

## Synthesis of $\gamma$ -Lactones and 3-Alkylidene-1-indanones

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$\gamma$ -Lactones are formed in high yields in the reactions of (*E*)-3-alkyl-3-phenylpropenoic acids in concentrated sulfuric acid if the alkyl groups contain a tertiary  $\gamma$ -hydrogen. If the alkyl groups bear secondary  $\gamma$ -hydrogens 3-alkylidene-1-indanones are formed almost exclusively. Reaction mechanisms for the cyclizations are discussed on the basis of deuteration experiments.

Acid catalyzed lactonizations of alkylidenemalonitriles<sup>1</sup> and dialkyl alkylidenemalonates<sup>2</sup> have been reported.

During the course of our investigation concerning the formation of  $\beta$ -alkylated ethyl (*Z*)- and (*E*)-cinnamates from ethyl (*Z*)- and (*E*)- $\beta$ -chlorocinnamates in CuI catalyzed Grignard reactions, it was of interest to find a method to unambiguously determine the configuration of *Z*- and *E*-isomers. Since NMR measurements of the ethyl  $\beta$ -alkylcinnamates did not always give unequivocal results, we tried some cyclizations in concentrated sulfuric acid with the intention of transferring the *Z*-isomers of the  $\beta$ -alkylcinnamic acids to the corresponding indenone derivatives. In these experiments we found that the *E*-isomers, which contained a tertiary  $\gamma$ -hydrogen, formed  $\gamma$ -butyrolactones and that the *E*-isomers with secondary  $\gamma$ -hydrogens did not cyclize to lactones but to 3-alkylidene-1-indanones (Scheme 1 and Table 1).  $\beta$ -Methylcinnamic acid did

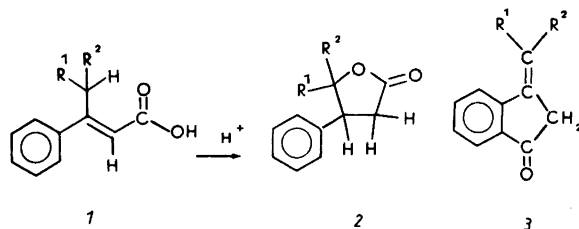
Table 1. Cyclization of  $\beta$ -alkylcinnamic acids in concentrated sulfuric acid according to Scheme 1.

Substituent	R <sup>1</sup>	R <sup>2</sup>	Reaction time h	Product	Yield <sup>a</sup> %
a	Me	Me	5	2a	93
b	Me	Et	5	2b	86
c	C-hexyl		5	2c	87
d	C-pentyl		5	2d	81
e	H	Et	24	3e	71
f	H	i-Pr	24	3f	68
g	H	sec-Bu	24	3g	64
h	H	H	48	unreacted	0

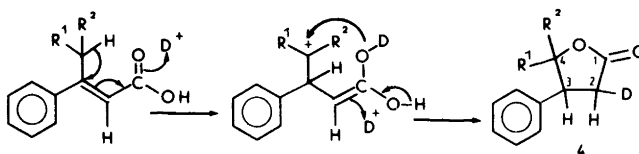
<sup>a</sup>As determined by <sup>1</sup>H NMR spectroscopy.

not undergo any cyclization when it was stirred for 48 h in concentrated sulfuric acid at 35°C. Neither did the ethyl  $\beta$ -alkylcinnamates form lactones, although the alkyl group contained a tertiary  $\gamma$ -hydrogen.

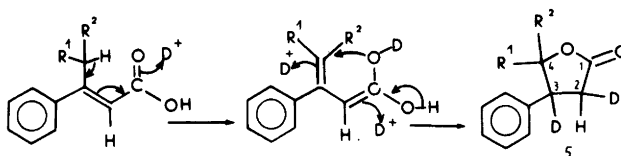
Several reaction mechanisms are possible for the formation of the lactones. According to the mechanism, reaction proceeds can be elucidated by carrying out the reaction in deuterated sulfuric acid. If the  $\beta$ -carbon of the lactone does not bear a deuterium atom the cyclization has to proceed by an internal hydride shift (Scheme 2) and not by a double bond migration which should lead to deuteri-



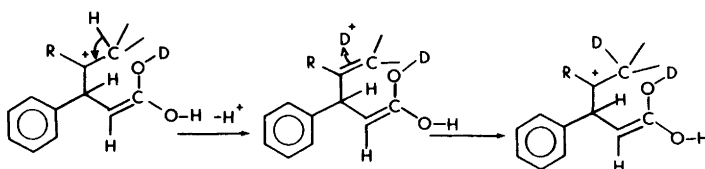
Scheme 1.



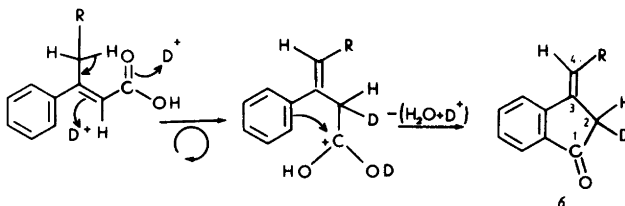
Scheme 2.



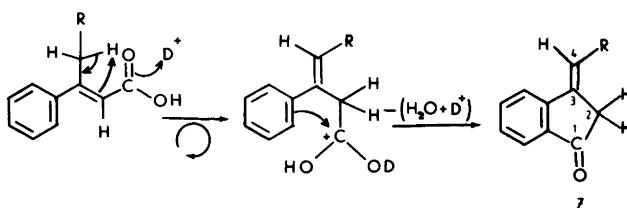
Scheme 3.



Scheme 4.



Scheme 5.



Scheme 6.

ation of the  $\beta$ -carbon (Scheme 3). The high-field part of the proton decoupled  $^{13}\text{C}$  NMR spectrum of the reaction products formed when (*E*)-3-isopropylcinnamic acid was allowed to react with deuteriated sulfuric acid is shown in Fig. 1 (spectrum B) together with the spectrum of 4-methyl-3-phenyl- $\gamma$ -valerolactone (*2a*) (spectrum C). The two upper-field signals in the spectrum of *2a* arise from methyl carbons. The signals at 34.4 ppm and 51.1 ppm belong to C-2 and C-3, respectively. The absorptions for C-2 from the deuteration experiment ap-

pear as a  $\text{CH}_2$  singlet and a CHD triplet centered 0.7 ppm upfield from the  $\text{CH}_2$  signal. A weak CD triplet can be discerned, not completely resolved, upfield from the CH signal of C-3. The low intensity of CD can be due to partial saturation because of long  $T_1$  for CD compared with that of CH. Neither can the relative intensities of CH and CD be compared because of differences in NOE. The deuterium content at C-3 is, however, small as determined from the decrease in intensity for the CH signal of the deuteriated sample relative to the intensity for the

CH signal of the undeuteriated sample. These results show that an internal hydride shift according, for instance, to Scheme 2 is the dominating pathway, although it cannot be the only reaction mechanism involved because the absorption for C-2 also appears as a CH<sub>2</sub> singlet identical with that from the undeuteriated sample. This shows that an internal hydride or proton shift to C-2 also oper-

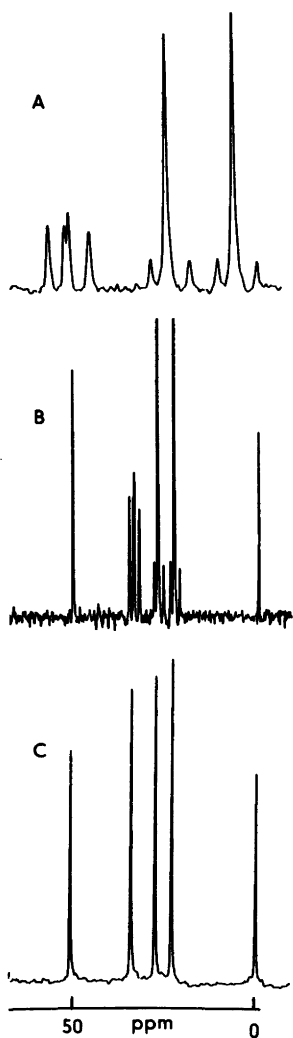


Fig. 1. High-field region of the proton decoupled 15.03 MHz <sup>13</sup>C NMR spectra C of 4-methyl-3-phenyl- $\gamma$ -valerolactone (2a) and B its deuterium derivative. Inset A is a 2.4-fold expansion of the methyl groups and C-2 to illustrate the effect of deuteration.

ates. The presence of two triplets upfield from the methyl signals reveals a <sup>2</sup>H exchange which can take place starting from the intermediary carbocation (Scheme 4). NMR and MS measurements also revealed that a <sup>2</sup>H exchange takes place in the phenyl ring.

Why the lactonization did not take place with the cinnamic acids which bear secondary or primary  $\gamma$ -hydrogens can be explained by the lower capacity of only one alkyl group or three hydrogens to stabilize the intermediary positive charge on the  $\gamma$ -carbon. A double bond migration with elimination of a proton from the  $\gamma$ -position is therefore more likely than an internal hydride shift. At least two reaction mechanisms can operate in this cyclization as is shown in the reaction of  $\beta$ -isobutyrcinnamic acid with deuteriated sulfuric acid (Schemes 5 and 6). The <sup>1</sup>H and <sup>13</sup>C NMR spectra of the deuteriated sample indicate that the reaction mechanism outlined in Scheme 6 is the dominating pathway, although secondary reactions are involved. For example, a complete <sup>2</sup>H exchange is observed at C-4 which most likely is a result of a <sup>2</sup>H exchange after the cyclization, because the same exchange was observed when 3-propylidene-1-indanone (3e) was treated with deuteriated sulfuric acid. A complete <sup>2</sup>H exchange at C-2 was also observed when  $\beta$ -propylcinnamic acid was stirred with deuteriated sulfuric acid for 36 h. This exchange has to be the result of a tautomerization.

## EXPERIMENTAL

Mass spectra were recorded on an LKB 9000 instrument (70 eV) equipped with a gas chromatograph (50 m  $\times$  0.2 mm glass capillary column, stationary phase SE-30). <sup>1</sup>H NMR spectra were obtained on a Jeol FX-60 FT NMR spectrometer at 59.75 MHz and <sup>13</sup>C spectra on the same instrument operating at 15.03 MHz. CDCl<sub>3</sub> was used as solvent and TMS as an internal standard.

The (*E*)- $\beta$ -alkylcinnamic acids were prepared by alkaline hydrolysis of the corresponding ethyl cinnamates which were prepared in good yields from ethyl (*Z*)-3-chloro-3-phenylpropenoate in CuI catalyzed Grignard reactions.

*General procedure for the preparation of  $\gamma$ -lactones and  $\beta$ -alkylidene-1-indanones.* The  $\beta$ -alkylcinnamic acid (1 g) was added to concentrated sulfuric acid (20 cm<sup>3</sup>) at 0°C. The reaction mixture was stirred for 5 h while the reaction temperature was allowed to reach 20°C. The reaction mixture was poured into ice and water, followed by extraction with di-

ethyl ether. The organic phase was extracted with sodium bicarbonate solution, dried with  $\text{Na}_2\text{SO}_4$  and the diethyl ether evaporated. The  $\gamma$ -butyrolactone was recrystallized from a mixture of light petroleum and diethyl ether. The  $\beta$ -alkylidene-indanones were prepared according to the same procedure except that the reaction time at  $20^\circ\text{C}$  was prolonged to 24 h.

**4-Methyl-3-phenyl- $\gamma$ -valerolactone (2a).**  $^1\text{H}$  NMR (59.75 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.04 ( $\text{CH}_3$ , s), 1.55 ( $\text{CH}_3$ , s), 2.93 ( $\text{CHCH}_2$ , q,  $J$  9.3 Hz), 3.55 ( $\text{CHCH}_2$ , q, 9.3 Hz).

$^{13}\text{C}$  NMR (15.03 MHz,  $\text{CDCl}_3$ ):  $\delta$  23.2 ( $\text{CH}_3$ ), 27.7 ( $\text{CH}_3$ ), 34.4 (C-2), 51.1 (C-3), 87.1 (C-4), 127.8, 128.6, 136.8 (aromatic), 175.3 (C-1);  $J$  (C-5, H-5) 127 Hz, (C-2, H-2) 134 Hz, (C-3, H-3) 134 Hz.

MS [IP 70 eV;  $m/e$  (% rel. int.)]: 190 (16, M), 175 (20, M- $\text{CH}_3$ ), 162 (46, M-CO), 132 (10), 131 (11), 104 (100, Ph-CH= $\text{CH}_2$ ), 91 (10), 78 (19), 77 (18), 43 (16).

**4-Methyl-3-phenyl-4-hexanolide (2b).** Two diastereomers were formed in the ratio 1:3 as determined by  $^{13}\text{C}$  NMR spectroscopy. The  $^1\text{H}$  NMR spectrum of these diastereomers is not easily interpreted.  $\text{H}_2-2$  and  $\text{H}-3$  gave rise to an  $\text{AB}_2$  system, in which the signals of the diastereomers appear as different peaks in the A part whereas the signals of the diastereomers coincide in the  $\text{B}_2$  part.  $\text{H}_2-5$  appears as a distorted quartet with the highest peak at 1.8 ppm.

$^1\text{H}$  NMR (59.75 MHz  $\text{CDCl}_3$ ):  $\delta$  1.0 ( $\text{CH}_3$ , s) 0.9, 1.1, 1.2 ( $\text{CH}_3\text{-CH}_2$ , distorted triplet), ( $\text{CH}_3\text{-CH}_2$ , distorted quartet between 1.6–2.0 ppm), ( $\text{CH-CH}_2$ ,  $\text{AB}_2$  system between 2.8–3.8 ppm), 7.1–7.4 (aromatic). The signals of the carbon atoms of the diastereomers appear, with some exceptions, as different peaks, *i.e.*, the signals of C-1, C-2 and the aromatic carbons except C-*ipso* coincide.

$^{13}\text{C}$  NMR of the diastereomer which was formed in higher yield (15.03 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.1 (C-6), 21.1 (C-5), 32.9 (C-5), 34.6 (C-2), 48.5 (C-3), 89.6 (C-4), 127.7, 127.9, 128.7, 137.1 (aromatic), 175.7 (C-1).  $^{13}\text{C}$  NMR of the diastereomer which was formed in lower yield (15.03 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.8 (C-6), 24.1 (C-5), 28.7 (C-5), 34.6 (C-2), 51.6 (C-3), 89.3, 127.7, 127.9, 128.7, 136.8 (aromatic), 175.7 (C-1).

MS [IP 70 eV;  $m/e$  (% rel. int.)]: 204 (3, M), 189 (1, M- $\text{CH}_3$ ), 176 (5), 175 (8, M-C $_2\text{H}_5$ ), 132 (5, PhCHCH $_2\text{CO}$ ), 131 (7, PhCHCHCO), 115 (2), 105 (18), 104 (100, PhCHCH $_2$ ), 91 (6), 78 (10), 77 (9).

**4-Spirocyclohexane-3-phenyl- $\gamma$ -butyrolactone (2c).**  $^1\text{H}$  NMR (59.75 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.5–1.8 (C-hexyl, broad), 2.8–3.4 ( $\text{CH-CH}_2$ ,  $\text{AB}_2$ -system), 7.2–7.4 (aromatic).

$^{13}\text{C}$  NMR (15.03 MHz,  $\text{CDCl}_3$ ):  $\delta$  21.7, 22.6, 24.9, 32.3, 36.8, 88.6 (C-hexyl), 34.7 (C-2), 51.2 (C-3), 127.6, 128.1, 128.6, 137.1 (aromatic), 175.9

(C-1);  $J$  (C-3, H-3) 132 Hz,  $J$  (C-2, H-2) 134 Hz,  $J$  (C-2, H-3) 5.5 Hz.

MS [IP 70 eV;  $m/e$  (% rel. int.)]: 230 (9, M), 202 (9, M-CO), 187 (2), 169 (3), 132 (18, PhCHCHCO), 105 (34), 104 (100, PhCHCH $_2$ ), 103 (20), 78 (17), 77 (11).

**4-Spirocyclopentane-3-phenyl- $\gamma$ -butyrolactone (2d).**  $^1\text{H}$  NMR (59.75 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.2–2.2 (cyclopentyl, broad), 2.8–3.6 ( $\text{CH-CH}_2$ ,  $\text{AB}_2$  system), 6.8–7.3 (aromatic).

$^{13}\text{C}$  NMR (15.03 MHz,  $\text{CDCl}_3$ ):  $\delta$  23.0, 23.3, 33.9, 38.0, 98.6 (C-pentyl), 36.2 (C-2), 48.7 (C-3), 127.7, 127.9, 128.7, 138.0 (aromatic, 176.0 (C-1);  $J$  (C-2, H-2) 136 Hz,  $J$  (C-2, H-3) 6 Hz,  $J$  (C-3, H-3) 136 Hz.

MS [IP 70 eV;  $m/e$  (% rel. int.)]: 216 (10, M), 188 (17, M-CO), 169 (6), 132 (21, PhC $_2\text{H}_3\text{CO}$ ), 131 (10, PhC $_2\text{H}_4\text{CO}$ ), 115 (9), 105 (54), 104 (100, PhC $_2\text{H}_4$ ), 103 (31), 91 (15), 78 (21), 77 (21), 55 (14).

**3-Propylidene-1-indanone (3e).**  $^1\text{H}$  NMR (59.75 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.1 ( $\text{CH}_3$ , t,  $J$  7.2 Hz), 2.2 ( $\text{CH}_2$ - $\text{CH}_3$ , K,  $J$  7.2 Hz), 3.1 ( $\text{CH}_2\text{CO}$ , d, 2.0 Hz), 6.2 ( $\text{CH}=\text{C}$ , tt,  $J$  7.3 and 2.0 Hz), 7.2–7.9 (aromatic).

$^{13}\text{C}$  NMR (15.03 MHz,  $\text{CDCl}_3$ ):  $\delta$  13.7 (C-6), 23.3 (C-5), 39.4 (C-2), 120.7 (C-4), 123.5, 126.5, 128.1, 134.7, 136.7, 150.9 (aromatic), 203.1 (C-1);  $J$  (C-6, H-6) 126 Hz,  $J$  (C-5, H-5) 123 Hz,  $J$  (C-2, H-2) 131 Hz,  $J$  (C-2, H-4) 8 Hz, (C-4, H-4) 161 Hz.

MS [IP 70 eV;  $m/e$  (% rel. int.)]: 172 (48, M), 157 (26, M- $\text{CH}_3$ ), 145 (11), 144 (100, M-C $_2\text{H}_4$ ), 141 (6), 129 (56), 128 (36), 127 (15), 115 (20), 102 (10), 77 (9), 76 (7).

**3-Isobutylidene-1-indanone (3f).**  $^1\text{H}$  NMR (59.75 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.1 ( $\text{CH}_3$ , d,  $J$  6.6 Hz), 1.4 [( $\text{CH}_3$ ) $_2\text{CH}$ , m], 3.2 ( $\text{CH}_2\text{CO}$ , d,  $J$  2 Hz), 6.1 ( $\text{CH}=\text{C}$ , dt 9.5 Hz and 2 Hz), 7.2–7.8 (aromatic).

$^{13}\text{C}$  NMR (15.03 MHz,  $\text{CDCl}_3$ ):  $\delta$  22.6 [( $\text{CH}_3$ ) $_2$ ], 29.6 (C-5), 39.3 (C-2), 120.7 (C-4), 123.5, 128.1, 131.9, 134.8, 136.7, 151.0 (aromatic), 203.2 (C-1);  $J$  (C-6, H-6) 126 Hz,  $J$  (C-5, H-5) 125 Hz,  $J$  (C-2, H-2) 131 Hz,  $J$  (C-2, H-4) 8 Hz,  $J$  (C-4, H-4) 161 Hz.

MS [IP 70 eV;  $m/e$  (% rel. int.)]: 186 (33, M), 171 (48, M- $\text{CH}_3$ ), 158 (8, M-CO), 144 [100, M-( $\text{CH}_3$ ) $_2\text{C}$ ], 143 [39, M-( $\text{CH}_3$ ) $_2\text{CH}$ ], 128 (35), 115 (27), 102 (8), 77 (8), 77 (6).

**3-(2-Methylbutylidene)-1-indanone (3g).**  $^1\text{H}$  NMR (59.75 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.0 ( $\text{CH}_3\text{CH}_2$ , t,  $J$  7.1 Hz), 1.1 ( $\text{CH}_3\text{C}$ , d,  $J$  7.1 Hz), 1.4 ( $\text{CH}_3\text{CH}_2$ , m), 2.4 ( $\text{CH}_3\text{CH}$ , m), 3.2 ( $\text{CH}_2\text{CO}$ , d,  $J$  2 Hz), 6.1 ( $\text{CH}=\text{C}$ , dt,  $J$  9.7 Hz and 2 Hz).

$^{13}\text{C}$  NMR (15.03 MHz,  $\text{CDCl}_3$ ):  $\delta$  12.0 (C-7), 20.4 ( $\text{CH}_3$ ), 30.1 (C-6), 36.6 (C-4), 39.7 (C-2), 120.8 (C-4).

MS [IP 70 eV;  $m/e$  (% rel. int.)]: 200 (23, M), 185 (4, M- $\text{CH}_3$ ), 171 (72, M-C $_2\text{H}_5$ ), 145 (16), 144 (100, M-C $_4\text{H}_8$ ), 143 (50), 141 (12), 129 (13), 127 (11), 116 (10), 115 (25), 77 (9).

*Deuteration experiments.* (*E*)-4-Methyl-3-phenyl-

2-pentenoic acid (300 mg) was added to deuteriated concentrated sulfuric acid (10 ml) at 0°C. The reaction mixture was stirred for 24 h while the reaction temperature was allowed to reach 20°C. The reaction mixture was poured into ice and water and extracted twice with chloroform. The combined chloroform phases were extracted with sodium bicarbonate solution, dried with sodium sulphate and the chloroform evaporated. NMR and MS analyses showed that the reaction mixture contained several deuteriated products, which could not be separated by capillary GLC. The main reaction product was a derivative of 2-deuterio-4-methyl-3-phenyl- $\gamma$ -valerolactone with varying degrees of deuteriation in the phenyl ring.

<sup>1</sup>H NMR (59.75 MHz, CDCl<sub>3</sub>):  $\delta$  1.03 (CH<sub>3</sub>, s), 1.54 (CH<sub>3</sub>C, s), 2.8–3.6 (CH-CHD, an AB-system, not completely resolved).

<sup>13</sup>C NMR (15.03 MHz, CDCl<sub>3</sub>):  $\delta$  23.2 (CH<sub>3</sub>), 27.7 (CH<sub>3</sub>), 34.2 (C-2), 51.1 (C-3), 87.3 (C-4), 175.4 (C-1); *J* (C-2, H-2) 132 Hz, *J* (C-2, D-2) 23 Hz, *J* (C-3, H-3) 133 Hz.

The main reaction product from the reaction of 5-methyl-3-phenyl-2-propenoic acid with deuteriated sulfuric acid was a derivative of 4-deuterio-5-methyl-3-propylidene-1-indanone with varying degrees of deuteriation in the phenyl ring.

<sup>1</sup>H NMR (59.75 MHz, CDCl<sub>3</sub>):  $\delta$  1.15 (CH<sub>3</sub>, d, *J* 6.6 Hz), 2.6 [(CH<sub>3</sub>)<sub>2</sub>CH, sep, *J* 6.6 Hz], 3.2 (CH<sub>2</sub>CO, s), 7.2–7.8 (aromatic).

<sup>13</sup>C NMR (15.03 MHz, CDCl<sub>3</sub>):  $\delta$  22.6 (CH<sub>3</sub>), 29.5 (C-5), 39.3 (C-2), 119.7–153.8 (aromatic, not completely resolved), 203.2 (C-1).

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