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4,4-Dimethyl Effect. (7).¹⁾ The A-Ring Conformation of 4,4-Dimethyl-3-keto Steroids in Solution. The Circular Dichroism Spectra of Onoceranediones²⁾

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The circular dichroism (CD) spectra of variously C-8 (and C-14) substituted onocerane-3,21-diones can be well interpreted by assuming that ring A (and ring D) of the compounds is in equilibrium between chair and twist (T_1) forms with variable ratios. This equilibrium was affected by minor structural changes at remote positions and by the polarity of the solvent. Increase of the steric bulkiness of the 8β -substituent increases the proportion of twist form. The A-ring conformation of compounds which carry an oxygenated function at 8β was greatly affected by changes of the solvent polarity, while that of the compounds without an 8β -oxygenated substituent was almost solvent-independent. These conclusions were supported by measurements of solvent shift in the proton nuclear magnetic resonance ($^1\text{H-NMR}$) spectra (TH-effect) of the compounds.

The presence of a new kind of steric effect, trivially named the "8 α -substituent effect" (for details, see the text), is proposed.

Keywords—4,4-dimethyl effect; 4,4-dimethyl-3-keto steroid; onoceranedione 8-substituted; conformation; conformational equilibrium; CD; NMR; TH-effect; 8 α -substituent effect

In a preceding paper,³⁾ we showed that the A-ring of 4,4-dimethyl-3-keto steroids is so flexible that its conformation easily changes into a T_1 or an FB^3 form as a consequence of remote structural changes. The anomalous behavior in the circular dichroism (CD) spectra of this system, *i.e.*, the "anomalous 4,4-dimethyl effect" or "4,4,8 β -trimethyl effect,"⁴⁾ was also explained in terms of such conformational changes. For example, reversal of the Cotton effect by introduction of an 8β -methyl group was attributed to the conformational change of ring A from chair to twist (T_1) form. Another important suggestion in that paper is that compounds which show a double-humped CD are in equilibrium between chair and twist forms at ring A in solution, while in a crystalline state they may adopt a flattened chair or a flattened boat conformation.

In continuing our study on the 4,4-dimethyl effect, we treat in this paper the CD spectra of onoceranediones, since the 4,4-dimethyl effect and its anomalies are known to be reflected in this bicyclic system.⁵⁾ The nuclear magnetic resonance (NMR) spectra are also discussed. An advantage of choosing this system is that the configuration and bulkiness of the C-8 substituent can be easily changed by means of chemical modifications. For this purpose the twelve compounds shown in Chart 1 were prepared.

Synthesis

The diones, **1**,^{5a,6)} **2**,^{5a,6)} **3**,^{5a,6)} **4**,⁷⁾ **10**,⁶⁾ **11**,⁶⁾ and **12**,⁸⁾ are known. The dione **5** was prepared by alkaline hydrolysis of **4**, and the diones **6**, **7**, **8**, and **9** were prepared from α -onocerin diacetate (**13**)⁶⁾ as follows.

Hydroboration of **13** followed by alkaline peroxide oxidation and hydrolysis yielded a tetraol which, after purification as the tetraacetate (**15**), was hydrolyzed to the pure tetraol

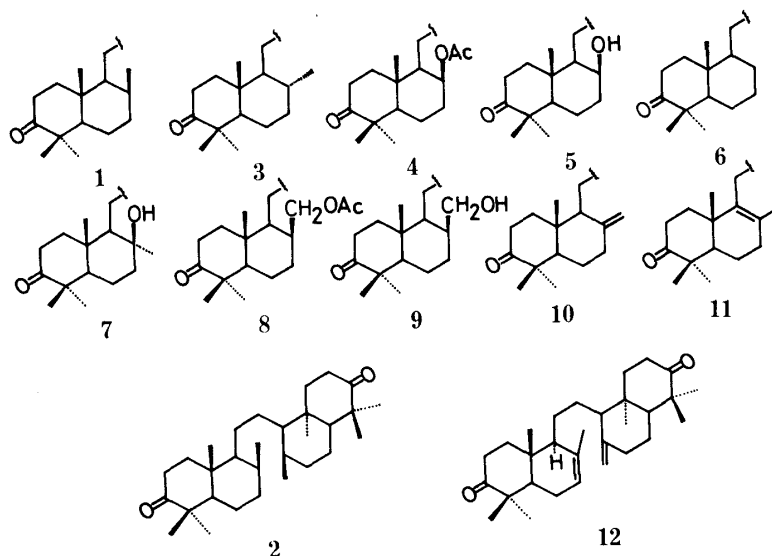


Chart 1

(14). Partial acetylation of this and Jones oxidation of the resulting diacetate (16) afforded the dione-diacetate (8). Saponification of 8 gave the diol (9). The stereochemistry of the CH_2OR group at C-8 was assigned as β and that at C-14 as α , since diborane should attack the *exo* double bonds from the less hindered side of the molecule. This assignment was supported by the CD spectra of the products (see below).

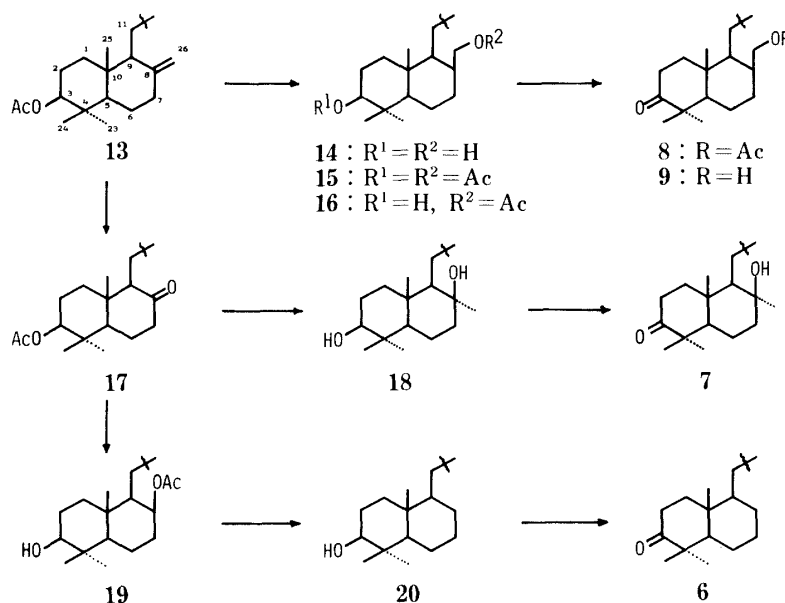


Chart 2

Grignard reaction on the bisnor-dione (17), the ozonolysis product of 13, with a large excess of methylmagnesium iodide effected the introduction of methyl groups at both the C-8 and C-14 carbonyls. The reaction should exclusively give, as discussed above, the product in which the methyl groups are introduced from the less hindered side of the molecule, *i.e.*, the α -face to C-8 and the β -face to C-14. The product was oxidized with CrO_3 -pyridine complex to the dione (7).

Preparation of the bisnor derivative (6) was more difficult. Attempted Wolf-Kishner

reduction of **17** failed even under forcing conditions, apparently because of the hindered nature of the ketones. Therefore, the photodeacetoxylation method⁹⁾ was applied to the diol-diacetate (**19**).⁷⁾ Irradiation of **19** in HMPT-H₂O (95:5) with a high pressure 300 W Hg-lamp without a filter afforded the expected diol (**20**), although the yield was low (8%). Jones oxidation of **20** afforded the bisnor-dione (**6**).

The conclusion that all the compounds except **2** and **12** have structures identical in the right and left halves was corroborated by the ¹H- and ¹³C-NMR spectra, both of which gave exactly half the number of peaks expected for C₃₀ or C₂₈ structures. The compounds which were composed of two different halves, **2** and **12**, showed complex spectra corresponding to both halves.

Results and Discussion

General Remarks

The CD spectra of the above diketones were measured in two solvent systems, methanol and dioxane. Figure 1 show the spectra of the saturated compounds and Fig. 4 show those of the unsaturated compounds.

Before detailed discussion, it is necessary to show that there is no mutual interaction between the C-3 and C-21 carbonyl groups. For this purpose, it seems sufficient to mention that the spectrum of the dione **2** (in methanol) coincides with half of the arithmetic sum of the spectra of the diones **1** and **3**.^{5a)} Since the diones **1** and **3** are both C₂ symmetrical, the above result means that each carbonyl group is contributing independently. Therefore, we can treat all compounds except unsymmetrical ones by considering half of the molecule.

When the solvent was changed from methanol to dioxane, all the compounds showed increased intensity of the negative peak (and decreased intensity of the positive peak) with a concomitant small shift of the absorption maximum to either side. Dissymetric solvation at the carbonyl group and solvent-dependent conformational change are possible reasons for this.¹⁰⁾

If the system in question is in equilibrium between two conformers (A) and (B), the CD rotational strength (R_0^T) of the system can be presented as indicated in eq. 1.¹¹⁾

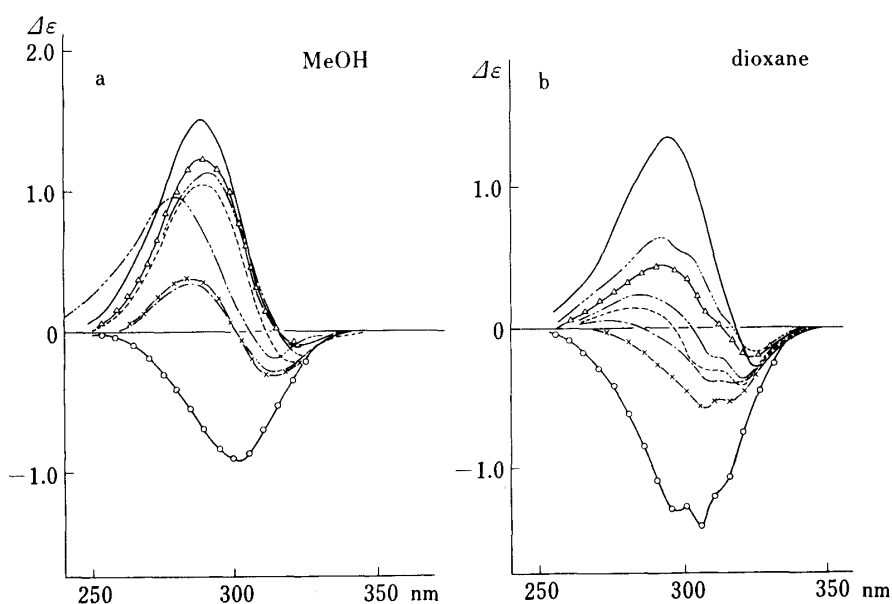


Fig. 1. CD Spectra of Onoceranediones in MeOH (a) and Dioxane (b)

1, —; 3, ○—○; 4, ———; 5, - - - -; 6, — · — ·; 7, ×—×; 8, △—△; 9, — · — ·.

$$R_0^T = N_A R_A + N_{A'} R_{A'} + N_B R_B + N_{B'} R_{B'} \quad (1)$$

where R_A and R_B are the rotational strengths of non-solvated forms A and B, $R_{A'}$ and $R_{B'}$ are those of solvated forms, and N_A , $N_{A'}$, N_B , and $N_{B'}$ are their populations, respectively.

Equation 1 can be replaced by eq. 2.

$$\Delta\epsilon = \alpha\Delta\epsilon_{(A)} + \beta\Delta\epsilon_{(B)} \quad (2)$$

where $\Delta\epsilon$ is the differential dichroic absorption of the system in a given solvent and $\alpha\Delta\epsilon_{(A)}$ and $\beta\Delta\epsilon_{(B)}$ are the contributions of the conformers (A) and (B), *i.e.*, $\Delta\epsilon_{(A)} = a\Delta\epsilon_A + b\Delta\epsilon_{A'}$ and $\Delta\epsilon_{(B)} = c\Delta\epsilon_B + d\Delta\epsilon_{B'}$, and $\alpha + \beta = 1$.

The conformational changes of the compound, if they occur on changing the solvent, must be observed as a change of α and β , otherwise the ratio β/α is constant.

Since the degree of dissymmetric solvation in a given solvent is difficult to estimate, in the discussion hereafter we compare the spectra of compounds in the same solvent, so that the factor of dissymmetric solvation can be neglected, or is at least minimized.

Equilibrium of Ring A Conformation between Chair and Twist

As is clear from Fig. 1, all spectra are more or less double-humped, and the introduction of an 8 β -substituent increases the positive contribution in the Cotton effect. All of the above spectra can be described by eq. 2 where one of the conformers has a single positive transition at *ca.* 290 nm and the other has a single negative transition at *ca.* 302 nm.

Although we do not know the real spectra of (A) and (B), they may be approximated by the spectra of **1** and **3**, respectively, since these are sufficiently positive (λ_{\max} at 289 nm in methanol and 293 nm in dioxane) and negative (λ_{\max} at 302 nm in methanol and 305 nm in dioxane), respectively. Then eq. 2 is transformed to eq. 3 by using $\Delta\epsilon_{(1)}$ and $\Delta\epsilon_{(3)}$.

$$\Delta\epsilon = \alpha\Delta\epsilon_{(1)} + \beta\Delta\epsilon_{(3)} \quad (3)$$

where $\alpha + \beta = 1$.

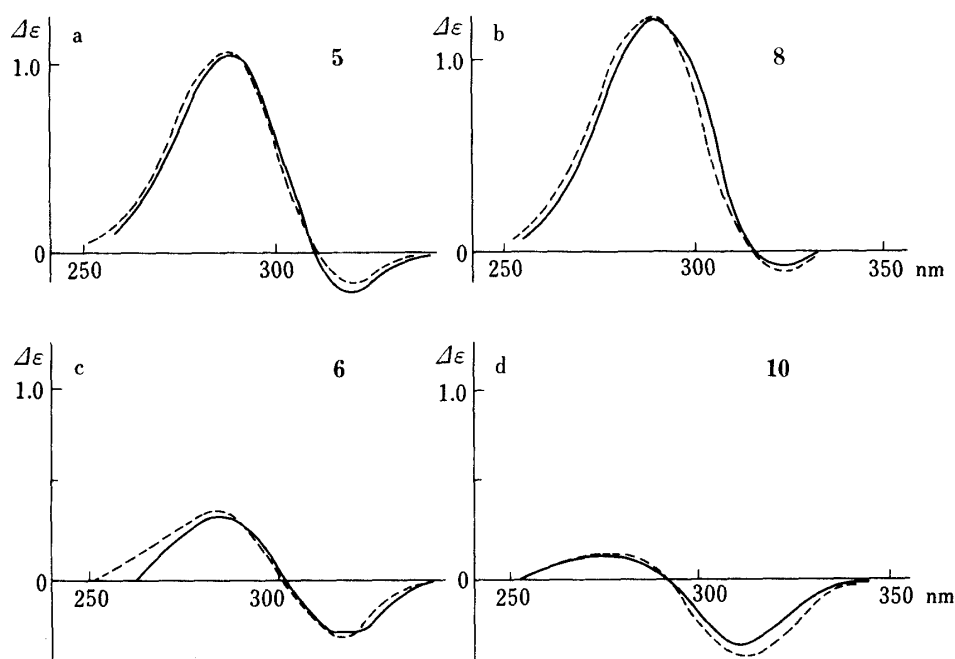


Fig. 2. Observed and Calculated CD Spectra in MeOH

—, obs. - - - - -, calc.

a: $\alpha = 0.8$, $\beta = 0.2$. b: $\alpha = 0.9$, $\beta = 0.1$. c: $\alpha = 0.46$, $\beta = 0.54$. d: $\alpha = 0.32$, $\beta = 0.68$.

This approximation is not correct in a strict sense, since each compound of different structure and/or conformation should have a different solvation mode. For example, the spectrum of **2** in dioxane is not exactly equal to the arithmetic sum of those of **1** and **3**, suggesting that the solvent differently affects **1**, **3**, and **2**, respectively. However, the above approximation is roughly valid, as will be shown below.

By adopting appropriate α and β , the spectrum of each compound in methanol was calculated and the resulting spectra were compared with the observed spectra; good agreement was found except for the 8β -acetoxyl compound.¹²⁾ Some examples are shown in Fig. 2.

The above result clearly indicates that the observed λ_{\max} 's correspond not to the real transitions but to apparent transitions caused by overlap of two slightly different transitions. Previously, Djerassi *et al.*¹³⁾ observed that the optical rotatory dispersion (ORD) transition of α -onoceradienedione (**10**) is unusually red-shifted. This is evidently due to the above phenomenon.

As shown by X-ray analysis,¹⁴⁾ ring A of compound **1** has a twist (T_1) or a flattened boat (FB^3) conformation in the crystalline state. It may be in equilibrium in solution as follows: $FB^3 \leftrightarrow (B^3) \leftrightarrow T_1$. In order to simplify the discussion, we roughly estimate the angle θ_β ³⁾ of this compound as 36° , *i.e.*, the mean of the observed FB^3 (40°) and T_1 (32°) forms, and we call this conformation "twist," since its CD curve is very similar to that of usual triterpenoid 3-ketones which were suggested to have T_1 geometries at ring A.³⁾

The spectrum of compound **3** is sufficiently negative for us to assume that it has a chair conformation, very close to an ideal chair, at ring A. For this compound we assume θ_β to be 110° .

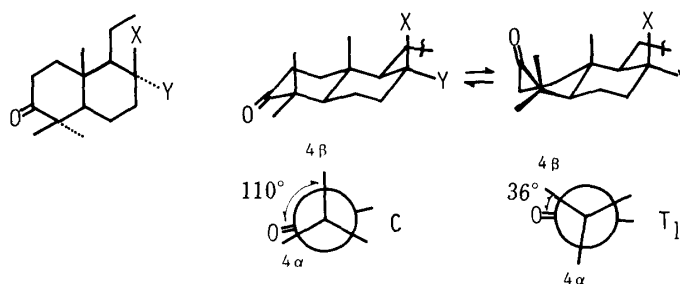


Chart 3

Then, eq. 3 means that ring A of a given compound is in equilibrium between the two conformations, chair (similar to that of **3**) and twist (similar to that of **1**), with the equilibrium constant $K = \beta/\alpha$. It should be noted that the above chair and twist do not necessarily correspond to the two real relaxed conformations of each compound, since compounds with different structures should have relaxed conformations which would differ from those corresponding to **1** and **3**. However, the real relaxed conformation of a given compound might not be greatly different from those anticipated.

The α , β values and energy differences of the above two conformers in methanol calculated according to eq. 4 are given in Table I.

$$-\Delta F(\text{kcal/mol}) = RT(\ln \beta - \ln \alpha) \quad (4)$$

Conformational Change Depending on the Solvent

On changing the solvent from methanol to dioxane, the spectra of both **1** and **3** showed a decreased positive contribution and an increased negative contribution. This may be due to a decrease of the degree of dissymmetric solvation at the carbonyl group in the latter solvent.

In spite of the changes of $\Delta\epsilon_{(1)}$ and $\Delta\epsilon_{(3)}$, the spectra of compounds **6** and **10**, which do not

TABLE I. Calculated Equilibrium Data in MeOH and Dioxane

Compd.	MeOH				Dioxane				
	α	β	$-\Delta F$ (at 20°C)	θ (°)	α	β	$-\Delta F$ (at 20°C)	θ (°)	
1	1.00	0		36	1.00	0		36	
8	0.90	0.10	-1.28	43	0.65	0.35	-0.36	62	a)
9	0.85	0.15	-1.00	47	0.72	0.28	-0.55	57	a)
4					0.55	0.45	-0.11	69	a)
5	0.80	0.20	-0.80	50	0.50	0.50	0	73	a)
6	0.46	0.54	0.09	76	0.46	0.54	0.09	76	
7	0.46	0.54	0.09	76	0.32	0.68	0.44	86	a)
10	0.32	0.68	0.44	86	0.32	0.68	0.44	86	
3	0	1.00		110	0	1.00		110	

$$-\Delta F(\text{kcal/mol}) = RT(\ln \beta - \ln \alpha).$$

$$\theta = 36\alpha + 110\beta.$$

a) Solvent-dependent conformational change.

carry oxygenated functions other than the C-3 carbonyl, are well represented by using the same coefficients as in methanol. This suggests that the conformations of these compounds are solvent-independent (or solvent dependent conformational changes, if they occur, show the same or similar character and extent).

In contrast to **6** and **10**, the spectra of the compounds bearing oxygenated functions at C-8, such as **4**, **5**, **7**, **8**, and **9**, changed markedly, depending on the solvent. The α and β values in methanol were no longer applicable, but when new parameters were adopted, the calculations again showed fairly good agreement with the observed spectra. The α , β values and the calculated energy difference of the two forms in dioxane are shown in Table I, which indicates increases of the chair (and hence decreases of the twist) contribution for **4**, **5**, **7**, **8**, and **9** in dioxane.

Those changes can be explained as follows. In addition to the usual solvation at the carbonyl group, the effective bulkiness of the C-8 oxygenated substituent is expected to be changed depending on the solvent. In a hydroxylic solvent such as methanol, the oxygen atom gains a trigonal character by solvation, thus increasing the bulkiness of the substituent, while in dioxane this solvation is not operating, but instead the 8-OH group interacts with the solvent in such a way as to change the bond character from O-H to O---H. This decreases the effective bulkiness of the OH group in dioxane. These changes of effective bulkiness of the C-8 substituent should produce changes of non-bonded interaction between 10 β -methyl and the 8 β -substituent, thus producing the conformational change of the compound.

We next wish to know which conformation is the most stable one in a given solvent and if the conformation in solution really corresponds to that in the crystalline state, as is frequently assumed.

As pointed out above, conformational change in compound **10** due to solvent is negligible. In such a case, the most stable conformation in solution should be similar to that indicated by X-ray analysis, unless special factors such as packing effect or unusual solvation in the crystalline state are operating. For the compounds whose A-ring conformation is solvent dependent, the conformations predicted from CD would not correspond to those from X-ray analysis. Generally speaking, the conformation in the crystalline state may be similar to that in non-polar solvents.

The conformations corresponding to **1** and **3** are not the real relaxed forms of each compound, but are forms arbitrarily adopted. Assuming that the most probable confor-

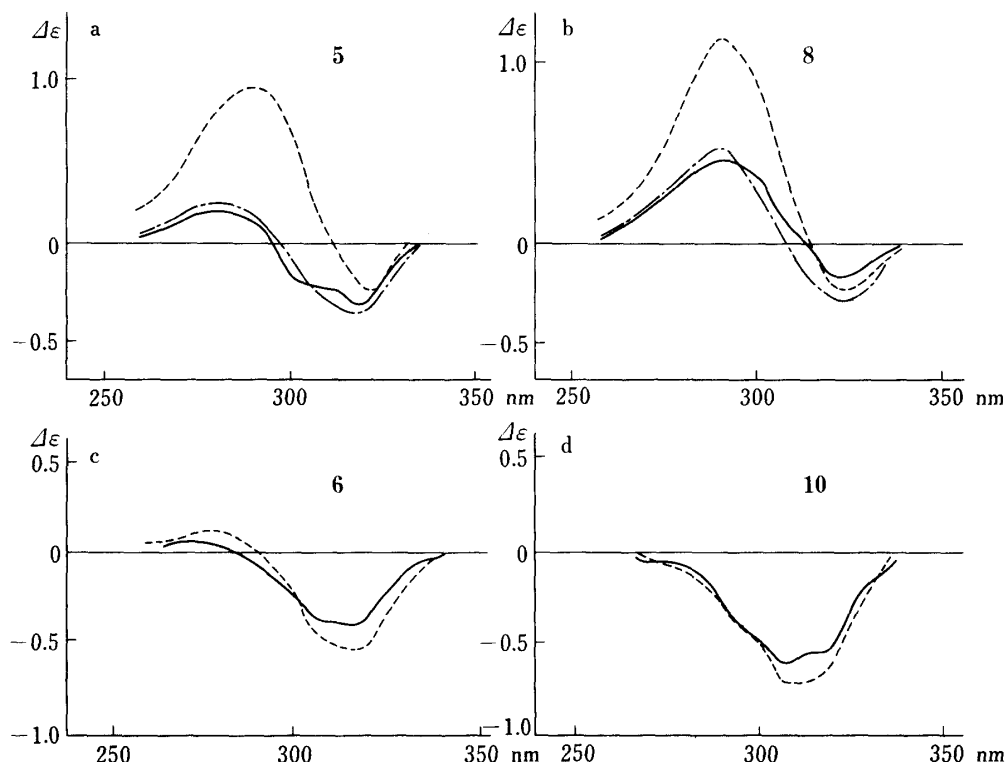


Fig. 3. Observed and Calculated CD Spectra in Dioxane

—, obs.; ----, — — —, calc.
 a: ----, $\alpha=0.8$, $\beta=0.2$; — — —, $\alpha=0.5$, $\beta=0.5$. b: ----, $\alpha=0.9$, $\beta=0.1$; — — —, $\alpha=0.65$, $\beta=0.35$. c: $\alpha=0.46$, $\beta=0.54$. d: $\alpha=0.32$, $\beta=0.68$.

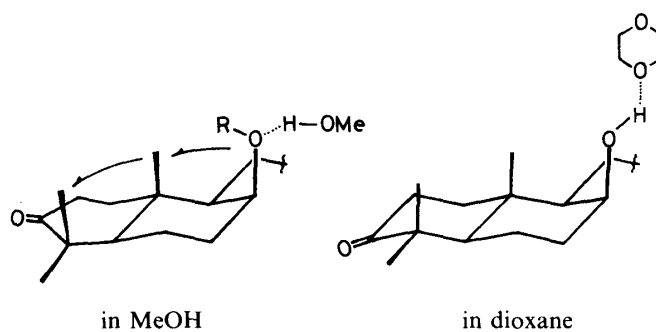


Chart 4

mation is midway between the above two extreme forms, we have estimated the following value θ , which is a measure of conformational distortion in a solvent, according to eq. 5:

$$\theta = 36\alpha + 110\beta \quad (5)$$

where 36 and 110 are the θ_β 's (dihedral angle between C=O and 4 β -methyl group) of compounds **1** and **3**, respectively.

In agreement with our expectation, the calculated value (86°) for compound **10** was found to be nearly equal to the θ_β (88°) obtained from X-ray analysis.³⁾ We therefore concluded that compound **6** took an almost flat form at ring A ($\theta = 76^\circ$).¹⁵⁾ This agreed with the prediction in the preceding paper³⁾ that "when a compound shows a clear double-humped CD, it should have an almost flat conformation (at A-ring)."

8 α -Substituent Effect

The spectra of compounds **6** and **7** were unexpected. Although we expected a negative

curve for **6** and a positive curve for **7**, the real spectrum of **6** was a double-humped one, indicating that the compound is in equilibrium between chair and twist forms in a ratio of *ca.* 1:1 in both the methanol and dioxane solvents. The spectrum of **7** in methanol again showed that the compound is in an equilibrium between chair and twist, but the ratio (*ca.* 1:1) changed to *ca.* 7:3 in dioxane, as expected from the change of effective bulkiness of the hydroxyl group in that solvent.

Comparing the spectra of **6** and **3** and those of **7** and **5** in the same solvent, we can conclude that introduction of the 8 α -methyl group increases the contribution of the chair conformation at ring A. Such an effect of an 8 α -substituent, a kind of conformational transmission,¹⁶⁾ which reduces steric compression at ring A, has never been recognized previously and, of course, cannot be attributed to a distortion of ring B, since even in compound **1** ring B was shown to have a good chair conformation (X-ray analysis).³⁾

Although the origin of this phenomenon is not completely clear, it may be due to a decrease of flexibility of ring B caused by the presence of an equatorial substituent at C-8. The C-8 equatorial substituent may reduce the flexibility of ring B by an anchoring effect, thus decreasing the interaction between the 10 β -methyl group and the 8 β -substituent. Molecular mechanics calculations are required to clarify this point.

Unsaturation at Ring B

The effect of unsaturation at ring B on the conformation of ring A in connection with the location of a double bond was fully discussed in the preceding paper.³⁾ In agreement with that discussion the 8-ene (**11**) gave strongly positive CD ($\Delta\epsilon = 1.59$ at 290 nm in methanol), suggesting that the compound has twist conformation at ring A, although the spectrum was affected by changing the solvent. The solvent effect on this compound was larger than that on compound **1**.

The spectrum of the 7-ene (onocera-7,14-diene-3,21-dione) was calculated by subtraction of $\Delta\epsilon$ of **10** from that of **12**, *i.e.*, $\Delta\epsilon = 2\Delta\epsilon_{(12)} - \Delta\epsilon_{(10)}$. It was strongly negative, indicating that ring A of this compound is a fairly good chair, as expected for usual 4,4-dimethyl- Δ^7 -3-keto steroids. The spectrum of the 8(26)-ene (**10**) was a hybrid of these, being a double-humped one, as discussed above.

The NMR Spectra of Onoceranediones

¹³C-NMR data for the diones in CDCl₃ are collected in Table II. The chemical shifts of

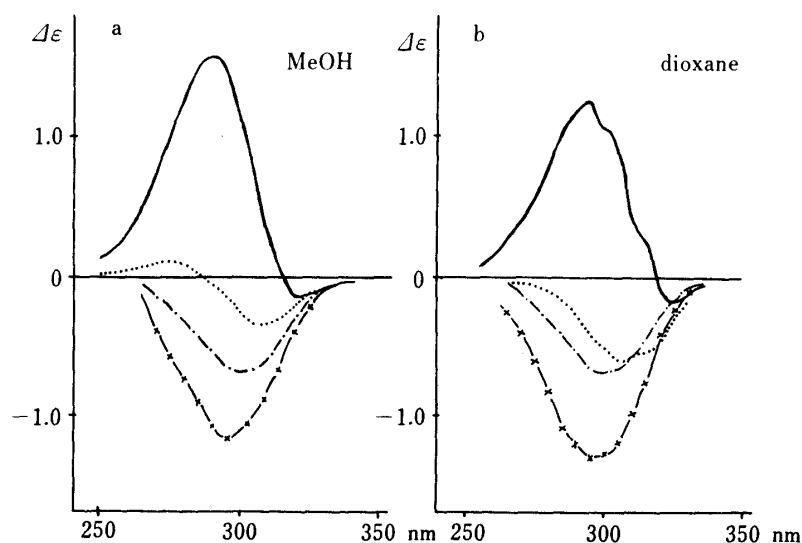


Fig. 4. CD Spectra of Unsaturated Onoceranediones in MeOH (a) and Dioxane (b)
10,; **11**, —; **12**, ---; onocera-7,14-diene-3,21-dione (calcd.), ×—×.

TABLE II. ^{13}C -NMR Chemical Shifts of Onoceranediones (in Chloroform- d)^{a)}

Carbon	1	2 (A/B)	2 (C/D)	3	4	5	6	7	8	9	10	11
1	38.9	38.9	38.0	38.1	38.1	38.3	37.8	38.4	38.3	38.3	37.9	35.9
2	34.2	34.2	34.5	34.5	34.1	34.1	34.6	34.0	34.2	34.2	34.7	34.4
3	217.6	217.6	217.0	216.9	216.6	217.1	217.2	216.7	216.9	216.9	216.6	217.7
4	47.5	47.5	47.7	47.7	47.3	47.5	47.7	47.6	47.5	47.5	47.7	47.1
5	55.5	55.5	55.4	55.3	54.7	55.1	55.1	55.4	55.4	55.4	55.2	51.4
6	18.5	18.5	22.7	22.7	18.3	17.9	23.0	19.3	18.5	18.9	25.1	20.5
7	34.1	34.1	36.6	36.6	31.6	34.9	28.0 ^{b)}	42.0	28.9	29.5	37.6	33.9
8	28.9	28.9	34.1	33.9	69.0	66.6	27.3 ^{b)}	72.4	34.8	39.3	147.4	138.8
9	52.8	54.2	58.2	58.8	52.9	53.4	50.6	59.5	52.5	53.0	56.5	127.6
10	37.6	37.5	37.5	37.9	37.2	37.2	37.1	38.3	37.2	37.4	39.2	38.6
11	23.8	28.2	29.1	32.5	23.1	22.4	27.1 ^{b)}	29.5	23.5	24.2	22.8	28.7
23	26.7	26.8	25.8	25.7	26.6	26.6	26.0	26.1	26.4	26.6	26.0	26.9
24	21.2	20.9	21.8	21.7	21.4	21.5	21.7	21.5	21.2	21.2	21.6	20.9
25	14.9	15.2	13.8	13.7	15.3	15.8	13.3	14.7	15.8	15.7	14.0	20.4
26	16.3	16.4	21.1	21.2	—	—	—	31.4	62.9	61.5	107.6	20.1

a) ^{13}C FT NMR (at 25.0 MHz) were recorded on a JEOL FX-100 spectrometer using a 5 mm spinning tube at 24°C under the following conditions: spectral width, 6024 Hz; pulse flipping angle, 45°; acquisition time, 0.6799 s, number of data points, 8192. Accuracies of δ values were about ± 0.1 . Assignments were confirmed by OFR and ^1H -hetero-spin decoupling methods.

b) Assignments may be interchanged.

TABLE III. ^1H -NMR Chemical Shifts of Onocerane-3,21-diones (in Chloroform- d)^{a)}

Compound	4 α -Me	4 β -Me	10 β -Me	Others ^{b)}
1	1.000 (-0.037)	1.044 (0.044)	0.951 (0.167)	
3	1.050 (-0.117)	1.023 (0.094)	0.947 (0.203)	
4	1.094 (-0.001)	1.065 (0.063)	1.065 (0.077)	
5	1.110 (-0.039)	1.079 (0.030)	1.121 (0.033)	4.08 (2H, br s)
6	1.068 (-0.074)	1.036 (0.090)	0.948 (0.225)	
7	1.089 (-0.068)	1.057 (0.043)	1.099 (0.015)	1.24 (6H, s)
8	1.090 (-0.020)	1.041 (0.139)	0.909 (0.221)	2.05 (6H, s), 4.1 (4H, m)
9	1.086 (-0.022)	1.025 (0.095)	0.808 (0.285)	3.6 (4H, m)
10	1.090 (-0.037)	1.012 (0.140)	0.823 (0.162)	
11	1.100 (0.012)	1.063 (0.026)	1.074 (0.086)	

a) The values in parentheses indicate the shift values in benzene- d_6 [$\Delta\delta_{(\text{CDCl}_3)} - \delta_{(\text{C}_6\text{D}_6)}$].

b) Data for new compounds only.

ring B carbons were markedly affected by the nature and stereochemistry of the C-8 substituent as expected, while those of the ring A carbons showed very little change for all compounds (except **11**) suggesting that either the conformational change of this ring or the effect thereof, if it occurs, is negligibly small in this solvent.

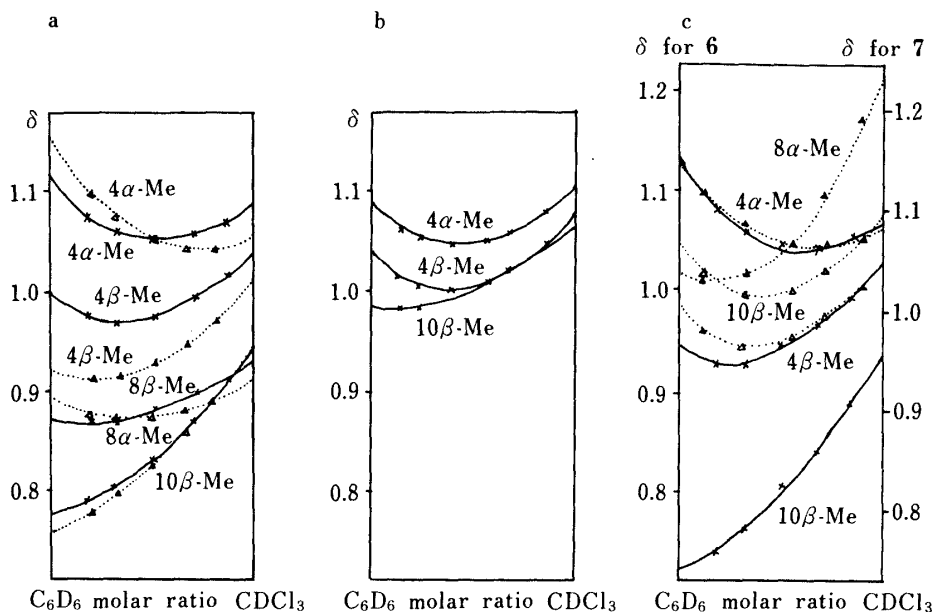


Fig. 5. TH-Effect of C-Methyl Groups in Compounds 1, 3, 6, 7, and 11

a: 1, —; 3, ----. b: 11, —. c: 6, —; 7, ----.

$^1\text{H-NMR}$ in CDCl_3 (Table III) again provided little conformational information. The 4α - and 4β -methyl groups showed no significant difference in any of the compounds (except for 11), as if all of them have the same conformational relationship under the NMR conditions.

In contrast, the TH-effect (ASIS shift on continuously changing the solvent from CDCl_3 to benzene)¹⁷⁾ was found to sensitively reflect minor conformational change, as suggested already.¹⁸⁾ For example, although the spectra of 1 and 3 in CDCl_3 were similar, those in benzene- d_6 were markedly different. The methyl groups at 4α and 4β in 3 experienced different TH-effect (down field shift $H = -12$ for 4α - and up field shift $H = 9$ for 4β -methyl), reflecting their different stereochemical situations with respect to the C-3 carbonyl group, whereas the H -values for the corresponding methyls in 1 were smaller ($H = -4$ for 4α - and $H = 4$ for 4β -methyl) suggesting that their stereochemical similarity is greater (Fig. 5a). This situation is pronounced in compound 11, whose 4α - and 4β -methyl groups showed almost the same H and T ($H = 1.2$, $T = 4.6$ for 4α - and $H = 2.6$, $T = 4.8$ for 4β -methyl) (Fig. 5b).

Interestingly, the 4α - and 4β -methyl groups of compounds 6 and 7 experienced similar TH-effects, suggesting conformational similarity at ring A (Fig. 5c). However, for many compounds the observed TH-effects did not correspond to the conformation predicted from the CD measurements, suggesting that the A-ring conformations in NMR measurement might possibly be different from those in CD measurements. This would be because the solvent polarity of chloroform is different from those of methanol and dioxane and the ASIS shift in NMR is attributable to a different type of solvation from that in CD measurement. In addition to this solvent-solute interaction, another factor which may influence the ring A conformation is solute-solute interaction, since the concentration for NMR measurement is extremely high compared to that for CD measurements. All of the above factors may produce conformational changes in such a flexible system. Lanthanide induced shifts may also be accompanied by conformational changes at ring A.

Conclusion

Various C-8 (and C-14) substituted onoceranediones provide good examples in which

the A-ring conformation is intermediate between those of 4,4-dimethyl-3-keto steroids and 4,4,8 β -trimethyl-3-keto steroids. Analyses of the CD spectra in two different solvent systems (methanol and dioxane) led to the conclusion that the A-ring conformation in solution is always in equilibrium between chair and twist with various ratios, which are greatly affected by the nature and stereochemistry of a substituent at ring B and the polarity of the solvent.

Increase of steric bulkiness of the 8 β -substituent increased the population of the twist form at ring A, thus increasing the intensity of the positive maximum. Apart from dissymmetric solvation at the carbonyl group, a solvent may change the steric bulkiness of a substituent by solvation; thus, polar substituents were more strongly influenced than non-polar substituents in terms of increase of their effective steric bulkiness when the solvent polarity was increased. This also increases the intensity of the positive maximum in the CD. Flexibility of ring B is another factor which influences the equilibrium. When ring B is more flexible, the A-ring conformation has an increased population of twist form as a result of increase of steric compression of the 10 β -methyl group. Introduction of an equatorial substituent on that ring decreases its flexibility, thus increasing the population of chair form at ring A. This effect, observed in 8 α -methyl compounds, which have an increased chair contribution at ring A, may be a general one for any 8 α -substituent, and is trivially called the "8 α -substituent effect."

The above results strongly support our previous conclusion that in 4,4-dimethyl-3-keto steroid derivatives, minor structural and/or conformational changes at remote positions markedly disturb the balance of chair and twist equilibrium at ring A, since the presence of the 4,4-dimethyl group appreciably reduces the energy difference between the chair and twist forms. This conformational transmission is best reflected in the CD spectrum of the compound, and is presumably the origin of the anomalous 4,4-dimethyl effect.

Experimental

Unless otherwise stated, the following procedures were adopted. Melting points were taken on a Yanagimoto micro hot-stage mp apparatus, and are uncorrected. Infrared (IR) spectra were taken in KBr disks and are given in cm^{-1} . ^1H -NMR (100 MHz) and ^{13}C -NMR (25.0 MHz) spectra were measured in CDCl_3 solution with tetramethylsilane as an internal standard on a JEOL FX-100 spectrometer, and are given in δ . High resolution mass spectra were taken with a Hitachi M-80 machine. Wakogel C-200 (silica gel) was used for column chromatography. For thin layer chromatography (TLC), Merck precoated plates GF₂₅₄ were used and spots were observed by spraying 1% ceric sulfate in 10% H_2SO_4 followed by heating at 100 °C until coloration appeared. All organic extracts were dried over Na_2SO_4 before concentration.

8 β ,14 α -Dihydroxy-26,27-bisnoronocerane-3,21-dione (5)—Compound **4** (20 mg) was hydrolyzed with 10% KOH–MeOH under reflux for 2 h to give **5** (12 mg), mp 120–122 °C, as prisms from *n*-hexane–acetone. IR: 3410, 1692. M^+ 446.3382 (Calcd for $\text{C}_{28}\text{H}_{46}\text{O}_4$ 446.3394).

3 β ,21 α -Dihydroxy-26,27-bisnoronocerane (20)—The diol-diacetate **19** (250 mg) in HMPT– H_2O (95 : 5, 300 ml) was irradiated with a 300 W high pressure Hg-lamp (without a filter) for 20 h while nitrogen was bubbled through the solution. A large amount of water was added to the reaction mixture, and the whole was repeatedly extracted with ether. The combined extract was washed with water and concentrated to give the residue (70 mg), which was chromatographed in benzene. The benzene–AcOEt (8 : 1) eluate gave **20** (17 mg), mp 165–168 °C, as needles from MeOH. IR: 3390. NMR: 0.74 (12H, s), 0.93 (6H, s), *ca.* 3.0 (2H, m). M^+ 418.3821 (Calcd for $\text{C}_{28}\text{H}_{50}\text{O}_2$ 418.3808).

26,27-Bisnoronocerane-3,21-dione (6)—Compound **20** (17 mg) in acetone (5 ml) was oxidized with the Jones reagent (5 drops) at 0 °C for 10 min, then the mixture was diluted with water, and extracted with ether. The product obtained from the ethereal extract was chromatographed to give **6** (11 mg) from the benzene–EtOAc (9 : 1) eluate. It formed prisms, mp 173–175 °C, from MeOH, and prisms, mp 143–145 °C, from *n*-hexane–ether. IR: 1695. M^+ 414.3485 (Calcd for $\text{C}_{28}\text{H}_{46}\text{O}_2$ 414.3495).

3 β ,8 β ,14 α ,21 α -Tetrahydroxyonocerane (18)—Compound **15** (300 mg) in ether (10 ml) was added slowly (for 20 min) to a stirred solution of MeMgI (prepared from 400 mg of Mg and 2.4 g of CH_3I) in ether (50 ml) at 0 °C, and the mixture was stirred for a further 1 h at room temperature, then under reflux for 2.5 h. After decomposition by addition of sat. NH_4Cl aq, the mixture was extracted with ether, and the extract was washed and concentrated to give a solid residue. Repeated chromatography of this in benzene– CH_2Cl_2 gave **18** (131 mg), mp 218–220 °C, as needles from CHCl_3 –MeOH. IR: 3430. NMR: 0.72 (6H, s), 0.90 (6H, s), 0.97 (6H, s), 1.18 (6H, s), *ca.* 3.1 (2H, m). M^+

478.4015 (Calcd for $C_{30}H_{54}O_4$ 478.4019).

8 β ,14 α -Dihydroxyonocerane-3,21-dione (7)—The tetraol **18** (120 mg) in pyridine (15 ml) and CrO_3 -pyridine complex (prepared from 1 g of CrO_3 and 14 ml of pyridine) were mixed and the mixture was kept at room temperature for 24 h. The mixture was poured into water, and extracted with CH_2Cl_2 , then the extract was washed with water, and concentrated. The residue was chromatographed in CH_2Cl_2 to give **7** (43 mg), mp 227–229 °C, as needles from benzene- CH_2Cl_2 , IR: 3450, 3380, 1685. MS m/z : 456 ($M^+ - 18$). Anal. Calcd for $C_{30}H_{50}O_4$: C, 75.90; H, 10.62. Found: C, 75.68; H, 10.78.

3 β ,21 α ,26,27-Tetraacetoxy-8 α H,14 β H-onocerane (15)— $BF_3 \cdot Et_2O$ (400 mg) in THF (10 ml) was added dropwise under stirring to a cooled (0 °C) mixture of α -onocerin diacetate **13** (500 mg) and $NaBH_4$ (80 mg) in THF (30 ml) during 1 h. After being stirred for a further 1 h, the mixture was basified with 3 N NaOH, 35% H_2O_2 (5 ml) was added and the stirring was continued for a further 3.5 h. NaCl was then added to the mixture and the separated THF layer was collected and concentrated to give a residue, which was partitioned between water and $CHCl_3$ -MeOH. Concentration of the organic layer gave the residue, which was acetylated with Ac_2O (8 ml)-pyridine (15 ml) at 90 °C for 1.5 h. After usual work-up and chromatography of the product with benzene-AcOEt (20:1), the tetraacetate **15** (300 mg), mp 212–215 °C, was obtained as needles from *n*-hexane-benzene. IR: 1725. NMR: 0.80 (6H, s), 0.85 (12H, s), 2.02 (12H, s), 4.08 (4H, m), ca. 4.5 (2H, m). M^+ 646.4438 (Calcd for $C_{38}H_{62}O_8$ 646.4441).

26,27-Diacetoxy-3 β ,21 α -dihydroxy-8 α H,14 β H-onocerane (16)—The tetraacetate **15** (140 mg) was hydrolyzed with 5% KOH-MeOH (20 ml) under reflux for 30 min. The precipitated tetraol **14** (90 mg) was collected by filtration, washed with water, dried, then acetylated with Ac_2O (1 ml) and pyridine (20 ml) for 30 min at 0 °C and for a further 1 h at room temperature. The mixture was poured into water and extracted with $CHCl_3$, and the product obtained from the extract on usual work-up was chromatographed in benzene. The benzene-EtOAc (5:1) eluate gave **16** (46 mg), mp 126–131 °C, as prisms from *n*-hexane-benzene. IR: 3400, 1721. NMR: 0.77 (12H, s), 0.97 (6H, s), 2.00 (6H, s), 3.17 (2H, m), 4.07 (4H, m). M^+ 562.4253 (Calcd for $C_{34}H_{58}O_6$ 562.4230).

26,27-Diacetoxy-8 α H,14 β H-onocerane-3,21-dione (8)—The diol **16** (60 ml) in acetone (10 ml) was oxidized with the Jones reagent (10 drops) at 0 °C for 20 min. After work-up as described for **6**, the product was chromatographed in CH_2Cl_2 to give **8** (40 mg), mp 210–213 °C, as prisms from MeOH. IR: 1689, 1727. MS m/z : 558 (M^+). Anal. Calcd for $C_{34}H_{54}O_6$: C, 73.08; H, 9.74. Found: C, 72.71; H, 9.83.

26,27-Dihydroxy-8 α H,14 β H-onocerane-3,21-dione (9)—The diacetoxy-dione **8** (25 mg) was hydrolyzed with 10% KOH-MeOH (10 ml) under reflux for 4 h. After usual work-up, the product was chromatographed in $CHCl_3$ on acid washed alumina to give **9** (15 mg), mp 275–278 °C, as prisms from *n*-hexane-acetone. IR: 3375, 1695. M^+ 474.3728 (Calcd for $C_{30}H_{50}O_4$ 474.3706).

CD Spectral Measurement—The CD spectra were taken in MeOH and dioxane on a Jasco J-20 spectrometer at 20 °C. Concentrations are in g/ml. Data are given as $\Delta\epsilon$ (λ nm).

8 α H,14 β H-Onocerane-3,21-dione (Onoceranedione-I) (1)—MeOH ($c = 0.336 \times 10^{-3}$): -0.06 (330), -0.12 (319), 0 (315), 0.96 (300), 1.50 (289), 0.76 (270), 0.08 (250). Dioxane ($c = 0.492 \times 10^{-3}$): -0.093 (335), -0.268 (322), 0 (316), 1.112 (300), 1.349 (293), 0.494 (270), 0.144 (255).

8 α H,14 β H-Onocerane-3,21-dione (Onoceranedione-II) (2)—MeOH ($c = 0.927 \times 10^{-3}$): -0.014 (340), -0.29 (315), 0 (302), 0.473 (283), 0.29 (270), 0.043 (250). Dioxane ($c = 0.491 \times 10^{-3}$): -0.065 (335), -0.362 (318), -0.308 (313), -0.329 (308), 0 (290), 0.068 (275), 0.022 (265).

8 α H,14 β H-Onocerane-3,21-dione (Onoceranedione-III) (3)—MeOH ($c = 0.604 \times 10^{-3}$): -0.033 (335), -0.902 (302), -0.731 (290), -0.198 (270), -0.022 (250). Dioxane ($c = 0.537 \times 10^{-3}$): -0.025 (340), -1.071 (315), -1.419 (305), -1.27 (300), -1.295 (295), -0.623 (280), -0.099 (260).

8 β ,14 α -Diacetoxy-26,27-bisnoronocerane-3,21-dione (4)—MeOH ($c = 0.174 \times 10^{-3}$): -0.11 (320), -0.18 (315–311), 0 (309), 0.96 (280), 0.46 (260), 0.13 (240). Dioxane ($c = 0.466 \times 10^{-3}$): -0.024 (340), -0.352 (319), 0 (302), 0.207 (290), 0.200 (287), 0.221 (283), 0.014 (155).

8 β ,14 α -Dihydroxy-26,27-bisnoronocerane-3,21-dione (5)—MeOH ($c = 0.454 \times 10^{-3}$): -0.015 (350), -0.224 (320–318), 0 (310), 1.043 (288), 0.477 (270), 0.149 (260). Dioxane ($c = 0.635 \times 10^{-3}$): -0.013 (340), -0.151 (300), -0.401 (318), 0 (295), 0.125 (282–280), 0.09 (270), 0.013 (255).

26,27-Bisnoronocerane-3,21-dione (6)—MeOH ($c = 0.389 \times 10^{-3}$): -0.013 (340), -0.284 (317), -0.271 (315), -0.290 (312), 0 (300), 0.361 (283), 0.077 (265). Dioxane ($c = 0.356 \times 10^{-3}$): -0.049 (335), -0.392 (314), -0.357 (312), -0.381 (308), 0 (283), 0.042 (273), 0.021 (265).

8 β ,14 α -Dihydroxyonocerane-3,21-dione (7)—MeOH ($c = 0.438 \times 10^{-3}$): -0.033 (335), -0.310 (315), -0.304 (310), 0 (300), 0.363 (283), 0.02 (260). Dioxane ($c = 0.437 \times 10^{-3}$): -0.062 (335), -0.527 (315), -0.508 (313), -0.595 (307), -0.453 (300), -0.031 (270).

26,27-Diacetoxy-8 α H,14 β H-onocerane-3,21-dione (8)—MeOH ($c = 0.567 \times 10^{-3}$): -0.045 (330), -0.097 (323), 0 (315), 1.222 (289), 0.507 (270), 0.075 (255). Dioxane ($c = 0.454 \times 10^{-3}$): -0.045 (335), -0.201 (320), 0 (312), 0.447 (292), 0.201 (270), 0.015 (255).

26,27-Dihydroxy-8 α H,14 β H-onocerane-3,21-dione (9)—MeOH ($c = 0.264 \times 10^{-3}$): -0.033 (335), -0.098 (323), 0 (315), 1.128 (292), 0.480 (270), 0.164 (260). Dioxane ($c = 0.264 \times 10^{-3}$): 0.033 (335), -0.167 (322), 0 (315), 0.643 (290), 0.109 (260).

Onocera-7(26),14(27)-diene-3,21-dione (α -Onoceradienedione) (10)—MeOH ($c=0.593 \times 10^{-3}$): -0.022 (340), -0.049 (330), -0.341 (305), 0 (287), 0.108 (275), 0.116 (272), 0.034 (250). Dioxane ($c=0.485 \times 10^{-3}$): -0.055 (335), -0.535 (315—312), -0.603 (306), -0.507 (300), -0.109 (280), -0.027 (265).

Onocera-8,13-diene-3,21-dione (β -Onoceradienedione) (11)—MeOH ($c=0.539 \times 10^{-3}$): -0.074 (330), -0.123 (320), 0 (315), 1.59 (290), 0.79 (270), 0.15 (250). Dioxane ($c=0.450 \times 10^{-3}$): -0.059 (335), -0.191 (324), 0 (318), 1.044 (300), 1.242 (294), 0.426 (270), 0.074 (255).

Onocera-7,14(27)-diene-3,21-dione (12)—MeOH ($c=0.925 \times 10^{-3}$): -0.057 (330), -0.672 (300), -0.043 (265). Dioxane ($c=1.056 \times 10^{-3}$): -0.044 (335), -0.643 (315), -0.920 (303), -0.454 (280), -0.038 (260).

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References and Notes

- 1) Triterpenoid Chemistry. XXIII. Part XXII: 4,4-Dimethyl Effect (6) (ref. 3).
- 2) A part of this work was presented at the 100th Annual Meeting of the Pharmaceutical Society of Japan, April 1980, Tokyo, Abstract p. 201, and at the 27th Symposium on the Chemistry of Terpenes, Essential Oils and Aromatics, Nagasaki, September 1983, Abstract p. 320.
- 3) Y. Tsuda and F. Kiuchi, *Chem. Pharm. Bull.*, **32**, 4806 (1984).
- 4) P. Witz, H. Hermann, J.-M. Lehn, and G. Ourisson, *Bull. Soc. Chim. Fr.*, **1963**, 1101.
- 5) a) Y. Tsuda and T. Sano, *Chem. Pharm. Bull.*, **28**, 3134 (1980). b) R. Hanna, J. Levisalles, and G. Ourisson, *Bull. Soc. Chim. Fr.*, **1960**, 1938.
- 6) D. H. R. Barton and K. H. Overton, *J. Chem. Soc.*, **1955**, 2639.
- 7) T. Sano, T. Fujimoto, and Y. Tsuda, *Chem. Pharm. Bull.*, **23**, 1784 (1975).
- 8) K. Habaguchi, M. Watanabe, Y. Nakadaira, and K. Nakanishi, *Tetrahedron Lett.*, **1968**, 3731.
- 9) H. Deshayes, J. P. Pete, C. Portella, and D. Scholler, *J. Chem. Soc., Chem. Commun.*, **1975**, 439.
- 10) D. N. Kirk, W. Klyne, and S. R. Wallis, *J. Chem. Soc. (C)*, **1970**, 350.
- 11) K. M. Wellmann, W. S. Briggs, and C. Djerassi, *J. Am. Chem. Soc.*, **87**, 73 (1965).
- 12) The observed spectrum of **8** in MeOH was apparently blue-shifted, probably due to the contribution of shorter wavelength transition of the OAc group. The same unusual blue-shift was observed in the spectrum of 3-oxo-16 β -acetoxy-urs-12-ene in MeOH [J. Sliwowski and Z. Kasprzyk, *Tetrahedron*, **28**, 991 (1972)]. However, the real reason for this phenomenon is not clear.
- 13) C. Djerassi, O. Halpern, V. Halpern, and B. Riniker, *J. Am. Chem. Soc.*, **80**, 4001 (1958).
- 14) Y. Tsuda, K. Yamaguchi, and S. Sakai, *Chem. Pharm. Bull.*, **32**, 313 (1984).
- 15) An alternative explanation is that one terminal ring takes a chair form and the other a twist. Even so, this also means that the A-ring chair conformation in compound **6** is less favored than that in compound **3**.
- 16) D. H. R. Barton, A. J. Head, and P. J. May, *J. Chem. Soc.*, **1957**, 935.
- 17) M. Hashimoto and Y. Tsuda, International Symposium on NMR, Preliminary Report, M-2-13, Tokyo, 1965.
- 18) Y. Tsuda, K. Yoshimoto, T. Yamashita, and M. Kaneda, *Chem. Pharm. Bull.*, **29**, 3238 (1981).