

## The Reaction of 1,3-Diphenyl-1-propanone with Ethanol

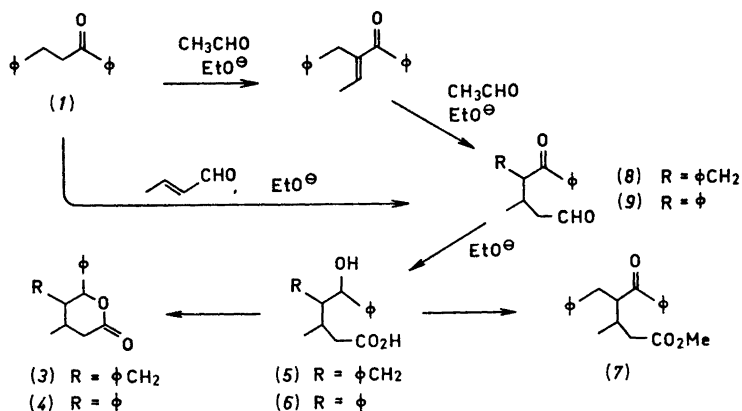
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1,3-Diphenyl-1-propanone reacts in ethanolic sodium ethoxide to give a single diastereomer of 4-benzyl-3-methyl-5-phenyl- $\delta$ -valerolactone (**3**). The configuration and conformation of an analogous reaction product (**4**) from benzyl phenyl ketone is deduced from IR and Eu(DPM)<sub>3</sub>-shifted NMR data, whereby stereochemistry for (**3**) is also implied. The mechanisms of the reactions are discussed.

During studies on the chemistry of chalcones and related compounds in this laboratory,<sup>1-3</sup> it was noticed that 1,3-diphenyl-1-propanone (**1**) has been reported<sup>4</sup> as furnishing an unidentified carbonyl-containing product A ( $\nu_{\max}$  1732 cm<sup>-1</sup>) on treatment with ethanolic sodium ethoxide. As it was possible that this behaviour might be connected with an anomaly in a chalcone reduction,<sup>2</sup> the reaction of (**1**) with base was reinvestigated.

As suggested in the original report,<sup>4</sup> compound A appeared to be a lactone, as the corresponding hydroxyacid (**5**) could be isolated from the reaction mixture by neutralisation, and cyclised to the lactone by warming. The neutral fraction obtained before neutralisation consisted of almost pure 1,3-diphenyl-1-propanol (**2**), thus implying that **1** and ethanol were involved in a base-catalysed reduction-oxidation reaction. Mass spectrometry of compound A indicated an MW of 280, and the NMR spectrum (see later) integrated for 20 protons. These facts can only be accommodated by C<sub>19</sub>H<sub>20</sub>O<sub>2</sub>, as was supported by combustion analysis. Consideration of possible structures for A, presumably formed by the reaction of **1** with acetaldehyde or crotonaldehyde, suggested 4-benzyl-3-methyl-5-phenyl- $\delta$ -valerolactone (**3**), which could have been formed as indicated. This was supported by further experiments which showed that (i) sodium methoxide in methanol or potassium *t*-butoxide in *t*-butanol failed to produce any reaction with **1**; (ii) sodium isopropoxide in isopropanol gave only **2**; and (iii) **1** reacted with acetaldehyde in methanolic sodium methoxide giving **3** in low yield. Furthermore, the hydroxy acid (**5**) could be methylated and oxidised to a ketoester (**7**) the IR spectrum of which ( $\nu_{\max}$  1670 cm<sup>-1</sup>) demonstrated that the hydroxy group in **5** must be benzylic.



More than a hundred years ago, benzyl phenyl ketone was found <sup>5</sup> to react analogously with ethanolic potassium ethoxide, and the reaction product was identified <sup>6,7</sup> as 4,5-diphenyl-3-methyl- $\delta$ -valerolactone (4). In addition, it was shown that benzyl phenyl ketone and crotonaldehyde react in methanolic sodium methoxide to give the ketoaldehyde (9) which, on treatment with KOH-containing methanol, furnished the hydroxy acid (6) and thence the lactone (4).<sup>6,7</sup>

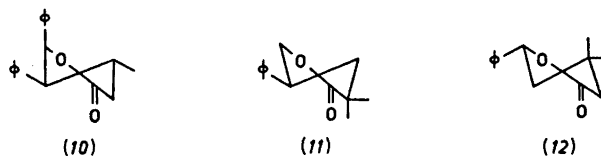
The spectra of the above products support the original structures, and leave little doubt that the lactone from 1,3-diphenyl-1-propanone is indeed 3.

In the NMR spectrum of 3 and 4 there is a doublet ( $\tau$  9.0,  $J = 6$  Hz) for the methyl group, and a low-field doublet ( $\tau$  4.4,  $J = 2.5$  Hz) for the  $\phi\text{-CH-O}$  proton. Unfortunately, the remaining aliphatic protons appear in a very complex pattern at  $\tau$  7.1–8.3. However, the use of the chemical shift reagent  $\text{Eu}(\text{DPM})_3$ <sup>8</sup> results in a first-order spectrum. Thus, for 4, all aliphatic protons appear at widely distributed chemical shift values and all coupling constants are readily extracted from the spectrum. As predicted on the basis of results with esters,<sup>8</sup>  $\text{Eu}(\text{DPM})_3$  seems to coordinate at the lactone carbonyl oxygen in 4, since the largest shifts are associated with the  $-\text{O}-\text{CO}-\text{CH}_2-$  protons.\*

The mass spectrum of 3, apart from providing  $\text{M}^+$  and a peak at  $m/e$  91 ( $\text{C}_7\text{H}_7^+$ , indicating the presence of a  $\text{C}_6\text{H}_5\text{CH}_2$  group), contains a number of features (for example, an  $\text{M} - 18$  peak) whose clarification requires further work.

As for the stereochemistry of 3 and 4, certain deductions can be made from the spectra, since the compounds are homogeneous by TLC criteria and the NMR spectrum indicates the presence of a single diastereomer. Half-chair conformations in solid  $\delta$ -lactones have been correlated <sup>9,10</sup> with  $\nu_{\text{C}=\text{O}}(\text{CHCl}_3)$  at  $1740\text{ cm}^{-1}$ , and half-boat conformations with  $\nu_{\text{C}=\text{O}}(\text{CHCl}_3)$  at  $1760\text{ cm}^{-1}$ . Compound 4 having  $\nu_{\text{C}=\text{O}}(\text{CHCl}_3)$  at  $1730\text{ cm}^{-1}$  evidently belongs to the former class. In a half-chair conformation (10) the 3-methyl group must be equatorial, on the basis of the large difference between  $J_{\text{AX}}$  (6.5 Hz) and  $J_{\text{BX}}$  (11.0 Hz) at the ABX system of H-2A, H-2B, and H-3. The coupling constant between H-3 and H-4 is 8.0 Hz, and molecular models indicate

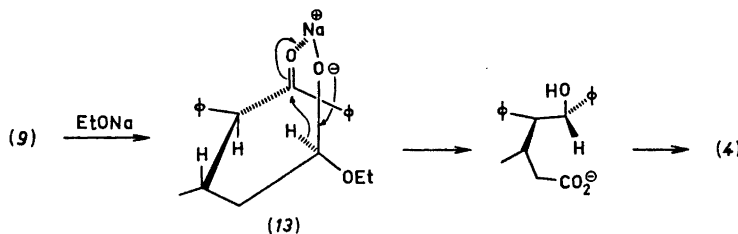
\* For related  $\text{Eu}(\text{DPM})_3$  work on lactones, see Ref. 11.



that the 4-phenyl substituent must be equatorial, although the  $J$  value does seem to be rather small (*cf.* 11,<sup>10</sup>  $J_{\text{H}-3\text{ax},\text{H}-4\text{ax}} = 11.0$  Hz). The remaining phenyl group of 4 at C-5 must then be axial, as  $J_{\text{H}-4,\text{H}-5} = 4.5$  Hz. These assignments are supported by the absence of long-range coupling in the spectrum of 4 that would have resulted from the W-shaped arrangement of H-2eq and H-4eq (in 12,<sup>10</sup> for instance,  $J_{\text{H}-2\text{eq},\text{H}-4\text{eq}} = 1.7$  Hz). Also, had the 5-phenyl substituent been equatorial, the resulting  $J_{\text{H}-4\text{ax},\text{H}-5\text{ax}}$  would have been much larger than 4.5 Hz; in (12), for instance, this  $J = 12.7$  Hz.

Although no detailed stereochemical analysis for 3 was undertaken, it is very probable that the above results imply the same stereochemistry for both 3 and 4. The stereochemical assignments presented require, of course, that the coordination of  $\text{Eu}(\text{DPM})_3$  with 4 does not involve conformational changes. This argument is supported by the fact that  $J_{\text{H}-4,\text{H}-5}$  (4.5 Hz) has the same value in both shifted and non-shifted spectra.

It is interesting that although the ketoaldehyde (9) is a 1:1 mixture of the diastereomers (by NMR), the hydroxyacid (6) consists of a single diastereomer (by NMR). This means that prior to the hydride transfer in the Cannizzaro reaction, the intermediate must assume, by epimerisation at  $\text{CH}-\text{CO}-\phi$ , a stable configuration as the two enantiomers (*e.g.*, 13).



## EXPERIMENTAL

For details in spectrometry, *etc.*, see Ref. 3.

*Experiments with 1,3-diphenyl-1-propanone (1).* A. 0.45 g of 1 was refluxed in ethanolic (50 ml) sodium ethoxide (from 0.15 g Na) for 52 h, cooled, poured into water and extracted with ether. The ethereal layer gave, after washing, drying and evaporating, 0.21 g of 1,3-diphenyl-1-propanol (2),  $\nu_{\text{max}}$  3470  $\text{cm}^{-1}$ ,  $\tau$  1.88 (5 H s), 2.93 (5 H s), 5.55 (1 H t 6.5 Hz), 7.10 (1 H br s, *exch.* w.  $\text{D}_2\text{O}$ ), 7.45 (2 H m), 8.10 (2 H m). The aqueous layer from above gave, after acidification, extraction in ether, drying and treatment with ethereal diazomethane, 0.19 g of methyl 4-benzyl-5-hydroxy-3-methyl-5-phenylvalerate as an oil,  $\nu_{\text{max}}$  3460, 1730  $\text{cm}^{-1}$ ,  $\tau$  2.80 (5 H s), 3.01 (5 H m), 5.22 (1 H d 3.5 Hz), 6.50 (3 H s), 7.1–8.1 (6 H m), 9.13 (3 H d 6.5 Hz). (Found: C 77.01; H 7.77.  $\text{C}_{20}\text{H}_{24}\text{O}_3$  requires C 76.89; H 7.74.)

B. When methanol was used instead of ethanol in the above reaction, no reaction took place.

C. 0.20 g of *I* was refluxed with potassium *t*-butoxide (0.1 g) in 50 ml of *t*-butanol. After 50 h only starting material was present (by TLC).

D. 0.29 g of *I* was refluxed with sodium isopropoxide (from 0.1 g of Na) in isopropanol (50 ml). After 26 h only 1,3-diphenyl-1-propanol was present (by TLC).

E. 0.29 g of *I* was dissolved in 50 ml of methanol, sodium methoxide (from 0.1 g of Na) added and 0.1 g of acetaldehyde in 5 ml of methanol was added with stirring during 8 h. TLC indicated that at least 8 components were present, one of them being the lactone (3).

*4-Benzyl-3-methyl-5-phenyl-δ-valerolactone (3)* was obtained by warming (30 min, 70°C) the acidified aqueous layer (see A, above), or less satisfactorily, by the original procedure.<sup>4</sup> It had m.p. 145°C (lit.<sup>4</sup> m.p. 145.5–146.6°C),  $\nu_{\max}(\text{CHCl}_3)$  1734  $\text{cm}^{-1}$ ,  $\tau$  2.7–3.5 (10 H m), 4.91 (1 H d 2 Hz), 7.05–8.25 (6 H m), 9.0 (3 H d 6.3 Hz). (Found: C 81.29; H 7.00.  $\text{C}_{18}\text{H}_{20}\text{O}_2$  requires C 81.37; H 7.19.) The mass spectrum had peaks at *m/e* 280, 262, 189, 188, 174, 132, 117, and 91.

*4,5-Diphenyl-3-methyl-δ-valerolactone (4)* was prepared as described.<sup>6,7</sup> It had m.p. 103°C (lit.<sup>9</sup> m.p. 103–104°C),  $\nu_{\max}(\text{CHCl}_3)$  1730  $\text{cm}^{-1}$ ,  $\tau$  2.9–3.5 (10 H m), 4.51 (1 H d 4.5 Hz), 6.95–7.95 (4 H m), 8.95 (3 H d 6.0 Hz);  $\tau$  (Eu(DPM)<sub>3</sub>:*A* = 1:4) 1.70 (2 H m), 2.5 (9 H m), 3.6 and 3.72 (each 1 H q, *ABX*,  $J_{AB} = 17$  Hz,  $J_{AX} = 6.5$  Hz,  $J_{BX} = 11.0$  Hz), 5.38 (1 H q, 8.0 and 4.5 Hz), 5.9 (1 H m), 8.35 (3 H d 6.5 Hz),  $\tau$  (Eu(DPM)<sub>3</sub>:*A* = 1:8) 3.65 (1 H d 4.5 Hz).

*Methyl 4-benzyl-3-methyl-5-oxo-5-phenylvalerate (7)*. The hydroxy ester (see A, above) was dissolved in acetone, Jones reagent added until the colour persisted, poured into water, taken up in ether, washed, dried, filtered and evaporated to give *7*, an oil,  $\nu_{\max}$  1730, 1675  $\text{cm}^{-1}$ ,  $\tau$  2.15 (2 H m), 2.68 (3 H m), 2.94 (5 H s), 6.1–7.8 (6 H m), 6.38 (3 H s), 9.03 (3 br d 6 Hz). (Found: C 77.29; H 6.98.  $\text{C}_{20}\text{H}_{22}\text{O}_3$  requires C 77.39; H 7.14.)

*4,5-Diphenyl-3-methyl-5-oxovaleraldehyde (9)* was prepared as described.<sup>6</sup> It had  $\nu_{\max}$  1718, 1675  $\text{cm}^{-1}$ ,  $\tau$  0.35 (1/2 H t 2 Hz), 0.41 (1/2 H t 2 Hz), 2.1 (2 H m), 2.7 (3 H m), 2.83 (5 H s), 5.42, 5.47, 5.59, 5.64 (4 lines of equal intensity, sum = 1 H), 6.7–7.4 (1 H m), 7.45–8.2 (2 H m), 8.92 (3/2 H d 6.5 Hz), 9.11 (3/2 H d 6.5 Hz).

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