U. D. C. 547.678.3.07

46. Michitoshi Ohta: Studies on Abietic Acid Derivatives. III.[1] Synthesis of Fluorenone Derivatives.

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It has earlier been reported[1] that the oxidation of methyl deisopropylallodehydroabietate (I) with chromium trioxide gives methyl 9,10-dioxodeisopropylallodehydroabietate (II) in a fair yield. (II) does not react even on boiling with acetic anhydride nor with *o*-phenylenediamine but its oxidation with hydrogen peroxide in sodium hydroxide alkalinity affords an acid (III), m.p. 239~241°. Boiling of (III) with potassium hydroxide in ethyleneglycol changes it to an acid (IV) of m.p. 234~235°(decomp.).

The analytical values of (III) agree with those for 2,6-dimethyl-2-(*o*-carboxyphenyl)-6-methoxycarbonylcyclohexanecarboxylic acid as anticipated. The analytical values of (IV) are identical with those of a tricarboxylic acid formed by saponification of the ester of (III), but the titration value for carboxyl group is 24.75% for (III) and 32.04% for (IV), being far smaller than those calculated for (III) (26.9%) and for (IV) (42.2%).[2] However, their titration with a solution of sodium methoxide in a mixture of methanol-benzene,[3] in ethylenediamine, with thymol blue as the indicator, gives values agreeing well with calculated values, being 26.64% for (III) and 42.08% for (IV).

Treatment of (III) and (IV) with diazomethane affords the same trimethyl ester (V), m.p. 71~71.5°, from both, so that the structures of (III) and (IV) are reliable. Saponification of (V) with ethanolic potassium hydroxide affords a dicarboxylic acid (VI), m.p. 241~243°, different from (III) and this acid gives normal value for titration of the carboxylic acid, as expected.

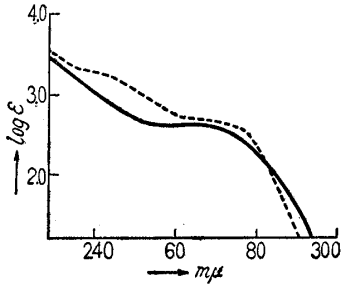

Fig. 1.
Ultraviolet Absorption Spectra
—— (III) (EtOH)
------ 2,4,6-tri-*tert*-butylbenzoic acid (cyclohexane)[4]

The ultraviolet spectrum of (III), as shown in Fig. 1, does not exhibit the absorption of aromatic carboxylic acids and this is thought to be due to the obstruction of resonance of the carboxylic acid in the aromatic ring with the ring by steric interference. Betts and others[4] reported that 2,4,6-tri-*tert*-butylbenzoic acid also does not exhibit absorption maximum in the ultraviolet region. On heating the tricarboxylic acid (IV) above its decomposition point under a reduced pressure, it forms a neutral substance (VII), m.p. 147~149°, with evolution of water and carbon dioxide, with a small amout of an acid (VIII), m.p. 130~131°, as a by-product. (VII) is easily saponified by 2% ethanolic

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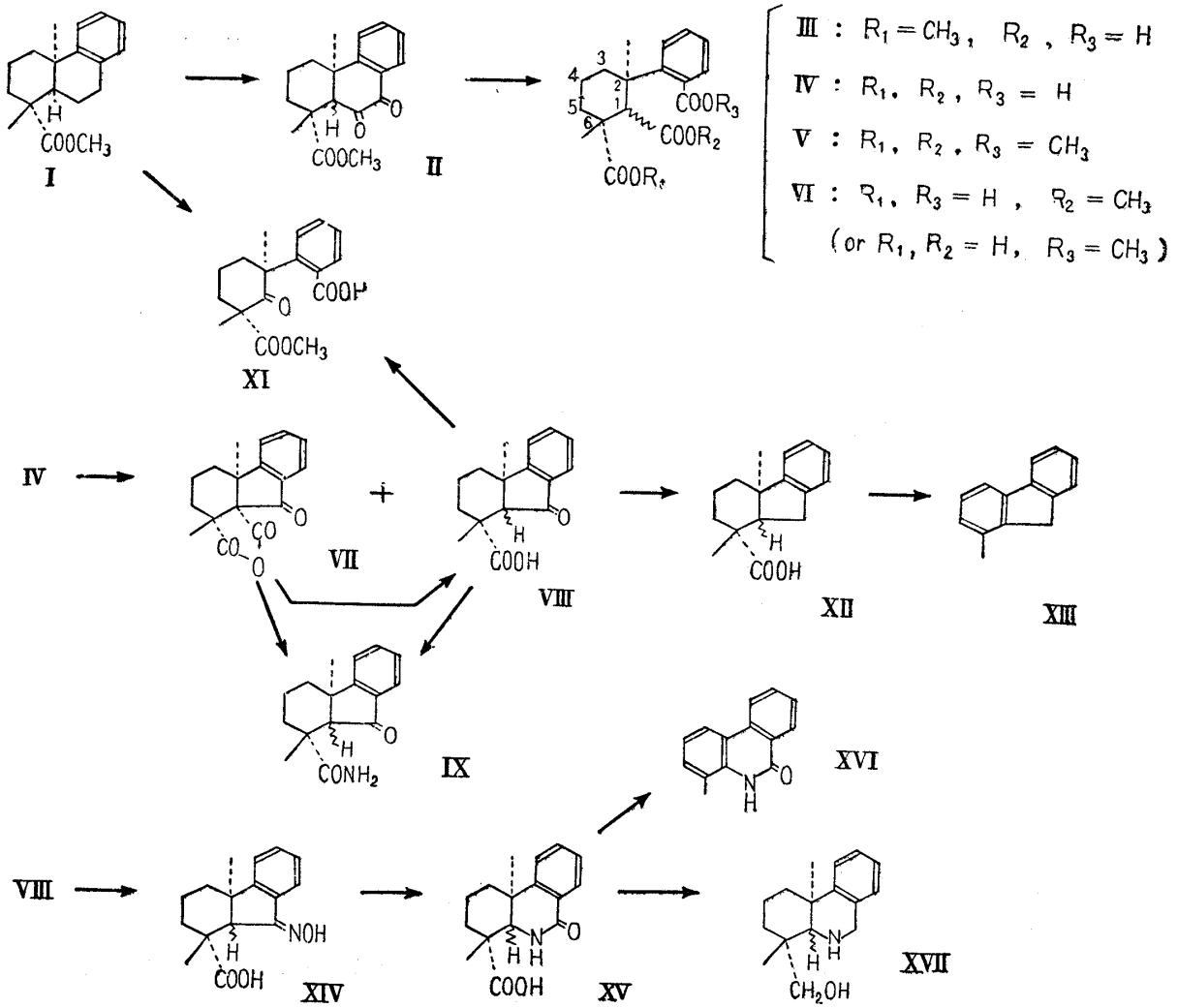
1) Part I. M. Ohta, L. Ohmori: This Bulletin, **5**, 91(1957). Part II. M. Ohta, L. Ohmori: *Ibid.*, **5**, 96(1957).
2) R. C. Cookson and others reported one example of a carboxylic acid that cannot be titrated with sodium hydroxide in connection with structural studies on delpheline (cf. J. Chem. Soc., **1956**, 3864).
3) J. S. Fritz, *et al.*: Anal. Chem., **24**, 306(1952), **25**, 179(1953).
4) E. E. Betts, *et al.*: Can. J. Chem., **33**, 1768(1955).

sodium hydroxide and the low-pressure distillation of the syrupy acid thereby obtained affords mainly (Ⅷ) with a small recovery of (Ⅶ).

(Ⅷ) is a monobasic acid corresponding to the formula $C_{16}H_{18}O_3$, exhibits absorption maximum at 291 mμ in its ultraviolet spectrum, and absorptions for -COOH and conjugated carbonyl at 5.93 and 5.90 μ in its infrared spectrum. Huang-Minlon reduction of (Ⅷ) gives an acid (Ⅻ), m.p. 162~163°, in a good yield and its dehydrogenation with palladium-carbon affords 1-methylfluorene (XIII). It follows, therefore, that (Ⅷ) is 1,4a-dimethyl-1-carboxy-1,2,3,4,4a,9a-hexahydrofluoren-9-one.

Since (Ⅷ) remains inert to boiling with hydroxylamine acetate in ethanol, the carboxyl in 9-position is thought to be sterically interfered by substituents in 1- and 4a-positions, but (Ⅷ) forms an oxime (XIV) of m.p. 225~228°(decomp.) on boiling with hydroxylamine hydrochloride in pyridine. Derivation of (Ⅷ) to its acid chloride by treatment with thionyl chloride and its treatment with ammonia water affords an acid amide (Ⅸ), m.p. 183~185°. Methylation of (Ⅷ) with diazomethane to its methyl ester and oxidation with chromium trioxide in acetic acid gives an acid of m.p. 129~131.5°, which was found to be identical with 2,6-dimethyl-2-(*o*-carboxyphenyl)-6-methoxycarbonylcyclohexanone (Ⅺ), obtained by the chromium trioxide oxidation of (I) reported in Part I of this series.[1] Therefore, the configurations at C_1 and C_{4a} still retain those of C_1 and C_{4a} in (I). (Ⅺ) is polymorphic and slow crystallization from isopropyl ether yields crystals melting at 129~131.5°, while rapid crystallization by scratching of the vessel wall gives crystals melting



at 104~106°.

As for the structure of (VII), its ultraviolet spectrum exhibits absorption maximum at 296 mμ and its infrared spectrum shows absorptions of conjugated carbonyl at 5.89 μ and that of a five-membered anhydride ring at 5.43 and 5.63 μ, so that it is assumed as 1,4a-dimethyl-9-oxo-1,2,3,4,4a,9a-hexahydrofluoren-1,9a-dicarboxylic anhydride. This structure for (VII) is supported by the fact that an amide (IX) is obtained on standing (VII) in ammonia water and that (VIII) is obtained on saponification of (VII), followed by low-pressure distillation.

Treatment of the afore-mentioned oxime (XIV) with thionyl chloride in dioxane to effect Beckmann rearrangement affords a lactam (XV), m.p. ca. 350°(decomp.), whose dehydrogenation with palladium-carbon gives 4-methyl-6(5*H*)-phenanthridone (XVI), m.p. 240.5~242°, thereby confirming the structure of (XV) as 4,10b-dimethyl-4-carboxy-1,2,3,4,4a,10b-hexahydro-6(5*H*)-phenanthridone. Methylation of (XV) with diazomethane to form its methyl ester and its reduction by boiling with lithium aluminum hydride in dioxane affords the corresponding amino alcohol (XVII), m.p. 128.5~129°.

The present series of studies were carried out under the kind guidance of Prof. Eiji Ochiai of the University of Tokyo for which the writer is deeply grateful. The writer expresses his gratitude to Mr. Y. Matsui of the Shionogi Research Laboratory for the infrared spectral measurements, to the members of the Analysis Room of this Laboratory for elemental analyses reported herein, and to Miss L. Ohmori for technical assistance.

Experimental[5]

2,6-Dimethyl-2-(*o*-carboxyphenyl)-6-methoxycarbonylcyclohexanecarboxylic Acid (III)—Three grams of the dioxo compound (II) was suspended in a mixture of 15 cc. of EtOH and 12 cc. of 30% H_2O_2, chilled in ice, and 8.4 cc. of 10% NaOH was added dropwise during 30 mins. The mixture was further stirred for 30 mins. to complete dissolution of the starting materials, acidified with 10% HCl, and the crystals that precipitated out were collected by filtration. After washing with water, the crystals were recrystallized from MeOH, affording 3.21 g. (96%) of (III), m.p. 238~240°. Further recrystallization raised the m.p. to 239~241°. *Anal.* Calcd. for $C_{18}H_{22}O_6$: C, 64.7; H, 6.6; OCH_3, 9.3; COOH, 26.9. Found: C, 64.59; H, 6.92; OCH_3, 9.32; COOH (titration with NaOH), 24.75; (titration with NaOMe), 26.64. $[\alpha]_D^{16}$ −84.7°(c=3.070, EtOH). U.V. λ_{max} 266 mμ (log ε 2.71) (cf. Fig. 1).

Tricarboxylic Acid (IV)—To a solution of 1.14 g. of (III) dissolved in 12 cc. of ethyleneglycol, 0.2 cc. of water and 2.5 g. of KOH were added, the mixture was boiled for 4 hrs., cooled, and acidified with HCl. This was extracted several times with ether, the combined extract was dried over anhyd. Na_2SO_4, and ether evaporated. The residue was recrystallized from MeOH-AcOEt to 0.72 g. of (IV), m.p. 234~235°(decomp.). Further crop of 0.26 g. of (IV), m.p. 232~234°, was obtained by the concentration of its mother liquor. Total yield, 0.98 g.(90%). *Anal.* Calcd. for $C_{17}H_{20}O_6$: C, 63.7; H, 6.3; COOH, 42.2. Found: C, 63.68; H, 6.45; COOH (by titration with NaOH), 32.04, (by titration with NaOMe), 42.08. $[\alpha]_D^{16}$ −63.7°(c=2.466, EtOH). U.V. λ_{max} 266 mμ (log ε 2.64). I.R. λ_{max} 5.88 μ(COOH).

Trimethyl Ester (V)—Prepared by the methylation of (IV) with ether solution of CH_2N_2 and recrystallized from petr. ether. m.p. 71~71.5°; $[\alpha]_D^{16}$ −41.1°(c=2.532, EtOH). *Anal.* Calcd. for $C_{20}H_{26}O_6$: C, 66.3; H, 7.2; OCH_3, 25.7. Found: C, 66.25; H, 7.23; OCH_3, 25.31.

Similar methylation of (III) and (VI) gave (V).

Dicarboxylic Acid (VI)—A mixture of 0.1 g. of (V) and 1 cc. of 16% ethanolic KOH was boiled for 2 hrs. on a water bath, treated as usual, and recrystallization from ether-petr. ether gave (VI), m.p. 241~243°, which showed depression on admixture with (III). *Anal.* Calcd. for $C_{18}H_{22}O_6$: C, 64.7; H, 6.6; COOH, 26.9. Found: C, 64.17; H, 6.91; COOH, 27.13.

1,4a-Dimethyl-9-oxo-1,2,3,4,4a,9a-hexahydrofluorene-1,9a-dicarboxylic Anhydride (VII)—(IV)(0.67 g.) placed in an Anschutz distillation flask was heated to 240~250° under low pressure (4 mm. Hg) by which the substance fused with vigorous effervescence and a distillate of b.p. ca. 220° was obtained. This distillate was dissolved in benzene and extracted with 5% Na_2CO_3 solution. The benzene layer was dried over anhyd. Na_2SO_4, the solvent was distilled off, and the residue (0.51 g.) was recrystallized from MeOH to 0.46 g.(77%) of (VII), m.p. 147~149°; $[\alpha]_D^{16}$ +26.4°(c=2.048, $CHCl_3$). *Anal.* Calcd. for $C_{17}H_{16}O_4$: C, 71.8; H, 5.7. Found: C, 71.86; H, 5.69. U.V. λ_{max} mμ (log ε): 255 (4.14), 296 (3.41). I.R. λ_{max}: 5.43, 5.63, 5.89 μ.

5) All m.p.s are uncorrected. Optical rotation was measured in a 1-dm. tube, ultraviolet spectrum in ethanol solution, and infrared spectrum in Nujol.

The carbonate extract was acidified with HCl, extracted with ether, and the solvent was distilled off from the extract after drying over anhyd. Na_2SO_4 The residue (0.08 g.) was recrystallized from ether-petr. ether to 0.06 g.(11%) of crystals melting at 129~131°, undepressed on admixture with (Ⅷ) described below.

1,4a-Dimethyl-1-carboxy-1,2,3,4,4a,9a-hexahydrofluoren-9-one (VIII)—A mixture of 1.14 g. of (Ⅶ) and 20 cc. of 2% ethanolic NaOH was boiled for 10 mins., EtOH distilled off under a reduced pressure, the residue was acidified with HCl, and extracted with ether. The extract was dried over anhyd. Na_2SO_4, the ether evaporated, and the syrupy residue was submitted to low-pressure distillation by which all distilled out at 197~200° at 3 mm. Hg. The distillate was dissolved in ether, extracted with 5% Na_2CO_3, and separated into acid and neutral portions by the usual method. The neutral portion was recrystallized from MeOH and 0.05 g.(4%) of the starting anhydride (Ⅶ), m.p. 147~149°, was recovered.

The acid portion was recrystallized from ether-petr. ether and afforded 0.88 g.(85%) of (Ⅷ), m.p. 130~131°; $[\alpha]_D^{16}$ +9.3°(c=2.582, EtOH). *Anal.* Calcd. for $C_{16}H_{18}O_3$: C, 74.4; H, 7.0; COOH, 17.4. Found: C, 74.32; H, 7.30; COOH, 17.82. U. V. λ_{max} mμ (log ε): 247 (4.09), 291 (3.40). I. R. λ_{max}: 5.90, 5.93 μ.

Oxidation of Methyl Ester of (VIII) with Chromium Trioxide—(VIII) was derived to its methyl ester by treatment with ether solution of CH_2N_2. b.p$_1$ 145~146°, $[\alpha]_D^{11}$ +4.4°(c=4.820, EtOH). To a solution of 0.77 g. of this methyl ester dissolved in 15 cc. of glacial AcOH, 1.68 g. of CrO_3 and 1 cc. of water were added and the mixture was heated at 80~85°(internal temp.) for 6 hrs. MeOH was added to the reaction mixture to decompose excess of CrO_3, the solvent was distilled off under a reduced pressure, and the residue, added with water, was extracted with ether. After drying over anhyd. Na_2SO_4, ether was evaporated, the residue was dissolved in isopropyl ether with application of heat, and the solution was allowed to cool, so as to precipitate out the crystals gradually, from which 0.50 g.(58%) of acid, m.p. 129~131.5°, was obtained. No depression of m.p. occurred on admixture with 2,6-dimethyl-2-(*o*-carboxyphenyl)-6-methoxycarbonylcyclohexanone[1] (Ⅺ), m.p. 128~131.5°, obtained by the oxidation of (I). On the other hand, rapid crystallization by stimulation of the vessel wall afforded crystals melting at 104~106°. *Anal.* Calcd. for $C_{17}H_{20}O_5$: C, 67.1; H, 6.6. Found: C, 66.98; H, 6.74.

Amide (IX)—i) To a solution of 0.3 g. of (Ⅷ) dissolved in 5 cc. of dehyd. ether, 1 cc. of $SOCl_2$ and 1 drop of pyridine were added and the mixture was allowed to stand at room temperature for 5 hrs. This was evaporated to dryness under a reduced pressure, 5 cc. of conc. ammonia and a small amount of MeOH were added to the residue under ice cooling, and the mixture was shaken. This solution was concentrated under a reduced pressure, the crystals that separated out were collected, washed with water and recrystallized from MeOH to 0.23 g.(77%) of (Ⅸ), m.p. 183~185°. *Anal.* Calcd. for $C_{16}H_{19}O_2N$: C, 74.7; H, 7.4. Found: C, 74.64; H, 7.26.

ii) A suspension of 0.2 g. of the anhydride (Ⅶ) in 4 cc. of conc. ammonia water was allowed to stand at room temperature for 2 weeks. The crystals obtained were recrystallized from MeOH to 0.16 g.(88%) of the amide, m.p. 183~185°, undepressed on admixture with (Ⅸ) obtained by the foregoing method. *Anal.* Calcd. for $C_{16}H_{19}O_2N$: C, 74.7; H, 7.4; N, 5.4. Found: C, 74.64; H, 7.42; N, 5.43.

1,4a-Dimethyl-1-carboxy-1,2,3,4,4a,9a-hexahydrofluorene (XII)—To a solution of 1.25 g. of (Ⅷ) dissolved in 15 cc. of diethyleneglycol, 1.5 cc. of hydrazine hydrate and 1.8 g. of KOH were added and the mixture was heated in an oil bath of 130~140° for 1.5 hrs., and then at 210~220° for 2 hrs. This was treated as usual and the product was recrystallized from dil. MeOH to 1.03 g.(87%) of (Ⅻ), m.p. 162~163°. *Anal.* Calcd. for $C_{16}H_{20}O_2$: C, 78.7; H, 8.3; COOH, 18.4. Found: C, 78.87; H, 8.53; COOH, 18.55; $[\alpha]_D^{15}$ −60.7°(c=2.088, EtOH). U. V. λ_{max} mμ (log ε): 259 (2.88), 265 (3.08), 272 (3.13).

1-Methylfluorene (XIII)—A mixture of 0.45 g. of (Ⅻ) and 0.1 g. of 10% Pd-C was heated in a metal bath at 280~300° for 5 hrs. and at 310~320° for 5 hrs., and the product was recrystallized several times from MeOH, affording 0.03 g. of (XIII), m.p. 86~86.5°, undepressed on admixture with an authentic sample of m.p. 86~87°. *Anal.* Calcd. for $C_{14}H_{12}$: C, 93.3; H, 6.7. Found: C, 92.85; H, 6.80.

Oxime (XIV) of (VIII)—A solution of 1 g. of (Ⅷ) dissolved in 7 cc. of pyridine and added with 0.6 g. of $NH_2OH \cdot HCl$ was boiled for 4 hrs., pyridine was distilled off under a reduced pressure, and acidified with 10% AcOH. The crystals that precipitated out were collected by filtration and recrystallized from EtOH to 0.53 g.(50%) of (XIV), m.p. 225~228°(decomp.). *Anal.* Calcd. for $C_{16}H_{19}O_3N$: C, 70.3; H, 7.0; N, 5.1. Found: C, 69.99; H, 6.96; N, 5.25.

4,10b-Dimethyl-4-carboxy-1,2,3,4,4a,10b-hexahydro-6(5*H*)-phenanthridone (XV)—To a suspension of 0.3 g. of (XIV) in 4 cc. of dioxane, 0.6 cc. of $SOCl_2$ was added dropwise under ice cooling, the mixture was allowed to stand over night, and the solvent was distilled off in vacuum. The residue was warmed with 5% NaOH solution on a water bath to dissolve resinous substance, the mixture was acidified with HCl, and the crystals that precipitated out were collected by filtration. Recrystallization from a large amount of EtOH afforded 0.21 g.(70%) of (XV), m.p. ca. 350°(decomp.). *Anal.* Calcd. for $C_{16}H_{19}O_3N$: C, 70.3; H, 7.0; N, 5.1. Found: C, 69.92; H, 7.05; N, 5.38.

4-Methyl-6(5*H*)-phenanthridone (XVI)—A mixture of 0.37 g. of (XV) and 0.2 g. of 10% Pd-C was heated in a metal bath at 300~310° for 15 hrs., cooled, and the content was dissolved in $CHCl_3$, removing Pd-C. The $CHCl_3$ solution was washed consecutively with 5% NaOH, 5% HCl, and water, dried over anhyd. Na_2SO_4, and $CHCl_3$ evaporated. The residue (0.16 g.) was recrystallized several times from $CHCl_3$ and gave 0.05 g. of (XVI), m.p. 240.5~242°, undepressed on admixture with an authentic sample, m.p. 240~242°. *Anal.* Calcd. for $C_{14}H_{11}ON$: C, 80.4; H, 5.3; N, 6.7. Found: C, 80.43; H, 5.36; N, 6.60.

4,10b-Dimethyl-4-hydroxymethyl-1,2,3,4,4a,5,6,10b-octahydrophenanthridine (XVII)—The lactam (XV) was treated with ether solution of CH_2N_2 to prepare the methyl ester (not crystallized) and the solution of 0.46 g. of this methyl ester dissolved in 40 cc. of dehyd. dioxane was boiled with 0.46 g. of $LiAlH_4$ for 8 hrs. Ice water was added to this mixture cautiously, inorganic matter was filtered off, and the filtrate was evaporated under a reduced pressure. The residue was recrystallized from acetone-petr. ether mixture to (XVII), m.p. 128.5~129°. *Anal.* Calcd. for $C_{16}H_{23}ON$: C, 78.3; H, 9.5; N, 5.7. Found: C, 78.74; H, 9.35; N, 5.64. $[\alpha]_D^{15}$ −44.5°(c=1.664, EtOH). U.V. λ_{max} mμ (log ε): 267 (2.58), 274 (2.51).

Hydrochloride: m.p. 215°(from dil. EtOH).

Diacetate: m.p. 100~101°(from ether-petr. ether). *Anal.* Calcd. for $C_{20}H_{27}O_3N$: C, 72.9; H, 8.3; N, 4.3. Found: C, 73.18; H, 8.13; N, 4.19.

Summary

Oxidation of methyl 9,10-dioxodeisopropylallodehydroabietate (II) with alkaline hydrogen peroxide yielded a dicarboxylic acid (III). Thermal decomposition of the tricarboxylic acid (IV) obtained by saponification of (III) afforded two kinds of fluorenone derivatives, (VII), m.p. 147~149°, and (VIII), m.p. 130~131°. Structures of these compounds were examined, together with the Beckmann rearrangement of the oxime of (VIII).

(Received March 4, 1957)

U.D.C. 615.782.54-092.21

47. Eigo Takabatake: Metabolism of Drugs. X.*[1] The Relationship between Hypnotic Activity and Metabolism of Ethylhexabital. (1). The Influence of Species, Sex, and Age on the Activity of Liver to Metabolize Ethylhexabital and the Isolation of an *in vitro* Metabolite.

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It is known that the duration of barbiturate hypnosis is regulated by the rate of their biotransformation in the body and influenced by several conditions. It was previously shown[1] by the use of paper chromatography and ultraviolet spectrophotometry that ethylhexabital J.P. (5-(1-cyclohexenyl)-5-ethylbarbituric acid, EHB) was converted by rat liver slices *in vitro* to 3-keto-EHB which was pharmacologically inactive. The isolation and identification of an *in vitro* metabolite as 3-keto-EHB are described in the present paper. The relationship between the duration of EHB hypnosis and the EHB-metabolizing activity of liver slices is also shown with regard to species, sex, and age differences.

Materials and Methods

Animal: A litter mates of rats born in the Institute were used. Other animals were used after breeding for at least one week under our controlled conditions. All animals were fasted for

* This constitutes a part of a series entitled "Metabolism of Drugs" by H. Tsukamoto.

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1) Part IX. E. Takabatake: J. Pharm. Soc. Japan, **76**, 511(1956).