

product, 0.71 g. of yellow needle-like crystals, m. p. 193–194°, was collected on a filter. The product was purified by several successive crystallizations from carbon tetrachloride and ethanol to a constant melting point, 198–199°. Melting points reported previously are 200°⁵ and 193°.²

p,p'-Dichlorotoluene.—A mixture of 2.0 g. of hexachlorobiphenyl (II) and 2.0 g. of zinc dust was refluxed for forty-eight hours in 200 ml. of anhydrous ethanol. The mixture was filtered hot to remove unused zinc and the filtrate cooled to room temperature. The platelets, 0.5 g., which precipitated, melted at 178–179°. The melting point previously reported² is 175–176°.

Synthesis of *p,p',α,α,α',α'*-Hexachlorobiphenyl from *α,α,α,β*-Tetrachlorotoluene.—This reaction was carried out according to the directions of Kenner and Witham² using 12 g. of *α,α,α,β*-tetrachlorotoluene (b. p. 152–155° (70 mm.)) and 8.3 g. of copper powder which was reduced⁶ by alcohol vapor in a heated tube. The product, 3.2 g., melted at 193–194° and gave no depression in melting point when mixed with the hexachlorobiphenyl from the rearrangement.

(5) Montagne, *Rec. trav. chim.*, [ii] **21**, 19 (1902).

(6) Eiloart, *THIS JOURNAL*, **12**, 239 (1890).

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Dehydrogenation of 1,5-Pentanediol

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Recently reported preparation of γ -butyrolactone² and γ -valerolactone³ by catalytic dehydrogenation of 1,4-butanediol and 1,4-pentanediol, respectively, suggested that δ -valerolactone might be prepared in a similar manner from the now readily available 1,5-pentanediol.⁴

Dehydrogenation was found to proceed smoothly on heating 1,5-pentanediol with a copper chromite⁵ catalyst, δ -valerolactone being obtained in 78% crude yield. It was found advantageous to stop the reaction after about 85% of the theoretical amount of hydrogen had been evolved. Attempts to carry the dehydrogenation to completion resulted in the formation of 30–35% of polymeric products.

Vacuum distillation of the dehydrogenation reaction mixture yielded a product which analyzed about 90% δ -valerolactone and 10% 1,5-pentanediol. Refractionation improved the purity up to 97–98%. Complete removal of contaminating diol was effected by adding a slight excess of phenyl isocyanate to the mixture, decomposing the excess with water and distilling the pure lactone from the residue of the bis-phenylurethan and diphenylurea. A 71% yield of pure δ -valerolactone was obtained by this procedure. This com-

(1) Formerly Chemist, Industrial Chemical Section, Agricultural Residues Division.

(2) (a) J. W. Reppe, *Chem. Industries*, **57**, 458 (1945). Condensation of translated report on advances in acetylene chemistry by Dr. J. W. Reppe, ORR Report No. G-1, Rubber Reserve Co. (July 25, 1945); (b) I. G. Callomon and G. M. Kline, *Modern Plastics*, **23**, No. 6, 174 (1946); (c) Krizikalla, OPB Report No. 11431, U. S. Department of Commerce (February 19, 1943).

(3) L. P. Kyrides and F. B. Zienty, *THIS JOURNAL*, **68**, 1385 (1946).

(4) L. E. Schiepp and H. H. Geller, *ibid.*, **68**, 1646 (1946).

(5) "Organic Syntheses," Coll. Vol. II, p. 142.

pared favorably with the method involving the hydrolysis of δ -chlorovaleronitrile.⁶

Dehydrogenation of 1,5-Pentanediol.—1,5-Pentanediol, 52 g. (0.50 mole), was thoroughly mixed with 1.5 g. of copper chromite and the mixture was heated under reflux. The top of the reflux condenser was connected to a gas-washing bottle, containing water, which was in turn connected to a wet-test meter. Vigorous evolution of hydrogen began when the temperature of the reaction mixture reached 210° and continued for about thirty minutes. At the end of this time the temperature had risen to 245° and gas evolution slowed down considerably. Meter readings showed that 21 liters of gas had been evolved. Heating was stopped and the reaction mixture subjected to vacuum distillation. The distillate, 43.2 g., was analyzed by saponification with 0.4 *N* sodium hydroxide and found to consist of 90.6% δ -valerolactone. Treatment of another sample with phenyl isocyanate yielded a precipitate of the bis-phenylurethan of 1,5-pentanediol. The weight of urethan obtained was roughly equivalent to 9.4% of diol in the original sample. Refractionation of this crude product gave a distillate analyzing 97–98% pure as the lactone. The yield of crude lactone based on the analysis of the original distillate was 78.3% of the theoretical.

Purification of δ -Valerolactone.—A sample of the crude distillate from the dehydrogenation was treated with a 10% excess of phenyl isocyanate over that calculated as necessary to react with the 1,5-pentanediol in the sample. This mixture was shaken and allowed to stand for thirty minutes after which sufficient water to react with the excess phenyl isocyanate was added. The resulting mixture was distilled under reduced pressure. The distillate analyzed as 100% δ -valerolactone by saponification and the yield calculated back to the original 1,5-pentanediol was 71.2% of the theoretical. The pure lactone had the following properties: b. p. 105° (8 mm.) (227° (750 mm.)), n_{D}^{25} 1.4553, d_4^{25} , 1.104.

The structure of the lactone was established by converting a sample to δ -iodovaleric acid, m. p. 56–57°. Mixed melting point with an authentic sample showed no depression.

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PEORIA 5, ILLINOIS RECEIVED FEBRUARY 24, 1947

(6) H. Kroper and Bretschneider, OPB Report No. 645, U. S. Department of Commerce (April 25, 1942).

(7) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

Estrogenic Action and Isomorphism

BY HERBERT E. UNGNADE AND FRANCIS V. MORRIS

The extraordinary agreement in the molecular dimensions of stilbestrol and estrone¹ and the dihydrostilbestrol isomers and estrone² as determined from crystallographic data has prompted a study of the melting behavior of mixtures of natural and synthetic estrogens.

The results prove that mixed crystals are formed between α -estradiol and the synthetic estrogens stilbestrol (Fig. 1) and *meso*-dihydrostilbestrol (Fig. 2) and hence the isomorphism of these substances, but it is uncertain whether the solid solutions are continuous or not at the melting temperatures. The same uncertainty holds for the system of mixed crystals between stilbestrol and *dl*-dihydrostilbestrol (Fig. 3), whereas the dia-

(1) Giacomello and Bianchi, *Gazz. chim. ital.*, **71**, 667 (1944).

(2) Carlisle and Crowfoot, *J. Chem. Soc.*, 5 (1941).

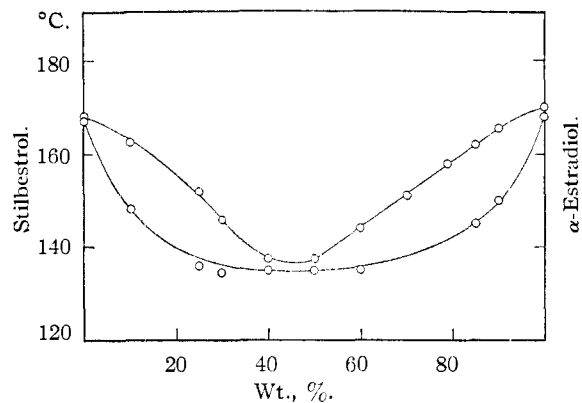


Fig. 1.

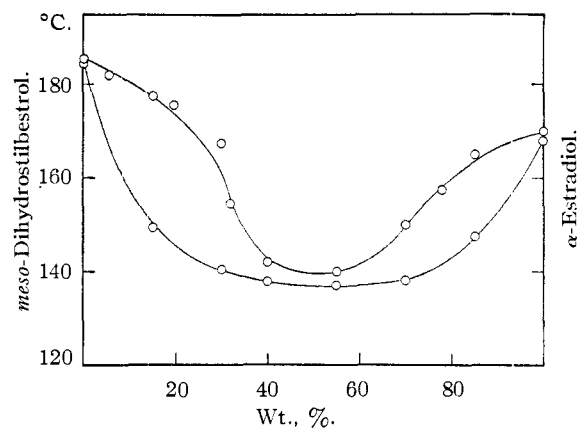


Fig. 2.

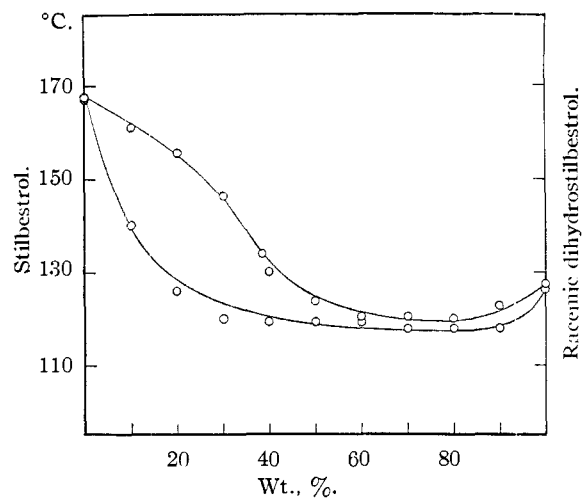


Fig. 3.

gram for the system stilbestrol-*meso*-dihydrostilbestrol (Fig. 4) is fairly conclusive as an indication of complete miscibility of the solids.

The observed formation of mixed crystals between stilbestrol and its dihydro compounds further substantiates the *trans*-configuration of the stilbestrol isomer melting at 171° ³ since *cis*-stil-

(3) Solmssen, *Chem. Rev.*, **37**, 504 (1945).

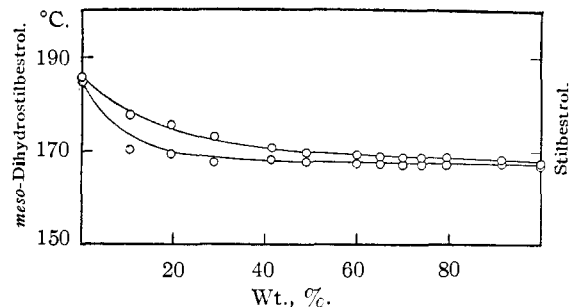


Fig. 4.

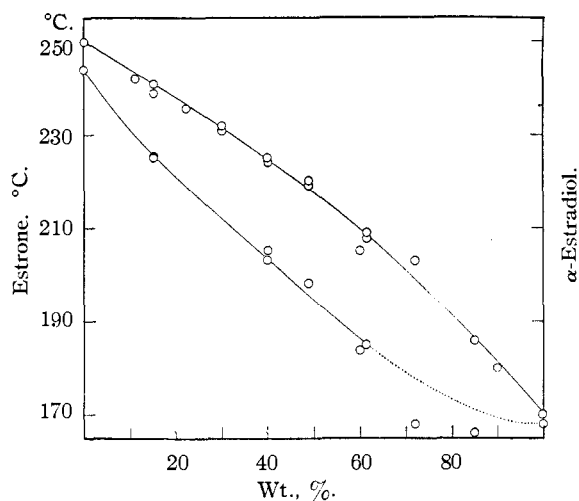


Fig. 5.

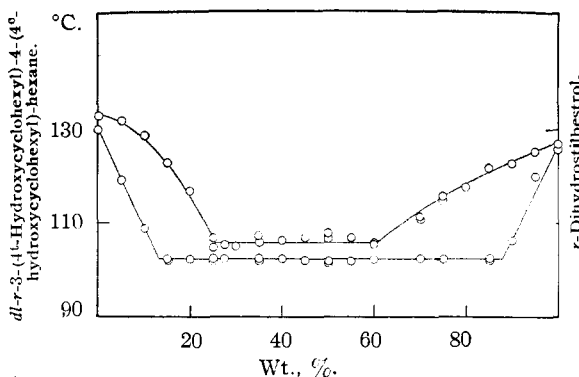


Fig. 6.

benes do not form solid solutions with the corresponding dihydro compounds.⁴

The natural estrogens estrone and α -estradiol give an indication of mixed crystal formation (Fig. 5). The experimental difficulties in this case are however so great that the data are subject to considerable uncertainty.

All of the compounds described above form mixed crystals and are biologically active as estrogens. The perhydrostilbestrol compounds⁵ which presumably have similar dimensions⁶ are biologi-

(4) Neuhaus, *Die Chemie*, **57**, 34 (1944).

(5) Ungnade and Ludutsky, *J. Org. Chem.*, **10**, 307 (1945).

(6) Schueler, *Science*, **103**, 221 (1946).

cally inactive.⁷ An investigation of one of these, *dl-r-3*(4^h-hydroxycyclohexyl)-4-(4^h-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^h-hydroxycyclohexyl)-4-(4^h-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).

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RECEIVED SEPTEMBER 9, 1946

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 C₁₅H₁₂O₆N₄: 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.