[Chem. Pharm. Bull.
32(1) 313—317 (1984)]

4,4-Dimethyl Effect. (5). The Conformation of 8αH,14βH-Onocerane-3,21-dione (Onoceranedione-I) in the Crystalline State[1]

YOSHISUKE TSUDA,*,[a] KEIICHI YAMAGUCHI,[b] and SHIN-ICHIRO SAKAI[b]

Faculty of Pharmaceutical Sciences, Kanazawa University,[a] 13-1 Takara-machi, Kanazawa 920, Japan, and Faculty of Pharmaceutical Sciences,[b] Chiba University, 1-33 Yayoi-cho, Chiba 260, Japan

(Received April 25, 1983)

Single crystals of onoceranedione-I grown in CH_2Cl_2–methanol are orthorhombic, $a=13.326$, $b=16.507$, $c=12.092$ Å, $U=2659.9$ Å^3, $D_c=1.11$ g/cm^3, $Z=4$, with space group $P2_12_12_1$. The structure, solved by use of the MULTAN program, revealed that the conformations of the two terminal rings are boat forms, which are flexible even in the crystalline state. The positive circular dichroism spectrum of the compound is discussed in connection with the above results.

Keywords——X-ray analysis; onoceranedione-I; 4,4-dimethyl-3-keto steroid ring A conformation; 4,4-dimethyl effect; boat form; 3-keto-onoceranoid; CD

The origin of 4,4-dimethyl effect in 4,4-dimethyl-3-keto steroids, particularly the anomalies in the circular dichroism (CD) and optical rotatory dispersion (ORD) spectra (the Cotton effect changes its sign depending on the presence or absence of the C_8-methyl group) has been a subject of continuing interest in relation to the conformation of ring A.[2] In a previous paper, we showed by X-ray analyses of some triterpenoid 3-ketones that ring A of 4,4,8β-trimethyl-3-keto steroids usually adopts a boat form in the crystalline state and we concluded that a similar conformation in solution is responsible for the positive Cotton effect in the CD of this system.[2] 4,4-Dimethyl-3-keto steroids without the C_8-substituent have a chair form at ring A and give a negative Cotton effect.[2]

On the other hand, it has been noted that the same anomalies of CD spectra as seen in 4,4-dimethyl-3-keto steroids are observed in some bicyclic systems such as onoceranoids: onoceranedione-I gives a positive and onoceranedione-III exhibits a negative Cotton effect. These results led to the correct stereochemical assignments of the above onoceranoids (onoceranedione-I as 8α*H*, 14β*H* and onoceranedione-III as 8β*H*, 14α*H* configurations)[3] and, at the same time, strongly suggest that the terminal rings (A and D) of onoceranedione-I have boat conformations.

In order to test the above suggestion that the same stereochemical relationship holds in 4,4-dimethyl-steroids and onoceranoids, X-ray analysis of onoceranedione-I was undertaken, since we consider that the result in the crystalline state should also be applicable to the conformation in solution in this case (see later).

Experimental

Crystallographic Measurements——Single crystals of onoceranedione-I were grown in CH_2Cl_2–methanol as colorless prisms. A computer-controlled Rigaku Denki AFC-5 four-circle X-ray diffractometer was used for all measurements. The intensities of all the reflections in the range of $3° < 2\theta < 55°$ were measured using the ω–2θ scan method with a scan speed of 2°/min in 2θ. Of the total 3477 reflections obtained by the use of monochromated Mo-$K\alpha$ radiation, 2327 had intensities $F_o > 3\sigma F_o$ and they were used in the calculation. No absorption correction was made.

Crystal Data——$C_{30}H_{50}O_2$. $M=442.7$. Orthorhombic. $a=13.326$ (5) $b=16.507$ (11), $c=12.092$ (14) Å, $U=$

TABLE I. Positional Parameters ($\times 10^4$) with Their Estimated Standard Deviations (in Parentheses) and Equivalent Isotropic Thermal Parameters (A^2) of Onoceranedione-I for Non-hydrogen Atoms

Atom	*X*	*Y*	*Z*	$B_{eq.}$[a)]
C1	2416 (7)	4437 (7)	5027 (9)	5.4
C2	1948 (10)	3636 (7)	5312 (11)	7.0
C3	2207 (9)	2953 (6)	4521 (10)	5.7
C4	3286 (8)	2820 (5)	4194 (9)	4.1
C5	3915 (6)	3627 (5)	4371 (7)	3.2
C6	4893 (7)	3603 (6)	3714 (9)	4.4
C7	5560 (7)	4340 (6)	4048 (10)	4.8
C8	5044 (7)	5147 (5)	3817 (8)	4.2
C9	4003 (6)	5146 (5)	4438 (8)	3.6
C10	3289 (6)	4407 (5)	4150 (7)	3.3
C11	3447 (7)	5973 (5)	4352 (9)	3.8
C12	4147 (7)	6676 (5)	4730 (9)	4.0
C13	3540 (6)	7412 (5)	5123 (7)	3.2
C14	2735 (6)	7716 (5)	4272 (8)	4.1
C15	2133 (6)	8418 (5)	4779 (8)	3.9
C16	2836 (7)	9105 (6)	5162 (9)	4.2
C17	3546 (6)	8771 (5)	6068 (7)	3.4
C18	4248 (6)	8091 (5)	5593 (8)	3.1
C19	4790 (8)	7699 (6)	6610 (9)	4.8
C20	5267 (12)	8277 (9)	7437 (13)	8.7
C21	5066 (8)	9162 (7)	7265 (8)	5.2
C22	4119 (7)	9471 (6)	6688 (9)	4.5
C23	3702 (10)	2178 (6)	4977 (10)	6.4
C24	3359 (10)	2474 (7)	2971 (9)	6.0
C25	2836 (7)	4442 (6)	2965 (9)	4.8
C26	5016 (11)	5357 (7)	2554 (10)	6.2
C27	3109 (9)	7915 (7)	3113 (9)	5.7
C28	5020 (7)	8397 (5)	4766 (8)	4.2
C29	3405 (10)	9767 (8)	7671 (11)	7.8
C30	4416 (10)	10193 (6)	5919 (12)	6.7
O1	1549 (7)	2528 (6)	4128 (10)	9.7
O2	5677 (9)	9614 (6)	7641 (10)	11.1

a) $B_{eq.} = (4/3)\Sigma_i\Sigma_j\beta_{ij}a_ia_j$

2659.9 Å^3, $D_c = 1.11$ g/cm^3, $Z = 4$. μ(Mo-$K\alpha$) $= 0.6$ cm^{-1}. Space group $P2_12_12_1$. Crystal size, $0.38 \times 0.63 \times 0.25$ mm.

Structure Analysis and Refinement——The structure was solved by the direct method using MULTAN[4)] and refined by the block-diagonal least-squares procedure with the assumption of positional anisotropic thermal parameters for all non-hydrogen atoms. The *R* factor was finally reduced to 0.094. The results are given in Tables I and II, and Figs. 1—3.

Results and Discussion

The results of X-ray analysis showed that ring A (and D) of onoceranedione-I is a deformed boat form, as expected, which accounts for the positive Cotton effect of the compound. Ring B (and C) has a chair form.

As in 4,4-dimethyl-3-keto steroids, an 8β-substituent (particularly 8β-methyl) in 3-keto-onoceranoids also causes the conformational change of ring A from chair to boat form, thus producing a reversal of the Cotton effect from negative to positive. Such a remarkable change

Table II. Endocyclic Torsional Angles with Their Standard Deviations (in Parentheses) of Onoceranedione-I

Atoms	Angle (°)	Atoms	Angle (°)
C1 -C2 -C3-C4	−48.0 (1.5)	C13-C14-C15-C16	−55.6 (1.0)
C1 -C10-C5-C4	−63.5 (0.9)	C14-C13-C18-C17	−53.7 (0.9)
C2 -C3 -C4-C5	22.2 (1.3)	C14-C15-C16-C17	61.7 (0.9)
C3 -C4 -C5-C10	33.5 (1.0)	C15-C16-C17-C18	−63.9 (0.9)
C5 -C6 -C7-C8	60.0 (1.0)	C16-C17-C18-C13	58.3 (0.9)
C5 -C10-C1-C2	37.8 (1.1)	C17-C18-C19-C20	48.6 (1.1)
C5 -C10-C9-C8	−54.4 (0.9)	C18-C13-C14-C15	53.4 (1.0)
C6 -C7 -C8-C9	−55.9 (1.0)	C18-C17-C22-C21	32.3 (1.1)
C7 -C8 -C9-C10	55.2 (1.0)	C18-C19-C20-C21	−6.9 (1.6)
C9 -C10-C5-C6	56.7 (0.9)	C19-C20-C21-C22	−27.0 (1.7)
C10-C1 -C2-C3	14.1 (1.4)	C20-C21-C22-C17	13.7 (1.4)
C10-C5 -C6-C7	−60.8 (1.0)	C22-C17-C18-C19	−62.1 (0.9)

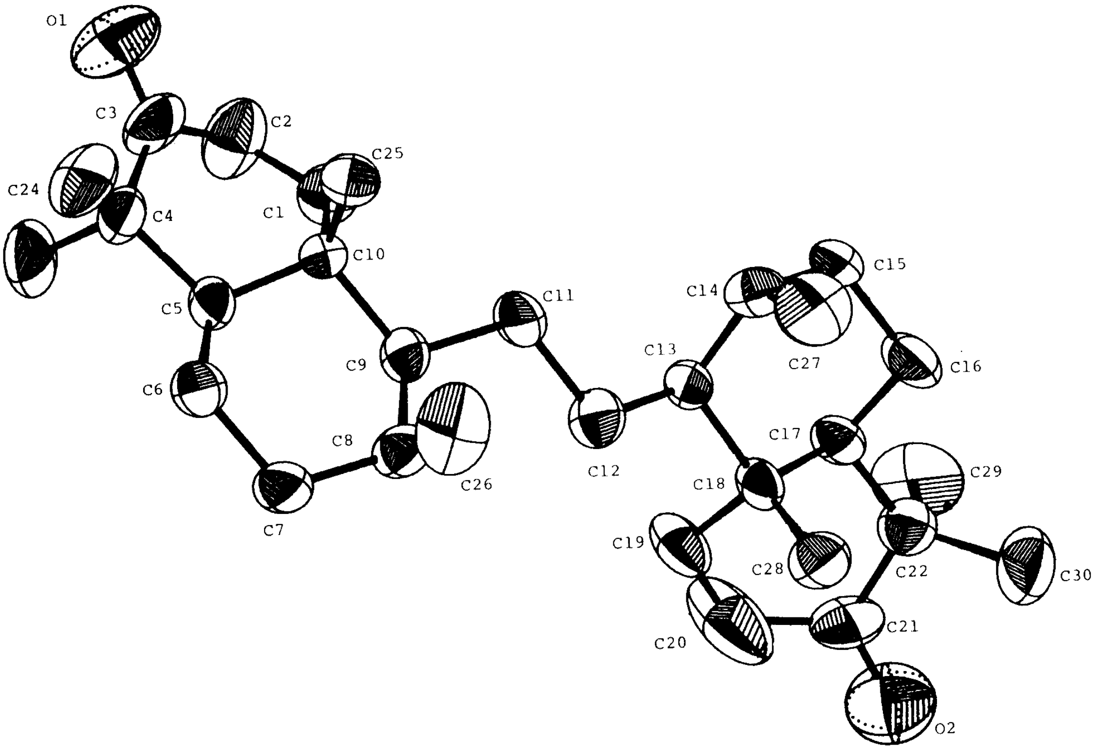

Fig. 1. Perspective Drawing of Onoceranedione-I

in the conformation of the terminal ring due to conformational transmission caused by introduction of an 8β-substituent is characteristic of the system bearing the 4,4-dimethyl group. This must be the origin of the anomalies (4,4-dimethyl effect) in the CD spectra.

Another interesting feature is that the two halves of onoceranedione-I in the crystalline state are not conformationally identical, thus losing the diad rotation axis, in contrast to the closely related compound, α-onoceradienedione, which has a diad rotation axis in the crystalline state.[1] Although the final reduction of R value was not sufficient to reveal very fine details of the conformation, the present results still indicates a conformational difference between the two terminal rings, particularly at the corresponding positions C_1–C_2–C_3 and

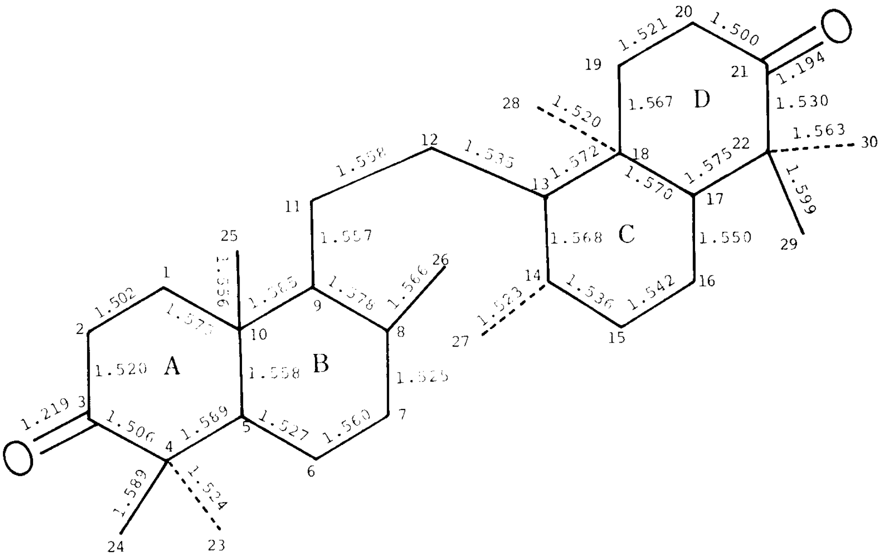

Fig. 2. Bond Lengths (Å) with Maximum Standard Deviation (0.018 Å)

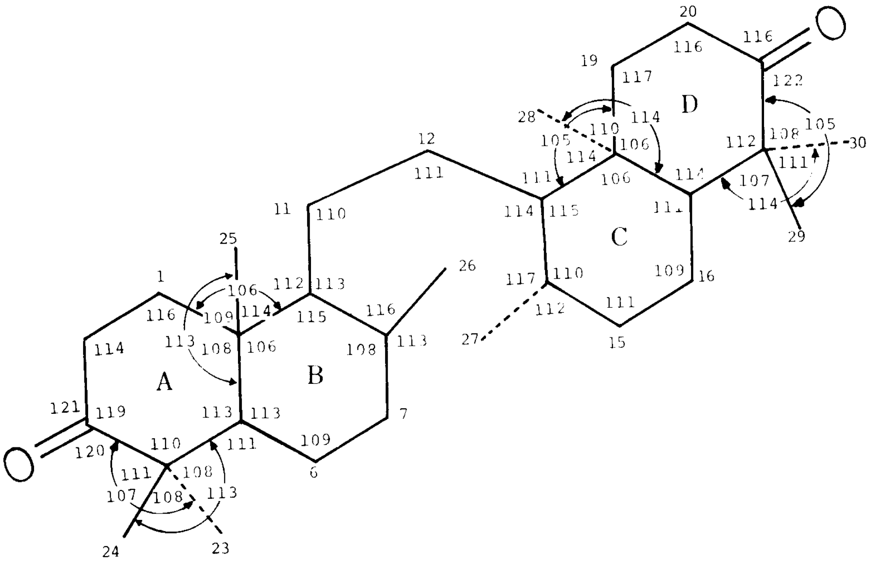

Fig. 3. Bond Angles ( ) with Maximum Standard Deviation (1.1)

C_{19}–C_{20}–C_{21} [for example, compare the torsional angles <C_{10}–C_1–C_2–C_3 (14°) and <C_{18}–C_{19}–C_{20}–C_{21} (−7°)]. This means that the terminal rings (for example, ring A) can adopt similar but distinct conformations even in the crystalline state. The larger thermal factors of C_2 and C_{20} along the z axis compared to the other atoms (see Fig. 1) are another indication of such flexibility of these atoms along this axis; in other words, flexibility of the terminal rings.

The above flexibility of the compound should increase in solution. The Cotton effect of onoceranedione-I should therefore correspond to the equilibrated boat forms of the terminal rings of the molecule. A more detailed discussion of the CD curve in connection with the ring A conformation will be given in a forthcoming publication.

References and Notes

1) Triterpenoid Chemistry. XXI. Part XX: 4,4-Dimethyl Effect (4): Y. Tsuda, N. Kashiwaba, and Y. Iitaka, *Chem.*

Pharm. Bull., **31**, 1370 (1983).

2) Y. Tsuda, N. Kashiwaba, and T. Hori, *Chem. Pharm. Bull.*, **31**, 1073 (1983), and references cited therein.

3) *a*) Y. Tsuda and T. Sano, *Chem. Pharm. Bull.*, **28**, 3134 (1980); *b*) H. Hanna, J. Levisalles, and G. Ourisson, *Bull. Soc. Chim. Fr.*, **1960**, 1938.

4) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr. Sect. A*, **27**, 368 (1971).