Acta Chemica Scandinavica B 33 (1979) 755—759

Stereochemistry of Some Substituted γ-Butyrolactones

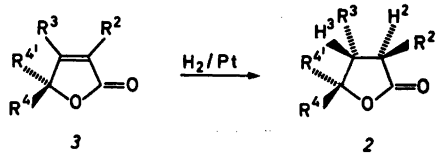
PER KOLSAKER [a] and ARNE STRØM BERG [b]

[a] Department of Chemistry, University of Oslo, Box 1033, Blindern/Oslo 3, Norway and
[b] Nyegaard & Co. A/S, Oslo 4, Norway

Some tri- and tetrasubstituted γ-butyrolactones were prepared by hydrogenation of the analogously substituted α,β-butenolides. Epimerization experiments indicated that the hydrogen atoms introduced were located *trans* to each other. In the tetrasubstituted γ-lactones a large vicinalcoupling constant (^{1}H NMR) indicated that the C_s-like conformer with both hydrogen atoms in pseudoaxial position was dominating at equilibrium. Comparison of the prepared γ-butyrolactones with others from the literature indicated that only when bulky substituents in 2- and 4-positions were *cis* to each other were such large vicinal coupling constants observed. The methoxycarbonyl group is not bulky enough in this respect, and it is necessary to have an additional substituent in 3-position to make the conformer with the 2- and 3-hydrogen in pseudoaxial position the thermodynamically more stable. Variations of the vicinal coupling constant with temperature and solvent were observed and discussed.

In an attempt to convert the cyano groups of malononitrile *1* into methoxycarbonyl groups (using MeOH/H_2SO_4) the substituted γ-butyrolactone *2a* was formed in good yield (Scheme 1).[1]

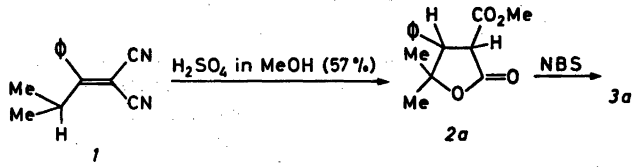
In view of the rather high value of the vicinal coupling constant ($J_{H_2H_3}$ = 12.5 Hz) we decided to look more closely into the subject. According to the Karplus equation, high vicinal coupling constants are associated with either large or small dihedral angles.[2] As the latter would imply severe steric contact between the substituents, a structure with *trans* configuration was considered to be most likely. In order to obtain a chemical confirmation of this assignment, the corresponding α,β-butenolide *3a* (easily prepared by the reaction of γ-butyrolactone *2a* with *N*-bromosuccinimide, see the experimental section) was hydrogenated using platinum as the catalyst (Scheme 2).



3 2

Scheme 2. *a*, $R^2 = CO_2Me$, $R^3 = Ph$, $R^4 = R^{4'} = Me$; *b*, $R^2 = CO_2Me$, $R^3 = H$, $R^4 = R^{4'} = Me$; *c*, $R^2 = CO_2Me$, $R^3 = R^4 = R^{4'} = Me$; *d*, $R^2 = CO_2Me$, $R^3 = Ph$, $R^4 = H$, $R^{4'} = Me$; *e*, $R^2 = H$, $R^3 = Ph$, $R^4 = R^{4'} = Me$; *f*, $R^2 = H$, $R^3 = 2$-Me-Ph, $R^4 = R^{4'} = Me$.

The only isolated product was identical to the γ-butyrolactone *2a* earlier obtained from malononitrile *1*.[1] This could mean that the initial assignment was wrong, *i.e.* that *2a* in fact was the *cis* isomer as catalytic hydrogenation of a double bond normally is considered to be a *cis* addition.[3] However, the transfer of hydrogen atoms to a molecule absorbed on a metal surface may occur in a stepwise manner enabling a *trans* addition to take place.[3] The



1 2a

Scheme 1.

0302-4369/79/100755-05$02.50

Table 1. Observed vicinal coupling constant $J_{H_3H_4}$ in γ-butyrolactones *2*.[a]

Compound	R^2	R^3	R^4	$R^{4'}$	$J_{H_3H_4}$/Hz	Ref.
2a	CO_2Me	Ph	Me	Me	12.5	*b*
2b	CO_2Me	H	Me	Me	9.3 and 9.5	*b*
2c	CO_2Me	Me	Me	Me	12.5	*b*
2d	CO_2Me	Ph	H	Me	8.0	*b*
2e	H	Ph	Me	Me	10.1 and 8.9	*b*
2f	H	2-Me-Ph	Me	Me	8.4 and 7.2	*b*
2g	*t*-Bu	H	*t*-Bu	H	12.8	*5*
2h	*t*-Bu	H	H	*t*-Bu	9.0	*5*
2i	Ph	H	Ph	H	12.9	*5,6*
2j	Ph	H	H	Ph	9.7	*5,6*
2k	Ph	H	Me	H	12.8	*5,6*
2l	Ph	H	H	Me	9.0	*5,6*
2m	Me	H	Ph	H	12.9	*5*
2n	Ph	H	Me	Me	12.2	*6*
2o	Ph	H	Ph	Me	12.1	*6*
2p	Ph	H	Me	Ph	13.1	*6*
2q	NHCOPh	H	Me	H	12.6	*7*
2r	NHCOPh	H	Ph	H	12.5	*7*

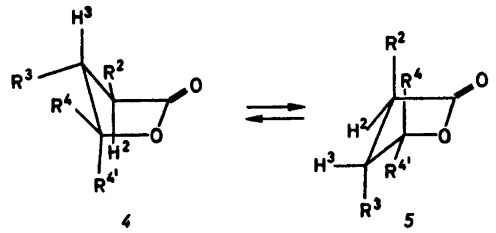
[a] Solvent: $CDCl_3$. [b] This work.

possibility of epimerization of the product on the catalyst cannot be ruled out either. That γ-butyrolactone *2a* most likely has the *trans* configuration was established by its failure to epimerize on prolonged treatment with sodium methoxide; sufficient acidity of the 2-proton was proved by deuterium exchange (^{1}H NMR).

γ-Butyrolactones *2b-f* were prepared (see the experimental section) and their vicinal coupling constants $J_{H_3H_4}$ are entered in Table 1 together with those of some representative γ-butyrolactones found in the literature.

Rapid pseudorotation usually makes the study on conformational behaviour of five-membered rings difficult.[4] However, in γ-butyrolactones resonance demands for planarity in the C2–C1(O)–O–C4 group make pseudorotation less probable.[5] In fact, in moderately strained γ-lactones like galactonolactone, this group is found to be planar by X-ray crystallographic analysis,[8] with C3 lying 0.64 Å above this plane. If the same situation is valid for the γ-butyrolactones *2* in solution, *4* and *5* should represent the two rapidly interconverting envelope forms (Scheme 3).

Steric interactions between pseudoaxial substituents in 2- and 4-positions will tend to favor conformer *4*. As the observed vicinal

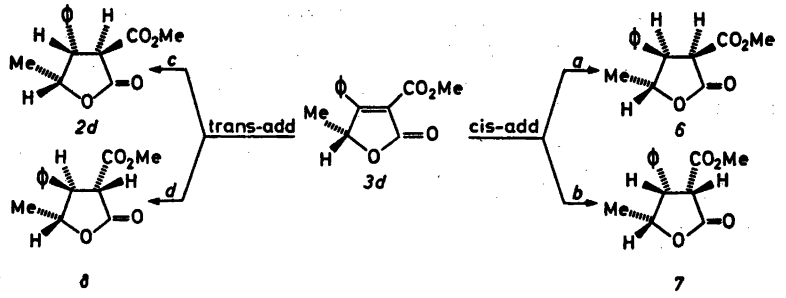


Scheme 3. Conformers of γ-butyrolactones *2*.

coupling constant $J_{H_3H_4}$ is the weighted mean of the larger pseudo-J_{aa}- and the smaller pseudo-J_{ee}-constant, a large observed value would indicate that the lower energy conformer *4* is predominating.

From Table 1 it can be seen that whenever R^3 and R^4 (*cis* to each other) are bulky groups, a large vicinal coupling constant (12–13 Hz) is observed.

The methoxycarbonyl group cannot be regarded bulky as compound *2b* has $J_{H_3H_4} = 9.3$ and 9.5 Hz. This is not unexpected, since the conformational energy (free energy differences between monosubstituted cyclohexane conformers) for this group is around 4.5 kJ/mol, compared to 7.0, 12.8 and 23 kJ/mol for the Me, Ph and *t*-Bu group, respectively.[9] In fact, it is apparently necessary to introduce an



Scheme 4. Hydrogenation of α,β-butenolide *3d*.

additional steric hindrance at C3 to make conformation *4* the predominant one (*2a* or *2c*). The importance of having substituents at C2 is demonstrated in butyrolactones *2e* and *2f*.

The formation of γ-butyrolactone *2d* deserves some comment. In principle, the hydrogenation of α,β-butenolide *3d* may give either of the four isomers *2d*, *6*, *7* or *8* (Scheme 4).

The choice of *2d* as the correct structure for the isolated compound was based on two arguments. Firstly, the failure of the product to epimerize should rule out structures *6* and *7*, which both have a *cis* configuration at the C2–C3 bond. Secondly, in analogy with the size of the vicinal coupling constant $J_{H_2H_3}$ for the isomer pairs *2g* and *2h*, *2i* and *2j*, *2k* and *2l*, (Table 1), the methyl group at C4 and the methoxycarbonyl group at C2 were chosen to be *trans* to each other.

As conformational equilibria are temperature dependent, decreasing temperatures should lead to an increase in the population of the lower energy conformer *4*. Increasingly higher values for the vicinal coupling constant with decreasing temperature were indeed observed as indicated in Table 2.

In principle, it should be possible to obtain the vicinal pseudodiaxial coupling constant by decreasing the sample temperature sufficiently.[10] It appears from Table 2 that for lactone *2a* this coupling constant is 13.3–13.4 Hz as the observed values are practically constant below −65 °C. Unfortunately, the inaccessability of the pseudoequatorial coupling constant makes it impossible for us to use the temperature dependence in calculating conformational energies. The polarity of the conformers *4* and *5* is probably quite different and as expected

Table 2. Temperature dependence of $J_{H_2H_3}$ in *2*.

2a		*2d*	
t/°C	$J_{H_2H_3}$/Hz	*t*/°C	$J_{H_2H_3}$/Hz
$CHCl_2CHCl_2$		$CHFCl_2$	
140	11.9	−8	9.0
102	12.3	−33	8.9
66	12.5	−46	9.1
		−63	9.2
$CHFCl_2$		−80	9.4
−10	13.1	−95	9.7
−65	13.4	−115	10.5
−105	13.4		
−123	13.3		

the observed coupling constant $J_{H_2H_3}$ shows solvent dependence. Conformer *4* is judged to be the more polar one as the observed coupling constant increases when changing from deuteriochloroform to tetradeuteriomethanol, Table 3.

The latter observation raises a question of the validity of calculated conformational energy in general using temperature-dependent parameters in solution chemistry. It is a well-known fact that solvent polarity increases with decreasing temperature, at least as indicated by *one* polarity parameter, the dielectric constant. This effect is more pronounced with polar

Table 3. Solvent dependence of $J_{H_2H_3}$ in *2a* at *t* = 33 °C.

Solvent	$CDCl_3$	$CHCl_2CHCl_2$	CD_3COCD_3	CD_3OD
$J_{H_2H_3}$/Hz	12.5	12.7	13.1	13.0

solvents. Since conformer population (at least for reasonably polar compounds) is affected by the polarity of the medium, the calculated free energy differences contain both a solvent-dependent and a temperature-dependent term. The sizes of these two terms are not easily accessible. Comparison of Tables 2 and 3 tells us, however, that the temperature influence is more important than change of solvent. The dielectric constant of tetrachloroethane increases from about 6.0 at 140 °C to 7.8 at 33 °C,[11] while the coupling constant change is 0.8 Hz in the same temperature interval. Changing the solvent from deuteriochloroform ($\varepsilon_{33} \sim 4.6$) [12] to hexadeuterioacetone ($\varepsilon_{33} \sim 20$)[12] causes a change in $J_{H_3H_5}$ of only 0.6 Hz. Although dielectric constants are poor measures of solvent polarities, it can be concluded that one has to be very cautious in using conformational energies in a quantitative manner when going from one solvent system to another.

EXPERIMENTAL

General. Melting points (uncorrected) were determined on a micro hot-stage. IR spectra were recorded on a Perkin-Elmer 457 Grating Infrared Spectrophotometer, ^{1}H NMR spectra on a Varian A60A Spectrometer and the mass spectra on an AEI MS902 instrument. Elemental analyses were performed by I. Beetz, West-Germany.

Butenolides 3b and *3d* were prepared by thermolysis of the proper γ-bromoalkylidene malonates.[13]

3a. γ,γ-Dimethyl-α-methoxycarbonyl-β-phenyl-γ-butyrolactone *2a*[1] (2 g, 8 mmol) and *N*-bromosuccinimide (1.4 g, 8 mmol) were refluxed in tetrachloromethane (10 ml) for 8 h. After filtering, the reaction solution was washed with water, dried ($MgSO_4$) and the solvent was evaporated. Ether was added to the residue and after cooling to 0 °C, *3a* crystallized out. Yield 0.48 g (24 %), m.p. 91 °C (ether–pentane). Anal. $C_{14}H_{14}O_4$: C, H. ^{1}H NMR ($CDCl_3$): δ 7.1–7.7 (5H,m), 3.72 (3H,s), 1.56 (6H,s), MS: *m/e* 246 (M^+, 69 %).

3c. Condensation of 3-bromo-3-methyl-2-butanone[14] with dimethyl malonate using titanium(IV) chloride–pyridine as catalyst,[15] gave a 25–30 % crude yield (^{1}H NMR) of dimethyl 2-bromo-1,2-dimethylpropylidenemalonate. Attempts to purify this ester by distillation at oil pump pressure led to formation of *3c* in 57 % yield (from the bromo ester). M.p. 64–65 °C. Anal: $C_9H_{12}O_4$: C, H. ^{1}H NMR ($CDCl_3$): δ 3.90 (3H,s), 2.36 (3H,s), 1.48 (6H, s). MS: *m/e* 184 (M^+, 2 %). IR (KBr): 1775, 1715, 1635 cm^{-1}.

Hydrogenation of butenolides (3). Butenolides *3* (on the scale of 2–20 mmol) were dissolved in MeOH (50 ml) and PtO_2 (50 mg) added. On shaking in a hydrogen atmosphere at room temperature and just above atmospheric pressure, one molar equivalent hydrogen was absorbed within 0.5 h. After filtering, MeOH was evaporated giving the butyrolactones *2* in moderate to good yields (after recrystallization).

2a. Yield 42 %, m.p. 127–128 °C (MeOH).[1]

2b. Yield 98 %, b.p. 107 °C/0.25 mmHg. Anal. $C_8H_{12}O_4$: C, H. ^{1}H NMR ($CDCl_3$): δ 3.82 (3H,s). ABX-system: 3.66 (H_X), 2.42 (H_B), 2.19 (H_A), J_{AX} 9.3 Hz, J_{BX} 9.5 Hz, J_{AB} 23.3 Hz; 1.54 (3H,s), 1.45 (3H,s). IR (film): 1775, 1740 cm^{-1}. MS: *m/e* 157 ($M^+ - CH_3$, 43 %).

2c. Yield 90 %, m.p. 56 °C (ether–pentane). Anal. $C_9H_{14}O_4$: C, H. ^{1}H NMR (CCl_4): δ 3.78 (3H,s), 3.27 (1H,d,*J* 12.5 Hz), 2.3–3.0 (1H, m), 1.47 (3H,s), 1.25 (3H,s), 1.08 (3H,d,*J* 5.5 Hz). IR (KBr): 1760, 1740 cm^{-1}. MS: *m/e* 186 (M^+ 0.2 %).

2d. Yield 75 %, m.p. 92–93 °C (ether–pentane or MeOH). Anal. $C_{13}H_{14}O_4$: C, H. ^{1}H NMR ($CDCl_3$): δ 7.0–7.6 (5H,m), 5.08 (1H,m), 4.21 (1H,t), 3.92 (1H,d,*J* 8.0 Hz), 3.80 (3H,s), 1.01 (3H,d,*J* 7.5 Hz). IR (KBr) 1775, 1720 cm^{-1}. MS: *m/e* 234 (M^+, 6 %).

γ,γ-Dimethyl-β-phenyl-γ-butyrolactone (2e).[16] A mixture of butyrolactone *2a* (1.5 g, 6 mmol), sodium chloride (0.44 g, 7.5 mmol), H_2O (0.4 g, 22 mmol) and DMSO (5 ml) was stirred at 170–210 °C for 3h. Chloroform and water were added. After washing twice with water and drying ($MgSO_4$), chloroform was evaporated, leaving crystals of *2e*. Yield 1.0 g (87 %), m.p. 96–97 °C (MeOH or ether–pentane). Found: C 76.3, H 7.4. Calc. for $C_{12}H_{14}O_2$: C 75.8; H 7.4. ^{1}H NMR (aceton-d_6, 60 MHz): δ 7.3 (5H,s). ABX-system: 3.62 (H_X), 3.07 (H_A), 2.82 (H_B), (J_{AX} 10.1 Hz, J_{BX} 8.9 Hz, J_{AB} 17.6 Hz); 1.52 (3H,s), 1.01 (3H,s). MS: *m/e* 190 (M^+, 4 %).

γ,γ-Dimethyl-β-(2-methylphenyl)-γ-butyrolactone (2f).[1,17] 2-Methyl-1-(2-methylphenyl)-propylidenemalononitrile (2.1 g, 0.01 mol) was dissolved in 20 % sulfuric acid–methanol (15 ml). After refluxing for 60 h, the solution was diluted with ice-cold $NaHCO_3$-solution. Extraction with chloroform with subsequent washing with water and drying ($MgSO_4$), gave after evaporation crystals of *2f*. Yield: 1.3 g (64 %), m.p. 89–90 °C (MeOH). Anal. $C_{13}H_{16}O_2$: C, H. ^{1}H NMR ($CDCl_3$, 60 MHz): δ 7.3 (4 H, s), ABX-system: 3.90 (H_X), 3.01 (H_A), 2.80 (H_B), (J_{AX} 8.4 Hz, J_{BX} 7.2 Hz, J_{AB} 17.6 Hz) 2.38 (3H,s), 1.55 (3H,s), 1.05 (3H,s). IR (KBr): 1770 cm^{-1}.

Base treatment of α-methoxycarbonyl-γ-butyrolactones (2a–d). (i) The butyrolactones were dissolved in deuteriochloroform and shaken with OD^-/D_2O for 1 h. The ^{1}H NMR signal from the α-proton disappeared. Subsequent shaking of the $CDCl_3$-solution with OH^-/H_2O confirmed the reversibility. (ii) Butyrolactones

2 (2 – 4 mmol) were dissolved in MeOH (50 ml) and equimolar amounts of sodium methoxide solution (0.43 M) were added. After stirring overnight at room temperature, the solution was worked up. The butyrolactones thus obtained were identical to the starting materials as indicated by the IR and ^{1}H NMR spectra.

REFERENCES

1. Kolsaker, P. and Berg, A. *Acta Chem. Scand. B 32* (1978) 61.
2. Karplus, M. *J. Chem. Phys. 30* (1959) 11; *J. Am. Chem. Soc. 85* (1963) 2870.
3. House, H. O. *Modern Synthetic Reactions*, 2nd Ed., Benjamin, California 1972, pp. 19 – 28.
4. Hendrickson, J. B. *J. Am. Chem. Soc. 83* (1961) 4537; *86* (1964) 4854; *89* (1967) 7036 and references therein.
5. Hussain, S. A. M. T., Ollis, W.D., Smith, C. and Stoddart, J. F. *J. Chem. Soc. Perkin Trans. 1* (1975) 1480 and references therein.
6. Johnson, R. N., Lowry, J. B. and Riggs, N. V. *Tetrahedron Lett.* (1967) 5113.
7. Altman, J., Gilboa, H. and Ben-Ishai, D. *Tetrahedron 33* (1977) 3173.
8. Jeffrey, G. A., Rosenstein, R. D. and Vlasse, M. *Acta Crystallogr. 22* (1967) 725; *cf.* Jeffrey, G. A. and Kim, S. H. *Chem. Commun.* (1966) 211.
9. Dale, J. *Stereochemistry and Conformational Analysis*, Universitetsforlaget, Oslo, Verlag Chemie, New York-Weinheim 1978.
10. Lambert, J. B., Papay, J. J., Khan, S. A., Kappauf, K. A. and Magyar, E. S. *J. Am. Chem. Soc. 96* (1974) 6112.
11. Höiendahl, K. *Dan. Kemi 16* (1935) 53.
12. Janz, G. T. and Tomkins, R. P. T. *Nonaqueous Electrolyte Handbook*, Academic, New York, London 1972.
13. Berg, A. and Kolsaker, P. *Acta Chem. Scand. B 32* (1978) 665.
14. Catch, J. R., Hey, D. H., Jones, E. R. H. and Wilson, W. *J. Chem. Soc.* (1948) 276.
15. Lehnert, W. *Tetrahedron 29* (1975) 635.
16. Krapcho, A. B. and Lovey, A. J. *Tetrahedron Lett.* (1973) 957.
17. Kolsaker, P. and Hellebostad, K. *Unpublished results.*

Received July 3, 1979.