

cally inactive.⁷ An investigation of one of these, *dl-r-3*(4⁺-hydroxycyclohexyl)-4-(4⁺-hydroxycyclohexyl)-hexane, has failed to show any appreciable mixed crystal formation with the corresponding active dihydro compound (Fig. 6).

Experimental⁸

The melting point diagrams (Figs. 1-6) were obtained in an ordinary melting point apparatus according to the procedure of Rheinboldt⁹ or Grimm.¹⁰ The lower curves in the diagrams (solidus curves) represent the thawing points (first appearance of liquid), the upper curves (liquidus curves) the final melting temperatures (clear melt). All mixtures were stirred continuously after thawing in order to insure equilibrium conditions. Fusing of the samples (method of Rheinboldt) was applicable only for mixtures of stilbestrol and *dl*-dihydrostilbestrol (Fig. 3). Mixtures containing α -estradiol resolidified only partially after melting. The determinations were therefore carried out with carefully ground mixtures (method of Grimm) which were heated to 125° for twelve hours prior to the determination.

Mixtures of *dl*-dihydrostilbestrol and *dl-r-3*-(4⁺-hydroxycyclohexyl)-4-(4⁺-hydroxycyclohexyl)-hexane did not solidify after melting, and a diagram obtained from freshly prepared mechanical mixtures showed considerable lack of equilibrium. The values in Fig. 6 were obtained from finely ground mechanical mixtures which were kept at room temperature for several months or which were maintained at 80° for twelve hours. The curves show two eutectic points and the formation of a compound. The maximum in this case is flattened out so that the eutectic points are connected by a nearly straight line. A diagram of this type has been described by Rheinboldt^{9a} for the system *m*-hydroxybenzaldehyde-picric acid. As in the example of Rheinboldt, the thaw curve in Fig. 6 does not coincide with the melting curve in the flat part between the two eutectic points. This is believed to be due to the fact that the perhydro compound was not entirely pure. A higher melting point (135°) has been reported for this compound.¹¹

The data in Fig. 5 were obtained by preheating the mixtures to 165° for at least twenty-four hours in an atmosphere of oxygen-free nitrogen. The uncertainties in this case are due to the fact that the samples darken during the determinations presumably due to oxidation. Mechanical mixtures which were not preheated gave thaw points which could not be reproduced for all percentages. Sufficient points were obtained to deduce at least limited miscibility.

Acknowledgment.—The authors are indebted to Dr. W. M. Hoehn, George Breon Co., Kansas City, Mo., for a supply of the hormones used in this investigation.

(7) Unpublished work by J. Leon Sealy, George Breon Co., Kansas City, Missouri.

(8) All temperatures uncorrected.

(9) (a) Rheinboldt, *J. prakt. Chem.*, [2] **111**, 242 (1925); (b) Rheinboldt, *ibid.*, **112**, 187 (1926); **113**, 199, 348 (1926).

(10) Grimm, Günther and Tittus, *Z. physik. Chem.*, **B14**, 180 (1931).

(11) Schoeller, Inhoffen, Steinruck, and Höss, U. S. Patent 2,392,846 (1946).

CHEMISTRY DEPARTMENT
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o-Acetobenzoic Acid, its Preparation and Lactonization. A Novel Application of the Doebner¹ Synthesis

BY HARRY L. YALE

We have found that phthalic anhydride and malonic acid, in the presence of pyridine and

(1) Roger Adams, editor, "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1942, volume 1, pp. 226, 233.

acetobenzoic acid in 48.5% yield; the only other product, aside from unreacted phthalic anhydride, is *o*-phthalic acid. The reaction probably proceeds through the intermediate formation of phthalylacetic acid since small amounts of that compound are obtained from the same reactants under special conditions. 3-Methylenephthalide is another intermediate whose transitory existence during this reaction is possible. Both of these compounds have been reported to yield *o*-acetobenzoic acid.^{1a,2}

We have also found that *o*-acetobenzoic acid lactonizes to 3-methylenephthalide when heated with acetyl chloride.

***o*-Acetobenzoic Acid.**—A finely ground mixture of 52.7 g. (0.36 mole) of phthalic anhydride and 44.0 g. (0.42 mole) of malonic acid (dried in an oven at 100° for two hours) was heated on a steam-bath for three hours with 35 ml. of Mallinckrodt reagent grade pyridine. Carbon dioxide was evolved during the entire heating period. The clear yellow solution was diluted with 300 ml. of water which caused a colorless solid, m. p. 124–126°, to separate. This was filtered and dried. The 10 g. of material thus obtained was identified as unreacted phthalic anhydride by a mixed melting point. When the filtrate was treated with 17 ml. of concentrated hydrochloric acid (pH of solution resulting was 3.9) and allowed to stand for three days at room temperature, clusters of needles formed on the sides of the flask. These were filtered off; weight 15.3 g. After one recrystallization from 100 ml. of benzene there was obtained 14.5 g. of colorless needles, m. p. 114–115°. *o*-Acetobenzoic acid is reported to melt at 115°.³

The filtrate from the acetobenzoic acid was treated with 18 ml. of concentrated hydrochloric acid. The solid which separated weighed 21.6 g. This was heated under reflux with 250 ml. of benzene and filtered hot. The benzene filtrate on cooling yielded an additional 10.5 g. of acetobenzoic acid, m. p. 114–115°. The benzene insoluble material, 11.1 g., was recrystallized from 110 ml. of boiling water, m. p. 200–201° (dec.). *o*-Phthalic acid is reported to have a m. p. of 206–208° (dec.).

Anal.⁴ Calcd. for C₈H₆O₄: C, 57.83; H, 3.62. Found: C, 57.75; H, 3.95. An additional 3.0 g. of crude acetobenzoic acid was obtained by the ether extraction of the filtrate from which the mixture of two acids had been obtained. The total yield of acetobenzoic acid was 48.5%.

o-Acetobenzoic acid forms a normal 2,4-dinitrophenyl-hydrazone, m. p. 185–186°.

Anal. Calcd. for C₁₃H₁₂O₆N₄: N, 16.28. Found: N, 15.93.

Isolation of Phthalylacetic Acid.—A mixture of 52.0 g. (0.5 mole) of malonic acid, 74.0 g. (0.5 mole) of phthalic anhydride and 50 ml. of pyridine was allowed to stand at room temperature for eleven days and was then diluted with 350 ml. of water. The solid which separated weighed 54.8 g. and was identified as phthalic anhydride. The filtrate was made acid to congo red and cooled. The solid obtained was collected, extracted with boiling benzene and filtered hot. On cooling there was obtained an additional 8.0 g. of phthalic anhydride. The benzene insoluble material was dissolved in 200 ml. of dioxane. On cooling, two types of crystals separated: (1) opaque plates and (2) large transparent clusters. These were separated mechanically. The plates, m. p. 270° (dec.), 2.0 g., were phthalylacetic acid.

Anal. Calcd. for C₁₀H₆O₄: C, 63.16; H, 3.16; neut.

(1a) Gabriel and Michael, *Ber.*, **10**, 1551 (1877).

(2) Gabriel, *ibid.*, **17**, 2521 (1884).

(3) Benneville, *J. Org. Chem.*, **6**, 462 (1941).

(4) The microanalyses were carried out by Mr. J. F. Alicino of this Institute.

equiv., 190. Found: C, 63.21; H, 3.31; neut. equiv., 188.

The large clusters, m. p. 197° (dec.), 7.0 g., were *o*-phthalic acid.

3-Methylenephthalide.—*o*-Acetobenzoic acid, 3.28 g. (0.02 mole), and 5.0 ml. of acetyl chloride were refluxed gently for one and one-half hours. An external bath temperature of 50° was maintained while the excess acetyl chloride was removed under reduced pressure. The oily residue was treated with 10 ml. of water and enough 10% aqueous ammonia to make the mixture alkaline to litmus. At this point the oil had partially solidified. The mixture was extracted with ether and the ether extracts dried over anhydrous sodium sulfate. The ether was distilled *in vacuo* leaving a semi-solid residue, 2.2 g. This was dissolved in 4.0 ml. of acetone, centrifuged and the clear

acetone solution decanted. When diluted with 10 ml. of water an oil separated and soon solidified, 1.5 g., m. p. 50–55°. It was sublimed at 1–2 mm. with a bath at 45–50° and 0.65 g., m. p. 57°, of product was obtained. Gabriel² reported a m. p. of 58–60°. The sublimed material could be crystallized from hexane.

Anal. Calcd. for C₉H₈O₂: C, 73.97; H, 4.11. Found: C, 73.38; H, 4.21.

The aqueous ammoniacal solution was evaporated to dryness. From the residue there was obtained 0.5 g. of *o*-acetobenzoic acid.

The yield of 3-methylenephthalide was 26.2%.

THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH
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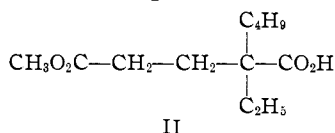
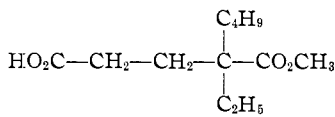
COMMUNICATIONS TO THE EDITOR

REARRANGEMENT IN PREPARATION OF ESTER ACID CHLORIDES

Sir:

In conversion of the half ester of a dibasic acid to the ester acid chloride, it has been assumed that the chlorine becomes attached to the carbon originally present as carboxyl. Thus, Bardhan¹ prepared acid chlorides from the two half esters of trimethylsuccinic acid, and treated each with methylzinc iodide. In each case there was obtained a "similar" mixture of ethyl α,α,β -trimethyllevulinate and ethyl α,β,β -trimethyllevulinate. This was ascribed to the half esters used as starting materials being a similar mixture of isomers, in spite of convincing evidence² that half esters so obtained are largely a single isomer.

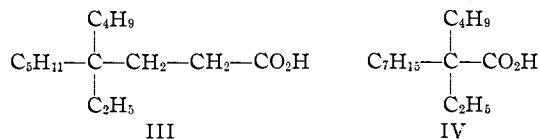
We have obtained the isomeric half esters, I and II, of α -butyl- α -ethylglutaric acid.³ Here the



hindrance around one carboxyl is so great that the essential homogeneity of the isomers is assured. Esterification of the acid with a large excess of methanol in presence of sulfuric acid gave a high yield of II after one hour under reflux, whereas a 10% yield of II remained after one hundred forty hours under reflux. Each isomer was converted to the acid chloride with thionyl chloride and these heated with tribromoaniline in xylene.

From each isomer was obtained a poor yield of a tribromoanilide, m. p. 127–128°, no depression on mixing the two. *Anal.* Calcd. for C₁₃H₂₄NO₃Br₃: C, 39.88; H, 4.45. Found: C, 39.94; H, 4.50. Thus, a mixture of ester acid chlorides must have been obtained from each isomer, and there was isolated only the tribromoanilide resulting from reaction with the unhindered acid chloride.

Further, the acid chloride from each isomeric half ester was treated with dibutylcadmium,⁴ and the resulting mixture of keto esters was reduced by the modified Wolff-Kishner procedure.⁵ There was obtained in the two cases nearly identical mixtures of acids of the expected equivalent weight and b. p. 148.5–149.5° (1.5 mm.). This mixture was separated into the acids, III (*ca.* 25%) and IV



(*ca.* 75%), by virtue of the rapid esterification of III and the very slow esterification of IV. When the esterification procedure used was repeated on the residual IV, no ester was detected. *Anal.* Calcd. for C₁₅H₃₀O₂: C, 74.32; H, 12.48; eq. wt., 242.4. Found for III: C, 74.09; H, 12.39; eq. wt., 245.7. Found for IV: C, 74.17; H, 12.01; eq. wt., 241.5; *n*^{27D} for III, 1.4533; for IV, 1.4472. *p*-Bromoanilide of III, m. p. 88.5–89.0°; of IV, m. p. 121.5–122°. *Anal.* Calcd. for C₂₁H₃₄NOBr: C, 63.62; H, 8.65. Found for deriv. of III: C, 64.11; H, 8.42. Found for deriv. of IV: C, 63.51; H, 8.72.

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(1) Bardhan, *J. Chem. Soc.*, 2604 (1928).

(2) Bone, Sudborough and Sprankling, *ibid.*, **85**, 534 (1904).

(3) Bruson and Riener, *THIS JOURNAL*, **66**, 56 (1944).

(4) Cason, *ibid.*, **68**, 2078 (1946).

(5) Huang-Minlon, *ibid.*, **68**, 2487 (1946).