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32. **Masao Sumi** : Studies on Anthelmintics. XXXIV.* Synthetic Studies on Stereoisomers of Artemisin.

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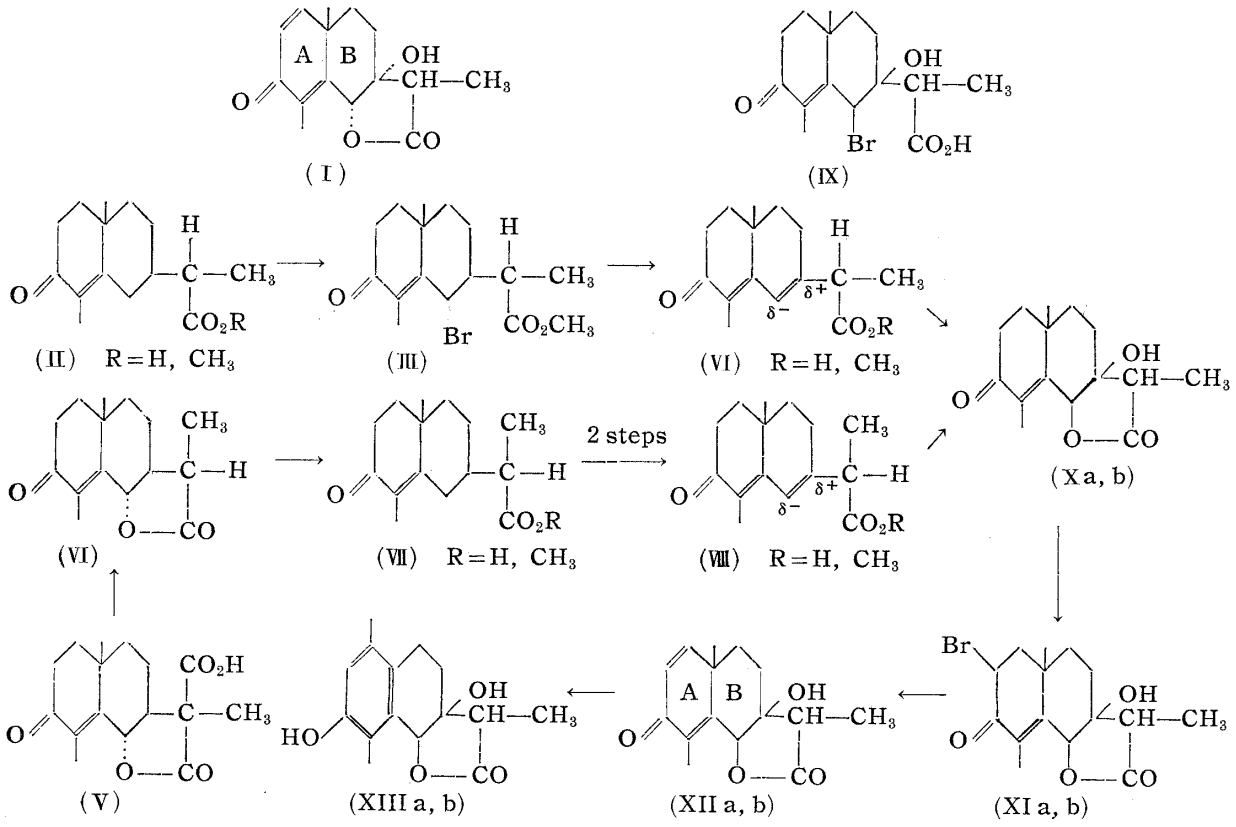
In 1894, a new substance named artemisin was found in the mother liquor left after the extraction of santonin from *Artemisia maritima* L.[1] By the investigations of Bertolo[2] and Wedekind, *et al.*,[3] it was shown that artemisin is a sesquiterpenic lactone with a structure of 7-hydroxysantonin. Recently, Barton[4] discussed the stereochemistry of artemisin and deduced that the lactone ring was *trans*-fused as in natural santonins, that the other stereochemical configurations were the same as in (−)-α-santonin, and, therefore, its structure could be represented by the formula (I). As for the synthesis of artemisin, however, nothing has been reported as yet.

In order to synthesize a compound with the artemisin structure, a hydroxyl group must be introduced into C_7 in santonins which possess a propionic acid side chain. To attain this purpose, 3-oxo-11-*epi*-eusantona-4,6-dienic acid (IV: R=H) and 3-oxoeusantona-4,6-dienic acid (VIII; R=H) were chosen as the starting materials. By the E effect of the C_3-carbonyl the C_6—C_7 double bond in both compounds is polarized



* This constitutes a part of a series entitled "Studies on Anthelmintics" by Yasuo Abe. Preliminary report of this work was made in Proc. Japan Acad., **31**, 309(1955).

** Juso, Osaka (角 正夫).

1) Elsevier's "Encyclopaedia of Organic Chemistry," Elsevier Publishing Company, Amsterdam, **12B**, 3828(1953).
2) P. Bertolo : Atti accad. Lincei, [5] **32** I, 618(1923); Gazz. chim. ital., **53**, 724(1923).
3) K. Tettweiler, O. Engel, E. Wedekind : Ann., **492**, 105(1932).
4) D. H. R. Barton : J. Org. Chem., **15**, 467(1950).

as shown in the formulae. Therefore, it was expected that the addition of hypobromous acid to the double bond would result in the formation of an intermediate (IX) or its stereoisomer, which would be subsequently lactonized to a compound with the dihydroartemisin structure.

3-Oxo-11-*epi*-eusatona-4,6-dienic acid (IV; R=H) was obtained by the hydrolysis of methyl 3-oxo-11-*epi*-eusantona-4,6-dienate (IV; R=CH_3) which had been prepared from the methyl ester (II; R=CH_3) of 3-oxo-11-*epi*-eusanton-4-enic acid[5,6] via its C_6-bromo compound. In a similar way 3-oxoeusantona-4,6-dienic acid (VIII; R=H) was derived from 3-oxoeusanton-4-enic acid[5] (VII; R=H). The preparation of the latter acid (VII) had been very difficult, but when dihydro-α-santonin (VI), which was produced by the stereospecific decarboxylation of 11-carboxy-6α-hydroxy-3-oxoeusanton-4-enic acid lactone[7] (V), was treated with zinc in acetic acid, (VII; R=H) was readily obtained in a pure state. The use of methanol[6] in place of acetic acid failed to cause the reductive fission of the lactone.

By the action of hypobromous acid on 3-oxo-11-*epi*-eusantona-4,6-dienic acid (IV; R=H), a substance with m.p. 192° was obtained from the neutral fraction of the product and a small amount of another substance with m.p. 150° was isolated from the mother liquor. As was expected, both compounds proved to be stereoisomers of α-(5,6-dihydroxy-4,9-dimethyl-3-oxo-1,2,3,5,6,7,8,9-octahydronaphthyl-6)propionic acid lactone* by their ultraviolet and infrared spectra as well as by the elementary analyses. The substance with m.p. 192° is tentatively called A-isomer** (Xa) and the one with m.p. 150°, B-isomer (Xb).

α-(5,6-Dihydroxy-4,9-dimethyl-3-oxo-1,2,3,5,6,7,8,9-octahydronaphthyl-6)propionic acid lactone-A (Xa) was brominated to the 2-bromo compound (XIa), which on dehydrobromination led to α-(5,6-dihydroxy-4,9-dimethyl-3-oxo-3,5,6,7,8,9-hexahydronaphthyl-6)propionic acid lactone-A (XIIa), m.p. 177°. It displayed a pink color by the action of ethanolic sodium hydroxide just as natural artemisin,[1] and its infrared spectrum revealed the presence of a hydroxyl, a γ-lactone, and an α,β-unsaturated ketone (Table I and Fig. 1). Further, the cross-conjugated dienone structure of (XIIa) was confirmed by the dienone-phenol rearrangement which gave rise to α-(3,5,6-trihydroxy-1,4-dimethyl-5,6,7,8-tetrahydronaphthyl-6)propionic acid lactone-A (XIIIa) under the same conditions as for natural artemisin.[3] Accordingly, (XIIa) is considered to be the first racemic stereoisomer of artemisin.

When α-(5,6-dihydroxy-4,9-dimethyl-3-oxo-1,2,3,5,6,7,8,9-octahydronaphthyl-6)-propionic acid lactone-B (Xb) was subjected to a reaction sequence similar to that

TABLE I.

	λ_{max}^{EtOH} (mμ)	log ε	ν_{max}^{Nujol} (μ)		
			OH	Lactonic CO	Conjugated CO
Artemisin[8]	240	4.09	2.90	5.60	6.00
A-Isomer (XIIa)	246.5	4.10	2.95	5.61	6.02
B-Isomer (XIIb)	246	4.21	2.90	5.62	6.03

* As the stereochemical configuration is not known, the compounds will be designated as the derivatives of naphthalene.

** To the name of compounds derived from A-isomer are suffixed the letter A, and to those from B-isomer the letter B.

5) Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi, T. Toga: J. Am. Chem. Soc., **78**, 1416(1956).
6) M. Nishikawa, K. Morita, H. Hagiwara: The work reported at the meeting of the Pharmaceutical Society of Japan, Osaka, March, 1955.
7) M. Sumi: This Bulletin, **4**, 152(1956).
8) H. Mitsuhashi: This Bulletin, **1**, 75(1953).

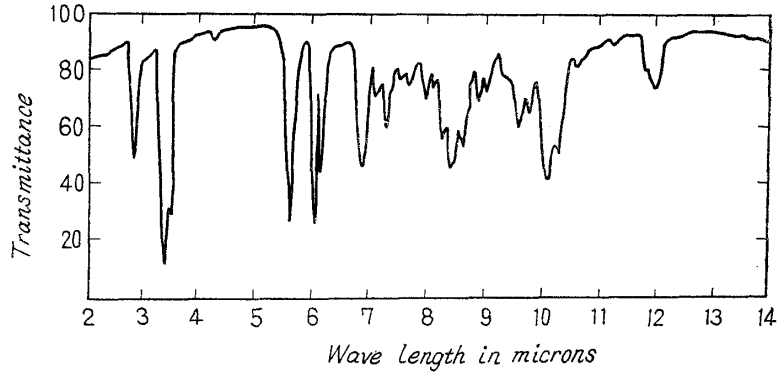


Fig. 1. Infrared Spectrum of the A-Isomer (XIIa) (Nujol mull)

for the A-isomer (Xa), it afforded α-(5,6-dihydroxy-4,9-dimethyl-3-oxo-3,5,6,7,8,9-hexahydronaphthyl-6)propionic acid lactone-B (XIIb), whose structure was evidenced by its infrared spectrum (Table I and Fig. 2). This substance also showed a pink color with ethanolic sodium hydroxide, and it was converted into α-(3,5,6-trihydroxy-1,4-dimethyl-5,6,7,8-tetrahydronaphthyl-6)propionic acid lactone-B (XIIIb) by the dienone-phenol rearrangement. Therefore, (XIIb) would probably be another racemic stereoisomer of artemisin.

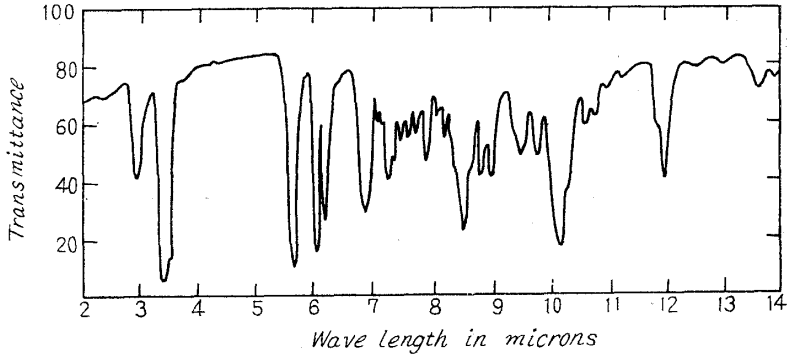


Fig. 2. Infrared Spectrum of the B-Isomer (XIIb) (Nujol mull)

As 3-oxoeusantona-4,6-dienic acid (VIII; R=H) is epimeric with (IV) (R=H) at C_{11}, it had been expected to produce the C_{11}-epimer of (Xa) or (Xb) by the addition of hypobromous acid, but this was not the case and only a neutral, crystalline product containing bromine was obtaind. Then, attention was turned to methyl 3-oxoeusantona-4,6-dienate (VIII; R=CH_3).

When it was treated with N-bromacetamide[8] in hydrous acetone, the same hydroxy-lactone (Xa) as derived from (IV; R=H) was formed. It is, therefore, predicted that the configuration at C_{11} of either (IV) or (VIII) suffers inversion during the addition of hypobromous acid, since the hydrogen atom at C_{11} which corresponds, in vinylogy, to the α-position of a β-keto acid is activated. The true mechanism, however, is still unknown.

Consequently, the stereochemical configurations of α-(5,6-dihydroxy-4,9-dimethyl-3-oxo-3,5,6,7,8,9-hexahydronaphthyl-6)propionic acid lactones-A and -B (XIIa and XIIb) cannot be assumed at the present stage, but the relative configuration of C_6-hydroxyl and C_{11}-hydrogen is evidently opposite in the two isomers, since the desmotropo compounds derived from (XIIa) and (XIIb) are different.[5] If (XIIa) and (XIIb) are actually stereoisomers of artemisin, the lactone ring in both substances would be

9) e.g. G. H. Ott, T. Reichstein: Helv. Chim. Acta, **26**, 1799(1943).

cis-fused by the following reasons. (XIIa) and (XIIb) possess the ultraviolet absorption maxima at 246.5 mμ and 246 mμ, respectively, differing considerably from natural artemisin (λ_{max} 240 mμ) with a *trans*-lactone. Just as in the case of santonins,[7] the B-ring and the lactone ring cannot be *trans*-fused in the diaxial configuration[5,10] in artemisin, so that, of the racemic stereoisomers of artemisin, only the racemate of the natural product and its C_{11}-epimer possess the *trans*-lactone. The stereochemical relationship between artemisin and the C_{11}-epimer is equal to that between α- and β-santonins, which exhibit the absorption maxima at almost the same wave length (241 mμ and 242 mμ,[9] respectively). It could therefore be considered that the C_{11}-epimer of artemisin would show an absorption maximum at about 240 mμ as artemisin itself.* Accordingly, both isomers (XIIa and XIIb) obtained above would probably have *cis*-lactone fusion.

Since, in close resemblance to desmotroposantonins,[4] desmotropoartemisin can exist in only two stereoisomeric forms as racemates, either of the above stereoisomers of α-(3,5,6-trihydoxy-1,4-dimethyl-3-oxo-5,6,7,8-tetrahydronaphthyl-6)propionic acid lactone should be the recemate of desmotropoartemisin derived from natural artemisin. It is hoped that this will be ascertained in the near future.

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Experimental**

Methyl 3-Oxo-11-*epi*-eusanton-4-enate (**II**; **R**=CH_3)—Twenty grams of 3-oxo-11-*epi*-eusanton-4-enic acid[5,6] (II; R=H) in ether was treated with diazomethane. The ether solution was washed with Na_2CO_3 and water, dried, and evaporated. The residual oil was distilled to give 19 g. of the methyl ester, b.p_4 168~170°. The 2,4-dinitrophenylhydrazone was recrystallized from MeOH-benzene to red plates, m.p. 174°. *Anal.* Calcd. for $C_{22}H_{28}O_6N_4$: C, 59.44; H, 6.35; N, 12.61. Found: C, 59.50; H, 6.17; N, 12.58.

Methyl 3-Oxo-11-*epi*-eusantona-4,6-dienate (**IV**; **R**=CH_3)—To methyl 3-oxo-11-*epi*-eusanton-4-enate (40 g.) in 40 cc. of Ac_2O was added 0.5 g. of H_2SO_4. The mixture was heated at 50~60° for 3 hrs., poured into ice-cold water, and extracted with ether. After the extract was washed with water and dried, 26.5 g. of Br_2 in 30 cc. of AcOH was added dropwise under stirring. The solution was washed with water, dried, and evaporated to leave an oily bromo compound, which was refluxed for 1 hr. with 150 cc. of picoline. The reaction mixture was cooled, poured into cold dil. H_2SO_4, and extracted with ether. The ether solution was washed with Na_2CO_3 and water, dried, and concentrated. The residue was distilled to give 20 g. of an oily ester, b.p_5 170~172°. λ_{max} 297 mμ (log ε 4.28), n_D^{33}: 1.547. *Anal.* Calcd. for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.09; H, 8.45.

3-Oxo-11-*epi*-eusantona-4,6-dienic Acid (**IV**; **R**=**H**)—The linear dienone ester (20 g.), obtained in the preceding experiment, was stirred with 100 cc. of 15% KOH solution for 15 hrs. at room temperature. After unchanged material was removed by shaking with ether, the alkaline solution was acidified and extracted with ether. The ether solution was worked up in the usual way to afford 18 g. of an oily acid (IV; R=H).

3-Oxoeusanton-4-enic Acid (**C-acid**[5]: **VII**; **R**=**H**)—A solution of 30 g. of dihydro-α-santonin[7] (VI) in 600 cc. of AcOH was stirred with 100 g. of Zn dust under reflux for 17 hrs. Zn was filtered off and the filtrate was concentrated under reduced pressure. The residue, after addition of dil. HCl, was extracted with ether, the ether extract was shaken with Na_2CO_3 solution, and the alkaline solution was acidified. The separated acid (15 g.) was recrystallized from aq. MeOH to colorless prisms, m.p. 146°, undepressed with an authentic sample of (VII)[5] (R=H).

* A sample of artemisin for determination of ultraviolet spectrum was kindly supplied by Dr. H. Mitsuhashi, for which the author is much indebted.

** All ultraviolet adsorption spectra were determined in EtOH solution.

10) M. Sumi: This Bulletin, **4**, 147(1956).

11) Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi, T. Toga: J. Am. Chem. Soc., **78**, 1422(1956).

Methyl 3-Oxoeusanton-4-enate (VII; R=CH_3)—3-Oxoeusanton-4-enic acid (20 g.) in ether was treated with CH_2N_2 to give 20 g. of the methyl ester (VII; R=CH_3), b.p_3 165~170°. The 2,4-dinitrophenylhydrazone was recrystallized from MeOH-benzene to red leaflets, m.p. 161°. *Anal.* Calcd. for $C_{22}H_{28}O_6N_4$: C, 59.44; H, 6.35; N, 12.61. Found: C, 59.71; H, 6.40; N, 12.58.

Methyl 3-Oxoeusantona-4,6-dienate (VIII; R=CH_3)—A solution of 5 g. of (VII: R=CH_3) in 50 cc. of CCl_4 was refluxed with 3.8 g. of N-bromosuccinimide for 40 mins. under illumination. The succinimide was filtered off and the filtrate was concentrated under reduced pressure. After the residue was refluxed for 1 hr. with 30 cc. of picoline, the reaction mixture was worked up in the same way as for (IV: R=CH_3) to afford 2.7 g. of an oily product (VIII: R=CH_3), b.p_4 161~166°. λ_{max} 295 mμ (log ε 4.22), n_D^{33}: 1.5331. *Anal.* Calcd. for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.17; H, 8.93.

When (VII: R=CH_3) was converted into the enol acetate and the latter was subjected to the bromination-dehydrobromination method, there was also obtained the same linear dienone-ester (VIII: R=CH_3), but the ultraviolet spectrum showed that the product was contaminated with some starting material.

3-Oxoeusantona-4,6-dienic Acid (VIII; R=H)—In the same way as for (IV), 10 g. of (VIII: R=CH_3) was hydrolyzed to give 8 g. of an oily acid (VIII: R=H).

α-(5,6-Dihydroxy-4,9-dimethyl-3-oxo-1,2,3,5,6,7,8,9-octahydronaphthyl-6)propionic Acid Lactones-A and -B (Xa and Xb)—(a) From 3-oxo-11-*epi*-eusantona-4,6-dienic acid (IV): Seventeen grams of (IV) was dissolved in a solution of 9.7 g. of K_2CO_3 in 170 cc. of water and to this was added hypobromous acid solution which was prepared from 11 g. of bromine, 14 g. of Na_2CO_3, and 170 cc. of water. After the solution was washed once with ether, another portion of ether was added, and dil. HCl was added in small portions under shaking until the aqueous layer became acidic. The ether layer was separated, washed with Na_2CO_3 solution and water, dried, and concentrated to give 1.9 g. of a crystalline material (A-isomer: Xa). This on recrystallization from EtOAc afforded colorless prisms, m.p. 192°. λ_{max} 245 mμ (log ε 4.13), ν_{max}^{Nujol} 2.89 (hydroxyl), 5.63 (lactonic CO), 6.02 (conjugated CO), and 6.14 μ (double bond). *Anal.* Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 67.94; H, 7.46.

After the A-isomer was removed, another crystalline material was isolated from the mother liquor. The fraction which was easily soluble in EtOAc was recrystallized from EtOAc-petr. ether to afford 0.5 g. of the B-isomer (Xb) as colorless prisms, m.p. ca. 122°(decomp.). *Anal.* Calcd. for $C_{15}H_{20}O_5 \cdot \frac{1}{2}H_2O$: C, 65.91; H, 7.74. Found: C, 65.76; H, 7.62. After it was dried at 110~115° for 4 hrs. *in vacuo*, it showed m.p. 150° (sintering at 145°). λ_{max} 245 mμ (log ε 4.11), ν_{max}^{Nujol} 2.90 (hydroxyl), 5.62 (lactonic CO), 6.01 (conjugated CO), and 6.18 μ (double bond). *Anal.* Calcd. for $C_{15}H_{20}O_5$: C, 68.16; H, 7.63. Found: C, 67.71; H, 7.69.

(b) From methyl 3-oxoeusantona-4,6-dienate (VIII; R=CH_3): A solution of 5.6 g. of (VIII: R=CH_3) in 300 cc. of acetone was treated with a mixture of 9 g. of N-bromacetamide, 200 cc. of water, and 2 g. of NaOAc for 40 hrs. at room temperature. The red solution was concentrated under reduced pressure below 35° and the separated oil was taken up in ether. The ether extract was washed with Na_2CO_3 solution and water, dried, and evaporated. After the residue was kept standing for a long time, there was obtained 0.5 g. of a crystalline product, which was recrystallized from EtOAc-petr. ether to colorless prisms, m.p. 192°, undepressed with the A-isomer obtained in (a).

When 3-oxoeusatona-4,6-dienic acid (VIII: R=H) was treated with hypobromous acid under the same conditions as in (a), only a bromo compound, m.p. 140°(decomp.), was isolated, which was not further investigated.

α-(2-Bromo-5,6-dihydroxy-4,9-dimethyl-3-oxo-1,2,3,5,6,7,8,9-octahydronaphthyl-6)propionic Acid Lactone-A (XIa)—To a solution of 2.0 g. of the hydroxylactone-A (Xa) in 700 cc. of ether was added dropwise 1.2 g. of Br_2 in 50 cc. of AcOH. The reaction mixture was washed with $NaHCO_3$ solution and water, dried, and concentrated to leave 1.5 g. of a crystalline material. Recrystallization from MeOH gave colorless prisms, m.p. 178°(decomp.). λ_{max} 249 mμ (log ε 4.12). *Anal.* Calcd. for $C_{15}H_{19}O_4Br$: C, 52.49; H, 5.58. Found: C, 52.71; H, 5.28.

α-(5,6-Dihydroxy-4,9-dimethyl-3-oxo-3,5,6,7,8,9-hexahydronaphthyl-6)propionic Acid Lactone-A (XIIa)—Bromohydroxylactone-A (XIa)(1.3 g.) was refluxed with 10 cc. of aldehyde-collidine for 25 mins. The mixture was poured into cold dil. H_2SO_4 and shaken with ether. The ether layer was washed with Na_2CO_3 solution and water, dried, and concentrated to give 0.4 g. of a crystalline product. This was recrystallized from EtOAc-petr. ether to colorless plates, m.p. 130~160°. After being dried at 110~125° for 4 hrs. *in vacuo*, it showed m.p. 177°. λ_{max} 246.5 mμ (log ε 4.10); ν_{max}^{Nujol} 2.95 (hydroxyl), 5.61 (lactonic CO), 6.02 (conjugated CO), and 6.15 μ (double bond) (Fig. 1). *Anal.* Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.67; H, 7.22. On heating with ethaolic NaOH it exhibited a pink color.

α-(3, 5, 6-Trihydroxy-1, 4-dimethyl-5, 6, 7, 8-tetrahydronaphthyl-6)propionic Acid Lactone-A (XIIIa)—To 200 mg. of the dienone(VIIa) suspended in 4 cc. of dil. H_2SO_4 (1 : 1) was added dropwise 1.5 cc. of water under cooling and shaking. The mixture was kept standing overnight at room temperature and then stirred at 50~55° for 5 hrs., and after addition of 5 cc. of water, it was allowed to stand 24 hrs. The separated solid was washed consecutively with Na_2CO_3 solution, water, dil. H_2SO_4, and water, and triturated with a small amount of cold EtOH. Filtration gave 50 mg. of a crystalline material, wich was recrystallized from EtOAc-petr. ether to colorless prisms, m.p. 223°. λ_{max} 288 mμ (log ε 3.48), λ_{min} 250 mμ (log ε 2.34). *Anal.* Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found : C,68.39; H, 7.22.

α-(2-Bromo-5, 6-dihydroxy-4, 9-dimethyl-3-oxo-1, 2, 3,5,6,7,8,9-octahydronaphthyl-6)propionic Acid Lactone-B (XIb)—Hydroxylactone-B (Xb) (1.5 g) was dissolved in 750 cc. of ether and 0.9 g. of Br_2 in 200 cc. of ether was added under boiling. Decolorization occurred in 80 mins. After cooling. the solution was washed with Na_2CO_3 and water. Drying and evaporation afforded 1.2 g. of a bromo compound, which was recrystallized from MeOH to colorless prisms, m.p. 191°(decomp.). λ_{max} 248 mμ (log ε 4.09). *Anal.* Calcd. for $C_{15}H_{19}O_4Br$: C, 52.49; H. 5.58. Found : C, 52.19; H, 5.47.

α-(5, 6-Dihydroxy-4, 9-dimethyl-3-oxo-3, 5, 6, 7, 8, 9-hexahydronaphthyl-6)propionic Acid Lactone-B (XIIb)—The bromohydroxylactone-B (1.2 g.) obtained in the preceding experiment was refluxed with 10 cc. of aldehyde-collidine for 30 mins. The reaction mixture was worked up in the same way as for the A-isomer and there was obtained 0.2 g. of a crystalline substance, which was recrystallized from EtOAc to colorless plates, m.p. 240°. λ_{max} 246 mμ (log ε 4.21); ν_{max}^{Nujol} 2.90 (hydroxyl), 5.62 (lactonic CO), 6.03 (conjugated CO), and 6.16 μ (double bond) (Fig. 2.). *Anal.* Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found : C, 68.45; H, 6.95. It showed a pink color when heated with ethanolic NaOH.

α-(3, 5, 6-Trihydroxy-1, 4-dimethyl-5, 6, 7, 8-tetrahydronaphthyl-6)propionic Acid Lactone-B (XIIIb)—The dienone (B-isomer, 263 mg.) was suspended in 4.2 cc. of dil. H_2SO_4 (1 : 1). After addition of 1.6 cc. of water under cooling, the mixture was kept standing overnight at room temperature and then stirred at 50~57° for 17 hrs. It was worked up in the same way as described for the A-isomer to give 150 mg. of a crude product. Recrystallizaton from benzene-MeOH gave colorless prisms, m.p. 198°. λ_{max} 290 mμ(log ε 3.47), λ_{min} 250 mμ(log ε 2.00). *Anal.* Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found : C, 68.66; H, 7.12.

Summary

Starting from 3-oxo-11-*epi*-eusantona-4,6-dienic acid (IV; R=H) and 3-oxoeusantona-4,6-dienic acid (VIII; R=H), α-(5,6-dihydroxy-4,9-dimethyl-3-oxo-3,5,6,7,8,9-hexahydronaphthyl-6)propionic acid lactones-A and -B (Xa and Xb) were synthesized, which would probably be racemic stereoisomers of artemisin.

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