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4,4-Dimethyl Effect. (3). The Ring A Conformation of 4,4-Dimethyl-Δ^7-3-keto Steroids and 4,4,8-β-Trimethyl-3-keto Steroids (3-Keto-triterpenoids). The Crystal Structure of Serratenedione[1]

YOSHISUKE TSUDA,*,[a] NORIAKI KASHIWABA,[a] and TOSHIHIKO HORI[b]

Faculty of Pharmaceutical Sciences, Kanazawa University,[a] Takara-machi, Kanazawa 920, Japan, and Rigaku Denki Co., Ltd.,[b] Matsubara-cho, Akishima, Tokyo 196, Japan

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Single crystals of serratenedione grown in methanol are orthorhombic, $a=14.506$, $b=10.558$, $c=16.296$ Å, $U=2495.8$ Å^3, $D_c=1.17$ g/cm^3, $Z=4$, with space group $P2_12_12_1$. The structure, solved by use of the MULTAN program, revealed the conformation of the compound to be as follows: ring A, deformed boat; B, chair; C, chair-like; D, half-chair; and E, distorted chair. Circular dichroism (CD) spectra of 4,4-dimethyl-3-keto steroids with Δ^7 or an 8β-methyl group are discussed in connection with the above results.

Keywords——4,4-dimethyl effect; ring A conformation of 4,4-dimethyl-Δ^7-3-keto steroid; ring A conformation of 4,4,8β-trimethyl-3-keto steroid; 3-keto-triterpenoid; CD spectra of 4,4-dimethyl-3-keto steroid; X-ray analysis; deformed boat form

The conformation of ring A of 4,4-dimethyl-3-keto steroids has been a subject of continuing interest,[2] particularly in relation to their unique properties (so-called "4,4-dimethyl effect") in the CD (or optical rotatory dispersion (ORD)) spectra; the Cotton effect changes its sign depending on the substituent at ring B or structure difference at the ring B/C junction.[3] For solving this problem, various methods, such as dipole moment, CD or ORD, nuclear magnetic resonance (NMR), X-ray analysis, and empirical force field (EFF) or extended Hückel molecular orbital (EFF-EHMO) calculation, have been proposed and accordingly, at one time or another, various conformations such as chair, deformed (flattened) chair (sofa), equilibrating boat and chair, and deformed (twist) boat conformations have been suggested.[2] Among those methods, X-ray analysis[4] must be the most direct and reliable method, though the information obtainable is limited to the crystalline state; however, such conformations are very often comparable with the conformations in solution.[4b,5] At present, the consensus seems to be that the deformed chair is the most probable conformation for ring A of 4,4-dimethyl-3-keto-5α-steroids (I) provided that the compound carries no extra substituent at ring B. Such compounds always show negative CD curves. The compounds with Δ^7 and Δ^8, II and III, were also suggested to take a similar conformation.[2] However, these compounds exhibit opposite Cotton effect to each other, negative for II and positive for III,[3] and the reason for this remains unclear. The X-ray analysis of these compounds to obtain precise information on ring A is therefore required.

On the other hand, very little is known about the conformation of ring A of 4,4-dimethyl-3-

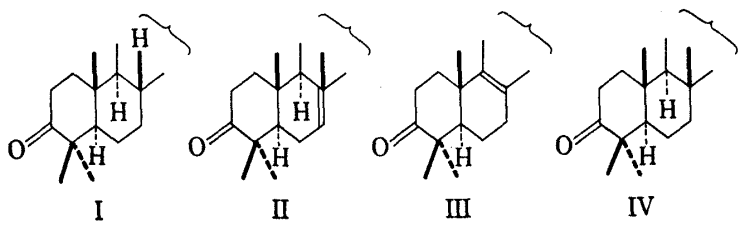
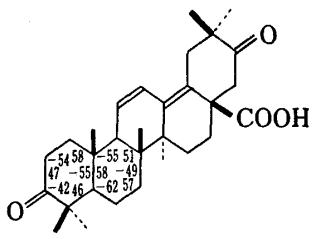


Chart 1



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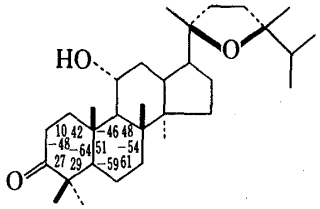

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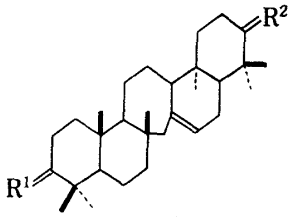


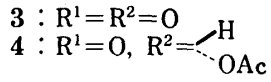
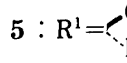
3 : $R^1=R^2=O$
4 : $R^1=O$, $R^2=$ 
5 : $R^1=$  , $R^2=O$

Chart 2

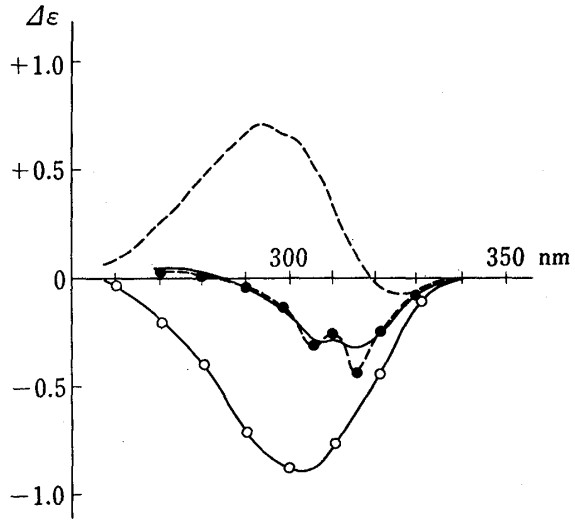


Fig. 1. CD spectra of 21α-Acetoxyserrat-14-en-3-one(4), 3β-Acetoxyserrat-14-en-21-one (5), and Serrat-14-ene-3,21-dione(Serratenedione)(3) in Dioxane

·····: 21α-Acetoxyserrat-14-en-3-one (4).
—○—: 3β-Acetoxyserrat-14-en-21-one (5).
···●···: 4+5 (calcd).
——: Serratenedione (3) (obs.).

keto steroids with an 8β-methyl group (IV). This partial structure is frequently encountered in triterpenoids. Undoubtedly, deformation of ring A due to conformational transmission originated by the creation of an additional 1,3-diaxial Me–Me interaction is expected and, in fact, such a deformation is suggested by the inversion of the Cotton effect from negative to positive.[3] Ourisson *et al.* have suggested a chair (70%)–boat 30(%) equilibrium[6] or deformed chair conformation[7] from dipole moment studies of 28-cyano-lupan-3-one. The same authors[3] again suggested a flattened chair conformation on the basis of comparisons of CD spectra of various 3-keto-triterpenoids and other 4,4-dimethyl-3-keto steroids. However, there are still some ambiguities, since dipole moment cannot in general be very accurately calculated from group moments and sometimes leads to an incorrect conclusion.[8]

Two X-ray analyses are now available, which surprisingly conflict with each other: papyriogenin-A (**1**)[9] has a chair, while alnuserol (**2**)[10] has a deformed boat conformation[11] at ring A.

Thus, we selected serratenedione (**3**)[12] for X-ray analysis. The compound has both 4,4-dimethyl-Δ^7-3-keto and 4,4,8β-trimethyl-3-keto systems at the opposite termini of one molecule and there is considered to be no mutual interaction between them, since the CD spectrum of serratenedione is very close to the arithmetic sum of the spectra of 21α-acetoxyserrat-14-en-3-one (**4**)[13] (positive curve) and 3β-acetoxyserrat-14-en-21-one (**5**)[14] (negative

curve) as shown in Fig. 1. Flexibility of the seven-membered middle ring presumably reduces the steric interactions between rings A/B and D/E. Hence, the conformations of ring E and ring A of serratenedione should reflect the ring A conformations of 4,4-dimethyl-Δ^7-3-keto and 4,4,8β-trimethyl-3-keto steroids, respectively.

Experimental

Crystallographic Measurements——Suitable crystals of serratenedione were grown in methanol as colorless prisms. A computer-controlled Rigaku Denki AFC-6A four-circle X-ray diffractometer was used for all measurements. The unit cell dimensions and orientation matrix were derived from a least-squares fit of the angular values of 19 reflections. The intensities of all the reflections in the range of $2\theta<135°$ were measured using the 2θ-ω scan technique. The scan speed was 2°/min for all reflections. Of 2581 reflections obtained by use of monochromated Cu-$K\alpha$ radiation, 2283 had $I>2\sigma(I)$ and were used in the calculation. No absorption correction was made.

Crystal Data——$C_{30}H_{46}O_2$, M=438.7. Orthorhombic, $a=14.506(5)$, $b=10.558(7)$, $c=16.296(7)$ Å, $U=2495.8$ Å^3, $D_c=1.17$ g/cm^3, $Z=4$; μ(Cu-$K\alpha$)=5.0 cm^{-1}. Space group $P2_12_12_1$. Crystal size, $0.40\times0.40\times0.35$ mm^3.

Structure Analysis and Refinement——The structure was solved by the direct method using MULTAN[15] and refined by the block-diagonal least-squares procedure with the assumption of positional and anisotropic thermal parameters for all non-hydrogen atoms. The R factor was finally reduced to 0.08. The results are given in Table I, and Figs. 2—5.

Table I. Positional Parameters ($\times10^4$) with Their Estimated Standard Deviations (in Parentheses) and Equivalent Isotropic Thermal Parameters (Å^2) of Serratenedione (3)

$$B_{eq}=\frac{4}{3}\Sigma_i\Sigma_j\beta_{ij}\mathbf{a}_i\mathbf{a}_j$$

	x	y	z	B_{eq}
O1	264(6)	8174(9)	2911(5)	4.98
O2	−543(7)	8572(8)	−4908(5)	5.38
C1	269(7)	6337(10)	1085(5)	2.93
C2	223(9)	6311(12)	2044(6)	4.35
C3	665(7)	7511(11)	2417(6)	3.26
C4	1666(7)	7763(0)	2180(6)	2.90
C5	1856(7)	7253(10)	1279(6)	2.52
C6	2693(7)	7874(11)	901(6)	3.14
C7	2934(7)	7212(11)	79(6)	3.27
C8	2140(6)	7315(10)	−562(6)	2.55
C9	1258(6)	6733(9)	−164(5)	2.36
C10	982(6)	7276(9)	711(5)	2.32
C11	403(7)	6681(10)	−724(5)	2.74
C12	516(7)	5946(10)	−1548(5)	3.00
C13	989(7)	6752(10)	−2218(6)	2.64
C14	2054(7)	6713(10)	−2137(6)	2.73
C15	2601(7)	6862(12)	−2768(6)	3.64
C16	2277(7)	7086(12)	−3648(6)	3.94
C17	1242(7)	7355(10)	−3677(6)	2.88
C18	679(7)	6417(10)	−3110(6)	2.67
C19	−353(7)	6700(11)	−3194(6)	3.08
C20	−683(7)	6687(12)	−4095(6)	3.78
C21	−167(8)	7685(11)	−4566(6)	3.41
C22	888(8)	7555(11)	−4599(6)	3.50
C23	2264(8)	6969(13)	2780(6)	4.10
C24	1888(8)	9210(11)	2300(7)	4.08
C25	555(7)	8659(11)	673(6)	3.35
C26	2067(8)	8736(10)	−867(6)	3.29
C27	2460(7)	6443(10)	−1282(6)	2.92
C28	863(8)	5026(10)	−3290(7)	3.18
C29	1098(8)	6373(11)	−5167(6)	4.35
C30	1333(9)	8767(11)	−4955(7)	3.74

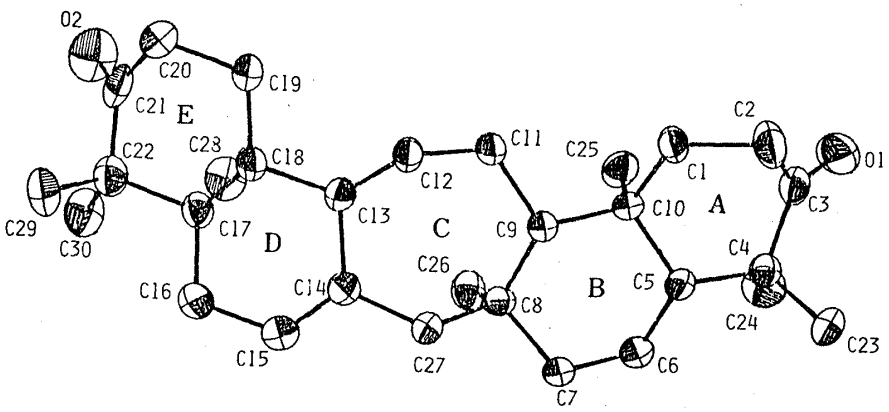


Fig. 2. A Perspective Drawing of the Molecule of Serratenedione with Hydrogen Atoms Omitted

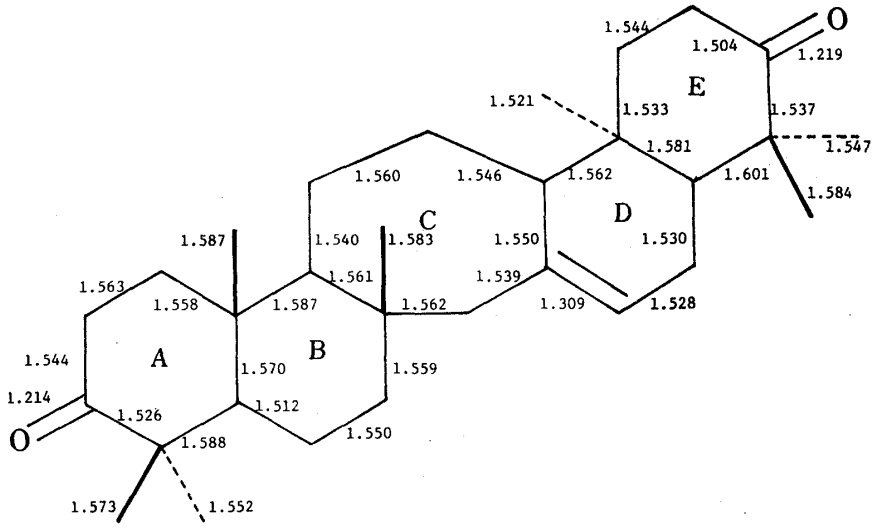


Fig. 3. Bond Lengths (Å)

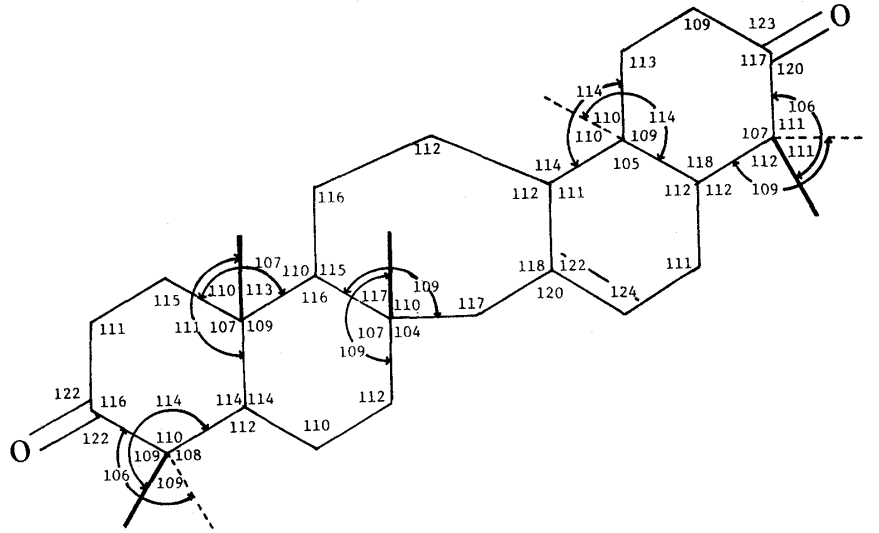


Fig. 4. Bond Angles (°)

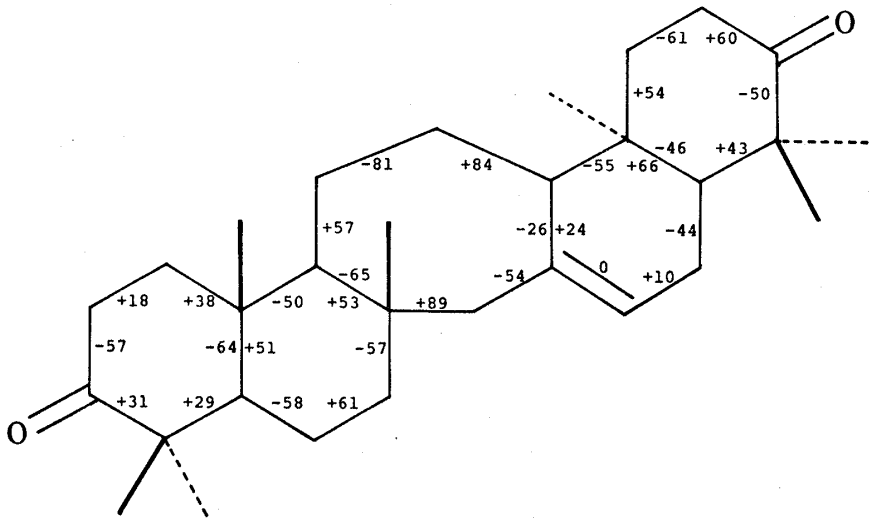


Fig. 5. Endo-cyclic Torsional Angles (°)

Results and Discussion

The endo-cyclic torsional angles of serratenedione (Fig. 5) clearly show that ring A of the compound is a deformed boat form, rings B and E are chair form, ring D is a half-chair form, and ring C has a chair-like conformation so as to make the whole molecule almost planar, but slightly bent.

Regarding the terminal rings, the chair conformation of ring E is slightly distorted from an ideal form, which presumably accounts for the negative CD contribution of ring A of 4,4-dimethyl-Δ^7-3-keto steroids. Most interestingly, ring A adopts a distorted boat conformation that is between two boat forms, V (boat) and VI (twist), but closer to V. Ring A of alnuserol, (2) also takes a similar conformation.[11] Therefore, the twisted boat form is the most probable conformation for ring A of 4,4,8β-trimethyl-3-keto-5α-steroids or 3-keto-triterpenoids.

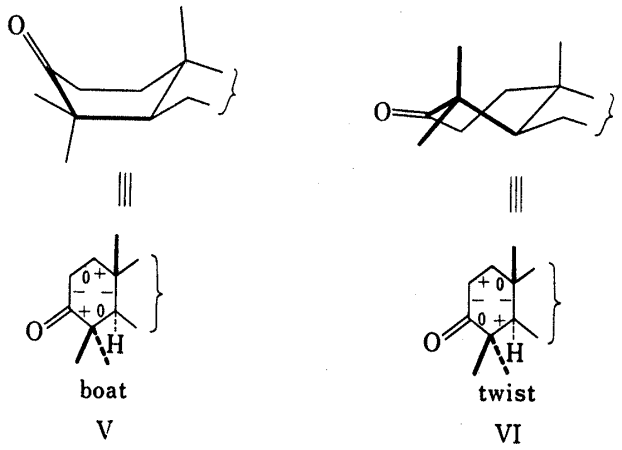


Chart 3

As suggested previously on the basis of EFF calculations,[16] the energy difference between chair and boat conformations at ring A of 4,4-dimethyl-3-keto steroids may be small. Creation of an extra non-bonded interaction by introducing an 8β-methyl group could be enough to invert the preferred conformation from distorted chair to twisted boat. The energy difference between those two conformations of 4,4,8β-trimethyl-3-keto compounds may still be so small

that another factor (such as deformation at remote rings) can produce reversal of the conformation of ring A to distorted chair. Papyriogenin-A (**1**) may be an example of such a case, its ring A being indicated to adopt a sofa conformation.[17]

In solution, the ring A conformation may also be affected and modified by other factors such as solvation of the carbonyl and other functional groups. However, it seems very likely that the conformation of serratenedione (**3**) in the crystalline state is similar to that in solution, and that the positive CD of 4,4,8β-trimethyl-3-keto-5α-steroids is attributable to their (distorted) boat conformation at ring A.

References and Notes

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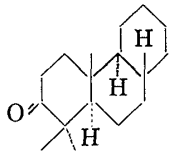

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