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98. Yoshisuke Tsuda and Kimiaki Isobe: Osmium Tetroxide Oxidation of Hopa-15,17(21)-diene, Dehydrozeorinin, and Hop-17(21)-ene.[*1]

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The structures of the diol and the conjugated ketone obtained from the osmium tetroxide oxidation of hopa-15,17(21)-dienes (I) were now revised and correctly assigned as IV and V, respectively, the former being obtained by lithium aluminum hydride decomposition and the latter by hydrogen sulfide decomposition of the intermediate osmate. Hop-17(21)-ene (VI) was also found to give the seco-diketone (VIII) in lesser yield. A probable mechanism for the formation of the seco-diketones was also discussed.

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In the study of structural elucidation of zeorin, Barton, de Mayo, and Orr[1)] reported the osmium tetroxide oxidation of dehydrozeorinin derivatives (I), where they obtained a mixture of a triol, m.p. 235～252°, and of its monobenzoate, m.p. 227～241°, by lithium aluminum hydride decomposition of the intermediate osmate from dehydrozeorinin benzoate (I; R=OCOPh), while a conjugated ketone, m.p. 141～142°, $\lambda_{\max}^{\mathrm{EtOH}}$ 230 mμ (ε ～9000), was produced when the osmate from dehydrozeorinin acetate (I; R=OAc) was decomposed by hydrogen sulfide. They considered that the glycol (II) could be dehydrated into the conjugated ketone (III) by an action of mineral acid, which is possibly entrained in the hydrogen sulfide gas stream, and based on this consideration they assigned the structures of the products as II and III, respectively. If their assignments are correct, the same reaction on hopa-15,17(21)-diene (I; R=H) would be expected to give hop-17(21)-en-15,16-diol (II; R=H) and 21α-hop-16-en-15-one (III; R=H), respectively, and the latter must be identical with isoanhydrodustaninone-A which we have already derived from dustanin.[2)] However, the ultraviolet absorption spectra of Barton's conjugated ketone ($\lambda_{\max}^{\mathrm{EtOH}}$ 230 mμ (ε ～9000)) and of isoanhydrodustaninone-A ($\lambda_{\max}^{\mathrm{EtOH}}$ 242 mμ (ε ～14000)) show significant difference, and the absorption maximum of the former seems to be too short for such a trisubstituted conjugated ketone chromophor; a fact which therefore presents some doubts to the assigned structures of the Barton's products.

Hence, we have examined the osmium tetroxide oxidation of hopa-15,17(21)-diene (I; R=H), and again confirmed that the intermediate osmate gives two products, a glycol, m.p. 208～210°, and a conjugated ketone, m.p. 102～104°, $\lambda_{\max}^{\mathrm{EtOH}}$ 232 mμ (ε ～9300), depending on the method of decomposition employed, the former being obtained by lithium aluminum hydride decomposition and the latter by hydrogen sulfide decomposition. The conjugated ketone, however, was not identical with isoanhydrodustaninone-A but analysed with one extra oxygen. In the infrared spectrum it exhibited two intense carbonyl absorptions at 1660 and 1700 cm^{-1}, the latter being attributable to an additional carbonyl group. The glycol, again contrary to the expectation, was not acetylated nor formed any ketonic function upon treatment with mineral acid, the acid treatment product being an unidentified hydrocarbon.

[*1] A part of the work was presented at the Kinki Branch Meeting of Pharmaceutical Society of Japan. November 23, 1965.

[*2] Toyonaka, Osaka (津田喜典, 磯部公明).

1) D.H.R. Barton, P. de Mayo, J.C. Orr: J. Chem. Soc., **1958**, 2239.

2) Y. Tsuda, K. Isobe: Tetrahedron Letters, No. **37**, 3337 (1965).

Conclusive evidences of their structures, (IV; R=H) for the glycol and (V; R=H) for the conjugated ketone, were obtained from their nuclear magnetic resonance spectra which showed two olefinic protons for either compound. The glycol exhibited an AB quartet at δ 5.82 (δ_{AB}=28 c.p.s., J_{AB}=11 c.p.s.) as that of hopa-15,17(21)-diene,[2] and the conjugated ketone showed two doublets at δ 6.94 and 5.82 (J=12 c.p.s.); the facts which indicate that the glycol is not 15,16-diol but 17,21-diol (IV; R=H), and the conjugated ketone must have the structure (V; R=H). In accord with this assignment, the glycol when treated with lead tetra-acetate quantitatively furnished the conjugated ketone (V; R=H).

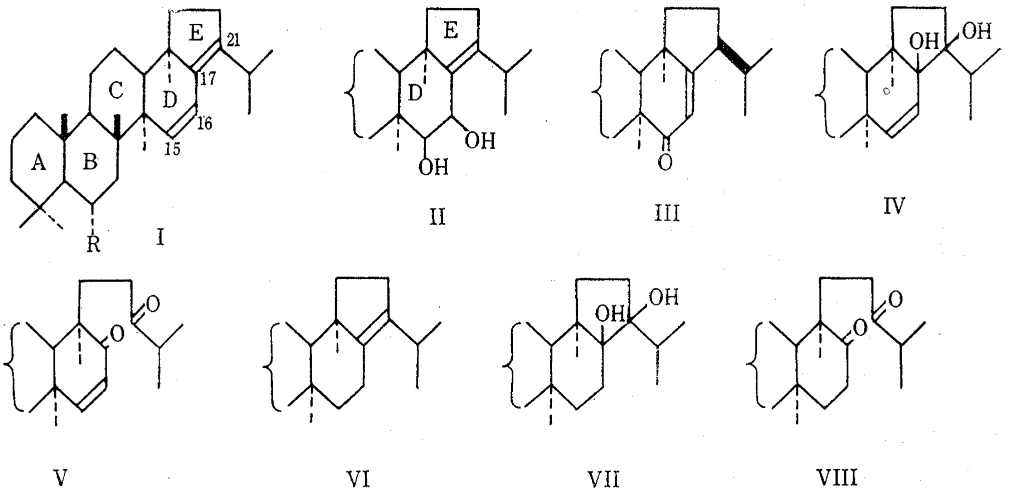

Chart 1.

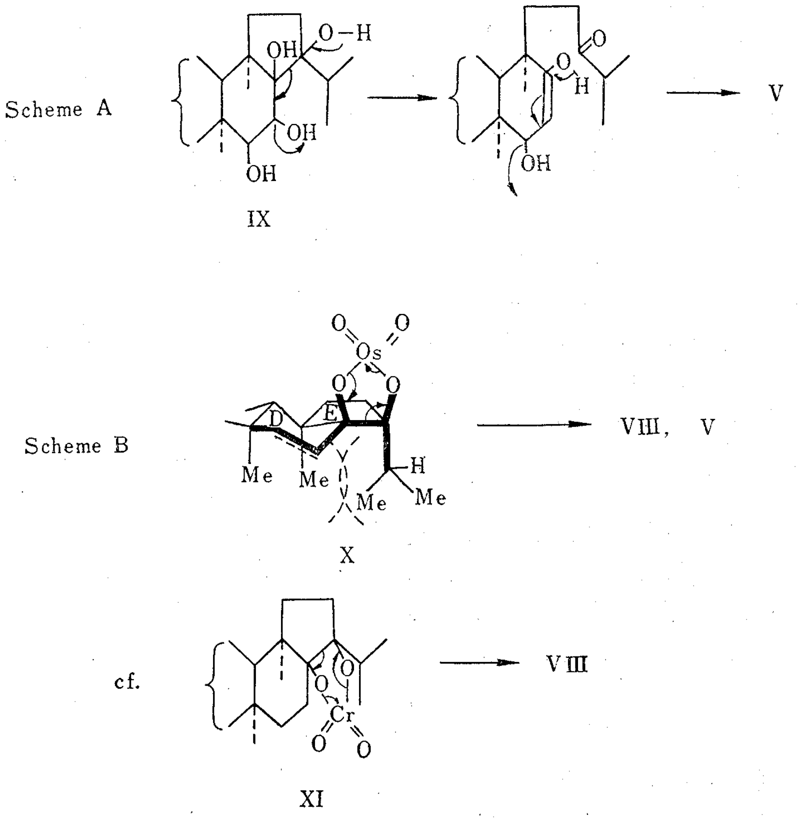

Chart 2.

Re-examination of the osmium tetroxide oxidation on dehydrozeorinin acetate (I; R=OAc) yielded the triol and the conjugated ketone depending on the method of decomposition employed, to which we now assign the structures (Ⅳ; R=OH) and (V; R=OAc), respectively. In the nuclear magnetic resonance spectra the triol-monoacetate (Ⅳ; R=OAc) exhibited two olefinic protons as an AB quartet at δ 5.90 (δ_{AB}=23 c.p.s., J_{AB}=12 c.p.s.) and the conjugated ketone did two doublets at δ 6.99 and 5.95 (J=11 c.p.s.), as expected. The triol monoacetate (Ⅳ; R=OAc) was again smoothly converted into the conjugated ketone (V; R=OAc) on treatment with lead tetraacetate.

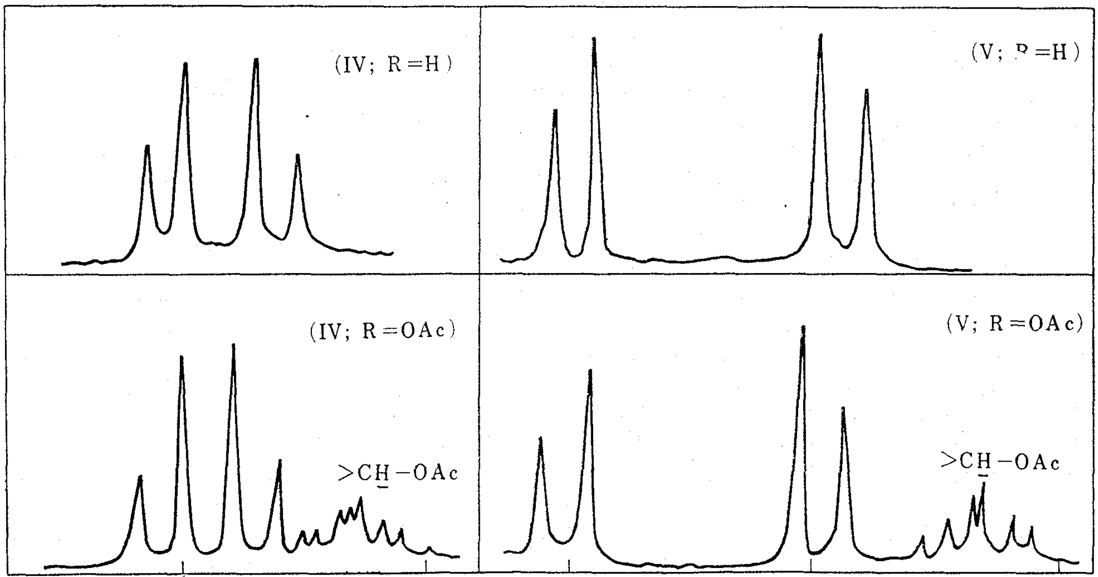

Fig. 1. Olefinic Proton Signal in NMR Spectra (in $CDCl_3$, 60 Mc.)

Why does one yield the seco-diketone (V) by hydrogen sulfide decomposition of the osmate? The first explanation that comes to mind is that it could be derived from a tetraol (Ⅸ) as indicated in scheme A. This possibility, however, was excluded from the following reasons: firstly it does not explain the formation of the glycol (Ⅳ) by hydride decomposition of the same osmate, secondly the glycol was recovered unchanged on further treatment with osmium tetroxide, and finally the seco-diketone (V) was isolated even after treatment with less than one mole of osmium tetroxide to the diene (I).

We have now found that the osmate from hop-17(21)-ene (Ⅵ; R=H) when decomposed by hydrogen sulfide also furnished *ca.* 20% of the seco-diketone (Ⅷ; R=H) along with 80% of the glycol (Ⅶ; R=H), although Barton, *et al.*[1] had isolated only one product (Ⅶ; R=OAc) from zeorinin acetate (Ⅵ; R=OAc). The structure of Ⅷ was proved from its infrared band at 1698 cm^{-1} and by lead tetraacetate oxidation of Ⅶ into Ⅷ. Hence a probable mechanism of the formation of the seco-diketone may be as follows. If we assume that the osmolation had occurred from the less hindered face of the molecule and the resulting osmate has the stereostructure (X), the steric compression between C_{18}-methyl and isopropyl groups will markedly increase the strains of ring E and the osmate ring, which will induce the self-cleavage of the central $C_{17\sim21}$ bond under influence of a mild reducing agent (scheme B), the product thus gaining a great relief of the steric compression. The presence of a double bond allylic to the central bond will facilitate its cleavage, so that the cooperation of the both steric and electronic effects will almost completely change the course of

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decomposition thus producing the seco-diketone (V) as a major product.*[3] Though the problem whether the cleavage is heterolytic or homolytic is still uncertain, the mechanism should be analogous to that of the observed cleavage of the cyclic chromic ester (Ⅺ) in oxidation of 17,21-diol.[1)]

Experimental

Osmium Tetroxide Oxidation of Hopa-15,17(21)-diene (I; R=H)——a) Hopadiene (I; R=H) (300 mg.) and OsO_4 (300 mg., 1.6 eq.) in abs. ether (20 ml.) and pyridine (8 ml.) were kept for 7 days at room temperature in the dark. Two-third of the mixture was evaporated to dryness and the residue in tetrahydrofuran heated with excess of $LiAlH_4$ under reflux for 30 min. After addition of a few drops of H_2O, the mixture was filtered, the residue throughly washed with $CHCl_3$, and the combined filtrate evaporated to dryness. Chromatography of the residue in *n*-hexane over acid-washed alumina and crystallization of the *n*-hexane-benzene and benzene eluates from *n*-hexane gave hopadiene glycol (Ⅱ; R=H) as needles, m.p. 208~210°, $[\alpha]_D$ +24°(c=0.67 in $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 3600~3700 (OH). *Anal.* Calcd. for $C_{30}H_{50}O_2$: C, 81.39; H, 11.38. Found: C, 81.30; H, 11.43. This glycol was recovered unchanged (a) on treatment with pyridine and Ac_2O at room temperature, and (b) with H_2S in the ethanolic solution.

To one-third of the above osmate mixture H_2S from a Kipp generator was passed in, then filtered. The residue was washed with $CHCl_3$, and the combined filtrate and washings evaporated to dryness. Since a preliminary experimentation had indicated that the product is a mixture of V and a small amount of Ⅳ, the residue was treated for 10 min. with 3% EtOH-HCl which converted Ⅳ to a hydrocarbon and left V unchanged. Chromatography of the acid treatment product in *n*-hexane over acid-washed alumina and crystallization of the benzene eluate from *n*-pentane yielded the seco-diketone (V; R=H) as prisms, m.p. 102~104°, $[\alpha]_D$ +58°(c=1.01 in $CHCl_3$). UV λ_{max}^{EtOH} mμ (ε): 232 (9300), $\lambda_{max}^{n\text{-hexane}}$ mμ (ε): 233 (10500). IR ($CHCl_3$) cm^{-1}: 1700, 1660. *Anal.* Calcd. for $C_{30}H_{48}O_2$: C, 81.76; H, 10.98. Found: C, 81.27; H, 11.13.

b) Hopadiene (I; R=H) (105 mg.) and OsO_4 (60 mg., 0.92 eq.) in dioxane (4 ml.) were kept for 36 hr. at room temperature in the dark, and the osmate formed was decomposed by H_2S. A thin-layer chromatography of the product showed the formation of the seco-diketone (V; R=H) and the glycol (Ⅳ; R=H). Working up as above, there was obtained the seco-diketone (V; R=H), m.p. and mixed m.p. 102~104°.

Attempted Oxidation of Hopadiene Glycol (IV; R=H) with Osmium Tetroxide——Hopadiene glycol (70 mg.) and OsO_4 (160 mg., 3 eq.) in pyridine-ether-dioxane were kept for 7 days at room temperature in the dark. By H_2S decomposition of the mixture, the starting material was recovered unchanged.

Reaction of Acid on Hopadiene Glycol (IV; R=H)——Hopadiene glycol (10 mg.) in EtOH (5 ml.) was treated with a few drops of conc. HCl at 80° for 1 hr. There was formed white precipitate of m.p. >300°, whose thin-layer chromatography in *n*-hexane showed a spot at Rf~1.0 suggesting that it is a hydrocarbon. The characterization of this was unsuccessful. No carbonyl compound was found in the reaction mixture.

Lead Tetraacetate Oxidation of Hopadiene Glycol (IV; R=H)——Hopadiene glycol (40 mg.) in benzene (2.5 ml.) and AcOH (2 ml.) containing 60 mg. of $Pb(OAc)_4$ was kept for 10 min. at room temperature. Ethylene glycol (2 drops) was added and the mixture was extracted with benzene which was washed with H_2O, dried over $MgSO_4$, and evaporated to dryness. Filtration of the residue in benzene through a short column of acid-washed alumina gave the seco-diketone (V; R=H), m.p. and mixed m.p. 102~104°. The IR spectrum was superimposible with that of the seco-diketone obtained above.

Dehydrozeorinin Acetate (I; R=OAc)——Dehydrozeorinin acetate was prepared from zeorinin acetate oxide by the method described by Ashina and Yoshioka.[3)] It crystallized in prisms from $CHCl_3$-MeOH, m.p. 219~221°(lit.[1)] m.p. 222~223°).

Osmium Tetroxide Oxidation of Dehydrozeorinin Acetate (I; R=OAc)——The solutions of dehydrozeorinin acetate (210 mg.) in pyridine (3 ml.) and OsO_4 (170 mg., 1.5 eq.) in dioxane (6 ml.) were mixed in hot, and the mixture was kept for 6 days at room temperature in the dark. About three-fifth of the mixture was treated with $LiAlH_4$ as described above, and the product was chromatographed over acid-washed alumina to give the triol (Ⅳ; R=OH), m.p. 220~250°(from benzene) (lit.[1)] m.p. 235~252°). This showed no carbonyl absorption in the IR spectrum. Acetylation of this with pyridine and Ac_2O gave the acetate (Ⅳ; R=OAc), as needles from *n*-hexane, m.p. 210~214°, $[\alpha]_D$ +61°(c=1.13 in $CHCl_3$). IR (Nujol) cm^{-1}: 1720 shoulder, 1710. *Anal.* Calcd. for $C_{32}H_{52}O_4$: C, 76.75; H, 10.47. Found: C, 76.43; H, 10.38.

A two-fifth of the osmate was decomposed by H_2S. The product on chromatography over acid-washed alumina yielded the triol monoacetate (Ⅳ; R=OAc) (20 mg.), m.p. and mixed m.p. 210~214°, and the seco-diketone (V; R=OAc) (70 mg.), m.p. 146~147°(lit.[1)] m.p. 141~142°) as needles from *n*-pentane or MeOH-H_2O. $[\alpha]_D$ +79°(c=0.74 in $CHCl_3$). UV λ_{max}^{EtOH} mμ (ε): 231 (12400). IR ($CHCl_3$) cm^{-1}: 1720 shoulder, 1705, 1660. *Anal.* Calcd. for $C_{32}H_{50}O_4$: C, 77.06; H, 10.11. Found: C, 76.86; H, 10.05.

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*[3] This may imply the 17β,21β-configuration for the diols (Ⅳ and Ⅶ).

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Lead Tetraacetate Oxidation of the Triol Monoacetate (IV; R=OAc)——A mixture of the triol monoacetate (40 mg.) and $Pb(OAc)_4$ (50 mg.) in benzene (3 ml.) and AcOH (3 ml.) were stirred for 10 min. at room temperature. After addition of ethylene glycol (2 drops), the product was isolated in the usual way to afford the seco-diketone (V; R=OAc), m.p. and mixed m.p. 145~147°. The IR spectrum was superimposable with that of the seco-diketone (V; R=OAc) obtained above.

Osmium Tetroxide Oxidation of Hop-17(21)-ene (VI; R=H)——Hop-17(21)-ene (135 mg.) and excess of OsO_4 in pyridine (5 ml.) and abs. ether (5 ml.) were kept for 7 days at room temperature in the dark. About one-third of the mixture was decomposed by $LiAlH_4$ and the product in ether was passed through a short column of acid-washed alumina to give the diol (VII; R=H), as colorless prisms from Me_2CO-MeOH, m.p. 230~231°, $[\alpha]_D$ +12.2°(c=1.2 in $CHCl_3$) (lit.[4] m.p. 225~226°, $[\alpha]_D$ +12.5°). *Anal.* Calcd. for $C_{30}H_{52}O_2$: C, 81.02; H, 11.79. Found: C, 80.96; H, 11.87.

The rest of the osmate was decomposed by H_2S. The product (76 mg.), which showed two closed spots in TLC, was crystallized from *n*-hexane to give the diol (VII; R=H) (53 mg.) which on recrystallization from Me_2CO-MeOH formed colorless prisms, m.p. and mixed m.p. 230~231°. The IR spectrum was superimposable with that of the diol obtained above. A hexane-soluble compound which showed almost one spot corresponding to the higher Rf in TLC, was again treated with cold MeOH to remove a insoluble substance (trace), then the MeOH-soluble fraction (13 mg.) was crystallized from MeOH-H_2O to give the seco-diketone (VIII; R=H) as colorless needles, m.p. and mixed m.p. 97~98°. The IR spectrum was superimposable with that of the seco-diketone obtained below.

Lead Tetraacetate Cleavage of the Diol (VII; R=H)——The diol (VII; R=H) (50 mg.) in benzene (3 ml.) and AcOH (3 ml.) was treated with an excess of $Pb(OAc)_4$ at room temperature for 30 min. Working up as usual, the product isolated was crystallized from MeOH to give the seco-diketone (VIII; R=H) as colorless needles, m.p. 98~100°, $[\alpha]_D$ −5.6°(c=0.8 in $CHCl_3$). IR (Nujol) cm^{-1}: 1698. *Anal.* Calcd. for $C_{30}H_{50}O_2$: C, 81.39; H, 11.38. Found: C, 81.55; H, 11.40.

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3) Y. Asahina, I. Yoshioka: Ber., **73**, 742 (1940).

4) H. Fazakerley, T.G. Halsall, E.R.H. Jones: J. Chem. Soc., **1959**, 1877.