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

By Masao NAKAZAKI and Sachihiko ISOE

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The chemical investigation of todomatuic acid (I) was initiated by Tuchihashi and Hanzawa,[1] who isolated an acid on the hydrolysis of the high boiling fraction (b. p. 207∼210°C/12 mmHg) of an oil which had been obtained as a by-product when *Abies sachalinensis* MAST. (todo matu) was digested with sulfite in the pulp industry. They described the sesquiterpene acid, todomatuic acid (m. p. 58.5°C; b. p. 200∼215°C/3 mmHg; n_D^{50} 1.4891, d_4^{50} 1.0233, $[\alpha]_D^{32.5}+85.84°$) and suggested the formula of $C_{15}H_{24}O_3$. They also established the presence of a carbonyl group by preparing various carbonyl derivatives: semicarbazone (m. p. 193°C), thiosemicarbazone (m. p. 149∼150°C), and *p*-nitrophenylhydrazone (m. p. 154∼155°C). That this compound was a ketone rather than an aldehyde was assumed as a results of its negative Schiff and Legal tests. Furthermore, the natural compound absorbed one mole of hydrogen over a palladium-on-carbon catalyst to give dihydrotodomatuic acid (b. p. 182∼183°C/3 mmHg).

These facts, together with other evidence (the molecular formula, the molecular refraction index, etc.) led them to conclude correctly that this natural product is an unsaturated monocyclic sesquiterpene carboxylic acid with one keto group. Some further observations on the structure of todomatuic acid, observations which eventually led to its correct structure assignment, are due to Momose.[2] He found that, on oxidative degradation with potassium permanganate, I gave oxalic acid and an acyclic saturated ketodicarboxylic acid, $C_{13}H_{22}O_5$ (semicarbazone, decomp. p. 185∼186°C). The further oxidation of $C_{13}H_{22}O_5$ with nitric acid gave isovaleric acid (IV) and racemic β-(α-carboxyethyl)glutaric acid (V), which was found to be identical with a synthetic specimen.[3]

These findings indicate that the acyclic saturated ketodicarboxylic acid $C_{13}H_{22}O_5$ could be either IIIa or IIIb, corresponding to structure I or II respectively for todomatuic acid. The structure formula I was Momose's choice, because I is compatible with the isoprene rule and several sesquiterpenes[4] (see Fig. 4) can be found posssesing the same carbon skeleton (bisabolene type) as I; of these, atlantone[5] (VI) is especially noteworthy, for in it the keto group and the endocyclic double bond are located in the same place as in I.

It seems desirable, however, to provide more convincing evidence to prove unambiguously[6]

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* For a preliminary account of this work, see M. Nakazaki and S. Isoe, This Bulletin, **34**, 741 (1961).

1) R. Tuchihashi and T. Hanzawa, *J. Chem. Soc. Japan* (*Nippon Kwagaku Kwaishi*), **61**, 1041 (1940).

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

3) Z. H. Skraup, *Monatsh.*, **21**, 907 (1900).

4) J. L. Simonsen and D. H. R. Barton, "The Terpenes," Vol. III, Cambridge Univ. Press, Cambridge (1952), pp. 9—25.

5) A. S. Pfau and P. A. Plattner, *Helv. Chim. Acta*, **17**, 129 (1934).

6) Momose's explanation for the formation of $C_{13}H_{22}O_5$ instead of a homologous ketodicarboxylic acid seems awkward.

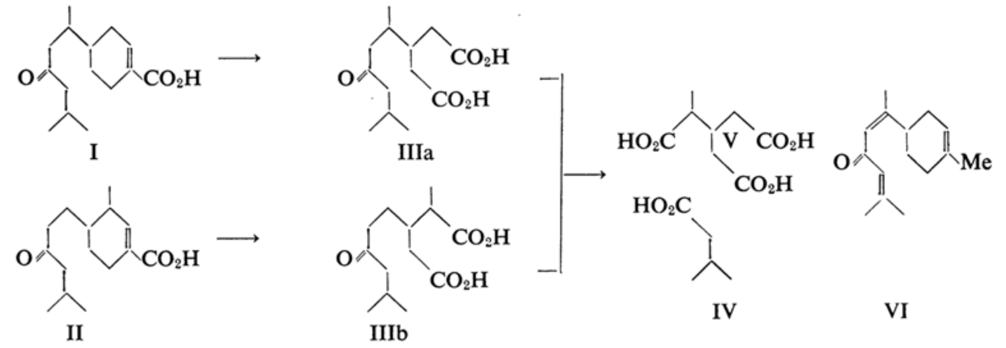


Fig. 1

the structure of this unusual monocyclic sesquiterpene carboxylic acid, preferably by a synthetic approach. In this paper, the synthesis of (±)-dihydro-desoxo-todomatuic acid and the establishment of the absolute configuration of todomatuic acid will be reported.

First we wanted to ascertain the exact location of the carboxyl group on the cyclohexene ring by means of Barbier-Wieland degradation, hoping that a cyclohexanone derivative, our prime objective, would prove to be a useful key substance for structure determination as well as for a synthetic approach.

The Wolff-Kishner reduction of todomatuic acid yielded desoxy-todomatuic acid (VIIa) (Fig. 2) (m. p. 59~60°C), which was esterified with diazomethane to afford the methyl desoxo-todomatuate (VIIc) (b. p. 130~131°C/1 mmHg). The catalytic hydrogenation of VIIc over an Adams catalyst gave methyl dihydro-desoxo-todomatuate (VIIIa) (b. p. 117~119°C/1 mmHg), which gave the carbinol VIIIc with phenylmagnesium bromide. The unsaturated compound VIIId, obtained from VIIIc on dehydration by boiling with acetic anhydride and pyridine, was ozonolyzed. After the ozonide had been decomposed with zinc powder, the neutral fraction boiling at 100~110°C/1 mmHg was purified by chromatography on alumina. An oil which showed infrared absorption at 1704 cm^{-1} (six-membered cyclic ketone) was converted directly into semicarbazone (m. p. 151~152°C). If the structure of todomatuic acid is represented correctly by I, this ketone should be 2-(4-oxocyclohexyl)-6-methylheptane (IX). Our next project was, therefore, the synthsis of this compound.

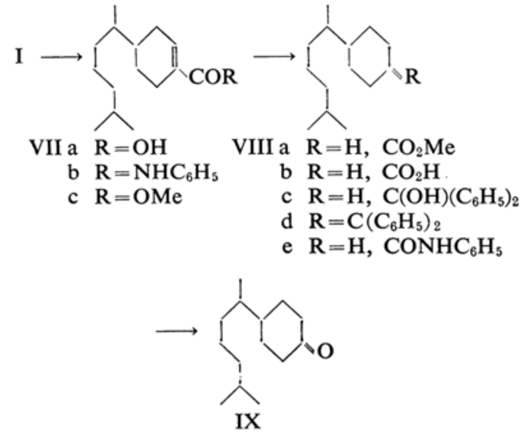


Fig. 2

p-Anisyl-isohexylketone (Xa) (Fig. 3), obtained by the Friedel-Crafts reaction of anisol

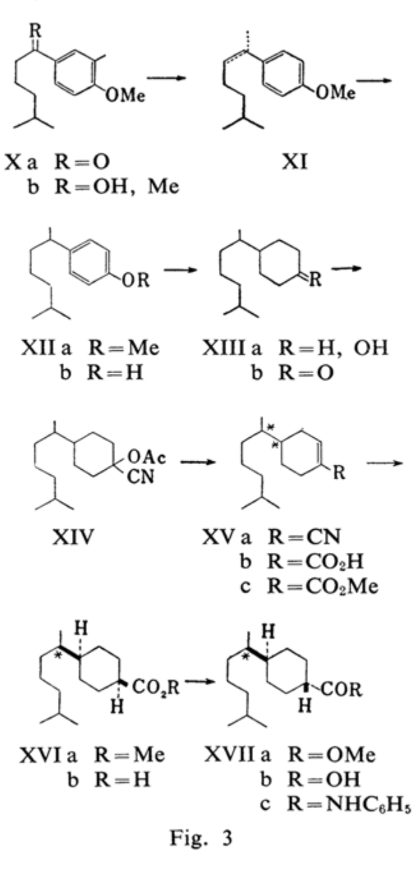


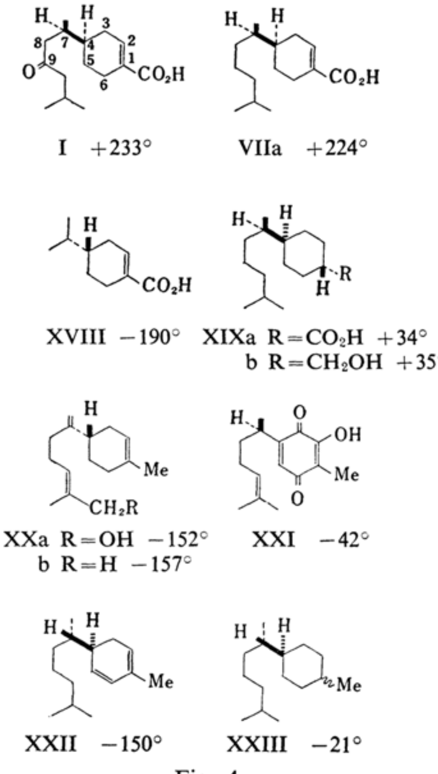
Fig. 3

and 5-methylhexanoyl chloride, was converted into the carbinol Xb with methylmagnesium bromide, and then Xb was dehydrated by boiling it with acetic anhydride to afford the unsaturated phenol ether XI. The catalytic hydrogenation of XI gave XIIa, which was hydrolyzed by boiling it with hydroiodic acid in an acetic acid solution to afford the phenol XIIb. The high pressure catalytic hydrogenation of XIIb (Raney nickel 130 atms., 140~150°C) yielded the alcohol XIIIa, which was oxidized with potassium dichromate in sulfuric acid to (±)-2-(4-oxocyclohexyl)-6-methylheptane (XIIIb) (b. p. 113~114°C/1 mmHg, semicarbazone, m. p. 149~150°C), whose infrared absorption spectrum was found superimposable on that of the ketone IX from the natural product. These findings firmly established the structure of todomatuic acid (I). Our attention was next directed to introduce a carboxyl group to the C_1 position of the ketone XIIIb in order to synthesize (±)-dihydro-desoxo-todomatuic acid (VIIIb).

The ketone XIIIb was heated with potassium cyanide in acetic anhydride to give the cyanohydrin acetate XIV, which was pyrolyzed at 1 mmHg by passing it through a heated Pyrex tube (600°C) packed with ceramic Rashig rings to afford the unsaturated cyanide XVa, which was then hydrolyzed to the unsaturated acid XVb (b. p. 163~165°C/1 mmHg). Although two racemic forms[7] were expected for the structure XVb because of the presence of two asymmetric carbon atoms, the infrared absorption spectrum of the synthetic XVb was found identical with that of (+)-desoxotodomatuic acid (VIIa).

In order to provide more unambiguous evidence, it seemed desirable to compare compounds with only one asymmetric center. The synthetic XVb was esterified with diazomethane, and the methyl ester thus obtained was catalytically hydrogenated on an Adams catalyst, affording the saturated methyl ester XVIa, probably the cis form predominantly. Equilibration of the methyl ester XVIa by boiling it with sodium ethoxide yielded the more stable trans methyl ester XVIIa, which was then saponified to (±)-*trans*-2-(4-carboxycyclohexyl)-6-methylheptane (XVIIb) (b. p. 152~155°C/1 mmHg; n_D^{18} 1.4723); its anilide XVIIc melted at 105~106°C. In order to compare the above mentioned synthetic XVIIb with the saturated acid VIIIb obtained from the natural product, it is necessary to convert VIIIb to the trans form; this was accomplished by the equilibration of the methyl ester VIIIa by boiling it with sodium ethoxide. Saponification of the optically active trans methyl ester thus prepared gave (+)-*trans*-dihydro-desoxo-todomatuic acid (XVIIb), b. p. 150~153°C/1 mmHg; $[\alpha]_D^{27}$ +14.1°; n_D^{18} 1.4723 (the anilide, m. p. 115~116°C), whose infrared spectrum was found to be superimposable on that of the synthetic XVIIb in every detail.

Having thus accomplished the synthesis of (±)-dihydro-desoxo-todomatuic acid, let us now proceed to discuss the absolute configuration of todomatuic acid. As can be seen from the structure formula of todomatuic acid (I) (Fig. 4; the molecular rotations are shown below the structure formula of the relevant compounds), it has two asymmetric centers (C_4 and C_7). The absolute configuration around C_4 will be discussed first. Since todomatuic acid (I) and desoxo-todomatuic acid (VIIa) show almost equal rotation values ($[M]_D$ +233° and $[M]_D$ +224° respectively), the keto groups on the side chains seem to have little effect on the optical rotations. The same is true for the asymmetric center at C_7; dihydro-desoxo-todomatuic acid XIXa, lacking the asymmetric center at C_4, exhibits very little rotation, showing a predominant contribution of the asymmetric center at C_4 to the optical rotation of the unsaturated compounds I and VIIa.



I +233° VIIa +224°

XVIII −190° XIXa R=CO_2H +34°
b R=CH_2OH +35°

XXa R=OH −152° XXI −42°
b R=H −157°

XXII −150° XXIII −21°

Fig. 4

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[7] Pyrolysis at 600°C can hardly be stereo-specific, and the products, XVa, XVb and XVc, may be a mixture of two racemic forms.

Therefore, it is safe to compare todomatuic acid (I) and desoxo-todomatuic acid (VIIa) with (−)-phellandric acid (XVIII) ($[M]_D$ −190°),[8] despite the fact that I and VIIa have extra asymmetric centers in the side chains. One of Mills' empirical rules[9] tells us that I and VIIa have the (R)-configuration opposite natural (−)-phellandric acid (XVIII) at the C_4 center. Among the four bisabolene type sesquiterpenes whose absolute configurations have been established (lancerol (XXa),[10] bisabolene (XXb),[11] perezone (XXI)[12] and zingiberene (XXII)[13]), is particularly suitable to compare zingiberene's asymmetric center in the side chain with that of todomatuic acid (I). Hexahydrozingiberene (XXIII) ($[M]_D$ −21°),[14] which has only one asymmetric center in the side chain, can be compared with (+)-dihydro-desoxo-todomatuic acid (XIXa), since the substitutions at C_1 are too remote from the asymmetric centers on C_7 to affect the signs of rotation in both compounds. A more relevant comparison is that of XXIII with the alcohol XIXb, $[M]_D$ +35°, prepared from XIXa by lithium aluminum hydride reduction. Since the hydroxymethyl group has almost the same polarizability as the methyl group,[15] the fact that XIXb and XXIII show opposite rotations of about the same order indicates that these compounds have opposite configurations in the side chains. This deduction assigns the (R)-configuration to the asymmetric center, C_7, of todomatuic acid. Although the specific rotation[5] reported for atlantone (VI) is very small (+1∼+6°),[16] it is very interesting to note that todomatuic acid and atlantone are the only two sesquiterpene ketones of the bisabolene type with a positive optical rotation so far isolated from conifers.

These facts are of interest in connection with the taxonomy of conifers,[17] suggesting the same absolute configuration at the C_4 asymmetric centers in both compounds.

Experimental*

Todomatuic Acid (I).—Crude todomatuic acid (80 g.), obtained from the hydrolysis of the high boiling fraction of sulfite oil, was recrystallized from petroleum ether (b. p. 35∼60°C) to give 41 g. of a pure compound, m. p. 57∼59°C, $[\alpha]^{13}_D$ +92.50° (*c* 1.2 in ethanol) (lit. :[1] m. p. 58.5°C, $[\alpha]_D$ +85.84° (in ethanol)).

Found: C, 71.56; H, 9.57. Calcd. for $C_{15}H_{24}O_3$: C, 71.38; H, 9.57%.

The semicarbazone prepared from I was recrystallized from diluted ethanol decomp. p. 190°C (lit. :[1] decomp. p. 193.2∼193.7°C).

Found: C, 61.92; H, 8.83; N, 13.42. Calcd. for $C_{16}H_{27}O_3N_3$: C, 62.09; H, 8.80; N, 13.59%.

(+)-Desoxo-todomatuic Acid (VIIa).—In a copper flask, 12 g. of sodium was dissolved in 230 cc. of diethylene glycol, and a mixture of 21 g. of todomatuic acid and 20 cc. of hydrazine (prepared from commercially available 80% hydrazine hydrate by azeotropic dehydration with toluene) was then added. The reaction mixture was heated at 180∼190°C, and the generated water was co-distilled with excess hydrazine. Heating was continues for 24 hr., and then 15 cc. of hydrazine was added. The reaction mixture was heated for another 24 hr. and then poured into ice water. After the aqueous solution was made acidic with concentrated hydrochloric acid, this was extracted with benzene. The benzene extract was dried over anhydrous magnesium sulfate. Removal of the solvent gave a viscous residue which distilled at 164∼166°C/1 mmHg to give 13.8 g. of a viscous oil. After this oil had stood at room temperature, the product crystallized. Recrystallization from diluted methanol gave crystals which melted at 50∼60°C, $[\alpha]^{27}_D$ +94.3° (*c* 1.18 in ethanol).

Found: C, 75.90; H, 11.18. Calcd. for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00%.

The anilide VIIIb was prepared by the usual procedure and recrystallized from petroleum ether and then from diluted methanol; m. p. 78∼79°C.

Found: C, 80.36; H, 10.15; N, 4.77. Calcd. for $C_{21}H_{31}ON$: C, 80.46; H, 9.97; N, 4.47%

(+)-*trans*-Dihydro-desoxo-todomatuic Acid (XVIIb).—To 40 cc. of an ether solution of diazomethane prepared from 4 g. of *N*-nitrosomethylurea, a solution of 2 g. of desoxo-todomatuic acid in 50 cc. of ether was added. After being kept at room temperature for 2 hr., the excess diazomethane was decomposed with acetic acid. After the mixture had been washed with water and dried over anhydrous magnesium sulfate, the solvent was removed

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[8] R. G. Cook, A. K. Macbeth and T. B. Swanson, *J. Chem. Soc.*, **1940**, 808.

[9] J. A. Mills, ibid., **1952**, 4976.

[10] A. Birch and A. R. Murray, ibid., **1951**, 1888. The absolute configuration was established by Mills[9] by comparing its rotation with that of limonene.

[11] A. Eschenmoser, J. Schreiber and W. Keller, *Helv. Chim. Acta*, **34**, 1667 (1951). The absolute configuration was established by Mills[9] by a comparison of its rotation with that of limonene.

[12] F. Kögl and A. G. Boer, *Rec. trav. chim.*, **54**, 779 (1935); cf. also Ref. 13.

[13] A. Eschenmoser and H. Schinz, *Helv. Chim. Acta*, **33**, 171 (1950); D. Arigoni and O. Jeger, ibid., **47**, 881 (1954). See also Ref. 11.

[14] F. W. Semmler and A. Becker, *Ber.*, **46**, 1816 (1913); L. Ruzicka and A. G. van Veen, *Ann.*, **468**, 143 (1929).

[15] J. Brewster. *J. Am. Chem. Soc.*, **81**, 5475 (1959).

[16] The fact that the proton at C_4 is labile might be responsible for the racemization through enolization. According to Mills,[9] an optically pure compound with the VI structure should show at least $[M]_D$+150°. Compare this with the molecular rotations of XXa and XXb (Fig. 4).

[17] H. Erdtman, "Chemistry of Some Heartwood Constitutions of Conifers and their Physiological and Taxonomic Significance," in A. Todd, Ed., "Progress in Organic Chemistry," Vol. I, Academic Press Inc., Pub., New York (1952), p. 22.

* The analyses were performed in the microanalytical laboratory of the Institute of Polytechnics, Osaka City University.

to afford a liquid which was distilled to give 1.9 g. of methyl desoxo-todomatuate (VIIc) (b. p. 130~131°C/1 mmHg). The catalytic hydrogenation of 1.9 g. of VIIc in 30 cc. of ethanol with 0.5 g. of an Adams catalyst gave 1.7 g. of methyl dihydro-desoxo-todomatuate, (VIII) (b. p. 117~119°/1 mmHg). To a sodium ethoxide solution prepared from 0.2 g. of sodium and 11 cc. of absolute ethanol, 1.7 g. of methyl dihydro-desoxo-todomatuate (VIIIa) was added. After the solution had been refluxed for 1 hr., the methyl ester was saponified by boiling it with 1 g. of potassium hydroxide and 5 cc. of water. After the ethanol had been distilled off, the reaction mixture was refluxed for 4 hr. and then diluted with 20 cc. of water. The alkaline solution was washed with ether and was made acidic with concentrated hydrochloric acid. After this solution had been extracted with ether and dried over anhydrous magnesium sulfate, the solvent was removed to give a viscous oil which distilled at 150~153°C/1 mmHg, affording 1.6 g. of an oil. $[\alpha]_D^{27}$ +14.1° (*c* 1.77 in ethanol), n_D^{18} 1.4723. The anilide prepared from XVIIb was recrystallized from ethanol, m. p. 115~116°C.

Found: C, 80.14; H, 10.62; N, 4.49. Calcd. for $C_{21}H_{33}ON$: C, 79.94; H, 10.54; N, 4.44%.

The Wieland-Barbier Degradation of Methyl (+)-Dihydro-desoxo-todomatuate (VIIIa).—To a Grignard solution prepared from 4 g. of magnesium, 30 g. of bromobenzene and 100 cc. of ether, a solution of 4 g. of the methyl ester VIIIa in 30 cc. of ether was added. After the solution had been refluxed for 15 min., the ether was removed and replaced by 50 cc. of benzene; then the reaction mixture was heated in an oil bath (110°C) for 12 hr. The Grignard complex was decomposed with cold diluted hydrochloric acid and extracted with ether. After being dried over anhydrous magnesium sulfate, the ether extract was concentrated to give an oil which was distilled to yield 4.5 g. of the tertiary alcohol VIIIc (b. p. 200~205°C/1 mmHg). The tertiary alcohol VIIIc (8.8 g.) was dehydrated by heating it with 200 cc. of acetic anhydride and 40 cc. of pyridine for 4 hr. The reaction mixture was poured into ice water and extracted with ether. The ether extract was washed with diluted hydrochloric acid and a 5% sodium carbonate solution successively and then dried over anhydrous magnesium sulfate. Removal of the solvent gave an oil which was then distilled to afford 7.2 g. of the unsaturated compound VIIId (b. p. 205~210°C/1 mmHg). To a solution of 7.2 g. of the unsaturated compound VIIId in 75 cc. of chloroform, a stream of ozone (2%) was passed for 1 hr. The ozonide was decomposed with 8 cc. of acetic acid and 6 g. of zinc powder. After being freed from the zinc powder, the chloroform solution was washed with a diluted sodium carbonate solution and then concentrated. The residue was distilled at 1 mmHg to give two fractions: 1. b. p. 100~110°C. 1 g; 2. b. p. 190~210°C. 5.4 g. The higher boiling fraction was shown to be recovered unsaturated compound VIIId by examination of its infrared spectrum; it was then ozonolyzed again to afford 0.7 g. of the low boiling fraction (b. p. 110~120°C/1 mmHg). The combined low boiling fractions were dissolved in 20 cc. of petroleum ether and passed through a column containing 35 g. of alumina. Elution with petroleum ether-ether (10 : 1) gave 0.2 g. of an oil which exhibited an absorption at 1704 cm^{-1} infrared spectrum; this was directly converted into semicarbazone. The semicarbazone was recrystallized from diluted ethanol, m. p. 151~152°C.

Found: C, 67.38; H, 11.02; N, 15.97. Calcd. for $C_{15}H_{29}ON_3$: C, 67.37; H, 10.93; N, 15.72%.

***p*-Anisyl-isohexylketone (Xa).** — A mixture of 44.3 g. of 5-methylhexanoic acid and 35 cc. of thionyl chloride was heated on a water bath for 30 min. After the excess thionyl chloride had been removed, the residue was distilled to yield 45 g. of 5-methylhexanoyl chloride (b. p. 70~71°C/1 mmHg). To a stirred mixture of 53.4 g. of aluminum chloride and 150 cc. of carbon disulfide, 45 g. of the acid chloride was added over a 10 min. period under cooling. After 36.7 g. of anisole had been added over a 30 min. period, stirring was continued for another 30 min.; then the temperature of the reaction mixture was gradually brought to room temperature. The reaction mixture was decomposed with ice and extracted with ether. The ether extract was washed with water, a 10% sodium hydroxide solution and water successively, and then dried over anhydrous magnesium sulfate. Removal of the solvent gave a residue which distilled to yield 56.6 g. of Xa, b. p. 131~133°C/1 mmHg.

Found: C, 76.27; H, 9.34. Calcd. for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15%.

The semicarbazone prepared from Xa was recrystallized from ethanol to give prisms, m. p. 124~125°C.

Found: C, 65.11; H, 8.54; N, 15.10. Calcd. for $C_{15}H_{23}O_2N_3$: C, 64.95; H, 8.36; N, 15.5%.

2-*p*-Anisyl-6-methylheptane (XIIa).—To a suspension of 18 g. of magnesium in 250 cc. of ether, a stream of methyl bromide was passed until the magnesium was consumed. A solution of 56 g. of the ketone Xa in 100 cc. of ether was added to the Grignard solution for over 1 hr., and the reaction mixture was refluxed for 2 hr. After diluted hydrochloric acid had been added to decompose the Grignard complex, the reaction mixture was extracted with ether. Removal of the solvent gave the crude alcohol Xb, which was refluxed with 150 cc. of acetic anhydride for 3 hr. The solution was concentrated at reduced pressure and the residual oil was distilled, giving 47.8 g. of the unsaturated compound XI (b. p. 107~113°C/1 mmHg). Two grams of Raney nickel were added to a solution of 47.8 g. of the unsaturated compound XI in 30 cc. of ethanol and hydrogenated in a steel bomb at 25 atm. of hydrogen at 30~40°C. The product boiled at 107~113°C/1 mmHg and weighed 47.5 g.

Found: C, 81.95; H, 11.13. Calcd. for $C_{15}H_{24}O$: C, 81.76; H, 10.98%.

2-(4-Hydroxyphenyl)-6-methylheptane (XIIb).—A mixture of 42 g. of XIIa, 115 cc. of hydroiodic acid (b. p. 127°C), 40 cc. of acetic anhydride and 1 g. of red phosphorus was refluxed for 2 hr. After 60 cc. of acetic anhydride had been added, heating was resumed for another 2 hr. The reaction mixture was then poured into ice water and extracted with benzene. The benzene extract was washed with water and dried over anhydrous magnesium sulfate. Removal of the solvent and distillation gave 38 g. of XIIb, b. p. 127~128°C/1 mmHg.

Found: C, 80.42; H, 10.80. Calcd. for $C_{14}H_{22}O$: C, 81.50; H, 10.75%.

2-(4-Hydroxycyclohexyl)-6-methylheptane(XIIIa).—The phenol (38 g.) XIIb was catalytically hydrogenated in 70 cc. of ethanol with 2 g. of Raney nickel in a steel bomb (140~150°C, 130 atm. of hydrogen) for 3 hr. After being freed from the catalyst, the product was distilled to give 37.5 g. of the cyclohexanol derivative XIIIa, b. p. 120~121°C/1 mmHg.

Found: C, 79.75; H, 12.19. Calcd. for $C_{14}H_{28}O$: C, 79.18; H, 13.29%.

2-(4-Oxocyclohexyl)-6-methylheptane (XIIIb).—To a solution of 18.5 g. of potassium dichromate in 142 cc. of water, 16.3 cc. of concentrated sulfuric acid was added. To the stirred dichromate solution, 37.0 g. of the alcohol XIIIa was added at 57~58°C. The mixture was then stirred for 20 min., cooled to room temperature and extracted with ether. The ether extract was washed with water and with a 5% sodium hydroxide solution successively, and then dried over anhydrous magnesium sulfate. Removal of the solvent and distillation gave 27.5 g. of XIIIb (b. p. 113~114°C/1 mmHg).

Found: C, 79.96; H, 12.91. Calcd: for $C_{14}H_{16}O$: C, 79.93; H, 12.46%.

The semicarbazone prepared from XIIIb was recrystallized from diluted ethanol, m. p. 149~150°C. The mixed melting point with the semicarbazone (m. p. 151~152°C) of IX from todomatuic acid was 149.5~150°C, and their infrared spectra in a Nujol mull or carbon disulfide were superimposable in every detail.

Found: C, 67.53; H, 10.78; N, 15.73. Calcd. for $C_{15}H_{29}ON_3$: C, 67.37; H, 10.93; N, 15.72%.

2-(4-Cyano-4-acetoxycyclohexyl)-6-methylheptane (XIV).—A mixture of 20 g. of the ketone XIIIb and 22.8 g. of acetic anhydride was added slowly to a chilled solution of 14.6 g. of potassium cyanide in 145 cc. of water and then stirred for 13 hr. at room temperature. The reaction mixture was neutralized with a sodium carbonate solution and extracted with ether. The ether extract was washed with water and dried over anhydrous magnesium sulfate. When the solvent was removed at reduced pressure, the cyanohydrin began to decompose. The crude cyanohydrin was directly acetylated by heating it with 10 cc. of acetic anhydride and 1.3 g. of acetyl chloride for 1 hr. After concentration at reduced pressure, the residue was distilled to give 3.5 g. of XIV, b. p. 145~147°C/1 mmHg. The ketone XIIIb was recovered from a low boiling fraction.

2-(4-Carboxycyclohex-3-enyl)-6-methylheptane (XVb).—Five grams of the acetate XIV were passed through a heated Pyrex tube (600°C) packed with ceramic Rashing rings at reduced pressure (1 mmHg) over 1.5 hr. The decomposition products were collected in a trap chilled in a dry ice-acetone bath. After being diluted with ether, the product was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed, and the residue was distilled to give 2.11 g. of the unsaturated cyanide XVa (b.p. 130~132°C/1 mmHg). The cyanide XVa (2.0 g.) was hydrolyzed by heating it with a solution of 1.5 g. of potassium hydroxide in 13 cc. of water with 15 cc. of diethylene glycol for 30 hr. After being made acidic with concentrated hydrochloric acid, the mixture was extracted with benzene. Removal of the solvent gave a residue which was hydrolyzed further by refluxing it with an ethanolic sodium ethoxide solution (prepared from 0.5 g. of sodium and 20 cc. of ethanol). The reaction mixture was diluted with water and washed with benzene. The unsaturated acid XVb precipitated by adding diluted hydrochloric acid was extracted with ether. Removal of the solvent gave an oil which distilled to afford 1.5 g. of XVb, b. p. 163~165°C/1 mmHg. The infrared spectrum was found superimposable on that of (+)-desoxo-todomatuic acid (VIIa).

Found: C, 75.34; H, 10.99. Calcd. for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00%.

***trans*-2-(4-Carboxycyclohexyl)-6-methylheptane (XVIIb).**—The unsaturated acid XVb (1.2 g.) was dissolved in 50 cc. of ether and esterifed with a diazomethane ether solution prepared from 2.4 g. of nitrosomethylurea. After the reaction mixture had been allowed to stand at room temperature for 3 hr., the excess diazomethane was decomposed with a small amount of acetic acid. The mixture was washed with a diluted sodium cabonate solution and then water. After being dried over anhydrous sodium sulfate, the solvent was removed to give an oil which distilled at 128~130°C/1 mmHg. The yield was 1.2 g. The methyl ester XVc was dissolved in 20 cc. of ethanol and catalytically hydrogenated with 80 mg. of an Adams catalyst for 12 hr. Removal of the catalyst and the solvent gave 1.1 g. of an oil which was distilled, b. p. 117~120°C/1 mmHg. The saturated ester (XVIa) (1.1 g.) was added to an ethanolic sodium ethoxide solution prepared from 0.1 g. of sodium and 5 cc. of ethanol, and the solution was refluxed for 1 hr. After a solution of 0.7 g. of sodium hydroxide in 8 cc. of water had been added, the mixture was refluxed for 8 hr. The solution was acidified with diluted hydrochloric acid and extracted with ether. Removal of the solvent and distillation of the residue gave an oil (1.0 g.) (b. p. 152~155°C/1 mmHg; n_D^{18} 1.4723) whose infrared absorption spectrum was found superimposable in every detail on that of natural (+)-*trans*-dihyro-desoxo-todomatuic acid. The anilide prepared from XVIIb was recrystallized from diluted methanol to give needles, m. p. 105~106°C. The mixed melting point with the anilide from natural (+)-*trans*-dihydro-desoxo-todomatuic acid (m. p. 115~116°C) was 103~104°C.

Found: C, 80.42; H, 10.76; N, 4.64. Calcd. for $C_{21}H_{33}ON$: C, 79.94; H, 10.54; N, 4.44%.

The Lithium Aluminum Hydride Reduction of Methyl (+)-*trans*-Dihydro-desoxo-todomatuate (XVIIa).—To a slurry of 0.57 g. of lithium aluminium hydride and 10 cc. of ether, a solution of 2.0 g. of the optically active methyl ester XVIIa in 10 cc. of ether was added over a 45 min. period.

After the reaction mixture had been refluxed for 1.5 hr. and then cooled in an ice bath, the excess lithium aluminum hydride was decomposed with ethyl acetate. Twenty cubric centimeters of 2 N hydrochloric acid were added, and the reaction mixture was extracted with ether. The ether extract was washed with water and dried with anhydrous sodium sulfate. Removal of the solvent gave a viscous oil which was then distilled to afford 1.5 g. of a liquid, b. p. 152∼155°C/4 mmHg; n_D^{31} 1.4663, $[\alpha]_D^{31}$ +15.5° (c 30.4 in chloroform).

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Department of Chemistry
Institute of Polytechnics
Osaka City University
Kita-ku, Osaka