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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 synthesized¹⁾ and investigation of the rotation of the optically active isomer predicted²⁾ that santonin A would have a *cis*-fused lactone and its C₇-C₁₁ 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 C₆-hydroxyl *trans* to the C₇-side chain. The present paper describes this work in detail.

Starting from 3-oxo-11-*epi*-isoeusanton-4-enic acid*** (I : R=H; A-acid¹⁾), Ishikawa⁴⁾ synthesized methyl 6 ξ -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 6 α -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 C₆-hydroxyl group *cis* to the propionic ester side chain at C₇. 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 C₁-C₂ of the C₆-epimer of (II) was unsuccessful,⁴⁾ there remained a route in which methyl 3-oxo-11-*epi*-isoeusanton-4-enate (I : R=CH₃) was first converted to a cross-conjugated dienone and subsequently a hydroxyl group was introduced into C₆. 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

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

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*** The investigation described below clarified that the compounds in the santonin A series possess an axial side chain at C₇ 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. Miki⁶⁾.

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 acetate⁴⁾(V) of methyl 3-oxo-11-*epi*-isoeusanton-4-enate (I : R=CH₃) possesses two α -positions (C₂ and C₇) relative to the conjugated double bond system and the C₇-position may be considerably hindered by a bulky side chain. Therefore, in the expectation that the C₂-position would be preferentially brominated and subsequent dehydrobromination would introduce a double bond into C₁-C₂, 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 ($\lambda_{\text{max}}^{\text{EtOH}}$ 240 m μ with a shoulder around 270 m μ). This, as well as the elementary analysis, clearly showed that it was methyl 3-oxo-11-*epi*-iso-

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

eousantona-1,4-dienate (XII). On the other hand, the oily product was found to be methyl 3-oxo-11-*epi*-eousantona-4,6-dienate (XI) with the linear dienone structure from the ultraviolet absorption spectrum ($\lambda_{\text{max}}^{\text{EtOH}}$ 265 m μ , 309 m μ , 403 m μ) 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 C₆-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-6 α -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 C₆-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 C₆ with the methyl santoninate isomer (III), m.p. 113°, obtained by Ishikawa, but unexpectedly it also afforded 6 α -hydroxy-3-oxo-11-*epi*-isoeusantona-1,4-dienic acid lactone (IV) by hydrolysis. The above assignment to the C₆-hydroxyl of (III) thus became doubtful and it was impossible to determine which of the two isomers would have the hydroxyl *trans* to the C₇-side chain. It is clear, however, that inversion occurred at C₆ 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 C₇-C₁₁ bond takes the axial position in 6 α -hydroxy-3-oxo-11-*epi*-isoeusantona-1,4-dienic acid lactone (IV), and also in (III), (XVI), etc. In regard to the configurations at C₆ of (III) and (XVI), the following assumption is tentatively made. As the C₇-side chain adopts the axial position in each of the two methyl santoninate isomers described above, the C₆-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 6 α -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 6 β -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 C₇. 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 acetate³⁾ (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 C₂ but also in C₇ by the action of NBS, since the subsequent dehydromination resulted in the formation of a com-

pound (VII) with the linear dienone structure as a minor product. In the case of (XVII), however, the introduction of a bromine atom into C₇ would have been prevented by the bulky C₇-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 acetate⁴⁾ (V) in 800 cc. of CCl₄ 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. H₂SO₄, Na₂CO₃ 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 m μ (log ϵ 4.14), 309 m μ (log ϵ 4.15), 403 m μ (log ϵ 4.48). *Anal.* Calcd. for C₂₂H₂₀O₆N₄: 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 m μ (log ϵ 4.00). *Anal.* Calcd. for C₁₆H₂₂O₃: 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 C₁₅H₂₀O₃: C, 72.55; H, 8.12. Found: C, 72.39; H, 8.47.

6 α -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 CHCl₃ was refluxed under illumination for 1 hr. After cooling, the solution was washed with NaHCO₃ 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 NaHCO₃ washings 0.1 g. of (XIII) was recovered.

Methyl 6 α -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 CCl₄ 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. Na₂SO₄) was stirred with 7.1 g. of dried Ag₂O for 60 hrs. at room temperature. Ag₂O 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 m μ (log ϵ 4.00). *Anal.* Calcd. for C₁₆H₂₂O₄: 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 6 α -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

* 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 monoenone⁷⁾ (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 $137\sim 143^\circ$. λ_{max} $241\text{ m}\mu$ ($\log \epsilon$ 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} $265\text{ m}\mu$ ($\log \epsilon$ 4.19), $306\text{ m}\mu$ ($\log \epsilon$ 4.16) $400\text{ m}\mu$ ($\log \epsilon$ 4.52). *Anal.* Calcd. for $\text{C}_{18}\text{H}_{20}\text{O}_4\text{N}_4$: 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} $223\text{ m}\mu$ ($\log \epsilon$ 4.29), $256\text{ m}\mu$ ($\log \epsilon$ 4.24), $307\text{ m}\mu$ ($\log \epsilon$ 3.90), $400\text{ m}\mu$ ($\log \epsilon$ 4.54). *Anal.* Calcd. for $\text{C}_{18}\text{H}_{20}\text{O}_4\text{N}_4$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.50; H, 5.38; N, 15.57. According to Gunstone⁷⁾ 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 acetate⁸⁾ (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.⁸⁾ λ_{max} $227\text{ m}\mu$ ($\log \epsilon$ 4.26), $255\text{ m}\mu$ ($\log \epsilon$ 4.23), $307\text{ m}\mu$ ($\log \epsilon$ 3.84), $396\text{ m}\mu$ ($\log \epsilon$ 4.52). The oily product was hydrolyzed to a dicarboxylic acid, m.p. 190° (decomp.), showing no depression when mixed with an authentic sample.⁸⁾ λ_{max} $241\text{ m}\mu$ ($\log \epsilon$ 3.99). *Anal.* Calcd. for $\text{C}_{16}\text{H}_{20}\text{O}_5$: 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 $\text{C}_7\text{--C}_{11}$ bond of santonin A. A novel route for the preparation of a cross-conjugated dienone is also described.

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