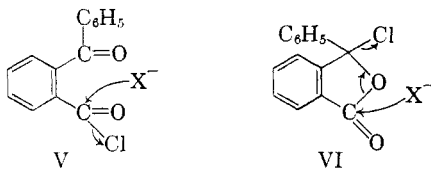



heated or kept too long, precipitates the compound unchanged.

Formation of I has no bearing on the true structure of *o*-benzoylbenzoyl chloride, as illustrated by V and VI.



Authentic ethyl 3-phenylphthalidylmalonate (II) can be obtained in good yield from ethyl *o*-benzoylbenzoate and ethyl sodiomalonate in alcohol. The properties of this substance are quite different from those of its isomer. Its infrared spectrum shows absorption at 1720 and 1770 cm^{-1} , corresponding to lactone and ester carbonyl groups. It gives no ferric chloride color and it is insoluble in cold dilute sodium hydroxide. When it is heated with the latter reagent, it dissolves, and acidification then precipitates 3-phenylphthalidyl malonic acid. Heating this acid yields the known² 3-phenylphthalidylacetic acid, also obtained directly from the malonic ester by acid hydrolysis.

By analogy with the present results, it is probable that the compound obtained from ethyl benzoylbenzoate and benzyl cyanide is not $\text{C}_6\text{H}_5\text{COC}_6\text{H}_4\text{-COCHCN}$,³ but rather $\text{HOOC}_6\text{H}_4\text{C}=\text{CCN}$ or  the corresponding lactone. The reported stability to hydrolysis then is easily understandable, and the methylation product is a methyl ester.

EXPERIMENTAL

Ethyl o-benzoylbenzoylmalonate (I). Slight modification of the original preparation¹ enables one to obtain yields of 90–95%. It was not necessary to avoid heating benzoylbenzoyl chloride, and the material was freed of thionyl chloride at 100° under reduced pressure, two portions of dry benzene being added to insure complete volatilization. As I is soluble in and rapidly altered by aqueous sodium carbonate, an excess must be avoided in final washing of the crude product; furthermore, the compound is quite soluble in ether and it is well to use 2:1 ether-ligroin (30–60°) for the first crystallization. The crude product obtained in the present research melted at 80–85°; recrystallization from ethyl acetate-ligroin gave clear prisms, m.p. 86–88° (lit.,¹ 77–79°).

Anal. Calcd. for $\text{C}_{21}\text{H}_{20}\text{O}_6$: C, 68.5; H, 5.5. Found: C, 68.4; H, 5.4.

Ethyl 3-phenylphthalidylmalonate (II). A solution of 10 g. of sodium in 100 ml. of absolute alcohol was treated with 70 g. of ethyl malonate and then 100 g. of ethyl benzoylbenzoate. The mixture was boiled for 1.5 hr. and then distilled to a sirup under reduced pressure. Addition of 400 ml. of

water gave a cloudy solution from which ether extraction (2×100 ml.) removed 9.1 g. of ethyl malonate and 20 g. of ethyl benzoylbenzoate. The product was precipitated by acidification as an oil which soon solidified; recrystallization from alcohol and then from ethyl acetate-ligroin gave 95 g. of colorless needles m.p. 100–102°.

Anal. Calcd. for $\text{C}_{21}\text{H}_{20}\text{O}_6$: C, 68.5; H, 5.5. Found: C, 68.5; H, 5.6.

When II was boiled with 10% sodium carbonate for about 5 min., it gave a colorless solution. Acidification gave an oil which solidified when it was dried and rubbed with ether. Crystallization from ethyl acetate-ligroin gave an *acid-ester*, colorless needles, m.p. 97–98° that frothed at about 145°.

Anal. Calcd. for $\text{C}_{19}\text{H}_{16}\text{O}_6$: C, 67.0; H, 4.7. Found: C, 66.7; H, 4.5.

When 1 g. of II was boiled for 1 hr. with 4 ml. of acetic acid and 4 ml. of 48% hydrobromic acid, it gave 3-phenylphthalide-3-acetic acid, needles from toluene, m.p. 177–178° with previous sintering (lit.,² m.p. 179–181°); boiling the acid with methanol-sulfuric acid gave *methyl 3*-phenylphthalid-3-acetate, needles from methanol, m.p. 86–87°; b.p. 230–232° at 10 mm.

Anal. Calcd. for $\text{C}_{17}\text{H}_{14}\text{O}_4$: C, 72.3; H, 5.0. Found: C, 72.0; H, 5.0.

When 6.7 g. of II was boiled 15 min. with 4 g. of sodium hydroxide in 25 ml. of water and the resulting solution was then cooled and acidified, there was obtained 5.3 g. crude *3*-phenylphthalidylmalonic acid, a white powder nearly insoluble in hot acetic acid, ethyl acetate, benzene, or chloroform. Acetone dissolved it easily, however, and crystallization from acetone-ligroin gave 4.1 g. of colorless needles, m.p. 160–164° with gas evolution; the melt resolidified and then melted again at 176–178°.

Anal. Calcd. for $\text{C}_{17}\text{H}_{12}\text{O}_6$: C, 65.4; H, 3.9. Found: C, 65.2; H, 3.9.

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Condensation Reactions of Phthalaldehydic Acid. I

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On the basis of certain reactions of phthalaldehydic acid several early investigators^{1,2} postulated a tautomeric closed-ring form for this compound. This view is substantiated in a recent paper by Wheeler, Young, and Erley,³ who have examined the infrared absorption of phthalaldehydic acid. These investigators also give data for a considerable number of substituted phthalides prepared by syntheses involving the very reactive 3-position in the 3-hydroxyphthalide form. However, in none of the phthalides which they describe is the carbon atom at the 3-position linked directly to carbon in the substituent.

The solubility and stability of phthalaldehydic

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acid in concentrated sulfuric acid, and even in mixtures of concentrated sulfuric acid and 20% fuming sulfuric, suggested that condensations might be carried out between phthalaldehydic acid and aromatic hydrocarbons, aryl halides, etc., not unlike the condensation occurring in the production of DDT. A search of the literature revealed that this approach to the synthesis of 3-substituted phthalides from phthalaldehydic acid has been examined only in condensations using certain phenols and phenolic ethers.^{2,4,5}

The experiments reported here show that sulfuric acid, which on occasion is bolstered with 20% fuming sulfuric acid, can be employed successfully as the medium for condensing phthalaldehydic acid with a number of aromatic hydrocarbons and aryl halides. Two of the phthalides synthesized and described, namely 3-(2,5-dichlorophenyl)phthalide and 3-(2,5-dibromophenyl)phthalide, are apparently unreported in the literature; the others have been prepared by more circuitous methods. Thus the preferred preparation for 3-phenylphthalide, possibly the most important of the phthalides described in this paper, has been the method of Ullman^{6,7} which involves the reduction of *o*-benzoylbenzoic acid. 3-Phenylphthalide has also been synthesized by the reaction of phthalaldehydic acid with phenylmagnesium bromide.⁸

The present study is being extended to determine the possibility of similar condensations of phthalaldehydic acid with other aromatics.

EXPERIMENTAL

The phthalaldehydic acid used in these experiments was purified by a single recrystallization from water. This afforded a white crystalline solid, m.p. 99–100°. The fuming sulfuric acid was Merck 20–23%, reagent grade.

3-Phenylphthalide. Five grams (0.033 mole) of phthalaldehydic acid was dissolved in 30 ml. of conc. sulfuric acid, 95–98%. To this solution was added 2.6 g. (0.033 mole) of benzene, and the mixture mechanically stirred at room temperature to disperse the benzene. After about 0.5 hr. the benzene disappeared, giving a homogeneous solution. Stirring was then continued for 0.5 hr.

The reaction mixture, light amber in color, was slowly poured with stirring into about ten times its volume of cold water. The product separated as a thick gum and quickly hardened to a granular solid. After standing until cool the solid was removed, crushed, and thoroughly washed with cold water. The crude product, m.p. 112–114°, weighed 6.9 g. (98%) and was nearly white in color. A single crystallization from ethanol gave 6.0 g. (86%) of white crystals, m.p. 116–117°; lit.,⁷ m.p. 115–116°.

Anal. Calcd. for C₁₄H₁₀O₂: C, 79.98; H, 4.79. Found: C, 80.12; H, 4.94.

To verify the product as 3-phenylphthalide 0.5 g. was oxidized with alkaline permanganate solution according to

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accepted procedure.⁹ This gave 0.45 g. of anhydrous *o*-benzoylbenzoic acid, m.p. 127°; lit.,¹⁰ m.p. 127°.

3-Tolylphthalide. Three grams (0.02 mole) of phthalaldehydic acid was dissolved in 30 ml. of 5:1 conc. sulfuric acid–water. To this was added 1.84 g. (0.02 mole) of toluene, and the mixture was mechanically stirred to disperse the insoluble toluene. After approximately 2 hr. the toluene disappeared, giving a clear green solution. This was permitted to stand for 1 hr., then poured into a large volume of cold water. The product separated as a yellow gum, soon hardening to a crumbly solid. When cold the solid was removed, pulverized, and washed with cold water. After air-drying the crude product, ivory in color, weighed 4.5 g. (100%). Crystallization from ethanol yielded 3.8 g. (85%) of a white powdery solid which showed no sharp melting point, but softened at 85° and became a clear liquid at ca. 115°. This behavior is not unexpected, as the synthesis permits formation of a mixture of the 3-tolylphthalides, particularly the *o*- and *p*-isomers. Reported melting points¹¹ for the isomers are as follows: 3-(*p*-tolyl)-phthalide, 130°; *o*-, 111°; *m*-, 86.6°.

Anal. Calcd. for C₁₅H₁₂O₂: C, 80.35; H, 5.39. Found: C, 79.86; H, 5.47.

3-(*p*-Xylyl)-phthalide. Three grams (0.02 mole) of phthalaldehydic acid was dissolved in 20 ml. of 9:1 conc. sulfuric acid–water. To this solution at room temperature was added 2.12 g. (0.02 mole) of *p*-xylene and the mixture was stirred to disperse the insoluble hydrocarbon. After about 30 min. the mixture became orange in color and homogeneous. The reaction product was then isolated in the same manner as described previously for 3-phenylphthalide. After air drying the crude product, ivory in color, weighed 4.5 g. (94%) and melted at 104–111°. Crystallization from ethanol yielded a white powder-like solid, m.p. 111–112°; lit.,¹² m.p. 112°.

Anal. Calcd. for C₁₆H₁₄O₂: C, 80.65; H, 5.92. Found: C, 80.84; H, 5.68.

To verify the product as 3-(*p*-xylyl)phthalide 0.5 g. was subjected to alkaline permanganate oxidation.⁹ This gave 0.48 g. of 2-(*o*-carboxybenzoyl)terephthalic acid (commonly called benzophenone-2,2',5'-tricarboxylic acid) m.p. 282° dec. Neut. equiv. Calcd.: 105; found: 108.

3-(Chlorophenyl)phthalide. Five grams (0.033 mole) of phthalaldehydic acid was dissolved in 30 ml. of 2:1 conc. sulfuric acid–20% fuming sulfuric acid. To this was added 3.75 g. (0.033 mole) of chlorobenzene, and the mixture was stirred to disperse the insoluble halide. As a slight temperature rise occurs, the reaction vessel was kept in a water bath at room temperature during the initial stages of the reaction. After some 45 min. the dispersed phase disappeared, leaving a homogeneous solution. The reaction product was then separated and dried as previously described for 3-phenylphthalide. The crude material weighed 8.2 g. (100%) and was nearly white in color. Crystallization from ethanol gave a white, microcrystalline solid. The purified product failed to melt sharply, softening at 85° and becoming completely liquid at 95°. This is to be expected, as the reaction for preparation permits formation of isomeric 3-(chlorophenyl)phthalides, the *o*- and *p*- in particular. Successive recrystallizations of first crops of crystals from ethanol gave a gradual rise of softening temperature. The melting point of 3-(*p*-chlorophenyl)phthalide reported¹³ is 124°. The product melting at 85–95° was used for the analysis.

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Anal. Calcd. for $C_{14}H_9O_2Cl$: C, 68.72; H, 3.71; Cl, 14.49. Found: C, 68.74; H, 3.90; Cl, 14.67.

3-(Bromophenyl)phthalide. Five grams (0.033 mole) of phthalaldehydic acid was dissolved in 30 ml. of 2:1 conc. sulfuric acid-20% fuming sulfuric acid. To this was added 5.23 g. (0.033 mole) of bromobenzene. Following essentially the same procedure outlined for the preparation of 3-(chlorophenyl)phthalide there was obtained 9.25 g. (96%) of crude product. Crystallization from ethanol yielded a white crystalline solid which did not show a sharp melting point but softened at 92° and finally became completely liquid ca. 105°, indicating a mixture of isomers. The reported¹⁴ melting point for 3-(*p*-bromophenyl)phthalide is 139–140°.

Anal. Calcd. for $C_{14}H_9O_2Br$: C, 58.16; H, 3.14; Br, 27.64. Found: C, 58.32; H, 3.07; Br, 27.47.

3-(2,5-Dichlorophenyl)phthalide. Five grams (0.033 mole) of phthalaldehydic acid was dissolved in 36 ml. of 1:1 concentrated sulfuric acid-20% fuming sulfuric acid. To this was added 4.9 g. (0.033 mole) of *p*-dichlorobenzene. In order to keep the insoluble *p*-dichlorobenzene in melted condition the reaction vessel was placed in a water bath maintained at 65–70°. The mixture was mechanically stirred, and after about 2 hr. the dispersed *p*-dichlorobenzene disappeared, yielding a homogeneous reddish-brown solution. The mixture was allowed to stand in the hot water bath for an additional hour, then cooled and poured slowly with stirring into about ten times its volume of cold water. The product separated as a gum which gradually hardened. When cold the solid was removed and the lumps crushed and washed several times with cold water. The crude product, light tan in color, weighed 8.4 g. (90%) and melted at 128–130°. Recrystallization from ethanol, with added Norit, gave colorless needles, m.p. 130–131°.

Anal. Calcd. for $C_{14}H_8O_2Cl_2$: C, 60.24; H, 2.89; Cl, 25.41. Found: C, 59.90; H, 2.80; Cl, 25.54.

3-(2,5-Dibromophenyl)phthalide. Five grams (0.033 mole) phthalaldehydic acid was dissolved in 45 ml. of 2:1 conc. sulfuric acid-20% fuming sulfuric acid. To this solution was added 7.86 g. (0.033 mole) of *p*-dibromobenzene, and the reaction vessel was then placed in an oil-bath at a bath temperature of 90–95° in order to maintain the insoluble *p*-dibromobenzene in a melted state for better dispersion. Following essentially the same procedure used in the preparation of 3-(2,5-dichlorophenyl)phthalide, there was obtained 12.2 g. (99%) of crude product, light ivory in color, m.p. 121–124°. Crystallization from ethanol, with added Norit, afforded colorless crystals, m.p. 124–125°.

Anal. Calcd. for $C_{14}H_8O_2Br_2$: C, 45.69; H, 2.19; Br, 43.43. Found: C, 45.49; H, 2.37; Br, 43.59.

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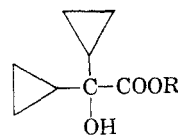
Dicyclopropylglycolic Acid

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The interesting physiological activity of certain basic esters of benzilic acid is well known.¹ The

availability of dicyclopropyl ketone through the convenient procedure of Hart and Curtis² has now made possible the preparation of the analog of benzilic acid, dicyclopropylglycolic acid (I).



- I. R = H
II. R = CH₃
III. R = -CH₂CH₂N(C₂H₅)₂HCl

Although Hart and Curtis showed that dicyclopropyl ketone reacts with the usual carbonyl reagents, we have been unable to prepare its cyanohydrin. Nor does it appear to form a chloroform addition product³ from which the hydroxyacid could be derived. In these respects dicyclopropyl ketone resembles benzophenone.

The desired acid I was finally secured through permanganate oxidation of 1,1-dicyclopropyl-2-propyn-1-ol, derived from dicyclopropyl ketone by addition of sodium acetylide.⁴ The yield of the oxidation step was only fair (40–45%).

Direct acid-catalyzed esterification of I could not be accomplished. Use of an ion exchange resin as the acid catalyst was no better. Likewise the action of either methyl iodide or dimethyl sulfate on the sodium salt of I produced no ester. Finally, however, II was obtained in 71% yield using diazomethane. The basic ester III was formed by treating the acid I with diethylaminoethyl chloride in isopropanol according to the method of Horenstein and Pählicke.⁵

EXPERIMENTAL

Dicyclopropylglycolic acid (I). To a stirred suspension of 40.8 g. (0.3 mole) of 1,1-dicyclopropyl-2-propyn-1-ol in 800 ml. of water held at 3–5° by means of an ice bath was added dropwise, over a period of 2.5 hr., a solution of 118.5 g. (0.75 mole) of potassium permanganate in 850 ml. of water. After stirring in the ice bath for another 1.5 hr., a large quantity of a filter aid (filtercel) was added and stirring was continued overnight in a refrigerated room.

The manganese dioxide and filter aid were collected at the filter and washed well with water. The combined filtrate and washings were decolorized with charcoal and extracted with ether from which, after drying and removal of ether by distillation, 6.0 g. (15%) of the acetylenic carbinol was recovered.

The ice-cold alkaline solution was acidified by the dropwise addition of cold concentrated sulfuric acid, and then extracted with five 200-ml. portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate. Filtration and removal of the ether by distillation gave

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