Chem. Pharm. Bull.
17(2) 291—295 (1969)

UDC 581.19 : 582.29 : 547.597.02

Lichen Triterpenoids. II.[1] The Stereostructure of Zeorin

Itiro Yosioka, Tsutomu Nakanishi, and
Isao Kitagawa

Faculty of Pharmaceutical Sciences, Osaka University[2]

(Received March 25, 1968)

The stereostructure of zeorin, a widely distributed triterpenoid in the lichen family, has been proposed as II in connection with the structure of leucotylin (I). In addition, a questionnaire has been presented concerning to the C_{21}–side chian configurations of hopane and isohopane frameworks.

In the preceding paper[1], we described the stereostructure of leucotylin (I) on the basis of chemical and X-ray crystallographical investigations and in addition postulated some discrepancy, concerning to the geometry of C_{21}– isopropanol side chain of zeorin and suggested the structure (II) with inverse C_{21}–configuration against the previous formulation. In the present report, the detail verifying II as the stereostructure of zeorin is afforded[3,4].

The structure of zeorin (II),[5] $C_{30}H_{52}O_3$, mp 228—229°, was first elucidated as III in 1958 by virtue of the extensive chemical study performed by Barton and his co-workers[6], in which the geometry at C_{17} and C_{21} was left unsolved. A few years later, a related triterpenoid named

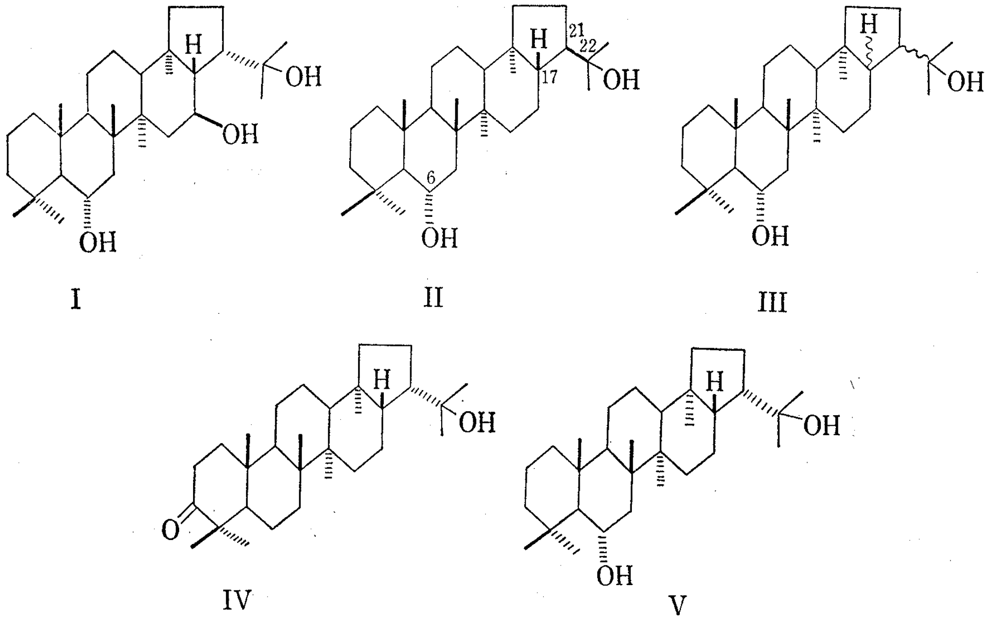

Chart 1. Proposed Structures by Previous Investigations

---

[1] Part I: I. Yosioka, T. Nakanishi, and I. Kitagawa, *Chem. Pharm. Bull.* (Tokyo), **17**, 279 (1969).

[2] Location: *Toneyama, Toyonaka, Osaka.*

[3] I. Yosioka, T. Nakanishi, and I. Kitagawa, *Chem. Pharm. Bull.* (Tokyo), **15**, 353 (1967). This corresponds to the preliminary account on the conversion of zeorin to hopane. Although the structure (V) having C_{21} α-isopropanol configuration was quoted therein, due to the proposed structure (XIII) of hopane, all the experimental evidences are valid as explicated in the present paper.

[4] I. Yosioka, T. Nakanishi, and I. Kitagaa, *Tetrahedron Letters*, **1968**, 1485 (Preliminary report on the revised stereostructure of zeorin).

[5] The newly proposed structure (II) is used for the discussion hereafter.

[6] D.H.R. Barton, P. de Mayo, and J.C. Orr, *J. Chem. Soc.*, **1958**, 2239.

hydroxyhopanone, one of the major triterpenic components of Dammar resins, was chemically assigned IV by Jones and his co-workers.[7] On the other hand at nearly the same time, Huneck suggested[8] the possible identity of 6-desoxyzeorin with hydroxyhopane on the basis of the chemical comparison among their corresponding derivatives, although the identity had once been suspected by Jones, *et al.*[9] and some ambiguities are found in view of the present knowledge. In 1963, Huneck and Lehn tried[10] to clarify the stereochemical problem of zeorin by the nuclear magnetic resonance (NMR) study, where they examined the C-methyl chemical shifts of several related derivatives of zeorin, hydroxyhopane and dammarane derivatives and concluded spectroscopically that zeorin possesses the identical carbon skeleton with hydroxyhopane as expressed by V. However, the chemical correlation between two triterpenes had not been provided until recently when the unambiguous conversion of zeorin to its skeletal hydrocarbon (=zeorinane) was accomplished by Tsuda, *et al.*[11] and by us[3] independently and the identity of zeorinane with hopane was established. It appeared hence that all the stereochemical problems had become beyond question.

As reported in the preceding paper[1], however, we found that (i) the carbon frameworks of zeorin and leucotylin differ only at C_{21} geometry and (ii) leucotylin possesses C_{21}-α-isopropanol moiety attached to the ring E of "C_2" (half-chair)[12] conformation. Therefore, it follows that the reactions described below lead us to propose II (having C_{21}-β-isopropanol side chain) for zeorin in the sequel.

On chromium trioxide oxidation, zeorin gave zeorinone (VI), mp 238—241° as reported previously[6]. Treatment of the ketone with phosphorus oxychloride-pyridine at room temperature furnished a mixture of dehydration products, which was successively separated into two components by silver nitrate impregnated silica gel column chromatography.[13] An earlier eluted compound VIII (named zeorininone-a) $C_{30}H_{48}O$, mp 196.5—197°, infrared (IR) spectrum[14]: 1699 ($\rangle$CO), NMR[14]: 9.35, 9.12, 9.05, 8.97, 8.82, 8.72 (3H each singlet, total six methyls), 8.22, 8.37 (3H each singlet, assignable to $\rangle C=C(C\underline{H}_3)_2$) was assigned VIII on the basis of its physical properties. Another dehydration product (eluted later, named zeorininone-b), $C_{30}H_{48}O$, mp 215—215.5°, IR: 1699 (CO), 1635, 889 ($\rangle C=CH_2$), NMR: 9.21, 9.13, 9.05, 8.97, 8.89, 8.72 (3H each singlet, total six methyls), 8.19 (3H, singlet, $H_2C=\overset{|}{C}-C\underline{H}_3$), 5.18 (2H, broad singlet, $H_3C-\overset{|}{C}=C\underline{H}_2$) was given the structure VII having C_{21}-isopropenyl function reasonably.

A saturated ketone (now termed as 22-desoxy-zeorinone),[15] $C_{30}H_{50}O$, mp 238—239°, obtained by catalytic hydrogenation of VII in the neutral solvent mixture, is surely believed to retain the original C_{21} geometry of zeorin as is expressed by IX. On the contrary, the isopropylidene derivative (VIII) was catalytically hydrogenated only in the acidic medium to another saturated ketone (termed here as 22-desoxy-21βH-zeorinone[16]). $C_{30}H_{50}O$, mp 204—207°, IR (KBr): 1704, and the former ketone (IX) was practically not produced in

---

[7] G.U. Baddeley, T.G. Halsall, and E.R.H. Jones, *J. Chem. Soc.*, **1961**, 3891, and literatures cited therein.

[8] S. Huneck, *Chem. Ber.*, **94**, 614 (1961).

[9] H. Fazakerley, T.G. Halsall, and E.R.H. Jones, *J. Chem. Soc.*, **1959**, 1877.

[10] S. Huneck and J.-M. Lehn, *Bull. Soc. Chim. France*, **1963**, 1702.

[11] Y. Tsuda, K. Isobe, S. Fukushima, H. Ageta, and K. Iwata, *Tetrahedron Letters*, **1967**, 23.

[12] E.L. Eliel, N.L. Allinger, S.J. Angyal, and G.A. Morrison, "Conformational Analysis," Interscience Publishers, New York, 1965, p. 200.

[13] T. Norin and L. Westfelt, *Acta Chem. Scand.*, 17, 1828 (1963).

[14] The IR spectra were taken in chloroform and expressed in cm^{-1}, and the NMR spectra were measured with the Hitachi H-60 spectrometer in deuteriochloroform with tetramethylsilane as an internal standard and given in τ-values unless specified otherwise.

[15] The ketone was previously designated by α-deoxyzeorinone in our preliminary report[3] since it was found that the ketone possesses the identical C_{21}-geometry with hydroxyhopane which was believed to possess C_{21} α-side chain configuration at that time. We wish to alter the name to 22-desoxy-zeorinone because IX preserves the carbon skeleton of zeorin.

[16] The termination was based on the similar reason as above, since the ketone (X) is believed to possess the inverted configuration at C_{21} against zeorin skeleton.

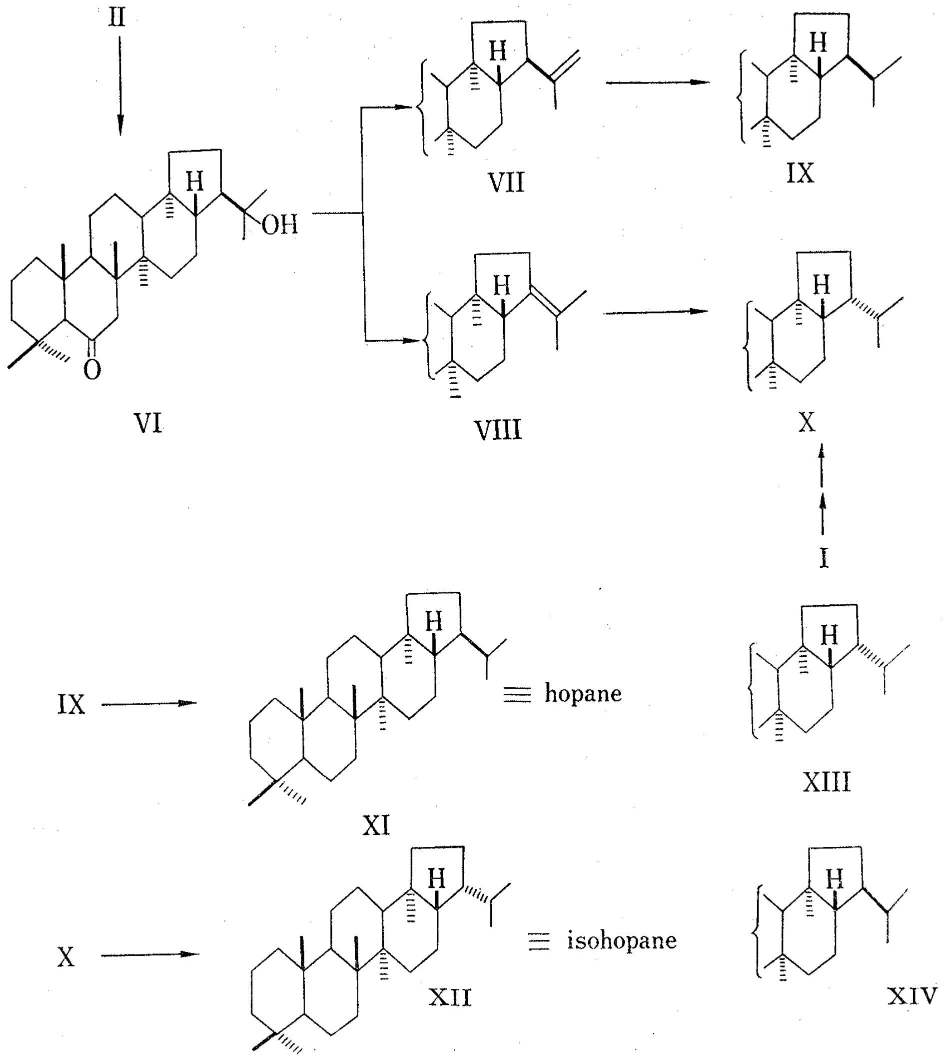

Chart 2

this case. Although two ketones (IX and X) thus obtained behave identically on thin–layer chromatogram (TLC), they are clearly discriminated each other by gas liquid chromatography (GLC) and IR spectral comparison. Besides the agreement assigning X to the second saturated ketone on the basis of its formation procedure[17] and physical properties, the established identity (mixed mp, IR, TLC and GLC) of the ketone (X) with the one keeping C_{21}-α-orientation of leucotylin (I) as described in the preceding paper[1], enables us to assume that the former ketone (IX), retaining C_{21} configuration of zeorin, should be formulated with C_{21}-β-isopropyl orientation.[18] Consequently, zeorin should be expressed by II in place of V contrary to the previous assignment.

Furthermore, the following conversions lead us to suspect the hitherto assigned C_{21} side chain configurations of hopane (XIII, C_{21}-βH)[7,20] and isohopane (XIV, C_{21}-αH)[7,21] and

---

[17] The hydrogenation seems to proceed from the less hindered β side as revealed by Dreiding model inspection. As was discussed in the preceding paper,[1] the double bond migration of $\Delta^{21,22}$ in VIII to $\Delta^{17(21)}$ during or before the hydrogenation procedure in AcOH–AcOEt mixture could be ruled out. The later derivation of X to isohopane (XII) also corroborates the assumption.

[18] It seems clear that isozeorininone and deoxyzeorinone appeared in the earlier paper[19] are mixtures of VII, VIII and IX, X respectively as were also pointed out in lit. 11).

[19] D.H.R. Barton and T. Bruun, *J. Chem. Soc.*, **1952**, 1683.

[20] G. Berti, F. Bottari, A. Marsili, J.-M. Lehn, R. Witz, and G. Ourisson, *Tetrahedron Letters*, **1963**, 1283.

[21] M.N. Galbraith, C.J. Miller, J.W. L. Rawson, E. Ritchie, J.S. Shannon, and W.C. Taylor, *Australian J. Chem.*, **18**, 226 (1965).

to revise their stereostructures to XI (C_{21}-αH) and XII (C_{21}-βH) respectively. Thus, the forced Huang–Minlon reduction of IX under the Nagata's procedure B[22] furnished a single hydrocarbon, mp 188—191°, identical with hopane[23] (GLC), while the other ketone X similarly afforded another single hydrocarbon, mp 188—190°, which was proved identical with isohopane (=moretane)[23] by GLC, although both of the conversions were proceeded with the most of the starting ketones recovered respectively.[24]

In conclusion, as is apparent from the discussion above, the present report offers a questionnaire on the hitherto believed carbon frameworks of hopane (XIII) and isohopane (XIV). Only anxiety, if any, of the presentation here lies in the low yield conversions of IX to XI and X to XII. Anyhow, the definite conclusion will be given by the X-ray analysis of a heavy atom induced derivative of 3,22-dihydroxyhopane, which is now in progress in this faculty.

Experimental[25]

Zeorin (II)——Zeorin used in this investigation was obtained from *Parmelia leucotyliza* Nyl.[1] and another lichen, *Anaptychia isidiophora* Vain,[26] which afforded zeorin and leucotylin from the neutral triterpenoid fraction with the yields of 0.77% and 0.36% respectively. Colorless needles from MeOH, mp 228—229°.

Zeorinone (VI)——Oxidation of zeorin (II) (1.2 g) with CrO_3 (260 mg)–AcOH (262 ml) mixture by keeping room temperature overnight followed by usual treatment yielded zeorinone (VI)[19] (870 mg) of melting at 238—241° (recrystallized with $CHCl_3$–MeOH).

Dehydration of Zeorinone (VI) with $POCl_3$ giving Zeorininone-a (VIII) and Zeorininone-b (VII)——To an ice-cooled solution of zeorinone (VI) (870 mg) in pyridine (40 ml) was added $POCl_3$ (4 ml) dropwise and the total mixture was allowed to stand room temperature one overnight. Checking the product by thin layer chromatography (TLC) (using silver nitrate impregnated silica gel G) disclosed that it contained two olefinic components and no more VI left. The crystalline precipitates (684 mg) obtained by treating the reaction mixture with ice–water was chromatographed on silver nitrate impregnated silica gel[13] (20 g) developing with *n*-hexane–benzene (10:1) and (3:1). From the earlier eluant zeorininone-a (VIII) was obtained (yield: 250 mg). Colorless needles, mp 196.5—197.5°, from $CHCl_3$–MeOH, positive to tetranitromethane test. *Anal.* Calcd. for $C_{30}H_{48}O$: C, 84.84; H, 11.39. Found: C, 84.61; H, 11.14. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1699 (CO). NMR (τ): 9.35, 9.12, 9.05, 8.97, 8.82, 8.72 (3H each singlet, total six methyls), 8.37, 8.22, (3H each singlet, $>C=C(C\underline{H}_3)_2$). The later eluant gave zeorininone-b (VII) (yield: 180 mg), mp 215—215.5° (colorless needles from $CHCl_3$–MeOH), positive to tetranitromethane test. *Anal.* Calcd. for $C_{30}H_{48}O$: C, 84.84; H, 11.39. Found: C, 84.65; H, 11.11. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1699 (CO), 1635, 889 ($>C=CH_2$). NMR (τ): 9.21, 9.13, 9.05, 8.97, 8.89, 8.72 (3H each singlet, total six methyls), 8.19 (3H singlet, $CH_2{=}\overset{|}{C}{-}C\underline{H}_3$), 5.18 (2H singlet, $H_3C{-}\overset{|}{C}{=}C\underline{H}_2$).

Hydrogenation of VII giving 22-Desoxy-zeorinone (IX)——A solution of zeorininone-b (VII) (80 mg) in EtOH (60 ml)–*n*-hexane (30 ml) mixture was shaken with PtO_2 (90 mg) under hydrogen atmosphere at room temperature until one mole of hydrogen was uptaken (6 hr). The product obtained after treatment in a usual manner was crystallized from EtOH yielding colorless leaflets of IX, mp 238—239°. *Anal.* Calcd. for $C_{30}H_{50}O$: C, 84.44; H, 11.81. Found: C, 84.20; H, 11.72. IR ν_{max}^{KBr} cm^{-1}: 1704 (CO).

Hydrogenation of VIII giving 22-Desoxy-21βH-zeorinone (X)——A mixture of zeorininone-a (VIII) (125 mg), PtO_2 (120 mg) in AcOH (30 ml)–EtOAc (20 ml) was shaken under hydrogen atmosphere for 7 hr at room temperature. After usual treatment, the product giving practically single peak on GLC was crystallyzed from EtOH to give colorless needles of X, mp 204—207°. *Anal.* Calcd. for $C_{30}H_{50}O$: C, 84.44; H, 11.81. Found: C, 84.31; H, 11.77. IR ν_{max}^{KBr} cm^{-1}: 1704 (CO).

---

22) W. Nagata and H. Itazaki, *Chem. Ind.* (London), **1964**, 1194.

23) Kindly provided by Dr. Y. Tsuda of Showa College of Pharmacy, to whom the authors deepest thanks are due.

24) The carbonyl function at C_6 has been known[19] quite resistant to the reduction under the ordinary Huang–Minlon condition.

25) Melting points were taken on the Yanagimoto Micromelting-point Apparatus (a hotstage type) and recorded as read. The GLC data were taken by the Yanagimoto Gas Chromatograph Model GCG-3DH with FID.

26) I. Yosioka, *et al,* unpublished data.

Comparison of 22-Desoxy-zeorinone (IX), 22-Desoxy-21βH-zeorinone (X) and the Corresponding Monoketone derived from Leucotylin (I)[1]

	mp	IR	GLC (column: 1% SE–30 on chromosorb W) temp. 242°	temp. 240°
IX	238—239°	1704		14 min 18 sec
X	204—207°	1704	10 min 24 sec	
Monoketone (A) from leucotylin	207—208°	1704	10 min 24 sec	11 min 24 sec

Mixed melting point of X and (A) was 204—207°. TLC could not differenciate IX from X or (A).

Forced Huang-Minlon Reduction of IX to XI——A solution of IX (15 mg) in triethyleneglycol (8 ml) was refluxed with anhydrous hydrazine (5.2 ml), EtOH 5 ml, hydrazine dihydrochloride (1.34 g), for 5 hr (bath temp. 130°). The reaction mixture was then added with KOH (1.58 g) and the excess hydrazine was removed by setting downward condenser as usual followed by heating of the mixture for additional 4 hr with reflux (bath temp. 240—245°). The product obtained by treating the reaction mixture with ice-water was extracted with ether. TLC of the ether extract indicated that most of IX was recovered but a minor less polar compound produced. The minor product was then isolated by TLC giving XI (less than one mg, colorless needles from EtOH), mp 188—191°.[27]

Forced Huang Hinlon Reduction of X to XII——A mixture of X (mp 204—207°) (15 mg), anhydrous hydrazine (7 ml), hydrazine dihydrochloride (1.01 g) in triethyleneglycol (8 ml) was refluxed for 7 hr (bath temp. 160—168°). After adding KOH (1.56 g) and removing the excess hydrazine as above the mixture was refluxed for additional 4 hr (bath temp. 240—245°), poured into ice-water, extracted with ether. TLC of the ether extract also showed that the most of X was recovered except that a minor less polar compound was procdued. The product was isolated by TLC and crystallized from EtOH giving colorless needles (XII, less than one mg), mp 188—190°.[27]

GLC Comparison of XI and XII with Hopane, Isohopane, IX and X——The comparison was performed under the condition below: column: 1% SE–30 on chromosorb W, 2 m, temp. 235°, carrier gas: N_2, flow rate 60 ml/min and the retention times were: XI and hopane: 12.8 min, XII and isohopane: 11.0 min, IX: 17.7 min, X: 14.0 min.

Acknowledgment The authors would like to express their sincere thankness to the members of the Analysis Room of this faculty for elementary analyses and spectral data, and to the Res. Lab. of Dainippon Pharmaceutical Co. for elementary analyses.

---

27) Although the hydrocarbons mentioned here are gas chromatographically pure, we were unable to raise their melting points as found in lit. 28) and 21), mp 213° for hopane and mp 192—194° for isohopane (=moretane) (both corrected values) respectively, due to the shortage of the material.

28) R.E. Corbett and H. Young, *J. Chem. Soc.* (*C*), **1966** 1556.