[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

REARRANGEMENT OF DIETHYL 3-PHENYLPHTHALIDYL-3-MALONATE TO DERIVATIVES OF 3-PHENYLINDONE-2-CARBOXYLIC ACID

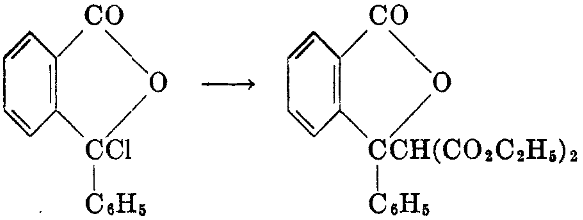
WILLIAM L. YOST[1] AND ALFRED BURGER

Received May 3, 1950

In contrast to the phthalein indicators in which the lactone ring is extremely sensitive to dilute alkali, 3,3-diphenylphthalide is remarkably stable to both acids and bases (1), and to amines, ammonia, and hydrazine (2). Certain 3,3-dialkylphthalides (3) possess nearly as great a stability.

It was desired to prepare a number of 3-alkyl-3-arylphthalides and to investigate the effect of various functional groups in the aliphatic side chain on the stability of the furanone ring. Of the 3-alkyl-3-arylphthalides, only 3-methyl-3-(α-naphthyl)phthalide (4) and 3-methyl-3-phenylphthalide (5) have previously been described.

Diethyl 3-phenylphthalidyl-3-malonate (I) was prepared by treatment of the pseudo chloride of *o*-benzoylbenzoic acid with diethyl ethoxymagnesium malonate in ethanol-ether solution. The structure of this pseudo chloride has been the subject of much consideration (6, 7) and the results of the present work support the earlier assignment of structures. The condensation with diethyl malonate was adapted from the method given by Hauser (8) for the preparation of substituted acetophenones.



I

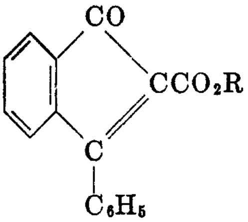
The colorless diethyl 3-phenylphthalidyl-3-malonate is accompanied in the preparation by a nearly equal amount of a deep yellow substance which has been shown to be ethyl 3-phenylindone-2-carboxylate (II). This compound is also formed with remarkable ease when the colorless phthalide derivative is warmed gently with dilute sodium carbonate solution. The rearrangement evidently takes place in acids as well, since acid hydrolysis of I produces the brilliant red 3-phenylindone-2-carboxylic acid (III).

The structure of the ester (II) was established by hydrogenation of the double bond and hydrolysis and decarboxylation to the known 3-phenyl-1-indanone (9). When hydrogenated, the red acid spontaneously decarboxylated to yield the same ketone. The latter was synthesized for comparison by cyclization of

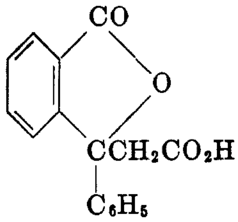
---

[1] Du Pont Research Fellow, 1947–1949.

β,β-diphenylpropionic acid, and its semicarbazone (10) was found to be identical with those of our two degradation products.



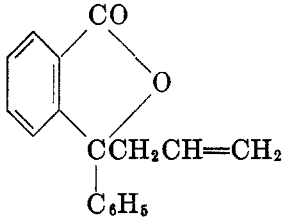
II. R = C_2H_5
III. R = H



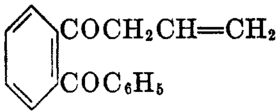
IV

When hydrolyzed with alcoholic potassium hydroxide, diethyl 3-phenylphthalidyl-3-malonate was extensively decomposed, but a very small amount of 3-phenylphthalidyl-3-acetic acid (IV) could be isolated. In order to establish with more certainty the cyclic nature of this latter compound, it was prepared independently by oxidation of 3-allyl-3-phenylphthalide (V), and the acids from the two sources were shown to be identical. Very recently, a synthesis of 3-phenylphthalidyl-3-acetic acid by another route has appeared in the literature (11).

That the previously unknown 3-allyl-3-phenylphthalide had the cyclic (V) rather than the tautomeric open structure (VI) was determined by comparing its ultraviolet absorption spectrum with those of 3-methyl-3-phenylphthalide and of phthalide itself (12).



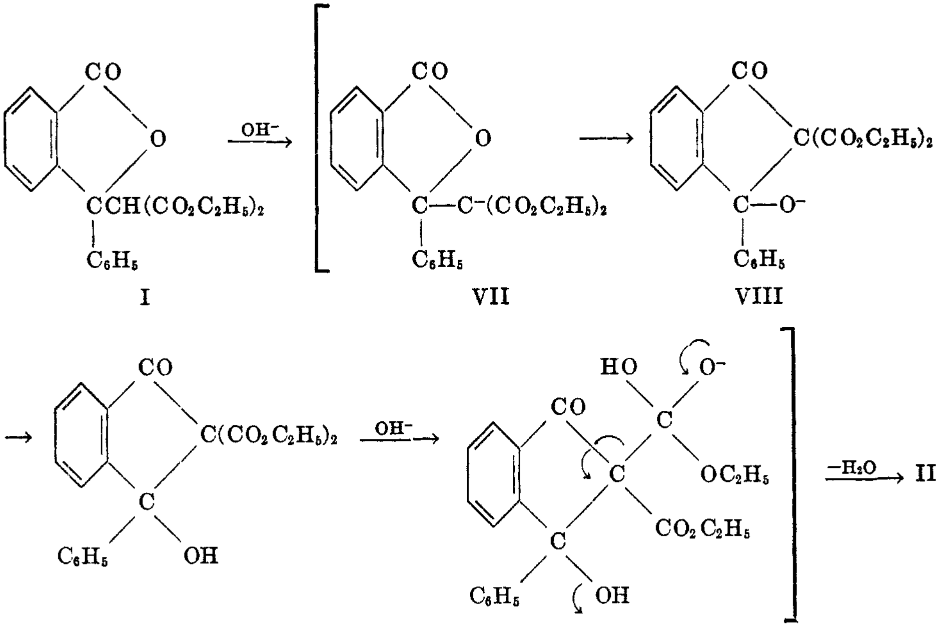
V



VI

In the light of the extraordinary inertness of 3,3-dialkylphthalides to bases, the solubility of diethyl 3-phenylphthalidyl-3-malonate in sodium carbonate solution indicates an initial attack of the base on the remaining active hydrogen atom of the malonic ester grouping. This observation is supported by the fact that 3-phenylphthalidyl-3-acetic acid, with less active *alpha* hydrogens, is quite stable to strong bases. If the carbanion VII is first formed, it might be expected to undergo an internal Claisen condensation. Attack by hydroxide ions on the ester carbonyl of the corresponding molecule IX would lead to X which must lose water in a process simulating the base-induced dehydration of an aldol.

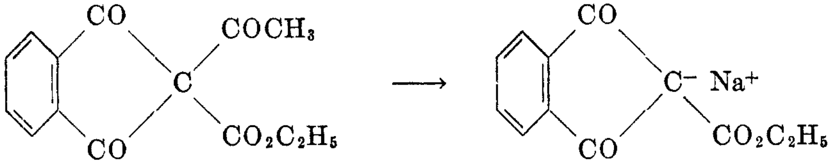
Once the ester II has been precipitated by acidification, it cannot be redissolved in base. This observation could be explained on the basis of its inability to form a sodium salt. Such salts have been shown to exist in other cases, for



I VII VIII

IX X

example, in XII which results from the loss of the acetyl group from 2-acetyl-2-carbethoxy-1,3-indandione (XI) in the presence of base (13).



XI XII

We wish to acknowledge valuable suggestions from Drs. T. A. Geissman of the University of California, and J. W. Wilson of Smith, Kline, and French Laboratories for the preparation of 3-allyl-3-phenylphthalide.

EXPERIMENTAL

Diethyl 3-phenylphthalidyl-3-malonate (I). The pseudo chloride of *o*-benzoylbenzoic acid was prepared by treating 45.2 g. (0.20 mole) of the keto acid with 95.2 g. (0.80 mole) of thionyl chloride at room temperature. The resulting solution was warmed to 50° and maintained at this temperature while a stream of carefully dried air, preheated to 50°, was passed over the surface at atmospheric pressure. After 20 hours dry air was sucked through the mixture for five hours, or until the excess thionyl chloride had apparently been removed. The amber syrupy residue was allowed to cool to room temperature. It was dissolved in 100 cc. of absolute ether and was added rapidly with good stirring to the magnesium diethyl malonate derivative prepared from 5.35 (0.22 atom) of magnesium and 35.2 g. (0.22 mole) of diethyl malonate according to the directions of Walker and Hauser (8). A pale, greenish, thick syrupy precipitate formed. Stirring and reflux were maintained for an additional hour, the reaction mixture was allowed to stand overnight cooled, and then decomposed with 130 cc. of ice-cold 37% sulfuric acid. The layers were separated, the aqueous solution was extracted with 25 cc. of ether, the ether layers were combined and washed with water, extracted with three 50-cc. portions of 10% sodium carbonate solution, and again washed with water. The oily residue from the ether was dried by distilling benzene from it to near dryness. Addition of absolute ether to this residue gave a precipitate of 17.6 g. (24%) of the colorless diethyl 3-phenylphthalidyl-3-malonate, which melted, after three recrystallizations from absolute ether, at 77–79°.

Anal. Calc'd for $C_{21}H_{20}O_6$: C, 68.47; H, 5.47.
Found: C, 68.74; H, 5.39.

Ethyl 3-phenylindone-2-carboxylate (II). (*a*) The sodium carbonate extracts and water washings from the preparation of diethyl 3-phenylphthalidyl-3-malonate were turbid and yellow. They were combined and washed with ether. Acidification caused the precipitation of a small amount of deep yellow, highly refractive crystals melting at 86–87.5°.

(*b*) The filtrate from the colorless diethyl malonate derivative was evaporated to near dryness. A dark viscous oil remained, which was distilled *in vacuo.* After removing a small amount of unreacted diethyl malonate, the distilland began to decompose. It was cooled, taken up in absolute ether, and refrigerated overnight. The solution deposited 13.0 g. (23.4%) of the same deep yellow crystals, m.p. 87–88° after recrystallization from absolute ether.

(*c*) Ten grams (0.0272 mole) of diethyl 3-phenylphthalidyl-3-malonate was dissolved in 100 cc. of 10% sodium carbonate solution by warming to about 50° for 20 minutes, during which time a yellow color developed and gradually deepened as the temperature increased. After the solution became clear, it was cooled to 15° and cautiously neutralized with 6 *N* hydrochloric acid. The ester crystallized directly at this temperature, melted at 84–87°, and weighed 6.7 g. (88.8%).

Anal. Calc'd for $C_{18}H_{14}O_3$: C, 77.68; H, 5.07.
Found: C, 77.81; H, 5.21.

3-Phenylindone-2-carboxylic acid (III). To a colorless solution of 3.68 g. (0.01 mole) of diethyl 3-phenylphthalidyl-3-malonate in 10 cc. of glacial acetic acid was added 1 cc. of water containing 5 drops of concentrated sulfuric acid. On heating, the color of the solution deepened quickly from yellow to deep vermillion. Distillation of ethyl acetate through a short column was complete after one hour. The cooled residue was diluted with 20 cc. of water, and the red oil which separated was dissolved in benzene, washed with water, and extracted into three 10-cc. portions of 10% sodium carbonate solution. Acidification of these extracts with 6 *N* hydrochloric acid caused the quantitative precipitation of the acid as brilliant red felted needles, which, after repeated recrystallization from 50% ethanol-water, melted at 153.5–156°.

Anal. Calc'd for $C_{16}H_{10}O_3$: C, 76.79; H, 4.03.
Found: C, 76.98; H, 4.35.

Structure of ethyl 3-phenylindone-2-carboxylate. Ethyl 3-phenylindone-2-carboxylate (1.8 g., 0.0065 mole) was hydrogenated in 25 cc. of absolute ethanol at atmospheric pressure and 34° in the presence of Raney nickel catalyst. The crude ethyl 3-phenylindanone-2-carboxylate was isolated as nearly colorless crystals, m.p. 86–87.5°, but decomposed as attempts were made to purify it. The ester was hydrolyzed in 10 cc. of glacial acetic acid containing a trace of 50% sulfuric acid by heating to 90° for one hour. The residue was diluted with water, and the liberated oil dissolved in benzene. After washing with water, the benzene solution was extracted with sodium carbonate solution, but only a trace of alkali-soluble material was isolated. The ketone, formed by decarboxylation during the hydrolysis, could not be isolated in a pure state, but was converted directly to the semicarbazone, m.p. 217.5–219.5° (sintering at 211.5°).

Structure of 3-phenylindone-2-carboxylic acid. This acid (1.28 g., 0.0051 mole) was hydrogenated in 25 cc. of absolute ethanol at atmospheric pressure and 34° in the presence of palladium chloride. Decarboxylation of the reduction product was detected in the readings of the hydrogen buret. The resulting ketone, after liberation from the catalyst and solvent, was converted to its *semicarbazone*. After purification, the latter melted at 218.5–220.5° (after sintering at 212°). The reported melting point of 3-phenyl-1-indanone semicarbazone is 225° (10).

Anal. Calc'd for $C_{16}H_{15}N_3O$: N, 15.84. Found: N, 15.66.

A mixture of this semicarbazone with that derived from ethyl 3-phenylindone-2-carboxylate (9, 10) melted at 217.5–219.5° (intering at 211.5°). A mixture of the authentic semicarbazone with that derived from the corresponding acid melted at 216–218° (sintering at 212°).

3-Phenylphthalidyl-3-acetic acid (IV). 1. *Hydrolysis of diethyl 3-phenylphthalidyl-3-malonate.* To a solution of 2.5 g. of the diester (I) in 10 cc. of absolute ethanol was added 10 cc. of 40% aqueous potassium hydroxide solution. The mixture began to darken instantly. It was refluxed gently for one hour during which time decomposition continued. Water was added portionwise, and water and ethanol were distilled out until a total of 30 cc. of water had been added and 30 cc. of distillate had been collected. The residue was extracted with benzene to remove tarry decomposition products, and the alkaline layer was acidified with concentrated hydrochloric acid. The liberated oil was extracted into benzene and the solution dried and evaporated. Addition of a small amount of chloroform to the residue caused precipitation of a microcrystalline material which was filtered, washed quickly with cold chloroform, and dried. After recrystallization from 50% ethanol-water, the acid melted constantly at 175–177°.

2. *Oxidation of 3-allyl-3-phenylphthalide.* A mixture of 1 g. of 3-allyl-3-phenylphthalide, 1.7 g. of potassium permanganate, and 20 cc. of water was refluxed for 35 minutes and then cooled. Manganese dioxide was removed by filtration, and the filtrate was acidified carefully with concentrated hydrochloric acid. The liberated oil was extracted into benzene and treated as under 1. Colorless crystals melting at 173–175° were obtained. A mixture melting point with the material obtained by the previous method showed no depression.

Anal. Calc'd for $C_{16}H_{12}O_4$: C, 71.63; H, 4.51; Neut. equiv., 268.24.
Found: C, 71.64; H, 4.44; Neut. equiv., 267.72.

3-Allyl-3-phenylphthalide. (V). Allylmagnesium chloride was prepared by an adaptation of the method of Van Campen (14) for the preparation of substituted benzylmagnesium halides. A suspension of 24.3 g. (1.0 atom) of magnesium turnings in 500 cc. of anhydrous ether was treated with a solution of 38.5 g. (0.5 mole) of allyl chloride in 450 cc. of anhydrous ether at the rate of about 2 cc. per minute. After addition of the allyl chloride was complete (3.5 hours), the mixture was stirred and refluxed for an additional 15 minutes, and then the yield was estimated by titration to be about 85%.

On the basis of this result, an amount of *o*-benzoylbenzoic acid was added so that the ratio of Grignard reagent to keto acid was approximately 3:1. A solution of 33.9 g. (0.15 mole) of *o*-benzoylbenzoic acid in 280 cc. of anhydrous ether was added to the suspension of Grignard reagent during 1.25 hours, and the ether was simultaneously distilled out at the same rate. After addition was complete, 930 cc. of anhydrous benzene was added portionwise and distillation of ether continued until the liquid temperature reached 80°. The solution was then refluxed for an additional 11 hours without stirring.

Hydrolysis of the reaction complex was effected by cautious addition of 100 cc. of ice-cold water. Excess magnesium was removed by decantation and the material further hydrolyzed with 300 cc. of 9% hydrochloric acid. The benzene layer was separated, washed with water, extracted with saturated sodium bicarbonate solution until neutral, and again washed with water. Acidification of the alkali extracts liberated 8.3 g. (24.4%) of starting acid.

The benzene layer was dried and evaporated at atmospheric pressure and the oily residue was distilled *in vacuo*. A first fraction boiled at 180–186° (1.0 mm.) and weighed 21.4 g. (57.1%), n_D^{25} 1.5797. A second fraction was very high-boiling, dark and viscous, and was discarded with the residue. A second fractionation through a short column gave a pale amber distillate boiling at 168–169.5° (0.4 mm.), n_D^{25} 1.5808, and this oil was finally obtained as a nearly colorless material, boiling at 153–154° (0.2 mm.), n_D^{25} 1.5848. It could also be purified by passing a solution in petroleum ether through a column packed with alumina.

Anal. Calc'd for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64.

Found: C, 81.03; H, 5.87.

SUMMARY

o-Benzoylbenzoic acid pseudo chloride condenses with diethyl ethoxymagnesium malonate to diethyl 3-phenylphthalidyl-3-malonate. This ester can either be hydrolyzed and decarboxylated to 3-phenylphthalidyl-3-acetic acid, or rearranged to ethyl 3-phenylindone-2-carboxylate. The structures of these two compounds have been established by independent methods, that of 3-phenylphthalidyl-3-acetic acid by oxidation of 3-phenyl-3-allylphthalide, and that of the indone derivative by conversion to the known 3-phenyl-1-indanone. A mechanism for the novel rearrangement reported in this work has been proposed.

CHARLOTTESVILLE, VIRGINIA

REFERENCES

(1) BAYER, *Ann.*, **202,** 50 (1880).
(2) TEPPEMA, *Rec. trav. chim.*, **42,** 30 (1923).
(3) TASMAN, *Rec. trav. chim.*, **46,** 653 (1927).
(4) NEWMAN, *J. Am. Chem. Soc.*, **59,** 1004 (1937); COOK, ROBINSON, AND GOULDEN, *J. Chem. Soc.*, 393 (1937).
(5) BERGMANN, *J. Org. Chem.*, **4,** 1 (1939); OSTERZETZER, *Monatsh.*, **34,** 795 (1913).
(6) MEYER, *Monatsh.*, **25,** 475, 1177 (1904); *Monatsh.*, **28,** 1231 (1907).
(7) AUWERS AND HEINZE, *Ber.*, **52,** 588 (1919); MARTIN, *J. Am. Chem. Soc.*, **38,** 1142 (1916).
(8) WALKER AND HAUSER, *J. Am. Chem. Soc.*, **68,** 1386 (1946).
(9) KOHLER, *Am. Chem. J.*, **31,** 649 (1904).
(10) AUWERS AND AUFFENBERG, *Ber.*, **52,** 110 (1919).
(11) JOHNSON, MCCLOSKEY, AND DUNNIGAN, *J. Am. Chem. Soc.*, **72,** 514 (1950).
(12) BUU-HOÏ AND CHE-KIN LIN, *Compt. rend.*, **209,** 221 (1939).
(13) RUGGLI AND ZICKENDRAHT, *Helv. Chim. Acta*, **28,** 1377 (1945).
(14) VAN CAMPEN, MEISNER, AND PARMERTER, *J. Am. Chem. Soc.*, **70,** 2296 (1948).