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# Cyclization of Polyenes. III[1] Cyclization of Squalene-oxides

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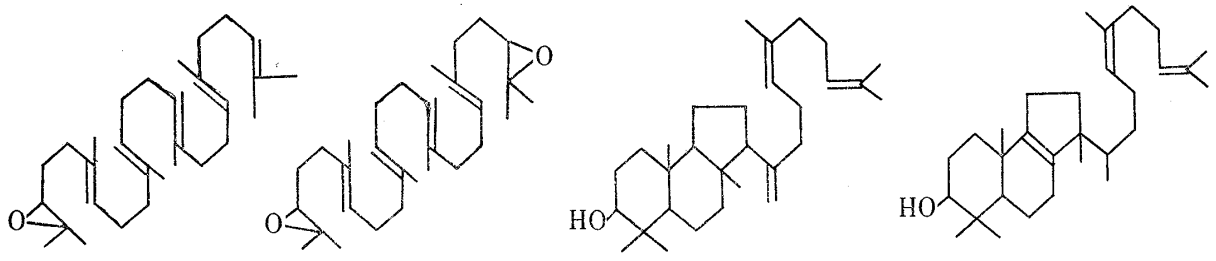
For the purpose of finding the optimum conditions of biogenetic-type synthesis of onocerin from squalene 2,3;22,23-dioxide (IV), acid-catalyzed cyclization ($BF_3$-etherate in water-saturated benzene) of squalene-2,3-oxide (I) was investigated to afford the compounds, III, V, VI, VII, VIII and IX.

The gross structure of these compounds was established by physical and chemical evidences. The cyclization of IV was also tried.

The interest in the biogenetic-type syntheses of some kinds of polycyclic terpenes have prompted us to investigate the acid-catalyzed cyclizations of the suitable polyenes including squalene-oxides[3] from the beginning of 1966. In those days little results concerning the laboratory cyclization of the oxide have been reported, even though the role of the squalene in the fields of the biosyntheses of triterpenes and steroids had been established.[4]

Recent biochemical tracer experiments have proved the intermediacy of squalene-2,3-oxide (I) in the biosyntheses of lanosterol[5] and other triterpene.[6] The non enzymic cyclization of the oxide with stannic chloride was also reported by van Tamelen, *et al.*[7] to afford the two tricyclic compounds, II and III.

During a search for optimum conditions on the biogenetic type synthesis of onocerin from squalene-2,3; 22,23-dioxide (IV), the present authors have independently found that the compound III was obtained from the 2,3-oxide by treatment with boron trifluoride-etherate in water-saturated benzene solution and a part of the results was reported in a preliminary communication.[8]




I IV II III

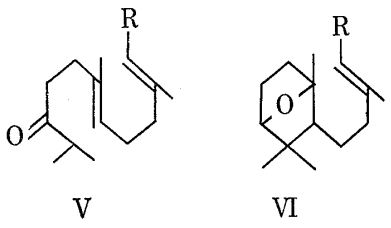
Chart 1

1) Part II of this series: S. Kanno, T. Kato and Y. Kitahara, *Chem. Commun.*, **1967**, 1257.
2) Location: *No.* 75, *Katahiracho, Sendai. a)* Present address: *Shionogi Research Laboratory, Shionogi Co., Ltd., Fukushima-ku, Osaka.*
3) E.E. van Tamelen and T.J. Curphey, *Tetrahedron Letters*, **1962**, 121.
4) R.G. Langdon and K. Bloch, *J. Am. Chem. Soc.*, **74**, 1869 (1952).
5) *a)* E.J. Corey and W.E. Russey, *J. Am. Chem. Soc.*, **88**, 4750 (1966); *b)* E.E. van Tamelen, J.D. Willet, R.B. Clayton and K.E. Lord, *ibid.*, **88**, 4752 (1966).
6) E.J. Corey and Paul R. Ortiz de Montellano, *J. Am. Chem. Soc.*, **89**, 3362 (1967).
7) E.E. van Tamelen, J. Willet, M. Schwarts and R. Nadeau, *J. Am. Chem. Soc.*, **88**, 5937 (1966).
8) M. Kishi, T. Kato and Y. Kitahara, *Chem. Pharm. Bull.* (Tokyo), **15**, 1071 (1967).

The present paper deals with the further investigations in the cyclization products from the oxide as well as the several trials of the biogenetic-type synthesis of onocerin.

**Cyclization of Squalene-2,3-oxide (I)**

Squalene-2,3-oxide (I) was treated with catalytic amounts of boron-trifluolide etherate in water-saturated benzene solution at room temperature and the reaction mixture was separated by silica-gel chromatography into ketone V, ether VI and alcoholic component with 9.3, 11.6 and 49.3% yield, respectively.



V VI

$R = -(CH_2 \cdot CH_2 \cdot CH=C(CH_3))_3-CH_3$

Chart 2

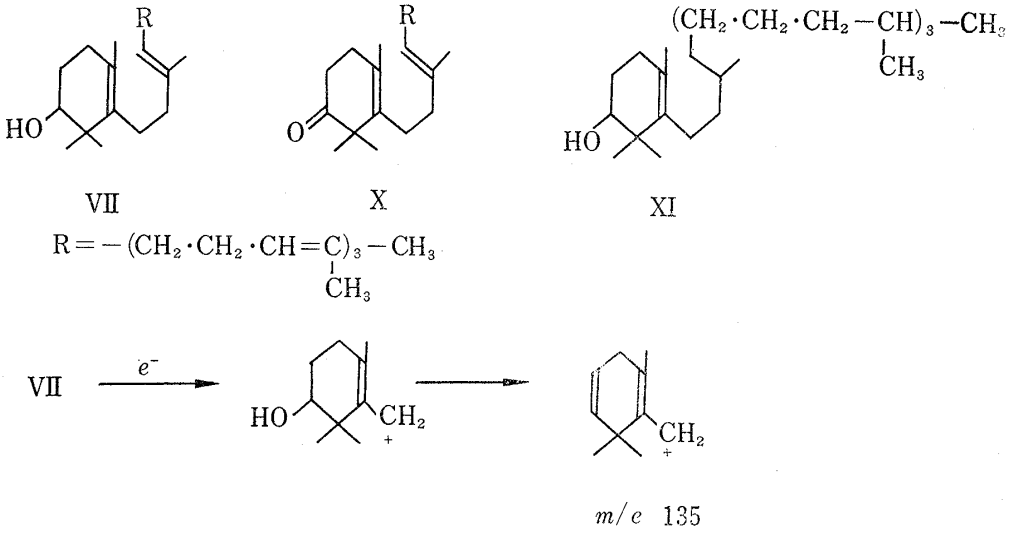
The alcoholic component was found to be the mixture and was further separated into four compounds VII, VIII, III and IX by the repeat of column chromatography with the different adsorbents.[9]

The gross structures of each component were deduced from the following spectroscopic and chemical evidences, respectively.

The compound V----$M^+$: *m/e* 426, IR: 1715 $cm^{-1}$ (carbonyl), NMR ($\delta$ ppm): 1.03 (6H, doublet, $J$=6.5 cps, methyls of isopropyl group), 1.55 (18H, singlet, methyls on double bond), 5.1 (5H, olefinic hydrogens).

The compound VI----$M^+$: *m/e* 426, IR: no absorption in the carbonyl and hydroxyl regions, NMR: 0.97 and 1.01 (3H each, singlet, tertiary methyls), 1.22 (3H, singlet, methyl geminal to an oxygen function), 1.55 (15H, methyls on double bond), 3.55 (1H, doublet, $J$=4 cps, hydrogen geminal to an oxygen), 5.1 (4H, olefinic hydrogens).

The compound VII----$M^+$: *m/e* 426, IR: 3350 $cm^{-1}$ (hydroxyl), NMR: 0.93 and 1.02 (3H each, singlet, tertiary methyls), 1.55 (18H, methyls on double bond), 3.34 (1H, doublet of doublets, $J$=5.0 and 7.5 cps, hydrogen geminal to hydroxyl group), 5.1 (3—4H, olefinic hydrogens). Oxidation of VII with chromium trioxide afforded the corresponding ketone X (IR: 1715 $cm^{-1}$, six-membered carbonyl) and on catalytic hydrogenation, VII was converted to the octahydroderivative XI ($M^+$: *m/e* 434, positive to tetranitromethane), the NMR spectrum of which showed no olefinic hydrogen. The presence of the strong peaks at *m/e* 135 in the mass spectra of both VII and XI support the assigned structure VII.



VII X XI

$R = -(CH_2 \cdot CH_2 \cdot CH=C(CH_3))_3-CH_3$

VII $\xrightarrow{e^-}$

*m/e* 135

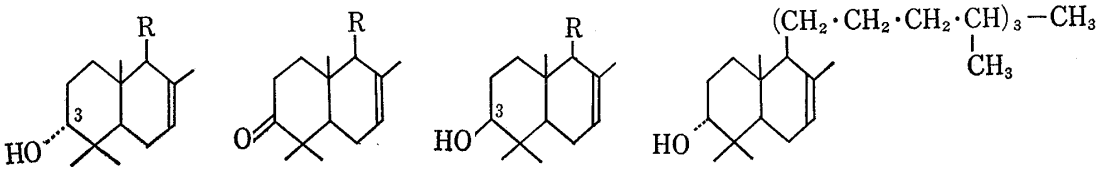
Chart 3

9) See experimental section.

The compound VIII——$M^+$: *m/e* 426, IR: 3350 $cm^{-1}$ (hydroxyl), NMR: 0.83, 1.04 and 1.05 (3H each, singlet, tertiary methyls), 3.31 (1H, doublet of doublets, $J$=2.0 and 3.0 cps, hydrogen geminal to the hydroxyl group), 5.03 (3H, olefinic hydrogens), 5.36 (1H, broad triplet, an olefinic hydrogen).

Conversions of VIII to the ketone XII (IR: 1712 $cm^{-1}$, six-membered carbonyl) and to the hexahydroderivative XIII ($M^+$: *m/e* 432) were carried out to support the bicyclic structure for the compound VIII. The NMR spectrum of XIII showed an olefinic hydrogen at 5.36 ppm, suggesting that the circumstance of one of the olefinic hydrogens of VIII is different from others. This sort of difference toward the catalytic hydrogenation was also observed in the double bond of compound IX.

The mass spectra of VIII (Fig. 1) and its hexahydroderivative XIII are quite similar and five intense peaks are observed, indicating that these fragment ions are derived from bicyclic skeleton. One of the possible features of fragmentations would be as follows.




VIII XII XIV XIII

R=-(CH₂·CH₂·CH=C)₃-CH₃ (H₃C)

Chart 4

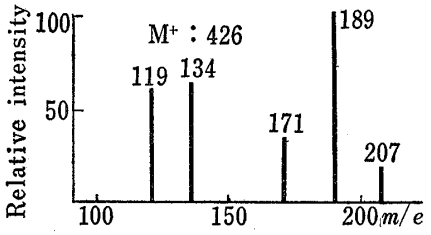



Fig. 1. Mass Spectrum of VIII

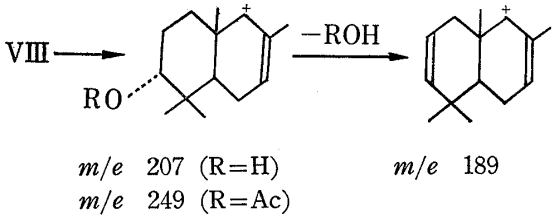
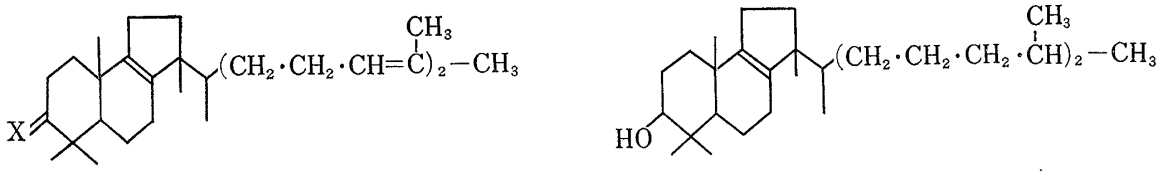



Chart 5

The aforementioned ketone XII was reduced with lithium tri-*tert*-butoxy aluminum hydride to the epimeric alcohol XIV, in the nuclear magnetic resonance (NMR) spectrum of which one hydrogen geminal to hydroxyl group appeared at 3.04 ppm as doublet of doublets with the coupling constants of 4.5 and 10 cps. Comparison of the chemical shifts and the coupling constants[10] of $C_3$-hydrogen of VIII and its epimer XIV suggests that the $C_3$-hydroxyl group of VIII has the axial configuration, while its epimer is equatorial, respectively.




III : X=OH, H
XV : X=O

XVI

Chart 6

10) *a*) N.S. Bhacca and D.H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, 1964, pp. 47, 51 and 77. *b*) J.I. Muscher, *J. Am. Chem. Soc.*, **83**, 1146 (1961).

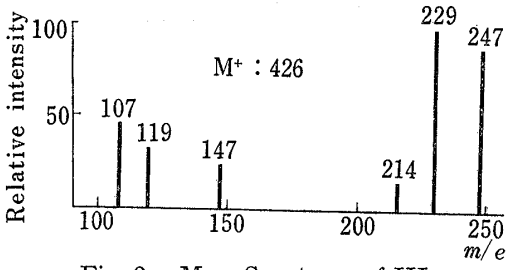



Fig. 2. Mass Spectrum of III

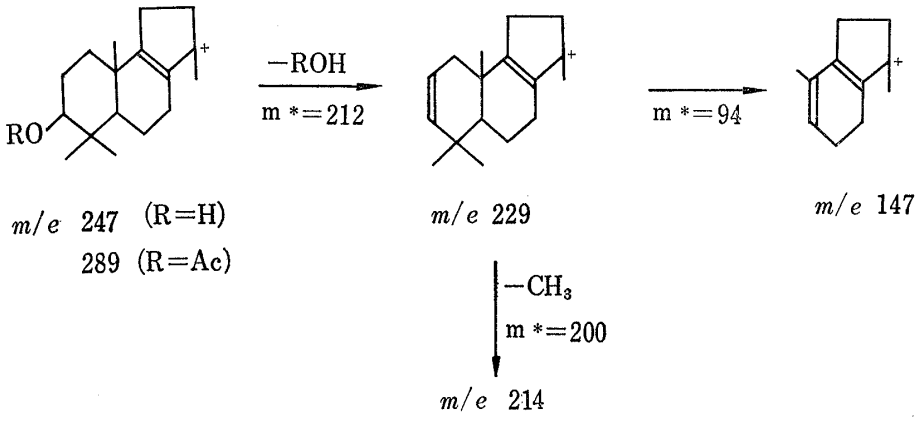


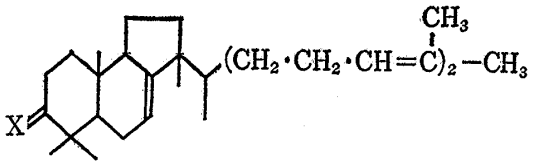

Chart 7

The compound III-----Mass: *m/e* 426 ($M^+$). IR: 3350 $cm^{-1}$, NMR: 0.8–1.1 (*ca.* 15 H, four tertiary methyls[11] and one secondary methyl), 3.08 (1H, doublet of doublets, $J$=6 and 8.5 cps, hydrogen geminal to hydroxyl group).

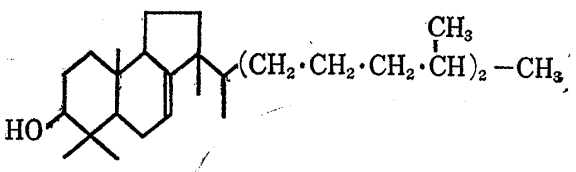
III was converted to the ketone XV (IR: 1708 $cm^{-1}$, six-membered carbonyl) and to the tetrahydroderivative XVI, ($M^+$: *m/e* 430). XVI was positive to tetranitromethane and showed no olefinic hydrogen in the NMR spectrum.

The fragmentations of III in its mass spectrum (Fig. 2) can be considered as shown above.

The compound IX-----Mass: *m/e* 426 ($M^+$), 247 and 229. IR: 3350 $cm^{-1}$, NMR: 0.7—1.0 (*ca.* 15H, four tertiary methyls and a secondary methyl), 5.0 (3H, olefinic hydrogen). IX was converted to the ketone XVII (IR: 1708 $cm^{-1}$) and to the tetrahydroderivative XVIII ($M^+$: *m/e* 430). The NMR spectrum of XVIII showed the presence of one hydrogen geminal to hydroxyl group at 3.03 as doublet of doublets with $J$=5.5 and 8 cps, and an olefinic hydrogen at 5.0 ppm.




IX : X=OH, H
XVII : X=O




XVIII

Chart 8

11) These assignments are confirmed by measuring the NMR spectrum in benzene solution.

The mass spectra of IX and III are similar indicating that IX and III have the same carbon skeletons.

**Cyclization Mechanism**

Although the formation of a new tricyclic compound was recognized[12] when the monocyclic alcohol VII was submitted to the same condition of cyclization as in the case of squalene 2,3-oxide, the rate of the formation of the new compound is quite slow as compared with those of the formation of the compounds III and IX. The isolation of a bicyclic alcohol with $C_3$-equatorial hydroxyl group could not be accomplished, III and IX might be transformed from the tricyclic intermediate XIX, which is most probably derived directly by the initiation of the ring opening with the concomitant stereospecific cyclization of squalene-2,3-oxide. The cyclization of the oxide and the migrations of hydride and methyl groups with stereospecificities are reasonably explained by assuming the chair, chair, boat conformation of the initial squalene-2,3-oxide as depicted below.

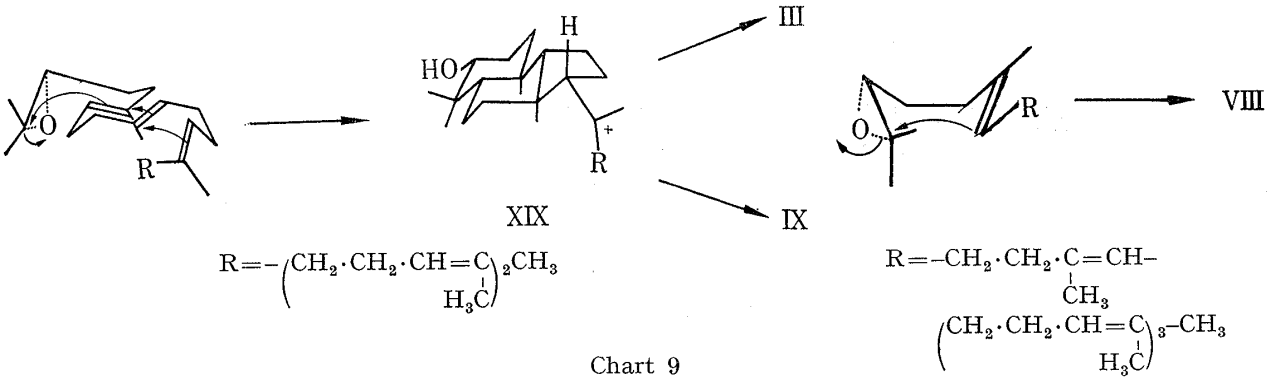



Chart 9

It is not apparent whether the monocyclic alcohol VII is the intermediate or not for the formation of the bicyclic alcohol VIII. However, the unexpected formation of the bicyclic alcohol with axial configuration of the $C_3$-hydroxyl group suggests one of the possible pathways of the formation of the A-ring of VIII would be the cyclization from the boat conformer of the oxide.

It is thus found that the laboratory cyclization of squalene-2,3-oxide proceeds stereospecifically to afford the cyclic compounds.

Applications of the same conditions to the squalene-2,3; 22,23-dioxide IV afforded the mixture, mainly the ketonic compounds. After several repeats of purification using column and thin-layer chromatography, a fraction having the same retention time and *Rf* values of gasliquid chromatography and thin-layer chromatography with $\beta$-onocerin was obtained. To our regret, however, the onocerin could not be isolated because of the low yield of the fraction (less than 1%).

## Experimental

Unless otherwise stated, NMR spectra were measured in $CS_2$ using TMS as an internal standard and mass spectra were measured at 200° and 25 eV by direct inlet method.

**Cyclization of Squalene-2,3-oxide (1)**——To 160 ml of water-saturated benzene was added 50 drops of boron trifluoride-etherate from capillary at 5° with stirring and the stirring was continued for 5 min. To this stirred mixture was added dropwise 7.25 g of (1) in 40 ml of water-saturated benzene at 5° and the reaction mixture was kept overnight at room temperature. The resulting mixture was poured into ice water and extracted with ether. The ether solution was washed with aqueous sodium bicarbonate solution and then water. After being dried over magnesium sulfate, the solvent was removed out to afford 7.1 g of brown oil which showed 4 spots on thin-layer chromatogram (TLC).

12) A tricyclic system was assigned by the mass spectrum, in which *m/e* 247 and 229, the characteristic fragment ions of III and IX, were also observed.

**Isolation of the Cyclized Products**——7.1 g of the above mentioned reaction mixture was dissolved in petroleum–ether and chromatographed on 140 g of silica gel. The continuous elutions with petroleum ether–benzene (1:1) gave the ketone V (0.68 g, 9.3%) and then the ether VI (0.84 g, 11.6%) with complete separation. The alcoholic components were eluted from benzene–ether (10:1), (3.5 g 49.3%).

**Purification of the Alcoholic Components**——The alcoholic components (3.5 g) were dissolved in benzene (30 ml) and chromatographed on 190 g of 20% silver nitrate–silica gel. Two fractions (A and B) were obtained by the elutions with the mixed solvents of 10% and then 20% ether in benzene, respectively. By the repetition of the infinitely developing preparative silica gel thin-layer chromatography (chloroform–*n*–hexane (4:1), developing time, 24 hr), VII (700 mg, 9.6%) and VIII (300 mg, 4.1%) were obtained from the fraction B. By the same methods (chloroform–benzene (3:1), developing time, 24 hr), III (415 mg, 5.7%) and IX (285 mg, 3.9%) were obtained from the the fraction A.

**Oxidation of the Alcohol VII**——To a stirred 2 ml of absolute pyridine was added 60 mg of chromium trioxide gradually at 0° and to this mixture was added dropwise 20 mg of VII in 1 ml of absolute pyridine at 0°. The resulting mixture was stirred for 5 hr at room temperature and then poured into ice water and extracted with ether. The ether solution was washed with 2N hydrochloric acid and then with water and dried over anhydrous magnesium sulfate. After evaporation of the solvent, the residue was dissolved in benzene–petroleum ether (7:3) and filtered through silica gel to give 9 mg of colorless oil X.

**Hydrogenation of VII**——10 mg of platinum dioxide in 2 ml of ethanol was shaken under hydrogen for an hour and to this was added 40 mg of VII in 1 ml of ethanol and then shaken under hydrogen overnight to absorb 11.0 ml (4.4 moles equivalent) of hydrogen at 18°. After the platinum dioxide was filtered off, the solvent was removed out to give 30 mg of colorless oil, XI.

Mass: *m/e* 434 ($M^+$).

**Tetranitromethane (TNM) Test of XI**——2 mg of XI was dissolved in 2 ml of carbon tetrachloride and to this was added one drop of TNM from capillary. The solution became yellow in contrast to the blank test.

**Oxidation of VIII**——By working up as described in VII, 20 mg of VIII gave 8 mg of colorless oil, XII.

IR: 1712 $cm^{-1}$.

**Reduction of XII with Lithium Tri-*tert*-butoxy Aluminum Hydride**——To a suspension of lithium tri-*tert*-butoxy aluminum hydride prepared from 18 mg of lithium aluminum hydride and 104 mg of anhydrous *tert*-butanol in 1 ml of anhydrous ether, 60 mg of the mixture of XII and X were added. After stirring at room temperature for 19 hr, the reaction mixture was poured into ice water and extracted with ether. The ether solution was washed with 2N hydrochloric acid and water and then dried over magnesium sulfate. After removal of the solvent, the residued oil was purified with silica gel chromatography to afford the colorless oil which consisted of VII and XIV.

**Hydrogenation of VIII**——40 mg of VIII in 3 ml of ethanol was subjected to the hydrogenation with 10 mg of platinum dioxide. VIII absorbed 6.3 ml (2.7 moles equivalent) of hydrogen at 25° to give 30 mg of colorless oil, XIII.

Mass: *m/e* 432 ($M^+$), 207 (21%), 189 (100%), 171 (45%), 134 (99%) and 119 (60%).

NMR: One olefinic hydrogen at 5.36 ppm.

**Acetylation of VIII**——10 mg of VIII was dissolved in 1 ml of absolute pyridine and to this was added 0.5 ml of acetic anhydride. The mixture was heated at 70° for 30 min. After evaporation of the solvent under diminished pressure, the residue was dissolved in benzene–petroleum ether (7:3) and filtered through silica gel to give 8 mg of colorless oil.

IR: 1735, 1250 $cm^{-1}$

Mass: *m/e* 468 ($M^+$), 249 (5%), 189 (70%), 171 (100%), 134 (75%) and 119 (65%).

**Acetylation of XIII**——3 mg of XIII were subjected to the acetylation (0.5 ml of absolute pyridine and 0.25 ml of acetic anhydride) to give 2 mg of colorless oil.

IR: 1735, 1250 $cm^{-1}$

Mass: *m/e* 474 ($M^+$), 249 (7%), 189 (51%), 171 (25%), 134 (100%) and 119 (60%).

**Oxidation of III**——30 mg of III was subjected to the oxidation with 60 mg of chromium trioxide in 3 ml of pyridine to afford 15 mg of colorless oil, XV.

IR: 1708 $cm^{-1}$

**Hydrogenation of III**——60 mg of III in 4 ml of ethanol was subjected to the hydrogenation with 10 mg of platinum dioxide. III absorbed 11.5 ml of hydrogen (3.5 moles equivalent) at 13° to give 58 mg of colorless oil, XVI.

Mass (70 eV): *m/e* 430 ($M^+$), 247 (90%), 229 (100%), 214 (14%), 147 (21%), 119 (31%) and 107 (37%).

**Acetylation of III**——10 mg of III was subjected to the acetylation with 0.5 ml of acetic anhydride in 1 ml of absolute pyridine to yield 8 mg of colorless oil.

IR: 1735, 1250 $cm^{-1}$.

Mass (70 eV): *m/e* 468 ($M^+$), 289 (61%), 229 (100%), 214 (9%), 147 (34%), 119 (86%) and 107 (61%).

**Acetylation of XVI**——10 mg of XVI was subjected to the acetylation to afford 7 mg of colorless oil.

IR: 1735, 1250 $cm^{-1}$.

Mass (70 eV): *m/e* 472 ($M^+$), 289 (66%), 229 (100%), 214 (9%), 147 (20%), 119 (34%) and 107 (25%).

**Oxidation of IX**——20 mg of IX was subjected to the oxidation to yield 8 mg of colorless oil, XVII.
IR: 1708 $cm^{-1}$.

**Hydrogenation of IX**——40 mg of IX in 3 ml of ethanol was subjected to the hydrogenation with 10 mg of platinum dioxide and IX absorbed 7.3 ml of hydrogen (3.0 moles equivalent) at 30° to yield 30 mg of colorless oil, XVIII.
Mass: *m/e* 430 ($M^+$), 247 (35%), 229 (100%).

**Acetylation of XVIII**——10 mg of XVIII was subjected to the acetylation with 0.5 ml of acetic anhydride in 1 ml of absolute pyridine to yield 8 mg of colorless oil.
IR: 1735, 1250 $cm^{-1}$.
Mass: *m/e* 472 ($M^+$), 289 (75%), 229 (100%).

**Isomerization of VII**——15 mg of VII in 0.4 ml of water-saturated benzene was treated with one drop of boron trifluoride–etherate from capillary as described in the cyclization of (1). 10 mg of pale yellow oil was obtained which showed 2 spots on silver nitrate–silica gel TLC. One spot was identical with VII and the other was very close to III or IX. The ratio of VII to the other was estimated to be nearly 10 to 1 by TLC.

**Cyclization of Squalene-2,3; 22,23-dioxide (IV)**——2.3 g of IV was dissolved in 120 ml of water-saturated benzene and to a stirred solution was added 50 drops of boron trifluoride–etherate dropwise from capillary at 0—5°. The resulting mixture was stirred for 8 hr at room temperature, poured into ice water and extracted with ether. The ether solution was washed with aqueous sodium bicarbonate solution and with water and then dried over anhydrous magnesium sulfate. The solvent was removed out to give 2.3 g of brown oil.

**Separation of Onocerin Derivative**——2.3 g of the reaction mixture was chromatographed on 70 g of silica gel. The fraction eluted with ether gave 320 mg of alcoholic substance which was further chromatographed on 50 g of silver nitrate–silica gel (2 times) to give 70 mg of colorless oil close to onocerin on TLC. Preparative TLC by infinite developing method (solvent benzene tetrahydrofuran 5:1, developed for 11 hr) gave three main fractions (C, 8 mg), (D, 10 mg) and (E, 6 mg). Fraction D contained a substance with the same *Rf* values (TLC and GLC) as the authentic *β*-onocerin.

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