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The Oxidation of the Methyl Group at C-5 in Friedelin and Shionone

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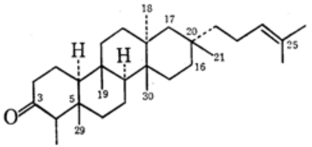
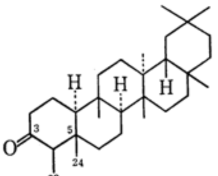
3β-Friedelanol (V, R=H) and 3β-shionanol (VIII, R=H) have been converted into γ-lactones, (VI) and (IX) respectively, either by lead tetraacetate-iodine oxidation followed by Jones' oxidation or by photolysis of their nitrites (V, R=NO and VIII, R=NO) followed by Jones' oxidation. These results confirm the presence of an axial methyl group at C-5 in friedelin (II) and shionone (I).

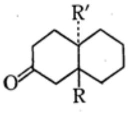
The structure (I)[*3] has been proposed[1a,1b] for shionone, a novel tetracyclic triterpene with a perhydrochrysene skeleton, on the following evidences; (a) the ORD and CD spectra of shionone are similar to those of friedelin (II), this means shionone has a *trans*-2-decalone ring system as



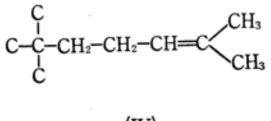
(I)



(II)



(III)



$C-\overset{C}{\underset{C}{C}}-CH_2-CH_2-CH=C\begin{matrix}CH_3\\CH_3\end{matrix}$

(IV)

Fig. 1.

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[*3] Nomenclature following biogenetic standpoint is applied here.

1) a) F. Patil, G. Ourisson, Y. Tanahashi and T. Takahashi, *Bull. Soc. Chim. France,* **1964**, 1422. b) Y. Tanahashi, Y. Moriyama, T. Takahashi, F. Patil, J.-F. Biellmann and G. Ourisson, *ibid.,* **1966**, 1670.

2) a) Y. Tanahashi, T. Takahashi, F. Patil and G. Ourisson, *ibid.,* **1964**, 584. b) P. Witz, H. Hermann, J.-M. Lehn and G. Ourisson, *ibid.,* **1963,** 1101. c) M. Takahashi, W. Kamisako, Y. Koyama and K. Miyamura, *J. Pharm. Soc. Japan,* **80**, 592 (1960).

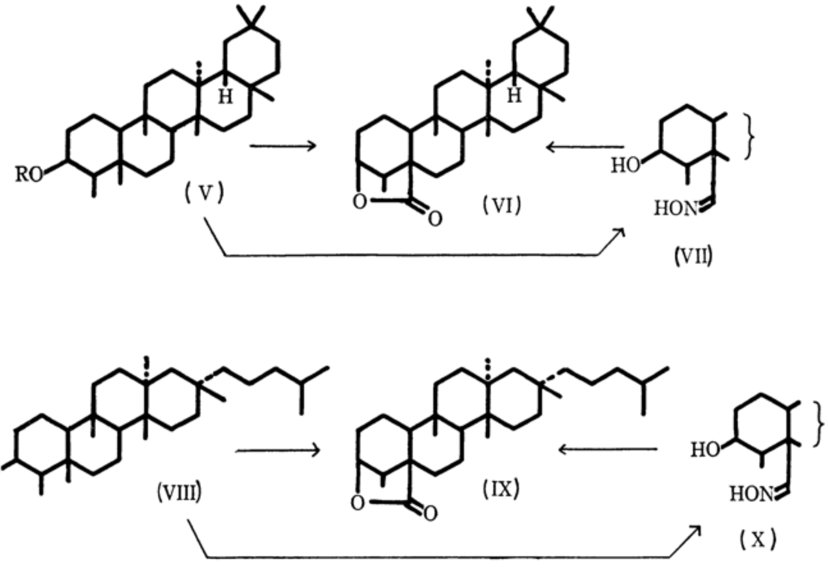

Fig. 2.

shown in (III),2) (b) chemical degradations coupled with spectral studies suggest B/C trans ring fusion1b) and an unusual side chain(IV),1,3,4) (c) the NMR spectrum of shionone in deuteriobenzene shows the presence of five tertiary methyl groups, two allylic methyl groups and one secondary methyl group; the latter has shown to be located at C-4 by degradative work.2a) Structure I is the only one that accounts for these facts and the modern biogenetical theory of higher terpenoids.

During the chemical degradation of shionone, we have attempted to prove the presence of an axial β-methyl group at C-5 in shionone; this aspect comprises the subject of this paper. Later, the NMR method was successfully applied to locate an axial methyl group on C-5.3)

There are many well known procedures for the oxidation of an angular methyl group which is situated at 1, 3-positions with respect to oxo- or axial hydroxyl groups.5a) We have carried out (a) lead tetraacetate-iodine oxidation5b) and (b) photochemical rearrangement of a nitrite according to Barton.5c)

At first, 3β-friedelanol (V, R=H) was subjected to these oxidations.6) 3β-Friedelanol (V, R=H) in cyclohexane was treated with lead tetraacetate in the presence of iodine and calcium carbonate under irradiation,7) followed by oxidation with Jones' reagent.8) The reaction mixture which showed many spots on thin layer chromatogram (TLC), furnished the γ-lactone, 3β-hydroxyfriedelan-24-oic acid lactone (VI), in a yield of 22% after separation by column chromatography and preparative TLC. On the other hand, 3β-friedelanol was converted into its nitrite (V, R=NO), and the nitrite was photolysed9) in benzene to furnish the rearranged product, 24-hydroxyimino-3β-friedelanol (VII). Jones' oxidation of this oxime (VII) yielded the same γ-lactone (VI). The structure of the γ-lactone was confirmed by its IR band at 1765 cm^{-1}, and by the disappearance of one methyl signal in its NMR spectrum.10) The nitrite procedure was better suited for obtaining the pure lactone because of easier separation of the product in each step. Anyhow, both methods were found to be suitable to prove the presence of an axial methyl group at C-5 in friedelane-type compounds.

Then, 3β-shionanol (VIII, R=H)2a) was subjected to the oxidation as in the case of 3β-friedelanol (V, R=H). The lead tetraacetate procedure furnished the γ-lactone, 3β-hydroxyshionan-29-oic acid lactone (IX) in a yield of 20%, while the Barton procedure furnished the same

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3) Y. Tanahashi, Y. Moriyama, T. Takahashi, F. Patil and G. Ourisson, *Bull. Soc. Chim. France,* **1966**, 2374.

4) W. Kamisako and M. Takahashi, *J. Pharm. Soc. Japan,* **85**, 888 (1965).

5) a) For example, C. Djerassi (ed.), "Steroid Reactions," Chap. 8, Holden-Day Inc., San Francisco (1963). b) K. Heusler and J. Kalvoda, *Angew. Chem.,* **76**, 518 (1964). c) A. L. Nussbaum and C. H. Robinson, *Tetrahedron,* **17**, 35 (1962).

6) In a preliminary form: T. Fukuda, T. Tsuyuki, Y. Tanahashi and T. Takahashi, This Bulletin, **38**, 1808 (1965).

7) K. Heusler, J. Kalvoda, P. Wieland, G. Anner and A. Wettstein, *Helv. Chim. Acta,* **45**, 2575 (1962).

8) K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.,* **1946**, 39.

9) D. H. R. Barton, J. M. Beaton, L. E. Geller and M. M. Pechet, *J. Am. Chem. Soc.,* **83**, 4076 (1961).

10) NMR spectra of friedelin derivatives will be discussed in a separate paper.

product in a smaller yield. The γ-lactonic nature of the product was confirmed by its IR and NMR spectra.

Thus, the presence of an axial β-methyl group at C-5 in shionone was confirmed. This result adds a further strong support to the proposed structure (I) of shionone.

Experimantal[*4]

Lead Tetraacetate Oxidation of 3β-Friedelanol (V, R=H). To cyclohexane (400 m*l*), boiled with lead tetraacetate (12 g, 27 mmol) and calcium carbonate (5 g) for 10 min, 3β-friedelanol (V, R=H, 2 g, 4.7 mmol) and iodine (2.6 g, 10 mmol) were added and heated under reflux with stirring under irradiation using a 250 W lamp. When the reaction was continued for 80 min, the purple color faded. To the reaction mixture, ether (*ca.* 1 *l*) was added and filtered. The precipitate was washed with ether and the washing was combined with the filtrate. The ether layer was washed with 10% sodium thiosulfate solution and then worked up in a usual manner. A yellow oily residue was dissolved in acetone (80 m*l*), to which Jones' reagent8) (3.2 m*l*) was dropped and stirred for 1 hr at 0°C. After addition of water (200 m*l*), the oxidation products were extracted with ether. An oily residue, dissolved in petroleum ether, was subjected to a column chromatography (alumina, Merck, neutral, activity II, 100 g). Elution with petroleum ether - benzene (8 : 2—7 : 3) gave white crystals (870 mg) and further elution with petroleum ether - benzene (6 : 4—5 : 5) afforded white crystals (780 mg). The latter showed two spots on TLC, therefore, they were separated by preparative TLC (Merck, silica gel G, 1 mm thick). A component with R_f 0.41 was extracted and recrystallized from acetone to give 3β-hydroxyfriedelan-24-oic acid lactone (VI, 450 mg), mp 286—287°C, ν_{max}^{Nujol} 1765 cm^{-1}.

Found: C, 82.20; H, 11.19%; mol wt (mass spectrometry), 440. Calcd for $C_{30}H_{48}O_2$: C, 81.76; H, 10.98%; mol wt, 440.68.

A component with R_f 0.55, extracted and recrystallized from methanol, showed a γ-lactone carbonyl band at 1765 cm^{-1}, and had mp 242—243°C. Its structure was not identified because of lack of the material.

3β-Hydroxyfriedelan-24-oic Acid Lactone (VI) by Nitrite Procedure. Excess nitrosyl chloride was passed through a solution of 3β-friedelanol (V, R=H, 1 g, 2.33 mmol) in pyridine (400 m*l*) at room temperature for about 8 min. The brown colored solution was poured into a large amount of water and filtered. The white precipitate was washed with water and dried over phosphorus pentoxide. TLC showed that this nitrite (V, R=H, 973 mg.) contained a small amount of 3β-friedelanol. On recrystallization from petroleum ether, it had mp 261—263°C, ν_{max}^{Nujol} 1645 and 1610 cm^{-1} (nitrite).

Found: N, 3.02%. Calcd for $C_{30}H_{51}O_2N$: N, 3.06%.

3β-Friedelanyl nitrite (V, R=NO, 973 mg) was dissolved in dry benzene (300 m*l*). The solution, which maintained at about 20°C, was irradiated according to the Barton procedure,9) using a 100 W, high pressure mercury lamp with bubbling nitrogen. After 1 hr, the disappearance of the nitrite was confirmed by TLC and the benzene solution was passed through a column of silica gel (Davison, 200 mesh, 5 g). After elution with benzene-ether (60 : 1, 800 m*l*), 3β-hydroxy-24-hydroxyiminofriedelane (VII) was obtained by further elution with benzene-ether (3 : 1, 600 m*l*) and was recrystallized from acetone. It weighed about 436 mg and contained acetone as crystallizing solvent. The crystals were dried under reduced pressure at 70°C for 5 hr, mp 249.5—250°C, ν_{max}^{Nujol} 3570 and 3300cm^{-1}.

Found: N, 3.11%. Calcd for $C_{30}H_{51}O_2N$: N, 3.06%.

To the ice-cooled solution of the oxime (VII, 150 mg) in acetone (50 m*l*), Jones' reagent (1.2 m*l*) was dropped and stirred for 45 min. The saturated sodium hydrogen carbonate solution was added and the product was extracted with ether. Crude products (114 mg), showing three spots on TLC, were purified by passing through a column of silica gel (Davison, 200 mesh, 15 g). Elution with benzene - petroleum ether (3 : 1, 400 m*l*) yielded pure γ-lactone (VI, 32 mg), which was recrystallized from petroleum ether, mp 287—287.5°C. This lactone was identical with that obtained by lead tetraacetate procedure.

Lead Tetraacetate Oxidation of 3β-Shionanol (VIII, R=H). To cyclohexane (100 m*l*), lead tetraacetate (3 g, 7 mmol) and calcium carbonate (1.3 g) were added, and heated under reflux for 10 min. After addition of iodine (660 mg, 2.6 mmol) and 3β-shionanol (VIII, R=H, 528 mg, 1.2 mmol), the same treatment was followed as in the case of 3β-friedelanol.

The crude products, thus obtained, were purified by column chromatography. Elution with petroleum ether - benzene (6 : 4—5 : 5) furnished white crystals (136 mg), which were shown to be a mixture by TLC. By preparative TLC (coated with Davison silica gel in 1 mm thickness, developed with benzene), a component with R_f 0.40 was collected and recrystallized from methanol to give 3β-hydroxyshionan-29-oic acid lactone (IX, 105 mg), in white needles, mp 189.5—191°C, ν_{max}^{Nujol} 1765 cm^{-1}.

Found: C, 81.05; H, 11.44%; mol wt (mass spectrometry), 442. Calcd for $C_{30}H_{50}O_2$: C, 81.39; H, 11.38%; mol wt, 442.70.

3β-Hydroxyshionan-29-oic Acid Lactone (IX) by Nitrite Procedure. A solution of 3β-shionanol (VIII, R=H, 250 mg) in pyridine (30 m*l*) was swirled while nitrosyl chloride was passed into it at room temperature, until the brown color persisted. Evaporation of pyridine in vacuo, followed by addition of water (*ca.* 1 *l*) gave crystals in leaflet, which were filtered and washed with water. The crystals were dissolved in petroleum ether and dried over sodium sulfate. Concentration of the solution furnished 3β-shionanyl nitrite (VIII, R=NO, 260 mg), mp 100—104°C, ν_{max}^{Nujol} 1640, 1610, 905, 810 and 760 cm^{-1}.

Found: N, 2.89%. Calcd for $C_{30}H_{53}O_2N$: N, 3.05%.

A solution of the nitrite (VIII, R=NO, 170 mg) in dry toluene (25 m*l*) was irradiated by means of a 100 W high pressure mercury lamp with agitation by

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[*4] All melting points were measured on a hot block and are uncorrected. Mass spectra were measured using the Hitachi Mass Spectrometer, RMU-6D Type, at the Naka Works, Hitachi Ltd., to which company the authors' thanks are due.

nitrogen stream. After 2 hr, the completion of the reaction was confirmed by TLC. Crude oxime fraction was separated by column chromatography (silica gel, Davison, 200 mesh, 15 g), followed by preparative TLC (silica gel G, Merck, 0.75 mm thickness, developed with benzene-ether-methanol in the ratio of 8 : 2 : 0.05). A component with R_f 0.15 was extracted and recrystallized from petroleumether - methanol, giving rise to 3β-hydroxy-29-hydroxyiminoshionane (X, 50 mg), mp 222—223°C, ν_{max}^{Nujol} 3215, 3175 and 940 cm^{-1}.

Found: C, 78.10; H, 11.55; N, 3.05%. Calcd for $C_{30}H_{53}O_2N$: C, 78.37; H, 11.62; N, 3.05%.

To a solution of the oxime (X, 40 mg) in acetone (10 m*l*), maintained at 0°C, Jones' reagent (0.5 m*l*) was added and stirred for 30 min. After addition of water, the product was extracted with ether. The residue, after evaporation of solvent, was separated by preparative TLC (silica gel G, Merck, 1 mm thickness, developed with benzene). A component with R_f 0.40 was extracted and recrystallized from methanol to afford γ-lactone, mp 190.5—191.5°C, which was identical with the γ-lactone prepared by lead tetraacetate procedure in respect to the melting point, IR spectrum and R_f value on TLC.