The Structure of Todomatuic Acid. Synthesis of (±)-Dihydro-desoxo-todomatuic Acid

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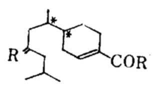
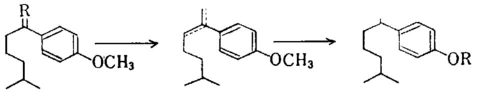
Todomatuic acid, $C_{15}H_{24}O_3$, monocyclic unsaturated keto-acid (m. p. 58.5°C, b. p. 200~215°C/3 mmHg, $[\alpha]_D^{32.5}+85.84°$; semicarbazone, m. p. 193.2~193.7°C), was first isolated by Tuchihashi and Hanzawa[1] on hydrolysis of the high boiling fraction of an oil, obtained as a by-product when *Abies sachalinensis* Mast. (to do matu) was digested with sulfite in pulp industry.



Ia R=O R′=OH
b R=H_2 R′=OH
c R=H_2 R′=OCH_3

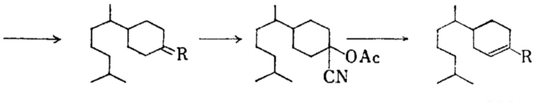
The structure Ia was advanced by Momose[2], mainly by the results of oxidative degradation of Ia with potassium permanganate which gave oxalic acid and an acyclic saturated keto-dicarboxylic acid (II), $C_{13}H_{22}O_5$ (semicarbazone, decomp. p. 185~186°C). Further oxidation of II with nitric acid gave isovaleric acid and β-(α-carboxyethyl)glutaric acid. Among various possible structures which satisfy the results of the degradation, Ia was favored because Ia is compatible with the isoprene rule.

In this communication, the synthesis of (±)-dihydro-desoxo-todomatuic acid (Xb) is reported.



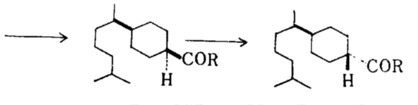
IIIa R=O IV Va R=CH_3
b R=OH, CH_3 b R=H

(4-Anisyl)-isohexyl ketone (IIIa) (b. p. 131~133°C/1 mmHg; semicarbazone, m. p. 124~125°C) obtained by Friedel-Crafts reaction of anisole with isocaproyl chloride, was converted into IIIb by Grignard reaction with methylmagnesium bromide, and then IIIb was dehydrated by boiling with acetic anhydride to the unsaturated phenol ether IV (b. p. 109~115°C/1 mmHg).



VIa R=OH, H VII VIIIa R=CN
b R=O b R=COOH

Catalytic hydrogenation of IV gave Va (b. p. 107~113°C/1 mmHg), which was hydrolyzed by boiling with hydroiodic acid in acetic acid to afford the phenol Vb (b. p. 127~128°C/1 mmHg). High pressure catalytic hydrogenation of Vb (Raney nickel, 130 atms., 30°C) yielded the alcohol VIa (b. p. 120~121°C/1 mmHg), which was oxidized with potassium dichromate in sulfuric acid to the ketone VIb (b. p. 113~114°C/1 mmHg; semicarbazone, m. p. 149~150°C). The cyanohydrin acetate VII (b. p. 145~147°C/1 mmHg) prepared from VIb with potassium cyanide and acetic anhydride, was pyrolyzed by passing through a heated Pyrex tube (600°C) packed with ceramic Raschig rings to give unsaturated cyanide VIIIa, which was then hydrolyzed to the unsaturated acid VIIIb (b. p. 163~165°C/1 mmHg).



IXa R=OH Xa R=OCH_3
b R=OCH_3 b R=OH
c R=NHC_6H_5
(or its antipode) (or its antipode)

Although two racemic forms are expected for the structure VIIIb, the infrared absorption spectrum of synthetic VIIIb was found superimposable on that of (+)-desoxo-todomatuic acid (Ib) (m. p. 59~60°C, $[\alpha]_D^{27}+94.3°$ in ethanol; anilide, m. p. 78~79°C) obtained by Wolff-Kishner reduction of Ia. Catalytic hydrogenation of the methyl ester Ic of natural Ib gave saturated methyl ester IXb in which only one asymmetric center remains.

Heating with sodium methoxide converted IXb into more stable methyl ester Xa, which was hydrolyzed to give (+)-dihydro-desoxo-todomatuic acid (Xb) (b. p. 150~153°C/1 mmHg, n_D^{18} 1.4723, $[\alpha]_D^{27}+14.1°$ in ethanol; anilide Xc, m. p. 115~116°C). Following the same procedure, racemic IXb gave (±)-dihydro-desoxo-todomatuic acid (Xb) (b. p. 152~155°C/1 mmHg, n_D^{18} 1.4723; anilide, Xc

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[1] R. Tuchihashi and T. Hanzawa, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **61**, 1041 (1940).

[2] T. Momose, *J. Pharm. Soc. Japan* (*Yakugaku Zasshi*), **61**, 288 (1941).

m. p. 105~106°C). The infrared absorption spectra of racemic Xb, Xc and natural Xb, Xc were found superimposable in every detail.

These findings firmly establish the structure of todomatuic acid.

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