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New Routes to Pyranotetrahydrofuran Derivatives

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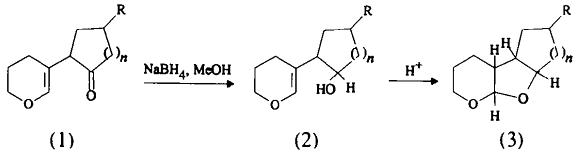
Abstract

The determination of the structure of (4a*RS*,4b*SR*,6*RS*,8a*RS*,9a*SR*)-6-methyl-3,4,4a,4b,5,6,7,8,8a,9a-decahydro-2*H*-benzofuro[2,3-*b*]pyran, $C_{12}H_{20}O_2$, has allowed us to interpret the stereochemistry of the elimination–addition process by which the compound is obtained from the reaction of 3-bromodihydropyran with ketone enolate and sodium amide. The conformation of the molecule in the solid state is discussed and compared with the conformation calculated by molecular-mechanics optimization.

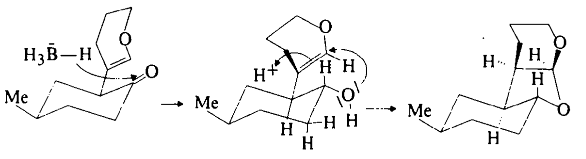
Comment

We showed previously (Jamart-Grégoire, Grand, Ianelli, Nardelli & Caubère, 1990; Jamart-Grégoire, Mercier-Girardot, Ianelli, Nardelli & Caubère, 1995) that dihydropyranyl ketones, (1), could be obtained easily by elimination–addition from 3-bromodihydropyran, ketone enolates and sodium amide. Ketones of type (1) are convenient starting materials for the synthesis of pyranotetrahydrofurans of type (3).



(1) (2) (3)

During the course of this study, we had to consider the determination of the structure of (3) (n = 2, R = Me). Although the nature of the ring junctions could easily be determined from ^{1}H NMR data, the position of the methyl substituent could not. Fortunately, we were able to obtain crystals suitable for an X-ray crystal structure analysis, from which the stereochemistry of the reactions could be deduced (see scheme below). The alcohol (2) is formed by the axial attack of a proton upon compound (1), with formation of the equatorial hydroxy group which was then protonated on the back side of the dihydropyran ring, giving a cationic species stabilized by the O atom on the front side, which was the only side accessible to the hydroxy group.



(1) (2) (3)

Table 3 gives the relevant parameters describing the conformation of the three rings forming the core of the molecule. The configuration at the C4—C5 junction is *cisoid*, while that at C6—C7 is *transoid*. The configurations at the chiral centres, with reference to the labelling of Fig. 1, are C4*R*, C5*S*, C6*R*, C7*S* and C9*R*. The other enantiomer is also present in the crystal, as a consequence of the centrosymmetric space group.

The molecular conformation can be deduced from the torsion angles given in Table 2. The C3—C4 bond is (−)synclinal to O2—C5 and (+)synclinal to C7—C8, while C5—O2 is (−)anticlinal to C6—C11 [O2—C5· · ·C6—C11 −121.0 (2)°] and C9—C12 is (+)-antiperiplanar to C7—C8.

To estimate the influence of packing forces on the molecular conformation, molecular-mechanics calculations were carried out using both *MMX* and *MM+* force fields of the *PCMODEL* (Serena Software, 1989) and *HYPERCHEM* (Autodesk Inc., 1992) suites of programs, respectively. In these calculations, isolated molecules were considered and program default parameters were used, beginning the energy minimization process from the molecular structures found experimentally in the X-ray diffraction analysis. (No allowance was made for non-bonded interactions in the crystal as none was conspicuously significant and any interactions involving charge polarization could only be described if the experimental electric potential distribution in the crystal was available, which is beyond the scope of the present analysis.) The results in terms of bond distances, bond angles and torsion angles are compared with those obtained from the experimental analysis in Table 2. From this comparison, the following general comments can be made. Firstly, a rough general evaluation of the disagreement between the experimental and calculated models is given by the following averages of the absolute values of the differences $|\Delta|$: $|\Delta|_{MMX}$ distances 0.015 Å, angles 1.3, torsions 3.2°; $|\Delta|_{MM+}$ 0.016 Å, 1.3, 3.5°. Second, all the bond-distance values observed, except those involving the O atoms, are less than those calculated and this can perhaps be justified by the fact that the experimental values have not been corrected for the effects of thermal motion. Third, the largest difference in bond angles is observed for the O1—C5—O2 angle, whose value is intermediate between those calculated by the two force fields, indicating that some default parameter used in these calculations was probably not strictly appropriate. Finally, the torsion angles show the largest discrepancies when the O atom of the furan ring is involved, indicating significant differences in the conformation of that ring, possibly due to packing effects; in this respect the comparison of puckering parameters of Table 3 is irrelevant.

Analysis of the thermal motion of the molecule in the crystal, carried out in terms of the Schomaker & Trueblood (1968) **TLS** rigid-body approximation using the *THMV* program (Trueblood, 1984), shows that there is no case of possible disorder, giving quite satisfactory agreements between the observed and calculated atomic displacement parameters. The overall residual disagreement index R_{wU} is only 0.058, in agreement with the low anisotropy of the atomic displacements, the $r_{\max}/r_{\min}$ ratio of the maximum and minimum r.m.s. displacements being in the range 1.34–2.15 with an average value of 1.77.

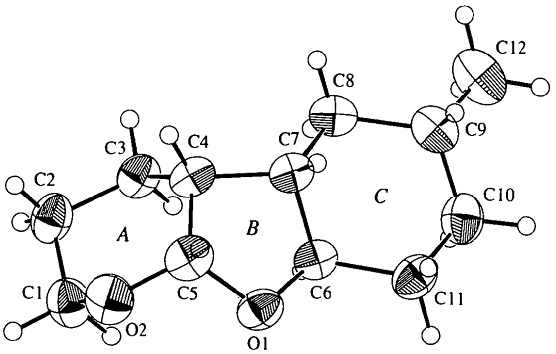


Fig. 1. *ORTEP* (Johnson, 1965) drawing of molecule (3). Ellipsoids are drawn at the 50% probability level.

Experimental

Compound (3) (R = Me, n = 2) was obtained by the action of two equivalents of $NaBH_4$ in EtOH at room temperature on 5-(5-methyl-2-oxocyclohexyl)-3,4-dihydropyran (prepared according to Jamart-Grégoire, Mercier-Girardot, Ianelli, Nardelli & Caubère, 1995), followed by cyclization with 0.1 equivalents of p-toluenesulfonic acid in CH_2Cl_2 for 2 h at room temperature.

Crystal data

$C_{12}H_{20}O_2$
$M_r = 196.29$
Monoclinic
$P2_1/n$
$a = 14.963\ (6)$ Å
$b = 6.093\ (3)$ Å
$c = 12.228\ (5)$ Å
$\beta = 100.14\ (2)°$
$V = 1097.4\ (8)$ Å^3
$Z = 4$
$D_x = 1.188$ Mg m^{-3}
D_m not measured

Cu $K\alpha$ radiation
$\lambda = 1.54178$ Å
Cell parameters from 29 reflections
$\theta = 17.03–39.87°$
$\mu = 0.620$ mm^{-1}
$T = 293\ (2)$ K
Prism
0.42 × 0.39 × 0.28 mm
Colourless

Data collection

Siemens AED diffractometer
$\theta/2\theta$ scans
Absorption correction: none
3953 measured reflections
2084 independent reflections
1917 observed reflections [$I > 2\sigma(I)$]
$R_{\rm int} = 0.0260$

$\theta_{\max} = 70.01°$
$h = -18 \rightarrow 18$
$k = -2 \rightarrow 7$
$l = -14 \rightarrow 14$
1 standard reflection monitored every 50 reflections
intensity decay: none

Refinement

Refinement on F^2
$R(F) = 0.0540$
$wR(F^2) = 0.1064$
$S = 1.227$
2084 reflections
208 parameters
All H-atom parameters refined
$w = 1/[\sigma^2(F_o^2) + (0.0377P)^2 + 0.174P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\max} < 0.001$

$\Delta\rho_{\max} = 0.13$ e Å^{-3}
$\Delta\rho_{\min} = -0.12$ e Å^{-3}
Extinction correction: *SHELXL93* (Sheldrick, 1993)
Extinction coefficient: 0.039 (2)
Atomic scattering factors from *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2)*

$$U_{\rm eq} = (1/3)\Sigma_i\Sigma_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	$U_{\rm eq}$
O1	0.16204 (8)	0.1966 (2)	0.2758 (1)	0.0560 (4)
O2	0.06674 (9)	0.2293 (3)	0.1041 (1)	0.0660 (5)
C1	−0.0178 (1)	0.2962 (4)	0.1332 (2)	0.0644 (7)
C2	−0.0769 (1)	0.1010 (4)	0.1441 (2)	0.0613 (7)
C3	−0.0303 (1)	−0.0462 (4)	0.2367 (2)	0.0526 (6)
C4	0.0655 (1)	−0.1090 (3)	0.2205 (1)	0.0485 (5)
C5	0.1169 (1)	0.0821 (3)	0.1790 (1)	0.0549 (6)
C6	0.1568 (1)	0.0645 (3)	0.3713 (1)	0.0463 (5)
C7	0.1307 (1)	−0.1625 (3)	0.3275 (1)	0.0452 (6)
C8	0.1045 (1)	−0.3041 (3)	0.4189 (2)	0.0533 (7)
C9	0.1849 (1)	−0.3173 (3)	0.5154 (2)	0.0562 (6)
C10	0.2225 (2)	−0.0897 (4)	0.5524 (2)	0.0647 (8)
C11	0.2421 (1)	0.0569 (4)	0.4579 (2)	0.0586 (7)
C12	0.1604 (2)	−0.4467 (5)	0.6124 (2)	0.0759 (9)

Table 2. *Comparison of observed and calculated bond distances (Å), angles (°) and selected torsion angles (°)*

MMX = force field of *PCMODEL*, *MM+* = force field of *HYPERCHEM* and Δ = obs.−calc. Distances: $|\Delta|_{\max}$ *MMX* 0.030 (C1—C2), *MM+* 0.028 (C1—C2). Angles: $|\Delta|_{\max}$ *MMX* 4.7 (O1—C5—O2), *MM+* 3.9 (O1—C5—O2). Torsion angles: $|\Delta|_{\max}$ *MMX* 8.9 (C5—O1—C6—C7), *MM+* 8.3 (C6—O1—C5—O2).

	X-ray obs.	*MMX* calc.	*MMX* Δ	*MM+* calc.	*MM+* Δ
O1—C5	1.437 (2)	1.429	0.008	1.411	0.026
O1—C6	1.432 (2)	1.420	0.012	1.408	0.024
O2—C1	1.433 (3)	1.419	0.014	1.406	0.027
O2—C5	1.401 (2)	1.422	−0.021	1.405	−0.004

C1—C2	1.502 (3)	1.532	−0.030	1.530	−0.028
C2—C3	1.515 (3)	1.529	−0.014	1.529	−0.014
C3—C4	1.530 (2)	1.536	−0.006	1.534	−0.004
C4—C5	1.531 (3)	1.548	−0.017	1.542	−0.011
C4—C7	1.523 (2)	1.532	−0.009	1.533	−0.010
C6—C7	1.510 (2)	1.531	−0.021	1.530	−0.020
C6—C11	1.509 (2)	1.531	−0.022	1.529	−0.020
C7—C8	1.517 (2)	1.528	−0.011	1.528	−0.011
C8—C9	1.531 (3)	1.544	−0.013	1.545	−0.014
C9—C10	1.534 (3)	1.545	−0.011	1.545	−0.011
C9—C12	1.521 (3)	1.538	−0.017	1.538	−0.017
C10—C11	1.529 (3)	1.541	−0.012	1.541	−0.012
C5—O1—C6	108.3 (1)	106.9	1.4	106.9	1.4
C1—O2—C5	114.6 (2)	113.6	1.0	115.1	−0.5
O2—C1—C2	110.8 (2)	109.8	1.0	109.8	1.0
C1—C2—C3	109.5 (2)	108.1	1.4	107.9	1.6
C2—C3—C4	111.7 (2)	110.0	1.7	109.7	2.0
C3—C4—C5	113.0 (1)	115.0	−2.0	115.3	−2.3
C3—C4—C7	114.5 (1)	113.8	0.7	114.2	0.3
C5—C4—C7	99.5 (1)	98.3	1.2	97.4	2.1
O1—C5—O2	110.3 (1)	115.0	−4.7	106.4	3.9
O1—C5—C4	106.7 (2)	109.0	−2.3	109.9	−3.2
O2—C5—C4	117.4 (1)	114.4	3.0	117.1	0.3
O1—C6—C7	105.8 (1)	105.6	0.2	105.7	0.1
O1—C6—C11	115.3 (2)	114.3	1.0	114.0	1.3
C7—C6—C11	110.8 (2)	109.9	0.9	110.1	0.7
C4—C7—C6	101.3 (1)	100.2	1.1	100.2	1.1
C4—C7—C8	123.1 (1)	121.3	1.8	121.6	1.5
C6—C7—C8	110.1 (1)	110.3	−0.2	110.2	−0.1
C7—C8—C9	109.2 (2)	108.4	0.8	108.4	0.8
C8—C9—C10	112.2 (2)	111.7	0.5	111.8	0.4
C8—C9—C12	111.3 (2)	110.6	0.7	110.6	0.7
C10—C9—C12	111.4 (2)	110.9	0.5	110.9	0.5
C9—C10—C11	114.5 (2)	113.0	1.5	113.1	1.4
C6—C11—C10	107.2 (2)	108.2	−1.0	108.0	−0.8
C6—O1—C5—O2	140.1 (1)	133.0	7.1	131.8	8.3
C6—O1—C5—C4	11.6 (2)	3.0	8.6	4.1	7.5
C5—O1—C6—C7	15.9 (2)	24.8	−8.9	23.9	−8.0
C5—O1—C6—C11	138.8 (2)	145.8	−7.0	144.9	−6.1
C3—C4—C5—O1	88.3 (2)	92.5	−4.2	91.7	−3.4
C3—C4—C5—O2	−36.0 (2)	−37.8	1.8	−29.8	−6.2
C7—C4—C5—O1	−33.5 (2)	−28.8	−4.7	−29.5	−4.0
C7—C4—C5—O2	−157.8 (2)	−159.1	1.3	−151.0	−6.8
C3—C4—C7—C6	−79.2 (2)	−81.1	1.9	−81.4	2.2
C3—C4—C7—C8	43.9 (2)	40.3	3.6	40.1	3.8
C5—C4—C7—C6	41.5 (2)	41.0	0.5	40.8	0.7
C5—C4—C7—C8	164.7 (2)	162.5	2.2	162.2	2.5
C7—C8—C9—C12	176.7 (2)	178.5	−1.8	178.3	−1.6

Table 3. *Conformation of the rings and dihedral angles (°) of their least-squares planes*

Q_T = total puckering amplitude (Å) (Cremer & Pople, 1975), DAP = minimum displacement asymmetry parameter (Nardelli, 1983*a*), C = chair, HC = half-chair, E = envelope, *MMX* = force field of *PCMODEL* and *MM+* = force field of *HYPERCHEM*.

Ring		Q_T	DAP	Conformation
A	X-ray	0.508 (2)	Δ_2(C2–C1) = 0.0007 (8)	HC/C
	MMX	0.546	0.0137	
	MM+	0.535	0.0067	
B	X-ray	0.420 (2)	Δ_2(O1) = 0.0124 (6)	E
	MMX	0.440	Δ_s(C7) = 0.0265	
	MM+	0.438	Δ_s(C7) = 0.0338	
C	X-ray	0.585 (2)	Δ_2(C9–C10) = 0.0060 (8)	C
	MMX	0.602	0.0025	
	MM+	0.603	0.0015	
	X-ray	*A*/*B* = 68.5 (1)	*B*/*C* = 9.8 (1)	*A*/*C* = 59.3 (1)
	MMX	66.1	6.5	60.2
	MM+	67.9	6.8	61.4

The integrated intensities were obtained by a modified version (Belletti, Ugozzoli, Cantoni & Pasquinelli, 1979) of the Lehmann & Larsen (1974) peak-profile analysis procedure and corrected for Lorentz and polarization effects, but not for absorption. The structure was solved by direct methods and refined by anisotropic full-matrix least squares. All the H atoms were found from a $\Delta\rho$ map and refined isotropically.

Data collection: local programs. Cell refinement: *LQPARM* (Nardelli & Mangia, 1984). Data reduction: local programs. Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1990). Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993). Molecular graphics: *ORTEP* (Johnson, 1965). Software used to prepare material for publication: *PARST* (Nardelli, 1983*b*) and *PARSTCIF* (Nardelli, 1991).

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry and atomic coordinates corrected for libration have been deposited with the IUCr (Reference: BM1023). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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