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177. **Akira Tanaka**[*1] : Anodic Synthesis of Fatty Acids. VII.[1] The Syntheses of the Analogs of Chaulmoogric and Hydnocarpic Acids.

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Since Demjanow and Dojarenko[2] reported, in 1907, the Hofer–Moest reaction of cyclobutane– and cyclohexane–carboxylic acids, extensive studies on the electrolysis of alicyclic compounds have been made by Fichter and his co–workers.[3,4]

More recently, chaulmoogric[5] and aleprestic acids,[6] the two representatives of a class of cyclopentenyl acids found in the Hydnocarpus oils, were prepared by anodic synthesis. In these cases, however, 1,2–dicyclopent–2–enylethane, a symmetrical coupling product of cyclopent–2–enylacetic acid, was not identified. Difficulty in purification and isolation of such an unsaturated compound as 1,2–dicyclopent–2–enylethane may be attributed to unsaturation in the five–membered ring.

In the present work, an attempt has been made to apply a similar procedure to the synthesis of saturated alicyclic fatty acids, including the reduction product of the homologs of chaulmoogric and hydnocarpic acids, and related acids. Up to now, many methods using malonic ester,[7] Grignard reagent, or acetoacetic ester[8] were examined for the synthesis of these acids. Lately, thiophene intermediates were also involved in new synthesis

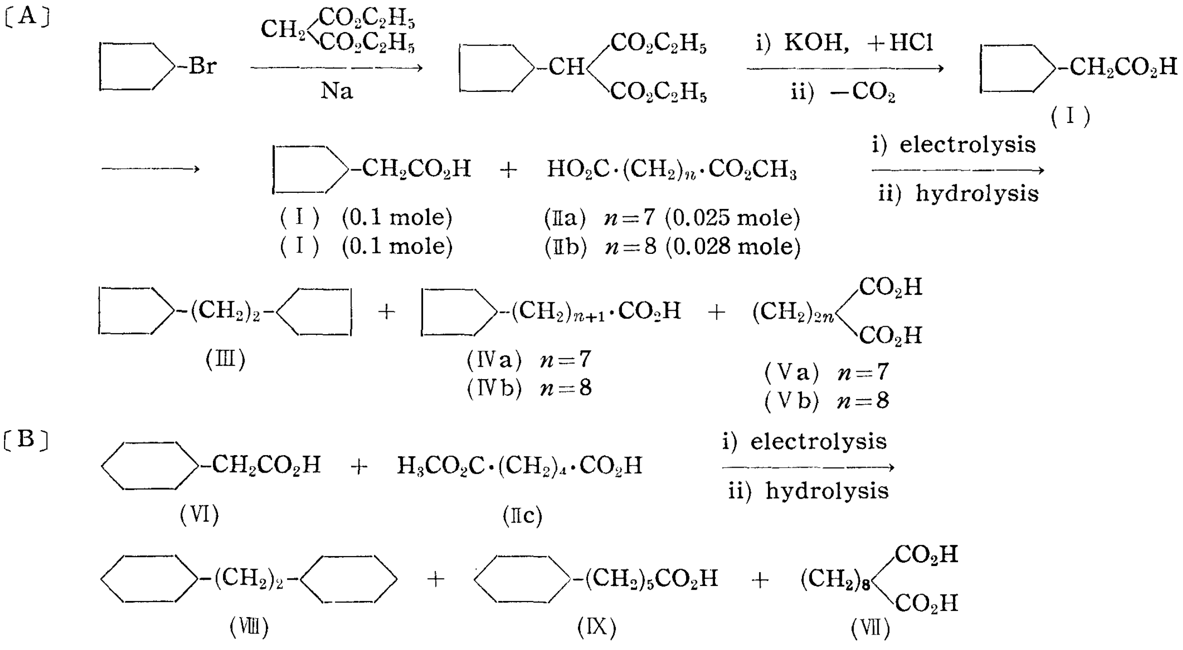

Chart 1.

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3) F. Fichter, *et al.* : Helv. Chim. Acta, **6**, 450(1923), **12**, 1152(1929), **15**, 698(1932), **17**, 1218(1934), **21**, 141(1938), **24**, 253(1941).
4) A. Petrovitch : *Ibid.*, **23**, 806(1940).
5) K. Mislow, I. V. Steinberg : J. Am. Chem. Soc., **77**, 3807(1955).
6) B. Wladislaw : J. Chem. Soc., **1955**, 4227.
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of dihydrochaulmoogric acid and the related compound.[9] However, these procedures described above are less convenient than anodic chain-extension method, which in a single stage leads directly to the desired product. With the starting material readily available, the simplest procedure is clearly the mixed Kolbe reaction.

Electrolysis of cyclopentylacetic acid (I) or cyclohexylacetic acid (VI) in the presence of an appropriate half-ester was carried out in methanol. The reaction proceeded without insurmountable difficulty, as shown in Chart 1.

By treatment of the reaction mixture with ethanolic potassium hydroxide solution, the required acid and neutral fractions were readily separated, and 1,2-dicyclopentylethane (III) and 1,2-dicyclohexylethane (VIII) were identified from the latter fraction as the symmetrical coupling product of (I) and (VI), respectively. No references have been found for preparation of these compounds (III and VIII) by electrolytic reaction. Physical constants of (III) and (VIII) are given in Table I.

TABLE I.

1,2-Dicyclopentylethane (III)		1,2-Dicyclohexylethane (VIII)	
Present sample	Literature[11]	Present sample	Literature[10]
b.p$_9$ 88°	b.p$_{17}$ 109~110°	b.p$_9$ 127~130°	b.p$_{12}$ 147~148.5°
n_D^8 1.4678	n_D^{20} 1.4657	n_D^{20} 1.4745	n_D^{18} 1.4760

Dihydroalepric acid (IVa), a reduction product of naturally occurring alepric acid, was prepared by electrolysis in methanol of a mixture of (I) and methyl hydrogenazelate (IIa) in 35.4% yield. Homodihydroalepric acid (IVb) was also obtained by the same procedure from a mixture of (I) and methyl hydrogensebacate (IIb) in 14.2% yield. New compounds, (IVa) and (IVb), were isolated in a highly pure state and identified as derivatives of *p*-bromophenacyl ester and S-benzylthiuronium salt as shown in Table II.

TABLE II.

	Acid m.p. (°C)	S-benzylthiuronium salt m.p. (°C)	*p*-Bromophenacyl ester m.p. (°C)
Dihydroalepric acid (IVa)	52~53.0	148.5	73.0
Homodihydroalepric acid (IVb)	57.0	143.0	76~77.0

ω-Cyclohexylhexanoic acid (IX), one of a series with a six-membered ring, was prepared by the cross-coupling reaction of ω-cyclohexylacetic acid[12] (VI) with methyl hydrogenadipate (VII). The objective (IX) melted at 33.0°, identical with the melting point given in the literature.[13] ω-Cyclohexylhexanoic acid (IX) is known as one of the compounds synthesized by Adams and his co-workers to investigate relation of chemical structure to bactericidal activity upon *B. leprae*.

Experimental[*3]

Apparatus—The apparatus used was the same as that reported before.[1]

Half ester—Methyl hydrogenadipate, methyl hydrogenazelate, and methyl hydrogensebacate were prepared by semi-esterification of the corresponding dicarboxylic acid.[*4]

[*3] All m.p.s and b.p.s are not corrected.

[*4] In this improved procedure, toluene was used instead of Bu_2O as a solvent and half esters were obtained in a high yield (calculated on free acids).

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10) R. Adams, J. R. Marshall : J. Am. Chem. Soc., **50**, 1972(1928).

11) P. S. Pinkney, C. S. Marvel : *Ibid.*, **59**, 2669(1937).

12) S. Ishiwata, Y. Nozaki : Yakugaku Zasshi, **71**, 1261(1951).

13) R. Adams, G. S. Hiers : J. Am. Chem. Soc., **48**, 2385(1926).

Cyclopentylacetic Acid (I)—87 g. of cyclopentanone[14] dissolved in EtOH was reduced over Raney Ni W-2 catalyst[15] in H_2 stream (60 atm.) at 65° for 7.5 hr. to give 61 g. of colorless cyclopentanol, b.p. 138~140°[16] (69.6%).

A mixture of 61 g. of cyclopentanol, 240 g. of 47% HBr (d:1.48), and 120 g. of conc. H_2SO_4 was allowed to stand overnight and refluxed for an additional 5 hr. to give 68 g. of cyclopentyl bromide with b.p. 137~139°. (I) was prepared by decarboxylation of cyclopentylmalonic acid, obtained by alkylation of sodioethylmalonic ester in xylene, with cyclopentyl bromide, followed by alkaline hydrolysis of the resulting cyclopentylmalonic ester, b.p$_6$ 114~124.° (I), b.p$_7$ 102~104°.[17] Overall yield, 31.0 g. (14.2%).

Dihydroalepric Acid (IVa)—A mixture of (I) (12.8 g., 0.1 mole) and methyl hydrogenazelate (IIa) (5.0 g., 0.025 mole) in 40 cc. of commercial MeOH containing 0.1 g. Na was electrolysed for 7 hr. with the average current of 0.7~0.8 amp. The solution at the end of the reaction was alkaline to litmus test paper. The MeOH solution was neutralized with glacial AcOH and after usual treatments, 10 g. of crude oil was obtained. The oil was hydrolysed, and the acid and neutral fractions were separated in the usual way. 5 g. of acid fraction was dissolved in petr. ether (b.p. 50~70°) and the cold petr. ether-insoluble fraction was filtered off. The cold petr. ether-soluble fraction was fractionally distilled to give 2 g. of crude dihydroalepric acid (IVa) (35.4%), b.p$_7$ 187°, which was recrystallized twice from Me_2CO and petr. ether (b.p. 50~70°) to give pure (IVa) as scaly platelets, m.p. 52~53.0°. *Anal.* Calcd. for $C_{14}H_{26}O_2$: C, 74.28; H, 11.58. Found : C, 74.10; H, 11.64.

p-Bromophenacyl ester : Recrystallized from 95% EtOH. m.p. 73.0°. *Anal.* Calcd. for $C_{22}H_{31}O_3Br$: C, 62.41; H, 7.33. Found : C, 62.46; H, 7.55.

S-Benzylthiuronium salt : White scaly plates, m.p. 148.5°, after two recrystallizations of the crude salt from EtOH. *Anal.* Calcd. for $C_{22}H_{36}O_2N_2S$: C, 67.31; H, 9.24; N, 7.12. Found : C, 67.01; H, 9.46; N, 7.29.

1,2-Dicyclopentylethane (III)—Distillation of the neutral fraction mentioned above gave (III), as a colorless oil of b.p$_9$ 88°. Yield, 2 g. (24.1%). n_D^8 1.4678. *Anal.* Calcd. for $C_{12}H_{22}$: C, 86.66; H, 13.34. Found : C, 86.94; H, 13.23.

Homodihydroalepric Acid (IVb)—A mixture of 12.9 g. of (I) (0.1 mole) and 6 g. of methyl hydrogensebacate (IIb) (0.028 mole) was electrolysed in 40 cc. of MeOH containing 0.1 g. of Na for 8.5 hr. with the average current 1.0 amp. By the usual treatment of the electrolyte, 11 g. of crude oil was obtained. Hydrolysis of the crude oil gave acid and neutral fractions which were separated without difficulty. The acid fraction was distilled to give 2.6 g. of a fraction showing b.p$_7$ 174~194° (mostly b.p$_7$ 192~194°), forming white crystals of m.p. 48~56°. Yield, 1.9 g. after recrystallization from Me_2CO (28.5% on cyclopentylacetic acid), m.p. 56.0°. When recrystallized further from petr. ether (b.p. 50~70°), the crystals formed white scaly plates, m.p. 57.0°. *Anal.* Calcd. for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found : C, 75.19; H, 11.84.

p-Bromophenacyl ester : m.p. 76~77.0°. *Anal.* Calcd. for $C_{23}H_{33}O_3Br$: C, 63.15; H, 7.60. Found: C, 63.33; H, 7.79.

S-Benzylthiuronium salt : m.p. 143.0°. *Anal.* Calcd. for $C_{23}H_{38}O_2N_2S$: C, 67.94; H, 9.42; N, 6.87. Found : C, 68.08; H, 9.59; N, 7.05.

Cyclohexylacetic Acid (VI)—Cyclohexylacetic acid, m.p. 28° (reported[12] m.p. 28°), was obtained by decarboxylation of cyclohexylmalonic acid, prepared by alkylation of sodioethylmalonic ester in EtOH with cyclohexyl bromide according to the method of Ishiwata and Nozaki.[12]

1,2-Dicyclohexylethane (VIII)—(VI) was dissolved in 35 cc. of commercial MeOH containing 30 mg. of Na. The MeOH solution was electrolysed for 2.75 hr. with the average current of 1.2~1.3 amp. When the MeOH solution was alkaline to litmus, the reaction was stopped and the cell content was neutralized with conc. HCl. This was extracted with Et_2O, which was washed with Na_2CO_3 solution and water, dried over $CaCl_2$, the Et_2O solution was allowed to stand overnight, and Et_2O was evaporated, leaving 6 g. of a crude oil. The oil was fractionally distilled under a reduced pressure. After distillation of 2.5 g. of forerun at b.p$_{11}$ 76~135°, 1,2-dicyclohexylethane (VIII) was obtained as a colorless oil, b.p$_{11}$ 135~140°. Yield, 2.2 g. (28.9%). (VIII) thus obtained, showed b.p$_9$ 127~130° when redistilled. n_D^{20} 1.4745. *Anal.* Calcd. for $C_{14}H_{26}$: C, 86.51; H, 13.49. Found : C, 86.60; H, 13.37.

ω-Cyclohexylhexanoic Acid (IX)—A mixture of 8 g. of (VI) and 20 g. of methyl hydrogenadipate (IIc) in 30 cc. of commercial MeOH containing 60 mg. of Na was electrolysed for 6 hr. with the average current of 1.2 amp. Color of the electrolyte at the end of the reaction was whitish yellow. The reaction mixture was treated as described above. The Et_2O extract was washed with water, dried over anhyd. Na_2SO_4, and evaporated. The residue, amounting to 10 g., was hydrolysed with 10%

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15) R. Mozingo : *Ibid.*, **21**, 15(1941).

16) F. Kögl, A. J. Ultée, Jr. : Rec. trav. chim., **69**, 1576(1950); G. E. Goheen : J. Am. Chem. Soc., **63**, 744(1941).

17) M. Jackman, A. J. Bergman, S. Archer : *Ibid.*, **70**, 497(1948). They reported b.p$_{27}$ 137° for (I).

ethanolic KOH and acid fraction was separated in the usual way. The fraction was distilled to give 2.5 g. of white crystals (IX), b.p$_{12}$ 167~169° (22.5%). Crude (IX) was purified through S-benzylthiuronium salt, followed by decomposition with conc. HCl. Pure (IX), m.p. 33.0°, was obtained after recrystallization from Me_2CO. *Anal.* Calcd. for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found : C, 72.43; H, 11.25.

S-Benzylthiuronium salt : m.p. 155.5° (from EtOH). *Anal.* Calcd. for $C_{20}H_{32}O_2N_2S$: C, 65.90; H, 8.85. Found : C, 65.45; H, 8.90.

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Summary

Anodic synthesis of saturated alicyclic compounds was carried out. Dihydroalepric acid and homodihydroalepric acid, analogs of chaulmoogric and hydnocarpic acids, were prepared by the mixed Kolbe reaction of cyclopentylacetic acid and half-ester of dibasic acid. ω-Cyclohexylhexanoic acid was obtained by the cross-coupling of cyclohexylacetic acid with methyl hydrogenadipate. 1,2-Dicyclopentylethane and 1,2-dicyclohexylethane were identified as the symmetrical coupling product of cyclopentylacetic acid and cyclohexylacetic acid, respectively.

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178. **Hisao Tsukamoto**[*1] **and Seisuke Terada**[*2] : Metabolism of Drugs. XXIII.[*3] Metabolic Fate of *p*-Hydroxybenzoic Acid and its Derivatives in Rabbit. (1).

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The alkyl *p*-hydroxybenzoates have been widely used as a preservative for galenicals, foods, and cosmetics. In the studies on the biotransformation of *p*-hydroxybenzoic acid in the animal body, unchanged *p*-hydroxybenzoic acid and *p*-hydroxyhippuric acid1~3) have been isolated from human and dog urine, and 3,4-dihydroxybenzoic acid4) has been detected in the urine of rabbit as the metabolites. On the occurrence of conjugated glucuronic acid, Quick3) also demonstrated the diglucuronide excretion in the urine of man and dog receiving *p*-hydroxybenzoic acid, but monoglucuronide of *p*-hydroxybenzoic acid has not yet been isolated as a urinary metabolite of *p*-hydroxybenzoic acid or its esters.

As *p*-hydroxybenzoic acid and its esters possess two functional groups which would conceivably be metabolized, two monoglucuronides are possible, the ether, *p*-carboxyphenyl glucuronide, and the ester, *p*-hydroxybenzoyl glucuronide. In the present paper is described the glucuronide formation in the metabolism of methyl *p*-hydroxybenzoate using

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[*3] Part XXII. H. Tsukamoto, H. Ide, E. Takabatake : This Bulletin, **8**, 236(1960).

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