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# 4-Epifriedelin and 4-Epishionone. Structure and Reflex Effect[1]

Reiko Aoyagi, Shūzō Yamada, Takahiko Tsuyuki, and Takeyoshi Takahashi

*Department of Chemistry, Faculty of Science, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo*

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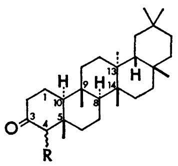
4-Epifriedelin (III) and 4-epishionone (VII) were prepared by photoepimerization of friedelin (I) and shionone (VI), respectively. On base treatment, III and VII were completely isomerized into I and VI, respectively; this observation was discussed based on reflex effect.

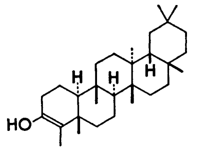
Friedelin (I), a pentacylic triterpene bearing 3-oxo-4-methyl substituents in A-ring, is widely distributed in the plant kingdom.[2] Especially it is well-known as one of the major constituents of cork.

Biosynthetic pathway of friedelin from squalene has been described.[3] Friedelin in enol form (II) may be derived from the protonated β-amyrin type intermediate by a sequence of 1,2-shifts of methyl groups and hydrogen atoms, followed by deprotonation in the last step.[3] It is, therefore, reasonable that the formation of 4α(axial)-methyl epimer (III, 4-epifriedelin) as well as that of friedelin (I) would be expected. Friedelin and several friedelin derivatives have been isolated from a large number of plants. However, isolation of 4-epifriedelin (III) from natural source has never been reported.

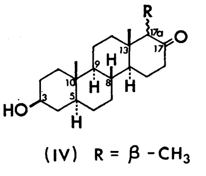
Ramirez and Stafiej described that D-homosteroid (IV) and its 17aα-methyl epimer (V) existed in a ratio of 70 : 30 under equilibrating conditions.[4] On the other hand, Ourisson *et al.* showed that friedelin (I) did not contain 4-epifriedelin (III) at equilibrium and this observation was explained by reflex effect.[5] The deformation of ring B caused by 1,3-diaxial interaction between the 5β- and 9β-methyl groups of III produces reflex effect which brings the 4α-methyl group nearer to the 10α-hydrogen atom, resulting in destabilization of III.[5] In the 17aα-methyl epimer (V), the corresponding 1,3-diaxial interaction (between 13β-methyl and 8β-hydrogen) should cause the reflex effect less severe.[5] These considerations were also supported by the equilibrating experiment on shionan-3-one (VI, with saturated side chain) with alkali; the 4α-epimer (VII, with saturated side chain) was not detectable at equi-



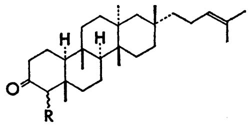
(I) R = β-CH$_3$
(III) R = α-CH$_3$



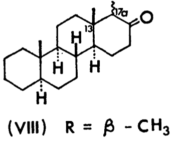
(II)



(IV) R = β-CH$_3$
(V) R = α-CH$_3$



(VI) R = β-CH$_3$
(VII) R = α-CH$_3$



(VIII) R = β-CH$_3$
(IX) R = α-CH$_3$

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[1] A preliminary account of this paper: T. Tsuyuki, R. Aoyagi, S. Yamada, and T. Takahashi, *Tetrahedron Lett.*, **1968**, 5263.

[2] *Cf. e. g.*, P. Boiteau, B. Pasich, and A. R. Ratsimamanga, "Les Triterpénoides en Physiologie végétale et animale," Ganthier-Villars, Paris (1964), p. 174.

[3] A. Eschenmoser, L. Ruzicka, O. Jeger, and D. Arigoni, *Helv. Chim. Acta*, **38**, 1890 (1955).

[4] F. Ramirez and S. Stafiej, *J. Amer. Chem. Soc.*, **77**, 134 (1955); **78**, 644 (1956).

[5] C. Sandris and G. Ourisson, *Bull. Soc. Chim. Fr.*, **1958**, 1524; *cf.* E. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, (1965), p. 345.

librium.[6a] This seems, therefore, to be the reason why neither the preparation of III[7] (and VII) nor the isolation of III (and VII) from natural source has yet been described.

In order to verify the exertion of the reflex effect in 4-epifriedelin (III) and 4-epishionone (VII), equilibration of these two compounds, as well as that of 17a$\beta$- and 17a$\alpha$-D-homo-5$\alpha$-androstan-17-ones (VIII and IX) as comparative compounds, was examined.

We have briefly reported a photochemical reaction of I in ethanol, in which III has been isolated together with A-norfriedelane, ethyl 3,4-seco-friedelan-3-oate, friedelin and 3$\beta$- and 3$\alpha$-friedelanols.[8] Friedelin (I) in ethanol, *n*-hexane or diethyl ether was irradiated with a high pressure mercury lamp under a nitrogen atmosphere at room temperature. The reaction products were subjected to silica gel column chromatographic separation and a ketone fraction was collected. The ketone fraction consisted of two components; the tlc examination showed two spots. A ketone with $R_f$ 0.52 was shown to be identical with I. The other ketone ($R_f$ 0.45), recrystallized from petroleum ether, showed mp 257.5°C, IR $\nu_{max}$ (Nujol) 1706 cm$^{-1}$. The molecular formula of $C_{30}H_{50}O$ was determined by the appearance of $M^+$ peak at *m/e* 426 in the mass spectrum, whose fragmentation pattern was very similar to that of I. These observations suggest that the photoepimerized ketone would be 4-epifriedelin (III). IR spectrum of III together with that of I is given in Fig. 1.

Further confirmation of the structure (III) was given by isomerization reaction of III. 4-Epifriedelin (III) in benzene was adsorbed on alumina overnight and then eluted with benzene to afford an isomerized product which was found to be identical (mp, mixed mp, IR, tlc and glc) with I, and no original ketone (III) was detectable by tlc examination. When silica gel was used no isomerization occurred. When III was treated with sodium methoxide in methanol–dioxane under reflux, it was completely isomerized to I. 4-Epifriedelin (III) was also thermally isomerized; on glc (Diasolid H–523, at 250°C) it gave two peaks at 36.6 and 41.1 min, due to III and I, respectively. These observations firmly confirm the Ourisson's reflex effect and lead to assignment of 4$\alpha$(axial)-methyl configuration (X) for 4-epifriedelin (III).

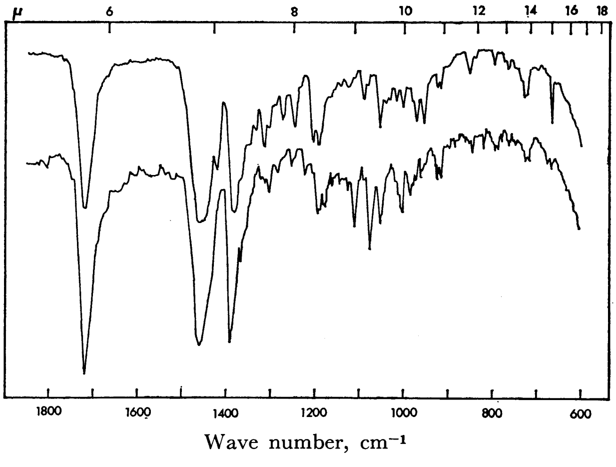
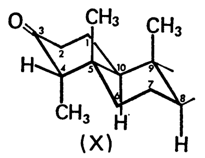
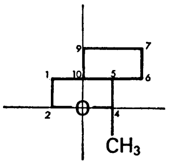


Fig. 1. IR spectra of friedelin (I, lower) and 4-epifriedelin (III, upper).

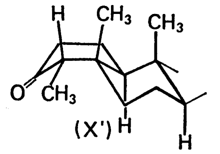
This assignment for III is compatible with optical rotatory dispersion (ORD) curve of III when compared with that of I(Fig. 2a). Both ORD curves show negative Cotton effect and the amplitude[9] of III ($a$=−43) is smaller than that of I($a$=−126). If one assumes a chair comformation such as X for both rings A and B, this evidence could be interpreted as that, while 4$\beta$-methyl group of I lies on octant plane, 4$\alpha$-methyl group of III contributes to the positive octant (Xa), resulting in reduction of absolute value of the amplitude for III. As positive Cotton effect is expected for conformations (X′ and X″) with ring A in boat form, these conformations can be excluded for III.



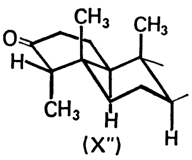
(X)



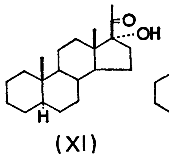
(Xa)



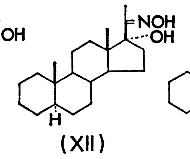
(X′)



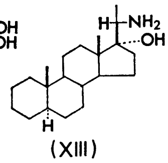
(X″)



(XI)



(XII)



(XIII)

4-Epishionone (VII) was prepared by photoepimerization of shionone (VI).[1] The same observations were obtained for VII as in the case of 4-epifriedelin (III), except the isomerization with alumina; VII was not isomerized with alumina. ORD curves of VI and VII are shown in Fig. 2b.

17a$\beta$- and 17a$\alpha$-methyl-D-homo-5$\alpha$-androstan-17-one (VIII and IX) were prepared as follows. Oximation of 17$\alpha$-hydroxy-5$\alpha$-pregnan-20-one (XI)[10] gave an oxime (XII), which on hydrogenation yielded 17$\alpha$-

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[6] a) Y. Tanahashi, T. Takahashi, F. Patil, and G. Ourisson, *Bull. Soc. Chim. Fr.*, **1964**, 584. b) Y. Moriyama, Y. Tanahashi, T. Takahashi, and G. Ourisson, *ibid.*, **1968**, 2890; T. Tsuyuki, T. Hoshino, M. Ito, and T. Takahashi, *ibid.*, **1968**, 2895; and the references cited therein.

[7] *Cf.* T. Brunn, *Acta Chem. Scand.*, **8**, 76 (1954). The corresponding hydrocarbon, "friedelane-II," was described. However, there seems to be lacking in spectral evidences to confirm this structure.

[8] T. Tsuyuki, S. Yamada, and T. Takahashi, This Bulletin, **41**, 511 (1968).

[9] The previously reported values (Ref. 1) were corrected by reinvestigation of ORD measurement.

[10] J. C. Danielwicz and W. Klyne, *J. Chem. Soc.*, **1962**, 4950.

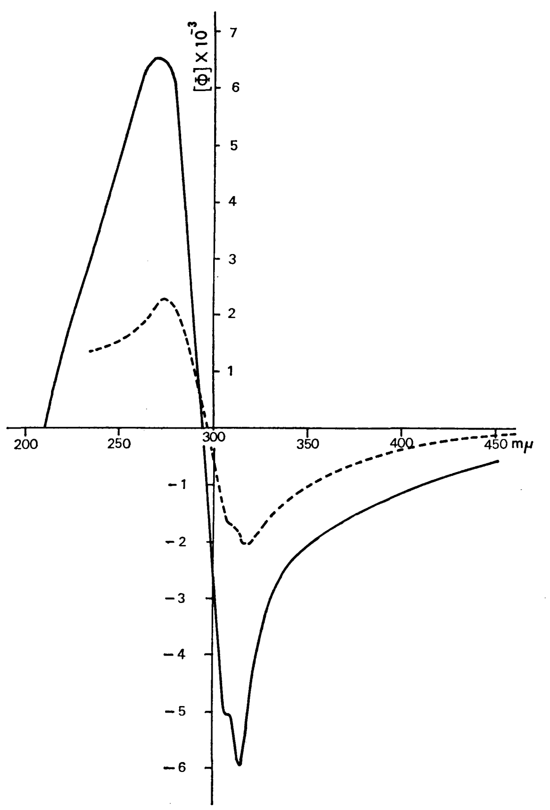

Fig. 2a. ORD curves of friedelin (I, solid line) and 4-epifriedelin (III, dotted line).

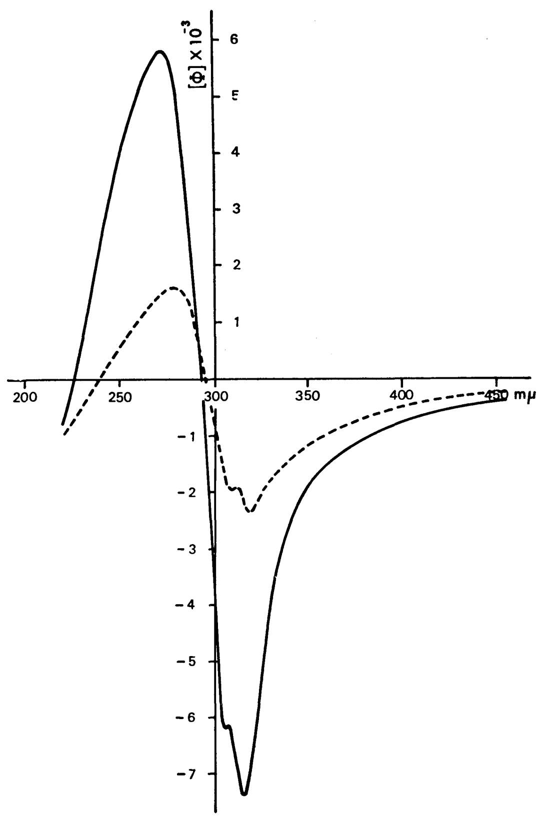

Fig. 2b. ORD curves of shionone (VI, solid line) and 4-epishionone (VII, dotted line).

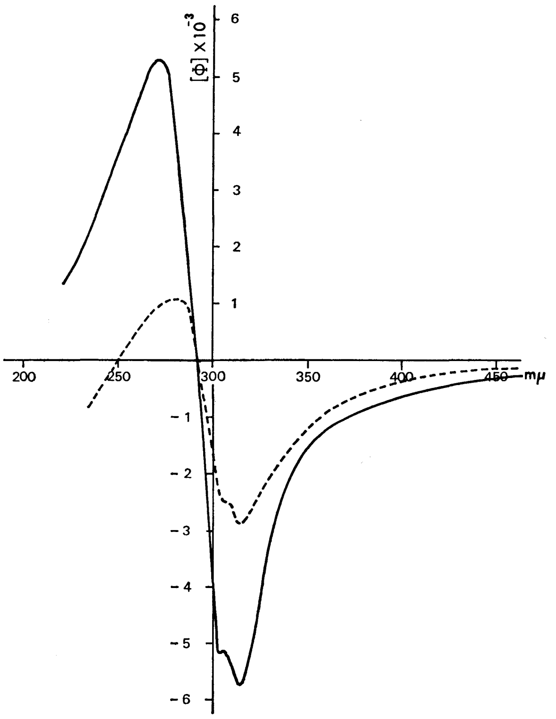

Fig. 2c. ORD curves of 17a$\beta$-methyl-D-homo-5$\alpha$-androstan-17-one (VIII, solid line) and 17a$\alpha$-methyl epimer (IX, dotted line).

hydroxy-20$\alpha$-amino-5$\alpha$-pregnane (XIII).[11] As in the case of the corresponding 3$\alpha$-hydroxy derivative[4] of XIII, when treated with nitrous acid XIII underwent the Demjanov ring enlargement to give 17a$\alpha$(axial)-methyl-D-homo-5$\alpha$-androstan-17-one (IX).[13] This ketone (IX) was treated with potassium hydroxide in ethanol under reflux to afford a mixture of 17a$\alpha$- and 17a$\beta$-methyl-D-homo-5$\alpha$-androstan-17-ones (IX and VIII). The same equilibrating mixture was also obtained by treatment of 17a$\beta$-methyl-D-homo-5$\alpha$-androstan-17-one (VIII) with alkali. The equilibrating mixture was separated into each component. ORD curves of VIII and IX are

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[11] The configuration at C-20 of XIII was deduced from the formation of 17a$\alpha$-methyl-D-homosteroid (IX) on nitrosation of XIII (*cf.* Ref. 4 and 12).

[12] D. N. Kirk and M. P. Hartshorn, "Steroid Reaction Mechanisms," Elsevier, Amsterdam (1968), p. 304.

[13] The location of ketone group on C-17 (not on C-17a) for IX was shown as follows. The mass spectrum of the ethylene ketal (XIV) of 17a$\beta$-methyl epimer (VIII) showed the presence of a characteristic peak at *m/e* 99 due to fragmentation "a" and absence of peak at *m/e* 113 due to fragmentation "b", which would be responsible for an alternative structure (XV). The 17a$\alpha$-(axial)-methyl configuration of IX was deduced from equilibration experiments.

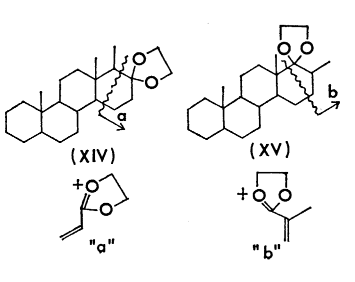

Table 1. PMR spectral data[a)]

| | | $\delta_{CDCl_3}$ | $\delta_{C_6D_6}$ | $\Delta$ | | $\delta_{CDCl_3}$ | $\delta_{C_6D_6}$ | $\Delta$ | | $\delta_{CDCl_3}$ | $\delta_{C_6D_6}$ | $\Delta$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| I | 4β-$CH_3$ | 0.87 | 0.97 | −0.10 | 5β-$CH_3$ | 0.72 | 0.63 | +0.09 | 9β-$CH_3$ | 0.87 | 0.74 | +0.13 |
| III | 4α-$CH_3$ | 1.11 | 0.86 | +0.25 | 5β-$CH_3$ | 0.87 | 0.69 | +0.18 | 9β-$CH_3$ | 0.92 | 0.85 | +0.07 |
| VI | 4β-$CH_3$ | 0.87 | 0.92 | −0.05 | 5β-$CH_3$ | 0.71 | 0.60 | +0.11 | 9β-$CH_3$ | 0.88 | 0.74 | +0.14 |
| VII | 4α-$CH_3$ | 1.11 | 0.86 | +0.25 | 5β-$CH_3$ | 0.90 | 0.74 | +0.16 | 9β-$CH_3$ | 0.90 | 0.83 | +0.07 |
| VIII | 17aβ-$CH_3$ | 0.87 | 0.98 | −0.11 | 13β-$CH_3$ | 0.60 | 0.51 | +0.09 | 10β-$CH_3$ | 0.72 | 0.66 | +0.06 |
| IX | 17aα-$CH_3$ | 1.08 | 0.85 | +0.23 | 13β-$CH_3$ | 0.81 | 0.70 | +0.11 | 10β-$CH_3$ | 0.77 | 0.66 | +0.11 |

a) Chemical shifts are expressed in $\delta_{ppm}$ downfield from TMS; $\Delta = \delta_{CDCl_3} - \delta_{C_6D_6}$.

given in Fig. 2c. The equilibrating mixture was shown to consist of 28% of 17aα- and 72% of 17aβ-isomers from ORD data. The fact that the amplitude of 17aα-methyl isomer (IX, $a=-40$) is smaller than that of 17aβ-methyl isomer (VIII, $a=-108$), indicates that 17aα(axial)-methyl group of IX contributes to the positive octant and 17aβ(equatorial)-methyl group of VIII lies on octant plane just as same as in the cases of friedelin and shionone series.

PMR spectral data of I, III, VI, VII, VIII, and IX are given in the Table. The solvent shift for a signal due to methyl group adjacent to carbonyl is well documented.[14)] Each of 4α-, 4α- and 17aα-methyl resonances of III, VII and IX, respectively, suffers an appreciable upfield shift ($\Delta=\delta_{CDCl_3}-\delta_{C_6D_6}=+0.23\sim+0.25$ ppm) on passing from deuteriochloroform to deuteriobenzene solution, showing that these methyl groups are in axial conformation. However, in I, VI and VIII, 4β-, 4β- and 17aβ-methyl resonances, respectively, suffer a small downfield shift ($\Delta=-0.05\sim-0.11$ ppm), suggesting an equatorial nature for these methyl groups. As to the other methyl signals, the solvent shifts ($\Delta$) of 5β- or 13β-methyl resonances are within $+0.09\sim+0.11$ ppm for I, VI or VIII, and within $+0.11\sim+0.18$ ppm for III, VII or IX. An upfield shift ($\Delta=+0.06\sim+0.14$ ppm) is observed for 9β- or 10β-methyl resonances of I, III, VI, VII, VIII or IX.

These observations exclude boat conformations of ring A for these six compounds, in agreement with the results obtained from ORD data. In conclusion, the most probable conformation of ring A of III and VII, and that of ring D of IX should be a deformed chair conformation.

## Experimental[15)]

*1. Friedelin Series.* *Isolation of 4-Epifriedelin (III).* Friedelin[2)] (I, 2.01 g) in ethanol (750 ml) was heated under reflux with introduction of nitrogen for 30 min and the resulting solution was irradiated with a high pressure mercury lamp under a nitrogen atmosphere at reflux temperature. After evaporation of the solvent under reduced pressure, the residue was dissolved in petroleum ether-benzene (1 : 1) and passed through a column (silica gel, 60 g). The elution with the same solvent gave hydrocarbons, ethyl 3,4-seco-friedelan-3-oate, ketones, and 3β- and 3α-friedelanols. The ketone fraction consisted of two components. A ketone ($R_f$ 0.52) which was eluted from the column, was collected and recrystallized from ethyl acetate to give 788 mg of white crystals which were shown to be identical with friedelin (I) in every respect. Further elution with the same solvent gave another ketone ($R_f$ 0.45), which was recrystallized from petroleum ether to afford 4-epifriedelin (III, 53.7 mg, 2.7%); IR (Nujol): $\nu_{C=O}$ 1706 cm$^{-1}$; Found: C, 84.31; H, 11.97%. Calcd for $C_{30}H_{50}O$: C, 84.44; H, 11.81%. MS: *m/e* 426 ($M^+$), 341 [$(M-85)^+$] and 302 [$(M-124)^+$]; PMR ($CDCl_3$): δ 0.87, 0.92, 0.95, 0.99, 1.00, 1.04, 1.17 (each singlet due to *t*-$CH_3$), 1.11 ppm (d, $J=7.0$ Hz, *sec*-$CH_3$); PMR ($C_6D_6$): δ 0.69, 0.85, 0.94, 1.01, 1.03, 1.09, 1.22 (each singlet due to *t*-$CH_3$), 0.86 ppm (d, $J=6.0$ Hz, *sec*-$CH_3$), ORD: $[\Phi]_{589}$ 0°, $[\Phi]_{318}^{\text{trough}}$ −2070°, $[\Phi]_{309}$ −1680° (sh), $[\Phi]_{275}^{\text{peak}}$ +2280° and $[\Phi]_{214}$ +1180°. Friedelin (I, 1.00 g) in *n*-hexane (500 ml) was irradiated under the same conditions. By the same separation procedure, 4-epifriedelin (III, 47 mg, 4.7%) was isolated from the photoreaction mixture.

*Isomerization of 4-Epifriedelin (III) into Friedelin (I).*

*a) With Sodium Methoxide*: 4-Epifriedelin (III, 5 mg) in dioxane (5 ml) and methanol (5 ml) was heated under reflux with sodium methoxide under a nitrogen atmosphere for 5.5 hr. The residue, after removal of the solvent, was extracted with ether. The ethereal extract was dried over sodium sulfate. Tlc ($SiO_2$) examination showed only one spot with $R_f$ 0.52, which corresponded to that of friedelin. The presence of 4-epifriedelin (III) was not detectable.

The isomerized product was isolated by $SiO_2$ preparative tlc to give friedelin (I), which was identified with an authentic sample by mp, IR and glc.

*b) With Alumina*: 4-Epifriedelin (III) was dissolved in benzene and the solution was divided into two portions. Each portion was poured into alumina (Showa Chemical, neutral) and silica gel columns, respectively, and adsorbed overnight. On elution with benzene, friedelin (I) was isolated from the eluent from the alumina-packed column. In the benzene eluent from the silica gel column, no friedelin (I) was detected; 4-epifriedelin (III) was recovered unchanged.

*c) Thermal Isomerization in Gas Chromatography*: 4-Epifriedelin (III) in acetone was injected into a column packed with Diasolid H-523 at 250°C. There appeared two peaks; one peak at $t_R$ 36.6 min due to III was exceedingly weak compared with the other one at $t_R$ 41.1 min due to friedelin

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14) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day (1964), pp. 164—169.

15) IR and mass spectra were measured using Hitachi EPI-G2 and Hitachi RMU-6 spectrometers, respectively. PMR spectra were taken on a JEOL-JNM-C-60 spectrometer at 60MHz using TMS as an internal standard. ORD measurement was carried out on a JASCO ORD/UV-5 spectrometer in dioxane solution (*c*: 2 mg/ml). All melting points were determined on a hot block and reported uncorrected. Silica gel column and thin layer chromatographies were carried out on Wakogel C-200 (Wako Pure Chem.) and Kieselgel G nach Stahl (E. Merck), respectively.

(I).

*2. Shionone Series. Isolation of 4-Epishionone (VII)* A solution of shionone[6] (VI, 1.00 g) in *n*-hexane (500 ml) was irradiated under the same conditions (*cf.* friedelin series) for 7 hr. This procedure was repeated and the combined residue, after the solvent had been removed, was chromatographed on silica gel. By the same procedures described for friedelin series, shionone (VI, $R_f$ 0.52) and 4-epishionone (VII, $R_f$ 0.45) were isolated. The latter (VII) was purified by recrystallization from ethyl acetate to give 93.1 mg of 4-epishionone (4.7%), mp 153.5—154°C; IR (Nujol): $\nu_{C=O}$ 1706 cm$^{-1}$; Found: C, 84.63; H, 11.61%. Calcd for $C_{30}H_{50}O$: C, 84.44; H, 11.81%. MS: *m/e* 426 ($M^+$); PMR ($CDCl_3$): δ 0.90, 0.92 (each singlet due to 2×*t*-$CH_3$), 1.15 (s, *t*-$CH_3$), 1.11 (d, $J$=7.0 Hz, *sec*-$CH_3$), 1.60, 1.67 ppm $\left(\text{each singlet, } \mathrm{C{=}C}\begin{matrix}\diagup\mathrm{CH_3}\\ \diagdown\mathrm{CH_3}\end{matrix}\right)$; PMR ($C_6D_6$): δ 0.74, 0.98, 1.10 (each singlet, *t*-$CH_3$), 0.83 (s, 2×*t*-$CH_3$), 0.86 (d, $J$=6.5 Hz, *sec*-$CH_3$), 1.62, 1.70 ppm (each singlet, $\mathrm{C{=}C}\begin{matrix}\diagup\mathrm{CH_3}\\ \diagdown\mathrm{CH_3}\end{matrix}$); ORD: $[\Phi]_{589}$ −130°, $[\Phi]_{319}^{\text{trough}}$ −2370°, $[\Phi]_{310}$ −1990° (sh), $[\Phi]_{278}^{\text{peak}}$ +1620° and $[\Phi]_{220}$ −1010°.

*Isomerization of 4-Epishionone (VII) into Shionone (VI).*
*a) With Sodium Methoxide*: 4-Epishionone (VII, 5 mg) was dissolved in a mixture of dioxane (5 ml) and methanol (5 ml) and the solution was heated with sodium methoxide under a nitrogen atmosphere for 5.5 hr. The reaction products were worked up as usual and examined by silica gel tlc. The presence of VII was not detectable and the spot due to VI appeared on tlc.

*b) With Alumina*: 4-Epishionone (VII) in benzene was adsorbed on alumina and silica gel, respectively, for 24 hr. The compound eluted with benzene from each column was shown to be identical with the starting material (VII), by tlc. In the case of 4-epishionone (VII), it was shown that alumina did not bring about isomerization of VII.

*3. D-Homosteroid Series. 17α-Hydroxy-20-hydroxyimino-5α-pregnane (XII).* A mixture of 17α-hydroxy-5α-pregnan-20-one[10] (X, 1.69 g), ethanol (60 ml), hydroxylamine hydrochloride (4.0 g) sodium acetate (4.7 g) and water (20 ml) was heated under reflux for 6 hr. On evaporation of some amount of solvent followed by cooling, crystals precipitated from the concentrated solution. Recrystallization from ethanol gave the oxime (XII, 1.59 g), mp 212.0—212.5°C; IR (Nujol): 3450 cm$^{-1}$ (broad). Found: C, 75.55; H, 10.67; N, 3.94%. Calcd for $C_{21}H_{35}O_2N$: C, 75.63; H, 10.58; N, 4.20%.

*17α-Hydroxy-20α-amino-5α-pregnane (XIII).* 17α-Hydroxy-20-hydroxyimino-5α-pregnane (XII, 1.59 g) in acetic acid (180 ml) was hydrogenated in the presence of platinum oxide with addition of two drops of concentrated hydrochloric acid (*cf.* Ref. 4). After the acetic acid had been removed under reduced pressure, the residue was washed with chloroform and recrystallized from methanol. The product XIII gave one spot on tlc, mp 290°C (with decomposition), IR (Nujol): 3300 and 3260 cm$^{-1}$. From the chloroform washings, the starting material (XII, 50 mg) was recovered.

*17aα-Methyl-D-homo-5α-androstan-17-one (IX).* A solution of 17α-hydroxy-20α-amino-5α-pregnane (XIII, 318 mg) in acetic acid (15 ml) and water (13 ml) was kept at 0°C. To this solution was added dropwise, with stirring, a solution of sodium nitrite (1.0 g) in water (5 ml). The mixture was stirred for 4 hr at 0°C and allowed to stand at room temperature for 10 hr. The reaction mixture was filtered and the precipitate was washed with chloroform. The filtrate and the washings were combined and neutralized with aqueous sodium hydrogen carbonate solution (*cf.* Ref. 4). After an usual work-up, recrystallization from acetone yielded 181 mg of a ketone (IX), mp 138.0—138.5°C; IR (Nujol): 1710 cm$^{-1}$; Found: C, 83.26; H, 11.49%. Calcd for $C_{21}H_{34}O$: C, 83.38; H, 11.33%. MS: *m/e* 302 ($M^+$) and 230 [$(M-72)^+$; base peak]; PMR ($CDCl_3$): δ 0.77, 0.81 (s, *t*-$CH_3$), 1.08 ppm (d, $J$=7.0 Hz, *sec*-$CH_3$); PMR ($C_6D_6$): δ 0.66. 0.70 (s, *t*-$CH_3$), 0.85 ppm (d, $J$=7.5 Hz, *sec*-$CH_3$); ORD: $[\Phi]_{589}$ −170°, $[\Phi]_{318}^{\text{trough}}$ −2870°, $[\Phi]_{308}$ −2410° (sh), $[\Phi]_{280}^{\text{peak}}$ +1120°, and $[\Phi]_{234}$ −420°.

*17aβ-Methyl-D-homo-5α-androstan-17-one (VIII).* A solution of 17aα-methyl-D-homo-5α-androstan-17-one (XI, 91.6 mg) and potassium hydroxide (400 mg) in ethanol (47 ml) was refluxed under nitrogen for 16 hr. The solution was concentrated, treated with 1 M-hydrochloric acid and diluted with water. The precipitate was extracted with ether and the ethereal extract was washed with water, dried over sodium sulfate and evaporated to dryness giving rise to 88 mg of product. This showed two spots ($R_f$ 0.5 and 0.4) on silica gel tlc developed with benzene and the lower spot was found to be identical with that of the starting material (IX). The mixture was separated by silica gel column chromatography into 17aα-methyl epimer (IX, 16.8 mg) and 17aβ-methyl epimer (VIII, 69 mg). The 17aβ-methyl epimer (VIII) showed mp 143.5°C; Found: C, 83.51; 11.44%. Calcd for $C_{21}H_{34}O$: C, 83.38; H, 11.33%. MS: *m/e* 302 ($M^+$) and 230 [$(M-72)^+$; base peak]; PMR ($CDCl_3$): δ 0.62, 0.72 (s, *t*-$CH_3$), 0.87 ppm (d, $J$=6.0 Hz, *sec*-$CH_3$); PMR ($C_6D_6$): δ 0.51, 0.66 (s, *t*-$CH_3$), 0.98 ppm (d, $J$=7.0 Hz, *sec*-$CH_3$); ORD: $[\Phi]_{589}$ −180°, $[\Phi]_{312}^{\text{trough}}$ −5740°, $[\Phi]_{304}$ −4980° (sh), $[\Phi]_{270}^{\text{peak}}$ +5010° and $[\Phi]_{222}$ +1660°.

*Equilibration of 17aβ-Methyl-D-homo-5α-androstan-17-one (VIII) with Alkali.* 17aβ-Methyl-D-homo-5α-androstan-17-one (VIII, 11.3 mg) was treated with potassium hydroxide (100 mg) in ethanol (2 ml) and subjected to equilibration for 17 hr. The equilibrating products were extracted and the ketone fraction was washed with water, dried and used for ORD measurement. ORD: $[\Phi]_{589}$ −175°, $[\Phi]_{314}^{\text{trough}}$ −4980°, $[\Phi]_{303}$ −3930° (sh), $[\Phi]_{270}^{\text{peak}}$ +3930° and $[\Phi]_{230}$ +1130°. These data show that the equilibrated ketone mixture consisted of 28% of 17aα- and 72% of 17aβ-epimers. On preparative tlc separation, the equilibrating mixture gave 17aα-methyl epimer (IX, 2.6 mg) and 17aβ-methyl epimer (VIII, 7.4 mg).

*Ethylene Ketal (XIV) of 17aβ-Methyl-D-homo-5α-androstan-17-one (IX).* 17aβ-Methyl-D-homo-5α-androstan-17-one (VIII, 10 mg) was dissolved in benzene (10 ml) and heated under reflux with ethylene glycol (4 ml) and *p*-toluenesulfonic acid (150 mg) for 13.5 hr under a nitrogen atmosphere. The reaction products were subjected to silica gel column chromatography and the ethylene ketal (XIV, 6.7 mg, recrystallized from acetone), mp 163°C; MS: *m/e* 346 ($M^+$) and 99 (fragment "a", base peak), was obtained.