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28. **Masao Sumi** : Studies on Anthelmintics.* XXX. The Synthesis of a New Stereoisomer of Methyl Santoninate.

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In the earlier stage of the synthetic studies on santonins, a stereoisomer called santonin A was first synthesized[1] and investigation of the rotation of the optically active isomer predicted[2] that santonin A would have a *cis*-fused lactone and its C_7–C_{11} bond would adopt the axial position. Although the configuration of this bond was later established by the total synthesis of santonins,[3] confirmation of this point in a chemical manner was required prior to exploration of the synthetic route. As was cited by Abe, *et al.* in Part XI of this series,[2] it was accomplished by examining the lactonization of methyl santoninate isomers with the C_6-hydroxyl *trans* to the C_7-side chain. The present paper describes this work in detail.

Starting from 3-oxo-11-*epi*-isoeusanton-4-enic acid*** (I : R=H; A-acid[1]), Ishikawa[4] synthesized methyl 6ξ-hydroxy-3-oxo-11-*epi*-isoeusanton-4-enate (II), which was further changed to an isomer (III) of methyl santoninate. Since the hydrolysis of this compound afforded 6α-hydroxy-3-oxo-11-*epi*-isoeusantona-1,4-dienic acid lactone (IV: santonin A) with *cis*-lactone fusion, the isomer was assumed to have the C_6-hydroxyl group *cis* to the propionic ester side chain at C_7. Consequently the synthesis of the isomer in which the hydroxyl and the side chain are *trans* became necessary for comparison with methyl santoninate derived from natural (−)-α-santonin in order to determine the configuration of the side chain in the santonin A series.

As an attempt to introduce a double bond into C_1–C_2 of the C_6-epimer of (II) was unsuccessful,[4] there remained a route in which methyl 3-oxo-11-*epi*-isoeusanton-4-enate (I : $R=CH_3$) was first converted to a cross-conjugated dienone and subsequently a hydroxyl group was introduced into C_6. However, the conversion of a monoenone like (I) into a cross-conjugated dienone had not been successful yet.**** For example, when 4,9-dimethyl-3-oxo-1,2,3,5,6,7,8,9-octahydronaphthalene (VI) was brominated and then dehydrobrominated, the product was a linear extended dienone (VII) and not

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* This constitutes a part of a series entitled "Studies on Anthelmintics" by Yasuo Abe. Part XXIX : J. Pharm. Soc. Japan, **76**, 507(1956).

** Juso-nishino-cho, Higashiyodogawa-ku, Osaka (角 正夫).

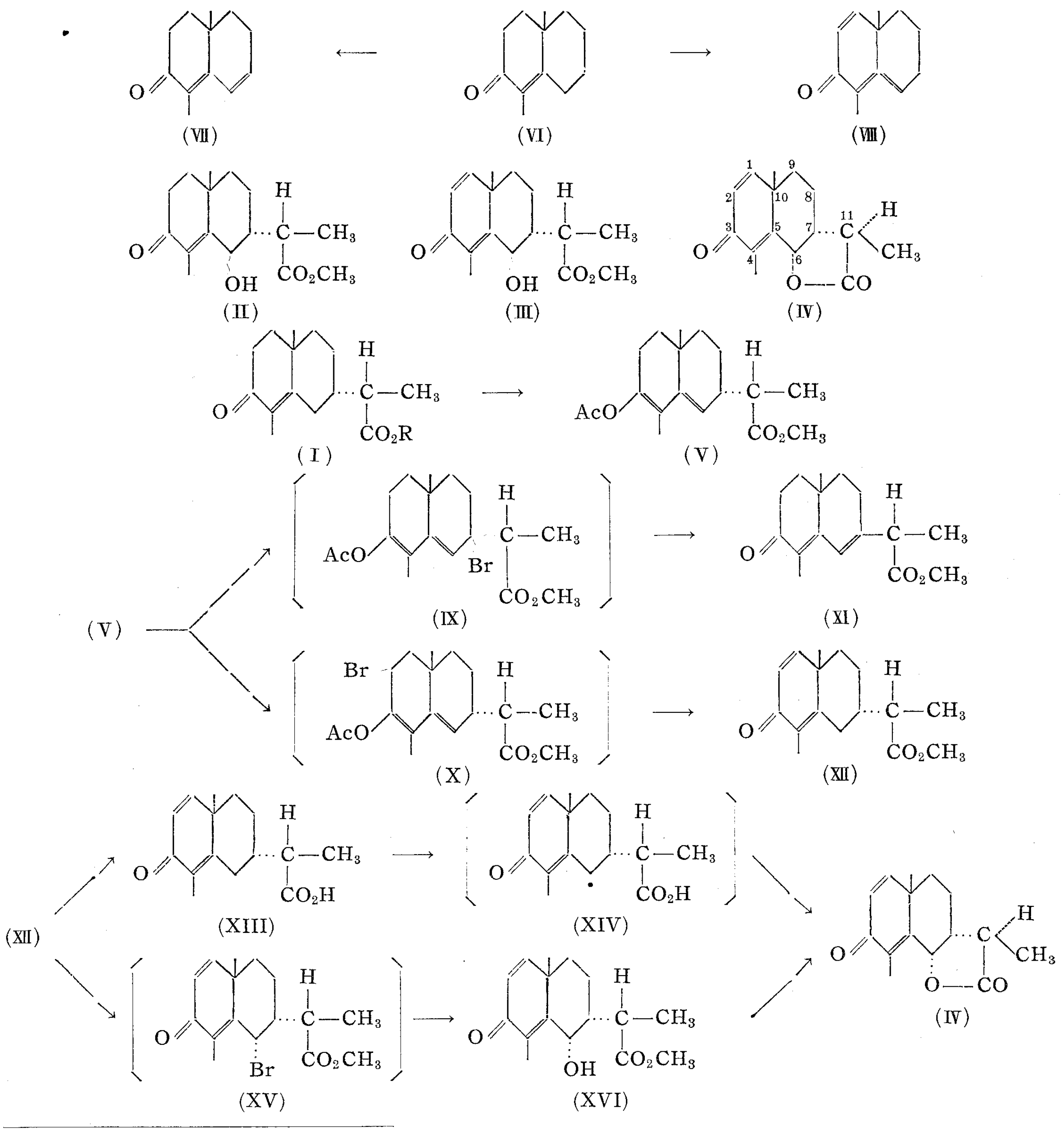
*** The investigation described below clarified that the compounds in the santonin A series possess an axial side chain at C_7 and, therefore, belong to the iso-series,[5] but, for simplification, correct names and formulae are used from the beginning.

**** After this work was finished, a more favorable method was found by T. Miki[6].

1) Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi, T. Toga : J. Am. Chem. Soc., **75**, 2567(1953).
2) Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi, T. Toga : *Ibid.*, **78**, 1416(1956).
3) Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi, T. Toga : *Ibid.*, **78**, 1422(1956).
4) H. Ishikawa : J. Pharm. Soc. Japan, **76**, 489(1958).
5) Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi : Chemistry & Industry, **1955**, 91.
6) T. Miki : J. Pharm. Soc. Japan, **75**, 403(1955).

a cross-conjugated dienone.[7]

The enol acetate[4](V) of methyl 3-oxo-11-*epi*-isoeusanton-4-enate (I : R = CH_3) possesses two α-positions (C_2 and C_7) relative to the conjugated double bond system and the C_7-position may be considerably hindered by a bulky side chain. Therefore, in the expectation that the C_2-position would be preferentially brominated and subsequent dehydrobromination would introduce a double bond into C_1-C_2, the enol acetate (V) was treated with N-bromosuccinimide (NBS) in carbon tetrachloride and the oily bromo compound was subjected to collidine-dehydrobromination. The product was chromatographed on alumina to give a crystalline material, m.p. 105°, and an oily substance. The former exhibited an ultraviolet absorption curve characteristic of a cross-conjugated dienone (λ_{max}^{EtOH} 240 mμ with a shoulder around 270 mμ). This, as well as the elementary analysis, clearly showed that it was methyl 3-oxo-11-*epi*-iso-



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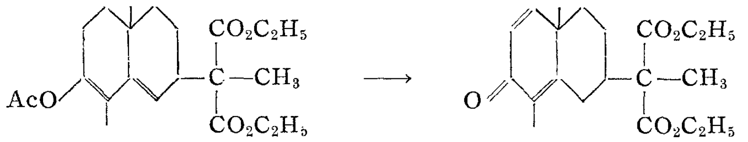
7) F. D. Gunstone, R. M. Heggie : J. Chem. Soc., **1952**, 1437.

eusantona-1,4-dienate (XII). On the other hand, the oily product was found to be methyl 3-oxo-11-*epi*-eusantona-4,6-dienate (XI) with the linear dienone structure from the ultraviolet absorption spectrum (λ_{max}^{EtOH} 265 mμ, 309 mμ, 403 mμ) and the elementary analysis of its 2,4-dinitrophenylhydrazone. Accordingly the above bromination product is considered to be a mixture of (IX) and (X).

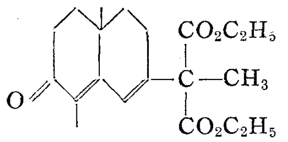
The introduction of a hydroxyl group into the C_6-position of the cross-conjugated dienone (XII) was then attempted. Methyl 3-oxo-11-*epi*-isoeusantona-1,4-dienate (XII) was hydrolyzed to 3-oxo-*epi*-isoeusantona-1,4-dienic acid (XIII), which was subsequently treated with NBS to give 3-oxo-6α-hydroxy-11-*epi*-isoeusantona-1,4-dienic acid lactone (IV, santonin A). It was probably produced via a free radical (XIV) in a way similar to the NBS-bromination of 3-oxo-11-*epi*-isoeusanton-4-enic acid.[2)]

When the dienone ester (XII) was directly brominated with NBS and the resulting C_6-bromo compound was treated with silver oxide in dry ether, the bromine atom was replaced by a hydroxyl to give rise to a new stereoisomer of methyl santoninate (XVI), m.p. 150°. It is evidently epimeric at C_6 with the methyl santoninate isomer (III), m.p. 113°, obtained by Ishikawa, but unexpectedly it also afforded 6α-hydroxy-3-oxo-11-*epi*-isoeusantona-1,4-dienic acid lactone (IV) by hydrolysis. The above assignment to the C_6-hydroxyl of (III) thus became doubtful and it was impossible to determine which of the two isomers would have the hydroxyl *trans* to the C_7-side chain. It is clear, however, that inversion occurred at C_6 by hydrolysis in the one with the *trans*-hydroxyl. Such an inversion is not observed by the hydrolysis of methyl santoninate derived from natural santonin where the relation of the hydroxyl and the side chain is *trans*. These facts evidently show that the C_7-C_{11} bond takes the axial position in 6α-hydroxy-3-oxo-11-*epi*-isoeusantona-1,4-dienic acid lactone (IV), and also in (III), (XVI), etc. In regard to the configurations at C_6 of (III) and (XVI), the following assumption is tentatively made. As the C_7-side chain adopts the axial position in each of the two methyl santoninate isomers described above, the C_6-hydroxyl is equatorially oriented when it is *cis* to the side chain, while the *trans*-hydroxyl is axially oriented. By inspection of molecular models it is readily understood that the equatorial hydroxyl can constitute a lactone ring with the carboxyl group of the side chain, but the axial hydroxyl makes it impossible on account of a long distance between the two groups. The isomer (XVI) obtained by the present author slowly lactonized only by standing at room temperature, while with (III), prepared by Ishikawa, such was not the case. Therefore, it would be reasonably predicted that the former is methyl 6α-hydroxy-3-oxo-11-*epi*-isoeusantona-1,4-dienate with the hydroxyl group *cis* (equatorial) to the side chain, and accordingly the latter is its 6β-isomer.

The above method for synthesizing a cross-conjugated dienone was found to be applicable to compounds without a side chain or with an equatorial side chain at C_7. The enol acetate of 4,9-dimethyl-3-oxo-1,2,3,5,6,7,8,9-octahydronaphthalene (VI) afforded 4,9-dimethyl-3-oxo-3,5,6,7,8,9-hexahydronaphthalene (VIII), and from the enol acetate[3)] (XVII) of ethyl 11-ethoxycarbonyl-3-oxoeusanton-4-enate, ethyl 11-ethoxycarbonyl-3-oxoeusantona-1,4-dienate (XVIII) was derived. In the former case a bromine atom would have been introduced not only into C_2 but also in C_7 by the action of NBS, since the subsequent dehydromination resulted in the formation of a com-



(XVII) (XVIII)



(XIX)

pound (VII) with the linear dienone structure as a minor product. In the case of (XVII), however, the introduction of a bromine atom into C_7 would have been prevented by the bulky C_7-side chain, and this would well explain the absence of the corresponding linear dienone (XIX) in the product. The 2,4-dinitrophenylhydrazone of (XVIII) prepared by the present method and the dienone acid obtained by the hydrolysis of (XVIII) were respectively identical with those synthesized through an alternative procedure.[3]

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Experimental*

Bromination of Methyl 3-Acetoxy-11-*epi*-isoeusantona-3,5-dienate (V)—To a solution of 16.7 g. of the enol acetate[4] (V) in 800 cc. of CCl_4 was added 9.5 g. of NBS and the mixture was refluxed under illumination for 15 mins. After cooled, the succinimide was filtered off and the filtrate was concentrated under reduced pressure. The residue was taken up in ether, washed with water, dried, and the ether was evaporated to give 19 g. of an oily bromo compound.

Methyl 3-Oxo-11-*epi*-isoeusantona-1,4-dienate (XII)—A mixture of 19 g. of the bromo compound obtained above and 70 cc. of collidine was refluxed for 30 mins. After the collidine hydrobromide was filtered off, the collidine was removed *in vacuo* from the filtrate. The residue was dissolved in ether and the ethereal solution was washed with dil. H_2SO_4, Na_2CO_3 solution, and water, dried, and evaporated. The residue, dissolved in benzene, was chromatographed over 150 g. of alumina. From the first benzene eluate there was obtained ca. 6 g. of an oily material, whose 2,4-dinitrophenylhydrazone was recrystallized from benzene-MeOH as dark red needles (the derivative of XI), m.p. 178°, λ_{max} 265 mμ (log ε 4.14), 309 mμ (log ε 4.15), 403 mμ (log ε 4.48). *Anal.* Calcd. for $C_{22}H_{20}O_6N_4$: C, 59.72; H, 5.92; N, 12.66. Found: C, 59.57; H, 5.74; N, 12.48.

The second benzene eluate afforded 0.3 g. of methyl 3-oxo-11-*epi*-isoeusanton-4-enate (I), which was characterized as its 2,4-dinitrophenylhydrazone. The benzene-ether (3 : 1 and 2 : 2) eluates gave 1.4 g. of methyl 3-oxo-11-*epi*-isoeusantona-1,4-dienate (XII). This was recrystallized from petr. ether to colorless prisms, m.p. 105°, λ_{max} 242 mμ (log ε 4.00). *Anal.* Calcd. for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.22; H, 8.47.

3-Oxo-11-*epi*-isoeusantona-1,4-dienic Acid (XIII)—To a solution of 1.2 g. of the dienone ester (XII) in 20 cc. of MeOH was added 10% aq. KOH solution and it was stirred for 8 hrs. at room temperature. The MeOH was removed under reduced pressure and the alkaline solution, washed with ether and after diluted to ca. 60 cc., acidified. The separated crystalline material (1 g.) was recrystallized from aq. MeOH to colorless prisms, m.p. 185°. *Anal.* Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.39; H, 8.47.

6α-Hydroxy-3-oxo-11-*epi*-isoeusantona-1,4-dienic Acid Lactone (IV: **Santonin A**)—A mixture of 1.0 g. of the dienone acid (XIII), 0.8 g. of NBS, and 100 cc. of $CHCl_3$ was refluxed under illumination for 1 hr. After cooling, the solution was washed with $NaHCO_3$ solution and water, dried, and concentrated to give 0.4 g. of crystals. Recrystallization from aq. MeOH afforded colorless prisms, m.p. 146°, undepressed on admixture with an authentic sample of (IV).[1] From the $NaHCO_3$ washings 0.1 g. of (XIII) was recovered.

Methyl 6α-Hydroxy-3-oxo-11-*epi*-isoeusantona-1,4-dienate (XVI)—To a solution of 1.3 g. of the dienone ester (XII) in 100 cc. of CCl_4 was added 0.9 g. of NBS and the mixture was refluxed under illumination for 25 mins. After the succinimide was filtered off, the filtrate was concentrated under reduced pressure and the residue taken into ether was purified. A solution of 1.7 g. of the resulting oily bromo compound in 200 cc. of ether (dried over anhyd. Na_2SO_4) was stirred with 7.1 g. of dried Ag_2O for 60 hrs. at room temperature. Ag_2O was removed by filtration and the filtrate was concentrated. When the residue was triturated with petr. ether and cooled, there was obtained 0.4 g. of a crystalline material, which was recrystallized to colorless plates, m.p. 150°, giving marked depression on admixture with (IV). λ_{max} 242 mμ (log ε 4.00). *Anal.* Calcd. for $C_{16}H_{22}O_4$: C, 69.09; H, 7.97. Found: C, 68.98; H, 8.09. After being kept standing for several days, its melting point became remarkably lower, and a band characteristic of a lactone appeared at 5.7 μ in its infrared spectrum.

Hydrolysis of Methyl 6α-Hydroxy-3-oxo-11-*epi*-isoeusantona-1,4-dienate (XVI)—To 0.2 g. of the ester (XVI) in 20 cc. of MeOH was added 0.2 g. of KOH in 2 cc. of water. After the mixture

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* All ultraviolet absorption spectra were measured in dehyd. EtOH.

was stirred for 6 hrs., MeOH was removed under reduced pressure. The alkaline solution was acidified and extracted with ether. The extract was washed with $NaHCO_3$ solution and water, dried, and evaporated to give 50 mg. of crystals. This was recrystallized from aq. MeOH to colorless prisms, m.p. 146°, undepressed on admixture with an authentic sample of (IV). Treatment of (XVI) with MeOH containing HCl also furnished the same product.

4,9-Dimethyl-3-oxo-3,5,6,7,8,9-hexahydronaphthalene (VIII)—A mixture of 19.5 g. of the monoenone[7] (VI), 154 cc. of Ac_2O, and 290 cc. of AcCl was refluxed gently for 4.5 hrs. After removal of the solvent *in vacuo*, the residue was taken into ether, washed with cold Na_2CO_3 solution, and ice-water. The ether solution was dried and concentrated, and distillation of the residual oil afforded 18.3 g. of the enol acetate (VI), b.p.$_5$ 137~143°. λ_{max} 241 mμ (log ε 3.85). 11 g. of the enol acetate was dissolved in 120 cc. of CCl_4 and 10.6 g. of NBS was added. The mixture was refluxed under illumination for 30 mins. The succinimide was filtered off and the filtrate was concentrated. The oily material thus obtained was chromatographed over 80 g. of alumina using benzene and benzene-ether (3 : 1 and 2 : 2). From the benzene eluates there was obtained 1.5 g. of a brown oil (VII), whose 2,4-dinitrophenylhydrazone was recrystallized from benzene-MeOH to dark red plates, m.p. 212°. λ_{max} 265 mμ (log ε 4.19), 306 mμ (log ε 4.16) 400 mμ (log ε 4.52). *Anal.* Calcd. for $C_{18}H_{20}O_4N_4$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.63; H, 5.56; N 15.82. The benzene-ether eluates afforded 1.2 g. of the cross-conjugated dienone (VIII), whose 2,4-dinitrophenylhydrazone recrystallized as dark red plates, m.p. 232°. λ_{max} 223 mμ (log ε 4.29), 256 mμ (log ε 4.24), 307 mμ (log ε 3.90), 400 mμ (log ε 4.54). *Anal.* Calcd. for $C_{18}H_{20}O_4N_4$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.50; H, 5.38; N, 15.57. According to Gunstone[7] the 2,4-dinitrophenylhydrazones of (VII) and (VIII) have melting points, 216° and 239°, respectively.

Ethyl 11-Ethoxycarbonyl-3-oxoeusantona-1,4-dienate (XVIII)—26 g. of the enol acetate[3] (XVII) of ethyl 11-ethoxycarbonyl-3-oxoeusanton-4-enate in 100 cc. of CCl_4 was refluxed under illumination for 40 mins. with 12.5 g. of NBS. The reaction mixture was worked up as described in the preceding experiment and there was obtained 30 g. of a bromo compound, which was heated for 50 mins. in 85 cc. collidine, and purification afforded 24 g. of an oily material. This was adsorbed on 240 g. of alumina and washed with benzene and benzene-ether (3 : 1 and 2 : 2). The benzene eluates contained impure (XVIII) (10.7 g.), which gave the 2,4-dinitrophenylhydrazone, m.p. 169°. From the benzene-ether eluates was obtained 6 g. of an oily product, whose 2,4-dinitrophenylhydrazone was recrystallized from benzene-MeOH as red prisms, m.p. 190°, undepressed on admixture with the derivative of (XVIII) which was prepared by an alternative path.[3] λ_{max} 227 mμ (log ε 4.26), 255 mμ (log ε 4.23), 307 mμ (log ε 3.84), 396 mμ (log ε 4.52). The oily product was hydrolyzed to a dicarboxylic acid, m.p. 190°(decomp.), showing no depression when mixed with an authentic sample.[3] λ_{max} 241 mμ (log ε 3.99). *Anal.* Calcd. for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.84; H, 7.07.

Summary

A new stereoisomer of methyl santoninate was synthesized and by the examination of the behavior of this substance as well as its C_8-epimer toward alkali, the axial position was assigned to the C_7–C_{11} bond of santonin A. A novel route for the preparation of a cross-conjugated dienone is also described.

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