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trans-3-Ethyl-*cis*-2,6,6-trimethyl-4-oxocyclohexanecarboxylic acid: an intermediate in the synthesis of a highly potent estrogen

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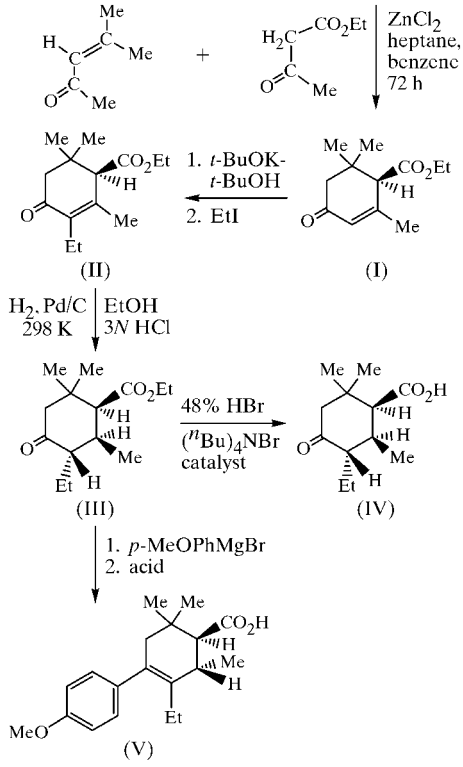
The title compound, $C_{12}H_{20}O_3$, (IV), the ethyl ester of which is an intermediate in the synthesis of a compound reported to be highly estrogenic, has been prepared. After the initial steps reported for the synthesis of this ester intermediate were followed, it was converted into the crystalline acid, (IV), for X-ray analysis. It was verified that (IV) was racemic when prepared. X-ray analysis showed that *anti*-hydrogenation of the double bond had occurred in the synthesis, making the orientation of the carboxyl group *cis* to the 2-methyl group and *trans* to the 3-ethyl group. NMR spectroscopy showed that the stereochemistry of (IV) was identical with that of its ester precursor. While the earlier report did not note the stereochemistry of this ester, it pointed out that the estrogenic product derived from it possessed the opposite carboxyl-2-methyl orientation, *i.e. trans*, although no X-ray analysis was performed. In the light of these results and the importance of correlating biological activity with compound structure, the unequivocal characterization of the highly estrogenic compound is warranted.

Comment

Some years ago, Crenshaw *et al.* (1974) reported syntheses of a series of *p*-methoxyphenylalkylcyclohexanecarboxylic and -cyclohexenecarboxylic acids, some of which they found to be highly estrogenic. Although they showed these compounds to be uterotropically potent, they presumed them to possess high estrogen-receptor binding affinity as well, but they did not test this property. In contrast, our more recent studies of estrogenic carboxylic acids have revealed that they exhibit the paradox of high uterotropic activity with very poor binding affinity for estrogen receptors (Meyers *et al.*, 1988, 1997, 2000; Banz *et al.*, 1998; Robinson *et al.*, 1999; Hou & Meyers, 2000), hence our interest in preparing the Crenshaw compounds, unequivocally determining their structures and correlating them with their uterotropic activities and estrogen-receptor binding affinities.



The syntheses are shown in the *Scheme* above. We repeated the methods used by Crenshaw *et al.* (1974) to prepare the initial ester intermediates (I), (II) and (III), then hydrolyzed ester (III) with aqueous HBr to give (IV). The Crenshaw group treated (III) with a Grignard reagent and hydrolyzed the product under acidic conditions to provide their carboxylic acid estrogen, (V), also shown in the *Scheme* above. Unlike ester (III), an oil, the corresponding carboxylic acid, (IV), is crystalline, permitting its diastereomeric structure to be unequivocally characterized by X-ray analysis.

The structure of (IV) is shown in Fig. 1. The space group for this chiral structure is $P2_12_12_1$. However, (IV) was racemic when prepared, as shown by polarimetric analysis, as well as

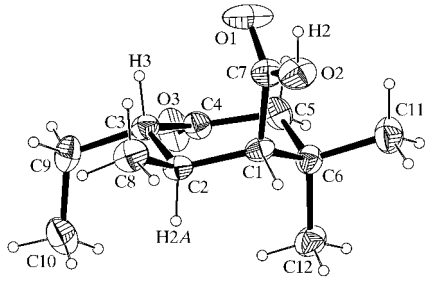


Figure 1
The molecular structure and atom-numbering scheme for (IV), with displacement ellipsoids at the 50% probability level. H atoms are shown as small spheres of arbitrary radii.

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by ^{1}H NMR shift analysis in the presence of a chiral amine. Thus, either the crystal used is the result of spontaneous resolution which produced a mechanical mixture of pure enantiomers (a 'conglomerate'; Jacques *et al.*, 1981), or it is an inversion twin (Flack & Bernardinelli, 1999). The latter choice is the more common, but we cannot be sure since the Flack parameter cannot discriminate in this case (Flack & Bernardinelli, 2000).

Fig. 1 shows the *trans* orientation of the C2-methyl group to the C3-ethyl group, indicating that *anti*-hydrogenation of the double bond occurred in converting (II) to (III), which is responsible for the *cis* orientation of the C1-carboxyl group to the C2-methyl group, likewise clearly exhibited. The stereochemistry of ester (III) is the same as that of its carboxylic acid, (IV), as ascertained from their virtually identical ^{1}H and ^{13}C NMR spectra, the only differences being the resonances of their different carboxyl groups.

The Crenshaw report provided no geometric characterization for their ester (III). In the absence of an unforseen isomerization, it is reasonable to believe that their Grignard reaction at the carbonyl group of (III), followed by acidification, dehydration to form the C3═C4 double bond, and ester hydrolysis, would provide estrogenic carboxylic acid (V) without altering the *cis* orientation of the C1-carboxyl group to the C2-methyl group. However, on the basis of the NMR H1–H2 coupling constant exhibited by (V), they reported a *trans* orientation for the C1-carboxyl to the C2-methyl. No X-ray crystal structure analysis was reported. In the light of these results and the importance of correlating biological activity with compound structure, the X-ray characterization of crystalline (V) is warranted so that the structure can be correlated with its uterotropic activity and receptor-binding affinity.

Fig. 1 also shows that (IV) has the chair conformation, in which the C1-carboxyl group is axial and the C2-methyl group equatorial, providing the *cis* configuration of these groups, while the C3-ethyl group is also equatorial, making it *trans* to both of these groups. Thus, the C6—C1—C2—C8 torsion angle subtended by the C2-methyl group with the ring is essentially linear [−179.0 (2)°], while the C1—C2—C3—C9 torsion angle subtended by the C3-ethyl group with the ring is somewhat less than linear [171.5 (2)°].

Bond distances and angles of interest are given in Table 1. It is noted that, while the angle subtended by the ring with all but one of the substituents is between 109.6 (2) and 111.8 (2)°, that involving the C3-ethyl group, C2—C3—C9, is 114.0 (2)°, suggesting a steric repulsion between this equatorial group and the vicinal equatorial C2-methyl group.

The molecular packing (Fig. 2) shows that the molecules of (IV) form infinite one-dimensional chains parallel to the *b* axis *via* intermolecular hydrogen bonding between the carbonyl O atom and the carboxyl H atom; Table 2 lists the hydrogen-bond geometry.

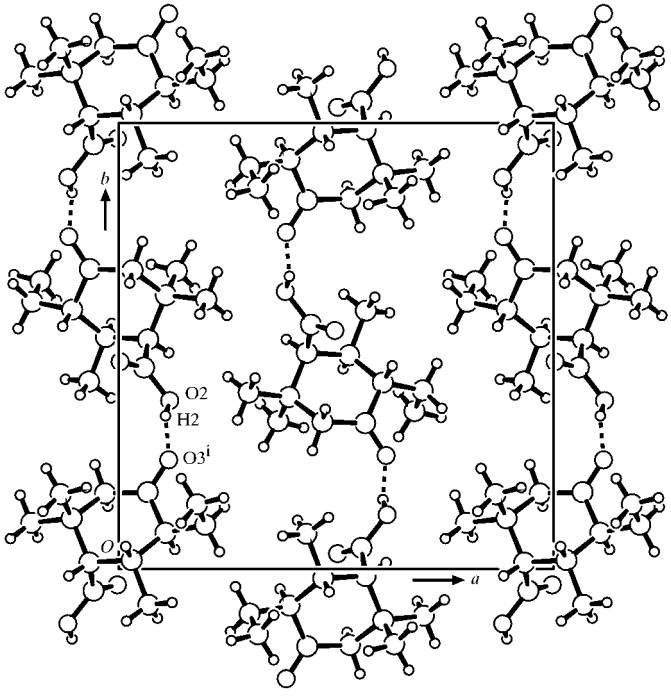

Figure 2
The molecular packing and hydrogen bonding in (IV), viewed down the *c* axis. Note the infinite one-dimensional molecular chains parallel to the *b* axis [symmetry code: (i) $-x, y-\frac{1}{2}, \frac{3}{2}-z$].

Experimental

Compound (I) was synthesized following the method reported by Surmatis *et al.* (1970), and was converted sequentially into compounds (II) and (III), as reported by Crenshaw *et al.* (1974). *Via* hydrolysis in refluxing 48% HBr containing a catalytic amount of $(^n\mathrm{Bu})_4\mathrm{NBr}$, (III) was converted into (IV). White crystals of (IV) were recrystallized twice from hexane (m.p. 394.8–396.2 K). Spectroscopic analysis: ^{1}H NMR ($CDCl_3$, δ, p.p.m.): 0.881 (*t*, *J* = 7.5 Hz, 3H), 0.986 (*s*, 3H), 1.096 (*s*, 3H), 1.123 (*d*, *J* = 6.9 Hz, 3H), 1.512 (*m*, 1H), 1.710 (*m*, 1H), 1.984 (*dd*, *J* = 13.5 and 1.8 Hz, 1H), 2.158 (*m*, 1H), 2.479 (*dd*, *J* = 4.5 and 1.5 Hz, 1H), 2.657 (*m*, 1H), 2.963 (*d*, *J* = 13.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, δ, p.p.m.): 10.51, 17.65, 17.88, 27.87, 28.83, 33.39, 36.44, 50.26, 50.93, 56.67, 179.66, 220.97. The racemic nature of (IV) as prepared was determined as follows: (i) an absolute ethanol solution of 0.046 mol l^{-1} of (IV), as prepared, exhibited an optical rotation of 0.0; (ii) the ^{1}H NMR ($CDCl_3$) resonance of H5 *cis* to the carboxyl of (IV), as prepared, δ 2.963 (*d*), became δ 3.032 (*d*) and δ 2.997 (*d*) in an approximately equimolar solution with (*S*)-(−)-1-phenylethylamine (Aldrich); (iii) likewise, the resonance of H5 *trans* to carboxyl, δ 1.984 (*dd*), became δ 1.897 and δ 1.863 in the same solution with (*S*)-(−)-1-phenylethylamine.

Table 1
Selected geometric parameters (Å, °).

C2—C8	1.538 (3)	C6—C12	1.526 (4)
C3—C9	1.533 (4)	C6—C11	1.533 (4)
C7—C1—C2	110.56 (19)	C9—C3—C2	114.0 (2)
C1—C2—C8	110.9 (2)	C12—C6—C1	109.6 (2)
C8—C2—C3	111.7 (2)	C11—C6—C1	110.33 (19)
C4—C3—C9	111.8 (2)		

Table 2
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
O2—H2···O3^{i}	0.82	1.91	2.712 (3)	164

Symmetry code: (i) $-x, y-\frac{1}{2}, \frac{3}{2}-z$.

Crystal data

$C_{12}H_{20}O_3$
$M_r = 212.28$
Orthorhombic, $P2_12_12_1$
$a = 13.716$ (3) Å
$b = 14.103$ (3) Å
$c = 6.214$ (4) Å
$V = 1202.0$ (9) Å^3
$Z = 4$
$D_x = 1.173$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
$\theta = 9.6$–$9.9°$
$\mu = 0.08$ mm^{-1}
$T = 296$ K
Irregular fragment, colorless
0.41 × 0.33 × 0.27 mm

Data collection

Rigaku AFC-5*S* diffractometer
ω scans
2313 measured reflections
1265 independent reflections
890 reflections with $I > 2\sigma(I)$
$R_{int} = 0.025$
$\theta_{max} = 25.1°$
$h = 0 \rightarrow 16$
$k = 0 \rightarrow 16$
$l = -7 \rightarrow 7$
3 standard reflections
every 100 reflections
intensity decay: 0.7%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.034$
$wR(F^2) = 0.092$
$S = 1.03$
1265 reflections
141 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0509P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.10$ e Å^{-3}
$\Delta\rho_{min} = -0.13$ e Å^{-3}

The absolute configuration of the title molecule could not be determined because of the lack of heavy atoms. The rotational orientations of the methyl and hydroxyl H atoms were refined by the circular Fourier method available in *SHELXL*97 (Sheldrick, 1997). All H atoms were treated as riding, with C—H = 0.96–0.98 Å and O—H = 0.82 Å.

Data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1996); cell refinement: *MSC/AFC Diffractometer Control Software*; data reduction: *PROCESS* in *TEXSAN* (Molecular Structure Corporation, 1997); program(s) used to solve structure: *SIR*92 (Burla *et al.*, 1989); program(s) used to refine structure: *LS* in *TEXSAN* and *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*III (Farrugia, 1997); software used to prepare material for publication: *TEXSAN*, *SHELXL*97 and *PLATON* (Spek, 2000).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK1530). Services for accessing these data are described at the back of the journal.

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