CHEMICAL
&
PHARMACEUTICAL BULLETIN

Vol. 8 No. 12 December 1960

UDC 547.473.07

176. Koiti Kimura,[*1] **Mitsuo Takahashi,**[*1] **and Akira Tanaka**[*2] **:**

Anodic Synthesis of Fatty Acids. VI.1) The Syntheses of ω-Hydroxylated Fatty Acids and ω,ω′-Diols.[*3]

(Faculty of Pharmacy, Kyoto University[*1]*)*

In the preceding paper,2) one of the authors reported the synthesis of the main constituents in conifer wax, such as juniperic acid, 1,16-hexadecanediol, and 1,12-dodecanediol. The present paper describes synthetic method for some ω-hydroxylated fatty acids and ω,ω′-diols which are of particular interest in the field of natural waxes or in perfume field. The desired ω-hydroxylated fatty acids and ω,ω′-diols were prepared in methanol by a mixed Kolbe reaction of the lower ω-acetoxy-fatty acid and an appropriate half ester of dibasic acid, followed by hydrolysis of the resulting reaction mixture with alcoholic potassium hydroxide solution. The synthetic route is shown in Chart 1.[*4]

$$\underset{\substack{\text{(I) } n=10\\ \text{(XIII) } n=11}}{CH_3CO_2(CH_2)_nCO_2H} + \underset{\substack{\text{(II) } m=2\\ \text{(III) } m=4}}{HO_2C(CH_2)_mCO_2CH_3} \xrightarrow[\text{ii) hydrolysis}]{\text{i) electrolysis}}$$

$$\underset{\substack{\text{(Va) } n=10\\ \text{(Vb) } n=11}}{HO(CH_2)_{2n}OH} + \underset{\substack{\text{(IVa) } n=10,\ m=2\\ \text{(IVb) } n=10,\ m=4\\ \text{(IVc) } n=11,\ m=4}}{HO(CH_2)_{n+m}CO_2H} + \underset{\substack{\text{(VIa) } m=2\\ \text{(VIb) } m=4}}{HO_2C(CH_2)_{2m}CO_2H}$$

Chart 1.

ω-Hydroxyl group of the starting acid was protected with acetyl group to prevent dehydrogenation of the hydroxyl group with a hydrogen of adjacent methylene group, followed by the formation of a double bond, and to avoid estolide formation during the reaction, but the protection of ω-hydroxyl group with benzoyl group is unsuitable for electrolysis in methanol because benzene ring is very sensitive to anodic oxygen and polymerizes easily at the anode-surface, causing current density to drop.

The mixture of diol diacetate, monoester, and diester, formed by both symmetrical

---

[*1] Yoshida-Konoe-cho, Sakyo-ku, Kyoto (木村康一, 高橋三雄).

[*2] Present address : National Institute of Hygienic Sciences, Tamagawa-Yoga-machi, Setagaya-ku, Tokyo (田中 彰).

[*3] Presented at the Kinki Local Meeting of the Pharmaceutical Society of Japan, Kyoto, March 20, 1959.

[*4] To obtain ω-hydroxy acid, another method was tried in which ω-bromo or ω-iodo acid, prepared by cross-coupling reaction of the lower ω-halogen acid with half ester of dibasic acid, was acetoxylated and saponified. However, this method did not seem desirable since the electrolytic synthesis of ω-halogen acids in methanol without diaphragm gave very low yield as in most cases.7,8)

1) Part V : Yakugaku Zasshi, **79**, 1445(1959).

2) A. Tanaka : *Ibid.*, **79**, 1327(1959).

and nonsymmetrical coupling of the two components, was separated readily by fractional distillation or crystallization and after hydrolysis of each fraction the objective products (IV, V, VI) were obtained in a pure state.

13-Hydroxytridecanoic acid (IVa), m.p. 78~79.0°, was prepared from methyl hydrogensuccinate (II) in the presence of acetylundecanoic acid (I), which was derived through ω-bromoundecanoic acid according to the method analogous to that of Jones.[3] 15-Hydroxypentadecanoic acid (IVb), m.p. 85~85.7°, was also synthesized by the cross-coupling of (I) with methyl hydrogenadipate (III) in methanol.[4]

Sabinic acid (XII) used as the starting acid for juniperic acid (IVc) was synthesized by Chuit and Hauser[5] by the condensation of 10-bromo-1-decanol with dimethyl malonate and also by the oxidation of 12-tridecenyl acetate. In the present work, the synthesis of (XII) was accomplished by the series of reactions shown in Chart 2.

$$\underset{(\mathrm{VII})}{\mathrm{CH_2{=}CH(CH_2)_8CO_2C_2H_5}} \xrightarrow[\mathrm{Na}]{tert\text{-}\mathrm{BuOH}} \underset{(\mathrm{VIII})}{\mathrm{CH_2{=}CH(CH_2)_8CH_2OH}} \xrightarrow{\mathrm{Ac_2O}}$$

$$\underset{(\mathrm{IX})}{\mathrm{CH_2{=}CH(CH_2)_8CH_2OAc}} \xrightarrow[\mathrm{BzOOH}]{\mathrm{HBr}} \underset{(\mathrm{X})}{\mathrm{Br(CH_2)_{11}OAc}} \xrightarrow{\mathrm{KCN}} \underset{(\mathrm{XI})}{\mathrm{NC(CH_2)_{11}OAc}}$$

$$\xrightarrow[+\mathrm{HCl}]{\mathrm{KOH}} \underset{(\mathrm{XII})}{\mathrm{HO(CH_2)_{11}CO_2H}} \xrightarrow{\mathrm{Ac_2O}} \underset{(\mathrm{XIII})}{\mathrm{AcO(CH_2)_{11}CO_2H}}$$

Chart 2.

Undecenol (VIII) was prepared in a good yield by reduction of ethyl undecenoate (VII) with sodium in *tert*-butanol and (VIII) was acetylated in 90% yield, further brominated in 94% yield with hydrogen bromide in the presence of benzoyl peroxide to give ω-acetoxyundecyl bromide (X). According to the usual procedure, (X) was converted to the corresponding cyanide, which in turn was hydrolyzed to give sabinic acid (XII) by the usual method. (XII), m.p. 83~83.5°, was obtained in 39.3% yield based on (VII). Juniperic acid (IVc) was obtained in 14.1% yield by the mixed Kolbe reaction of 1 mole of acetylsabinic acid (XIII) and 2 moles of methyl hydrogenadipate (III). (IVc) thus obtained melted at 95.5° and its methyl ester and acetyl derivative showed m.p. 54~55.5° and 63.0°, respectively. Infrared spectra of (XII) and (IVc) were similar to those of the corresponding natural samples.

On the other hand, ω,ω'-diol, a symmetrical coupling product of ω-acetoxy acid, was isolated from the neutral fraction after alkaline hydrolysis of the reaction mixture and some new derivatives are shown in Table I.

Table I.

Diol	m.p. (°C)	Acetate, m.p. (°C)	Benzoate, m.p. (°C)
$\mathrm{HO(CH_2)_{20}OH}$	102.5[a]	64.5	58~58.5
$\mathrm{HO(CH_2)_{22}OH}$	105~105.5[b,c]	66~67.0[d]	

a) m.p. 103° by Chuit and Hauser (*loc. cit.*); m.p. 102.4~102.6° by S. Shiina (*loc. cit.*). *b*) m.p. 105.6~105.7° by K.E. Murry and R. Schoenfeld (Australian J. Chem., **8**, 432(1955)). *c*) m.p. 105.5° by N.L. Drake, *et al.* (J. Am. Chem. Soc., **63**, 620(1941)). *d*) m.p. 66~67.0° by K.E. Murry and R. Schoenfeld (*loc. cit.* (b)).

---

[3] R.G. Jones : J. Am. Chem. Soc., **69**, 2350(1947).

[4] G.E. Svadkovskaya, *et al.* : Zhur. Obshcheĭ Khim., **27**, 2146(1957) (C.A., **52**, 6192(1958)). After this work had been completed, the authors learned that (IVa) was prepared by the Soviet chemists by the condensation of (I) with ethyl hydrogenadipate in hydr. ethanolic medium.

[5] P. Chuit, J. Hauser : Helv. Chim. Acta, **12**, 856(1929).

These diols have been prepared by the reduction of the corresponding diester by some investigators,[5,6] but it is noteworthy to learn that this synthetic method of diols in a single stage suggests possible application to the synthesis of aliphatic alcohols by the mixed Kolbe reaction of monobasic acid and the easily available ω-acetoxy acid. 1,22-Docosanediol (Vb) is contained in Carnauba wax and has also been known as a reduction product of phellonic acid or phellogenic acid, whereas 1,20-eicosanediol (Va) has not been found in naturally occurring oils, fats, or waxes. 1,20-Dichloroeicosane was newly prepared by the reaction of (Va) with thionyl chloride in the usual way. Melting points of 1,20-haloeicosanes are listed in Table II.

TABLE II.

Dihalides	$F(CH_2)_{20}F$[8]	$Cl(CH_2)_{20}Cl$	$Br(CH_2)_{20}Br$[7]	$I(CH_2)_{20}I$[6]
m.p.(°C)	46.0∼46.5	59.0∼60.0	67.4∼68.0	67.4∼67.6

Although the Hunsdicker-Simonini reaction has been known as an important stage in the synthetic procedure for higher ω-lactones which have a musk-like odor, the reaction described here also suggests a convenient route to provide starting materials for the preparation of lactones or to obtain pure samples necessary for studying natural wax constituents.

Experimental*5

The apparatus consisted of a 50-cc. wide-mouthed, cylindrical glass cell with a U-type water-cooled condenser, a 110-V source of D.C. current, an ammeter, and a variable resistor. The electrodes consisted of a platinum sheet anode ($2 \times 2\ cm^2$) with a platinum sheet cathode of the same area, at a distance of 3 mm. The electrolyte was maintained at a temperature not exceeding 60° by external and internal cooling. A current was passed until the electrolyte became slightly alkaline to Phenol Red test paper. When the electrolyte became alkaline, of above pH 8, the diol diacetate, a symmetrical coupling product of ω-acetoxy acid, was deacetylated and precipitated in warm MeOH (solvent). The precipitated diol interfered with smooth electrolysis and dropped current density.

ω-Acetoxyundecanoic Acid (I)—(I) was obtained from a mixture of 38 g. ω-bromoundecanoic acid, 64 g. AcOK, and 80 cc. glacial AcOH according to the modified Jones' method.[3] Yield, 28 g. (80.2%). m.p. 36.0°, b.p$_5$ 194∼195°. *Anal.* Calcd. for $C_{13}H_{24}O_4$: C, 63.90; H, 9.90. Found : C, 63.99; H, 10.15.

Methyl Hydrogensuccinate (II)—Succinic anhydride was cleaved by MeOH to the monoester, m.p. 57.0° (reported[9] m.p. 58.0°).

Methyl Hydrogenadipate (III)—(III) was prepared according to the method of Swann, *et al.*,[10] b.p$_7$ 135∼138°. *Anal.* Calcd. for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found : C, 52.46; H, 7.78.

Acetylsabinic Acid (XIII)—Reduction of 50 g. of ethyl undecenoate (VII) with 25 g. of Na and 40 cc. of *tert*-BuOH in 180 cc. of xylene gave undecenol (VIII), b.p$_6$ 120∼123°. Yield, 32 g. or 76%. (VIII) was refluxed with 96 g. of Ac_2O in the presence of pyridine for 5 hr. and 36 g. of (IX), b.p$_5$ 109∼117°, was obtained in 90% yield. Addition of HBr to (IX) in the presence of Bz_2O as a catalyst gave 46 g. of (X), b.p$_4$ 146∼162°, n_D^{30} 1.4647. Crude yield, 94%. A mixture of 46 g. of crude (X) and 20 g. of KCN was refluxed in 130 cc. of 95% EtOH and hydrolyzed with KOH-EtOH solution for 28 hr. to give 35 g. of sabinic acid (XII). The product (XII) was recrystallized from dehyd. benzene to pure (XII), m.p. 83∼83.5°. *Anal.* Calcd. for $C_{12}H_{24}O_3$: C, 66.63; H, 11.18. Found : C, 66.91; H, 11.47.

Overall yield was 20 g. or 34.1% (based on 50 g. of undecenoic acid). (XII) was acetylated with Ac_2O and AcONa to give (XIII), m.p. 45.0°.

13-Hydroxytridecanoic Acid (IVa)—Electrolysis of 7.7 g. of (I) and 13.2 g. of (II) in 40 cc. of MeOH containing 0.1 g. Na was carried out with the average current of 1.1 amp. for 4.5 hr., as described above. The crude oil (16 g.) was distilled under a reduced pressure to give the following fractions; (1) small amount of liquid, b.p. ∼90°, (2) 6 g. of liquid, b.p$_{7\sim6}$ 90∼98°, (3) residue, 5 g.

---

*5 All m.p.s are uncorrected.

[6] S. Shiina : Kogyo Kagaku Zasshi, **40**, 708(1937).

[7] H. Korshing : Ber., **86**, 944(1953).

[8] F.L.M. Patterson, *et al.* : J. Am. Chem. Soc., **78**, 2255(1956).

[9] J. Cason : Org. Syntheses, **25**, 19(1945).

[10] S. Swann, *et al.* : *Ibid.*, Coll. Vol. **II**, 276(1943).

The residue was saponified with 10% KOH-EtOH solution, and the neutral and acid fractions were separated with hot benzene. Upon careful treatment of acid fraction with benzene, crude crystals, m.p. 67~68.0°, weighing 3 g., were obtained. The crystals were recrystallized twice from AcOEt to pure (IVa), m.p. 78~79.0°. Yield, 0.6 g. (7.8%). *Anal.* Calcd. for $C_{13}H_{26}O_3$: C, 67.78; H, 11.38. Found : C, 67.52; H, 11.31.

The methyl ester was prepared with CH_2N_2 in Et_2O in the usual way, m.p. 40.5~41.5°. *Anal.* Calcd. for $C_{14}H_{28}O_3$: C, 68.81; H, 11.55. Found : C, 68.59; H, 11.52.

1,20-Eicosanediol (Va)—Crystals from the above neutral fraction were recrystallized from Me_2CO and then from dehyd. benzene to give pure (Va), m.p. 102.5°. Yield, 0.5 g.

The dibenzoate was prepared in the usual manner, m.p. 58~58.5° (from EtOH). *Anal.* Calcd. for $C_{34}H_{50}O_4$: C, 78.12; H, 9.64. Found : C, 78.01; H, 9.46.

Adipic acid (VIa)—Obtained by hydrolysis of the fraction of b.p$_{7\sim6}$ 90~98°; m.p. 152.0°.

15-Hydroxypentadecanoic Acid (IVb)—7.0 g. of (I) and 10.0 g. of (III) were dissolved in 45 cc. of MeOH containing 0.1 g. of Na. This solution was electrolysed for 4.5 hr. with electric current of 1.2 amp. by the same method as described above. After the termination of electrolysis, the electrolyte was treated in the usual way and the resulting oil was fractionally distilled to give 5.0 g. of liquid, b.p$_7$ 120~178°, and 4.0 g. of crystalline residue. The residue was saponified with 10% KOH-EtOH and an acid fraction (1.7 g.) was obtained as crystals of m.p. 68~69.0°. The crystals were purified from dehyd. benzene to white scaly crystals, m.p. 85~85.7° Yield, 0.6 g. *Anal.* Calcd. for $C_{15}H_{30}O_3$: C, 69.72; H, 11.70. Found : C, 69.79; H, 11.88.

1,20-Eicosanediol (Va)—Crystals from the neutral fraction were purified from a mixture of EtOH-benzene (1:1), m.p. 98~99.0°. Yield, 0.35 g. Recrystallization from dehyd. benzene afforded white crystals of (Va), m.p. 102.5°; yield, 0.3 g. (6.7%). The diacetate was prepared from (Va), Ac_2O, and, conc. H_2SO_4 in the usual manner, m.p. 64.5°. *Anal.* Calcd. for $C_{24}H_{46}O_4$: C, 72.31; H, 11.63. Found: C, 72.60; H, 11.79.

1,20-Dichloroeicosane (Vc)—A mixture of (Va) and $SOCl_2$ was refluxed in the presence of pyridine and the precipitated crystals were recrystallized from Me_2CO, m.p. 59~60.0°. *Anal.* Calcd. for $C_{20}H_{40}Cl_2$: C, 68.35; H, 11.47. Found : C, 68.06; H, 11.40.

Juniperic acid (IVc)—To a solution of 6.1 g. of (XIII) and 9.0 g. of (III) dissolved in 35 cc. of MeOH, 0.1 g. of Na was added to neutralize one part of the total acids used. The mixture was electrolysed for 4.5 hr. with electric current of 1.3 amp. After termination of the electrolysis, the mixture was neutralized with glacial AcOH and extracted with Et_2O. The combined Et_2O extract was washed with K_2CO_3 solution and H_2O, dried over $CaCl_2$, and Et_2O was distilled off. The residue was distilled under a reduced pressure to give 4.2 g. of a liquid, b.p$_6$ 80~152°, and 4.0 g. of residual white crystals.

The white crystals were hydrolyzed with 10% KOH-EtOH solution, and the acid and neutral fractions were separated using hot AcOEt. Acid fraction (caustic alkali-soluble) was extracted with Et_2O in acid medium and dried over Na_2SO_4. After evaporation of Et_2O, crystals obtained were recrystallized from dehyd. benzene to white scaly crystals, m.p. 95.0°. Yield, 1.0 g. (14.8%). *Anal.* Calcd. for $C_{16}H_{32}O_3$: C, 70.54; H, 11.84. Found : C, 70.77; H, 12.04.

Methyl ester : m.p. 54~54.5°. *Anal.* Calcd. for $C_{17}H_{34}O_3$: C, 71.28; H, 11.96. Found : C, 71.56; H, 12.11.

1,22-Docosanediol (Vb)—From the above neutral fraction (hot AcOEt-soluble products) white crystals were obtained on cooling. The crystals were collected and recrystallized from a mixture of benzene and EtOH (1:1) to form pure white crystals (Vb), m.p. 105~105.5°. Yield, 0.8 g. *Anal.* Calcd. for $C_{22}H_{46}O_2$: C, 77.12; H, 13.33. Found : C, 77.35; H, 13.53.

Diacetate of (Vb) : Prepared in the same way as described before, m.p. 66~67.0°. *Anal.* Calcd. for $C_{26}H_{50}O_4$: C, 73.19; H, 11.81. Found : C, 73.10; H, 12.02.

Sebatic acid (VIb)—Saponification of the fraction of b.p$_6$ 80~152° with KOH-EtOH solution gave (VIb), m.p. 130~132°.

The authors express their deep gratitude to Dr. Tatsuo Kariyone for his guidance and encouragement throughout this work. They are grateful to the members of the Analysis Center of the Kyoto University for the microanalyses.

Summary

ω-Hydroxy acids, $HO(CH_2)_nCOOH$ (n=12, 14, 15), and ω,ω'-diols, $HO(CH_2)_mOH$ (m=20, 22), were prepared in a single step by a mixed Kolbe reaction of ω-acetoxy acid and half-ester of dibasic acid. Several derivatives of these synthesized diols were also obtained.

(Received February 23, 1960)