in a usual manner by use of dimethyl sulfate, and was further converted into 4-(2-methoxy-4-methylphenyl)-3-butenoic acid (VI) by heating at 140° in a sealed tube with sodium succinate and acetic anhydride. The compound (VI) was reacted with sodium pyruvate and acetic anhydride, in the same manner as the above-mentioned synthesis of methylstyrylmaleic anhydride (X), to give methylanhydroitaconitin (VII). The identity of synthetic methylanhydroitaconitin and the one derived from I was demonstrated by mixed fusion and comparison of infrared spectra (Fig. 1).

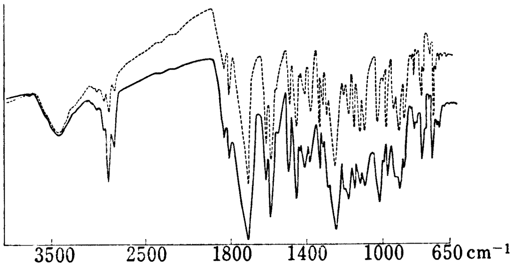

Fig. 1. Infrared Spectra of Methylanhydroitaconitin (KBr)

------: derived from itaconitin
——: synthesized

Prior to the above-mentioned successful preparation of 4-(2-methoxy-4-methylphenyl)-3-butenoic acid (VI), the authors tried to obtain this compound by heating the same starting materials at a different temperature, *i.e.* 160°, in an autoclave. However, the compound obtained by this reaction, yellow needles of mp 178°, showed no carbonyl absorptions in the infrared spectrum. Mass spectrum indicated its molecular weight to be 294. Furthermore, the NMR spectrum showed signals of two aromatic methyls at 7.69 τ as a singlet and of two methyls at 6.19 τ as a singlet, together with those of aromatic olefinic protons ten in all.

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6) K. Kinoshita and S. Nakajima, *Chem. Pharm. Bull.* (Tokyo), **6**, 31 (1958).
7) G.P. Chiusoli and G. Agnes, *Z. Naturforsch.*, **17B**, 852 (1962); *Proc. Chem. Soc.*, **1963**, 310.
8) R. Fittig and H.W. Jayne, **Ann.**, **216**, 97 (1883).
9) S. Nakajima, *Chem. Pharm. Bull.* (Tokyo), **13**, 69 (1965).
10) F. Timann and C. Schotten, *Ber.*, **11**, 773 (1878).

In view of these observations, this compound was considered to be 1,4-bis(2-methoxy-4-methylphenyl)-1,3-butadiene (VIII), which resulted from the following reaction:

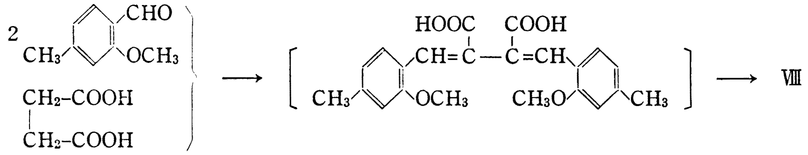
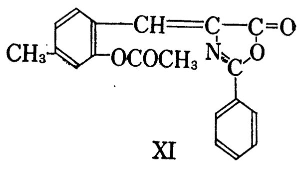


Chart 2



XI

A reaction of this type was reported by Kuhn, *et al.*,[11] who obtained 1,8-diphenyl-1,3,5,7-octatetraene together with 1,8-diphenyl-1,3,5,7-octatetraene-4,5-dicarboxylic acid anhydride by the action of cinnamic aldehyde, sodium succinate and acetic anhydride.

In an attempt to synthesize VII by another method, 2-phenyl-4-(2-acetoxy-4-methyl)-benzylidene-5(4H)-oxazolone (XI) was prepared by Erlenmeyer reaction of II with hippuric acid. However, further conversion of XI into VII *via* a keto acid could not be accomplished.

Experimental[12]

Methylstyrylmaleic Anhydride (X)——A mixture of 100 mg of 4-phenyl-3-butenoic acid (IX), 68 mg of sodium pyruvate and 1 ml of acetic anhydride was heated on a steam bath for 5 hr. After cool, the orange-yellow reaction solution gave crystals deposited, which were collected and recrystallized thrice from ethanol to orange leaflets of mp 152°, yield 35 mg. *Anal.* Calcd. for $C_{13}H_{10}O_3$: C, 72.89; H, 4.71. Found: C, 72.34; H, 5.23. IR ν_{max}^{KBr} cm^{-1}: 1835, 1807, 1759 (anhydride), 1640, 1608 (sh), 1572 (aromatic and double bond), 968 (*trans* double bond).

2-Hydroxy-4-methylbenzaldehyde (II) by Tiemann-Reimer Reaction——Industrial cresol mixture was distilled to remove *ortho* isomer. The *meta* and *para* mixture (7:5) boiling between 200° and 203° (150 g) was put in a flask together with 480 ml of water and 480 g of NaOH. Heating in a boling water bath under vigorous stirring was added 360 g of $CHCl_3$ in a period of 6 hr. After acidification with HCl, steam was passed in to give an oily product upon the surface of the distillate. The aqueous layer was extracted with ether and combined with the oil, and the ether was evaporated off. This oily product containing 60 g of isomeric aldehydes was mixed with 44 g of *p*-toluidine, and warmed in a boiling water bath for 30 min. The orange-yelllow crystalline mass thus produced was recrystallized once from ethanol to give almost pure crystals of yellow needles of N-(2-hydroxy-4-methylbenzylidene)-*p*-toluidine (III). Further crystallyzation gave pure samples for elemental analysis, mp 136°. Yield 23 g. *Anal.* Calcd. for $C_{15}H_{15}ON$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.61; H, 6.70; N, 6.24. The Schiff base (III) was suspended in water and distilled with steam. Extraction of the distillate with ether, removal of the solvent, and recrystallization from hexane gave pure crystals of II, mp 60°. Yield 8.2 g.

2-Hydroxy-4-methylbenzaldehyde by Ozonolysis of 2-Hydroxy-4-methyl-*trans*-cinnamic Acid (IV) Thirty gram of 2-hydroxy-4-methyl-*trans*-cinnamic acid (IV) was dissolved in 250 ml of acetone, and a stream of ozone was passed in for 4 hr. During this time, the color of the reaction mixture changed into reddish brown, then into faint yellow. The brown resin obtained after evaporation of the solvent *in vacuo* was mixed with small amount of water and warmed for a little while. The crystalline mass (13.9 g) that deposited after ice cool was collected on filter, and recrystallized from hexane to give pure crystals of II, mp 60°. The melting point was undepressed on admixture with the compound prepared by the method described above.

4-(2-Methoxy-4-methylphenyl)-3-butenoic Acid (VI)——A mixture of 2.9 g of 2-methoxy-4-methylbenzaldehyde (V), 3.2 g of sodium succinate and 2 g of acetic anhydride was put in a sealed tube, and heated in a boiling bath of ethylene bromide (bp 140°) in a period of 45 hr. The black-colored reaction mixture was warmed with 50 ml of 20% Na_2CO_3, and filtered from black residue. The orange-colored solution thus

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[11] R. Kuhn and A. Winterstein, *Helv. Chim. Acta*, **11**, 87 (1928).

[12] Koken model DS-301 and Hitachi model 215, Hitachi-Perkin-Elmer R-20, and Hitachi RMS-4 apparatus were used for measurement of infrared, NMR, and mass spectra, respectively. All melting points are uncorrected.

obtained was extracted twice with 50 ml of ether to remove impurities, and was acidified with HCl to give brown crystals after ice cool, 750 mg. After recrystallized twice from MeOH, it gave colorless prisms of mp 102°. *Anal.* Calcd. for $C_{12}H_{14}O_3 \cdot H_2O$: C, 64.27; H, 7.19. Found: C, 64.72; H, 6.41.

Methylanhydroitaconitin (VII)——A mixture of 192 mg of 4-(2-methoxy-4-methylphenyl)-3-butenoic acid (VI). 110 mg of sodium pyruvate and 2 ml of acetic anhydride was heated in a boiling water bath for 40 hr. The brown reaction mixture was mixed with 10 ml of water and boiled to remove acetic acid. Another 10 ml of water was added during this distillation. The resinous product after cool was taken on filter, washed with water, dried and purified on silica gel thin-layer plate using $CHCl_3$ as the solvent. The yellow band, whose *Rf* was identical with that of the methylanhydroitaconitin, was extracted with acetone, and recrystallized from ethanol to yellow needles, mp 154°, undepressed on admixture with methylanhydroitaconitin derived from itaconitin of natural origin.

1,4-Bis(2-methoxy-4-methylphenyl)-1,3-butadiene(VIII)——A mixture of 4.37 g of 2-methoxy-4-methylbenzaldehyde (V), 4.82 g of sodium succinate and 3.02 g of acetic anhydride was heated at 160° in an autoclave for 45 hr. The resinous product was washed with 10% Na_2CO_3 then with water and dried. The $CHCl_3$ solution of this resinous substance was chromatographed on the column of $CaHPO_4$. From the eluent was isolated the aldehyde unchanged and crude 1,4-bis(2-methoxy-4-methylphenyl)-1,3-butadiene (VIII). The latter compound was purified by recrystallization from methanol to yellow prisms of mp 178°, yield 1.0 g. *Anal.* Calcd. for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 81.04; H, 8.16. IR ν_{max}^{KBr} cm^{-1}: 1600, 1563 (aromatic and double bond), 1256, 1035 (phenolic ether). NMR (60 Mc, in $CDCl_3$) τ: 7.69 (6H, singlet, Ar-CH_3), 6.19 (6H, singlet, OCH_3). Mass Spectrum *m/e*: 294 (M^+).

2-Phenyl-4-(2-acetoxy-4-methylbenzylidene)-5(4H)-oxazolone (XI)——A mixture of 781 mg of 2-hydroxy-4-methylbenzaldehyde, 947 mg of hippuric acid, 500 mg of freshly melted sodium acetate and 5 ml of acetic anhydride was heated in a boliling water bath for 10 min. The yellow reaction mixture was cooled, poured into water, and the precipitate was collected on filter, washed with $NaHCO_3$ solution, then with water. The crude crystalline mass thus obtained was purified through chromatography on $CaHPO_4$ column using benzene as solvent. Crystallization from ethanol gave yellow cubes of mp 128°, yield 590 mg. *Anal.* Calcd. for $C_{19}H_{15}O_4N$: C, 71.02; H, 4.71. Found: C, 71.43; H, 4.47.

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