The authors wish to thank Professor Tzeng Kuan-fong, Professor Kao Yee-sheng, and Dr, Chou Yun-lee of Institute of Materia Medica Academic Sinica, Shanghai for supplying the authentic samples of liensinine and its perchlorate.

Thanks are also due to Dr. K. Konobu and his coworkers of this Faculty for the microanalyses.

Summary

Isoliensinine, a new phenolic biscoclaurine type alkaloid, was isolated from Formosan "Lien Tze Hsin," loti embryo (embryo of the seed of *Nelumbo nucifera* GAERTN., Fam. Nymphaeaceae) and its structure was assigned to the formula II on the basis of the cleavage reaction by sodium in liq. ammonia of its O,O-diethyl ether (IV) and of the synthesis of its O,O-dimethyl ether (III).

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8. **Takayuki Wada** : Structure of Digiprolactone.*1

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Digiprolactone is a component of *Digitalis purpurea* L., (Scrophulariaceae).[1~3] As is well known, this plant contains the cardiac glycosides together with the glycosides of some pregnane modifications. Digiprolactone (I), colorless needles, m.p. 149~151°, $[\alpha]_D$ −100.5° (from acetone-petroleum ether) was obtained from the mother liquor of diginin[4] and digifolein,[5] which belong to the latter group of glycosides. The molecular formula of I, $C_{11}H_{16}O_3$, was determined on the basis of elemental analysis and vapour pressure osmometry. The presence of a secondary hydroxyl group in I was deduced from the following data : Infrared bands of I at 3580 cm^{-1} and 3440 cm^{-1}; formation of monoacetate (II) of I, m.p. 86.5°, $[\alpha]_D$ −68.5°, with pyridine acetic anhydride; reversion of II by hydrolysis with sodium carbonate to I; formation of a six membered ring ketone (III), m.p. 101.5°, $[\alpha]_D$ −162.4°, IR : ν_{max} 1715 cm^{-1}, by oxidation of I with Jones reagent (oxime of III, (IV), m.p. 156~159°); and reduction of III with sodium borohydride to I.

The nuclear magnetic resonance spectra of I, II and III show three singlet signals due to three methyl groups. Infrared peaks[6] of I at 1741 cm^{-1} and 1632 cm^{-1} and ultraviolet absorption maximum of I at 214 mμ (log ε 4.15) infer the presence of an α,β-butenolide ring. The presence of a lactone group in digiprolactone was confirmed by hydrolysis and relactonisation of its dihydroderivative (V), m.p. 85.5~86°, $[\alpha]_D$ +10.6°,

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*1 This paper is the Part XXII of "Studies on Digitalis Glycosides" by Daisuke Satoh (Part XXI, T. Wada, D. Satoh : This Bulletin, in press.

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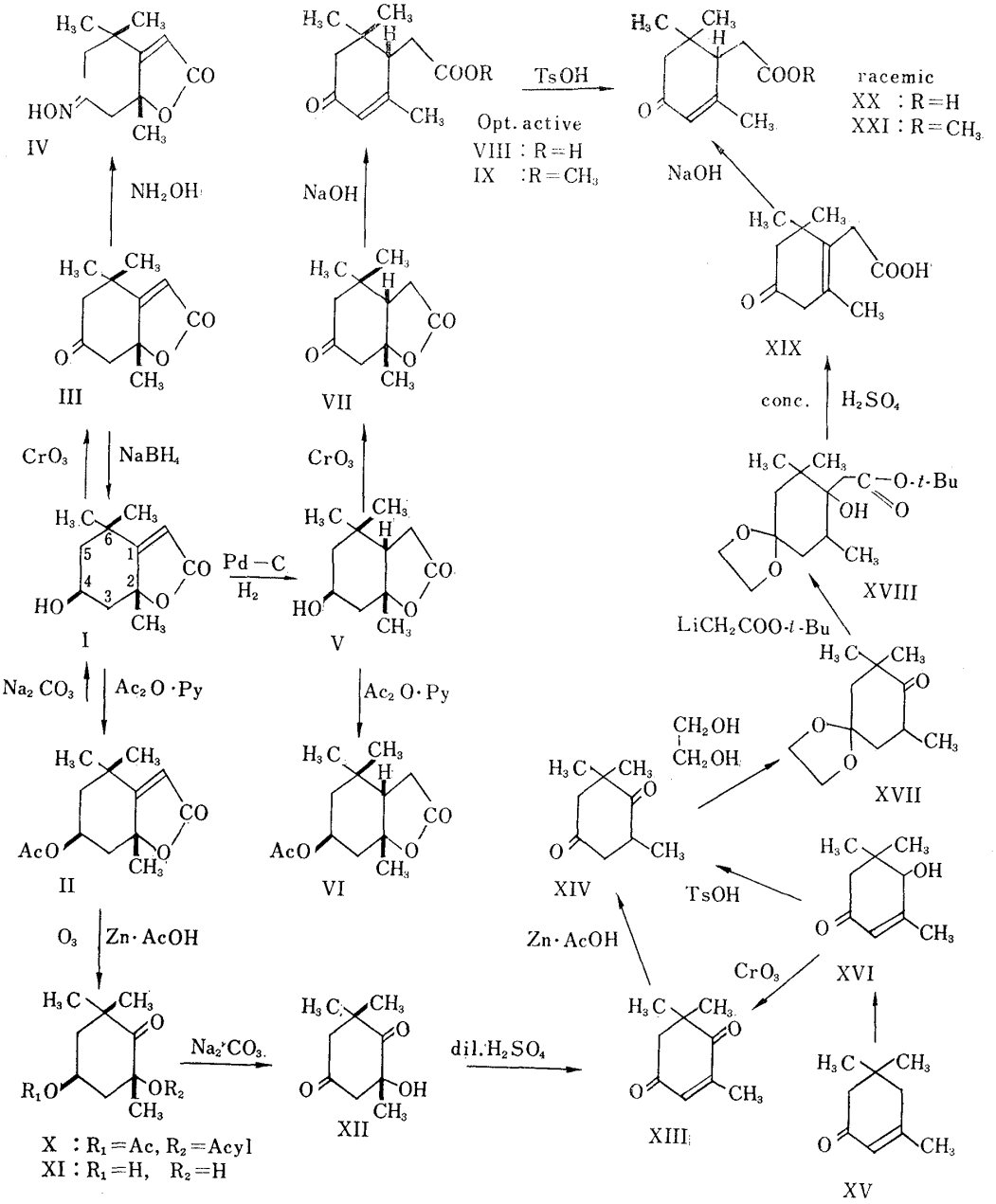
1) D. Satoh, H. Ishii, Y. Oyama, T. Wada, T. Okumura : This Bulletin, **4**, 284 (1956).
2) T. Wada, D. Satoh : This Bulletin, **12**, 752 (1964).
3) Y. Wada : *Ibid.*, **12**, 1117 (1964).
4) C. W. Shoppee, R. E. Lack, A. V. Robertson : J. Chem. Soc., **1962**, 3610.
5) C. W. Shoppee, R. E. Lack, S. Sternhell : *Ibid* **1963**, 3281.
6) The infrared spectra of I, II, III and IV show weak doublet at 1880 cm^{-1}, instead of singlet at 1780 cm^{-1}, expected for this type of α,β-butenolide rings.

(no maximum in 210~300 mμ region of ultraviolet spectrum), obtained by hydrogenation of I over palladium-charcoal.[7] The carbonyl band of V at 1765 cm^{-1} refers to a γ-lactone ring.

Acetylation of V with pyridine-acetic anhydride afforded dihydrodigiprolactone acetate (VI), m.p. 69°, $[\alpha]_D$ +16.9°. Oxidation of V with chromium trioxide in sulfuric acid gave a dihydroketone (VII), m.p. 94°, $[\alpha]_D$ −59.5°, IR : ν_{max} 1721 cm^{-1}, and a conjugated oxocarboxylic acid(VIII). A brief treatment of VII with alkali gave VIII in good yield, which was methylated with diazomethane to give an optically active conjugated oxocarboxylic acid methyl ester (IX), m.p. 29~31°, $[\alpha]_D$ −58.6°, UV : λ_{max} 236 mμ (log ε 4.12), IR ν_{max} cm^{-1} : 1740, 1675, 1640. The optical activity of IX was lost by refluxing with *p*-toluenesulfonic acid in benzene to give racemic IX (XXI), m.p. 49°. The nuclear magnetic resonance spectra of IX and XXI show signals of two tertiary methyl groups and a methyl group on a double bond, respectively.



7) T. Wada, D. Satoh : This Bulletin, **11**, 544 (1963).

Ozonisation of II, followed by reductive fission of ozonide with zinc in acetic acid yielded an oxoester (X), which was hydrolysed without purification to give a dihydroxy ketone (XI), m.p. 119°, $[\alpha]_D$ +22.2°, in 80% yield from II. The nuclear magnetic resonance spectrum of XI shows three singlet signals of tertiary methyl groups. Oxidation of XI with chromium trioxide furnished a hydroxydione (XII), m.p. 72~72.3°, $[\alpha]_D$ −13.1°. The presence of a hydroxyl band in the infrared spectrum of XII indicates that one of the two hydroxyls in XI is secondary and the other is tertiary. This tertiary hydroxyl of XII, which originates from hydrolysis of the lactone ring was dehydrated with diluted sulfuric acid to isolate a chromatographically pure oil, enedione (XIII), UV : λ_{max} 238 mμ, IR ν_{max} cm^{-1} : 1685, 1625, which gave a diketone (XIV), m.p. 66°, IR : ν_{max} 1720 cm^{-1}, by reduction with zinc in acetic acid. These results prove the 1,4-location of the two keto groups and 2-location for the tertiary hydroxyl group in XII.

From these reactions, the structure of XIV was anticipated to be (±)-2,6,6-trimethyl-1,4-cyclohexanedione and identification of XIV was made by infrared spectroscopy and mixed melting point determination with the authentic sample synthesized from isophorone (XV)[8] *via* hydroxyisophorone (XVI).[9] From above results, it can be deduced that the tertiary hydroxyl group in XI and XII, which forms the γ-lactone ring with the adjacent acetic acid group, is located at C-2.

Determination of the cyclohexane moiety of I gave rise to the assumed structure 4-oxo-2,6,6-trimethyl-2-cyclohexeneacetic acid methyl ester for the esters (IX and XXI). An authentic specimen of the compound was synthesized by the following sequences: The monoketal of XIV (XVII) was refluxed with *tert*-butyl lithioacetate[10] in ether to yield 1-hydroxy-4-oxo-2,6,6-trimethylcyclohexaneacetic acid *tert*-butyl ester 4-ethyleneketal (XVIII), which was treated with concentrated sulfuric acid to isolate 4-oxo-2,6,6-trimethyl-1-cyclohexeneacetic acid (XIX), m.p. 84°, followed by migration of the double bond with alkali to give a conjugated ketoacid (XX), which was methylated with diazomethane to separate (±)-4-oxo-2,6,6-trimethyl-2-cyclohexeneacetic acid methyl ester (XXI), m.p. 49°, UV : λ_{max} 236 mμ (log ε 4.14), IR ν_{max} cm^{-1} : 1740, 1675, 1640. This compound was identical with XXI from digiprolactone in all respects.

These results establish the structure of I as 2,4-dihydroxy-2,6,6-trimethyl-$\Delta^{1,\alpha}$-cyclohexaneacetic acid γ-lactone.

In general, α,β-butenolides give a positive Legal test and positive color reactions with alkaline nitrobenzenes. Because of structural deficiency,[11,12] digiprolactone gives negative results for these color reactions. No coloration is also observed with 82% sulfuric acid at room temperature.

The plain structure of the α,β-butenolide ring requires an equatorial 2-oxygen function and an axial 2-methyl group for I and II, with respect to the cyclohexane ring. The nuclear magnetic resonance spectra of I and II show proton signals at C-4 as a quintet (J=3.3 c.p.s.; 3.5 c.p.s., due to equatorial proton between two methylene groups). Two of the three methyl signals in II were shifted to the higher field (5 c.p.s. and 4 c.p.s.) when compared with the corresponding signals of I. This datum suggests the 1,3-diaxial relationship of 4-hydroxyl and two methyl groups at C-2 and C-6.[13] These evidences infer a chair conformation of the cyclohexane ring of I and II. The infrared spectrum of XI shows peaks of hydroxyl at 3624 cm^{-1} and 3600 cm^{-1} (shoulder) along with

8) O. Isler, H. Lindlar, M. Montavon, R. Rüegg, G. Saucy, P. Zeller : Helv. Chim. Acta, **39**, 2041 (1956).
9) M. S. Kharasch, E. K. Fields : J. Am. Chem. Soc., **63**, 2308 (1941).
10) C. R. Heuser, W. H. Puterburgh : *Ibid.*, **75**, 1068 (1953).
11) M. Kimura : This Bulletin, **3**, 75 (1955).
12) M. Frérejacque : Compt. rend., **234**, 2639 (1952).
13) Y. Kawazoe, Y. Sato, M. Natsume, H. Hasegawa, T. Okamoto, K. Tsuda : This Bulletin, **10**, 338 (1962).

weak absorption of hydrogen bonding at 3515 cm^{-1}, accompanied by corresponding hydrogen-bonded carbonyl at 1700 cm^{-1}, as a weak shoulder of a six membered ring ketone at 1710 cm^{-1}. From the absence of a peak of 1,3-*cis* OH-OH hydrogen bonding, *trans*-configuration of the two hydroxyls at C-2 and C-4 is assumed, which provides support for the conclusion from the nuclear magnetic resonance spectra of I and II.

Reversion of III by sodium borohydride reduction to I having 4-axial hydroxyl group in 85% yield is a reaction intrinsic to a hindered ketone.

Table I. The Nuclear Magnetic Resonance Spectra of Digiprolactone and Its Derivatives (τ-value of main signals)

	=CH (1H)	ROCH (1H)	C-methyl (3H)				
I	4.35	5.74 (q, J=3.3)	8.20	8.51	8.72		
II	4.31	4.76 (q, J=3.5)	8.30	8.62	8.74	AcO	7.92 (3H)
III	4.08	——	8.40	8.59	8.71		
V	—	5.93 (t-t, J=9, 4.5)	8.52	8.96	9.10		
VI	—	4.90 (t-t, J=8, 4)	8.48	8.93	9.02	AcO	7.97 (3H)
IX	4.15	——	8.05 (d, J=1.3)	8.92	9.01	MeO	6.29 (3H)
XI	—	5.58 (t-t, J=8, 5)	8.54	8.69	8.75		
XXI	4.15	——	8.05 (d, J=1.3)	8.93	9.02	MeO	6.29 (3H)

All the spectra were determined at 60 Mc., on a Model Varian A-60 spectrometer in $CDCl_3$ with tetramethylsilane as internal reference.
The signals are singlet, unless otherwise specified.
d: doublet t-t: triplet of triplets q: quintet J in c.p.s.

These data show that the cyclohexane moiety of I and II takes chair conformation with 2,4,6-triaxial substituents.

In contrast to butenolides (I and II), nuclear magnetic resonance spectra of the saturated derivatives (V and VI) show signals of a proton at C-4 as a triplet of triplets (J=9 c.p.s., 4.5 c.p.s.; 8 c.p.s., 4 c.p.s.) due to an axial-like proton between two methylene groups, and by acetylation, all the methyl signals shift to lower field, suggesting the absence of 1,3-diaxial relationship of methyl groups to the 4-hydroxyl group. Assuming *trans*-junction of the two rings in V or VI, these data require a boat form of the cyclohexane moiety, which is untenable by analogy to conformations of I and II, and by presence of 1,4-*cis* flagpole hydrogen atoms in this conformation.[14] Although the

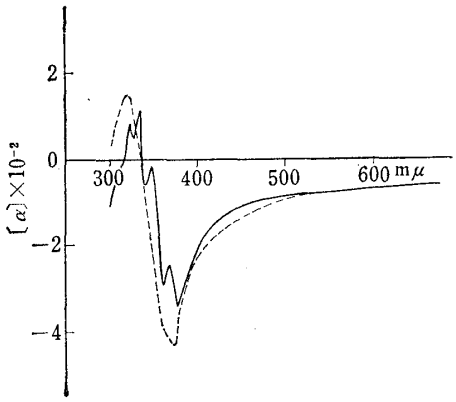


Fig. 1. The RD curve of IX
..... in MeOH ——— in dioxane

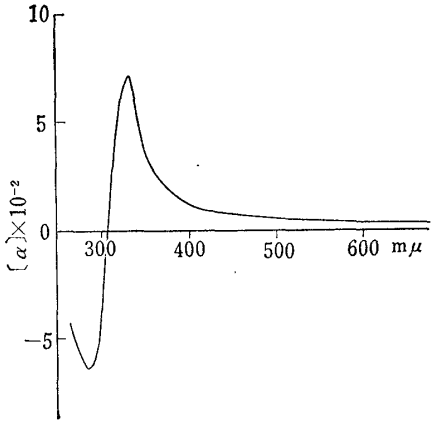


Fig. 2. The RD curve of XI
——— in MeOH

14) D. H. R. Barton, G. A. Morrison: Fortschr. Chem. org. Naturstoffe, **19**, 165 (1961).

conformation of *cis*-hydrindane is not fixed,[15] equatorial-like OR groups are more probable in the case of V and VI, with reversed chair form of cyclohexane ring as compared with I and II. This result strongly suggests *cis*-junction of the two rings of V or VI.

The RD curves of IX and XI are shown in Fig. 1 and Fig. 2.

The structure and stereochemistry of digiprolactone and its derivatives are given as illustrated in the chart on the basis of the present experiments.

After completion of this work, Hodges and Porte reported on loliolide from *Lolium perenne*,[16] which was identical with a compound from *Digitalis lanata* obtained by Tschesche and Buschauer (unpublished work; G. Snatzke : private communication). As the plane structure of loliolide*3 is quite identical with that of digiprolactone, further confirmation of the identity of these substances was made by mixed melting point determination and by comparison of the infrared spectra. Therefore, the name of digiprolactone should be cancelled after now.

Experimental

All the melting points were determined in capillary in concentrated sulfuric acid bath and are uncorrected.

UV spectra were determined in 95% EtOH and specific rotations were measured in $CHCl_3$.

Isolation of Digiprolactone (I)——The mother liquor of diginin and digifolein was swirled with ether-petr. ether (1:1) repeatedly. The solution was evaporated to yellow oil, which separated crystals of I on storage for a week or two. The crystal was freed from oily resin and recrystallized from Me_2CO-petr. ether to give colorless needles (I), double melting point at 149° and 151°. Tests with Keller-Kiliani, Baljet and Legal reagents were negative. No coloration was seen with 82% sulfuric acid at room temperature. $[\alpha]_D^{25}$ −100.5° (c=1.103), UV : λ_{max} 214 mμ (log ε 4.15), IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3580, 3440, 1840, 1741, 1632. *Anal.* Calcd. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found : C, 67.42; H, 8.24.

Digiprolactone Acetate (II)——A solution of I (100 mg.) in 0.5 ml. of pyridine and 0.5 ml. of acetic anhydride was kept at room temperature for 40 hr. The solvent was removed, the residue was dissolved in EtOAc and washed with hydrochloric acid, sodium carbonate and water, dried over sodium sulfate and evaporated to give colorless glass (118 mg.), which gave 100 mg. of prisms (II), m.p. 86.5°, $[\alpha]_D^{25}$ −68.5° (c=1.065), UV : λ_{max} 212 mμ (log ε 4.23), IR ν_{max}^{Nujol} cm^{-1} : 1855, 1830, 1745, 1628, 1260, 1250. *Anal.* Calcd. for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61; Mol wt. 238.27. Found : C, 65.65; H, 7.66; Mol. wt. 238.

II (8 mg.) in 1 ml. of MeOH was hydrolysed with 1.5 ml. of 5% sodium carbonate at room temperature for 14 hr. to give 5 mg. of prisms, m.p. 149/151°, identical with I.

Oxidation of I to III——To a solution of 100 mg. of I in 1.5 ml. of Me_2CO was added a slight excess of Jones' reagent at 0°. After 5 min., solution was diluted with water, extracted with EtOAc, and the organic layer was washed with water, dried over sodium sulfate and concentrated to dryness. The residue was recrystallized from Me_2CO-petr. ether to give 80 mg. of ketone (III), plates, m.p. 101.5°, $[\alpha]_D^{25}$ −162.4° (c=1.014),[17] UV : λ_{max} 212 mμ (log ε 4.19), IR ν_{max}^{Nujol} cm^{-1} : 1870, 1830, 1755, 1715, 1625. *Anal.* Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found : C, 68.22; H, 7.35.

Reduction of III (100 mg.) with 50 mg. of sodium borohydride in aqueous MeOH gave 65 mg. of prisms, m.p. 149/151°, identical with I. The second crop, m.p. 148~150° (20 mg.), showed no depression of melting point on admixture with I. As the NMR spectrum and IR spectrum were superimposible with those of I, the second crop of crystal had chiefly, if not entirely, the same stereochemistry with I.

III gave monoxime (IV), m.p. 156~159°, IR ν_{max}^{Nujol} cm^{-1} : 3230, 3080, 1874, 1837, 1745, 1630. *Anal.* Calcd. for $C_{11}H_{15}O_3N$: N, 6.69. Found : N, 6.64.

Dihydrodigiprolactone (V)——A solution of 100 mg. of I in 10 ml. of EtOH was shaken with previously reduced 2% palladium-charcoal (50 mg.) in hydrogen atmosphere. Hydrogen uptake ceased after 4 hr., absorbing 125 ml. (1 mole). The catalyst was removed, solution was evaporated *in vacuo* to give 100 mg. of glass, which gave 85 mg. of plates (V), m.p. 85.5~86° from ether-petr. ether. (The second crop of crystal (10 mg.) exhibited an identical NMR spectrum with that of the first crop). $[\alpha]_D^{25.5}$ +10.6° (c=1.070), UV : no maximum in 210~300 mμ region, IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3630, 3440, 1765. *Anal.* Calcd. for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found : C, 66.73; H, 9.23.

*3 The sample of loliolide was kindly supplied by Prof. R. Tschesche.

15) T. Norin : Acta Chem. Scand., **17**, 738 (1963).

16) R. Hodges, A. L. Porte : Tetrahedron, **20**, 1463 (1964).

17) The specific rotation of III minimized sharply by contact with alumina for a short time.

A solution of 17 mg. of V in EtOH was refluxed with 0.1*N* KOH for 40 min. After cooling, the solution was diluted with water and titrated with 0.01*N* HCl (0.8 ml. KOH was consumed; 0.9 mole). The neutral solution was extracted with EtOAc to afford V.

Dihydrodigiprolactone Acetate (VI)——A mixture of 60 mg. of V, 0.3 ml. of pyridine and 0.3 ml. of acetic anhydride was left standing for 30 hr. at room temperature. The solution was poured into ice water and dried *in vacuo*. The product was recrystallized from EtOAc-petr. ether to give 45 mg. of plates (VI), m.p. 69°, $[\alpha]_D^{26.5}$ +16.9°(c=1.052), IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1783, 1740, 1232. *Anal.* Calcd. for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.16; H, 8.54.

Dihydroketone (VII) from V——A solution of 100 mg. of V in 1 ml. of Me_2CO was oxidized with slight excess of Jones' reagent. After 30 sec., the solution was poured into ice water to give 80 mg. of solid, which was recrystallized from petr. ether to furnish 50 mg. of needles (VII), m.p. 94°, $[\alpha]_D^{29.9}$ −59.5° (c=0.511), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1770, 1721. *Anal.* Calcd. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22 Found: C, 67.32; H, 8.34. RD (c=0.66, MeOH): $[\alpha]_{700}$ −30, $[\alpha]_{311.5}$ −1224, $[\alpha]_{269.5}$ +932, a= −42.3.

The mother liquor of VII showed a prominent peak at 1670 cm^{-1}.

(−)-4-Oxo-2,6,6-trimethyl-2-cyclohexeneacetic Acid Methyl Ester (IX)——VII (360 mg.) was dissolved in 10 ml. of MeOH and 5% sodium hydroxide was added until the solution was neutral to phenolphthalein. After addition of another 1 ml. of sodium hydroxide, the solution was left standing for 5 min. at room temperature, then acidified with 10% sulfuric acid, freed from MeOH at room temperature *in vacuo*, and extracted with ether. The ether layer was washed with saturated sodium sulfate to pH 5, dried and evaporated to give 328 mg. of residue (VIII), IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1720, 1650 (lactone band was absent). The acid (VIII) was dissolved in absolute ether, and a solution of diazomethane in ether was added until the solution was faintly colored. After 15 min., the solution was washed with water, dried and evaporated to afford colorless oil, which was purified by silica gel chromatography and vacuum distillation. The product crystallized slowly to give 200 mg. of prisms (IX), m.p. 29~31°, $[\alpha]_D^{26.5}$ −58.6° (c=0.836), UV: λ_{max} 236 mμ (log ε 4.12), IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1740, 1675, 1640. *Anal.* Calcd. for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.69; H, 8.66. RD (c=0.836, $CHCl_3$): $[\alpha]_{700}$ −45, $[\alpha]_{369}$ −432, $[\alpha]_{318}$ +148, a=−11.6. RD (c=0.947, dioxane): $[\alpha]_{700}$ −55, $[\alpha]_{378}$ −345, $[\alpha]_{366}$ −243, $[\alpha]_{359}$ −284, $[\alpha]_{348}$ −11, $[\alpha]_{343}$ −61, $[\alpha]_{334}$ +116, $[\alpha]_{327}$ +50, $[\alpha]_{322}$ +82.

The NMR spectrum and IR spectrum of IX were identical with those of synthetically prepared XXI and racemized IX (*vide infra*).

Racemization of IX to XXI——To a cooled solution of IX (50 mg.) in dry benzene (2 ml.), 10 mg. of *p*-toluenesulfonic acid was added. The solution was refluxed under nitrogen atmosphere for 4 hr. After cooling to room temperature, the mixture was diluted with EtOAc, washed with saturated sodium sulfate, dried and evaporated to dryness. The residue was recrystallized from petr. ether to give 35 mg. of prisms (XXI), m.p. 49°, $[\alpha]_D^{31}$ −0.4°±4°(c=0.521), IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1740, 1675, 1640. *Anal.* Calcd. for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.78; H, 8.76.

This crystal showed no melting point depression on admixture with synthetic XXI (*vide infra*). The NMR spectrum and IR spectrum of this crystal was indistinguishable with those of the optically active isomer (IX) and those of synthetic XXI.

(±)-2,4-Dihydroxy-2,6,6-trimethylcyclohexanone (XI)——A solution of 364 mg. of II in 40 ml. of methylene chloride and 20 ml. of carbon tetrachloride was cooled to −80° and treated with 1 mole of ozone. After the mixture was brought to room temperature, the solvent was evaporated *in vacuo*, and the residue was stirred with 200 mg. of zinc dust in 5 ml. of acetic acid for 3 hr. The precipitation was filtered off and the solvent was removed from filtrate *in vacuo*. The residue was taken up in EtOAc, washed with sodium carbonate and water, dried over sodium sulfate and evaporated to dryness. The product (X) was hydrolysed with 5% sodium carbonate in aqueous MeOH for 13 hr. at room temperature. The reaction mixture was freed from MeOH and extracted with EtOAc. The organic layer was washed with water, dried over sodium sulfate and concentrated to dryness to leave colorless needles, which was recrystallized from Me_2CO-petr. ether to afford 211 mg. of needles (XI), m.p. 119°, $[\alpha]_D^{24}$ +22.2°(c=1.067), IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3624, 3600 (shoulder), 3515 (weak), 1710, 1700 (shoulder). (0.002 mole/L. CCl_4 in 50 mm. cell). *Anal.* Calcd. for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.99; H, 9.39. RD (c=0.298, MeOH): $[\alpha]_{650}$ +30, $[\alpha]_{332}$ +705, $[\alpha]_{284}$ −634, a=+23.0. RD (c=0.220, CCl_4): $[\alpha]_{700}$ +36.3, $[\alpha]_{332}$ +708, $[\alpha]_{279}$ −954, a=+28.6.

(+)-2-Hydroxy-2,6,6-trimethyl-1,4-cyclohexanedione (XII)——To a solution of 75 mg. of XI in 1.5 ml. of Me_2CO, a slight excess of Jones' reagent was added at 0°. After 30 sec., the reaction mixture was diluted with water and extracted with ether. The ether layer was washed with water, dried over sodium sulfate and evaporated to dryness. The residue was recrystallized from ether-petr. ether to afford 58 mg. ofneedles (XII), m.p. 72~72.3°, $[\alpha]_D^{24.5}$ −13.1° (c=1.063),[18] IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3570, 1715. *Anal.* Calcd. for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.67; H, 8.57.

18) The specific rotation of XII in methanol was positive.

(±)-2,6,6-Trimethyl-1,4-cyclohexanedione (XIV) *via* 2,6,6-Trimethyl-2-cyclohexene-1,4-dione (XIII)——A solution of 59 mg. of XII in 0.5 ml. of EtOH was refluxed with 0.5 ml. of 10% sulfuric acid for 1 hr. The reaction mixture was freed from EtOH and extracted with EtOAc. The extract was washed with water, dried and concentrated to give an oil (XIII), UV : λ_{max} 238 mμ, IR $\nu_{max}^{CCl_4}$ cm^{-1} : 1685, 1625. (IR spectrum of XIII was identical with that of the oxidation product of XVI). This oil was stirred with zinc in acetic acid at 100° for 4 hr. to give 10 mg. of prisms (XIV), m.p. 66°, IR : $\nu_{max}^{CCl_4}$ 1720 cm^{-1}, which was identified with the authentic sample of (±)-2,6,6-trimethyl-1,4-cyclohexanedione by comparison of IR spectra and by mixed melting point. Authentic sample of XIV, prisms, m.p. 65°, UV : λ_{max} 289 mμ (log ε 1.65), IR : $\nu_{max}^{CCl_4}$ 1720 cm^{-1}. *Anal.* Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found : C, 70.29; H, 9.33, was synthesized from isophorone (XV)[5] through hydroxyisophorone (XVI).[6]

(±)-1-Hydroxy-4-oxo-2,6,6-trimethylcyclohexaneacetic Acid *tert*-Butyl Ester 4-Ethyleneketal (XVIII)——The ether solution of 4 g. of (±)-2,6,6-trimethyl-1,4-cyclohexanedione 4-ethyleneketal (XVII), synthesized from XIV by the known procedure,[6] was refluxed for 2 hr. with *tert*-butyl lithioacetate, prepared from 3 g. of *tert*-butyl acetate.[7] The reaction mixture was poured into ice cold hydrochloric acid. The product was taken up in ether, washed with sodium bicarbonate and water, dried and concentrated to give an oil (XVIII), which was purified by silica gel chromatography and vacuum distillation. IR $\nu_{max}^{CCl_4}$ cm^{-1} : 3420, 1705. *Anal.* Calcd. for $C_{17}H_{30}O_5$: C, 64.94; H, 9.62. Found : C, 64.88; H, 9.76.

(±)-4-Oxo-2,6,6-trimethyl-2-cyclohexeneacetic Acid Methyl Ester (XXI)——To 50 ml. of cooled concentrated sulfuric acid, 3 g, of XVIII was added with stirring. After 30 min., the reaction mixture was poured into ice water and the separated oil was collected in ether, washed twice with water, extracted in aqueous sodium hydroxide. The alkaline solution was neutralized with sulfuric acid to pH 4 and extracted again with ether, washed, dried over sodium sulfate and evaporated to give an oil, from which a small amount of crystal, 4-oxo-2,6,6-trimethyl-1-cyclohexeneacetic acid (XIX), m.p. 84°, IR $\nu_{max}^{CCl_4}$ cm^{-1} : 1720, 1670 (XX), was separated. The solution of the oily material in aqueous MeOH was added with 10% sodium hydroxide and kept standing for 2 hr. at room temperature. Extraction of acidified solution gave a conjugated ketoacid (XX) when mixed with slight excess of diazomethane in ether for 15 min., afforded the methyl ester. Purification by chromatography and vacuum distillation gave 540 mg. of prisms (XXI), m.p. 49°, UV : λ_{max} 236 mμ (log ε 4.14), IR $\nu_{max}^{CCl_4}$ cm^{-1} : 1740, 1675, 1640 (shoulder). *Anal.* Calcd. for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found : C, 68.53; H, 8.77.

This product showed no depression of melting point on admixture with XXI from IX. IR, UV and NMR spectra of this product was identical with those of XXI from IX, and those of optically active isomer, IX, from digiprolactone.

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Summary

Digiprolactone is 2,4-dihydroxy-2,6,6-trimethyl-$\Delta^{1,\alpha}$-cyclohexaneacetic acid γ-lactone and identical with loliolide. The stereochemistry of this compound was also discussed.

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