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Biochemical Studies on "Bakanae" Fungus. Part 55 Synthesis of Gibberellins.

Part II. Infrared Spectra of the Lactones of Cyclohexane Series.*

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In order to clarify the structure of ring A of gibberellins, thirteen lactones of cyclohexane series, of which eight were new, were prepared to examine their infrared spectra. So far as the experiment is concerned, γ -lactones show the characteristic absorption band in the range $1775\sim 1782\text{ cm}^{-1}$ in dioxane, while δ -ones in the range $1730\sim 1762\text{ cm}^{-1}$. Since the absorption band due to lactone carbonyl of gibberellins occurs at the range $1777\sim 1786\text{ cm}^{-1}$ in dioxane, the lactone ring of gibberellins seems to be γ .

The chemical structure of gibberellins has recently been elucidated to a great extent and formulae were assigned by Japanese and British workers, respectively, which differed slightly each other (Fig. 1).

Cross et al.^{1,2)} had assigned the formula (I) for gibberellin A₃ (=gibberellic acid), while the formula (II) was assigned for GA₃** in our previous reports^{3,4)}. The British workers,

then, revised the formula as (III) in Fig. 1.^{5~8)}

Differences between British and Japanese structures lie in the attaching positions and the size of the lactone ring in ring A as well as the position of carbon-carbon double bond which should be located at the allylic position with alkoxy of the lactone.

Cross et al. reported γ -lactone structure, but, on the other hand, δ -lactone structure was insisted in our previous papers.

Infrared absorption band of lactone carbonyl of gibberellins occurs at $1750\sim 1770\text{ cm}^{-1}$

* A preliminary report of this paper has already been published [This Journal, **24**, 631 (1960)]

** The following abbreviations are used throughout this paper, GA₁, gibberellin A₁; GA₂, gibberellin A₂; GA₃, gibberellin A₃ and so forth.

1) B.E. Cross, J.F. Grove, J. MacMillan and T.P.C. Mulholland, *Chem. and Ind.*, **36**, 954 (1956).

2) B.E. Cross, J.F. Grove, J. MacMillan, T.P.C. Mulholland and N. Sheppard, *Proc. Chem. Soc.*, **1958**, 221.

3) N. Takahashi, Y. Seta, H. Kitamura and Y. Sumiki, This Journal, **22**, 432 (1958).

4) H. Kitamura, N. Takahashi, Y. Seta, A. Kawarada and Y. Sumiki, *ibid.*, **23**, 344 (1959).

5) B.E. Cross, J.F. Grove, J. MacMillan, J.S. Moffatt, T.P.C. Mulholland, J. Seaton and N. Sheppard, *Proc. Chem. Soc.*, **1959**, 302.

6) G. Stork, H. Newman, *J. Am. Chem. Soc.*, **81**, 3168 (1959).

7) G. Stork, H. Newman, *ibid.*, **81**, 5518 (1959).

8) B.E. Cross, J.F. Grove, P. McCloskey, T.P.C. Mulholland and W. Klyne, *Chem. and Ind.*, **1959**, 1345.

FIG. 1. Structure of Gibberellins.

which was attributed to γ -lactone by Cross et al. Based on the same evidence, Japanese group assigned strained δ -lactone structure, considering the lactone carbonyl frequencies of two other natural products [rosenolactone (γ -lactone) 1786 cm^{-1} ⁹; columbin (δ -lactone)

1750 cm^{-1} ¹⁰].

In order to clarify this point, reliable data were necessary concerning the infrared frequencies of the authentic lactones of cyclohexane series. This led us to the syntheses and infrared measurements of thirteen lac-

FIG. 2. Structures of Synthesized Lactones and Alcohol.

⁹ A. Harris, A. Robertson and W.B. Whalley, *J. Chem. Soc.*, **1958**, 1799.

¹⁰ D.H.R. Barton and D. Elad, *ibid.*, **1956**, 2085.

tones of cyclohexane series (Fig. 2). Methods of preparations are described afterwards. Among them, the lactone (VIII) corresponded to the ring A of GA_1 represented by Cross' first formula and the lactone (X) to that by the second formula, respectively. The infrared spectra of the mixtures of 6-methylbicyclo [3,2,1] octanol-(6) (XVIII) and each of the thirteen lactones were also examined. The alcohol has the same structure as that of the rings C and D of GA_2 (IV).

Infrared spectra of the lactones are illustrated in Fig. 3. Carbonyl frequencies of the lactones and their derivatives are listed in

Table I. Lactone-carbonyl frequencies of gibberellins are also summarized in Table II.

Carbonyl stretching band of γ -lactones of cyclohexanol carboxylic acids occurs in the range $1742\sim 1770\text{ cm}^{-1}$ (Nujol mull or liquid film). A considerable shift towards lower frequencies was observed in the lactones which have free hydroxyl group. However, even in these hydroxy-lactones absorption occurs at $1772\sim 1792\text{ cm}^{-1}$ (Nujol mull) if the free hydroxyl is masked as acetate, tosylate or phenylurethan. All γ -lactones, whether they have free hydroxyl or not, absorb at $1775\sim 1782\text{ cm}^{-1}$ in dioxane solutions. This indicates

FIG. 3. Infrared Spectra of Synthesized Lactones and Alcohol (Solid Samples=Nujol mulls, Liquid Samples=Liquid films)

FIG. 3.—(1) Cyclohexanol-(3)-carboxylic acid lactone.

FIG. 3.—(2) 1-Methylcyclohexanol-(3)-carboxylic acid lactone.

FIG. 3.—(3) Cyclohexane-*trans*-diol-(1,3)-carboxylic acid lactone. FIG. 3.—(4) 1-Methylcyclohexane-*trans*-diol-(2,3)-carboxylic acid lactone. FIG. 3.—(5) 1-Methylcyclohexane-*cis*-diol-(2,3)-carboxylic acid lactone.

FIG. 3.—(6) 1-Methylcyclohexane-*cis*(?)-diol-(2,5)-carboxylic acid lactone.

FIG. 3.—(7) Cyclohexanol-(4)-carboxylic acid lactone.

FIG. 3.—(8) 1-Methylcyclohexanol-(4)-carboxylic acid lactone.

FIG. 3.—(9) 3-Methylcyclohexanol-(4)-carboxylic acid lactone.

FIG. 3.—(10) Cyclohexane-*trans*-diol-(1,4)-carboxylic acid lactone. FIG. 3.—(11) *trans*-Cyclohexanol-(2)-acetic acid lactone.

 FIG. 3.—(12) *cis*(?) -Cyclohexanol-(2)-acetic acid lactone.

FIG. 3.—(13) Cyclohexanol-(3)-acetic acid lactone.

 FIG. 3.—(14) A Mixture of 1-Methylcyclohexane-*cis*(?) -diol-(2,5)-carboxylic acid lactone and 6-Methylbicyclo [3,2,1] octanol-(6).

TABLE I. POSITIONS OF CARBONYL STRETCHING BAND OF THE OBTAINED LACTONES

Name of the Compound	Wave Number	(cm ⁻¹)
A. γ -Lactones of cyclohexanolcarboxylic acids		
Cyclohexanol-(3)-carboxylic acid lactone	1770(N*),	1778(D*)
1-Methylcyclohexanol-(3)-carboxylic acid lactone	1768(N),	1775(D)
Cyclohexane- <i>trans</i> -diol-(1, 3)-carboxylic acid lactone	1755(N),	1782(D)
acetate	1790(N)	
tosylate	1792(N)	
1-Methylcyclohexane- <i>trans</i> -diol-(2, 3)-carboxylic acid lactone	1745(N),	1790(D)
phenylurethan	1780(N)	
1-Methylcyclohexane- <i>cis</i> -diol-(2, 3)-carboxylic acid lactone	1768(F*) (broad),	1778(D)
phenylurethan	1778(N)	
1-Methylcyclohexane- <i>cis</i> (?) -diol-(2, 5)-carboxylic acid lactone	1742(N),	1778(D)
tosylate	1772(N)	
B. δ -Lactones of cyclohexanolcarboxylic acids		
Cyclohexanol-(4)-carboxylic acid lactone	1740(N),	1752(D)
1-Methylcyclohexanol-(4)-carboxylic acid lactone	1742(N),	1750(D)
3-Methylcyclohexanol-(4)-carboxylic acid lactone	1740(N),	1752(D)
Cyclohexane- <i>trans</i> -diol-(1, 4)-carboxylic acid lactone	1745(N),	1762(D)
acetate	1766(N)	
tosylate	1768(N)	
C. Lactones of cyclohexanolacetic acids		
<i>trans</i> -Cyclohexanol-(2)-acetic acid lactone	1778(F),	1780(D)
<i>cis</i> (?) -Cyclohexanol-(2)-acetic acid lactone	1780 (1754. sh) (F),	1780(D)
Cyclohexanol-(3)-acetic acid lactone	1730(N),	1730(D)

* "N" refers to values determined in nujol mull, "F" in the state of liquid film and "D" in dioxane.

TABLE II. POSITIONS OF LACTONE CARBONYL STRETCHING BAND OF GIBBERELLINS AND RELATED COMPOUNDS.

(Wave number (cm⁻¹), determined in nujol mull)

GA ₁ methyl ester	1763 ¹¹⁾	GA ₃ methyl ester acetate	1761 ¹³⁾
	1759 ¹²⁾	GA ₄ methyl ester	1770 ¹⁴⁾
GA ₂ methyl ester	1755 ¹¹⁾	GA ₅	1765 ¹⁶⁾
GA ₃	1746 ¹³⁾	GA ₅ methyl ester	1748 ¹⁶⁾
	1784D* ¹³⁾	Dihydro GA ₁	1770 ¹²⁾
GA ₃ methyl ester	1766 ¹²⁾	Dihydro GA ₁ methyl ester	1760 ¹²⁾
	1770 ¹³⁾	Pseudo GA ₁ **	1760 ¹⁵⁾
	1777D ¹³⁾	Monobromo GA ₁	1760 ¹⁵⁾
GA ₃ acetate	1765 ¹³⁾	GC***	1760 ¹⁵⁾
	1786D ¹³⁾	Iso GA ₁ ***	1750 ¹⁵⁾

* "D" refers to values determined in dioxane.

** Pseudo GA₁ is the secondary-hydroxyl epimer of GA₁

*** GC is obtained from GA₁ by acid-catalyzed rearrangement.

**** Iso GA₁ is the secondary-hydroxyl epimer of GC.

that the shift towards lower frequencies owing to a free hydroxyl group is due to its dipolar interaction or hydrogen bonding. A molecular model of the lactone (X) which is the epimer of the ring A of Cross' second formula (III), suggests a strong hydrogen bonding between lactone carbonyl and free hydroxyl. From a study of a molecular model, the epimeric lactone, which could not be synthesized but will be derived from *trans*-diol, seems to form a weak hydrogen bonding and, therefore, it is expected to have its carbonyl absorption at higher frequencies than the lactone (X). In fact, the lactone (X'), which is probably a *cis*, *trans* mixture, shows a broad absorption

11) H. Kitamura, Y. Seta, N. Takahashi, Y. Sumiki, This Journal **23**, 408 (1959).

12) N. Takahashi, Y. Seta, H. Kitamura, Y. Sumiki, *ibid.* **23**, 509 (1959).

13) B.E. Cross, *J. Chem. Soc.*, **1** 54, 4670.

14) N. Takahashi, Y. Seta, H. Kitamura, Y. Sumiki, This Journal **23**, 405 (1959).

15) N. Takahashi, Y. Seta, H. Kitamura, A. Kawarada, Y. Sumiki, *ibid.* **23**, 493 (1959).

16) J. MacMillan, J.C. Seaton, P.J. Suter, *Proc. Chem. Soc.* **1959** 325.

at 1760~1775 cm^{-1} besides an absorption at 1742 cm^{-1} .

δ -Lactones of cyclohexanolcarboxylic acids absorb in the range 1740~1745 cm^{-1} . Tosylation or acetylation of a hydroxy lactone causes a shift towards higher frequencies. However, infrared absorption of δ -lactones always occurs at lower frequencies than that of γ -lactones. This is also true for the lactones of cyclohexanolacetic acids.

Infrared spectrum of a mixture of lactone (X) and alcohol (XVIII) is also shown in Fig. 3 as an example. It resembles that of GA_2 to a certain extent. Consequently, it is probable to draw the following conclusion.

- (i) γ -Lactones generally exhibit the absorption bands at higher frequencies than δ -lactones, although there are some which absorb at approximately the same frequencies as δ -ones owing to the interaction of free hydroxyl group.
- (ii) γ -Lactones can easily be distinguished from δ -ones by examining their infrared spectra measured in dioxane solutions, because in that solution dipolar interactions are nearly eliminated.
- (iii) Lactone carbonyl of gibberellins shows its absorption band in the range 1777~1786 cm^{-1} in dioxane. Therefore, the lactone ring in gibberellins seems to be γ .

METHODS OF PREPARATIONS

i) **Lactone of Cyclohexanol-(3)-carboxylic Acid (V):** Catalytic hydrogenation, followed by hydrolysis and lactonization, of ethyl *m*-hydroxybenzoate afforded the lactone (V).¹⁷⁻¹⁹⁾

ii) **Lactone of 1-Methylcyclohexanol-(3)-carboxylic Acid (VI):** Ethyl 1-methylcyclohexanone-(2)-carboxylate (XX) was prepared by methylation of ethyl cyclohexanone-(2)-carboxylate (XIX)²⁰⁾ with sodium sand and methyl iodide. The methylated keto ester

(XX) was then reduced either catalytically or with sodium borohydride to afford ethyl 1-methylcyclohexanol-(2)-carboxylate (XXI). Chlorination of the hydroxy ester (XXI) with phosphorus pentachloride, followed by dehydrochlorination in collidine, gave ethyl 1-methylcyclohexene-(2)-carboxylate (XXII), which was hydrolyzed to the corresponding unsaturated acid (XXIII). Lactonization was effected by heating the acid (XXIII) in 60% sulfuric acid (Fig. 4).

iii) **γ -Lactone of Cyclohexanediol-(1,3)-carboxylic Acid (VII):** Corresponding cyanohydrin (XXV) was prepared from 3-benzoyloxycyclohexanone (XXIV) which was obtained according to Clarke et al.²¹⁾ and Rigby²²⁾. Subsequent acid-hydrolysis gave the lactone (VII).

iv) **γ -Lactone of 1-Methylcyclohexane-*trans*-diol-(2,3)-carboxylic Acid (VIII):** Oxidation of ethyl 1-methylcyclohexene-(2)-carboxylate (XXII) with performic acid gave two isomeric *trans*-diols, one of which afforded the lactone (VIII) by subsequent hydrolysis and lactonization.

v) **γ -Lactone of 1-Methylcyclohexane-*cis*-diol-(2,3)-carboxylic Acid (IX):** Oxidation of the olefinic ester (XXII) with neutral aqueous solution of potassium permanganate at a low temperature gave two isomeric *cis*-diols, one of which afforded the lactone (IX) by subsequent treatments.

vi) **γ -Lactone of 1-Methylcyclohexane-*cis*-(2)-diol-(2,5)-carboxylic Acid (X):** Dimethyl γ -ethylenedioxy-pimelate (XXVI), which was prepared according to Lukes et al.²³⁾, gave methyl 5-ethylenedioxy-cyclohexanone-(2)-carboxylate (XXVII) by a self-condensation using sodium sand in toluene. The keto ester (XXVII) was methylated with sodium and methyl iodide to afford methyl 1-methyl-5-ethylenedioxy-cyclohexanone-(2)-carboxylate (XXVIII). It was then hydrogenated to afford the hydroxy ester (XXIX). Subsequent hydrolysis gave a keto acid (XXX) which was hydrogenated and lactonized to yield the lactone (X). Hydroxyl at C(2) of the lactone (X) may be equatorial one owing to the alkaline media during hydrolysis, therefore, hydroxyls at C(2) and C(5) may possess *cis*-configuration. This means that the lactone is epimeric with ring A of Cross' second formula concerning the C(2) hydroxyl. Several attempts were

17) M.F. Clarke and L.M. Owen, *J. Chem. Soc.*, **1950**, 2111.

18) E.J. Boorman and R.P. Linstead, *ibid.*, **1935**, 258.

19) W.H. Perkin, Jr. and G. Tattersal, *ibid.*, **91**, 480 (1907).

20) H.R. Snyder, L.A. Brooks and S.H. Shapiro, *Org. Synth.*, Coll. Vol. 2, P. 531 (John Wiley, New York, 1948).

21) M.F. Clarke and L.N. Owen, *J. Chem. Soc.*, **1950**, 2103.

22) W. Rigby, *ibid.*, **1949**, 1586.

23) R.M. Lukes, G.I. Poos and L.H. Sarett, *J. Am. Chem. Soc.*, **74**, 1401 (1952).

FIG. 4. Synthesis of Lactones from Ethyl Cyclohexanone-(2)-carboxylate.

made to obtain the epimer of the lactone (X): Epimerization with hot concentrated sodium hydroxide solution or Walden inversion by tosylation accompanied with successive hydrolysis led only to the recovery of unchanged lactone. Epimerization of C(2) hydroxyl of the keto-acid (XXX) with alkali gave only resinous substances. A liquid lactone (X') which was obtained by hydrogenation of the dione (XXXI) seems to be a mixture of *cis* and *trans* lactones from an infrared evidence.

vii) **Lactone of Cyclohexanol-(4)-carboxylic Acid (XI):** Ethyl *p*-hydroxybenzoate was hydrogenated, hydrolyzed and lactonized to yield the lactone (X)²⁴

viii) **Lactone of 1-Methylcyclohexanol-(4)-carb-**

oxylic Acid (XII): Bromination of ethyl 1-methylcyclohexene-(2)-carboxylate (XXII) with *N*-bromosuccinimide gave 4-bromo ester (XXXII), which was then treated with silver carbonate suspended in acetone to afford the corresponding olefinic hydroxy ester (XXXIII). Catalytic hydrogenation of the ester (XXXIII) gave ethyl 1-methylcyclohexanol-(4)-carboxylate (XXXIV), of which hydrolysis and lactonization afforded the lactone (XII).

ix) **Lactone of 3-Methylcyclohexanol-(4)-carboxylic Acid (XIII):** 3-Methylcyclohexanone-(4)-carboxylic acid (XXXV), which was prepared according to Perkin, Jr.²⁵ was hydrogenated and lactonized.

24) L.N. Owen and P.A. Robins, *J. Chem. Soc.*, 1949, 330.

FIG. 5. Synthesis of 1-Methylcyclohexanediol-(2, 5)-carboxylic acid.

x) **δ -Lactone of Cyclohexanediol-(1,4)-carboxylic Acid (XIV):** Bisulfite adduct of 4-benzoyloxycyclohexanone, which was prepared according to Jones and Sondheimer²⁶⁾, was treated with potassium cyanide to afford the corresponding cyanohydrin (XXXVI), of which acid-hydrolysis gave the lactone (XIV).

xi) **Lactone of *trans*-Cyclohexanol-(2)-acetic Acid (XV):** This was prepared according to Newman and VanderWerf²⁷⁾.

xii) **Lactone of *cis*-Cyclohexanol-(2)-acetic Acid (XVI):** The lactone, which was prepared by hydro-

prepare the *cis*-lactone according to them. However, it was found that the substance which was obtained by treating *trans*-cyclohexanol-(2)-acetamide with tosyl chloride was not identical with what they claimed to be [Formula (XXXVIII)]. The substance was shown to be tosylate of cyclohexanol-(2)-acetonitrile (XXXIX) (absorption at 2230 cm^{-1}). Hydrolysis of this tosylate (XXXIX) gave mainly an unsaturated acid instead of the lactone. The following procedure was devised to prepare a lactone which has probably *cis*-configuration: Ethyl cyclohexanone-(2)-carboxylate (XIX) was con-

genation of 2-hydroxycyclohexylidene acetic acid lactone (XXXVII) with Adams' platinum oxide catalyst according to Newman et al.²⁷⁾, shows infrared absorption due to lactone carbonyl at 1778 cm^{-1} and 1754 cm^{-1} , the former being stronger. Brewster and Kucera²⁸⁾ reported that the infrared absorption of the *cis*-lactone occurs at 1754 cm^{-1} . So the attempts were made to

densed with ethyl chloroacetate to afford a dicarboxylic ester (XL). It was then refluxed with concentrated hydrochloric acid to effect hydrolysis and decarboxylation. Cyclohexanone-(2)-acetic acid (XLI) thus obtained was hydrogenated to the corresponding hydroxy acid (XLII). Its lactonization with diluted hydrochloric acid gave a lactone (XLIII). Infrared absorption of its lactone carbonyl occurs at 1780 cm^{-1} with a shoulder at 1754 cm^{-1} . Its absorption in finger-print region is identical with that of *cis*-lactone prepared according to Newman et al.²⁷⁾ When this lactone

25) W.H. Perkin, Jr, *J. Chem. Soc.*, **85**, 422 (1904).

26) E.R.H. Jones and F. Sondheimer, *ibid.*, **1949**, 615.

27) M.S. Newman and C.A. VanderWerf, *J. Am. Chem. Soc.*, **67**, 233 (1945).

28) J.H. Brewster and H. Kucera, *ibid.*, **77**, 4564 (1955).

FIG. 6. Synthesis of 6-Methylbicyclo [3, 2, 1] octanol-(6).

(XLIII) was refluxed with concentrated aqueous ammonia, viscous oil was obtained instead of fine crystals of *trans*-amide. Infrared absorption of the oil showed that it mainly consisted of lactone with a small amount of amide and acid. If the lactone had had *trans*-configuration, it should have afforded amide in good yield²⁹. Therefore, the lactone (XLIII) seems to be *cis*.

xiii) Lactone of Cyclohexanol-(3)-acetic Acid (XVIII): Diethyl cyclohexanone-(3)-malonate (XLIV), which was prepared according to Bartlett et al.²⁹, was hydrolyzed and decarboxylated to afford cyclohexanone-(3)-acetic acid (XLV) only in poor yield. Its hydrogenation and distillation gave the lactone (XVII). In another attempt, the malonate (XLIV) was hydrogenated to afford diethyl cyclohexanol-(3)-malonate (XLVI). The corresponding malonic acid (XLVII) was obtained by hydrolysis, which was then heated to effect decarboxylation and lactonization. The lactone (XVII) was obtained in good yield by this method. From a study of molecular model, this lactone seems to be *cis*.

xiv) 6-Methylbicyclo [3,2,1] octanol-(6) (XVIII):

Diethyl homoisophthalate (XLVIII) was obtained from homoisophthalic acid which was prepared according to Ipatieff et al.³⁰ Catalytic hydrogenation of the ester (XLVIII) gave diethyl 3-carbethoxycyclohexanecarboxylate (XLIX). A keto ester (L) obtained by a self-condensation of the ester (XLIX) was hydrolyzed and decarboxylated to afford bicyclo [3,2,1] octanone-(6) (LI). Subsequent Grignard reaction gave the alcohol

(XVIII).

Several attempts were made to prepare a δ -lactone which has a hydroxyl adjacent to lactone carbonyl [see the ring A of formula (II)]. (i) Catalytic hydrogenation of corresponding aromatic hydroxy ester (LIIa and LIIb) with various catalysts; (ii) Catalytic hydrogenation of a diketone ester (LIII) and its reduction with calcium borohydride in methanol or sodium borohydride in pyridine; (iii) Substitution of chlorine atom in a chloride (LIV) by acetoxy or hydroxyl group, and (iv) Addition of formic acid to an olefin (LV). All of these were in vain.

EXPERIMENTAL

All melting points are not corrected. Infrared frequencies refer to nujol mulls for solid samples and to liquid films for liquid samples.

Lactone of Cyclohexanol-(3)-carboxylic Acid (V): Sixty grams of *cis*, *trans* mixture of the acid were heated at 160°C for some time with removal of water formed. The resulting lactone was distilled in vacuo, b.p. 138~140°C/33 mm or 118~120°C/6 mm. Yield, 21 g. Solidified distillate was recrystallized from petro-

leum ether. Needles with sticky nature, m.p. 118~120°C (lit.¹⁸ 119°C). *Anal.* Found: C, 66.49; H, 8.31. Calcd. for $C_7H_{10}O_2$: C, 66.64; H, 7.99%.

Ethyl 1-Methylcyclohexanone-(2)-carboxylate (XX): Into a suspension of finely powdered sodium (13.6 g) in anhydrous benzene (500 cc), ethyl cyclohexanone-(2)-carboxylate (XIX, 100 g) was added with stirring and heating under reflux for 2 hrs. Then, methyl iodide (100 g) was added dropwise to the voluminous suspension of sodium enolate and refluxing was continued for additional 3 hrs. with stirring. After cool-

29) P.D. Bartlett, G.F. Woods, *J. Am. Chem. Soc.*, **62**, 3933 (1940).

30) V.N. Ipatieff, J.E. Germain, W.W. Thompson and H. Pines, *J. Org. Chem.*, **17**, 272 (1952).

ing, water (300 cc) was added to the reaction mixture to dissolve sodium iodide. The benzen layer separated was washed with diluted sulfuric acid and then with water. Benzene was removed and the residue was distilled in vacuo, b.p. 129~135°C/28 mm. Yield, 98 g (92%). Redistillation gave a colorless liquid, b.p. 131~133°C/30 mm. n_D^{29} 1.4478. *Anal.* Found: C, 65.15; H, 8.95. *Calcd.* for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75%.

Ethyl 1-Methylcyclohexanol-(2)-Carboxylate (XXI):

(A) Eighty grams of the keto ester (XX) in 250 cc of 99% ethanol were hydrogenated at 100°C and an initial pressure of 50 kg/cm² for 2 hrs. over Raney nickel W-7 (10 g). The hydroxy ester obtained by the distillation of the product had the b.p. 106~107°C/6 mm. Yield, 77 g (95%).

Anal. Found: C, 64.68; H, 9.47. *Calcd.* for $C_{10}H_{18}O_3$: C, 64.53; H, 9.74% (B) Sodium borohydride (12 g) was added in small portions to the keto ester (150 g) in methanol (200 cc) at 5~10°C. After standing overnight at room temperature, diluted hydrochloric acid (1:50, 500 cc) was added to the reaction mixture and the separated oil was extracted with benzene. The obtained hydroxy ester was distilled in vacuo, b.p. 115~117°C/14 mm. Yield, 110 g (69%). n_D^{28} 1.4550.

Anal. Found: C, 64.08; H, 9.97. *Calcd.* for $C_{10}H_{18}O_3$: C, 64.53; H, 9.74%.

Ethyl 1-Methylcyclohexene-(2)-carboxylate (XXII):

The hydroxy ester (XXI, 108 g) was added dropwise to a suspension of phosphorus pentachloride (120 g) in anhydrous ether (300 cc) at 5~10°C with stirring. The reaction mixture was refluxed for 2 hrs. after the addition and then poured into ice-water (500 g). After separating the ether layer, the aqueous layer was extracted with ether. The combined ethereal solution was washed with sodium bicarbonate solution and dried with sodium sulfate. After the removal of ether, the residue was distilled in vacuo, b.p. 82~115°C/14 mm, giving a mixture of a chloro ester and an olefinic ester. Yield, 94 g (76%). The obtained crude mixture (100 g) was heated with freshly distilled collidine (250 cc) at 160°C for 30 min. After cooling, the reaction mixture was washed with diluted sulfuric acid to remove collidine. After separating the oily layer, the aqueous layer was extracted with ether. The combined ethereal solution was dried with sodium sulfate and distilled. The olefinic ester had b.p. 90~105°C/18 mm. Yield, 64 g. n_D^{20} 1.4560. Several times of rectification gave pure ester, b.p. 87~90°C/20 mm

or 82~84°C/15 mm. n_D^{26} 1.4556.

Anal. Found: C, 70.90; H, 9.53. *Calcd.* for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59%.

1-Methylcyclohexene-(2)-carboxylic Acid (XXIII):

The corresponding olefinic ester (XXII, 16 g) was refluxed with aqueous potassium hydroxide (8 g in 30 cc) for 9 hrs. The mixture was acidified with hydrochloric acid and extracted with ether. Ethereal solution was dried with sodium sulfate and distilled, b.p. 130~135°C/15 mm. Yield, 9.4 g (76%) n_D^{21} 1.4756.

Anal. Found: C, 68.06; H, 8.80. *Calcd.* for $C_9H_{12}O_2$: C, 68.54; H, 8.63%.

Lactone of 1-Methylcyclohexanol-(3)-carboxylic Acid

(VI): The olefinic acid (XXIII, 8 g) and 60% (vol.) sulfuric acid (32 cc) were heated on an asbestos wire gauze for 5 mins. After cooling, the reaction mixture was diluted with water (100 cc) and saturated with ammonium sulfate. Extraction with ether, followed by the removal of acid fraction with sodium bicarbonate solution, gave the lactone. b.p. 100~112°C/9 mm. Yield, 4.2 g (53%). It solidified after standing in a refrigerator. Needles from petroleum ether, m.p. 34~35°C.

Anal. Found: C, 68.49; H, 8.40. *Calcd.* for $C_8H_{12}O_2$: C, 68.54; H, 8.63%.

3-Benzoyloxycyclohexanone Cyanohydrin (XXV):

Fifty grams of 3-benzoyloxycyclohexanone [prisms from ether-petroleum ether, m.p. 62~63°C (lit.¹⁶ 63.5°C)], which was prepared from cyclohexanediol-(1,3) adopting the same procedures as described for 4-benzoyloxy isomer by Jones et al.²⁰, were melted and added to an aqueous solution of sodium bisulfite (40 g in 60 cc). The solidified adduct was transferred on a Buchner funnel and washed with a small amount of cold water and then with ether. The powdered adduct was placed in a round-bottomed flask, shaken with aqueous potassium cyanide (36 g in 90 cc) and ether (200 cc). Within an hour the adduct was converted into cyanohydrin which was in the ether layer. The aqueous layer was once extracted with ether (100 cc). The combined ethereal solution was washed with diluted sulfuric acid and then with saturated sodium chloride solution. After drying with sodium sulfate, ether was removed. The cyanohydrin solidified after standing in a refrigerator. Yield, 54 g (96%). Prisms from ethyl acetate-petroleum ether. M.p. 112~116°C (sinter at 93°C). *Anal.* Found: C, 68.75; H, 6.42; N, 5.67. *Calcd.* for $C_{14}H_{18}O_3N$: C, 68.55; H, 6.16; N, 5.71%.

Infrared frequencies; 3408 (OH), 2234 (CN), 1722 (CO), 1605 (benzene ring) cm^{-1} .

Lactone of Cyclohexane-*trans*-diol-(1, 3)-carboxylic Acid (VII): The cyanohydrin (XXV, 45 g) was refluxed with 20% hydrochloric acid (200 cc) for 4.5 hrs. After cooling, the precipitated benzoic acid was filtered off and the filtrate was concentrated in vacuo to 50 cc. The neutral fraction was extracted with ethyl acetate. The extract was dried with sodium sulfate. Crude lactone was obtained after the removal of the solvent in vacuo. Yield, 3.1 g (12%). Leaflets from ethyl acetate-petroleum ether, m.p. 165~165.5°C (sinter at 146°C). *Anal.* Found: C, 59.67; H, 7.63. Calcd. for $\text{C}_7\text{H}_{10}\text{O}_3$: C, 59.14; H, 7.09%.

Acetate: Prisms from ethyl acetate-petroleum ether, m.p. 72~74°C. *Anal.* Found: C, 58.85; H, 7.21. Calcd. for $\text{C}_9\text{H}_{12}\text{O}_4$: C, 58.67; H, 6.57%.

Tosylate: Needles from ethyl acetate-petroleum ether, m.p. 135~136°C. *Anal.* Found: C, 56.90; H, 6.30; S, 10.53. Calcd. for $\text{C}_{11}\text{H}_{10}\text{O}_6\text{S}$: C, 56.74; H, 5.44; S, 10.82%.

Lactone of 1-Methylcyclohexane-*trans*-diol-(2, 3)-carboxylic Acid (VIII): Ethyl 1-methylcyclohexene-(2)-carboxylate (XXII, 34 g) was added with shaking to a mixture of 30% hydrogen peroxide (26 g) and 80% formic acid (200 cc). An exothermic reaction occurred within 15 min. and the mixture became homogeneous. After standing 4 days at room temperature, formic acid was removed in vacuo. The residue was refluxed with 3*N*-methanolic potash (150 cc) for 5 hrs. After the removal of methanol, the acid was lactonized with 20% hydrochloric acid (120 cc). The neutral fraction was extracted with ethyl acetate. The extract was dried with sodium sulfate. The lactone was distilled in vacuo, b.p. 160~162°C/8 mm or 146~148°C/5 mm. Yield, 4.2 g (13%). It solidified after standing in a refrigerator. Plates from ether-petroleum ether, m.p. 72~73°C. *Anal.* Found: C, 61.51; H, 7.88. Calcd. for $\text{C}_8\text{H}_{12}\text{O}_3$: C, 61.52; H, 7.75%.

Phenylurethan: Needles from ether-petroleum ether, m.p. 143~144°C. *Anal.* Found: C, 65.70; H, 6.26; N, 5.34. Calcd. for $\text{C}_{15}\text{H}_{17}\text{O}_4\text{N}$: C, 65.44; H, 6.22; N, 5.09%.

Lactone of 1-Methylcyclohexane-*cis*-diol-(2, 3)-carboxylic Acid (IX): A solution of potassium permanganate (26 g) and magnesium sulfate (20 g) in water (500 cc) was added dropwise in the course of 1.5 hrs. to the olefinic ester (XXII, 34 g) in acetone (400 cc) at -40°C with stirring. After standing overnight in a

refrigerator, the precipitated manganese dioxide was filtered off. The filtrate was concentrated in vacuo. The lactone was obtained through hydrolysis, lactonization and extraction of neutral fraction as usual. B.p. 158~165°C/4 mm or 173~177°C/10 mm. Yield, 2.6 g (9%). n_D^{25} 1.4945. *Anal.* Found: C, 61.62; H, 8.24. Calcd. for $\text{C}_8\text{H}_{12}\text{O}_3$: C, 61.52; H, 7.75%.

Phenylurethan: Needles from ethyl acetate-petroleum ether, m.p. 129~130°C. *Anal.* Found: C, 66.01; H, 6.14; N, 5.07. Calcd. for $\text{C}_{15}\text{H}_{17}\text{O}_4\text{N}$: C, 65.44; H, 6.22; N, 5.09%.

Methyl 5-Ethylenedioxycyclohexanone-(2)-carboxylate (XXVII): Dimethyl γ -ethylenedioxypimelate (XXVI, 165 g) and finely powdered sodium (23 g) in anhydrous toluene (500 cc) were heated in an oil bath at 115°C with stirring. Within a short time a vigorous reaction started and the reaction mixture solidified with evolution of hydrogen. (When less pure pimelate was used, the reaction took place less vigorously and the yield was lower.) The heating was continued for additional 3 hrs. at 110°C. After cooling, the yellow solid was decomposed by adding 50% acetic acid (150 cc) cautiously. The toluene layer was separated and the aqueous layer was extracted 3 times with benzene (150 cc each). The combined benzene-toluene solution was washed with sodium bicarbonate solution and dried with sodium sulfate. Distillation gave the ester, b.p. 137°C/4 mm or 154°C/6 mm. Yield, 84 g (61%). It solidified after cooling and showed a positive ferric chloride test. Long prisms from ether-petroleum ether, m.p. 59~60°C. *Anal.* Found: C, 56.37; H, 6.73. Calcd. for $\text{C}_{10}\text{H}_{14}\text{O}_5$: C, 56.15; H, 6.51%. Infrared frequencies: 1750, 1726, 1672, 1626 cm^{-1} (enolized β -keto ester).

Methyl 1-Methyl-5-ethylenedioxycyclohexanone-(2)-carboxylate (XXVIII): The keto ester (XXVII, 82 g) in anhydrous toluene was added to a suspension of finely powdered sodium (10 g) in anhydrous toluene (300 cc) at 110°C with stirring. Immediately the sodium salt precipitated as a thick mass with a brisk evolution of hydrogen. Methyl iodide (100 g) was added dropwise and the stirring and refluxing were continued for additional 6 hrs. at 110°C. After cooling, water was added cautiously to the reaction mixture to dissolve sodium iodide. The toluene layer was separated and the aqueous layer was extracted with benzene. The combined benzene-toluene solution was washed with water. Distillation gave an oily product, b.p. 145°C/5 mm, with a negative ferric chloride test.

Yield, 76 g (86%). Since it did not solidify after standing several days in a refrigerator, it was employed for the next reaction without further purification. Infrared frequencies: 1748, 1734 cm^{-1} (CO).

Methyl 1-Methyl-5-ethylenedioxcyclohexanol-(2)-carboxylate (XXIX): The methylated keto ester (XXVIII, 75 g) in methanol (200 cc) was hydrogenated at 100°C and an initial pressure of 65 kg/cm^2 for 6 hrs. over Raney nickel W-7 (15 g). The solvent was removed in vacuo. The residue solidified when cooled. Yield, 71 g (93%). Long prisms from ether-petroleum ether, m.p. 59~60°C. *Anal.* Found: C, 57.71; H, 8.13. Calcd. for $\text{C}_{11}\text{H}_{18}\text{O}_5$: C, 57.38; H, 7.88%. Infrared frequencies: 3568 (OH), 1724 (CO) cm^{-1} .

1-Methylcyclohexanon-(5)-ol-(2)-carboxylic Acid (XXX): The hydroxy ester (XXIX, 70 g) was refluxed with 20% potassium hydroxide solution (200 cc) for 30 min. Unsaponified impurities were removed with ether. The aqueous layer was acidified with concentrated hydrochloric acid. After filtering off the precipitated potassium chloride, the mother liquor was extracted continuously with ether for 3 days. The crystalline mass separated in the flask was collected on a Buchner funnel and was washed with a small amount of ether. Yield, 35 g (67%). Needles from ethyl acetate-petroleum ether, m.p. 155~156°C. *Anal.* Found: C, 55.60; H, 6.99. Calcd. for $\text{C}_8\text{H}_{12}\text{O}_4$: C, 55.80; H, 7.03%. Infrared frequencies: 3376 (OH), 1724 (CO), 1690 (COOH) cm^{-1} .

Lactone of 1-Methylcyclohexane-*cis*(?)-diol-(2,5)-carboxylic Acid (X): The keto acid (XXX, 5 g) in 4% potassium hydroxide solution (50 cc) was hydrogenated at room temperature and atmospheric pressure for 3 hrs. over Raney nickel W-7 (5 g). 650 cc of hydrogen was absorbed. After removing the catalyst, the aqueous solution was acidified with concentrated hydrochloric acid (10 cc) and was heated in a boiling water bath for 30 min. The lactone was extracted with ethyl acetate after neutralizing the solution with sodium bicarbonate. The extract was dried with sodium sulfate. Crude lactone was obtained by the removal of the solvent. Yield, 700 mg (16%). Leaflets from ethyl acetate-petroleum ether, m.p. 101.0~101.5°C. *Anal.* Found: C, 61.66; H, 7.81. Calcd. for $\text{C}_8\text{H}_{12}\text{O}_3$: C, 61.52; H, 7.75%.

Tosylate: Needles from ethyl acetate, m.p. 156.5~157.0°C. *Anal.* Found: C, 58.53; H, 6.06; S, 11.53. Calcd. for $\text{C}_{15}\text{H}_{18}\text{O}_5\text{S}$: C, 58.05; H, 5.84; S, 10.33%.

Lactone of Cyclohexanol-(4)-carboxylic Acid (XI): Needles from ether, m.p. 108~110°C (lit.²⁴) 108~112°C). *Anal.* Found: C, 65.89; H, 8.08. Calcd. for $\text{C}_7\text{H}_{10}\text{O}_3$: C, 66.64; H, 7.99%.

Ethyl 1-Methyl-4-bromocyclohexene-(2)-carboxylate (XXXII): Ethyl 1-methylcyclohexene-(2)-carboxylate (XXII, 7.5 g) in carbon tetrachloride (30 cc) was heated with *N*-bromosuccinimide (8.5 g) in the presence of a small amount of benzoyl peroxide (0.1 g) for 2.5 hrs. After cooling, succinimide was filtered off and the solvent was removed from the filtrate. Distillation gave the bromide, b.p. 122~128°C/7 mm. Yield, 9.0 g (80%). Redistillation gave a colorless liquid, b.p. 125°C/7 mm. n_D^{18} 1.4992. *Anal.* Found: C, 48.67; H, 6.23; Br, 32.84. Calcd. for $\text{C}_{10}\text{H}_{15}\text{O}_2\text{Br}$: C, 48.59; H, 6.12; Br, 32.34%.

Ethyl 1-Methylcyclohexene-(2)-ol-(4)-carboxylate (XXXIII): The bromo ester (XXXII, 68 g) in acetone (150 cc) was treated with freshly prepared silver carbonate (77.5 g) and water (3 cc) at 5~10°C for 2 hrs. with stirring. The reaction mixture was then refluxed for 1 hr. with stirring. The precipitated silver bromide was filtered off. Distillation after the removal of acetone gave the hydroxy ester, b.p. 115~120°C/5 mm with a small amount of forerun, b.p. 95~115°C/5 mm (7 g). Yield, 32 g (63%). Redistillation gave a purer fraction (b.p. 109~113°C/6 mm, n_D^{18} 1.4722), which was still contaminated with the bromo ester. *Anal.* Found: C, 61.64; H, 8.09. Calcd. for $\text{C}_{10}\text{H}_{16}\text{O}_3$: C, 65.19; H, 8.75%.

Ethyl 1-Methylcyclohexanol-(4)-carboxylate (XXXIV): The olefinic hydroxy ester (XXXIII, 30 g) in 99% ethanol (200 cc) was hydrogenated at 50°C and an initial pressure of 50 kg/cm^2 for 3 hrs. over Raney nickel W-7 (5 g). After removing the solvent, the residue was fractionally distilled in vacuo. A fraction collected at a lower boiling range (b.p. 85~95°C/5 mm, 5 g) showed an additional infrared frequency in carbonyl region (1780 cm^{-1} γ -lactone) other than that of the hydroxy ester. Another fraction collected at a higher boiling range (b.p. 95~110°C/5 mm, 15 g) was chiefly consisted of the saturated hydroxy ester. Redistillation gave 13.2 g of colorless liquid, b.p. 107~108°C/5 mm, n_D^{18} 1.4640. *Anal.* Found: C, 64.55; H, 9.78. Calcd. for $\text{C}_{10}\text{H}_{18}\text{O}_3$: C, 64.53; H, 9.74%. Infrared frequencies: 3440 (OH), 1730 (CO) cm^{-1} .

Lactone of 1-Methylcyclohexanol-(4)-carboxylic Acid (XII): The hydroxy ester (XXXIV, 13 g) was refluxed with a potassium hydroxide solution (8 g in

50 cc) for 1 hr. After removing the unsaponified impurities with ether, the aqueous layer was acidified with concentrated hydrochloric acid (20 cc) and was extracted continuously with ether overnight. Ether was removed and the residue was heated until no more water distilled out. The residue, dissolved in ether, was shaken with a solution of sodium bicarbonate to remove *trans*-acid. Distillation of the ethereal solution after drying with sodium sulfate gave the lactone, b.p. 80~90°C/4 mm. Yield, 4.5 g (46%). It immediately solidified. Plates from ether, m.p. 54.5~56.5°C. *Anal.* Found: C, 68.54; H, 8.88. Calcd. for $C_8H_{12}O_2$: C, 68.54; H, 8.63%.

Lactone of 3-Methylcyclohexanol-(4)-carboxylic Acid (XIII): 3-Methylcyclohexanone-(4)-carboxylic acid (XXXV, m.p. 91~92°C, 11 g) in 4% sodium hydroxide (100 cc) was hydrogenated at room temperature and atmospheric pressure for 10 hrs. over Raney nickel W-7 (5 g). 1400 cc of hydrogen was absorbed. After removing the catalyst, the aqueous solution was acidified with concentrated hydrochloric acid (15 cc) and was extracted continuously with ether for 17 hrs. Treatment of the ether extract as described above for 1-methyl isomer afforded the lactone, b.p. 106~110°C/4~5 mm. Yield, 4.5 g (39%). It solidified after standing several days in a refrigerator. Needles from petroleum ether, m.p. 46~47°C. *Anal.* Found: C, 68.25; H, 8.82. Calcd. for $C_8H_{12}O_2$: C, 68.54; H, 8.63%.

4-Benzoyloxycyclohexanone Cyanohydrin (XXXVI): 4-Benzoyloxycyclohexanone [m.p. 62~63°C, lit.²⁰ 63°C, 168 g] in benzene (300 cc) was shaken with sodium bisulfite in water (120 g in 150 cc). The mixture soon solidified. The solid adduct was treated with 120 g of potassium cyanide in the same way as described for 3-benzoyloxy isomer. The obtained oily product solidified after standing in a refrigerator. Yield, 178 g (95%). Powders from ethyl acetate-petroleum ether, m.p. 92~98°C (sinter at 70°C). *Anal.* Found: C, 68.95; H, 6.26; N, 6.04. Calcd. for $C_{14}H_{15}O_3N$: C, 68.55; H, 6.16; N, 5.71%. Infrared frequencies: 3430 (OH), 2244 (CN) cm^{-1} .

Lactone of Cyclohexane-*trans*-diol-(1, 4)-carboxylic Acid (XIV): Treatment of the cyanohydrin (XXXVI, 30 g) in the same way as described for 3-benzoyloxy isomer gave the lactone. Yield, 1.5 g (8.6%). Leaflets from ethyl acetate-petroleum ether, m.p. 152~153°C (sinter at 123°C). *Anal.* Found: C, 59.20; H, 7.09. Calcd. for $C_7H_{10}O_3$: C, 59.14; H, 7.09%.

Acetate: Prisms from ethyl acetate-petroleum ether,

m.p. 84~85°C. *Anal.* Found: C, 58.49; H, 7.19. Calcd. for $C_{10}H_{12}O_4$: C, 58.69; H, 6.57%.

Tosylate: Needles from ethyl acetate, m.p. 129~130°C. *Anal.* Found: C, 56.80; H, 5.64; S, 10.71. Calcd. for $C_{14}H_{16}O_6S$: C, 56.74; H, 5.54; S, 10.82%.

1-Cyano-4-benzoyloxycyclohexene-(1) (LV): Thionyl chloride (150 g) was added dropwise to the cyanohydrin (XXXVI, 176 g) in pyridine (300 cc) in the course of 1.5 hrs. at 5~10°C with stirring. Then the reaction mixture was refluxed for 1.5 hrs. with stirring. After cooling, the dark and viscous reaction mixture was poured into ice-cold diluted sulfuric acid (150 cc of concentrated acid in 1 kg of crashed ice) and was extracted with ether. The separation of ether from the aqueous layer was possible only when the resinous impurities were removed by treating with activated charcoal. The separated ether layer was washed with water and dried with sodium sulfate. A white solid product was obtained after removing the ether. Yield, 113 g (70%). Needles from ether-petroleum ether, m.p. 66.5~67.5°C. *Anal.* Found: C, 74.21; H, 5.94; N, 6.13. Calcd. for $C_{14}H_{13}O_2N$: C, 73.99; H, 5.77; N, 6.16%. Infrared frequency: 2230 (CN, strong) cm^{-1} . Partial hydrolysis of this unsaturated nitrile in 80% formic acid afforded 4-benzoyloxycyclohexene-(1)-carboxylic acid amide. Needles from ethyl acetate, m.p. 168~169°C. *Anal.* Found: C, 68.54; H, 5.90; N, 5.82. Calcd. for $C_{14}H_{15}O_3N$: C, 68.55; H, 6.16; N, 5.71%. Infrared frequencies: 3428, 3240 (amide II and amide I) cm^{-1} .

1-Cyano-2-chloro-4-benzoyloxycyclohexane (LIV): Dry hydrogen chloride gas was introduced into a solution of the cyclohexene (LV, 65 g) in anhydrous ether (450 cc) at 0~5°C with stirring. White crystals started to separate as the solution was saturated with hydrogen chloride. The reaction mixture was left standing overnight in an ice bath. The product was collected on a Buchner funnel and washed with a small amount of ether. White, fine crystals from ethyl acetate-petroleum ether, m.p. 135~136°C. *Anal.* Found: C, 64.12; H, 5.43; Cl, 13.04. Calcd. for $C_{14}H_{14}O_2NCl$: C, 63.76; H, 5.35; Cl, 13.45%. Infrared frequency: 2238 (CN) cm^{-1} .

Lactone of *trans*-Cyclohexanol-(2)-acetic Acid (XV): A colorless liquid, b.p. 104°C/5 mm. n_D^{18} 1.4760. *Anal.* Found: C, 68.36; H, 8.77. Calcd. for $C_8H_{12}O_3$: C, 68.54; H, 8.63%.

Tosylate of Cyclohexanol-(2)-acetonitrile (XXXIX): Needles from ethyl acetate, m.p. 86°C (lit.²⁸) 84.5~

85.5°C). *Anal.* Found: C, 61.51; H, 6.55; N, 4.70. Calcd. for $C_{15}H_{19}O_5NS$: C, 61.42; H, 6.53; N, 4.78%. Infrared frequencies: 2230 (CN), 1362, 1185, 1171 (sulfonate) cm^{-1} .

Ethyl 1-Carbethoxycyclohexanone-(2)-acetate (XL): Ethyl cyclohexanone-(2)-carboxylate (XIX, 70 g) was added to a suspension of finely powdered sodium (9.7 g) in anhydrous benzene (400 cc) with stirring and refluxing. After 2 hrs., ethyl chloroacetate (51.5 g) was added to the reaction mixture and the refluxing was continued for additional 4 hrs. with stirring. After cooling, the benzene solution was washed with water and dried with calcium chloride. Distillation gave the diester, b.p. 142~150°C/5 mm. Yield, 50.2 g (48%). Redistillation gave a colorless liquid, b.p. 148~150°C/6 mm. n_D^{22} 1.4620. *Anal.* Found: C, 61.37; H, 8.04. Calcd. for $C_{18}H_{26}O_5$: C, 60.92; H, 7.87%. Infrared frequencies: 1745, 1730, 1715 (CO) cm^{-1} .

Cyclohexanone-(2)-acetic Acid (XLI): The diester (XL, 45 g) was refluxed with concentrated hydrochloric acid (150 cc) for 6 hrs. Hydrochloric acid was removed in vacuo. Distillation of the residue gave the keto acid, b.p. 160°C/5 mm. Yield, 22 g (80%). It solidified after standing. Needles from ethyl acetate-petroleum ether, m.p. 74~75°C. *Anal.* Found: C, 61.58; H, 8.01. Calcd. for $C_8H_{12}O_3$: C, 61.52; H, 7.75%.

Lactone of *cis*(?)-Cyclohexanol-(2)-acetic Acid (XLIII=XVI): The keto acid (XLI, 20 g) in sodium hydroxide solution (6 g in 200 cc) was hydrogenated at room temperature and an initial pressure of 70 kg/cm² for 8 hrs. over Raney nickel W-7 (5 g). After filtering off the catalyst, the aqueous solution was slightly acidified with hydrochloric acid. The solution was neutralized with sodium bicarbonate and the lactone was extracted with ether. The ethereal solution was dried with sodium sulfate and then was distilled, b.p. 120°C/9 mm. Yield, 12.5 g (72%). n_D^{22} 1.4760. *Anal.* Found: C, 68.70; H, 8.81. Calcd. for $C_8H_{12}O_2$: C, 68.54; H, 8.63%.

Diethyl Cyclohexanone-(3)-malonate (XLIV): A colorless liquid, b.p. 158~160°C/6 mm. (lit.²⁰) 135~137°C/12 mm). $n_D^{23.5}$ 1.4600. *Anal.* Found: C, 60.80; H, 8.14. Calcd. for $C_{18}H_{26}O_5$: C, 60.92; H, 7.87%.

Cyclohexanone-(3)-acetic Acid (XLV): Hydrolysis and decarboxylation of the malonate²⁰ gave the product in 37% yield. Prisms from benzene-petroleum ether, m.p. 78~80°C. *Anal.* Found: C, 61.99; H, 7.65.

Calcd. for $C_8H_{12}O_3$: C, 61.52; H, 7.75%.

Lactone of Cyclohexanol-(3)-acetic Acid (XVII): The keto acid (XLV, 6 g) in sodium hydroxide solution (1.6 g in 50 cc) was hydrogenated at room temperature and atmospheric pressure for 4 hrs. over Raney nickel W-7 (6 g). After filtering off the catalyst, the aqueous solution was acidified with hydrochloric acid and was extracted continuously with ether for 18 hrs. Removal of ether gave 6 g of oily product, which was heated at 160°C to effect lactonization. Distillation gave an oil, b.p. 126~130°C/4 mm. A small amount of crystals (50 mg) separated after cooling. Plates from ether-petroleum ether (10 mg), m.p. 116~119°C. *Anal.* Found: C, 69.07; H, 8.89. Calcd. for $C_8H_{12}O_2$: C, 68.54; H, 8.63%.

Diethyl Cyclohexanol-(3)-malonate (XLVI): Diethyl cyclohexanone-(3)-malonate (XLIV, 120 g) in 95% ethanol (200 cc) was hydrogenated at 100°C and an initial pressure of 75 kg/cm² for 2 hrs. over Raney nickel W-7 (10 g). Distillation gave the hydroxy ester, b.p. 150~160°C/0.1 mm (with decomposition). Yield, 44 g (36%). Redistillation gave a colorless liquid, b.p. 158°C/0.1 mm. n_D^{24} 1.4646. *Anal.* Found: C, 59.91; H, 8.83. Calcd. for $C_{18}H_{26}O_5$: C, 60.44; H, 8.59%. Infrared frequencies: 3430 (OH), 1756, 1730 (CO) cm^{-1} .

Cyclohexanol-(3)-malonic Acid (XLVII): The ethyl ester (XLVI, 40 g) was refluxed for 1 hr. with potassium hydroxide solution (30 g in 100 cc). The solution was neutralized with concentrated hydrochloric acid and was extracted continuously with ether for 2 days. A crystalline mass separated in the receiving flask. Yield, 27 g (86%). M.p. 172~173°C (dec.). *Anal.* Found: C, 53.96; H, 7.08. Calcd. for $C_9H_{14}O_5$: C, 53.46; H, 6.98%. Infrared frequencies: 3440 (OH), 1715 (CO) cm^{-1} .

Lactone of Cyclohexanol-(3)-acetic Acid (XVII): The malonic acid (XLVII, 25 g) was heated at 180~200°C for 30 min. to effect decarboxylation and lactonization. Subsequent distillation gave an oil, b.p. 150~156°C/15 mm, which immediately solidified. This was shown to be identical with the lactone prepared by the former method (infrared absorption and mixed melting point). Yield, 4.2 g (24%). Plates from ether-petroleum ether, m.p. 124~125°C, mixed m.p. 122°C. *Anal.* Found: C, 68.58; H, 8.64. Calcd. for $C_8H_{12}O_2$: C, 68.54; H, 8.63%.

Diethyl Homoisophthalate (XLVIII): Homoisophthalic acid (35.5 g) was refluxed with 99% ethanol

(150 cc) in the presence of a small amount of concentrated sulfuric acid (2 cc) for 10 hrs. The excess ethanol was removed in vacuo. Water was added and the separated ester was extracted with ether. The ethereal solution was washed with sodium carbonate solution and was dried with sodium sulfate. Distillation gave the ester, b.p. 160~161°C/7 mm. Yield, 44.5 g (96%). n_D^{21} 1.5010. *Anal.* Found: C, 65.94; H, 6.99. Calcd. for $C_{18}H_{10}O_4$: C, 66.08; H, 6.83%.

Ethyl 3-Carbethoxycyclohexaneacetate (XLIX): The aromatic diester (XLVIII, 30 g) in 99% ethanol (150 cc) was hydrogenated at 180°C and an initial pressure of 70 kg/cm² for 3 hrs. over Raney nickel W-7 (10 g). Distillation gave the diester, b.p. 160°C/11 mm, with a small amount of forerun, b.p. 120°C/11 mm (4 g). Yield, 23 g (75%). n_D^{23} 1.4786. *Anal.* Found: C, 64.82; H, 9.34. Calcd. for $C_{18}H_{22}O_4$: C, 64.44; H, 9.15%.

Ethyl Bicyclo [3, 2, 1] octanone-(6)-carboxylate-(7) (L): The diester (XLIX, 18.5 g) was added to a suspension of finely powdered sodium (5 g) in anhydrous toluene (100 cc) at 110°C with stirring. Refluxing was continued for 8 hrs. with stirring. Yellow solids separated in the course of reaction. After cooling, the sodium salt was carefully decomposed with diluted sulfuric acid. The toluene layer was separated and the aqueous layer was extracted with benzene. The solvents were removed from the combined benzene-toluene solution. Distillation gave an oil, b.p. 121~

123°C/5 mm, with a small amount of forerun, b.p. 78~120°C/5 mm (0.7 g). Yield, 4.5 g (30%). *Anal.* Found: C, 66.95; H, 8.69. Calcd. for $C_{11}H_{10}O_3$: C, 63.72; H, 8.22%.

Bicyclo [3, 2, 1] octanone-(6) (LI): The keto ester (L, 4.2 g) was refluxed with concentrated hydrochloric acid (20 cc) for 8 hrs. The ketone formed was purified by steam-distillation, m.p. 150~152°C. Yield, 1.5 g (53%). *Anal.* Found: C, 77.69; H, 9.70. Calcd. for $C_8H_{12}O$: C, 77.37; H, 9.74%. Infrared frequency: 1756 (CO) cm⁻¹.

6-Methylbicyclo [3, 2, 1] octanol-(6) (XVIII): The ketone (LI, 1.2 g) in anhydrous ether (10 cc) was added to a solution of methyl magnesium iodide (3 g of methyl iodide and 0.6 g of magnesium) in anhydrous ether (20 cc) at 0~5°C. After standing for 3 hrs., the reaction mixture was refluxed for 40 min. A grayish mass in the flask was decomposed with 3 N-sulfuric acid (20 cc) at 0~5°C. The ether layer was separated and the aqueous layer was extracted with ether. The combined ethereal solution was washed with a saturated solution of sodium bicarbonate and was dried with sodium sulfate. Evaporation of ether gave a crystalline mass. Yield, 1.0 g (76%). Needles from petroleum ether, m.p. 82~83°C. *Anal.* Found: C, 77.30; H, 11.86. Calcd. for $C_9H_{16}O$: C, 77.14; H, 11.43%. Infrared frequency: 3360 (OH) cm⁻¹.