864. *The Reaction between Styrene Oxide and Malonic Ester.*

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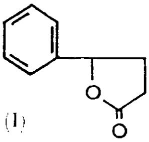
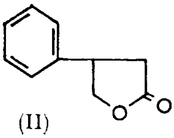
Contrary to literature reports, the base-catalysed reaction between styrene oxide and malonic ester gives almost equal amounts of γ-phenyl-γ-butyrolactone and β-phenyl-γ-butyrolactone.

During the evaluation of synthetic routes to γ-phenyl-γ-butyrolactone (I), suitable for the production of tonnage quantities, we re-examined the reaction between styrene oxide and malonic ester in the presence of strong base. According to Russell and VanderWerf[1] and Van Zyl and Van Tamelen,[2] the first-formed hydroxy-ester was saponified, lactonized, and decarboxylated to give the lactone (I) in a yield of 72%. Quoting Russell and VanderWerf from their summary, " . . . the attack of the nucleophilic anion of malonic ester occurs exclusively on the terminal (unsubstituted) carbon atom of the epoxide ring." These conclusions have been quoted widely (*e.g.*, refs. 3 and 4; also cf. refs. 5 and 6), but as a result of our experience we cannot agree with them.

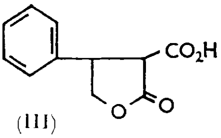
Small-scale experiments following the published method[1] established that the reaction between styrene oxide and malonic ester gave oily lactone which only partially crystallized when cooled strongly. Since infrared spectra suggested the presence of an isomeric lactone, pure specimens of compounds (I) and (II) were prepared. γ-Phenyl-γ-butyrolactone (I), obtained by reducing β-benzoylpropionic acid with sodium borohydride, crystallized readily and had m. p. 35—36°, in agreement with the literature.[7,8] β-Phenyl-γ-butyrolactone (II) was prepared from β-phenylglutaric acid[9] by application of the Simonini reaction,[10] this method having been employed for the synthesis of other β-substituted-γ-butyrolactones.[11] Attemps to reduce phenylsuccinic anhydride with aluminium amalgam[12] were not successful. The lactone (II) has been described only once previously, phenacyl acetate being employed as starting material, and the reported[13] m. p. 39° is rather lower than the figure we recorded for our synthetic material (47—48°).



(I)



(II)



(III)

The infrared spectra of standard mixtures of synthetic lactones (I) and (II) were recorded and used to analyse the oily lactone. By these means it was shown to contain 35—50% of compound (II), small variations being associated with changes in the reaction temperature and solvent (methanol, ethanol, or isopropyl alcohol). The yields of lactone mixture varied between 20 and 45% and at no time approached 70% (cf. ref. 1). Pilot plant experiments carried out to provide large amounts of lactone mixture for other purposes allowed a more accurate analysis to be made, and the data obtained using isopropyl

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[1] Russell and VanderWerf, *J. Amer. Chem. Soc.*, 1947, **69**, 11.

[2] Van Zyl and Van Tamelen, *J. Amer. Chem. Soc.*, 1950, **72**, 1357.

[3] Parker and Isaacs, *Chem. Rev.*, 1959, **59**, 737.

[4] Ingold, " Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, New York, 1953, p. 342.

[5] Adams and VanderWerf, *J. Amer. Chem. Soc.*, 1950, **72**, 4368.

[6] Barlow and MacLeod, *J.*, 1964, 141.

[7] Julia, Julia, and Bémont, *Bull. Soc. chim. France*, 1960, **27**, 304.

[8] Pernot and Willemart, *Bull. Soc. chim. France*, 1953, **20**, 321.

[9] Altschul, Bernstein, and Cohen, *J. Amer. Chem. Soc.*, 1956, **78**, 5094.

[10] Wilson, *Org. Reactions*, 1957, **9**, 332.

[11] Pattison and Saunders, *J.*, 1949, 2745.

[12] Haworth and Woodcock, *J.*, 1939, 154; Zimmer, Rothe, and Holbert, *J. Org. Chem.*, 1960, **25**, 1235.

[13] Kariyone and Fukui, *J. Pharm. Soc. Japan*, 1946, **66**, 42.

alcohol as solvent are summarized in the Experimental section. The lactone-acid (III) separated out from the aqueous mother-liquors remaining after extraction of the hydroxy-acids. Its structure follows from elemental analyses and its ready decarboxylation to β-phenyl-γ-butyrolactone (II), oxidation of which with alkaline permanganate gives phenylsuccinic acid.

Our results differ markedly from those reported in the literature[1,2] and it is possible that other nucleophilic ring-opening reactions of styrene oxide, which have been summarized in an excellent review,[3] require re-investigation. Although Russell and VanderWerf[1] carried out degradations on their lactone, it is not clear if they used crude or crystalline lactone for these experiments. In our hands crystallization of the oily lactones gave impure β-phenyl-γ-butyrolactone (II) rather than the γ-phenyl-isomer (I), and the melting point (45·5—46·0°) recorded by Russell and VanderWerf suggests that they, too, obtained only (II) in a state of purity. It seems certain that compounds synthesized[1,2,6] from crude lactone have unestablished structures.

The boron trifluoride-catalysed reaction between styrene oxide and malonic ester has been reported[14] to give γ-phenyl-γ-butyrolactone. Since the isomeric lactones (I) and (II) have similar melting points, this report also requires confirmation.

Attack on the α-carbon atom of styrene oxide by nucleophiles varies from 4% for piperidine[15] to essentially 100% for azide ion.[16] Our results for malonic ester anion (35—50%) fall into line with the relative nucleophilicities of the attacking species.

EXPERIMENTAL

Melting points were obtained using an "Electrothermal" apparatus equipped with a thermometer calibrated for stem exposure. Quantitative infrared spectra were recorded for solutions in nitromethane using a Hilger H-800 spectrophotometer.

Mixed Lactones (I) *and* (II).—The conditions described[1] for the reaction between styrene oxide and malonic ester were varied to include methanol, ethanol, and isopropyl alcohol as solvents,* at temperatures from ambient up to reflux. Effects of variations in the proportion of alkoxide were also investigated. From these results, which showed small variations in the ratio (I)/(II) + (III), the following conditions suitable for use on a large scale were developed: A 50-gallon stainless-steel vessel equipped with an efficient propeller stirrer and reflux condenser was purged with nitrogen and charged with isopropyl alcohol (114 l.). Sodamide (10 kg.) was added slowly (caution—copious evolution of ammonia) and the reaction completed by boiling under reflux for 3·5 hr. Final traces of ammonia were removed by slow distillation of isopropyl alcohol (18 l.) in a brisk current of nitrogen. Diethyl malonate (36·3 kg.) was added at a rate sufficient to maintain reflux (20 min.) followed by styrene oxide (28·1 kg.) during 40 min. Reaction was completed by boiling under reflux for a further 2 hr. Next morning the mixture was again brought to boiling under reflux and a solution of sodium hydroxide (13·6 kg.) in water (63 l.) added slowly, reflux being maintained by the heat of reaction. Aqueous alcohol (125 l.) was removed by slow distillation and the residue diluted with water (65 l.) to maintain homogeneity. This solution was added slowly to a vigorously stirred pre-cooled mixture of concentrated hydrochloric acid (42 l.) and water (45 l.), the temperature being maintained below 10°. The hydroxy-acids were extracted into isopropyl acetate (4 × 30 l.) and the aqueous layer diluted with more concentrated hydrochloric acid (4·5 l.) and set aside. The isopropyl acetate extracts were evaporated under reduced pressure and the residue decarboxylated by heating, initially at 95 and finally at 110°, the pressure being maintained between 300 and 550 mm. Distillation and combination on the basis of refractive indices gave two main fractions: (i) b. p. 105—120°/0·65—0·8 mm., assaying 70% as phenylbutyrolactones; (ii) b. p. 120—150°/1·25 mm., assaying 86% as phenylbutyrolactones. Samples (500 g.) of (i) and (ii) were subjected to precise fractionation and the fractions analysed by infrared spectroscopy and gas-liquid chromatography. Duplicate experiments, each using 28·1 kg. styrene oxide, gave the following

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* Dried by distillation from diethyl oxalate and alkoxide.

[14] Oda, Muneimiya, and Okano, *J. Org. Chem.*, 1961, **26**, 1343.

[15] Chapman, Isaacs, and Parker, *J.*, 1959, 1925.

[16] VanderWerf, Heisler, and McEwen, *J. Amer. Chem. Soc.*, 1954, **76**, 1231; McEwen, Conrad, and VanderWerf, *ibid.*, 1952, **74**, 1168.

results: phenylisopropoxyethanols, b. p. 163—165°/20 (8, 4%); lactone-acid (see below) (5·2, 4·2%); mixed lactones, b. p. 180—182°/20 (46, 47%) containing 27, 28% (I), 19, 19% (II).

α-Carboxy-β-phenyl-γ-butyrolactone (III).—During 7 days the aqueous mother-liquors deposited a white solid which was spun off, washed with water, and dried. Crystallization from acetone-benzene gave the *acid* as white needles (2·24 kg.), m. p. 143—145° (decomp.) (Found: C, 64·1; H, 5·1. $C_{11}H_{10}O_4$ requires C, 64·1; H, 4·9%). Assay as acid, 99·6%; by saponification, 100·4%.

β-Phenyl-γ-butyrolactone (II).—(*a*) β-Phenylglutaric acid [8] (97 g.) was stirred with 30% aqueous sodium hydroxide to give a solution just basic to phenolphthalein. Dilute nitric acid was added until an acid reaction was obtained, followed by dilute ammonia to give an alkaline solution once more. The solution was brought to neutrality by boiling, cooled to 30°, and a solution of silver nitrate (180 g.) in water (500 ml.) added. The heavy precipitate of the silver salt was collected, washed with cold water, and dried, first at 100°/20 mm. and finally over phosphorus pentoxide.

A portion of the silver salt (80 g.) was ground with dry sand (300 g.) and iodine (56 g.) and the mixture transferred to a 1-litre flask equipped with a reflux condenser. The flask was immersed for 1 hr. in an oil-bath maintained at 150°. After being cooled, the contents of the flask were boiled with ether (2 × 500 ml.) and the extracts washed successively to completion with potassium carbonate solution, sodium metabisulphite solution, and water. Evaporation of the dried (K_2CO_3) extracts left a dark oil (5 g.), which was boiled under reflux for 1 hr. with sodium hydroxide (10 g.) in 50% aqueous methanol (50 ml.). Alcohol was removed by distillation and, after being cooled, the residue was extracted with ether and then made strongly acid (HCl). An oil precipitated during 30 min. warming on the steam-bath; this was separated and purified by chromatography (hexane–acid-washed alumina). Crystallization of the eluted material from benzene–hexane gave the lactone as lustrous plates (1·4 g.), m. p. 47—48° (Found: C, 74·0; H, 6·0. Calc. for $C_{10}H_{10}O_2$: C, 74·05; H, 6·2%). Assay by saponification: 99·2%. The infrared spectrum of a solution in nitromethane showed a strong peak at 857 cm.$^{-1}$, not present in the spectrum of γ-phenyl-γ-butyrolactone, which was used to analyse lactone mixtures.

The sand and residues were extracted with dilute aqueous sodium hydroxide and the extracts purified by treatment with charcoal, filtered, and made strongly acid (HCl), precipitating phenylglutaric acid (18 g., 45%).

(*b*) The lactone acid (III) (50 g.) was distilled at 30 mm., giving an oil (37 g., 94%), which soon crystallized, m. p. 39—41°. One crystallization from benzene gave lustrous plates, m. p. 41—42°, not depressed when mixed with synthetic lactone (II) (above); the crystals liquefied when mixed with an equal weight of γ-phenyl-γ-butyrolactone. The infrared spectra of this lactone and authentic compound (II) were identical. Oxidation of the lactone (1 g.) in water (10 ml.) containing sodium hydroxide (5 g.) with 5% aqueous potassium permanganate gave phenylsuccinic acid (0·2 g.), m. p. and mixed m. p. 163—165°.

(*c*) Mixed lactones (I) and (II) (230 g.), assaying 98·4% by saponification, was cooled strongly in an acetone—" Dry Ice " bath. Scratching induced crystallization of a white solid which was largely freed from oil by decantation. Low temperature crystallization from hexane gave impure lactone (II) (7 g.), m. p. 31—37°, identified by its infrared spectrum and by oxidation to phenylsuccinic acid.

γ-Phenyl-γ-butyrolactone (I).—β-Benzoylpropionic acid was reduced with a solution of sodium borohydride in 40% aqueous sodium hydroxide.[6,7] Crystallization of the distilled lactone from hexane gave lustrous plates, m. p. 36—37°. Oxidation with alkaline permanganate as described for lactone (II) gave benzoic acid as the only isolable product.

Infrared Spectra.—These were obtained on a Hilger H-800 infrared spectrophotometer. For quantitative analysis of mixtures of compounds (I) and (II), spectra were determined of solutions in nitromethane and compared with those of standard mixtures. The peak at 857 cm.$^{-1}$ in the spectrum of lactone (II) was particularly useful. These results agreed well with those obtained by gas–liquid chromatographic analysis, with a column of Celite and 2·5% tritolyl phosphate at 140° as stationary phase. The following spectral details served for characterization purposes (frequencies, cm.$^{-1}$):

I, as Nujol mull: 1780*, 1763 (vs), 1720 (m), 1702 (m), 1619 (w), 1495 (w), 1457 (m), 1420 (m), 1369 (m), 1330 (m), 1312 (w), 1297 (m), 1270 (w), 1217 (m), 1184 (s), 1178 (s), 1143 (m), 1080 (w), 1057 (w), 1022 (s), 999 (w), 982 (m), 940 (m), 917 (w), 891 (m), 825 (m), 806 (w), 763 (s), 696 (s).

* Shoulder.

II, as Nujol mull: 1761 (vs), 1727 (s), 1707 (m), 1600 (w), 1496 (m), 1484 (m), 1458 (s), 1423 (m), 1408 (w), 1378 (m), 1356 (s), 1308 (m), 1289 (m), 1251 (m), 1225 (m), 1211 (m), 1173 (vs), 1164 (vs), 1157 (vs), 1082 (w), 1072 (m), 1041 (m), 1009 (vs), 1000 (s), 997 (w), 935 (m), 918 (w), 901 (w), 857 (s), 814 (m), 758 (s), 700 (s), 677 (m).

III, as KBr disc: 1777 (vs), 1740 (vs), 1602 (w), 1586*, 1497 (m), 1470 (m), 1457 (m), 1400 (m), 1356 (s), 1309 (w), 1287 (w), 1257 (s), 1222 (s), 1182 (w), 1150 (vs), 1122 (m), 1081 (m), 1063 (m), 1033 (s), 1005 (w), 992 (w), 942 (w), 910 (w), 897 (w), 852 (m), 779*, 757 (s), 740 (w), 685 (s).

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