The Stereochemistry of 2,4- and 2,3-Disubstituted-γ-butyrolactones

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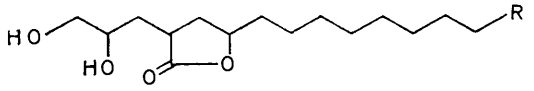
Relative configurational assignments have been made to the 2,4-dimethyl- (7), 2,4-di-t-butyl- (8), 2,4-diphenyl- (9), 4-methyl-2-phenyl- (10), and 2-methyl-3-phenyl- (31) γ-butyrolactones on the basis of the stereoselective synthesis of their *cis*-isomers, from the corresponding disubstituted but-2-en-4-olides (2)—(5) and 2-methylene-3-phenyl-γ-butyrolactone (41) by hydrogenation over palladium. The characteristic features from the ^{1}H n.m.r. spectra of the *cis*- and *trans*-isomers of (7)—(10) have been employed to assign relative configurations to the 2-methyl-4-phenyl- (11), 2,4-diethyl- (12), 2-ethyl-4-methyl- (13), and 2-butyl-4-methyl- (14) γ-butyrolactones. Equilibration studies on seven 2,4-disubstituted γ-butyrolactones [(7)—(10) and (12)—(14)] indicate that (i) the free energy differences between *cis*- and *trans*-isomers are small, and (ii) the *cis*- is thermodynamically more stable than the *trans*-isomer in all cases. The opposite situation is true of the 2-methyl-3-phenyl-γ-butyrolactones (31) where the *trans*-isomer is found to predominate at equilibrium. ^{1}H N.m.r. spectroscopic data suggest that the conformational behaviour of the five-membered ring in 2,4-disubstituted γ-butyrolactones is different for diastereoisomers but is not influenced to any great extent by the nature of the substituent groupings.

THE constitutions of the natural products, rubrenolide (1a) and rubrynolide (1b), isolated from the trunk wood of the Amazonian tree, *Nectandra rubra* (Mez) C. K. Allen [1] (Lauraceae), have been established [2] recently. In order to facilitate an investigation of the relative configurations associated with the substituents attached to the γ-lactone rings in these compounds, it was decided to synthesise some model 2,4-disubstituted γ-butyrolactones by stereoselective routes and examine their *cis–trans* isomerism under conditions of thermodynamic control.[3]



(1) a; R = CH_2=CH
b; R = HC≡C

RESULTS AND DISCUSSION

The 2,4-dimethyl- (2),[4] 2,4-di-t-butyl- (3),[5] 2,4-diphenyl- (4),[6-8] 4-methyl-2-phenyl- (5),[9] and 2-methyl-4-phenyl- (6) derivatives of but-2-en-4-olide were synthesised by standard procedures (see below and Experimental section). In all cases except one, hydrogenation over palladium yielded preferentially (Table 1) one isomer of the corresponding 2,4-disubstituted γ-butyrolactone. Assuming that the hydrogenation proceeds by *cis*-addition from the least hindered side of the 2,3-double bond,[10] the major isomer was assigned (Table 1 and Scheme 1) the *cis*-configuration.

TABLE 1

Stereoselective hydrogenation (over Pd–$BaSO_4$) of 2,4-disubstituted but-2-en-4-olides in ethanol [a]

Lactone	Mol. equiv. of H_2 absorbed	Isomer ratio (*cis* : *trans*)
(2)	1·05	98 : 2 [b]
(3)	1·05	≫99 : ≪1 [b]
(4) [c]	0·5	88 : 12 [d,e]
(5)	1·0	84 : 16 [f]
(6) [c]	0·6	50 : 50 [f,g]

[a] See Scheme 1. [b] By g.l.c. (see Experimental section). [c] Pd–C catalyst. [d] Based on yields after column chromatography on silica gel. [e] 2,4-Diphenylbutyric acid [13] was also characterised [14] as a product. [f] By ^{1}H n.m.r. spectroscopy. [g] 2-Methyl-4-phenylbutyric acid was also characterised as a product.

Mixtures of *cis*- (a) and *trans*- (b) isomers of 2,4-dimethyl- (7),[11,12] 2,4-di-t-butyl- (8), 2,4-diphenyl- (9),[6,13-18] 4-methyl-2-phenyl- (10),[16] 2-methyl-4-phenyl- (11),[19,20] 2,4-diethyl- (12),[21] 2-ethyl-4-methyl- (13),† and 2-butyl-4-methyl- (14) † γ-butyrolactones were also synthesised by known procedures. Only in the case of the 2,4-diphenyl-γ-butyrolactones (9) have the separation and characterisation of two isomers been reported.[16-18] The assignment of relative configurations to the two isomers was based [16] on the somewhat dubious information provided by the magnitude of vicinal ^{1}H n.m.r. coupling constants. In the present investigation, assignments are based on the stereo-

† Samples of these lactones were kindly provided by Professor C. Szántay, Technical University, Budapest.

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[2] N. C. Franca, O. R. Gottlieb, D. T. Coxon, and W. D. Ollis, *J.C.S. Chem. Comm.*, 1972, 514.
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[7] P. Yates and T. J. Clark, *Tetrahedron Letters*, 1961, 435.
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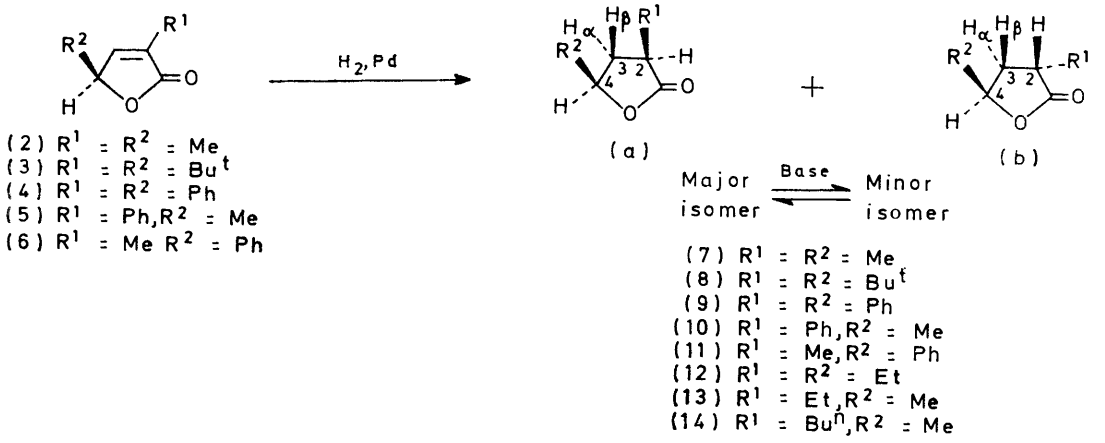
[12] R. Trave and L. Garanti, *Rend. ist Lombardo Sci., Pt.* 1, *Classe sci. mat. e nat.*, 1960, **94A**, 309 (*Chem. Abs.*, 1961, **55**, 14324).
[13] F. Bergmann, H. E. Eschinazi, and D. Schapiro, *J. Amer. Chem. Soc.*, 1942, **64**, 557; H. M. Crawford, *ibid.*, 1939, **61**, 608.
[14] W. Davey and D. J. Tivey, *J. Chem. Soc.*, 1958, 1230.
[15] R. Anschütz and W. F. Montfort, *Annalen*, 1895, **284**, 1.
[16] R. N. Johnson, J. B. Lowry, and N. V. Riggs, *Tetrahedron Letters*, 1967, 5113.
[17] R. N. Johnson and N. V. Riggs, *Austral. J. Chem.*, 1971, **24**, 1643.
[18] R. S. Givens and W. F. Oettle, *J. Amer. Chem. Soc.*, 1971, **93**, 3301; *J. Org. Chem.*, 1972, **37**, 4325.
[19] O. Mumm and K. Brodersen, *Ber.*, 1923, **56**, 2295.
[20] E. E. van Tamelen and S. R. Bach, *J. Amer. Chem. Soc.*, 1955, **77**, 4683.
[21] S. Obata, *J. Pharm. Soc. Japan*, 1953, **73**, 1295.

selective synthesis of a chosen number of key compounds [(7)—(11)] and these have been related to a wider range of compounds [(12)—(14)] by the characteristic features which emerge from an empirical evaluation of the ^{1}H n.m.r. spectra of *cis*- and *trans*-isomers.

In view of the confusion which exists in the literature regarding the identity of many of the compounds in Scheme 1 and the failure by most investigators to concentrated sulphuric acid at 100° to yield the αβ-unsaturated lactone (2).[4] Treatment of the oxo-diester (15) with *ca.* 6N-hydrochloric acid under reflux afforded the trisubstituted αβ-unsaturated lactone (17) [characterised as its methyl ester (18)] in addition to 2-methyl-4-oxopentanoic acid (16). Catalytic hydrogenation of the αβ-unsaturated lactone (2) gave two compounds in the ratio 98 : 2. The major product was assigned



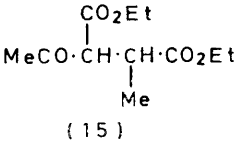
(2) $R^1 = R^2 = Me$
(3) $R^1 = R^2 = Bu^t$
(4) $R^1 = R^2 = Ph$
(5) $R^1 = Ph, R^2 = Me$
(6) $R^1 = Me\ R^2 = Ph$

(7) $R^1 = R^2 = Me$
(8) $R^1 = R^2 = Bu^t$
(9) $R^1 = R^2 = Ph$
(10) $R^1 = Ph, R^2 = Me$
(11) $R^1 = Me, R^2 = Ph$
(12) $R^1 = R^2 = Et$
(13) $R^1 = Et, R^2 = Me$
(14) $R^1 = Bu^n, R^2 = Me$

SCHEME 1 Stereoselective catalytic hydrogenation of 2,4-disubstituted but-2-en-4-olides (2)—(6) and base-catalysed equilibration of 2,4-disubstituted γ-butyrolactones (7)—(14)

separate and characterise *cis*- and *trans*-isomers, we shall now consider the synthesis, separation, and characterisation of each of the lactones (7)—(14).

Synthesis, Separation, and Characterisation.—(a) *2,4-Dimethyl-γ-butyrolactones* (7). 2,4-Dimethylbut-2-en-4-olide (2) was obtained by the following sequence: (i) base-catalysed condensation of ethyl 2-bromopropionate with ethyl acetoacetate to give the oxo-diester (15),[22] (ii) base-catalysed hydrolysis of (15), followed by decarboxylation



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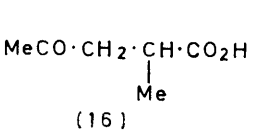

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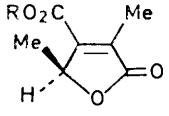
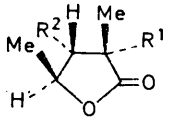
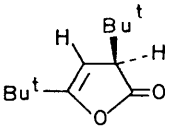


(17) R = H
(18) R = Me



(19) $R^1 = R^2 = D$
(20) $R^1 = D, R^2 = H$
(21) $R^1 = H, R^2 = D$



(22)

with hydrochloric acid, to afford 2-methyl-4-oxopentanoic acid (16),[23] and (iii) dehydration of (16) with acetic anhydride containing glacial acetic acid and (Table 1) as *cis*-2,4-dimethyl-γ-butyrolactone (7a) and the minor product the *trans*-isomer (7b).

Reduction of 2-methyl-4-oxopentanoic acid (16) with sodium borohydride followed by acidification also gave the 2,4-dimethyl-γ-butyrolactones (7), which were

TABLE 2

Assignment of the ring proton signals in the ^{1}H n.m.r. spectra of *cis*-2,4-disubstituted γ-butyrolactones (a)

Lactone	τ H-2	H-3α	H-3β	H-4
(7a)	7·08—7·63	7·08—7·63	8·30—8·94	5·30—5·72
(8a)	7·55 [a] (7·57) [b]	7·97 [a]	8·23 [a] (8·24) [c]	6·06 [a] (6·07) [c]
(9a)	5·99 [a,d,e]	6·96 [a,d]	7·64 [a,d] (7·64) [f]	4·48 [a,d] (4·52) [f]
(10a)	6·15 [d,g]	7·27 [d,g]	8·02 [d,g]	5·22 [d,g]
(11a)	7·14 [g]	7·28 [g]	8·18 [g]	4·66 [g]
(12a)	7·28—7·76	7·28—7·76	7·84—8·78	5·50—5·88
(13a)	7·46—7·80 [h]	7·46—7·80 [h]	7·90—8·80 [h]	5·46—5·80 [h]
(14a)	7·27—7·87 [h]	7·27—7·87 [h]	7·87—8·87 [h]	5·47—5·87 [h]

[a] Computed as a 4-spin system using LAOCOON II.[58] [b] From *cis*-3,4-dideuterio-2,4-di-t-butyl-γ-butyrolactone (24). [c] From *cis*-2,3-dideuterio-2,4-di-t-butyl-γ-butyrolactone (23). [d] Qualitatively, this assignment agrees with that of Johnson, Lowry, and Riggs.[16] [e] This signal disappears as a result of D–H exchange in CD_3OD–CD_3ONa. [f] From *cis*-2,3-dideuterio-2,4-diphenyl-γ-butyrolactone (28a). [g] Computed as a 7-spin system (ring protons and Me group) using LAOCOON II.[58]

separated into their *cis*- (7a) and *trans*- (7b) isomers by g.l.c. Although the 2,4-dimethyl-γ-butyrolactones (7) have been prepared previously by similar [11] and different [12] routes, the separation of the isomers is

[22] C. Bischoff, *Annalen*, 1880, **206**, 313.
[23] C. Pascual, D. Wegmann, U. Graf, R. Scheffold, P. F. Sommer, and W. Simon, *Helv. Chim. Acta*, 1964, **47**, 213.

reported here for the first time. The assignment (Table 2) of the ^{1}H n.m.r. signals of *cis*-2,4-dimethyl-γ-butyrolactone (7a) to the ring protons was aided by carrying out a catalytic reduction of the αβ-unsaturated lactone (2) with deuterium gas. The ^{1}H n.m.r. spectrum of the product was complex and indicated that it was a mixture of *cis*-2,3-dideuterio- (19), *cis*-2-monodeuterio- (20), and *cis*-3-monodeuterio- (21) 2,4-dimethyl-γ-butyrolactones. Nonetheless, the low-field multiplet could be assigned unambiguously to H-4. The ^{1}H n.m.r. assignments for the *trans*-lactone (7b) are given in Table 3.

TABLE 3

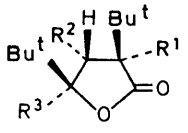
Assignment of ring proton signals in the ^{1}H n.m.r. spectra of *trans*-2,4-disubstituted γ-butyrolactones (b)

	τ			
Lactone	H-2	H-3α	H-3β	H-4
(7b)	7·22—7·64 [a]	7·82—8·16 [a]	7·82—8·16 [a]	5·28—5·64 [a]
(8b)	7·63 [b]	7·95 [b]	7·99 [b]	5·94 [b]
(9b)	6·08 [b,c]	7·18 [b,c] (7·21) [d]	7·31 [b,c]	4·35 [b,c] (4·36) [d]
(10b)	6·10 [c,e]	7·50 [c,e]	7·68 [c,e]	5·24 [c,e]
(11b)	7·34 [e]	7·60 [e]	7·70 [e]	4·46 [e]
(12b)	7·27—7·62	7·86—8·06	7·86—8·06	5·42—5·76
(13b)	7·39—7·70 [a]	7·91—8·60 [a]	7·91—8·60 [a]	5·30—5·57 [a]
(14b)	7·37—7·77 [a]	7·91—8·15 [a]	7·91—8·15 [a]	5·29—5·67 [a]

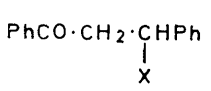
[a] In CCl_4. [b] Computed as a 4-spin system using LAOCOON II.[58] [c] Qualitatively, this assignment agrees with that of Johnson, Lowry, and Riggs.[16] [d] From *trans*-2,3-dideuterio-2,4-diphenyl-γ-butyrolactone (28b). [e] Computed as a 7-spin system (ring protons and Me group) using LAOCOON II.[58]

(b) 2,4-*Di-t-butyl-γ-butyrolactones* (8). U.v. irradiation of diazomethyl t-butyl ketone gave[5] the βγ-unsaturated lactone (22), which isomerised[5] to the αβ-unsaturated lactone (3) on heating in basic solution. Catalytic hydrogenation of both unsaturated lactones yielded the same crystalline product,[5] which was assigned (Table 1) as *cis*-2,4-di-t-butyl-γ-butyrolactone (8a). Isomerisation under basic conditions gave a mixture of isomers from which the *trans*-lactone (8b) was isolated crystalline in low yield.

Catalytic reduction of the αβ- (3) and βγ- (22) unsaturated lactones with deuterium gas to give the *cis*-2,3-dideuterio- (23) and *cis*-3,4-dideuterio- (24) 2,4-di-t-butyl-γ-butyrolactones permitted an unequivocal assignment (Table 2) of the ^{1}H n.m.r. signals of the *cis*-lactone (8a). The ^{1}H n.m.r. assignments for the *trans*-lactone (8b) are given in Table 3.



(23) $R^1 = R^2 = D, R^3 = H$
(24) $R^2 = R^3 = D, R^1 = H$



(25) X = CN
(26) X = CO_2Me
(27) X = CO_2H

(c) 2,4-*Diphenyl-γ-butyrolactones* (9). 2,4-Diphenylbut-2-en-4-olide (4) was obtained by the following sequence: (i) addition of hydrogen cyanide to benzylideneacetophenone to give the nitrile (25),[14,15,18,24-29] (ii) conversion of (25) into the methyl ester (26),[6,14,15,24,27] (iii) de-esterification of (26) to afford 4-oxo-2,4-diphenylbutyric acid (27),[6,13-15,18,24-27] and (iv) dehydration of (27) by refluxing with acetic anhydride to yield the αβ-unsaturated lactone (4),[6-8] m.p. 109—110°.[14,15,26,29-32] Catalytic reduction of (4) under conditions which permitted the absorption of 0·5 mol. equiv. of hydrogen afforded three products together with some starting material. One compound was identified as 2,4-diphenylbutyric acid [6,13] and was characterised previously [14] as the sole product of reduction following the absorption of 2 mol. equiv. of hydrogen by the αβ-unsaturated lactone (4). Hydrogenolysis of the C(4)–O single bond obviously competes with hydrogenation of the 2,3-double bond. The other two reduction products were isolated by column chromatography on silica gel in yields corresponding to an 88 : 12 ratio. The major product was assigned (Table 1) as *cis*-2,4-diphenyl-γ-butyrolactone (9a) [18] and the minor product as the *trans*-isomer (9b).[17,18] This assignment agrees (*cf.* ref. 18) with that originally proposed [16] on the basis of ^{1}H n.m.r. vicinal coupling constant data.

Reduction of 4-oxo-2,4-diphenylbutyric acid (27) with sodium borohydride followed by acidification also gave the 2,4-diphenyl-γ-butyrolactones (9), which were separated into their crystalline *cis*- (9a) and *trans*- (9b) isomers by column chromatography on silica gel (*cf.* ref. 18). The assignments (Tables 2 and 3) of the ^{1}H n.m.r. signals of both these isomers were aided by catalytic reduction of the αβ-unsaturated lactone (4) with deuterium gas. Both *cis*- (28a) and *trans*- (28b) 2,3-dideuterio-2,4-diphenyl-γ-butyrolactones were isolated and characterised.

TABLE 4

Chemical shifts (in p.p.m. from Me_4Si) for the ring carbon atoms in the ^{13}C n.m.r. spectra of *cis*- (9a) and *trans*- (9b) 2,4-diphenyl-γ-butyrolactones and of the *cis*-2,3-dideuterio-derivative (28a)

	$\delta_c(CDCl_3)$			
Compound	C-1	C-2	C-3	C-4
(9a)	176·3	47·5 [a]	40·4 [a]	79·1 [a]
(28a)	176·4	47·8, 47·4, 47·0 [b]	40·8, 40·0, 39·2 [b]	78·8
(9b)	176·9	45·1 [a]	39·2 [a]	78·8 [a]

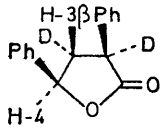
[a] Assignments were confirmed by off-resonance decoupling. [b] Triplets because of C,D-coupling.

Regarding the stereochemical evaluation of natural products containing 2,4-disubstituted γ-butyrolactone rings, ^{13}C n.m.r. spectra of *cis*- (9a) and *trans*- (9b) 2,4-diphenyl-γ-butyrolactones were obtained in order to assess whether this spectroscopic technique was liable to

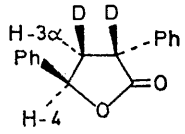
[24] H. Ruppe and F. Schneider, *Ber.*, 1895, **28**, 957.
[25] A. C. O. Hann and A. Lapworth, *J. Chem. Soc.*, 1904, **85**, 1355.
[26] A. Lapworth and E. Wechsler, *J. Chem. Soc.*, 1910, **97**, 38.
[27] M. S. Newman, *J. Amer. Chem. Soc.*, 1938, **60**, 2947.
[28] C. F. H. Allen and R. K. Kimball, *Org. Synth.*, 1943, Coll. Vol. II, p. 498.
[29] M. Robertson and H. Stephen, *J. Chem. Soc.*, 1931, 863.
[30] E. Yoshisato, M. Ryang, and S. Tsutsumi, *J. Org. Chem.*, 1969, **34**, 1500.
[31] F. G. Badder and S. Sherif, *J. Chem. Soc.*, 1960, 2309.
[32] R. Pummerer and E. Buchta, *Ber.*, 1936, **69**, 1005.

be diagnostic of configurational differences. Comparison (Table 4) of the chemical shifts for the ring carbon atoms of (9a) and (9b) indicates that ^{13}C n.m.r. is, in fact, less sensitive than is ^{1}H n.m.r. spectroscopy to configurational differences.

(d) *4-Methyl-2-phenyl-γ-butyrolactones* (10). 4-Methyl-2-phenylbut-2-en-4-olide (5) was obtained by



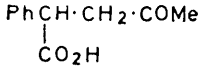
(28a)



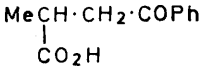
(28b)

the following sequence: (i) addition of hydrogen cyanide to benzylideneacetone to give a nitrile which was hydrolysed *in situ* to yield 2-phenyl-4-oxopentanoic acid (29),[33-36] and (ii) dehydration of (29) by refluxing with acetyl chloride to afford the non-crystalline αβ-unsaturated lactone (5),[9] previously reported [9] as a crystalline compound, m.p. 53°.[37] Catalytic hydrogenation of (5) gave two compounds in the ratio 84 : 16. The major product was assigned (Table 1) as *cis*-4-methyl-2-phenyl-γ-butyrolactone (10a) and the minor as the *trans*-isomer (10b). This assignment of configuration agrees with that previously proposed [16] on the basis of ^{1}H n.m.r. vicinal coupling constant data.

Reduction of 2-phenyl-4-oxopentanoic acid (29) with sodium borohydride followed by acidification also gave the 4-methyl-2-phenyl-γ-butyrolactones (10). The non-crystalline *cis*- (10a) and *trans*- (10b) isomers were separated by column chromatography on silica gel and the assignments of their ^{1}H n.m.r. signals are given in Tables 2 and 3 respectively.



(29)



(30)

(e) *2-Methyl-4-phenyl-γ-butyrolactones* (11). 2-Methyl-4-phenylbut-2-en-4-olide (6) was obtained by the following sequence: (i) addition of hydrogen cyanide to crotonophenone [38] to give a nitrile which was hydrolysed *in situ* to yield 2-methyl-4-oxo-4-phenylbutyric acid (30), and (ii) dehydration of (30) by refluxing with acetic anhydride [39] to afford the αβ-unsaturated lactone (6). Catalytic hydrogenation of (6) under conditions which permitted the absorption of 0·6 mol. equiv. afforded three products together with some starting material. One compound was identified as 2-methyl-4-phenylbutyric acid, *i.e.* the product of hydrogenolysis and reduction. The other two were present in the ratio 50 : 50 and were identified as the *cis*- (11a) and *trans*- (11b) 2-methyl-4-phenyl-γ-butyrolactones by comparison (Tables 2 and 3) of ^{1}H n.m.r. spectra with those of the 2,4-diphenyl-γ-butyrolactones (9). A *cis* : *trans* ratio of 50 : 50 probably does not reflect stereoselectivity of hydrogenation at the 2,3-double bond in view of the competing hydrogenolysis of the C(4)–O single bond of (11a and b) as well as of (6).

Reduction of 2-methyl-4-oxo-4-phenylbutyric acid (30) with sodium borohydride followed by acidification also gave the 2-methyl-4-phenyl-γ-butyrolactones (11).[19,20] The non-crystalline *cis*- (11a) and *trans*- (11b) isomers were separated by column chromatography on silica gel. The ^{1}H n.m.r. assignments are given in Tables 2 and 3.

An attempt to prepare the 2-methyl-4-phenyl-γ-butyrolactones by the method of van Tamelen and Bach [20] resulted (Scheme 2) in the isolation and characterisation of the constitutionally isomeric 2-methyl-3-phenyl-γ-butyrolactones (31). Reaction of the diethyl malonate anion with styrene oxide [40] proceeds *via* both possible modes [41] of attack by the anion on the epoxide ring to give an approximately 1 : 1 mixture of 2-ethoxycarbonyl-4-phenyl- (32) and 2-ethoxycarbonyl-3-phenyl- (33) γ-butyrolactones. The mixture of carboxylic acids [(34) and (35)] obtained on acid hydrolysis was subjected to the sequence of reactions (Scheme 2) reported by van Tamelen and Bach: [20] [(34) and (35)] ⟶ [(38) and (39)] ⟶ [(40) and (41)]. Compounds (40) and (41) were readily separated by column chromatography on silica gel and were assigned as 2-methylene-4-phenyl-γ-butyrolactone (40) and 2-methylene-3-phenyl-γ-butyrolactone (41) on the basis of their ^{1}H n.m.r. spectra (see Experimental section). This assignment was confirmed by the following chemical means.

Catalytic hydrogenation of (40) (uptake 0·5 mol. equiv.) afforded the isomeric αβ-unsaturated lactone (6), *cis*-2-methyl-4-phenyl-γ-butyrolactone (11a), a trace of the *trans*-isomer (11b), and 2-methyl-4-phenylbutyric acid. The high stereoselectivity exhibited during this hydrogenation is surprising in view of (i) the lack of stereoselectivity observed during the hydrogenation of (6) discussed earlier, and (ii) the fact that the chiral centre at C(4) is β to the double bond in (40).*

Catalytic hydrogenation of (41) with just less than 1 mol. equiv. afforded three compounds. One compound, present in small amounts, was characterised as the isomeric αβ-unsaturated lactone (42) by ^{1}H n.m.r. spectroscopy (see Experimental section). The other two products were present in the reaction mixture in the ratio of 73 : 27. The major product was assigned as

* The possibility that double bond isomerisation, *i.e.* (40) ⟶ (6), is fast compared with hydrogenation of (40) to give (11) is ruled out because hydrogenation of (6) should lead to almost equal proportions of (11a) and (11b) as shown earlier. In fact, only a trace of the *trans*-isomer (11b) is found.

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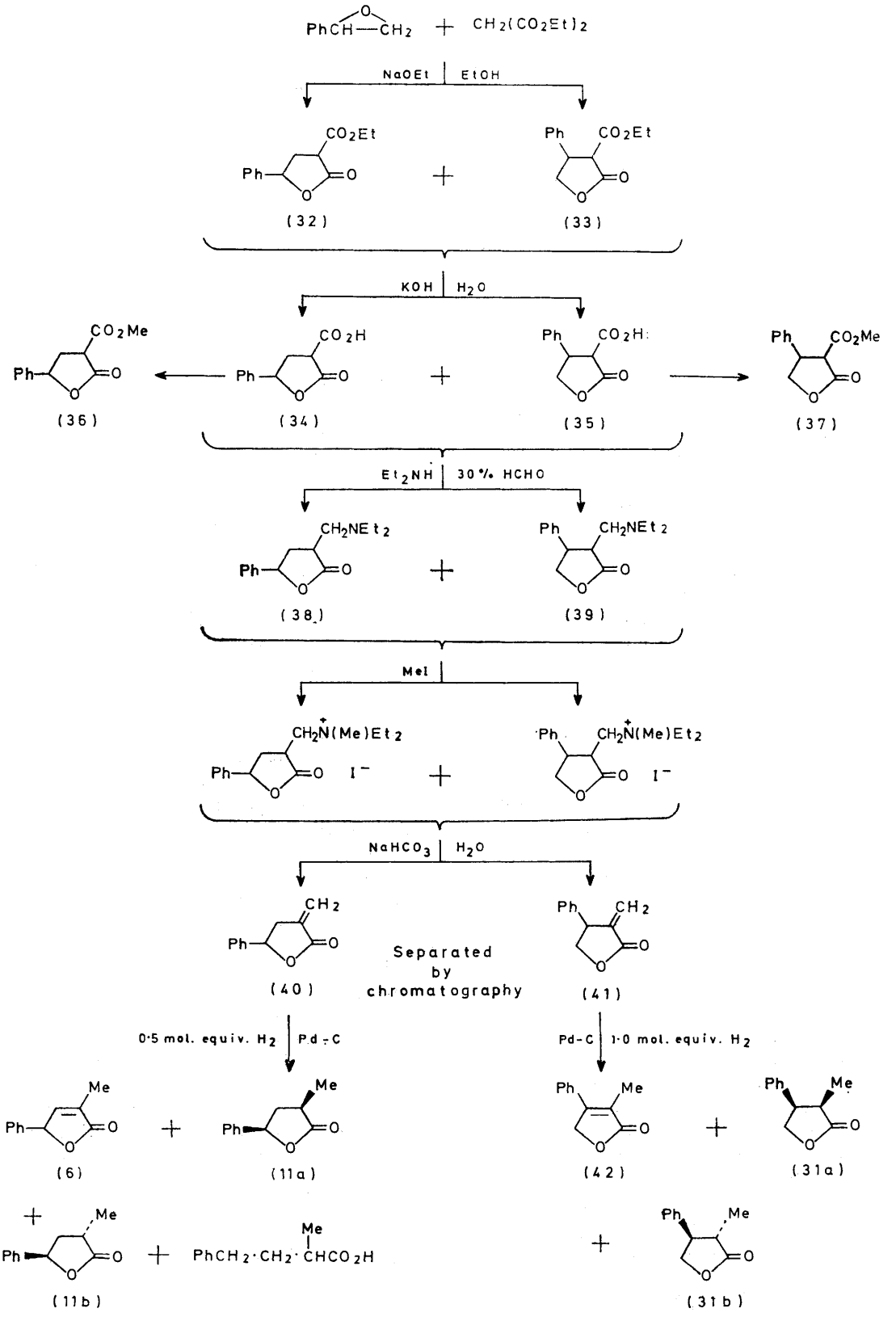
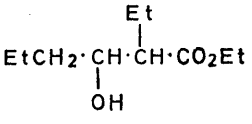


SCHEME 2 Synthesis of 2-methyl-4-phenyl- (11) and 2-methyl-3-phenyl- (31) γ-butyrolactones

cis-2-methyl-3-phenyl-γ-butyrolactone (31a) and the minor as the *trans*-isomer (31b).

Isomerisation of the exocyclic double bonds in the α-methylene derivatives (40) and (41) appears to occur quite readily on palladium catalysts to give the constitutionally isomeric αβ-unsaturated lactones (6) and (31) with endocyclic double bonds. There is adequate precedent for double-bond isomerisation on hydrogenation catalysts.[10]

(f) 2,4-*Diethyl-γ-butyrolactones* (12). A mixture of the *cis*- (12a) and *trans*- (12b) isomers of 2,4-diethyl-γ-butyrolactone was obtained by a published procedure [21] involving: (i) a Reformatsky reaction between ethyl 2-bromobutyrate and butyraldehyde to yield ethyl 2-ethyl-3-hydroxyhexanoate (43), and (ii) acid-catalysed dehydration of this β-hydroxy-ester (43) to afford the 2,4-diethyl-γ-butyrolactones (12). The isomers were partially separated by column chromatography on silica gel before being purified by preparative g.l.c. Configurations were assigned to the two isomers on the basis of a comparison (Tables 2 and 3) of their ^{1}H n.m.r. spectra with those of *cis*- (7a) and *trans*- (7b) 2,4-dimethyl-γ-butyrolactones. ^{1}H N.m.r. assignments are given in Tables 2 and 3.



(43)

(g) 2-*Ethyl*-4-*methyl*- (13) *and* 2-*butyl*-4-*methyl*- (14) *γ-butyrolactones*. Both these lactones were separated into their *cis*- and *trans*-isomers by preparative g.l.c. In each case, configurations were assigned on the basis of a comparison (Tables 2 and 3) of ^{1}H n.m.r. spectra with those of the 2,4-dimethyl- (7) and 2,4-diethyl- (12) γ-butyrolactones. ^{1}H N.m.r. assignments are given in Tables 2 and 3.

Equilibration Studies.—Base-catalysed equilibrations were performed on seven 2,4-disubstituted-γ-butyrolactones [(7)—(10) and (12)—(14)]. The results (Table 5) indicate that (i) the free energy differences between *cis*- and *trans*-isomers are small, and (ii) the *cis*- is thermodynamically more stable than the *trans*-isomer in all cases. Apart from the 2,4-di-t-butyl-γ-butyrolactones (8), the free energy differences lie within 0·24 kcal mol^{-1} of each other. This suggests that substituent effects are small and that only when substituent groups are large (*e.g.* t-butyl) do they influence the position of equilibrium.

The conformational behaviour of five-membered rings is generally accepted to be more complex and less well understood than that of six-membered rings. The reason for this is thought to be associated with the flexible nature of five-membered rings which permits rapid pseudorotation [42] involving interconversion of numerous conformations of similar energies. However, in 2,4-disubstituted-γ-butyrolactones, pseudorotation is probably severely impaired by (i) the presence of substituents [43] on C-2 and C-4, and (ii) the resonance demands

TABLE 5

Base-catalysed equilibrations (Bu^{t}OH–Bu^{t}OK) of the 2,4-disubstituted γ-butyrolactones [(7)—(10) and (12)—(14)] and 2-methyl-3-phenyl-γ-butyrolactone (31) at 25°

Lactone	Isomer ratio (*trans* : *cis*)	*K*	$\Delta G°_{25}$/ kcal mol^{-1}
(7)	44 : 56 [a]	1·27	−0·14
(8)	12 : 88 [b]	7·33	−1·20
(9)	40 : 60 [c]	1·50	−0·24
(10)	42 : 58 [d]	1·38	−0·19
(12)	43 : 57 [b]	1·33	−0·17
(13)	49 : 51 [b]	1·04	−0·002
(14)	42 : 58 [e]	1·38	−0·19
(31)	83 : 17 [f]	0·20	+0·95

[a] By g.l.c. (10% polyethylene glycol adipate on 80—100 mesh Chromosorb W at 80°). [b] By g.l.c. (capillary column of diethylene glycol succinate at 130°). [c] By ^{1}H n.m.r. spectroscopy from integration of the signals for H-4. [d] By ^{1}H n.m.r. spectroscopy from integration of the methyl doublets. [e] By g.l.c. (capillary column of diethylene glycol succinate at 140°). [f] By g.l.c. (capillary column of diethylene glycol succinate at 200°). A ratio of *ca.* 80 : 20 was obtained by ^{1}H n.m.r. spectroscopy from integration of the methyl doublets.

of the –C–CO–O–C– group for planarity.[44,45] If this constraint is imposed on γ-lactone rings then it is possible to discuss their conformational behaviour in terms of envelope conformations in which the –C(2)–CO–O–C(4)– fragment lies in a plane from which C-3 is displaced. Although this description undoubtedly represents an oversimplification of the problem, it does allow some qualitative conclusions to be drawn. *cis*-2,4-Disubstituted γ-lactones can exist in a conformation (44) in which both substituents are quasi-equatorial (*cf.* *cis*-1,3-disubstituted cyclohexanes), whereas in the *trans*-isomers one of the two substituents must be quasi-axial in conformations (45) and (46) (*cf.* *trans*-1,3-disubstituted cyclohexanes) and these conformations may be considered to be rapidly interconverting. On the basis of this model, a destabilising feature in the *trans*-isomers would appear to be the 1,3-nonbonded interactions between R^1 and H-4 in (45) and between R^2 and H-2 in (46). However, this interaction must be small as it takes a bulky substituent (*e.g.* t-butyl) to

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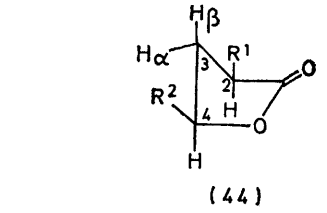
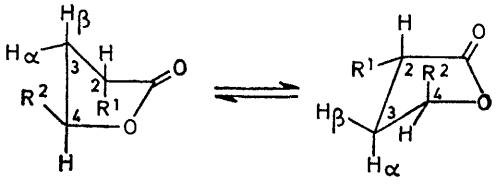
bring about a small displacement in the equilibrium towards the *cis*-isomer.*



(44)



(45) (46)

Although calculation of specific torsional angles in flexible systems from vicinal coupling constants is a dangerous procedure [46] and is to be avoided, the relative magnitudes (see Tables 6 and 7) indicate that (i) our

TABLE 6

Vicinal coupling constants (Hz) [a] of the *cis*-2,4-disubstituted γ-butyrolactones (8a)—(11a)

Lactone	$J_{2,3\alpha}$	$J_{2,3\beta}$	$J_{3\alpha,4}$	$J_{3\beta,4}$
(8a)	8·5	12·8	6·0	10·8
		(12·8) [b]		(10·8) [c]
(9a)	8·1 [d]	12·9 [d]	5·7 [d]	10·8 [d]
				(10·8) [e]
(10a)	8·5 [f]	12·8 [f]	5·7 [f]	10·8 [f]
(11a)	8·1	12·9	5·8	10·8

[a] Computed using LAOCOON II [58] as 4-spin systems for (8a) and (9a), and as 7-spin systems in the case of (10a) and (11a). [b] From *cis*-3,4-dideuterio-2,4-di-t-butyl-γ-butyrolactone (24). [c] From *cis*-2,3-dideuterio-2,4-di-t-butyl-γ-butyrolactone (23). [d] Johnson, Lowry, and Riggs [16] report 8·2, 13·0, 5·5, and 10·9 Hz, respectively, for $J_{2,3\alpha}$, $J_{2,3\beta}$, $J_{3\alpha,4}$, and $J_{3\beta,4}$. [e] From *cis*-2,3-dideuterio-2,4-diphenyl-γ-butyrolactone (28a). [f] Johnson, Lowry, and Riggs [16] report 8·4, 12·7, 5·2, and 10·3 Hz, respectively, for $J_{2,3\alpha}$, $J_{2,3\beta}$, $J_{3\alpha,4}$, and $J_{3\beta,4}$.

qualitative proposals regarding the conformational behaviour of the *cis*- and *trans*-isomers are reasonable [*e.g.* $J_{2,3\beta}$ and $J_{3\beta,4}$ are significantly larger than $J_{2,3\alpha}$ and $J_{3\alpha,4}$ in the *cis*-isomers, pointing to a significant contribution from conformation (44); this is not so in the *trans*-isomers where the values for $J_{2,3\alpha}$ and $J_{2,3\beta}$, and for $J_{3\alpha,4}$ and $J_{3\beta,4}$, are of the same order of magnitude and accommodate a description where conformations (45) and (46) are rapidly interconverting], and (ii) the conformational behaviour within the series of the *cis*-isomers is similar, and so is that in the series of *trans*-isomers, although the two diastereoisomers probably differ quite significantly from each other; indeed, the magnitudes of the vicinal coupling constants characterise the diastereoisomers.†

TABLE 7

Vicinal coupling constants (Hz) [a] of the *trans*-2,4-disubstituted γ-butyrolactones (8b)—(11b)

Lactone	$J_{2,3\alpha}$	$J_{2,3\beta}$	$J_{3\alpha,4}$	$J_{3\beta,4}$
(8b)	8·0	9·0	7·5	7·0
(9b)	8·1 [b]	9·7 [b]	7·8 [b]	5·8 [b]
			(7·8) [c]	
(10b)	7·0 [d]	9·0 [d]	6·8 [d]	6·2 [d]
(11b)	7·0	9·0	7·5	5·5

[a] Computed using LAOCOON II [58] as 4-spin systems for (8b) and (9b), and as 7-spin systems in the case of (10b) and (11b). [b] Johnson, Lowry, and Riggs [16] report 7·3, 9·7, 7·6, and 5·5 Hz, respectively, for $J_{2,3\alpha}$, $J_{2,3\beta}$, $J_{3\alpha,4}$, and $J_{3\beta,4}$. [c] From *trans*-2,3-dideuterio-2,4-diphenyl-γ-butyrolactone (28b). [d] Johnson, Lowry, and Riggs [16] report 6·7, 9·7, 6·9, and 5·6 Hz, respectively, for $J_{2,3\alpha}$, $J_{2,3\beta}$, $J_{3\alpha,4}$, and $J_{3\beta,4}$.

There are few instances where the relative stabilities of similar systems have been measured precisely, but where they have been obtained [47-55] there is a degree of correlation with the present results. The most detailed analysis [54] has been carried out on 2,4-disubstituted 1,3-dioxolans. Our observations should be compared with the exclusive preference for *cis*-isomers in these more highly flexible systems on acid-catalysed equilibration with their *trans*-isomers where it was also found that (i) free energy differences between diastereoisomers are small, and (ii) only bulky substituents show signs of specific steric interactions.

There are even fewer instances (for an exception, however, see ref. 56) where the relative stabilities of *cis*- and *trans*-isomers with vicinal substituents on five-membered rings have been measured accurately, but the expected preference for the *trans*-isomer has been more than adequately demonstrated in the prostaglandin field. In the case of the 2-methyl-3-phenyl-γ-butyrolactones (31), the *trans*-isomer (31b) is found (Table 5) to predominate at equilibrium.

EXPERIMENTAL

M.p.s were determined using a Reichart hot-stage apparatus. T.l.c. was carried out on glass plates (20 × 5 cm) coated with Merck silica gel G. Developed plates were air-dried, sprayed with cerium(IV) sulphate–sulphuric acid reagent, and heated with a naked flame. Hopkin and Williams silica gel (M.F.C. grade) was used as the chromatographic medium for all column separations. G.l.c. analyses of an analytical nature were carried out using a Perkin-Elmer F11 gas chromatograph equipped with a

* This is not surprising since the quasi-axial bonds on C-2 and C-4 in conformations (44)—(46) are directed away from each other to some extent.

† The chemical shift differences between H-3α and H-3β (Tables 2 and 3) also characterise [16] the diastereoisomers.

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flame-ionisation detector. Preparative g.l.c. was carried out on a Pye automatic preparative series 105 chromatograph. Low resolution mass spectra were determined with an A.E.I.-MS12 spectrometer, and high resolution spectra with an A.E.I.-MS9 instrument. I.r. spectra were recorded on a Perkin-Elmer 137 sodium chloride spectrophotometer with reference to polystyrene as standard. Lactone C=O absorption frequencies were characteristic [57] of the nature of the γ-lactone ring (*i.e.* saturated, αβ-unsaturated, or βγ-unsaturated). ^{13}C N.m.r. spectra were recorded on a JEOL-PS-100 spectrometer with deuteriochloroform as 'lock' and tetramethylsilane as internal standard. ^{1}H N.m.r. spectra were recorded on a Varian HA 100 spectrometer with tetramethylsilane as 'lock' and internal standard. Theoretical ^{1}H n.m.r. spectra were calculated with an ICL 1907 computer by using the LAOCOON II program.[58]

Diethyl 2-Acetyl-3-methylsuccinate (15).[22]—Ethyl acetoacetate (190 ml) was added to a solution of sodium ethoxide (102 g) in ethanol (1 l). This solution was stirred under reflux while ethyl 2-bromopropionate (250 g) was added dropwise during *ca.* 1 h. Refluxing and stirring were continued until a sample of the solution was neutral to moist litmus paper. The reaction was complete after 10 h. The mixture was then cooled and decanted from the precipitated sodium bromide. The salt was washed with ethanol (2 × 20 ml) and the washings were added to the decanted solution. Evaporation of the ethanol under reduced pressure gave an oil, which was distilled under reduced pressure to give the *diester* (15) (140 g, 68%), b.p. 144—150° at 0·2 mmHg (lit.,[22] 225—228° at 135 mmHg) (Found: *M*, 230. $C_{11}H_{18}O_5$ requires *M*, 230).

2-Methyl-4-oxopentanoic Acid (16) [23] *and 3-Carboxy-2,4-dimethylbut-2-en-4-olide* (17).—A mixture of the oxo-diester (15) (23 g), conc. hydrochloric acid (88 ml), and water (40 ml) was heated under reflux with stirring overnight. After cooling, water and ethanol were evaporated off under reduced pressure. The residue was extracted with ether (500 ml) and the extract was dried (Na_2SO_4) and evaporated to yield a mixture of a yellow oil and colourless crystals. The oil was filtered off from the crystals and was distilled under reduced pressure to give the *acid* (16) (5·0 g, 39%), b.p. 94—98° at 0·2 mmHg (lit.,[23] 106—108° at 0·7 mmHg) (Found: *M*, 130. $C_6H_{10}O_3$ requires *M*, 130), $\nu_{max.}$ ($CHCl_3$) 1740 and 1700 cm^{-1} (2 × CO), τ ($CDCl_3$) 0·61br (1H, s, CO_2H), 6·85—7·67 (3H, m, CH_2·CH), 7·75 (3H, s, CH_3CO), and 8·81 (3H, d, *J* 6·2 Hz, CH_3·CH).

The crystals were recrystallised from ether–hexane to give the carboxy-lactone (17) (2·2 g, 14%), m.p. 172—174° (Found: *M*, 156. $C_7H_8O_4$ requires *M*, 156), $\nu_{max.}$ ($CHCl_3$) 1750 (CO) and 1700 cm^{-1} (CO_2H), τ [$(CD_3)_2CO$] 4·84 (1H, m, CH_3·CH), 7·90 (3H, d, *J* 2 Hz, 2-Me), and 8·51 (3H, d, *J* 6·2 Hz, CH_3·CH). The *methyl ester* (18) (obtained by treatment with ethereal diazomethane) was a liquid, b.p. 118—120° at 0·4 mmHg (Found: *M*, 170. $C_8H_{10}O_4$ requires *M*, 170), $\nu_{max.}$ ($CHCl_3$) 1750 (CO) and 1710 cm^{-1} (CO_2Me), τ ($CDCl_3$) 4·86 (1H, m, CH_3·CH), 6·12 (3H, s, CO_2CH_3), 7·82 (3H, d, *J* 2·4 Hz, 2-Me), and 8·48 (3H, d, *J* 6·4 Hz, CH_3·CH).

2-Methyl-4-oxopentanoic Acid (16).[23]—The oxo-diester (15) (45 g) in 4% sodium hydroxide solution (300 ml) was heated for 3 h. After cooling, the mixture was treated again with 4% sodium hydroxide (100 ml) and refluxed for an additional 2 h. The mixture was then cooled and washed with ether (2 × 100 ml). The aqueous phase was acidified with conc. hydrochloric acid while the flask was cooled in an ice-bath; vigorous evolution of carbon dioxide occurred. The aqueous phase was extracted with ether (4 × 400 ml) and the combined extracts were washed with a little water, dried (Na_2SO_4), and evaporated to afford a deep yellow oil, which, on distillation under reduced pressure, yielded the acid (16) (17 g, 67%), b.p. 93—95° at 0·2 mmHg, identical (spectral characteristics) with the sample described above.

2,4-Dimethylbut-2-en-4-olide (2).[4]—A mixture containing 2-methyl-4-oxopentanoic acid (16) (10 g), acetic anhydride (40 ml), glacial acetic acid (40 ml), and conc. sulphuric acid (5 drops) was heated on a steam-bath for 3 h, cooled, diluted with water, and extracted with ether (250 ml). The extract was washed with saturated sodium hydrogen carbonate solution, dried (Na_2SO_4), and evaporated to leave a yellowish oil, which was purified by column chromatography on silica gel (chloroform as eluant) to give, as a colourless oil, the *lactone* (2) (2·6 g, 30%) (Found: *M*, 112·0523. $C_6H_8O_2$ requires *M*, 112·0524), $\nu_{max.}$ ($CHCl_3$) 1750 cm^{-1} (CO), τ ($CDCl_3$) 2·99 (1H, m, H-3), 5·03 (1H, m, H-4), 8·09 (3H, m, 2-Me), and 8·61 (3H, d, *J* 6·4 Hz, 4-Me).

Hydrogenation of 2,4-Dimethylbut-2-en-4-olide (2).—The lactone (2) (1·0 g) was dissolved in ethanol (25 ml) containing 5% palladium–barium sulphate (300 mg). Hydrogenation at atmospheric pressure resulted in the uptake of 1·05 mol. equiv. in 1·5 h. Filtration and evaporation yielded a product (700 mg, 70%) (Found: *M*, 114·0679. $C_6H_{10}O_2$ requires *M*, 114·0681), $\nu_{max.}$ ($CHCl_3$) 1760 cm^{-1} (CO), τ ($CDCl_3$) 5·30—5·72 (1H, m, H-4), 7·08—7·63 (2H, m, H-2 and -3α), 8·30—8·94 (1H, m, H-3β), 8·60 (3H, d, *J* 6·2 Hz, 4-Me), and 8·75 (3H, d, *J* 6·5 Hz, 2-Me). G.l.c. analysis (10% polyethylene glycol adipate on 80—100 mesh Chromosorb W at 80°) indicated the presence of two components in the ratio 98 : 2. The major component was assigned as *cis*-2,4-dimethyl-γ-butyrolactone (7a) and the minor as the *trans*-lactone (7b). The 2% of the *trans*-isomer (7b) was not detected in the ^{1}H n.m.r. spectrum of the product and was not considered to constitute a sufficient quantity to merit separation by preparative g.l.c.

Catalytic Reduction of 2,4-Dimethylbut-2-en-4-olide (2) *with Deuterium Gas.*—The lactone (2) (200 mg) was reduced with deuterium gas over 5% palladium–barium sulphate to yield a product which ^{1}H n.m.r. spectroscopy indicated was a mixture of *cis*-2,3-dideuterio- (19), *cis*-2-monodeuterio- (20), and *cis*-3-monodeuterio- (21) 2,4-dimethyl-γ-butyrolactones; τ ($CDCl_3$) 5·30—5·72 [1H, m (br owing to deuterium coupling), H-4], 7·14—7·63 [*ca.* 1H, m (br due to deuterium coupling), H-2 and -3α], and 8·31—8·87 [7H, m, d (*J* 6·2 Hz), d (*J* 6·5 Hz), and s for H-3β, 4-Me, and 2-Me].

cis- (7a) *and* trans- (7b) *2,4-Dimethyl-γ-butyrolactones.*—A solution of sodium borohydride (4 g) in 2N-sodium hydroxide (4 ml) diluted with water (36 ml) was added dropwise very slowly to a stirred solution of 2-methyl-4-oxopentanoic acid (16) (8 g) in methanol (50 ml) and stirring was continued overnight. Methanol and water were evaporated off and water was added to the residue; the mixture was then acidified with dilute hydrochloric acid and extracted with ether (3 × 500 ml). The combined extracts were washed with a small amount of water, dried (Na_2SO_4), and concentrated to give a colourless oil. Distillation under reduced

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[58] S. Castellano and A. A. Bothner-By, *J. Chem. Phys.*, 1964, **41**, 3863.

pressure yielded 2,4-dimethyl-γ-butyrolactone (7) (6 g, 85%), b.p. 80—82° at 18·1 mmHg (lit.,[12] 88—90° at 20 mmHg), shown by g.l.c. (10% polyethylene glycol adipate on 80—100 mesh Chromosorb W at 80°) to contain two components in the ratio *ca.* 3 : 2. These were separated by preparative g.l.c. (30% polyethylene glycol adipate on 60—80 mesh Chromosorb W at 130°). The first was identified by comparison with the major product obtained on catalytic hydrogenation of 2,4-dimethylbut-2-en-4-olide (2) as the cis-*isomer* (7a) (Found: *M*, 114·0679. $C_6H_{10}O_2$ requires *M*, 114·0681), $\nu_{max.}$ ($CHCl_3$) 1760 cm^{-1} (CO), τ (CCl_4) 5·40—5·84 (1H, m, H-4), 7·20—7·74 (2H, m, H-2 and -3α), 8·36—8·94 (1H, m, H-3β), 8·61 (3H, d, *J* 6·2 Hz, 4-Me), and 8·78 (3H, d, *J* 6·5 Hz, 2-Me); the second component was the trans-*isomer* (7b) (Found: *M*, 114·0679), $\nu_{max.}$ ($CHCl_3$) 1760 cm^{-1} (CO), τ (CCl_4) 5·28—5·64 (1H, m, H-4), 7·22—7·64 (1H, m, H-2), 7·82—8·16 (2H, m, H-3α and β), and 8·68 and 8·80 (2 × 3H, 2 × d, *J* 6·3 and 7·1 Hz, 2 × CH_3).

2,4-*Di-t-butylbut*-3-*en*-4-*olide* (22).[5]—Irradiation of diazomethyl t-butyl ketone [5] (16 g) in a quartz test tube with a Hanovia medium-pressure mercury vapour lamp as described by Wiberg and Hutton [5] gave a white solid, which, on crystallisation from ethanol–water, afforded crystals of the lactone (22) (6·2 g, 25%), m.p. 38—40° (lit.,[5] 41·5—42°) (Found: *M*, 196·1454. Calc. for $C_{12}H_{20}O_2$: *M*, 196·1463), $\nu_{max.}$ ($CHCl_3$) 1786 cm^{-1} (CO), τ ($CDCl_3$) 4·96 (1H, d, *J* 2·4 Hz, H-3), 7·08 (1H, d, *J* 2·4 Hz, H-2), and 8·87 and 9·01 (18H, 2 × s, 2 × Me_3C).

2,4-*Di-t-butylbut*-2-*en*-4-*olide* (3).[5]—The lactone (22) (2 g) was heated on a steam-bath for 6 h with 15% sodium hydroxide solution (56 ml) as described in ref. 5 to give white crystals of the lactone (3) (1·44 g, 72%), m.p. 92—94° (lit.,[5] 92·5—93·5°) (Found: *M*, 196·1461. $C_{12}H_{20}O_2$ requires *M*, 196·1463), $\nu_{max.}$ ($CHCl_3$) 1750 cm^{-1} (CO), τ ($CDCl_3$) 3·10 (1H, d, *J* 1·7 Hz, H-3), 5·54 (1H, d, *J* 1·7 Hz, H-4), and 8·76 and 9·07 (18H, 2 × s, 2 × Me_3C).

Hydrogenation of 2,4-*Di-t-butylbut*-3-*en*-4-*olide* (22).[5]—The lactone (22) (2 g) was hydrogenated in ethanol (25 ml) over 5% palladium–barium sulphate (250 mg) (uptake 1·05 mol. equiv. in 2 h). The catalyst was filtered off and the filtrate was examined by g.l.c. on (i) a capillary column of diethylene glycol succinate at 130°, and (ii) polyethylene glycol adipate on 80—100 mesh Chromosorb W at 105°. In each case, only one component was observed and it was assigned as *cis*-2,4-di-t-butyl-γ-butyrolactone (8a). Water was added to the filtrate before extracting it three times with pentane. The combined pentane extracts were dried (Na_2SO_4) and evaporated to afford *cis*-2,4-di-t-butyl-γ-butyrolactone (8a) (1·7 g, 85%), m.p. 86—88° (lit.,[5] 82—83°) (Found: *M*, 198·1618. $C_{12}H_{22}O_2$ requires *M*, 198·1620), $\nu_{max.}$ ($CHCl_3$) 1760 cm^{-1} (CO), τ ($CDCl_3$) 6·06 (1H, q, $J_{3\alpha,4}$ 6·0, $J_{3\beta,4}$ 10·8 Hz, H-4), 7·55 (1H, q, $J_{2,3\alpha}$ 8·5, $J_{2,3\beta}$ 12·8 Hz, H-2), 7·97 (1H, m, $J_{2,3\alpha}$ 8·5, $J_{3\alpha,4}$ 6·0, $J_{3\alpha,3\beta}$ 13 Hz, H-3α), 8·23 (1H, m, $J_{2,3\beta}$ 12·8, $J_{3\beta,4}$ 10·8, $J_{3\alpha,3\beta}$ 13·0 Hz, H-3β), and 8·96 and 9·08 (18H, 2 × s, 2 × Me_3C).

Catalytic Reduction of 2,4-*Di-t-butylbut*-3-*en*-4-*olide* (22) *with Deuterium Gas.*—The lactone (22) (250 mg) was reduced with deuterium over 5% palladium–barium sulphate to yield a product which afforded crystals of cis-3,4-*dideuterio*-2,4-*di-t-butyl*-γ-*butyrolactone* (24) (150 mg, 60%), m.p. 85—87° (from hexane–ether), τ ($CDCl_3$) 7·57 [1H, d (br owing to deuterium coupling), $J_{2,3\beta}$ 12·8 Hz, H-2], 8·16—8·46 [1H, d (vbr owing to deuterium coupling), $J_{2,3\beta}$ 12·8 Hz, H-3β], and 8·96 and 9·08 (18H, 2 × s, 2 × Me_3C). No *trans*-3,4-dideuterio-2,4-di-t-butyl-γ-butyrolactone was formed.

Hydrogenation of 2,4-*Di-t-butylbut*-2-*en*-4-*olide* (3).[5]—The lactone (3) (2 g) was hydrogenated as described for the lactone (22) for 2·5 h (uptake 1·05 mol. equiv.). The catalyst was filtered off and the filtrate was examined by g.l.c. as for the hydrogenation of (22). Once again, only one component was observed and its retention time corresponded to that of *cis*-2,4-di-t-butyl-γ-butyrolactone (8a). The compound was isolated from the filtrate to give crystals (1·7 g, 85%), m.p. 86—88° (lit.,[5] 82—83°), with spectroscopic properties identical with those already reported for the lactone (8a).

Catalytic Reduction of 2,4-*Di-t-butylbut*-2-*en*-4-*olide* (3) *with Deuterium Gas.*—The lactone (3) (250 mg) was reduced catalytically with deuterium gas as described for the lactone (22) to give crystals of 2,3-*dideuterio*-2,4-*di-t-butyl*-γ-*butyrolactone* (23) (160 mg, 64%), m.p. 76—78°, τ ($CDCl_3$) 6·07 [1H, d (br owing to deuterium coupling), $J_{3\beta,4}$ 10·8 Hz, H-4], 8·24 [1H, d (br owing to deuterium coupling), $J_{3\beta,4}$ 10·8 Hz, H-3β], and 8·95 and 9·05 (18H, 2 × s, 2 × Me_3C). No *trans*-2,3-dideuterio-2,4-di-t-butyl-γ-butyrolactone was formed.

trans-2,4-*Di-t-butyl*-γ-*butyrolactone* (8b).—*cis*-2,4-Di-t-butyl-γ-butyrolactone (8a) (450 mg) was dissolved in a 3% solution of potassium t-butoxide in t-butyl alcohol (10 ml) and the mixture was kept in a constant temperature bath at 25°. After 24 h it was treated with Zeocarb-325 resin and filtered, and the filtrate was evaporated. T.l.c. of the residue indicated the presence of two components, of which one (the slower moving) was the starting material. Column chromatography on silica gel with chloroform as eluant separated the two components. Fraction 1 slowly crystallised and was characterised as the trans-*lactone* (8b) (28 mg, 6%), m.p. 66—68° (Found: *M*, 198·1618. $C_{12}H_{22}O_2$ requires *M*, 198·1620), $\nu_{max.}$ ($CHCl_3$) 1760 cm^{-1} (CO), τ ($CDCl_3$) 5·94 (1H, t, $J_{3\alpha,4}$ 7·5, $J_{3\beta,4}$ 7·0 Hz, H-4), 7·63 (1H, t, $J_{2,3\alpha}$ 8·0, $J_{2,3\beta}$ 9·0 Hz, H-2), 7·95 (1H, m, $J_{2,3\alpha}$ 8·0 Hz, $J_{3\alpha,4}$ 7·5, $J_{3\alpha,3\beta}$ 13·0 Hz, H-3α), 7·99 (1H, m, $J_{2,3\beta}$ 9·0, $J_{3\beta,4}$ 7·0, $J_{3\alpha,3\beta}$ 13·0 Hz, H-3β), and 8·96 and 9·09 (18H, 2 × s, 2 × Me_3C). Fraction 2 slowly crystallised (250 mg, 55%) and was identical (spectra) with the *cis*-lactone (8a), m.p. 84—85°.

4-*Oxo*-2,4-*diphenylbutyronitrile* (25).[14,15,18,24-29]—Compound (25), m.p. 125—126° (lit.,[25] 126—127°), τ ($CDCl_3$) 2·18—2·98 (10H, m, 2 × Ph) and 5·52—6·86 (3H, XAB system, J_{AB} 18·0, J_{AX} 7·8, J_{BX} 6·6 Hz, $-CH_AH_B{\cdot}CH_X<$), was prepared by the method of ref. 25.

Methyl 4-*Oxo*-2,4-*diphenylbutyrate* (26).[6,14,15,24,27]—Compound (26), m.p. 103—104° (lit.,[6] 103—104°), τ ($CDCl_3$) 2·00—2·94 (10H, m, 2 × Ph), 5·72, 6·08, and 6·78 (3H, XAM system, J_{AM} 18·0, J_{AX} 10·0, J_{MX} 4·0 Hz, $-CH_AH_M{\cdot}CH_X<$), and 6·37 (3H, s, CO_2Me) was prepared by the method of ref. 6.

4-*Oxo*-2,4-*diphenylbutyric Acid* (27).[6,14,15,18,24-27]—Compound (27), m.p. 152—153° (lit.,[18] 152—155°), τ ($CDCl_3$) 0·18—0·78br (1H, s, CO_2H), 2·02—2·88 (10H, m, 2 × Ph), and 5·73, 6·15, and 6·78 (3H, XAM system, J_{AM} 18·0, J_{AX} 10·0, J_{MX} 4·2 Hz, $-CH_AH_M{\cdot}CH_X<$) was prepared by the method of ref. 6.

2,4-*Diphenylbut*-2-*en*-4-*olide* (4).[6-8]—4-Oxo-2,4-diphenylbutyric acid (27) (5·0 g) was dissolved in acetic anhydride (25 ml) and refluxed for 3 h. The mixture was then cooled, poured into ice–water, and left for 1 h. The precipitate was filtered off, dried in air, and purified by column chro-

matography on silica gel (150 g) with chloroform as eluant, to yield crystals of the *lactone* (4) (3·5 g, 78%), m.p. 109—110° (from ethanol) (lit.,[15] 109—110°) (Found: *M*, 236·0844. $C_{16}H_{12}O_2$ requires *M*, 236·0837), $\nu_{max.}$ ($CHCl_3$) 1750 cm^{-1}, τ ($CDCl_3$) 2·04—2·70 (10H, m, 2 × Ph), 2·41 (1H, d, *J* 2·0 Hz, H-3), and 4·01 (1H, d, *J* 2·0 Hz, H-4) (*cf.* ref. 30).

Hydrogenation of 2,4-*Diphenylbut*-2-*en*-4-*olide* (4).[14]—The lactone (4) (1·0 g) was dissolved in ethanol and 10% palladium–carbon (300 mg) was added. The mixture was hydrogenated for 10 min (uptake 0·5 mol. equiv.), filtered, and evaporated. The residue was shown by t.l.c. to contain four components. A sample was retained for ^1H n.m.r. spectroscopy (see below). The mixture was separated by column chromatography on silica gel with chloroform as eluant. Component 1 crystallised from ether–hexane to afford pure *trans*-2,4-diphenyl-γ-butyrolactone (9b) (30 mg, 3%), m.p. 67—68° (lit.,[18] 68—69°; lit.,[17] 74°) (Found: *M*, 238·0995. Calc. for $C_{16}H_{14}O_2$: *M*, 238·0993), $\nu_{max.}$ ($CHCl_3$) 1770 cm^{-1} (CO), τ ($CDCl_3$) 2·66 and 2·70 (10H, 2 × s, 2 × Ph), 4·35 (1H, q, $J_{3\beta,4}$ 5·8, $J_{3\alpha,4}$ 7·8 Hz, H-4), 6·08 (1H, q, $J_{2,3\alpha}$ 8·1, $J_{2,3\beta}$ 9·7, $J_{3\beta,4}$ 5·8, $J_{3\alpha,3\beta}$ 13·0 Hz, H-3α), and 7·31 (1H, m, $J_{2,3\alpha}$ 8·1, $J_{3\alpha,4}$ 7·8, $J_{3\alpha,3\beta}$ 13 Hz, H-3β), δ_C (p.p.m. from Me_4Si) ($CDCl_3$) 176·9 (CO), 139·4, 136·6, 129·0, 128·9, 128·4, 127·7, and 125·1 (aromatics), 78·8 (C-4), 45·1 (C-2), and 39·2 (C-3). The assignment of resonances to C-2, -3, and -4 was confirmed by off-resonance decoupling. Component 2 crystallised from ether–hexane to afford pure *cis*-2,4-diphenyl-γ-butyrolactone (9a) (225 mg, 22·5%), m.p. 103—105° (lit.,[18] 106—107°) (Found: *M*, 238·0995. Calc. for $C_{16}H_{14}O_2$: *M*, 238·0993), $\nu_{max.}$ ($CHCl_3$) 1770 cm^{-1} (CO), τ ($CDCl_3$) 2·64 and 2·70 (10H, 2 × s, 2 × Ph), 4·48 (1H, q, $J_{3\alpha,4}$ 5·7, $J_{3\beta,4}$ 10·8 Hz, H-4), 5·99 (1H, q, $J_{2,3\alpha}$ 8·1, $J_{2,3\beta}$ 12·9 Hz, H-2), 6·96 (1H, m, $J_{2,3\alpha}$ 8·1, $J_{3\alpha,4}$ 5·7, $J_{3\alpha,3\beta}$ 13·0 Hz, H-3α), and 7·64 (1H, m, $J_{2,3\beta}$ 12·9, $J_{3\beta,4}$ 10·8, $J_{3\alpha,3\beta}$ 13·0 Hz, H-3β). When the ^1H n.m.r. spectrum of the *cis*-isomer (9a) was run in CD_3OD–CD_3ONa after 15 min in solution, the signal at τ 5·99 was absent; this confirmed the assignment of this signal to H-2. Signals at τ 4·36 (t) and 4·48 (q) indicated the presence of both the *cis*- (9a) and the *trans*- (9b) isomer in approximately equimolar proportions in the basic solution. ^{13}C N.m.r. data: δ_C ($CDCl_3$) 176·3 (CO), 138·8, 136·2, 128·8, 128·1, 127·7, and 125·5 (aromatics), 79·1 (C-4), 47·5 (C-2), and 40·4 (C-3). The assignment of resonances to C-2, -3, and -4 was confirmed by off-resonance decoupling. Components 3 and 4, which corresponded to the starting material (4) and 2,4-diphenylbutyric acid,[6,13,14] respectively, were not investigated further. Integration of the H-4 signals of 2,4-diphenyl-γ-butyrolactone (9) in the ^1H n.m.r. spectrum ($CDCl_3$) gave a *cis–trans* isomer ratio of 88 : 12. The assumption was made that the major product of the hydrogenation is the *cis*-isomer (9a).

Catalytic Reduction of 2,4-*Diphenylbut*-2-*en*-4-*olide* (4) *with Deuterium Gas*.—The lactone (4) (1·0 g) was dissolved in ethanol (50 ml) and 10% palladium–carbon (300 mg) was added. Reduction with deuterium was performed for 10 min (uptake 0·6 mol. equiv.). The mixture was then filtered and evaporated and the residue was subjected to column chromatography on silica gel with chloroform as eluant. The *cis*- (28a) and *trans*- (28b) isomers of 2,3-dideuterio-2,4-diphenyl-γ-butyrolactone were characterised as described for the unlabelled compounds obtained on hydrogenation. trans-2,3-*Dideuterio*-2,4-*diphenyl*-γ-*butyrolactone* (28b) (30 mg, 3%) was crystallised from ether–hexane; m.p. 67—68° (Found: *M*, 240·1119. $C_{16}H_{12}D_2O_2$ requires *M*, 240·1119), τ ($CDCl_3$) 2·67 and 2·71 (10H, 2 × s, 2 × Ph), 4·36 (1H, d, $J_{3\alpha,4}$ 7·8 Hz, H-4), and 7·21 [1H, d (br owing to deuterium coupling), $J_{3\alpha,4}$ 7·8 Hz, H-3α]. A doublet of very low intensity centred on τ 6·09 (H-2) indicated that a small amount of H–D exchange had occurred during the catalytic reduction. The cis-*lactone* (28a) (350 mg, 35%) was crystallised from ether–hexane; m.p. 105—107° (Found: *M*, 240·1121), τ ($CDCl_3$) 2·63 and 2·71 (10H, 2 × s, 2 × Ph), 4·52 (1H, d, $J_{3\beta,4}$ 10·8 Hz, H-4), and 7·64 [1H, d (br due to deuterium coupling), $J_{3\beta,4}$ 10·8 Hz, H-3β]. No evidence for H–D exchange during the reduction was obtained. ^{13}C N.m.r. data: δ_C ($CDCl_3$) 176·4 (CO), 138·7, 136·1, 128·8, 128·6, 128·0, 127·7, and 125·5 (aromatics), 78·8 (C-4), 47·8, 47·4, and 47·0 (C-2 as a triplet owing to C,D-coupling), and 40·8, 40·0, and 39·2 (C-3 as a triplet owing to C,D-coupling).

cis- (9a) *and* trans- (9b) 2,4-*Diphenyl*-γ-*butyrolactone*.[18]—A solution of sodium borohydride (2·5 g) in 2N-sodium hydroxide (3 ml) diluted with water (22 ml) was added dropwise slowly to a stirred solution of 4-oxo-2,4-diphenylbutyric acid (27) (5·0 g) in methanol (33 ml) and stirring was continued overnight. Methanol and water were removed by evaporation and water was added to the residue, which was then acidified with dilute hydrochloric acid. The mixture was then extracted with ether (3 × 500 ml). The combined extracts were washed with a small amount of water, dried (Na_2SO_4), and concentrated to give an oil which solidified. T.l.c. indicated the presence of two components. These were separated by column chromatography on silica gel (chloroform as eluant). Component 1 crystallised when kept in the refrigerator for a few hours (*cf.* ref. 17) and was recrystallised from ether–hexane to give *trans*-2,4-diphenyl-γ-butyrolactone (9b) (1·3 g, 30%), m.p. 68—69° (lit.,[18] 68—69°; lit.,[17] 74°). Component 2 crystallised and was recrystallised from ether–hexane to give the *cis*-lactone (9a) (2·1 g, 40%), m.p. 105—107° (lit.,[18] 106—107°).

2-*Phenyl*-4-*oxopentanoic Acid* (29).[33-36]—A solution of potassium cyanide (65 g) in water (100 ml) was added dropwise with stirring to benzylideneacetone (64 g) in 95% ethanol (450 ml) and glacial acetic acid (29 ml) at 55°. After 30 min the ethanol was removed under reduced pressure and the residue was treated with sodium hydroxide (90 g) in water. The mixture was heated under reflux for 3 h and set aside overnight. Addition of conc. hydrochloric acid to the cooled, well-stirred solution yielded a solid, which was filtered off and dissolved in hot sodium carbonate solution. Treatment with charcoal and reprecipitation by dropwise addition of conc. hydrochloric acid (150 ml) gave a dark impure product, which crystallised from water to give 2-phenyl-4-oxopentanoic acid (29) (3·0 g, 3·5%), m.p. 125—127° (lit.,[33] 126°), τ ($CDCl_3$) 0·30br (1H, s, CO_2H), 2·74 (5H, s, Ph), 5·88, 6·66, and 7·30 (3H, XAM system, J_{AM} 17·4, J_{AX} 10·0, J_{MX} 4·8 Hz, $-CH_AH_M{\cdot}CH_X<$), and 7·88 (3H, s, CH_3CO).

cis- (10a) *and* trans- (10b) 4-*Methyl*-2-*phenyl*-γ-*butyrolactone*.—A procedure analogous to that employed in the preparation of *cis*- (9a) and *trans*- (9b) 2,4-diphenyl-γ-butyrolactone was followed, starting with 2-phenyl-4-oxopentanoic acid (29) (1·0 g). T.l.c. indicated that the oily product contained two components. These were separated by column chromatography on silica gel (chloroform as eluant). Component 1 was an oil, trans-4-*methyl*-2-*phenyl*-γ-*butyrolactone* (10b) (250 mg, 28%) (Found: *M*, 176·0830.

$C_{11}H_{12}O_2$ requires *M*, 176·0837), $\nu_{max.}$ ($CHCl_3$) 1760 cm^{-1} (CO), τ ($CDCl_3$) 2·74 (5H, s, Ph), 5·24 (1H, m, $J_{3\alpha,4}$ 6·8, $J_{3\beta,4}$ 6·2, J_{CHMe} 6·0 Hz, H-4), 6·10 (1H, q, $J_{2,3\alpha}$ 7·0, $J_{2,3\beta}$ 9·0 Hz, H-2), 7·50 (1H, m, $J_{2,3\alpha}$ 7·0, $J_{2,3\beta}$ 9·0, $J_{3\alpha,3\beta}$ 12·8 Hz, H-3α), 7·68 (1H, m, $J_{2,3\beta}$ 9·0, $J_{3\beta,4}$ 6·8, $J_{3\alpha,3\beta}$ 12·8 Hz, H-3β), and 8·56 (3H, d, J_{CHMe} 6·0 Hz, CH_3). Component 2, also an oil, was the cis-*lactone* (10a) (200 mg, 22%) (Found: *M*, 176·0830), $\nu_{max.}$ ($CHCl_3$) 1760 cm^{-1} (CO), τ ($CDCl_3$) 2·73 (5H, s, Ph), 5·22 (1H, m, $J_{3\alpha,4}$ 5·7, $J_{3\beta,4}$ 10·8, J_{CHMe} 6·0 Hz, H-4), 6·15 (1H, q, $J_{2,3\alpha}$ 8·5, $J_{2,3\beta}$ 12·8 Hz, H-2), 7·27 (1H, m, $J_{2,3\alpha}$ 8·5, $J_{3\alpha,4}$ 5·7, $J_{3\alpha,3\beta}$ 12·8 Hz, H-3α), 8·02 (1H, m, $J_{2,3\beta}$ 12·8, $J_{3\beta,4}$ 10·8, $J_{3\alpha,3\beta}$ 12·8 Hz, H-3β), and 8·55 (3H, d, J_{CHMe} 6·0 Hz, CH_3). The configurational assignments are based on the result of hydrogenation of 4-methyl-2-phenylbut-2-en-4-olide (5) (see below).

4-Methyl-2-phenylbut-2-en-4-olide (5).—2-Phenyl-4-oxopentanoic acid (29) (500 mg) was mixed with acetyl chloride (3 ml) and heated carefully on a sand-bath. The excess of acetyl chloride was distilled off until the temperature of the contents of the flask reached 130°. The residue was extracted with ether. The extract was washed with water, dried (Na_2SO_4), and evaporated. The crude product which was purified by preparative t.l.c. on silica gel (chloroform as developing solvent) to afford the lactone (5) (350 mg, 87%) as an oil which failed to crystallise although it has been reported previously as a crystalline compound (lit.,[9] m.p. 52—52·5°) (Found: *M*, 174·0676. $C_{11}H_{10}O_2$ requires *M*, 174·0681), $\nu_{max.}$ ($CHCl_3$) 1750 cm^{-1} (CO), τ ($CDCl_3$) 2·08—2·72 (5H, m, Ph), 2·50 (1H, d, $J_{3,4}$ 2·0 Hz, H-3), 4·88 (1H, q × d, $J_{3,4}$ 2·0, J_{CHMe} 6·1 Hz, H-4), and 8·51 (3H, d, J_{CHMe} 6·1 Hz, CH_3).

Hydrogenation of 4-Methyl-2-phenylbut-2-en-4-olide (5).—The lactone (5) (100 mg) dissolved in ethanol (20 ml) containing 5% palladium–barium sulphate (50 mg) was hydrogenated at atmospheric pressure (uptake of 1·0 mol. equiv.). Filtration and evaporation left a product which was examined by t.l.c. and by ^1H n.m.r. spectroscopy. Both indicated the presence of *cis-* (10a) and *trans-* (10b) 4-methyl-2-phenyl-γ-butyrolactone. Integration of the signals for the methyl protons in the ^1H n.m.r. spectrum ($CDCl_3$) gave a *cis–trans* isomer ratio of 84 : 16. [The assumption was made that the major product is the *cis*-isomer (10a).]

2-Methyl-4-oxo-4-phenylbutyric Acid (30).—Compound (30), m.p. 140—141° (lit.,[39] 140—141°), τ ($CDCl_3$) 1·90—2·70 (6H, m, Ph and CO_2H), 6·30—7·20 (3H, m, CH_2·CH), and 8·69 (3H, d, *J* 6·1 Hz, CH_3), was prepared by the method of ref. 39.

cis- (11a) *and* trans- (11b) *2-Methyl-4-phenyl-γ-butyrolactone*.—A procedure analogous to that employed in the preparation of *cis-* (9a) and *trans-* (9b) 2,4-diphenyl-γ-butyrolactone was followed, starting with 2-methyl-4-oxo-4-phenylbutyric acid (30) (1·0 g). T.l.c. indicated that the oily product contained two components. These were separated by column chromatography on silica gel (chloroform as eluant). Component 1 was an oil, trans-*2-methyl-4-phenyl-γ-butyrolactone* (11b) (200 mg, 22%) (Found: *M*, 176·0830. $C_{11}H_{12}O_2$ requires *M*, 176·0837), $\nu_{max.}$ ($CHCl_3$) 1763 cm^{-1} (CO), τ ($CDCl_3$) 2·69 (5H, s, Ph), 4·46 (1H, q, $J_{3\alpha,4}$ 7·5, $J_{3\beta,4}$ 5·5 Hz, H-4), 7·34 (1H, m, $J_{2,3\alpha}$ 7·0, $J_{2,3\beta}$ 9·0, J_{CHMe} 6·0 Hz, H-2), 7·60 (1H, m, $J_{2,3\alpha}$ 7·0, $J_{3\alpha,4}$ 7·5, $J_{3\alpha,3\beta}$ 12·8 Hz, H-3α), 7·70 (1H, m, $J_{2,3\beta}$ 9·0, $J_{3\beta,4}$ 5·5, $J_{3\alpha,3\beta}$ 12·8 Hz, H-3β), and 8·69 (3H, d, J_{CHMe} 6·0 Hz, CH_3). Component 2, also an oil, was the cis-*lactone* (11a) (250 mg, 28%) (Found: *M*, 176·0830), $\nu_{max.}$ ($CHCl_3$) 1763 cm^{-1} (CO), τ ($CDCl_3$) 2·67 (5H, s, Ph), 4·66 (1H, q, $J_{3\alpha,4}$ 5·8, $J_{3\beta,4}$ 10·8 Hz, H-4), 7·14 (1H, m, $J_{2,3\alpha}$ 8·1, $J_{2,3\beta}$ 12·9, J_{CHMe} 6·0 Hz, H-2), 7·28 (1H, m, $J_{2,3\alpha}$ 8·1, $J_{3\alpha,4}$ 5·8, $J_{3\alpha,3\beta}$ 12·4 Hz, H-3α), 8·18 (1H, m, $J_{2,3\beta}$ 12·9, $J_{3\beta,4}$ 10·8, $J_{3\alpha,3\beta}$ 12·4 Hz, H-3β), and 8·68 (3H, d, J_{CHMe} 6·0 Hz, CH_3). The configurational assignments are based on a comparison of the ^1H n.m.r. spectra with those of the 2,4-diphenyl-γ-butyrolactones (9).

2-Methyl-4-phenylbut-2-en-4-olide (6).—2-Methyl-4-oxo-4-phenylbutyric acid (30) (1·0 g) was refluxed with acetic anhydride (5 ml) as described by Ramirez and Rubin [39] to give a crude product. This was purified by column chromatography on silica gel (chloroform as eluant) to give, as an oil, the lactone (6) (600 mg, 65%) [Ramirez and Rubin [39] reported two crystalline compounds: one, with m.p. 84—86°, assigned as 2-methyl-4-phenylbut-3-en-4-olide lactone; the other, with m.p. 226—227°, assigned as the lactone (6)] (Found: *M*, 174·0676. Calc. for $C_{11}H_{10}O_2$: *M*, 174·0681), $\nu_{max.}$ ($CHCl_3$) 1750 cm^{-1} (CO), τ ($CDCl_3$) 2·54—2·84 (5H, m, Ph), 2·86—2·93 (1H, m, H-3), 4·08—4·22 (1H, m, H-4), and 7·92—8·08 (3H, m, CH_3).

Hydrogenation of 2-Methyl-4-phenylbut-2-en-4-olide (6).—The lactone (6) (200 mg) was dissolved in ethanol and 10% palladium–carbon (50 mg) was added. The mixture was hydrogenated for 15 min (uptake 0·6 mol. equiv.), filtered, and evaporated. The residue was shown by t.l.c. to contain at least two ' fast-moving ' components and one ' slow-moving ' component. The former were separated from the latter by preparative t.l.c. (chloroform as developing solvent). Fraction 1 was shown by ^1H n.m.r. spectroscopy in $CDCl_3$ to contain 2-methyl-4-phenylbut-2-en-4-olide (6) and the 2-methyl-4-phenyl-γ-butyrolactones (11) in the ratio *ca.* 4 : 1 (obtained by integration of the CH_3 signals). Integration of the H-4 signals of the 2-methyl-4-phenyl-γ-butyrolactones (11) gave a *cis–trans* ratio of *ca.* 1 : 1. Fraction 2 was identified as 2-methyl-4-phenylbutyric acid, *M* 178.

2-Ethoxycarbonyl-4-phenyl-γ-butyrolactone (32) [20] *and its 3-Phenyl Isomer* (33).—Diethyl malonate (96·0 g) was added to a solution of sodium ethoxide (42·0 g) in ethanol (300 ml). The mixture was stirred and styrene oxide (72·0 g) was added dropwise during 2 h. The temperature of the mixture was maintained at 40° during the addition and then the mixture was set aside overnight at room temperature. After cooling to 15°, cooled glacial acetic acid was added slowly until the solution was slightly acidic. The excess of alcohol was removed under reduced pressure and water was added to dissolve the precipitated sodium acetate. The oily layer which formed was separated from the aqueous layer and the latter was extracted once with ether. The ethereal solution was added to the oily product and the resulting solution was dried (Na_2SO_4) and evaporated. The crude product was distilled under reduced pressure to yield, as an oil, a *ca.* 1 : 1 mixture of the 4-phenyl (32) and the 3-phenyl lactone (33) (80 g, 57%), b.p. 160—165° at 1 mmHg (lit.,[20] 188—191° at 3·0 mmHg), *M* 234. ^1H N.m.r. spectroscopy in $CDCl_3$ indicated that the product was a mixture of *cis-* and *trans*-isomers of both constitutional isomers (32) and (33). The H-4 signals at τ 4·58 and 4·31 for the 4-phenyl lactone (32) showed a *cis–trans* isomer ratio of *ca.* 56 : 44. Separation of the two constitutional isomers (32) and (33) was attempted by t.l.c. and g.l.c. but was not successful.

2-Carboxy-4-phenyl-γ-butyrolactone (34) [20] *and the 3-Phenyl Isomer* (35).—The oil containing the lactones (32)

and (33) (11·2 g) was shaken with potassium hydroxide (15·0 g) in water (30 ml) until the mixture became homogeneous. It was set aside overnight at room temperature and was then acidified with conc. hydrochloric acid and cooled to give a crystalline solid. The crude product was recrystallised from water to yield a mixture of the acids (34) and (35) (6·5 g, 66%), m.p. 148—150° (lit.,[20] 149·3—150°). T.l.c. indicated the presence of two components. These were separated by preparative t.l.c. [benzene–dioxan–acetic acid (95 : 25 : 4) as developing solvent]. The slower-moving component was shown (see below) to be the acid (34), m.p. 94—96°, *M* 206, and the faster moving component the acid (35), m.p. 144—146°, in the mass spectrum of which a molecular ion was not detected.

The constitutional isomers [(34) and (35)] were characterised as their methyl esters, prepared by treatment with diazomethane in ether. *2-Methoxycarbonyl-4-phenyl-γ-butyrolactone* (36), an oil, showed $\nu_{max.}$ ($CHCl_3$) 1770 cm^{-1} (CO). ^1H N.m.r. spectroscopy in $CDCl_3$ indicated (*e.g.* two signals at τ 6·22 and 6·24 for the CO_2Me groups) that the product was a mixture of *cis*- and *trans*-isomers. The H-4 signals at τ 4·58 and 4·31 showed a *cis–trans* ratio of *ca.* 54 : 46. *2-Methoxycarbonyl-3-phenyl-γ-butyrolactone* (37) was also an oil, $\nu_{max.}$ ($CHCl_3$) 1770 cm^{-1} (CO). ^1H N.m.r. spectroscopy in $CDCl_3$ indicated (*e.g.* a broad signal at τ 6·23 for the CO_2Me groups) that the product was a mixture of *cis*- and *trans*-isomers.

2-Methylene-4-phenyl-γ-butyrolactone (40)[20] *and the 3-Phenyl Isomer* (41).—Diethylamine (7·5 g) was added to the mixture (3·5 g) of acids (34) and (35), and then 30% formaldehyde solution (3·7 g) was added with stirring. The mixture of acids dissolved while the mixture effervesced and evolved heat. After 2 days at room temperature, the aqueous layer was saturated with potassium carbonate and the upper organic layer was separated from it and diluted with ether. The ethereal solution was washed twice with water. The combined ethereal extracts were dried (Na_2SO_4) and evaporated. Distillation of the residue yielded an oil containing 2-diethylaminomethyl-4-phenyl-γ-butyrolactone (38) and the 3-phenyl isomer (39) (1·6 g, 40%), b.p. 112—116° at 1 mmHg (lit.,[20] 116—118° at 0·2 mmHg), *M* 247. These two constitutional isomers [(38) and (39)] could not be separated by t.l.c. or g.l.c. Accordingly, they (1·5 g) were mixed with methyl iodide (7 ml); after a few minutes, a pale yellow solid separated out. It was washed with ether to give the crystalline quaternary salts. A 5% sodium hydrogen carbonate solution (35 ml) was added to this product with stirring. A thick yellow oil separated out. Next day this was extracted with ether and the extract was dried (Na_2SO_4) and evaporated to leave a yellow oily mixture (750 mg, 75%). T.l.c. and g.l.c. on a capillary column of diethylene glycol succinate at 220° indicated the presence of two components, which were separated by column chromatography on silica gel [ethyl acetate–light petroleum (b.p. 60—80°) (1 : 4) as eluant]. Component 1 yielded *2-methylene-3-phenyl-γ-butyrolactone* (41) as an oil (Found: *M*, 174·0676. $C_{11}H_{10}O_2$ requires *M*, 174·0681), $\nu_{max.}$ ($CHCl_3$) 1760 cm^{-1} (CO), τ ($CDCl_3$) 2·40—3·00 (5H, m, Ph), 3·66 and 4·56 (2H, 2 × d, $J_{allylic}$ 2·8 Hz in each case, $H_2C{=}C\langle$), and 5·14—5·90 (3H, m, H-3, H-4α, and -4β). Component 2 yielded a crystalline product which was recrystallised from ether–hexane to give *2-methylene-4-phenyl-γ-butyrolactone* (40), m.p. 50—51° (Found: *M*, 174·0676), $\nu_{max.}$ ($CHCl_3$) 1770 cm^{-1} (CO), τ ($CDCl_3$) 2·42—2·96 (5H, m, Ph), 3·72 and 4·35 (2H, 2 × t, $J_{allylic}$ 2·7 and 2·5 Hz, $H_2C{=}C\langle$), 4·50 (1H, q, *J* 7·0 and 8·0 Hz, H-4), and 6·42—7·36 (2H, m, H-3α and -3β).

Hydrogenation of 2-Methylene-4-phenyl-γ-butyrolactone (40).—The lactone (40) (100 mg) was dissolved in ethanol and 10% palladium–carbon (25 mg) was added. The mixture was hydrogenated for 6 min (uptake 0·5 mol. equiv.), filtered, and evaporated; the residue was shown by t.l.c. to contain at least two ' fast-moving ' components and one ' slow-moving ' component. The former were separated from the latter by preparative t.l.c. (chloroform as developing solvent). Fraction 1 was shown by ^1H n.m.r. spectroscopy in $CDCl_3$ to contain 2-methyl-4-phenylbut-2-en-4-olide (6) and *cis*-2-methyl-4-phenyl-γ-butyrolactone (11a) in the ratio *ca.* 57 : 43 (obtained by integration of the H-4 signals). A trace (<3%) of *trans*-2-methyl-4-phenyl-γ-butyrolactone (11b) was observed. Fraction 2 was identified as 2-methyl-4-phenylbutyric acid, *M* 178.

Hydrogenation of 2-Methylene-3-phenyl-γ-butyrolactone (41).—The lactone (41) (200 mg) was dissolved in ethanol and 10% palladium–carbon (50 mg) was added. The mixture was hydrogenated for 15 min (uptake 1·0 mol. equiv.), filtered, and evaporated. The residue was examined by t.l.c. and ^1H n.m.r. spectroscopy. Both indicated the presence of *cis*- (31a) and *trans*- (31b) 2-methyl-3-phenyl-γ-butyrolactone as well as a trace of a third component thought to be 2-methyl-3-phenylbut-2-en-4-olide (42). Integration of the signals for the methyl protons in the ^1H n.m.r. spectrum ($CDCl_3$) gave product ratios of *ca.* 62 : 30 : 8 for (31a) : (31b) : (42). The assumption (*cf.* ref. 59) was made that the major product is the *cis*-isomer (31a). G.l.c. analysis on a capillary column of diethylene glycol succinate at 200° indicated a *cis–trans* isomer ratio of 73 : 27. The three components were isolated by preparative t.l.c., first with ethyl acetate–petroleum (b.p. 60—80°) (1 : 4) as developing solvent, to give pure *trans*-isomer (31b) as the faster-moving component, and secondly with chloroform as developing solvent, to give pure *cis*-isomer (31a) and the αβ-unsaturated lactone (42) from the slower-moving component. *cis*-2-Methyl-3-phenyl-γ-butyrolactone (31a) had m.p. 33—34° (from ether–hexane), $\nu_{max.}$ ($CHCl_3$) 1770 cm^{-1} (CO), τ ($CDCl_3$) 2·55—2·96 (5H, m, Ph), 5·30—5·60 (2H, m, 2 × H-4), 6·20—6·43 (1H, m, H-3), 6·86 (1H, quintet, H-2), and 9·13 (3H, d, *J* 7·0 Hz, CH_3); the *trans*-isomer (31b) was an oil, $\nu_{max.}$ ($CHCl_3$) 1770 cm^{-1} (CO), τ ($CDCl_3$) 2·50—2·90 (5H, m, Ph), 5·34—5·98 (2H, m, 2 × H-4), 6·53—6·88 (1H, m, H-3), 7·10—7·48 (1H, m, H-2), and 8·75 (3H, d, *J* 7·0 Hz, CH_3). The *αβ-unsaturated lactone* (42) slowly crystallised and was recrystallised from ether–hexane; m.p. 115—117°, *M* 174, τ ($CDCl_3$) 2·56 (5H, s, Ph), 4·97 (2H, m, 2 × H-4), and 7·88 (3H, m, CH_3).

Ethyl 2-Ethyl-3-hydroxyhexanoate (43).[21]—Granular zinc (15·0 g) and a small amount of iodine were treated dropwise with one-fifth of a mixture of butyraldehyde (10·5 g) and ethyl 2-bromobutyrate (30·0 g) in dry benzene (75·0 ml). The rest of this mixture was then added to the reaction mixture, which was heated for 1 h under reflux. Ice and water were then added, and the mixture was acidified with dilute sulphuric acid. The aqueous layer was separated from the organic layer, which was washed with water, dried (Na_2SO_4), and evaporated to give a pale yellow oil. Distillation under reduced pressure afforded the ester (43) as an oil (15 g, 54%), b.p. 75—80° at 0·7 mmHg.

cis- (12a) *and* trans- (12b) *2,4-Diethyl-γ-butyrolactone*.—

[59] E. Tedeschi, J. Kamionsky, D. Zeider, and S. Fackler, *J. Org. Chem.*, 1974, **39**, 1864.

Sulphuric acid (85%; 5·0 g) was added dropwise with stirring to ethyl 2-ethyl-3-hydroxyhexanoate (43) (5·0 g) and the mixture was heated under reflux for 5 h. It was then poured into ice–water and extracted with ether (3 × 250 ml). The combined extracts were washed with saturated sodium hydrogen carbonate solution, then with water, dried (Na_2SO_4), and evaporated. Distillation of the crude product yielded 2,4-diethyl-γ-butyrolactone (12) (2·0 g, 53%) as an oil, b.p. 60—62° at 1 mmHg (lit.,[21] 88—90° at 5 mmHg). This product was shown by g.l.c. on a capillary column of diethylene glycol succinate at 130° to contain two components in the ratio *ca.* 3 : 2. These were separated by column chromatography on silica gel (1500 g) with chloroform as eluant. The first fractions to be eluted were shown by g.l.c. to be considerably enriched with respect to the major component. This was obtained pure by preparative g.l.c. (30% polyethylene glycol adipate on 60—80 mesh Chromosorb W at 130°) and was identified (see Discussion) as cis-2,4-*diethyl-γ-butyrolactone* (12a) (Found: *M*, 142·0993. $C_8H_{14}O_2$ requires *M*, 142·0994), $\nu_{max.}$ ($CHCl_3$) 1770 cm^{-1} (CO), τ ($CDCl_3$) 5·50—5·88 (1H, m, H-4), 7·28—7·76 (2H, m, H-2 and H-3α), 7·84—8·78 (5H, m, H-3β and 2 × CH_3·CH_2), and 8·86—9·04 (6H, 2 × t, 2 × CH_3·CH_2). The later fractions to be eluted were shown by g.l.c. to be considerably enriched with respect to the minor component. This was obtained pure by preparative g.l.c. (see above) and was identified (see Discussion) as the trans-*lactone* (12b) (Found: *M*, 142·0993), $\nu_{max.}$ ($CHCl_3$) 1770 cm^{-1} (CO), τ ($CDCl_3$) 5·42—5·76 (1H, m, H-4), 7·26—7·62 (1H, m, H-2), 7·86—8·06 (2H, m, H-3α and -3β), 8·06—8·76 (4H, m, 2 × CH_3·CH_2), and 8·86—9·02 (6H, 2 × t, 2 × CH_3·CH_2).

cis- (13a) *and* trans- (13b) 2-*Ethyl*-4-*methyl*-γ-*butyrolactone*.—A sample of 2-ethyl-4-methyl-γ-butyrolactone (13) kindly provided by Professor C. Szántay was shown by g.l.c. on a capillary column of diethylene glycol succinate at 130° to contain two components in the ratio *ca.* 3 : 2. These were separated by preparative g.l.c. (30% polyethylene glycol adipate on 60—80 mesh Chromosorb W at 130°). The first component was identified by comparison of its ^1H n.m.r. spectrum with that of *cis*-2,4-dimethyl-γ-butyrolactone (7a) as cis-2-*ethyl*-4-*methyl*-γ-*butyrolactone* (13a) (Found: *M*, 128·0835. $C_7H_{12}O_2$ requires *M*, 128·0837), $\nu_{max.}$ ($CHCl_3$) 1770 cm^{-1} (CO), τ (CCl_4) 5·46—5·80 (1H, m, H-4), 7·46—7·80 (2H, m, H-2 and -3α), 7·90—8·80 (6H, m and d, *J* 6·2 Hz, H-3β, CH_3·CH_2, and CH_3), and 9·04 (3H, t, *J* 7·0 Hz, CH_3·CH_2). The second component was identified by comparison of its ^1H n.m.r. spectrum with that of the *trans*-lactone (8b) as the trans-*lactone* (13b) (Found: *M*, 128·0835), $\nu_{max.}$ ($CHCl_3$) 1770 cm^{-1} (CO), τ (CCl_4) 6·30—5·57 (1H, m, H-4), 7·39—7·70 (1H, m, H-2), 7·91—8·60 (4H, m, H-3α, H-3β, and CH_3·CH_2), 8·65 (3H, d, *J* 6·4 Hz, CH_3), and 9·00 (3H, t, *J* 7·0 Hz, CH_3·CH_2).

cis- (14a) *and* trans- (14b) 2-*Butyl*-4-*methyl*-γ-*butyrolactone*.—A sample of 2-butyl-4-methyl-γ-butyrolactone (14) kindly provided by Professor C. Szántay was shown by g.l.c. on a capillary column containing diethylene glycol succinate at 140° to contain two components in the ratio *ca.* 3 : 2 plus traces of three impurities. These components were separated by preparative g.l.c. (30% polyethylene glycol adipate on 60—80 mesh Chromosorb W at 140°). The first component was identified by comparison of its ^1H n.m.r. spectrum with that of *cis*-2,4-dimethyl-γ-butyrolactone (7a) as cis-2-*butyl*-4-*methyl*-γ-*butyrolactone* (14a) (Found: *M*, 156·1151. $C_9H_{16}O_2$ requires *M*, 156·1150), $\nu_{max.}$ ($CHCl_3$) 1770 cm^{-1} (CO), τ (CCl_4) 5·47—5·87 (1H, m, H-4), 7·27—7·81 (2H, m, H-2 and -3α), 7·87—8·87 (10H, m and d, *J* 6·2 Hz, H-3β, CH_3·CH_2·CH_2·CH_2, and CH_3), and 9·08 (3H, t, *J* 6·5 Hz, CH_3·CH_2·CH_2·CH_2). The second component was identified by comparison of its ^1H n.m.r. spectrum with that of the *trans*-lactone (7b) as the trans-*lactone* (14b) (Found: *M*, 156·1151), $\nu_{max.}$ ($CHCl_3$) 1770 cm^{-1} (CO), τ (CCl_4) 5·29—5·67 (1H, m, H-4), 7·37—7·77 (1H, m, H-2), 7·91—8·15 (2H, m, H-3α and -3β), 8·17—8·77 (9H, m and d, *J* 6·5 Hz, CH_3·CH_2·CH_2·CH_2 and CH_3), and 9·08 (1H, t, *J* 6·0 Hz, CH_3·CH_2·CH_2·CH_2).

Equilibration Studies.—Base-catalysed equilibrations of the 2,4-disubstituted γ-butyrolactones [(7)—(10) and (12)—(14)] and of 2-methyl-3-phenyl-γ-butyrolactone were carried out at 25·0 ± 0·1°. In all cases, the equilibrium situation was approached starting with (i) pure *cis*-isomer and (ii) pure *trans*-isomer. Equilibrations were followed by taking samples at suitable time intervals and analysing their isomeric composition. Two methods were employed.

Method 1. In a typical experiment, the lactone (10—25 mg) was added to a 3% solution of potassium t-butoxide in t-butyl alcohol (10—25 ml). Samples (2—5 ml) were analysed at suitable time intervals, after quenching the reaction with Zeocarb 325 and filtering off the resin.

Method 2. In the cases of the lactones (9) and (10), the pure isomer (200 mg) was added to a 10% solution of triethylamine in carbon tetrachloride (25 ml). Samples (2·5 ml) were analysed at suitable time intervals, after quenching the reaction with Zeocarb 325 and filtering off the resin.

Isomer ratios were determined either (procedure 1) by g.l.c., from the integrated intensities of the peaks corresponding to the *cis*- and *trans*-isomers (in all cases, the assumption was made that the detector response was the same for both isomers); or (procedure 2) by ^1H n.m.r. spectroscopy from the integrated intensities of signals due to suitably chemically shifted protons or groups in the *cis*- and *trans*-isomers. The results are summarised in Table 5.

We thank Professor C. Szántay (Institute of Organic Chemistry, Technical University, Budapest) for supplying samples of mixtures of *cis*- and *trans*-2-ethyl-4-methyl-γ-butyrolactone and 2-butyl-4-methyl-γ-butyrolactone. Their synthesis will be described in a forthcoming publication.

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