Substituted γ-Lactones. VIII.[1] Condensation between Phthalide and Aromatic Aldehydes[2]

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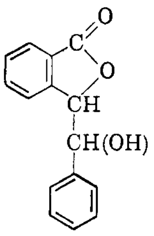
A study of the aldol-type condensation of phthalide (I) with aromatic aldehydes showed that the corresponding diastereoisomeric 3-(α-hydroxybenzyl)phthalides are formed in high yields. In the condensation reaction between I and benzaldehyde, and I and 2-methylbenzaldehyde, the corresponding *d,l-erythro* and *d,l-threo* isomers were separated and characterized. Their structures were confirmed by an independent synthesis.

In our investigations concerning the chemistry of γ-lactones we found that phthalide condensed with certain aromatic aldehydes in the presence of equimolar amounts of sodium methoxide to yield the corresponding aldol-type compounds(I). This observation is remarkable for two reasons. First, it has been repeatedly stated in the literature[4-7] that phthalide does not undergo aldo-type condensations with aldehydes, and second, the isolation of aldols in this type of reaction is not common. Especially this is the case if the corresponding olefin, obtainable through dehydration of the aldol, is in conjugation with an aromatic system. Recently, we found that γ-butyrolactone and *o*-ethoxybenzaldehyde condensed under alkaline conditions to yield isolatable amounts of the corresponding aldol.[8] We also found that this is the case in the phthalide series. In recent articles the same observation was made by two different groups of authors. Horton and Murdock[9] as well as Shapiro, Geiger, and Freedman[10] reported the isolation of aldols in such a reaction. This prompts us to report some of the results we have obtained so far.



I

The aldols isolated by us in high yields from such a condensation can occur in two different sets of diasteroisomers, namely the *d,l-erythro* and the *d,l-threo* compounds. In order to obtain more insight into the stereochemistry of the transition state of this reaction, it was decided to analyze the composition of the mixture of the aldols. The separation of the *d,l-threo* from the *d,l-erythro* isomers was achieved chromatographically on alumina and by fractional crystallization. Typical results for a condensation with benzaldehyde and 2-methylbenzaldehyde are summarized in Table I.

TABLE I

Compound	M.P.	Yield, %
d,l-erythro-3-(α-Hydroxybenzyl)-phthalide	148–149°	39
d,l-threo-3-(α-Hydroxybenzyl)-phthalide	102–103°	35
2-Phenyl-1,3-indanedione	147–148°	3
Recovered phthalide	73°	12
"Unidentified"[a]	182°	(11)
d,l-erythro-3-(α-Hydroxy-2-methyl-benzyl)phthalide	115–117°	27
d,l-threo-3-(α-Hydroxy-2-methyl-benzyl)phthalide	167–168°	38
2-(2-Methylphenyl)-1,3-indanedione	146–150°	2
Recovered phthalide	73°	33

[a] See ref. 11.

The configuration of the diastereoisomers was established by an independent synthesis similar to one given by Berti.[12] However, the ratios of the diastereoisomers are considered as semiquantitative in nature. Work on a quantitative method for determining the yields of the isomers is underway in this laboratory.[13]

With 1-naphthaldehyde, α-hydroxy-α-phthalidyl 1-methylnaphthalene, and with 3-nitrobenzaldehyde, 3-(α-hydroxy-3-nitrobenzyl)phthalide were obtained. These two compounds were not separated into the corresponding stereoisomers.

The occurrence of the aldols in this reaction

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[1] Paper VII in this series: H. Zimmer, M. E. Aler, and J. Rothe, *Chem. Ber.*, **94**, 2569 (1961).

[2] Presented before the Division of Medicinal Chemistry, American Chemical Society National Meeting, St. Louis, Missouri, March, 1961.

[3] Taken in part from the Ph.D. thesis of R. D. Barry, Univ. of Cincinnati (1960); 1957–1959, Chattanooga Medicine Co. Fellow; 1959–1960, Ethyl Corp. Fellow. Present address: Organic Research Laboratories, Department of Obstetrics and Gynecology, University Hospital, The Ohio State University, Columbus, Ohio.

[4] R. L. Shriner and S. Keyser, *J. Org. Chem.*, **5**, 200 (1940).

[5] W. Borsche, K. Diacont, and H. Hanau, *Ber.*, **67**, 675 (1934).

[6] W. Dieckmann, *Ber.*, **47**, 1439 (1914).

[7] W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.*, **99**, 775 (1911).

[8] H. Zimmer and J. Rothe, *J. Org. Chem.*, **24**, 28 (1959).

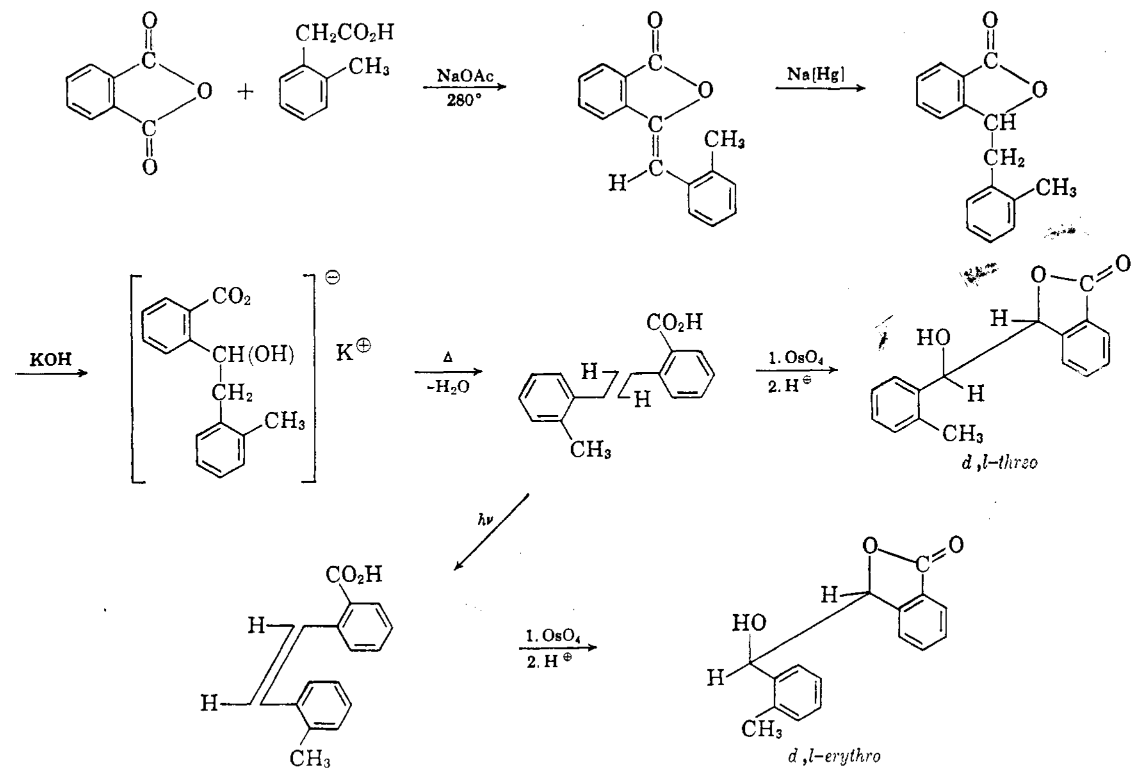
[9] R. L. Horton and K. C. Murdock, *J. Org. Chem.*, **25**, 938 (1960).

[10] S. L. Shapiro, K. Geiger, and L. Freedman, *J. Org. Chem.*, **25**, 1860 (1960).

[11] This portion appears to be a mixture of isomeric 3,3-bis(α-hydroxybenzyl)phthalides, giving an infrared spectrum with OH bands at 2.99 and 3.19 μ, and a carbonyl band at 5.72 μ.

[12] G. Berti, *Tetrahedron*, **4**, 393 (1958).

[13] H. Zimmer and R. Barry, Abstract of Paper, American Chemical Society National Meeting, St. Louis, March, 1961, p. 23N.



under the conditions described therefore seems to be a general one.

It is also noteworthy that the recovered phthalide is greater in the case of the condensation of 2-methylbenzaldehyde with phthalide, in accordance with the increased steric effect of the *ortho*-methyl group.

Experimental[14]

Reaction between Phthalide and Benzaldehyde.—A solution of 100 ml. of anhydrous methanol (distilled from magnesium) containing 0.1 mole of sodium methoxide (prepared by adding 2.3 g., 0.1-g.-atom, sodium to the methanol) was treated with 13.4 g. (0.1 mole) of phthalide and warmed until all of the phthalide dissolved. The yellow solution was cooled to room temperature, treated with 10 ml. (0.1 mole) of benzaldehyde, and left 24 hr. at room temperature. The orange mixture was acidified with 100 ml. of 20% sulfuric acid, methanol removed *in vacuo*, and the residue of orange oil and an aqueous layer was shaken with 200 ml. of ether. The clear aqueous layer was discarded, and the orange ether layer was shaken with three 50-ml. portions of 20% sodium carbonate solution (until the orange color was removed from the ether layer). Acidification of the sodium carbonate extracts furnished 0.75 g. (3.6% based on 0.1 mole of phthalide) of 2-phenylindane-1,3-dione, m.p. 148° (from ethanol; literature m.p. 147–148° [6]).

The yellow ether solution was extracted with five 50-ml. portions of 10% sodium bisulfite solution to remove the unchanged benzaldehyde, then dried. Removal of the ether gave a yellow oil which yielded some crystals when dried *in vacuo*. The oily mixture (21.12 g.) was boiled with 30 ml. of hot benzene, treated with about 3 ml. of petroleum ether (b.p. 40–60), and left overnight at room temperature. The crystals were collected and identified as *d,l-erythro*-3-(α-hydroxybenzyl)phthalide (8.50 g., 35% based on 0.1 mole of phthalide), m.p. 148–150° (from methanol; literature m.p. 148–149° [12]), λ_{max} 283 (ε 1970), 275 (1970), 269 (1450, shoulder), 264 (1150, shoulder), 259 (850, shoulder), 252 (660, shoulder), 228 mμ (1080); $\bar{\nu}_{max}$ 2.99, 5.79 μ. A mixed melting point with authentic material was not depressed.[12,15] Treatment of *d,l-erythro*-3-(α-hydroxybenzyl)phthalide with acetic anhydride gave *d,l-erythro*-3-(α-acetoxybenzyl)phthalide, m.p. 115° (from aqueous ethanol), λ_{max} 282 mμ (ε 1760), 274 (1780), 268 (1400, shoulder), 264 (1220, shoulder), 258 (930, shoulder), 252 (740), 228 (1150); $\bar{\nu}_{max}$ 5.65, 5.75 μ.

Anal. Calcd. for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. Found: C, 72.34; H, 5.12.

Pyrolysis of 0.5 g. of *d,l-erythro*-3-(α-acetoxybenzyl)-phthalide at 400–450° for 20 min. gave 0.17 g. (43%) of *trans*-3-benzylidenephthalide, m.p. 101–103° (from ethanol).

The yellow filtrate above, from the collection of *d,l-erythro*-3-(α-hydroxybenzyl)phthalide, was chromatographed on a 3.5 × 15.0 cm. column of neutral alumina. Elution with petroleum ether (b.p. 40–60°)-benzene mixtures gave 1.7 g. (12%) of phthalide, and elution with chloroform–benzene mixtures gave 8.29 g. (35% based on 0.1 mole phthalide) of *d,l-threo*-3-(α-hydroxybenzyl)phthalide, m.p. 102–103°, (from methanol; literature m.p. 102–103° [12]); $\bar{\nu}_{max}$ 2.95, 5.75 μ. A mixed melting point with authentic material was not depressed.[12,15] Treatment of *d,l-threo*-3-(α-hydroxybenzyl)-phthalide with acetic anhydride furnished *d,l-threo*-3-(α-acetoxybenzyl)phthalide, m.p. 125° (from aqueous ethanol), $\bar{\nu}_{max}$ 5.70, 5.80 μ.

Anal. Calcd. for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. Found: C, 72.48; H, 5.12.

An additional 0.87 g. (4%) of *d,l-erythro*-3-(α-hydroxybenzyl)phthalide was also obtained, along with 1.03 g. of unidentified material which furnished some crystals from petroleum ether (b.p. 40–60°)-benzene, m.p. 182°, $\bar{\nu}_{max}$ 2.99, 3.49, 5.72 μ, and tentatively identified as one of the isomers of 3,3-bis(α-hydroxybenzyl)phthalide.

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[14] Analyses by A. Bernhardt, Max-Planck Institut, Mülheim, Ruhr, Germany. Melting points are not corrected. The infrared spectra were determined as Nujol mulls with a Baird infrared spectrophotometer and the ultraviolet spectra measured in 95% ethanol with the Cary Model II or II PM spectrophotometer.

[15] We thank Dr. G. Berti for furnishing us with authentic samples of *d,l-erythro-* and *d,l-threo*-3-(α-hydroxybenzyl)phthalide.

Reaction between 2-Methylbenzaldehyde and Phthalide.—This reaction was carried out exactly as for the condensation of benzaldehyde with phthalide. After acidification of the reaction mixture and removal of methanol, the mixture was shaken with 200 ml. of ether and crystals of *d,l-threo*-3-(α-hydroxy-2-methylbenzyl)phthalide, (8.21 g., 32% based on 0.1 mole of phthalide), m.p. 167–168° (from methanol), λ_{max} 282 (ϵ 2160), 274 (2400), 268 (1870, shoulder), 228 mμ (11400, shoulder); $\bar{\nu}_{max}$ 2.90, 5.69 μ. A mixed melting point with *d,l-threo*-3-(α-hydroxy-2-methylbenzyl)phthalide, prepared by *cis*-hydroxylation of *trans*-2′-methylstilbene-2-carboxylic acid, was not depressed.

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.73; H, 5.80.

Treatment of *d,l-threo*-3-(α-hydroxy-2-methylbenzyl)phthalide with acetic anhydride furnished *d,l-threo*-3-(α-acetoxy-2-methylbenzyl)phthalide, m.p. 139° (from methanol), $\bar{\nu}_{max}$ 5.65, 5.75 μ.

Anal. Calcd. for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.97; H, 5.63.

The aqueous layer was discarded and the orange ether layer was extracted with two 100-ml. portions of 20% sodium carbonate solution (until the orange color was removed). Acidification of the sodium carbonate extracts gave 0.39 g. (1.7% based on 0.1 mole of phthalide) of 2-(2-methylphenyl)indane-1,3-dione, m.p. 146–150° (literature m.p. 179–180°[16,17]). The yellow ether layer was dried and evaporated *in vacuo*. The residual oil (12.64 g.) was dissolved in 20 ml. of benzene, left overnight, and the crystals of *d,l-threo*-3-(α-hydroxy-2-methylbenzyl)phthalide, (0.09 g.) m.p. 166–167° (from methanol), were collected. The yellow mother liquor was chromatographed on a 3.5 × 15.0 cm. column of neutral alumina, analogous to the method described for the separation of the mixture obtained from the condensation of phthalide with benzaldehyde. In this manner, 6.89 g. (27% based on 0.1 mole of phthalide) of *d,l-erythro*-3-(α-hydroxy-2-methylbenzyl)phthalide, m.p. 115–117° (from methanol), $\bar{\nu}_{max}$ 2.99, 5.70 μ.

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.79; H, 5.59.

Treatment of *d,l-erythro*-3-(α-hydroxy-2-methylbenzyl)phthalide with acetic anhydride gave *d,l-erythro*-3-(α-acetoxy-2-methylbenzyl)phthalide, m.p. 136° (from methanol), $\bar{\nu}_{max}$ 5.66, 5.75 μ.

Anal. Calcd. for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.59; H, 5.63.

Preparation of *d,l-threo*-3-(α-Hydroxy-2-methylbenzyl)phthalide. A. 2-Methylphenylacetic Acid.—A mixture of 42.5 g. (0.65 mole) of potassium cyanide and 50 ml. of water was warmed until most of the solid dissolved, then a solution of 75 ml. (0.57 mole) of α-bromo-*o*-xylene in 125 ml. of 95% ethanol was added. The mixture was refluxed for 9 hr., left at room temperature overnight, and the solution decanted from the precipitate. The alcoholic solution was steam distilled, the 2-methylphenylacetonitrile was separated from the aqueous layer, and refluxed with 510 ml. of 55% sulfuric acid for 8 hr. Upon cooling, the oily layer crystallized giving 62 g. (72%) of crude 2-methylphenylacetic acid, m.p. 75° (literature m.p. 88°[16]).

B. 3-(2-Methylbenzylidene)phthalide.—A mixture of 14.8 g. (0.1 mole) of phthalic anhydride, 15.0 g. (0.1 mole) of crude 2-methylphenylacetic acid, and 0.1 g. of anhydrous sodium acetate was heated at 280° for 8 hr., then cooled to 90° and treated with 100 ml. of 95% ethanol. The mixture was cooled to room temperature, the brown solid collected, and once recrystallized from a mixture of ethanol and Methyl Cellosolve, furnishing 5.4 g. (23%) of crude 3-(2-methylbenzylidene)phthalide, m.p. 121° (literature m.p. 136.5°[16]).

C. *trans*-2-Methylstilbene-2-carboxylic Acid.—An orange solution of 5.4 g. (0.023 mole) of 3-(2-methylbenzylidene)phthalide and 5 g. (0.091 mole) of potassium hydroxide in 100 ml. of 95% ethanol was diluted with 200 ml. of water and added to 100 ml. of 2% sodium amalgam (covered with a 1-cm. layer of mineral oil). The mixture was stirred vigorously for 5 hr., the mercury removed, the aqueous layer was extracted with ether to remove the mineral oil, then the mixture was filtered, and acidified with 300 ml. of 20% sulfuric acid. An oil separated which was collected, treated with a solution of 20 ml. of 95% ethanol and 2 g. of potassium hydroxide, and heated to 180° during 2 hr. The residue was treated with 50 ml. of 20% sulfuric acid and the precipitate of 1 g. (19%) of *trans*-2′-methylstilbene-2-carboxylic acid, m.p. 163–165° [from petroleum ether (b.p. 40–60°)–benzene; literature m.p. 169°[16]] collected.

D. *d,l-threo*-3-(α-Hydroxy-2-methylbenzyl)phthalide.—A solution of 0.05 g. (0.00021 mole) of *trans*-2′-methylstilbenecarboxylic acid in 3 ml. of anhydrous ether containing 0.1 ml. of pyridine, was treated with 0.06 g. (0.00024 mole) of osmium tetroxide in 9 ml. of anhydrous ether. A light brown precipitate separated and changed to dark brown during 2 days. The precipitate was collected, washed with ether, dissolved in 5 ml. of methylene chloride, and shaken with a solution of 0.2 g. of sodium hydroxide, 0.5 g. of mannitol, and 8 ml. of water for 10 min. Acidification of the basic layer gave 0.03 g. (57%) of *threo*-3-(α-hydroxy-2-methylbenzyl)phthalide, m.p. 164–167° (mixed melting point with the alcohol, m.p. 167–168°, obtained from the condensation of 2-methylbenzaldehyde with phthalide, was not depressed).

Reaction between Phthalide and 1-Naphthaldehyde.—This reaction was carried out exactly as described for the condensation of benzaldehyde with phthalide. The oil obtained after removal of the ether partially crystallized, was stirred with 10 ml. ethanol, and the crystals of one of the diastereoisomers of α-hydroxy-α-phthalidyl-1-methylnaphthylene, (9.0 g., 31% based on 0.1 mole of phthalide), m.p. 174–175° (from methanol), were collected.

Anal. Calcd. for $C_{19}H_{14}O_3$: C, 78.60; H, 4.85. Found: C, 78.29; H, 5.07.

The mother liquor was not further investigated.

Reaction between Phthalide and 3-Nitrobenzaldehyde.[18]—This reaction was carried out in the same manner as those described above, furnishing one of the diastereoisomers of 3-(α-hydroxy-3-nitrobenzyl)phthalide, m.p. 243–244°.

Anal. Calcd. for $C_{15}H_{11}NO_4$: C, 66.91; H, 4.12; N, 5.20. Found: C, 67.58; H, 3.25; N, 5.40.

The mother liquor was not further investigated.

Treatment of the above alcohol with acetic anhydride gave 3-(α-acetoxy-3-nitrobenzyl)phthalide, m.p. 120–121°.

Anal. Calcd. for $C_{17}H_{13}NO_6$: C, 62.38; H, 4.00; N, 4.28. Found: C, 62.47; H, 3.82; N, 4.39.

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(16) F. Bethmann, *Ber.*, **32**, 1104 (1899).

(17) This material was not further purified but gave an infrared spectrum in accordance with an indane-1,3-dione structure, and gave an orange color in ethanol, characteristic of indane-1,3-diones.

(18) Synthesis performed by Mr. J. Lang as a senior research project.