

X-Ray Crystallographic Determination of the *cis* Form and ^1H NMR Investigation of the *cis* and *trans* Forms of (5*S*)-2-*t*-Butyl-5-carboxymethyl-1,3-dioxolan-4-one

MARTIN VAHL GABRIELSEN

The Royal Danish School of Pharmacy, Chemical Laboratory C, DK-2100 Copenhagen, Denmark

Synthesis and high resolution ^1H NMR investigation of *cis* and *trans* (5*S*)-2-*t*-butyl-5-carboxymethyl-1,3-dioxolan-4-one are described. An X-ray crystallographic investigation of the (2*S*,5*S*)-form of the compound has been performed. Long range coupling between the two ring protons is found to be stronger for the *trans* form (2*R*,5*S*), than for the *cis* form (2*S*,5*S*), the values are 1.8 and 1.25 Hz, respectively.

Crystals of (2*S*,5*S*)-2-*t*-butyl-5-carboxymethyl-1,3-dioxolan-4-one are monoclinic space group $P2_1$, $a=5.775(3)$, $b=8.534(2)$, $c=10.276(3)$ Å, $\beta=91.27(5)^\circ$, $Z=2$. The structure has been solved by direct methods using X-ray diffraction data and has been refined by full-matrix least-squares method to a final R value of 0.071. The molecules adopt an O_1 -envelope conformation (E_0) in the crystalline state.

2,5-Disubstituted 1,3-dioxolan-4-ones contain a ring with two asymmetric carbon atoms; one pair of enantiomers, with the hydrogen atoms to the same side of the mean ring plane, constitutes the *cis* forms and the other pair of enantiomers the *trans* forms. The possibility of being able to discriminate between the two forms on the basis of ^1H NMR data has been discussed by several authors.¹⁻⁵ When spectra of both the *cis* and the *trans* forms have been available it has been shown that the chemical shift of the ring protons are different for the two forms.¹⁻⁵ In some cases chemical shift differences have also been observed for protons attached to carbon atoms in the substituents.¹

High resolution ^1H NMR spectroscopy has shown that long range coupling between the two ring protons is present in many, 2,5-

disubstituted 1,3-dioxolan-4-ones.²⁻⁶ In most cases where both forms have been investigated the coupling is stronger for the form, which is believed to be *trans*.

The coupling mechanism has been regarded^{1,6} as similar to that in 2,5-dihydrofurans; this requires that the lactone function is approximately planar, *i.e.* the 1,3-dioxolan-4-ones which show long range coupling should adopt an O_1 -envelope conformation.

RESULTS AND DISCUSSION

(5*S*)-2-*t*-Butyl-5-carboxymethyl-1,3-dioxolan-4-one (I) (Fig. 1) was synthesized by condensation of L-malic acid and 2,2-dimethylpropanal using a slight modification of the general method given by Salomaa and Sallinen.⁷

Heating of I at a temperature just above the melting point caused partial isomerization to II.

An X-ray analysis proved I to be the *cis* form; as it is reasonable to assume that no inversion takes place at C(2) in L-malic acid during the preparation of I, the absolute configuration of I is (2*S*,5*S*). The numbering of I [given as O(1), O(2), C(3) *etc.*] appears from Fig. 3.

The ^1H NMR spectrum of I consists of five groups of lines (Table 1). The ring proton H(51) and the two geminal methylene protons in the carboxymethyl substituent constitute an ABX system. The two ring protons H(51) and H(71) couple weakly; thus the signal from H(71) is a doublet, while the X part of the ABX system is further split to a total of eight lines.

Table 1. Chemical shift and coupling constants in *cis* and *trans* (5*S*)-2-*t*-butyl-5-carboxymethyl-1,3-dioxolan-4-one (Fig. 1).

Compound	Chemical shift (δ)		Coupling constants (Hz) ^b	
	COOH (ring)	H(51) (ring)	C-CH ₂ -COOH	Long range ABX system (-CH-CH ₂ -)
<i>cis</i> (I)	9.88	5.19	3.01	1.25
<i>trans</i> (II) ^a	9.88	5.34	1.01 1.01	1.8

$|J_{AB}| = 17.19$ $J_{AX} = \pm 3.67$ $J_{BX} = \pm 7.38$

^a Data on the *trans* form were obtained from a (5:1) mixture of the *cis* and the *trans* form. Chemical shifts and coupling constants are only given where assignment of frequencies were unambiguous. ^b Probable errors on coupling constants are 0.02 for the *cis* form and 0.07 for the *trans* form.

Table 2. Final positional and thermal (A^2) parameters for non-hydrogen atoms. The estimated standard deviations of positional ($\times 10^4$) and thermal ($\times 10$) parameters are given in parentheses. The temperature expression is of the form: $\exp\{-2\tau^2 h^2 a^2 U_{11} + k^2 b^2 *2 U_{22} + \dots + 2klb^*c^* U_{33}\}$.

	x/a	y/b	z/c	$U_{11} \times 100$	$U_{22} \times 100$	$U_{33} \times 100$	$U_{12} \times 100$	$U_{13} \times 100$	$U_{23} \times 100$
O(1)	0.9783(7)	0.5211(8)	0.9702(4)	3.9(2)	9.9(4)	5.1(3)	-0.5(2)	0.5(2)	1.3(3)
O(2)	0.8195(7)	0.4005(8)	1.1386(4)	4.9(2)	8.2(3)	6.6(3)	0.5(3)	-0.1(2)	2.5(3)
C(3)	0.8143(10)	0.4906(9)	1.0337(5)	4.5(3)	5.0(3)	3.5(3)	0.3(3)	-0.4(3)	-0.8(3)
C(4)	0.5736(9)	0.5500(9)	1.0040(5)	4.6(3)	4.9(4)	3.4(3)	-0.1(3)	0.3(2)	-0.2(3)
C(5)	0.5177(8)	0.5542(8)	0.8596(4)	3.6(3)	3.6(3)	3.8(3)	0.2(3)	0.3(2)	-0.1(3)
O(6)	0.5468(5)	0.3997(6)	0.8055(3)	4.0(2)	3.4(2)	3.5(2)	-0.7(2)	0.9(2)	0.0(2)
C(7)	0.6165(9)	0.4219(9)	0.6752(5)	3.8(3)	3.7(3)	3.5(3)	0.1(3)	0.5(2)	0.1(3)
O(8)	0.7389(6)	0.5682(6)	0.6751(3)	4.9(2)	3.8(2)	5.0(2)	-0.5(2)	1.7(2)	0.3(2)
C(9)	0.6805(9)	0.6524(8)	0.7803(6)	3.2(3)	4.0(3)	4.9(4)	0.1(3)	-0.7(3)	0.6(3)
O(10)	0.7440(7)	0.7823()	0.7993(4)	5.9(3)	3.6(2)	6.8(3)	-1.2(2)	0.6(2)	0.1(2)
C(11)	0.7608(9)	0.2886(10)	0.6275(5)	4.2(3)	4.3(3)	3.8(3)	-0.4(3)	1.2(3)	0.4(3)
C(12)	0.3256(13)	0.3211(9)	0.4864(7)	11.7(6)	5.9(5)	6.5(4)	1.3(4)	4.8(4)	0.0(4)
C(13)	0.6176(13)	0.1403(9)	0.6318(6)	8.1(5)	4.9(4)	6.0(4)	0.5(4)	1.8(4)	-0.9(3)
C(14)	0.9758(11)	0.2663(10)	0.7143(7)	5.5(4)	8.0(5)	10.6(6)	3.4(4)	-0.7(4)	-2.7(5)

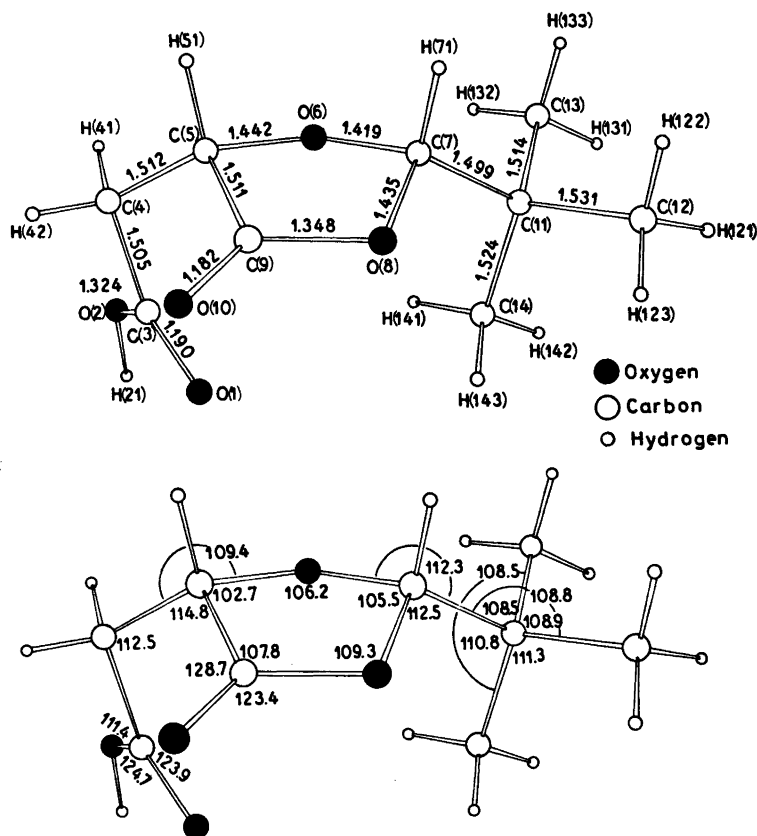


Fig. 3. Bond lengths (Å) and valency angles (°) for (2*S*,5*S*)-2-*t*-butyl-5-carboxymethyl-1,3-dioxolan-4-one.

Bond distances and valency angles for the molecule are given in Tables 3 and 4, the geometry is further illustrated by Fig. 3.

The bond lengths are close to normally accepted values and the valency angles in the ring system show no significant deviations from previously reported values.⁸

EXPERIMENTAL

Melting points were determined with a hot stage microscope (Mikroskop Heitzsch Ernst Leitz G.m.b.H., Wetzlar). The computations were performed on a GIER and an IBM 370/165 computer using *INDIFF*,⁹ a local version of *The N.R.C. 2A Picker Data Reduction Program*,¹⁰

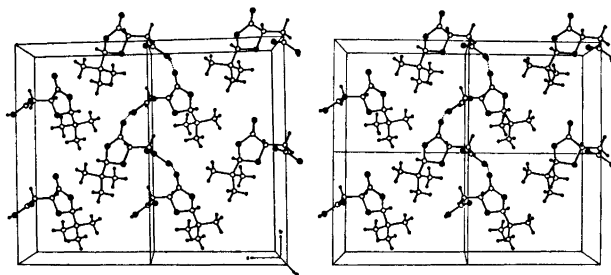


Fig. 4. Stereoscopic pair showing the crystal structure as seen from the direction of the *a*-axis. Hydrogen bonds are indicated by dotted lines.

Table 3. Intramolecular distances (Å) and valency angles (°). The estimated standard deviations are given in parenthesis.

O(1)–C(3)	1.190(7)	C(7)–O(8)	1.435(8)
O(2)–C(3)	1.324(8)	C(7)–C(11)	1.499(10)
C(3)–C(4)	1.505(8)	O(8)–C(9)	1.348(7)
C(4)–C(5)	1.512(7)	C(9)–O(10)	1.182(7)
C(5)–O(6)	1.442(9)	C(11)–C(12)	1.531(9)
C(5)–C(9)	1.511(8)	C(11)–C(13)	1.514(11)
O(6)–C(7)	1.419(6)	C(11)–C(14)	1.524(8)
O(1)–C(3)–O(2)	124.7(6)	C(7)–O(8)–C(9)	109.3(4)
O(1)–C(3)–C(4)	123.9(6)	C(5)–C(9)–O(8)	107.8(5)
O(2)–C(3)–C(4)	111.4(5)	C(5)–C(9)–O(10)	128.7(5)
C(3)–C(4)–C(5)	112.5(4)	O(8)–C(9)–O(10)	123.4(5)
C(4)–C(5)–O(6)	109.4(5)	C(7)–C(11)–C(12)	108.8(6)
C(4)–C(5)–C(9)	114.8(5)	C(7)–C(11)–C(13)	108.5(5)
O(6)–C(5)–C(9)	102.7(4)	C(7)–C(11)–C(14)	110.8(5)
C(5)–O(6)–C(7)	106.2(5)	C(12)–C(11)–C(13)	108.9(5)
O(6)–C(7)–O(8)	105.5(5)	C(12)–C(11)–C(14)	111.3(5)
O(6)–C(7)–C(11)	112.3(5)	C(13)–C(11)–C(14)	108.5(6)

Table 4. Hydrogen atoms: Positional and thermal parameters, bond distances and valency angles. Parameters for hydrogen atoms are not refined. For the *t*-butyl and methylene groups the values were determined by fitting a tetrahedral model with distances to hydrogen atoms *ca.* 0.96 Å to the difference fouriers.

Positional and thermal (Å ²) parameters				
	<i>x/a</i>	<i>y/b</i>	<i>z/c</i>	<i>U</i> × 100
H(21)	0.9691	0.3884	1.1604	6
H(41)	0.4644	0.4825	1.0453	4
H(42)	0.5598	0.6542	1.0382	4
H(51)	0.3526	0.5880	0.8359	4
H(71)	0.4713	0.4392	0.6222	3
H(121)	0.8858	0.2274	0.4481	6
H(122)	0.6905	0.3546	0.4377	6
H(123)	0.9409	0.4020	0.4852	6
H(131)	0.7066	0.0550	0.5985	6
H(132)	0.5767	0.1187	0.7201	6
H(133)	0.4790	0.1535	0.5795	6
H(141)	0.9313	0.2575	0.8032	7
H(142)	1.0560	0.1733	0.6887	7
H(143)	1.0754	0.3557	0.7046	7
Bond distances (Å)				
O(2)–H(21)				0.89
C(5)–H(51)				1.02
C(7)–H(71)				1.00
Valency angles (deg.)				
C(3)–O(2)–H(21)				106
C(4)–C(5)–H(51)				115
O(6)–C(5)–H(51)				106
C(9)–C(5)–H(51)				108
O(6)–C(7)–H(71)				106
O(8)–C(7)–H(71)				106
C(11)–C(7)–H(71)				114

The X-Ray System,¹¹ and ORTEP.¹² The X-ray atomic scattering factors used were those listed in International Tables for X-Ray Crystallography (1962).

Synthesis. To a solution of 5.5 g (75 mmol) of 2,2-dimethylpropanal in 75 ml of benzene were added 6.6 g (50 mmol) of L-malic acid, 0.4 g of *p*-toluenesulfonic acid and 20 g of molecular sieve (Union Carbide 3A). After refluxing for 3 h the benzene was decanted and the residue refluxed for further 10 min with 50 ml of benzene. The combined benzene phases were filtered and concentrated *in vacuo* to give a yellow oil, which was then dissolved in benzene. After slow evaporation of the benzene at room temperature colourless plate shaped crystals were obtained. Yield 1 g, m.p. 102–103 °C. Recrystallization of 0.1 g from diethyl ether-ligroin (1:1) resulted in the formation of short thick monoclinic needles of (2*S*,5*S*)-2-*t*-butyl-5-carboxymethyl-1,3-dioxolan-4-one (proved by X-ray analysis) m.p. 103 °C. Some of the crude product was heated at 120 °C for 1 h, cooled and recrystallized from diethyl ether-ligroin (1:1). Long thin colourless needles were obtained. From ¹H NMR investigations it could be concluded, that the latter crystals were a 5:1 mixture of *cis* and *trans* (5*S*)-2-*t*-butyl-5-carboxymethyl-1,3-dioxolan-4-one.

¹H NMR spectra. ¹H NMR spectra were recorded in a Varian HA 100 spectrometer¹³ operating at 31 °C in frequency sweep mode. The sample was dissolved in CDCl₃, and TMS was added as internal standard. The concentrations of the sample of the pure *cis* form and the sample of the mixture (5:1) of the *cis* and *trans* forms were 5 and 20 W/V %, respectively. Coupling constants were obtained from spectra recorded with 1 Hz/cm. Simulation and itera-

Table 5. Conformation of (2*S*,5*S*)-2-*t*-butyl-5-carboxymethyl-1,3-dioxolan-4-one.

Distances of atoms from least squares planes in the dioxolane ring			
Atom	Deviation	Atom	Deviation
Plane 1			
C(5)	-0.004	O(8)	-0.004
O(6) ^a	0.326	C(9)	0.014
C(7) ^a	-0.099	O(10)	-0.006
Plane 2			
C(5)	-0.126	C(4) ^a	0.811
O(6)	0.171	C(11) ^a	0.679
C(7)	-0.145	O(10) ^a	0.091
O(8)	0.061	H(51) ^a	-1.12
C(9)	0.039	H(71) ^a	-1.13

Equation in direct (unit cell) space for the dioxolane ring:
 Plane 1. $4.479x - 3.090y + 5.135z = 5.024$
 Plane 2. $4.807x - 2.612y + 4.555z = 5.083$

Torsion angles (deg.)

O(1) - C(3) - C(4) - C(5)	+38.4	O(6) - C(7) - C(11) - C(14)	-58.1
O(2) - C(3) - C(4) - C(5)	-141.6	H(71) - C(7) - C(11) - C(14)	-178.7
C(3) - C(4) - C(5) - H(51)	+176.7	O(8) - C(7) - C(11) - C(14)	+60.7
C(3) - C(4) - C(5) - O(6)	+57.2	O(6) - C(7) - C(11) - C(12)	+179.2
C(3) - C(4) - C(5) - C(9)	-57.7	O(6) - C(7) - C(11) - C(13)	+61.0
C(9) - C(5) - O(6) - C(7)	-26.6	H(121) - C(12) - C(11) - C(7)	-167
C(5) - O(6) - C(7) - O(8)	+29.1	H(131) - C(13) - C(11) - C(7)	+178
O(6) - C(7) - O(8) - C(9)	-19.8	H(141) - C(14) - C(11) - C(7)	-53

^a The coordinates did not contribute to the least squares matrix.

tion on the spin system were performed using LAOCOON III.¹⁴

Crystal data. (2*S*,5*S*)-2-*t*-Butyl-5-carboxymethyl-1,3-dioxolan-4-one, C₈H₁₄O₅, M = 202.21. Monoclinic, space group *P*2₁, *a* = 5.775(3), *b* = 8.534(2), *c* = 10.276(3) Å, β = 91.27(5)°, *V* = 506.3 Å³, *D*_m = 1.31 g cm⁻³, *Z* = 2, *D*_c = 1.33 g cm⁻³, linear absorption coefficient (λ(MoKα) = 0.7107 Å) μ = 1.2. The unit-cell dimensions were determined from least-squares refinement of diffractometer measured theta values for 43 reflections. The crystal density was measured by flotation in an aqueous KI solution.

X-Ray data collection. The intensity data were obtained from a single crystal with approximate dimensions 0.3 × 0.2 × 0.2 mm mounted on a Nonius three-circle automatic diffractometer using graphite monochromatized MoKα radiation (λ = 0.7107 Å). The crystal was mounted with the crystal *a*-axis along the φ-axis of the goniometer, the ω-scan technique with a fixed scan range of 1.0° and a scan speed of 1.2 deg. min⁻¹ was employed, background intensity was measured for half the scanning time at the scan range limits. The intensity of one reference reflection was measured for every 25th reflection.

Out of the 1567 independent reflections in the range 2.5 ≤ θ ≤ 30.0°, 910 had an intensity greater than 1.5 times the estimated standard deviation, and were considered observed. The data were corrected for Lorentz and polarization effects.

STRUCTURE DETERMINATION

Normalized structure amplitudes, |*E*(*h*,*k*,*l*)|, were calculated using the results from application of Wilson statistics. The structure was solved by direct methods. Preliminary symbolic addition by hand suggested eight likely combinations of phases for a starting set consisting of eight structure factors. These starting sets were then expanded and refined by application of the tangent formula to the 150 largest *E* values (|*E*(*h*,*k*,*l*)| ≥ 1.56). Due to the few strong interactions involving reflections with *k*-index equal to one, the position of the origin on the screw-axis was fixed by assigning the phase π/4 to *E*(241) and restricting the phase of *E*(212) to the range 0 < φ ≤ π/2.

Parts of the structure (9 of the total 14 non-hydrogen atoms) were found in an *E*-map based on the solution with the lowest *R*-value

($R = \sum(|E_o| - |E_c|) / \sum |E_o|$). The five remaining non-hydrogen atoms of the molecule appeared clearly in a subsequent electron density map.

Full-matrix least-squares refinements (minimizing $\sum w(|F_o| - |F_c|)^2$, with weights equal to unity) using individual isotropic temperature factors converged at $R = 0.12$. Anisotropic thermal parameters were then introduced for the oxygen atoms and the carbon atoms in the terminal methyl groups. After three cycles of least-squares refinement, a difference Fourier was calculated using structure factors in the range $\sin \theta / \lambda \leq 0.35$. In the difference map the fourteen largest maxima were found in regions where hydrogen atoms would be expected to contribute.

As the small number of observed reflections made least-squares refinement on the parameters of the hydrogen atoms impossible, it was decided to determine the positions of the hydrogen atoms in the *t*-butyl and methylene groups by fitting a tetrahedral model with carbon-hydrogen bond distances of 0.96 Å to the corresponding positive regions. The parameters for the three remaining hydrogen atoms were taken directly from the difference map.

Individual isotropic thermal parameters, approximately equal to those calculated for the corresponding heavier atoms, were assigned to the hydrogen atoms. Refinement on the positional and individual anisotropic thermal parameters for all non-hydrogen atoms converged at $R = 0.071$ (weighted $R = 0.050$; values of average and maximum shift/error were 0.01 and 0.05, resp.). On the last cycles empirical weights were introduced in order to make $w(|F_o| - |F_c|)^2$ independent of $|F_o|$ and $\sin \theta$. The weight scheme chosen was: $w = 1 / (1 + (|F_o| - b) / a)^2$, with $a = 3.0$ and $b = 12.0$.

The final atomic parameters are listed in Tables 2 and 4; tables of the structure factors are available on request.

Acknowledgement. The author wishes to thank Dr. M. Bàron, Facultad de Ciencias y Naturales, Buenos Aires, for his interest in this work. Thanks are also due to the staff of the Chemical Laboratory C, Royal Danish School of Pharmacy, and Dr. K. Schaumburg, University of Copenhagen, for fruitful discussions.

REFERENCES

1. Farines, M. and Soulier, J. *Bull. Soc. Chim. Fr.* (1970) 332.
2. Cort, L. A. and Stewart, R. A. *J. Chem. Soc. C* (1971) 1386.
3. Brettle, R. J. *J. Chem. Soc. Perkin Trans. 1* (1972) 611.
4. Baron, M. *J. Mol. Struct.* 12 (1972) 71.
5. Brettle, R. and Logan, I. D. *J. Chem. Soc. Perkin Trans. 2* (1973) 687.

6. Asano, R., Moritani, I., Fujiwara, Y. and Teranishi, S. *Bull. Chem. Soc. Jap.* 46 (1973) 663.
7. Salomaa, P. and Sallinen, K. *Acta Chem. Scand.* 19 (1965) 1054.
8. Haagensen, C. O. and Danielsen, J. *Acta Chem. Scand.* 18 (1964) 581.
9. Sørensen, A. M. *INDIFF, An Algol Nonius Three Circle Diffractometer Input Data Program*, Chemical Laboratory C, The Royal Danish School of Pharmacy, DK-2100 Copenhagen 1968.
10. Ahmed, F. R. *N.R.C. Crystallographic Program System*, National Research Council, Ottawa, Canada 1968.
11. Stewart, J. M., Kruger, C. J., Ammon, H. L., Dickinson, C. and Hall, S. R. *X-Ray 72 Crystal Structure Calculation System*, Computer Science Center, University of Maryland, June 1972.
12. Johnson, C. K. *ORTEP: A Fortran Thermal Ellipsoid Plot Program for Crystal Structure Illustrations*, Oak Ridge National Laboratory, Oak Ridge 1965.
13. Gillein, D. and Schaumburg, K. *Rev. Sci. Instrum.* 39 (1968) 262.
14. Manschen, O. H. *Thesis*, University of Copenhagen, Copenhagen 1971.

Received July 5, 1974.