Configurational Equilibria in 2,4-Disubstituted-γ-Butyrolactones

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Summary Equilibration studies on seven 2,4-disubstituted-γ-butyrolactones indicate that the *cis*-isomer is thermodynamically more stable than the *trans*-isomer in all cases.

RECENTLY, we established[1] the constitutions of the natural products, rubrenolide and rubrynolide, isolated from *Nectandra rubra* (Lauraceae). In order to investigate the relative configurations associated with the lactone rings in

these compounds, it became necessary to synthesise some model 2,4-disubstituted-γ-butyrolactones by stereoselective routes and examine their base-catalysed equilibration.

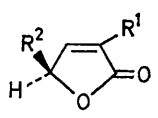
TABLE 1

Stereoselective hydrogenation (Pd–$BaSO_4$) of 2,4-disubstituted-4-hydroxybut-2-enoic lactones in ethanol.

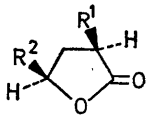
Lactone R^1	Lactone R^2	*cis*-Isomer M.p.	*trans*-Isomer M.p.	Isomer ratio (*cis* : *trans*)
Me	Me (**1**)	Oil	Oil	98 : 2[e]
Bu^t	Bu^t (**2**)	87—88°[b]	66—68°	>99 : <1[e]
Ph	Ph (**3**)[a]	105—107°[c]	68—69°[d]	88 : 12[f]
Ph	Me (**4**)	Oil	Oil	84 : 16[f]

[a] Pd–C catalyst. [b] Ref. 3. [c] Ref. 9. [d] Refs 8 and 9. [e] By g.l.c. [f] By ^{1}H n.m.r. spectroscopy.

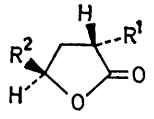
Compounds (**1**),[2] (**2**),[3] (**3**),[4] and (**4**)[5] were prepared by known routes. In all cases, hydrogenation over a palladium catalyst yielded preferentially (Table 1) one isomer of the corresponding 2,4-disubstituted-γ-butyrolactones. Assuming that the catalytic hydrogenation of the αβ-unsaturated lactones, (**1**)—(**4**), proceeds from the least hindered side of the carbon–carbon double bond, the major isomer obtained after each reduction was assigned the *cis* configuration.



(1) $R^1 = R^2 = Me$
(2) $R^1 = R^2 = Bu^t$
(3) $R^1 = R^2 = Ph$
(4) $R^1 = Ph; R^2 = Me$



(5a) $R^1 = R^2 = Me$
(6a) $R^1 = R^2 = Bu^t$
(7a) $R^1 = R^2 = Ph$
(8a) $R^1 = Ph; R^2 = Me$
(9a) $R^1 = R^2 = Et$
(10a) $R^1 = Et; R^2 = Me$
(11a) $R^1 = Bu^n; R^2 = Me$



(5b) $R^1 = R^2 = Me$
(6b) $R^1 = R^2 = Bu^t$
(7b) $R^1 = R^2 = Ph$
(8b) $R^1 = Ph; R^2 = Me$
(9b) $R^1 = R^2 = Et$
(10b) $R^1 = Et; R^2 = Me$
(11b) $R^1 = Bu^n; R^2 = Me$

Mixtures of *cis*- and *trans*-isomers of (**5**),[6] (**7**),[7–9] (**8**),[5,7] (**9**),[10] (**10**),† and (**11**)† were obtained by known routes. Separation of isomers was achieved by preparative g.l.c. in the case of lactones (**5**), (**9**), (**10**), and (**11**), and by silica gel chromatography in the case of lactones (**7**) and (**8**). Our assignment (Table 1) of configuration to the two isomers of 2,4-diphenyl-γ-butyrolactone (**7**) agrees (*cf.* ref. 9) with that originally proposed by Johnson, Lowry, and Riggs[7] on the basis of ^{1}H n.m.r. vicinal coupling constant data.

TABLE 2

Base-catalysed equilibrations (Bu^{t}OH–Bu^{t}OK) of 2,4-disubstituted-γ-butyrolactones at 25°.

Lactone R^1	Lactone R^2	Isomer ratio (*trans* : *cis*)	K	ΔG^0_{25} kcal mol^{-1}
Me	Me (**5**)	44 : 56	1·27[b]	−0·14
Bu^t	Bu^t (**6**)	12 : 88	7·33[b]	−1·20
Ph	Ph (**7**)[a]	40 : 60	1·50[c]	−0·24
Ph	Me (**8**)	42 : 58	1·38[c]	−0·19
Et	Et (**9**)	43 : 57	1·33[b]	−0·17
Et	Me (**10**)	49 : 51	1·04[b]	−0·002
Bu^n	Me (**11**)	42 : 58	1·38[b]	−0·19

[a] Equilibrated in CCl_4–Et_3N. [b] By g.l.c. [c] By ^{1}H n.m.r. spectroscopy.

Base-catalysed equilibrations were performed on all seven pairs of isomers. The results (Table 2) indicate that the *cis*-isomer is always favoured thermodynamically over the *trans*-isomer. The substituents on C-2 and C-4 in the case of the *cis*-isomers can assume quasi-equatorial orientations in an envelope conformation in which the C–C(O)–O–C group is planar;[11] in the *trans*-isomers one of the substituents must be quasi-axial in such an envelope conformation.

Our observations should be compared with the exclusive configurational preference for the *cis*-isomers in the more highly flexible 2,4-disubstituted-1,3-dioxolans[12] on acid-catalysed equilibration with their *trans*-isomers.

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[1] N. C. Franca, O. R. Gottlieb, D. T. Coxon, and W. D. Ollis, *J.C.S. Chem. Comm.*, 1972, 514.
[2] C. Armengaud, *Compt. rend.*, 1962, **254**, 3696.
[3] K. B. Wiberg and T. W. Hutton, *J. Amer. Chem. Soc.*, 1954, **76**, 5367.
[4] E. P. Kohler and R. H. Kimball, *J. Amer. Chem. Soc.*, 1933, **55**, 4632.
[5] S. Eskola, *Suomen Kemistilehti*, 1959, **B32**, 105.
[6] E. Honkanen, T. Moisio, and P. Karvonen, *Acta Chem. Scand.*, 1969, **23**, 531.
[7] R. N. Johnson, J. B. Lowry, and N. V. Riggs, *Tetrahedron Letters*, 1967, 5113.
[8] R. N. Johnson and N. V. Riggs, *Austral. J. Chem.*, 1971, **24**, 1643.
[9] R. S. Givens and W. F. Oettle, *J. Amer. Chem. Soc.*, 1971, **93**, 3301; *J. Org. Chem.*, 1972, **37**, 4325.
[10] S. Obata, *J. Pharm. Soc. Japan*, 1953, **73**, 1295.
[11] S. H. Kim, G. A. Jeffrey, R. D. Rosenstein, and P. W. R. Corfield, *Acta Cryst.*, 1967, **22**, 733.
[12] E. L. Eliel and W. E. Willy, *Tetrahedron Letters*, 1969, 1775; W. E. Willy, G. Binsch, and E. L. Eliel, *J. Amer. Chem. Soc.*, 1970, **92**, 5394; Y. Rommelaere and M. Anteunis, *Bull. Soc. Chim. Belge*, 1970, **79**, 11.