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Stereochemical Studies of some 12a-Substituted Rotenoid Derivatives

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The absolute configuration at 6a and 12a positions as well as the conformation of rings B and C of some *cis* fused 12a-substituted (OH, CH_2OH, CH_2OCOR') synthetic derivatives of natural rotenoids, rotenone and amorphigenin, are discussed on the basis of ^1H NMR, CD and molecular mechanics studies.

The CD Cotton effects above 300 nm of all 12a-substituted derivatives, compared with those of the parent natural rotenoids, show an unexpected sign inversion and cannot be used for reliable configurational assignment. This has been achieved in a nonempirical way by application of the exciton chirality method.

INTRODUCTION

Natural rotenoids and their synthetic analogues are compounds of biological importance.[1] The well-known rotenone *1* and amorphigenin *2* of established absolute stereochemistry[2] have been subjects of different chemical transformations and structural studies.[3]

In a previous paper, we discussed the determination of the absolute stereochemistry of the 12a-CH_2OH compounds *3*, *5*, *10*, *12* and their acetates *4*, *6*, *11* and *13* on the ground of ^1H NMR-data and the similarity of their CD spectra in CH_3CN solution to those of the parent natural compounds *1* and *2* within the 300–200 nm region.[3a] A more detailed investigation of the CD-spectra of the parent compounds *1* and *2* and the 12a-substituted *3*, *5*, *6*, *8*, *12* and *14* revealed unexpected differences in the region above 300 nm.[4]

The aim of the present study is to provide an additional unambiguous determination of the absolute configuration of the above mentioned 12a-substituted derivatives applying the exciton chirality method, as well as to find out a possible reason for the different CD-behaviour of the parent compounds *1* and *2* and the 12a-substituted derivatives within 300–350 nm, where the $n \rightarrow \pi^{*-}$ transition of the acetophenone chromophore and the longest wavelengths $\pi \rightarrow \pi^*$ transitions of the tetrasubstituted phenyl moiety appear.

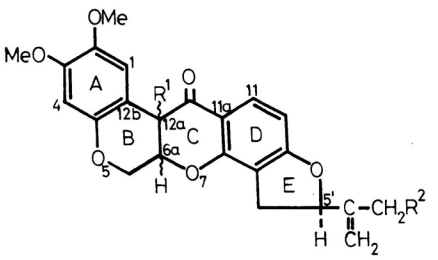
MATERIALS

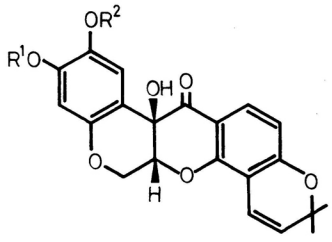
The natural compounds rotenone *1* and amorphigenin *2* have been used as model compounds. The absolute configuration of rotenone *2*, the main member of this group, is established as 6aS,12aS,5'R (6aβ,12aβ,5'β) by chemical degradation, ORD, CD, ^{1}H NMR and X-ray studies.[2] The same absolute configuration was confirmed[3c] for *2* and all other natural rotenoids.

The preparation and the TLC resolution of the 12a-CH_2OH derivatives *3*, *5*, *10*, *12* and the corresponding acetates *4*, *6*, *11* and *13* were described in a previous paper.[3a] The *cis* configuration of these compounds was assigned on the basis of ^{1}H NMR-data – the chemical shift of 1-H and the splitting pattern of 6a and 6-H_2 protons. Furthermore, the CD-spectra below 300 nm of the 6a-βH, 12a-βR^1–diastereomers (*3*, *5*, and *6*) revealed a close similarity in sign and magnitude to those of *1* and *2*, while the CD-spectrum of the 6a-αH,12a-αCH_2OH-diastereomer *12* showed an almost antipodal character.*

The 12a-$CH_2OCOC_6H_5$-derivative *7* is a new compound prepared for the purpose of this study by treatment of *3* with C_6H_5COCl in pyridine at 90 °C for 2 hours.

The preparation and the separation of the four 12a-OH diastereomers *8*, *14*, *16* and *17* was achieved by using a known procedure by air oxidation of *2* in mild alkaline medium.[3C] The *cis* configuration 6a-βH, 12a-βOH for *8* and 6a-αH, 12a-αOH for *14* was confirmed by comparison with SeO_2 oxidation products of compounds *9* and *15*, both of reliably determined absolute configuration.[3C]





18. $R^1 = R^2 = CH_3$
23. $R^1 = R^2 = -CH_2-$

* All synthetic derivatives discussed in this study retain the 5'R-configuration of natural rotenoids.

Comp.	R^1	R^2	Stereochemistry 6a	12a
1	H	H	β	β
2	H	OH	β	β
3	CH_2OH	H	β	β
4	CH_2OAc	H	β	β
5	CH_2OH	OH	β	β
6	CH_2OAc	OAc	β	β
7	$CH_2OCOC_6H_5$	H	β	β
8	OH	OH	β	β
9	OH	H	β	β
10	CH_2OH	H	α	α
11	CH_2OAc	H	α	α
12	CH_2OH	OH	α	α
13	CH_2OAc	OAc	α	α
14	OH	OH	α	α
15	OH	H	α	α
16	H	OH	β	α
17	H	OH	α	β
22	H	Br	β	β

RESULTS AND DISCUSSION

^{1}H NMR Studies

Previous ^{1}H NMR support[2d] for the *cis* B/C ring fusion in natural rotenoids was the chemical shift of 1-H in $CDCl_3$ or C_6D_6, $J_{6a,12a} \sim 4.0$ Hz and the small coupling constants $J_{6a,6ax} \sim 1.0$ Hz and $J_{6a,6eq} \sim 4.0$ Hz. The B- and C-ring conformations arrived at on the basis of these coupling constants were appropriately described with dihedral angles of 65 ° and 55 °, estimated from a Dreiding model (Figure 1, conformation G$^-$). X-ray studies confirmed the predominance of this conformer, as well as the bent nature of the rotenone molecule consequent upon the *cis* B/C-fusion.[2e]

As we have already discussed earlier,[3a] the ^{1}H NMR-spectra in $CDCl_3$ and C_6D_6 of rotenone *1* and the 12a-CH_2OH derivatives *3–6* and *10–13* revealed coupling constants $J_{6a,6ax} \sim 1.0$ Hz and $J_{6a,6eq} \sim 3.0$ Hz.

The present detailed investigation of the 250 MHz proton spectra (Table I) in C_6D_6 of 12a-OH compounds *8* and *14* revealed coupling constants $J_{6a,6ax}$ = 1.0–1.1 Hz and $J_{6a,6eq}$ = 2.3–2.4 Hz (Table I). These constants are very close to those observed[2d] for tephrosin *18* (1.2 Hz and 2.1 Hz) and for rotenone *1*, that we measured in the same solvent ($J_{6a,6ax}$ = 1.0 Hz and $J_{6a,6eq}$ = 3.0 Hz).

In order to rule out the influence of the solvent on the ^{1}H NMR parameters of the studied compounds, the NMR spectra in CD_3CN of selected compounds *1*, *4*, *7*, *8*, *12* and *14* (Table I) were recorded. The analysis of these spectra showed no solvent due conformational changes and yielded coupling constants $J_{6a,6ax}$ = 1.0–1.4 Hz and $J_{6a,6eq}$ = 2.3–2.4 Hz, except for *7* ($J_{6a,6ax} = J_{6a,6eq}$ = 1.8 Hz). The magnitude of the observed coupling constants between 6a-H and the geminal 6-H_2 protons corroborates the *cis*-configuration of the studied compounds and indicates a similar conformation of ring B in the natural rotenone *1* and the 12a-substituted derivatives. Moreover, irradiation of 6a-H in *1* and the 12a-CH_2OH compound *12* showed almost equal NOE

TABLE I

^1H NMR parameters (δ(ppm) and J(Hz)) of compounds 1, 4, 7, 12 *and* 14

Comp. No	Solv.	1	4	10	11	6a	6ax	6eq	12a-H or 12a-CH_2	$^3J_{6a6ax}$	$^3J_{6a6aq}$
1	CD_3CN[a]	6.67 s	6.48 s	6.51 d	7.77 d	5.01 ddd	4.20 ddd	4.52 dd	3.84 dd	1.0	3.0
4	CD_3CN	6.65 s	6.51 s	6.53 d	7.78 d	4.94 bs	4.47 dd	4.51 dd	4.84 d 4.28 d	1.3	2.3
7	CD_3CN	6.75 s	6.56 s	6.57 d	7.84 d	5.26 t	4.59 d	(2H)	5.17 d 4.54 d	1.8	1.8
	$CDCl_3$	6.76 s	6.47 s	6.51 d	7.87 d	4.98 dd	4.53 dd	4.59 dd	5.11 d 4.64 d	1.2±0.2	2.5±0.2
8	CD_3CN	6.59 s	6.55 s	6.59 d	7.81 d	4.69 dd	4.45 dd	4.57 dd		1.1	2.4
	C_6D_6	6.93 s	6.50 s	6.32 d	8.02 d	4.12 dd	4.44 dd	4.33 dd		1.1±0.1	2.4±0.1
12	CD_3CN	6.67 s	6.45 s	6.51 d	7.75 d	5.10 dd	4.46 dd	4.50 dd	4.38 d 3.64 d	1.4	2.4
14	CD_3CN	6.56 s	6.50 s	6.56 d	7.78 d	4.66 dd	4.41 dd	4.54 dd		1.0	2.3
	C_6D_6	6.89 s	6.41 s	6.33 d	7.99 d	4.27 dd	4.47 dd	4.36 dd		1.0±0.3	2.3±0.3

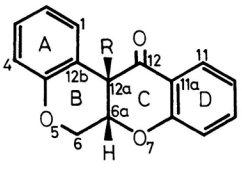
[a] Digital resolution of all spectra in CD_3CN being ±0.1 Hz
[b] For all compounds $^3J_{10,11}$ = 8.5 Hz
[3] $J_{12a',12a''}$ = 11.5–12.5 Hz
[2] $J_{6ax,6eq}$ = 12.0–12.5 Hz

enhancement of the two 6-H_2 protons. This is in accordance with the observed *J*-values and supports the *gauche* orientation of the two ring oxygens in *1* and *12*. In view of the *cis* B/C fusion and the retention of the preferred B-ring conformation upon substitution at C_{12a}, significant changes in the C-ring conformation are not to be expected. The ^1H NMR evidence indicates that introduction of 12a-substituents has no marked conformational effect and cannot explain the observed sign inversion of the longest wavelength Cotton effect.

Molecular Mechanics Studies

The basic skeleton of rotenoids, the four-ring chromanochromanone system *19* with different substitution at 12a-position (R = H(*19*), CH_2OCOCH_3(*20*), $CH_2OCOC_6H_5$(*21*)) served as model compounds for computations, carried out with the MM2 force field.[5]

Starting conformations were generated by combinations of different conformations of the two *cis*-fused B- and C-rings and by rotations around the C_{12a} — CH_2OCOR' and the CH_2 — OCOR'-bonds (R' = CH_3(*20*), C_6H_5(*21*)). The electrostatic interactions were estimated with an effective dielectric constant of 4.0. The results of the empirical energy calculations are presented in Table II. Designation of the conformations is given in Figures 1 and 2.



19. R = H
20. R = CH_2OCOR', R' = CH_3
21. R = CH_2OCOR', R' = C_6H_5

TABLE II

Computed low-energy conformers of 19–21

Compound	Relative steric energy (kcal/mol)			
	Conformer G(–)		Conformer T	
19	0.00		0.71	
20 (21)[a]	g(+)t	0.00 (0.00)	g(–)t	0.83 (0.74)
	g(+)g(–)	0.68 (0.97)	g(+)t	1.49 (1.00)
	tt	0.74 (0.54)	g(–)g(–)	1.66 (1.77)
	tg(+)	1.15 (1.12)	g(–)g(+)	1.68 (1.81)
	g(–)t	1.58 (1.23)	g(+)g(–)	2.22 (1.69)
	g(–)g(–)	1.96 (1.76)	g(+)g(+)	2.41 (1.78)
			tt	2.50 (2.33)
			tg(–)	2.51 (2.66)

[a] Values for compound *21* are given in parentheses

Four conformations resulted for the unsubstituted compound *19* (Table II). Two of them were found to have energies more than 5.0 kcal/mol above the lowest energy conformer *19*.G(–), and most probably these are saddle points along the path for interconversion between the two conformers *19*.G(–) and *19*.T. The lowest energy conformer *19*.G(–) has the two ring oxygens *gauche* to each other, while these are *anti* dispositioned in *19*.T (Figure 2). The energy difference between the two low energy conformers is mainly due to differences in the torsional energy contributions. Computations with the MMP2-version of the programme did not alter the conformational preferences.[6] Assignment of bond dipole moments to the C_{ar} — H-bonds, according to ref. 7, further increases the energy of conformer *19*.T. The computed lowest energy conformer *19*.G(-) has the geometry corresponding to the observed two small $J_{6a,6ax}$ and $J_{6a,6eq}$ constants (Table I).

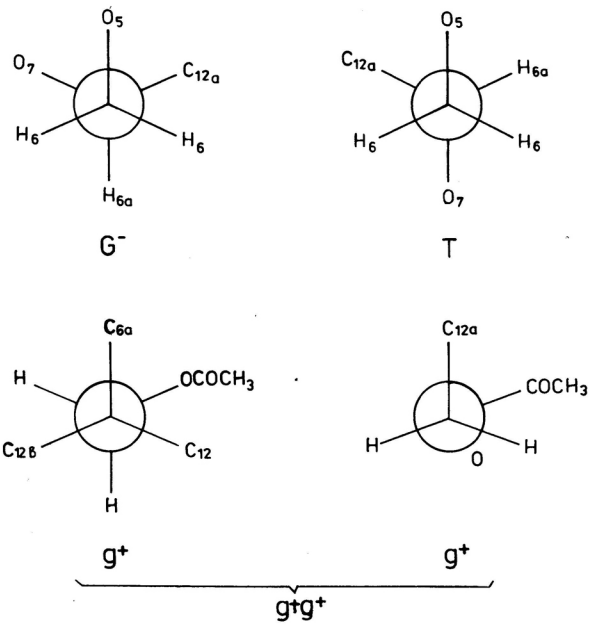


Figure 1. Description of the geometry and designation of the torsional angles in the case of compound *20*. G (*gauche*) and T (*anti*) refer to the four-atom unit $O_5-C_6-C_{6a}-O_7$. Assuming the positive values of the torsional angles to correspond to clockwise rotation, g^+ refers to a *gauche*-(+) disposition $C_{6a}/OCOCH_3$ (rotation around the $C_{12a}-CH_2OCOCH_3$ bond), respectively, $C_{12a}/COCH_3$ (rotation around the $CH_2-OCOCH_3$ bond); t and g^- designate the other two staggered conformations for these rotations.

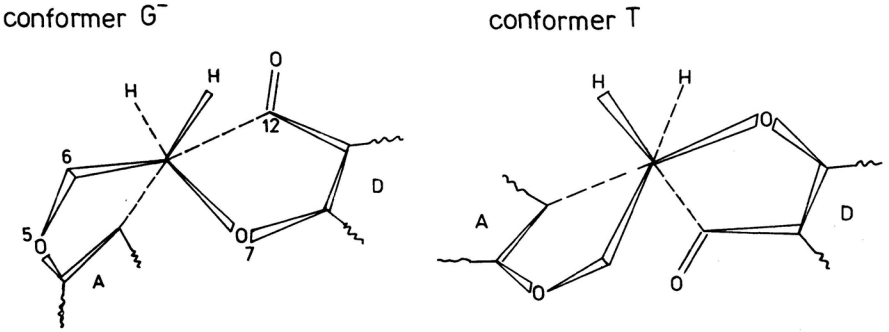


Figure 2. Computed lowest energy conformers, G^- and T, of compound *19*.

Different substitution at 12a-position retains the same conformer, *20*.G(–) and *21*.G(–). as the preferred one. Assignment of bond dipole moments to the C_{ar} — H-bonds[7] has no influence on the results, even for the extreme case of *21*, where additional bond-dipole/bond-dipole interactions occur of the benzoyl group with the A- and D-rings. Lower values of the dielectric constant resulted at even higher energies for

the conformers of type T. In this particular case, *21*, the lowest energy conformers G(–) g(+)t, G(–)tt and Tg(–)t have the benzoyl ring perpendicularly oriented with respect to the average plane of rings C and D (*21*.G(–)g(+)t), or held apart from the aromatic rings A and D (*21*.G(–)tt and *21*.Tg(–)t).

The main conformers G(–) and T only slightly differ with respect to the helicity of ring C. The torsional angle O=C—C_{11a}—C_{11} has the value –2.9 ° for conformer *19*.G(–) and 0.6 ° for conformer *19*.T, and these values practically do not change upon substitution at 12a-position. X-ray data[2e] for 8'-bromorotenone *22* are also indicative of a slight deviation of the C=O-bond from coplanarity with the plane of ring D.

Circular Dichroism Studies

The CD-data of compounds *1–3*, *5-8*, *12* and *14* are presented in Table III. Because of the presence of several chromophores with relatively strong absorption in the spectral range from 360 to 190 nm, all studied compounds show CD-spectra with many Cotton effects.

The model compounds *1* and *2* of unambiguously determined 6a-βH,12a-βH-absolute configuration[2] show two bands (Figure 3) above 300 nm: the longer wavelength CE around 350 nm arising from n→π^*-transition of the acetophenone chromophore (R-band)[8,9] and the CE with maximum at 307 nm, associated with the longest wavelength aromatic $\pi\rightarrow\pi^*$-transitions of ring A. The found position agrees well with the value expected according to Petruska.[10]

Below 300 nm, both *1* and *2* show a relatively strong negative CD-band at 276–277 nm, which coincides well with the literature data for the longest wavelength aromatic transitions (B-band) of the acetophenone chromophore (270–290 nm)[8] As these two longest wavelength ^1L_b-transitions (at 277 nm and 307 nm) are associated with relatively weak UV-absorbance (small ε values, *c.f.* $PhCOCH_3$, $\varepsilon\sim1000$ (278 nm); PhOMe $\varepsilon\sim1400$ (269 nm)), there are no reasons for expecting an exciton interaction between them. This conclusion is based on the exciton theory and other experimental data, where also the bisignate curves within ^1L_b-band do not arise from exciton coupling (see ref. 9, p. 149–169 and ref. 11, p. 32–46). The expected stronger ^1L_a-transition of the same chromophore, called sometimes charge-transfer or K-band, appears in *1* and *2* around 240 nm as a very intense positive CD-band.

In addition, two very strong bands of more complex origin (a negative around 210 nm and a positive one around 190 nm) have been found in both cases. The positive band around 240 nm and the negative one around 210–220 nm in CD-spectra of *1*, *2*, *3*, *5* and *8* could be in principle rationalized as resulting from exciton interactions, namely between the electric transition dipoles of ring A and the acetophenone chromophore within ^1L_a and ^1B bands. However, the analysis of possible mutual orientation of these chromophores in the most preferred conformation derived from NMR and molecular mechanic studies, indicates nearly *coplanar location* of the electric dipoles μ. In such a case, according to the exciton theory, only negligible coupling could be expected.

It is evident from Table III, that the CD-spectra of the 12a-substituted analogues *3*, *5* and *6* below 300 nm are very similar to those of the parent *1* and *2* (including B-band, which remains unaffected by 12a-substitution). This fact has been used for empirical correlation of their 12aS-absolute configuration.[3a] However, the clearly observed sign inversion of the CEs above 300 nm in all *cis* 6a-βH,12a-βR^1-derivatives *3*,

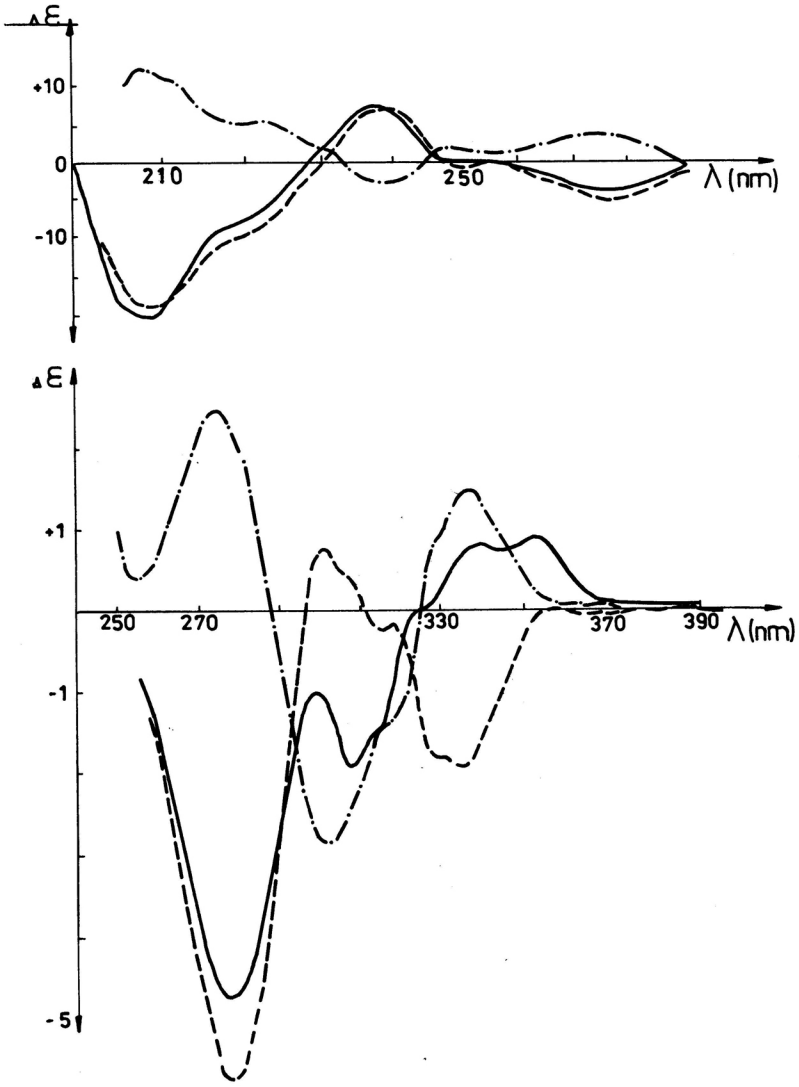


Figure 3. CD-spectra of compounds *2* (———), *5* (– – – –) and *12* (–·–·–) in CH_3CN.

5–6 and *8*, as compared with the parent *1* and *2*, forced us to check the above mentioned configurational assignment using the exciton chirality method. For this purpose, we prepared the *O*-benzoyl-derivative *7*. A comparison of the CD-spectra of *7* and the starting *3* (Figure 4) showed that the bands at 336, 308, 278, 242 and 208 nm, common to both compounds, are more intensive for *7*. The *O*-benzoylation leads to a positive band at 242 nm ($\Delta\varepsilon$ = +13.4) and a negative one at 222 nm ($\Delta\varepsilon$ = –21.4), both much more intensive than the observed bisignate curve of *3* in the same region. We regard this as a clear indication of exciton coupling interaction between ^1L_a (CT) – band of the benzoate chromophore (UV λ_{max} 230 nm, ε = 15300) and ^1L_a (CT)-band of the

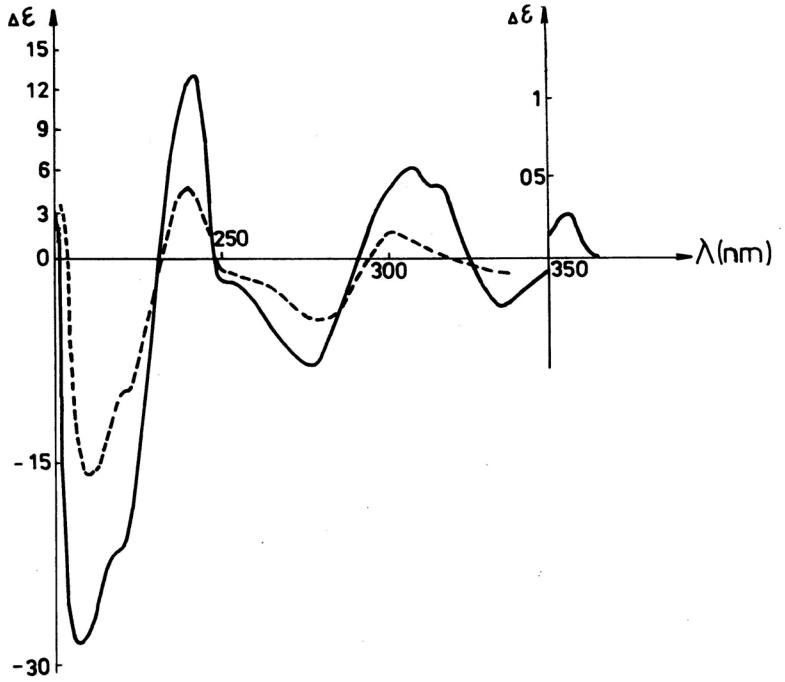


Figure 4. CD-spectra of compounds *3* (– – –) and *7* (——) (benzoyl derivative of *3*) in CH_3CN.

acetophenone chromophore (UV λ_{max} 243 nm, ε = 12600). It is obvious from Figure 4 that the difference CD between *7* and 3 below 245 nm leads to a net positive split band. This result becomes understandable considering the most preferred conformer G(–)gt, where the electric dipoles, almost parallel to the long axes of Ph-rings, are suitably oriented for exciton interaction. The other less preferred conformation G(–)tt has the benzoyl group outside of the ring system in achiral position towards the acetophenone chromophore. The possible exciton interaction of the opposite sign to the benzoate group in *7* with the sum electric dipole associated with ^1L_a-transition of ring A in G(–)gt conformer seems to have a much weaker contribution due to less suitable geometry.

This leads, in a nonempirical way, to the solution on the 12aS-configuration of *7* and all related compounds. This supports the previously made empirical correlation between *1*, *2*, *3*, *5* and *6*.

As expected, the compound *12*, heterochiral to *5* at C_{12a} and C_{6a}, gives an almost antipodal CD-spectrum. The same holds for the CEs of the 12a-OH – derivatives *8* (6a-βH, 12a-βOH) and *14* (6a-αH,12a-αOH). In this case, however, a considerable difference of the relative intensity of both CEs between 270–300 nm is observed.

Although homochiral at C_6 and C_{12a}, the model compounds *1* and *2* and the 12a-substituted derivatives *3*, *5–8* show antipodal CEs above 300 nm (see Table III and Figures 3 and 4). Actually, a positive CE for rotenone *1* and negative ones for the homochiral 6a-βH,12a-βOH - derivatives tephrosin *18* and milletosin *23* within n→π^* -transition around 350 nm has been recorded by Ollis and co-workers.[2c] However, be-

TABLE III

CD-data of 1, 2, *and some 12a-substituted derivatives in acetonitrile*

Compound	$\lambda_{max}(\Delta\varepsilon_{max})$
1	352(+1.21), 338sh(+1.04), 307(–2.07), 276(–5.98), 237(+9.10), 209(–25.07). 192(+23.33).
2	352(+0.86), 338sh(+0.76), 307(–1.91), 276(–4.62), 237(+6.70), 208(–19.70), 194(+18.23).
3	336(–1.36), 331(–1.36), 301(+1.43), 280(–4.03), 273(–3.78), 250(–0.86), 239(+5.18), 220(–9.36), 207(–16.22), positive below 200 nm.
5	364(–0.05), 334(–1.92), 315sh(–0.25), 301(+0.73), 278(–5.62), 250sh(–1.39), 238(+6.38), 208(–18.8).
6	356(+0.23), 334(–2.63), 308(+2.19), 277(–8.00), 208(–30.50), 194(+27.87).
7	354(+0.27), 336(–3.10), 317sh(+5.74), 308(–6.45), 304sh(+6.12), 279(–7.91), 251sh(–2.07), 242(+13.37), 222(–21.36), 208(–28.48).
8	355(+0.22), 329(–4.47), 297(+0.63), 276(–2.97), 242(+6.35), 221(–12.43), 206(–13.00), positive below 200 nm.
12	336(+1.44), 301(–2.83), 274(+2.40) 249(+1.43), 238(–3.28), 222sh(+4.70), 208(+11.62).
14	355(–0.43), 330(+5.38), 297(–6.59), 272(+0.84), 243(–6.95), 223(+15.57), 206(+13.42), negative below 200 n.

cause of the old instrumentation used by these authors a reliable comparison of their data with ours is not possible. It is known[8,9,12] that the sign of n→π^*-CE strongly depends on the helicity of the nonplanar acetophenone chromophore, namely the sign of the torsional angle $O=C_{12}—C_{12a}—C_{11a}—C_{11}$, which agrees well with the observed positive CE at 330 nm of *1* and *2*. The very close values of the coupling constants $J_{6a,6ax}$ and $J_{6a,6eq}$ of the parent compounds *1* and *2* and the 12a-substituted derivatives *4*, *5*, *7*, *8* and *14*, however, do not support directly the earlier assumption[4] that the main reason for the observed sign inversion of the CE above 300 nm in the 12a-substituted compounds is a change of the preferred sofa-conformation of ring C and, consequently, of the helicity of the acetophenone chromophore.

Moreover, according to our computed results, the mentioned torsional angle in the main conformer of *19* (near analogue of *1*), namely G(–), is of very small absolute value and even of opposite sign (–2.9 °) to that expected for the experimentally observed positive CE at 338 nm for *1*.

CONCLUSION

The reason for the observed sign inversion of the CEs above 300 nm in the 12a-substituted analogues of *1* and *2* remains still obscured and cannot be used for reliable configurational assignments. It could be due either to subtle conformational changes, undetectable by other methods, leading to inversion of the helicity of acetophenone chromophore and consequently of ring B, and/or to the electronic influence of 12a-substituents on the corresponding n→π^*- and π→π^*-transitions.

EXPERIMENTAL

Melting point (uncorrected): Kofler hot stage microscope. TLC: Silica gel GF_{254}, Merck, UV detection. All NMR-spectra were recorded at ambient temperature on a Bruker WM-250 spectrometer supplied with an Aspect 2000 Data System. Accuracy of the published coupling constants and chemical shifts – 0.1 Hz and 0.0004 ppm, respectively. For the NOE experiments, the standard Bruker programme NOEDIFF was used with typical parameters; decoupling power 50 L, preirradiation time 5 s, total number of scans 320. The CD-spectra in a range 400–190 nm (λ (nm)/$\Delta\varepsilon$) were obtained in CH_3CN solution on a Jobin Yvon Mark III dichrograph.

Preparation of 6aβ-H,12aβ-$CH_2OCOC_6H_5$ Rotenone(7)

Treatment of 6aβ-H,12aβ-CH_2OH rotenone *3* with C_6H_5COCl/pyridine at 90 °C for 2 hours. The usual work-up, followed by TLC-purification (C_6H_6:acetone = 12:1) yielded pure *7* – m.p. 202–204 °C (EtOH); *MS* (*m/z*, rel,. int., %): 528(M^+, 34), 326(RDA,100), 204(72), 105(C_6H_5CO,105), 77(C_6H_5,24).

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SAŽETAK

Stereokemijske studije nekih 12a-supstituiranih rotenoidnih derivata

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Na osnovi ^1H NMR, CD i molekulsko-mehaničkih studija razmatra se apsolutna konfiguracija položaja 6a i 12a, kao i konformacija protena B i C nekih *cis*-kondenziranih 12a-supstituiranih derivata (OH, CH_2OH, CH_2OCOR') prirodnih rotinoida, rotenona i amorfigenina.

Cottonovi efekti u CD iznad 300 nm pokazje za sve 12a-supstituirane rotenoide, za razliku od polaznih prirodnih spojeva, neočekivanu promjenu predznaka i ne može se koristitii za pouzdano utvrđivanje konfiguracije. To je postignuto neempirijskim putem, primjenom ekscitonske kiralne metode.