

SERRATENEDIOL :

A NEW SKELETAL TRITERPENOID CONTAINING A SEVEN MEMBERED RING

Y. Inubushi, T. Sano and Y. Tsuda

Faculty of Pharmacy, Osaka University, Toyonaka, Osaka, Japan

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RECENTLY, the isolations of several new triterpenoids from some pteridophytes have been reported.⁽¹⁾ They may be classified as hopane or modified hopane group and have a close biogenetical relationship with α -onocerin which can also be isolated from Lycopodium clavatum,⁽²⁾ since the two were chemically interrelated by a simple transformation.⁽³⁾ Serratenediol is another new triterpenoid isolated⁽⁴⁾ from a kind of club moss, Lycopodium serratum THUNB. var. Thunbergii MAKINO. In this paper the complete structure of this triterpenoid is shown to be represented by (I).

We shall start elaborating the argument by showing that serratenediol has an entirely different skeletal structure from the triterpenoids known at present.

Serratenediol (I), m.p. 300°, $C_{30}H_{50}O_2 \cdot 1/2H_2O$ has two hydroxyl groups, (diacetate (II), $C_{34}H_{54}O_4$,* m.p. 336-338°) and a trisubstituted double bond (4.69 τ , 1H),*¹ hence the compound is pentacyclic. Oxidation of (I) with chromium trioxide-

* All compounds given by formulae in this communication gave correct elementary analysis.

*¹ All NMR spectra were taken on Varian A-60 machine in $CDCl_3$ with $SiMe_4$ as internal standard by Mr. T. Shingu, Kyoto University, to whom we express our thanks; UV spectra were measured in ethanol and IR spectra on nujol mull unless otherwise stated.

pyridine complex gave serratenedione (III), $C_{30}H_{46}O_2$, m.p. $209-210^\circ$, ν_{max} 1709 cm^{-1} . The inertness of (III) to the base suggested that the double bond in the molecule is separated from each carbonyl groups by more than two carbon atoms. Wolff-Kishner reduction of the diketone (III) gave an unsaturated hydrocarbon, serratene (IV), $C_{30}H_{50}$,^{*2} m.p. $237-239^\circ$, $[\alpha]_D -19^\circ$, which could be hydrogenated over Adams catalyst to give two stereoisomeric saturated hydrocarbons, $C_{30}H_{52}$, α -serratane, m.p. $198-200^\circ$, and β -serratane, m.p. $184-187^\circ$ in the ratio of about 1 : 20.

The striking feature of this triterpene is that serratenediol has seven methyl groups^{*3} in contrast to known triterpenoids which all have eight methyl groups or their equivalents, since the NMR spectrum of diacetate (II) showed methyl groups at 9.21 , 9.16 and $9.11\ \tau$ in the ratio of 1 : 5 : 1 together with two acetyl methyls at $7.97\ \tau$. This was not completely certain because of the overlapping some of these groups. However, this conclusion was confirmed from transformations described later. All methyl groups in serratenediol are quaternary because there was no occurrence of coupling in the derivatives presented in this communication, except (VIII).

Treatment of serratenediol (I), and its hydrogenation product, serratenediol (V), $C_{30}H_{52}O_2 \cdot H_2O$, m.p. $264-265^\circ$, with phosphorous pentachloride in benzene caused dehydration accompanied by ring contraction producing bis-isopropylidene derivatives (VI), $C_{30}H_{46}$, m.p. $221-223^\circ$, and (VII), $C_{30}H_{48}$, m.p. $184-186^\circ$. Confirmation of the number of methyl groups was provided from the NMR spectra of (VI) and (VII) which exhibited two peaks at 8.42 (6H) and $8.29\ \tau$ (6H) indicating the formation of two isopropylidene groupings. There remained three methyl groups above the $9.00\ \tau$ region, which appeared as singlets at 9.46 , 9.40 and $9.11\ \tau$ in (VI) and at 9.40 , 9.11 and

*2 Dr. H. Ageta (private communication) has also confirmed the molecular weight of serratene by mass spectroscopy.

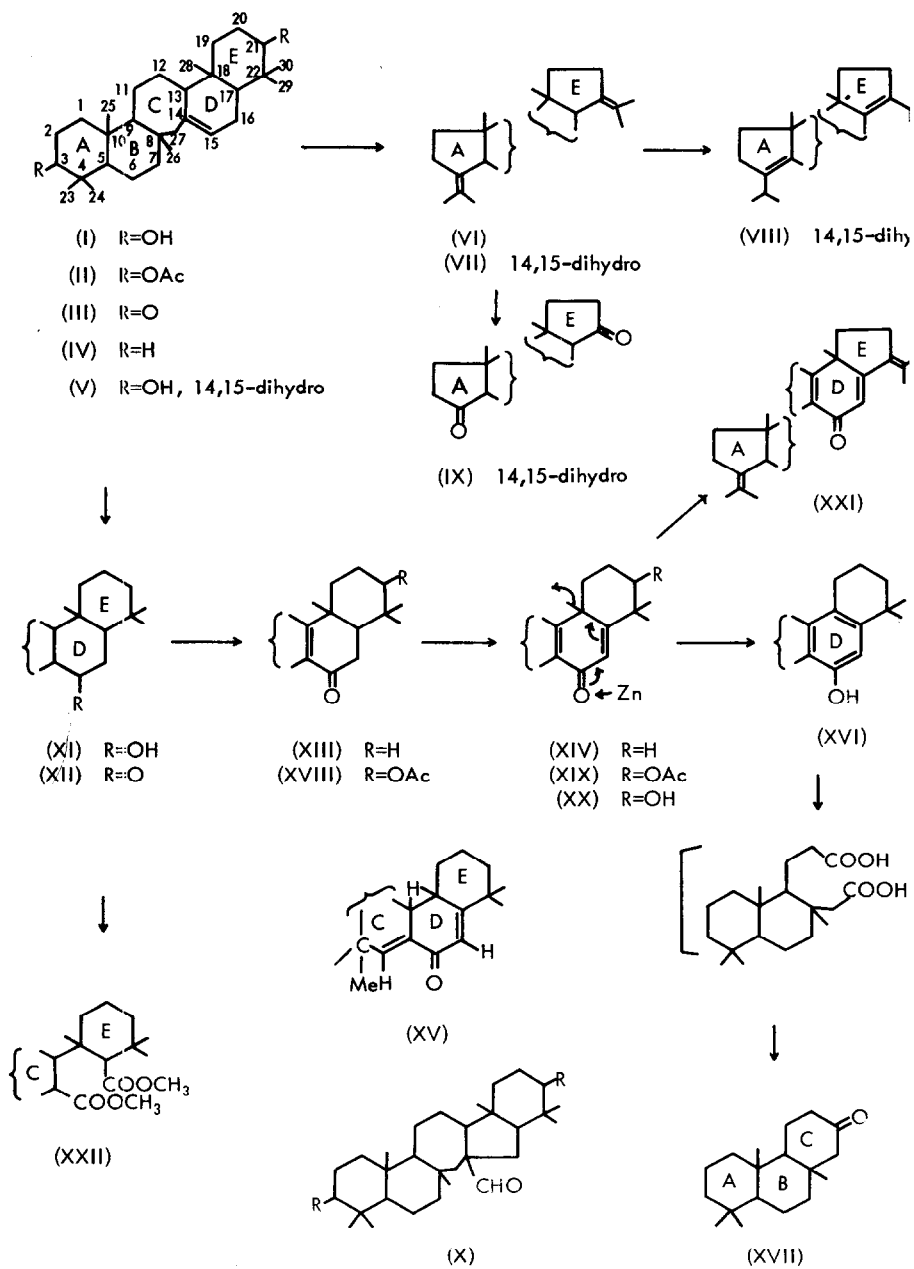
*3 Dr. H. Ageta (private communication) has also reached the same conclusion.

9.05 τ in (VII), and gave ratios exactly correspond to 1:1:1. No other methyl group could be found in the spectra. The bis-isopropylidene derivative (VII) when heated with 3% alcoholic hydrochloride rapidly isomerized to (VIII), $C_{30}H_{48}$, m.p. 119-121°, in which that the double bonds had migrated to the endo from the exo cyclic form was shown by regeneration of seven methyl groups above 8.90 τ in its NMR spectrum. Osmolation of (VII) and lead tetraacetate cleavage of the resulting tetra-ol gave acetone and C_{24} -diketone (IX), $C_{24}H_{36}O_2$, m.p. 173-176°. Single carbonyl absorption ($\nu_{\max}^{KBr} 1736 \text{ cm}^{-1}$) in IR of (IX) indicated that both the ketones formed are on five-membered rings. These transformations proved that both the terminal rings in serratenediol are six-membered and arranged as ring A in normal triterpenoid, e.g. β -amyrin, as represented in (I).

The trisubstituted double bond in serratenediol is probably far from the terminal rings, since neither the bis-isopropylidene derivative (VI), nor its acid isomerization product showed any conjugation in the UV spectra.

Attempts to form serratanone (XII) via peracid oxidation or ozonization were unsuccessful. The reaction unexpectedly resulted in an alkyl shift and produced an aldehyde (X).^{*4} However, hydroboration of serratene (IV) followed by peroxide oxidation and chromium trioxide-pyridine oxidation of the resulting alcohol (XI), $C_{30}H_{52}O$, m.p. 173-175°, furnished the desired ketone (XII), $C_{30}H_{50}O$, m.p. 202-204°, which on Wolff-Kishner reduction gave α -serratane indicating that no skeletal change took place during the above transformations. The IR spectrum of (XII) showed that the carbonyl formed must be on a six-membered or larger ring ($\nu_{\max} 1692 \text{ cm}^{-1}$). Methyl groups in this compound gave four peaks at 9.33, 9.20, 9.14 and 9.10 τ in

^{*4} We do not wish to discuss the structure and mechanism of formation of (X) in this communication. These will be presented in full publication.



ratio of 1:2:1:3.

Various oxidation studies on serratanone (XII) provided detailed information on the structure of ring D.

Nitric acid oxidation gave a dicarboxylic acid (dimethyl ester (XXII), $C_{32}H_{54}O_4$, m.p. 146-149°, ν_{\max} 1732 cm^{-1}) indicating the presence of a $-CO-CH_2-$ grouping in (XII).

Oxidation with selenium dioxide in acetic acid yielded three well defined compounds, (A), $C_{30}H_{48}O$, m.p. 247-249°, (B), $C_{30}H_{46}O$, m.p. 228-229°, and (C), $C_{30}H_{46}O$, m.p. 189-191° in yields of 16, 46 and 3%, respectively. They were separated from the reaction product by careful chromatography over silica gel and alumina.

Compound A is a conjugated ketone, λ_{\max} 259 $m\mu$ ($\log \epsilon$, 4.00), ν_{\max} 1645 and 1613 cm^{-1} , but showed no vinyl proton in the NMR spectrum, thus the double bond must be tetra-substituted. The same compound could be prepared in excellent yield from (XII) by bromination and dehydrobromination, or directly from serratene (IV) by sodium dichromate-acetic acid oxidation, though the yield was ca. 20%. Hence we can ascribe structure (XIII) to compound A. Methyl groups appeared as singlets at 8.97, 9.11 (6H), 9.15, 9.22, 9.26 and 9.35 τ .

Compound B had a λ_{\max} 256 $m\mu$ and a shoulder at 282 $m\mu$ ($\log \epsilon$, 4.13 and 3.67) and three strong absorptions at ν_{\max} 1647, 1623 and 1613 cm^{-1} . One vinyl proton was observed as a sharp singlet at 3.74 τ . Hence, it could be a dienone (XIV) which accordingly should be produced by further oxidation of (XIII). The correctness of this assignment was proved by further selenium dioxide oxidation of compound A to compound B, as the only isolable product, no other compound, e.g. compound C, being found in the mixture. The dienone (XIV) when heated with zinc dust in acetic

acid, spontaneously lost one methyl group and aromatized into a tetra-substituted phenol (XVI), $C_{29}H_{42}O$, m.p. 238-239°, λ_{\max} 285, 291 $m\mu$ ($\log \epsilon$, 3.45, 3.49), ν_{\max} 3484 (OH), 1600 and 1582 cm^{-1} (aromatic), NMR : 3.44 (1H, sharp singlet), 5.62 τ (OH, broad singlet, disappeared on D_2O treatment). As the reaction is well known in steroid and lanosterol chemistry,⁽⁵⁾ this aromatization unambiguously established the presence of a methyl group on the D/E ring juncture and also the structure of the ring with which we are concerned (ring D). In the NMR spectra below 9.00 τ region, the dienone (XIV) gave rise three methyl peaks at 8.73 (6H) and 8.77 τ and the phenol (XVI) at 8.75 and 8.78 τ , in contrast to serrataneone (XII), in which all the methyl groups appeared at above 9.10 τ . The low field shift (-0.3 ppm.) of these methyl groups suggested that the dienone or aromatic system may be situated at the α -position to one gem-dimethyl group on the terminal ring E. This relationship of ring D to ring E was rigidly established by ring contraction of serratadienediol (XX).

Oxidation of serratenediol diacetate (II) with sodium dichromate in acetic acid gave serratenediol diacetate (XVIII), $C_{34}H_{52}O_5$, m.p. 312-314°, λ_{\max} 256 $m\mu$ ($\log \epsilon$, 3.97), ν_{\max} 1650 and 1616 (C=C-CO), 1724 and 1250 cm^{-1} (OAc), NMR : no vinyl proton. Selenium dioxide oxidation of (XVIII) gave a dienone (XIX), $C_{34}H_{50}O_5$, m.p. 295-297°, λ_{\max} 248 $m\mu$, shoulder at 281 $m\mu$ ($\log \epsilon$, 4.20, 3.76), ν_{\max} 1647, 1613 and 1603 (dienone), 1724 and 1247 cm^{-1} (OAc), NMR 3.7 τ (1H, vinyl proton, sharp singlet). Hydrolysis of (XIX) and application of phosphorus pentachloride to the resulting diol (XX), $C_{30}H_{46}O_3 \cdot H_2O$, m.p. 296-298° gave a bis-isopropylidene derivative (XXI), $C_{34}H_{52}O$, m.p. 225-228°, in which one of the newly formed double bonds was evidently conjugated to the dienone system as shown by a marked bathochromic shift of its UV spectrum, λ_{\max} 276 and 320 $m\mu$ ($\log \epsilon$, 4.04 and 4.00). IR : ν_{\max} 1647, 1618 and 1597 cm^{-1} . NMR : 3.78 (1H, vinyl proton, singlet), 8.14 (6H), 8.43,

8.26 (C=C-CH₃), 8.88 (C=C- $\overset{|}{\underset{|}{\text{C}}}$ -CH₃), 9.34 and 9.48 τ ($-\overset{|}{\underset{|}{\text{C}}}$ -CH₃).

Compound C is isomeric to compound B, but its UV maximum was more bathochromic, λ_{max} 266 $m\mu$ (log ϵ , 4.11), and had two strong absorptions in the IR (1650 and 1597 cm^{-1}). The NMR spectrum in the vinyl proton region showed a sharp singlet at 3.89 τ and a clean doublet ($J=2.5$ c/s) at 3.35 τ , each corresponding to one proton. Coupling of the latter seems to be typical allylic coupling⁽⁶⁾ rather than attributable to an adjacent hydrogen. The methyl region of the spectrum provided further information of the structure. It clearly showed three high methyl groups at 9.20, 9.16 and 9.14 τ , and four low methyl groups at 8.97, 8.90, 8.83 and 8.79 τ . The low field shift of the fourth methyl group, in contrast to that in compound B (see above), suggested that this methyl group could also be a to the double bond, the remaining three high methyl groups, therefore, are most likely on ring A. We, hence extend the structure of compound C to (XV). In accordance with structure (XV) a clean doublet in (XIII) (7.25 τ , $J=13$ c/s) and in (XIV) (7.01 τ , $J=13$ c/s) which may be assigned to one component of AB-coupling of the C₂₇ methylene group was completely absent in compound C.

Confirmatory evidence of a seven-membered character of ring C was obtained from the following transformation of the phenol (XVI). Vigorous ozonization followed by peracid oxidation of the phenol (XII) gave a dicarboxylic acid which was pyrolysed into a ketone C₁₈H₃₀O, m.p. 156-158°. The ORD curve of this compound showed unambiguously its ketonic character by its typical peak at 314 $m\mu$, $[\alpha] +1700$ and IR absorption at 1721 cm^{-1} (in a KBr disc) confirmed that it is a cyclohexanone rather than a cyclopentanone. In the NMR spectrum two sharp peaks corresponding to four methyl groups were observed at 9.15 (6H) and 9.12 τ (6H). Therefore, the ketone must be represented by the structure (XVII).

There is no direct evidence about ring B. However, it is clear that from a consideration of triterpene biogenesis there is no other rational choice of structures for serratenediol except (I). The validity of structure (I) was proved by synthesis of serratenediol from α -onocerin. This will be presented in the forthcoming communication.

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