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Stereoisomerism and Crystal Structure of (1*R*,2*S*,5*R*)-(+)-4-(Benzoyloxymethylene)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-one {(1*R*,2*S*,5*R*)-(+)-4-(Benzoyloxymethylene)-3-pinanone}

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Synopsis. Conjugated esters from (+)-isopinocamphone, with a terpenic skeleton which is easily epimerizable may theoretically exist as four diastereomers (2*R*,4*E*; 2*R*,4*Z*; 2*S*,4*E*; 2*S*,4*Z*). X-Ray analysis shows that the reaction leads to a single isomer, namely an isopinocamphone derivative (2*S*,4*E*).

The study of some conjugated esters obtained from 3-pinanone [(1*R*,2*R*,5*S*)-(+)-isopinocamphone] showed that their stereochemistry is somewhat complicated. Three points had to be defined:

i) configuration around the double bond (*Z* or *E*)

ii) chirality of the conjugated system due to flexibility of the terpenic cycle (right or left-handed helix) and

iii) configuration of the chiral center C-2 (*R* or *S*).

(+)-Isopinocamphone¹⁾ is indeed a terpenic bicyclic ketone in which the α-carbon atom bearing the methyl group epimerizes easily during reactions in basic media. Many authors showed that at room temperature and in presence of sodium alcoholate,²⁾ (+)-isopinocamphone leads to a mixture of (1*R*,2*R*,5*S*)-(+)-isopinocamphone (75%) and (1*R*,2*S*,5*S*)-(+)-pinocamphone (25%).

On the other hand, Hirata³⁾ laid the stress upon the difficulties of structural elucidation due to conformational mobility.

This is why, besides studying NMR spectra and circular dichroism (CD) of these compounds, we called, at last, upon X-ray analysis to achieve structure determination of one of these esters.

Results and Discussion

Synthesis of esters has been performed as follows. The formyl ketone⁴⁾ was transformed to ester by acylation in pyridine. The ester has the *E* configuration (presence in the ^{1}H NMR spectrum of a lone signal for the ethylenic proton at about δ 8.3). In the *Z* configuration the signal would appear at higher field. In fact, a comparative study of the ^{1}H NMR spectra of two phenylmethylenepinocamphone⁵⁾ and nopinone⁶⁾ *Z* and *E* showed for the *Z* isomer an ethylenic proton at δ 6.10 and for the *E* isomer at δ 8.3 due to downfield effect of the two double bonds. This result will be confirmed in this paper by X-ray analysis. Thus, the *E* isomer is formed alone in this reaction. The greater stability of the *E* isomer is consistent with i) the less steric hindrance and ii) the less electric interaction between C=O and C–O dipole in this isomer than in the *Z* one.

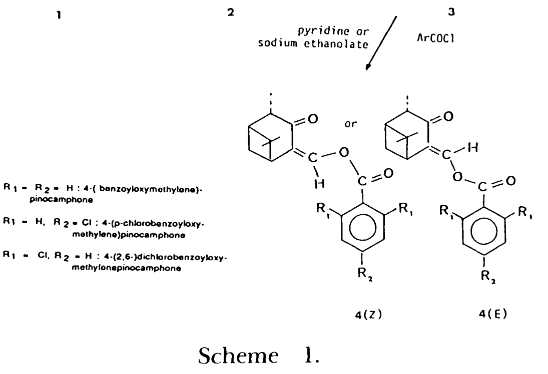
Synthesis of the (*Z*)-ester (even as a mixture *Z*/*E*) failed although two attempts were performed: photoisomerization of the (*E*) isomer and acylation at low temperature (−70 °C) of the sodium salt of 4-(hydroxymethylene)isopinocamphone. The latter was obtained by reaction with sodium alcoholate. This technique was successful with similar 2- and 3-bornanone derivatives.⁷,⁸⁾

Concerning now the configuration of the C-2 chiral center ^{1}H NMR spectra (300 MHz) of the isolated products give some interesting informations.

The *p*-chlorobenzoate revealed in its spectrum the presence of two doublets with the same coupling constant J=6.5 Hz at δ 1.20 and 1.30 in a ratio 89/11. Unlike to the *p*-chloro derivative the benzoate and 2,6-dichlorobenzoate purified under the same conditions show a single doublet at δ 1.20 with J=6.50 Hz proving the presence of a lone isomer. It was thus interesting to determine precisely the configuration of one of these pure isomers by X-ray analysis.

X-Ray Analysis. A white crystal with approximate dimensions of 0.2×0.25×0.3 mm was used for the data collection. The intensity was measured using a CAD4-ENRAF-NONIUS⁹⁾ four circles diffractometer with graphite monochromated Mo*K*α radiation (λ=0.71073 Å) by means of the ω-2θ scan technique up to 70° in 2θ (scan speed for the pre-scan 10° min^{-1}) at room temperature.

Crystal Data. $C_{18}H_{20}O_3$ crystallizes in orthorhombic system, space group $P2_12_12_1$ with: a=10.425(6), b=11.049(7), c=13.725(7) Å, V=1581(3) Å^3 with Z=4, F(000)=608, d_{cal}=1.19 g cm^{-3}, μ(Mo *K*α)=0.7 cm^{-1}.



Scheme 1.

Among the 3889 reflections measured 1509 independant reflections with $I > 3\sigma(I)$ were used to refine the 190 variable parameters.

The measured intensities were corrected for the Lorentz and polarization factors, no absorption correction was performed according to the small value of the absorption coefficient.

All calculations were performed using a DIGITAL Vax 730 computer, by means of SDP (Structure Determination Package) of ENRAF-NONIUS system. This structure was solved using direct method and refined by full matrix least-squares procedure.

In the last refinement all of the positions and thermal parameters of the nonhydrogen atoms were refined, for the hydrogen atoms their contributions were only introduced but not refined (R=0.055).

The final atomic parameters of the carbon and oxygen atoms are given in Table 1, according with labeling of these atoms shown in Fig. 1.

Analysis shows that the isolated ester obtained from (+)-isopinocamphone is in fact a pinocamphone derivative. Thus, epimerization took place during the reaction. In addition the conjugated system OC-C=C incorporated in the ring is not planar but skewed in the sense of a right-handed helix (torsional angle +11.89°) (Table 2). The skewness in this case is consistent with the sign of the Cotton effect of the $\pi \rightarrow \pi^*$ transition.

Table 1. Positional Parameters and Their Estimated Standard Deviations

Atom	x	y	z	$B/\text{Å}^2$
O1	0.3650(3)	1.0026(3)	0.7930(2)	6.96(8)
O2	0.5369(2)	0.8810(3)	0.7821(2)	4.62(6)
O3	0.6395(3)	0.9639(3)	1.0646(2)	6.85(8)
C1	0.9391(4)	0.8509(4)	0.9611(3)	5.6(1)
C2	0.8609(5)	0.9181(4)	1.0381(3)	5.12(9)
C3	0.7204(4)	0.9261(4)	1.0092(3)	4.85(9)
C4	0.6884(4)	0.8861(4)	0.9081(3)	4.29(8)
C5	0.7946(4)	0.8240(4)	0.8543(3)	5.5(1)
C6	0.9190(4)	0.9016(5)	0.8575(3)	6.1(1)
C7	0.8620(5)	0.7374(4)	0.9292(4)	6.7(1)
C8	1.0217(5)	0.8562(7)	0.7862(4)	9.6(2)
C9	0.9031(5)	1.0383(5)	0.8434(4)	7.7(1)
C10	0.8732(6)	0.8618(5)	1.1397(4)	7.3(1)
C11	0.5746(4)	0.9130(4)	0.8748(3)	4.58(9)
C12	0.4249(4)	0.9288(4)	0.7486(3)	4.58(9)
C13	0.3894(4)	0.8798(4)	0.6530(3)	4.50(8)
C14	0.2899(4)	0.9354(5)	0.6026(4)	6.3(1)
C15	0.2543(5)	0.8929(6)	0.5115(4)	7.8(1)
C16	0.3149(5)	0.7949(5)	0.4713(4)	7.3(1)
C17	0.4132(5)	0.7396(5)	0.5200(3)	6.5(1)
C18	0.4513(4)	0.7815(4)	0.6109(3)	5.1(1)

Anisotropically refined atoms are given in the form of the isotropic equivalent displacement parameter defined as: $(4/3)\cdot[a^2\cdot B(1,1)+b^2\cdot B(2,2)+c^2\cdot B(3,3)+ab(\cos\gamma)\cdot B(1,2)+ac(\cos\beta)\cdot B(1,3)+bc(\cos\alpha)\cdot B(2,3)]$

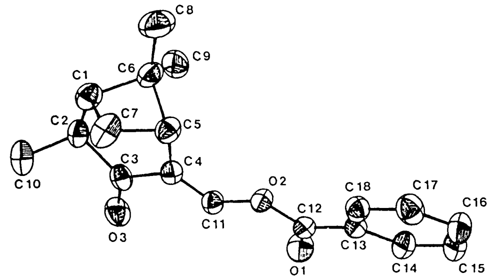


Fig. 1. Perspective view of **4a** and the numbering of the atoms.

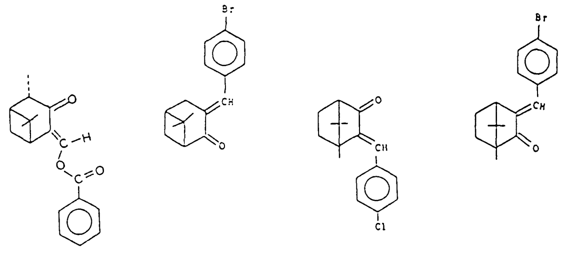
Table 2. Torsion Angles

Atom 1	Atom 2	Atom 3	Atom 4	Angle (ϕ/°)
C12	O2	C11	C4	189.89 (0.38)
C11	O2	C12	O1	5.69 (0.58)
C11	O2	C12	C13	185.08 (0.33)
C6	C1	C2	C10	175.77 (0.40)
C7	C1	C2	C3	316.10 (0.47)
C1	C2	C3	O3	171.82 (0.40)
C1	C2	C3	C4	351.01 (0.50)
C10	C2	C3	O3	46.04 (0.54)
C10	C2	C3	C4	225.24 (0.38)
O3	C3	C4	C11	11.89 (0.61)
C2	C3	C4	C11	192.70 (0.37)
C3	C4	C11	O2	179.36 (0.35)
C5	C4	C11	O2	2.48 (0.67)
C4	C5	C7	C1	276.31 (0.38)
O1	C12	C13	C14	10.32 (0.66)
O1	C12	C13	C18	189.97 (0.43)
O2	C12	C13	C14	190.95 (0.37)
O2	C12	C13	C18	10.59 (0.56)
C12	C13	C14	C15	179.22 (0.44)
C12	C13	C18	C17	180.14 (0.42)

However we have to put us in mind of the fact that the CD sign of this transition in conjugated ketones does not reflect always the true chirality of the enone system (many exceptions have been reported[10,11]).

In effect, inspection of Scheme 2 reveals that although the sign of the $\pi \rightarrow \pi^*$ transition in 2-(p-chlorobenzylidene) 3-bornanone **6**[12] and 4-(benzoyloxymethylene) 3-pinanone **4** shows the true skewness of the enone system, unfortunately in the case of 3-(p-bromobenzylidene) nopinone **5**[13] the CD sign is negative while the conjugated system has a right-handed skewness.

On the other hand, in a similar camphor (bornanone-2) derivative **7**[14] while the enone grouping is planar, the $\pi \rightarrow \pi^*$ transition still has a positive CD.



	4(E)	5(E)	6(E)	7(E)
conjugated system	right-handed skewness	right-handed skewness	left-handed skewness	planar
torsion angle	+11°89	+17°	-4°	0
transition	$\Delta\varepsilon > 0$	$\Delta\varepsilon < 0$	$\Delta\varepsilon < 0$	$\Delta\varepsilon > 0$
Derivatives of :	pinocamphone	nopinone	3-bornanone	2-bornanone

Scheme 2.

These results show undoubtedly that there is no direct correlation between the sign of the CD of the $\pi\rightarrow\pi^*$ transition and the chirality of the conjugated system in enones.

To the best of our knowledge there is yet no satisfactory explanation of these facts.

X-Ray analysis shows also that the aromatic ring is twisted by 10.32° and is no more coplanar with the ester carbonyl group.

At last, the angle between CH_3-10 and the ketone carbonyl group (46°) implies a pseudoequatorial or a pseudoaxial position for this methyl and would explain, in part, the weak values of the CD of the $n\rightarrow\pi^*$ transition.

Experimental

General. Melting points were determined on a oil bath. Values are uncorrected. Rotatory power was measured with a Rudolf type polarimeter and Circular Dichroism with Dichrograph Mark V Jobin-Yvon. IR spectra were recorded on a Perkin-Elmer 1600 FTIR, and NMR spectra on a Bruker AM 300 WB in $CDCl_3$. Shifts are given in parts per million.

The Preparation of (+)-Isopinocamphone (2): (+)-Isopinocamphone [(+)-3-pinanone] was prepared by oxidation with chromium trioxide of (1*R*,2*R*,3*R*,5*S*) (−)-isopinocampheol [mp: 51—53 °C, $[\alpha]^{20}_{\mathrm{D}}$ (*c* 20, ethanol)] by the procedure of Brown et al. (loc. cit.), $[\alpha]^{20}_{\mathrm{D}}=+19°$ (*c* 3, ethanol).

The Preparation of 4-(Hydroxymethylene) Isopinocamphone (3): Formylation of (+)-isopinocamphone has been performed according to the procedure of Bessière-Chrétien et al. (loc. cit.) using sodium amide in the place of sodium ethanolate: yield 75%, $[\alpha]^{20}_{\mathrm{D}}=+52°$ (*c* 3.6, cyclohexane).

The Preparation of Esters of 4-(Benzoyloxymethylene) (4a), 4-(*p*-Chlorobenzoyloxymethylene) (4b), and 4-(2,6-Dichlorobenzoyloxymethylene)pinocamphone (4c). To a stirred solution of **3** (6 g, 0.0209 mol) was added dropwise the acid chloride (6 g, 0.03 mol). A white precipitate is formed. The mixture is kept at room temperature for 12 h, acidified with 100 ml of a 50% hydrochloric acid solution and extracted with ether. The ether solution was washed with a saturated aqueous sodium hydrogencarbonate and water, dried and evaporated. The white residue in recrystallized from cyclohexane: yield 60%.

4a. Mp: 123 °C, $[\alpha]^{20}_{\mathrm{D}}=+112°$, (*c* 3.3, dioxane), IR ($CHCl_3$): C=O ester 1743, C=O terp. 1701, C=C 1629, C-O 1256 and 1149 cm^{-1}; CD (*c* 3.33, dioxane) $\Delta\varepsilon_{333}=+0.85$, (*c* 0.33, dioxane) $\Delta\varepsilon_{270}=+6.1$; ^{1}H NMR ($CDCl_3$): $\delta=0.88$ (3H, s, C_9H), 1.17 (3H, d, $C_{10}H$, *J*=7.26 Hz), 1.37 (2H, d, C_7H, *J*=10.7 Hz), 1.44 (3H, s, C_8H), 2.01 (1H, m, C_1H, *J*=6.27 and 2.35 Hz), 2.41 (1H, m, C_2H), 2.74 (1H, m, C_7H), 3.25 (1H, t, C_5H, *J*=6.07 Hz), 7.48 (2H, t, *J*=7.8 Hz aromatic protons), 7.62 (1H, dd, *J*=6.19 Hz aromatic protons), 8.07 (2H, m, aromatic protons), 8.37 (1H, s, $C_{11}H$). Found: C, 75.52; H, 7.05; O, 17.43%. Calcd for $C_{18}H_{22}O_3$: C, 75.52; H, 7.69; O, 16.18%.

4b. Mp: 131 °C $[\alpha]^{20}_{\mathrm{D}}=+85.8°$, (*c* 1.3, dioxane), IR ($CHCl_3$): C=O ester 1741, C=O terp. 1701, C=C 1630, C-O 1254 and 1150 cm^{-1}; CD (*c* 1.03, dioxane), $\Delta\varepsilon_{343}=0.52$, (*c* 0.10, dioxane), $\Delta\varepsilon_{266}=5.30$; ^{1}H NMR ($CDCl_3$): $\delta=0.88$ (3H, s, C_9H), 1.17 (3H, d, $C_{10}H$, *J*=7.2 Hz), 1.37 (2H, d, C_7H, *J*=10.7 Hz), 1.44 (3H, s, C_8H), 2.01 (1H, d, C_1H, *J*=6.22 and 2.39 Hz), 2.63 (1H, m, C_2H), 2.74 (1H, m, C_7H), 3.23 (1H, t, C_5H, *J*=5.90 Hz), 7.47 (2H, t, *J*=7.94 Hz aromatic protons), 8.01 (2H, m, aromatic protons), 8.34 (1H, s, $C_{11}H$). Found: C, 67.11; H, 5.89; O, 14.01; Cl, 12.97%. Calcd for $C_{18}H_{21}O_3Cl$: C, 67.89; H, 6.55; O, 14.97; Cl, 11.07%.

4c. Mp: 108 °C, $[\alpha]^{20}_{\mathrm{D}}=+29°$, (*c* 2.4, dioxane), IR ($CHCl_3$): C=O ester 1763, C=O terp. 1704, C=C 1633, C-O 1249—1154 cm^{-1}; CD (*c* 0.24, dioxane), $\Delta\varepsilon_{345}=+0.42$; (*c* 0.24, dioxane) $\Delta\varepsilon_{258}=+3.90$; ^{1}H NMR ($CDCl_3$): $\delta=0.80$ (3H, s, C_9H), 1.12 (3H, d, $C_{10}H$, *J*=7.25 Hz), 1.27 (1H, d, C_7H, *J*=10.80 Hz), 1.31 (3H, s, C_8H), 1.93 (1H, m, C_1H, *J*=6.29 and 2.34 Hz), 2.50 (1H, m, C_2H), 2.66 (1H, m, C_7H), 3.25 (1H, t, C_5H, *J*=6.02 Hz), 7.34 (3H, m, aromatic protons), 8.27 (1H, s, $C_{11}H$). Found: C, 61.23; H, 5.12; O, 13.61; Cl, 20.04%. Calcd for $C_{18}H_{20}O_3Cl_2$: C, 61.18; H, 5.13; O, 13.59; Cl, 20.11%.

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