[CONTRIBUTION FROM THE CENTRAL RESEARCH LABORATORIES OF THE MONSANTO CHEMICAL COMPANY]

Vinyl Aromatic Compounds. VI. Alkylidenephthalides and Related Compounds[1]

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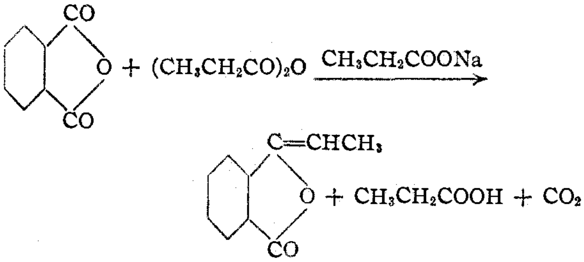
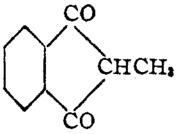
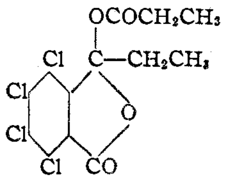
The Gabriel modification of the Perkin reaction, in which phthalic anhydride is substituted for benzaldehyde, has been reviewed briefly.[3]

We have selected the preparation of 3-ethylidenephthalide from phthalic anhydride, propionic anhydride and sodium propionate,[4,5] for study as representative of the Gabriel method of alkylidenephthalide formation. Although Gottlieb[4] reported an 88% crude yield, we have found that only 40–50% could be isolated as a pure product having a melting point of 64–65°. 2-Methyl-1,3-indandione (I), m. p. 84°, has been identified as one of the by-products and was easily separated by virtue of its solubility in cold aqueous alkali. The principal impurity, however, was an oil which could not be satisfactorily separated and purified by crystallization or distillation.





I



II

In order to elucidate the nature of this by-product, tetrachlorophthalic anhydride was condensed with a 200% excess of propionic anhydride under similar conditions to give a mixture of products from which 10% of 3-ethylidene-4,5,6,7-tetrachlorophthalide, m. p. 161°, and 14% of a neutral substance, $C_{13}H_{10}O_4Cl_4$, m. p. 107–108°, were isolated by fractional crystallization. The neutral by-product was easily saponified to 2-propionyl-3,4,5,6-tetrachlorobenzoic acid, m. p. 178–180°, which was independently prepared from 3-ethylidene-4,5,6,7-tetrachlorophthalide. Hence, the by-product is probably 3-propionoxy-3-ethyl-4,5,6,7-tetrachlorophthalide (II) which may have been formed by the addition of propionic acid to the ethylidenephthalide. The oily by-product formed in the preparation of 3-ethylidenephthalide probably has an analogous structure.

The phthalic anhydride–propionic anhydride reaction conditions have been varied with respect to catalyst, reagent ratios, and reaction times. Using 1.1 moles of propionic anhydride, 0.5 mole of sodium propionate and a reaction time of five hours at 180° there was obtained an 80% yield of crude distilled product, b. p. 154–162° (11 mm.) and a 58% yield of pure 3-ethylidenephthalide, m. p. 64–65°. The use of potassium propionate gave similar results, while sodium acetate was markedly inferior. Pyridine did not catalyze the reaction, although this catalyst recently has been reported,[6] to be satisfactory for the condensation of phthalic anhydride with malonic acid. No improvement in yield was obtained by increasing the reaction time.

On standing for several months 3-ethylidenephthalide is slowly transformed to a sticky resinous material.[7] This appears to be a low molecular weight polymer, $(C_{10}H_8O_5)_x$, of considerably higher oxygen content than the monomeric substance. It forms phthalic anhydride on destructive distillation. This transformation is caused by atmospheric oxygen since samples of ethylidenephthalide stored for six months in sealed evacuated ampoules showed no evidence of change.

By similar techniques, phthalic anhydride has been condensed with butyric anhydride and heptanoic anhydride to give propylidene- and *n*-hexylidene-phthalides. Attempts to prepare cyanomethylenephthalide from cyanoacetic acid and phthalic anhydride have been unsuccessful.[8] Thiophthalic anhydride reacted normally with propionic anhydride to give 3-ethylidenethiophthalide, but maleic and dichloromaleic anhydride gave only intractable tars. 3-Benzal-4,5,6,7-tetrachlorophthalide has been prepared from phenylacetic acid and tetrachlorophthalic anhydride in 60% yield.

We have attempted to prepare the ethyl ester of phthalideneacetic acid by direct esterification using acid catalysts. However, a hydration and decarboxylation took place with the formation of ethyl *o*-acetylbenzoate. A similar hydration and decarboxylation is reported by Yale,[6] who prepared *o*-acetylbenzoic acid directly from phthalic anhydride and malonic acid in pyridine

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[1] Preceding paper of this series: THIS JOURNAL, **70**, 1916 (1948).

[2] Present address: Department of Chemistry, The Ohio State University, Columbus, Ohio.

[3] Johnson, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, pp. 222–223.

[4] Gottlieb, *Ber.*, **32**, 958 (1899).

[5] Kohlrausch and Seka, *ibid.*, **77**, 469 (1944).

[6] Yale, THIS JOURNAL, **69**, 1547 (1947).

[7] Auwers and Auffenberg, *Ber.*, **51**, 1109 (1918).

[8] Pascual Vila and Ballester, *Anales fis. y quim.* (*Madrid*), **42**, 1097 (1946); *C. A.*, **41**, 6549 (1947), also failed to obtain a condensation product from 3,3-diethoxy-4,5,6,7-tetrachlorophthalide and cyanoacetic ester.

solution. 3-Methylenephthalide may have been the intermediate since the crude distillate on some runs formed a glassy polymer on standing. The desired esters of phthalideneacetic acid were prepared in satisfactory yields by treating phthalideneacetyl chloride with methyl, ethyl and *n*-hexyl alcohols. However, an attempted esterification of the acid chloride with phenol by the Schotten-Baumann technique was unsuccessful.

Experimental Part[9]

3-Ethylidenephthalide.—The following is a typical procedure for the preparation of ethylidenephthalide.[4,5] Phthalic anhydride (296 g., 2.0 moles) and propionic anhydride (286 g., 2.2 moles) were placed in a two-liter three-necked flask equipped with a stirrer, thermometer, reflux condenser and funnel for addition of solids. After heating to 150–160°, 96 g. (1.0 mole) of dry sodium propionate was added in four portions over a period of thirty minutes, taking care to allow the evolution of carbon dioxide to subside after each addition. After heating at slow reflux (170–180°) for five hours, the reaction was cooled somewhat and stirred vigorously with 700 cc. of hot water. The organic layer was taken up in 200 cc. of carbon tetrachloride and separated and washed with warm water. The product was then distilled to give 256 g. (80%) of crude ethylidenephthalide, b. p. 154–162° (11 mm.). Two recrystallizations from a mixture of benzene and hexane gave 130 g. of white crystals, m. p. 64–65°. An additional 55 g., m. p. 62–63° was obtained from the mother liquors, giving a total yield of 58%.

Extraction of the yellow oil remaining in the mother liquors with sodium hydroxide gave, after acidification, 12 g. (4%) of white crystals, b. p. 150° (17 mm.), m. p. 84–85°. This was 2-methyl-1,3-indandione, which Nathanson[10] prepared from sodium methylate and ethylidenephthalide.

The following table gives the crude (distilled) and pure (fraction melting above 60°) yields of ethylidenephthalide based on phthalic anhydride which were obtained under various conditions of catalyst concentration, reagent ratios, and reaction times at 170–180°.

Phthalic anhydride, moles	Propionic anhydride moles	Sodium propionate, moles	Time, hr.	Crude yield, %	Pure yield, %
1.0	1.1	0.1	5	<5	..
1.0	1.1	.5	2	71	43
1.0	1.1	.5	5	80	58
1.0	1.1	.5[a]	6	43	25
1.0	1.1	.5[b]	3	65	50
1.0	1.1	.5[c]	5	0[d]	..
1.0	1.1	1.0	5	75	50
1.0	1.1	1.0	24	78	46
1.0	1.5	0.5	3	..	45
1.2	1.0	0.5	3	62	41

[a] Sodium acetate. [b] Potassium propionate. [c] Pyridine. [d] Essentially all the phthalic anhydride was recovered unchanged.

The gummy resinous material formed by ethylidenephthalide[7] on standing in contact with air at room temperature for several months was washed with hot benzene. The insoluble portion was a white powder which melted at 196–199°, and a 2% solution in dioxane had a specific viscosity at 25° of 0.067 compared to 0.018 for unchanged ethylidenephthalide. Analysis indicated that this low polymer contained considerably more oxygen than the monomer.

Anal. Calcd. for $(C_{10}H_8O_5)_x$: C, 57.7; H, 3.8. Calcd. for $(C_{10}H_8O_4)_x$: C, 62.5; H, 4.6. Found: C, 58.5; H, 3.97.

Destructive distillation of the crude gummy material was effected under vacuum using an open flame. About fifty weight per cent. of phthalic anhydride, m. p. 129–131° after recrystallization, was obtained in the distillate.

3-Ethylidene-4,5,6,7-tetrachlorophthalide and 3-Ethyl-3-propionoxy-4,5,6,7-tetrachlorophthalide.—One mole (286 g.) of tetrachlorophthalic anhydride and 390 g. (3.0 moles) of propionic anhydride were heated with stirring to 160°. Then 60 g. (0.63 mole) of sodium propionate was added in five portions over a period of one hour. The reaction was then refluxed for five hours before distilling off the excess propionic anhydride and propionic acid under reduced pressure. The residue was washed with 500 cc. of water at reflux, dissolved in a little carbon tetrachloride and separated. The organic layer was distilled and a fraction boiling at 210–230° (5–8 mm.) was collected. This was dissolved in hot acetone and cooled to give white crystals which were recrystallized once from acetone and again from a mixture of benzene and hexane. There was obtained 29 g. (10%) of 3-ethylidene-4,5,6,7-tetrachlorophthalide, m. p. 161–162°.

Anal. Calcd. for $C_{10}H_4O_2Cl_4$: C, 40.3; H, 1.34; Cl, 46.7. Found: C, 40.5; H, 1.54; Cl, 48.2.

The filtrate from the first acetone recrystallization was diluted with water and the resultant solid collected and recrystallized several times from dilute ethanol to give 51 g. (14%) of 3-ethyl-3-propionoxy-4,5,6,7-tetrachlorophthalide, white crystals, m. p. 107–108°.

Anal. Calcd. for $C_{13}H_{10}Cl_4O_4$: C, 42.0; H, 2.70; Cl, 38.2; mol. wt., 372. Found: C, 42.26; H, 2.78; Cl, 38.33; mol. wt. (Rast), 395.

Although this material was not soluble in aqueous alkali it instantly formed a reddish yellow solution in alcoholic sodium hydroxide. After warming for fifteen minutes it was acidified and the solid was recrystallized from dilute alcohol to give yellow crystals, m. p. 178–180°, which were soluble in sodium bicarbonate. This was 2-propionyl-3,4,5,6-tetrachlorobenzoic acid and was identical with a sample prepared by the saponification of 3-ethylidene-4,5,6,7-tetrachlorophthalide.

Anal. Calcd. for $C_{10}H_6O_3Cl_4$: C, 38.0; H, 1.90. Found: C, 38.2; H, 2.09.

3-Propylidenephthalide.—Phthalic anhydride (296 g., 2.0 moles) was treated with butyric anhydride (348 g., 2.2 moles) in the presence of sodium butyrate (110 g., 1.0 mole) at 150–180° for five hours. The product was recovered as described above to give 217 g. (62%) of 3-propylidenephthalide, b. p. 142–145° (4.0 mm). Careful refractionation through a one-meter column packed with glass helices gave an analytical sample b. p. 143° (4 mm.), $n^{25}\mathrm{D}$ 1.5859, f. p. 5°. Bromberg[11] reported b. p. 169–170° (12 mm.) for a product obtained in 41% yield.

3-*n*-Hexylidenephthalide.—This compound was prepared from 1.0 mole of phthalic anhydride, 1.1 moles of heptanoic anhydride and 0.5 mole of sodium heptanoate in the same manner as described for ethylidenephthalide. There was obtained a 54% yield of 3-*n*-hexylidenephthalide, b. p. 175–176° (5 mm.), $n^{25}\mathrm{D}$ 1.5585, f. p. 5–6°.

Anal. Calcd. for $C_{14}H_{16}O_2$: C, 77.7; H, 7.41. Found: C, 77.42; H, 7.42.

3-Ethylidenethiophthalide.—Thiophthalic anhydride[12] (91 g., 0.55 mole, m. p. 108°) was treated with 170 g. (1.3 moles) of propionic anhydride and 53 g. (0.55 mole) of sodium propionate at 160° for three hours. The product was recovered in the usual fashion and boiled at 155–160° (6 mm.) with slight decomposition. The crude product was recrystallized twice from hexane to give 3-ethylidenethiophthalide, m. p. 56–57°, in 31% yield. The white crystals assumed an orange color on exposure to light.

Anal. Calcd. for $C_{10}H_8OS$: S, 18.2. Found: S, 18.43.

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[9] Analyses by Oakwold Laboratories, Alexandria, Va. All melting points corrected.

[10] Nathanson, *Ber.*, **26**, 2581 (1893).

[11] Bromberg, *Ber.*, **29**, 1436 (1896).

[12] Reissert and Holle, *Ber.*, **44**, 3029 (1911).

3-Benzal-4,5,6,7-tetrachlorophthalide.—The procedure of Weiss[13] for benzalphthalide was used. Phenylacetic acid (136 g., 1.0 mole), tetrachlorophthalic anhydride (238 g., 0.84 mole) and 3 g. of sodium acetate were heated at 230 to 260° for several hours using a short column and downward condenser to remove the water formed. The molten residue was then poured out and recrystallized from five liters of xylene. The product, 173 g. (53%) melted at 300°.

Anal. Calcd. for $C_{15}H_6O_2Cl_4$: C, 50.0; H, 1.67; Cl, 39.5. Found: C, 50.6; H, 2.26; Cl, 39.40.

Ethyl Phthalideneacetate.—Phthalideneacetic acid[14] (170 g., 0.9 mole) and 225 cc. of thionyl chloride were refluxed for four hours and the excess thionyl chloride was evaporated under water-pump vacuum. The resultant crystalline solid was broken up and treated with 300 cc. of cold absolute ethanol. After stirring for several hours the yellow solid was filtered and recrystallized from a mixture of benzene and hexane to give 90 g. (46%) of yellow crystals, m. p. 131–133°. The analytical sample after two more recrystallizations melted at 134–135°.

Anal. Calcd. for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62; sapn. no., 218. Found: C, 66.33; H, 4.62; sapn. no., 212.

Earlier attempts to esterify phthalideneacetic acid directly with an excess of ethanol using sulfuric acid as a catalyst gave a good yield of ethyl *o*-acetylbenzoate, b. p. 112–115° (2 mm.), $n^{25}D$ 1.5122.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.8; H, 6.32; sapn. no., 192. Found: C, 68.92; H, 6.55; sapn. no., 199.

Saponification of a small sample with alcoholic potassium hydroxide gave *o*-acetylbenzoic acid,[15] m. p. 115°. In one esterification run the crude distilled product having $n^{25}D$ 1.5238 was thought to contain some methylenephthalide since the material polymerized to an insoluble incompatible mass on standing at room temperature for several days.

Methyl Phthalideneacetate.—Treatment of phthalideneacetyl chloride with methanol at 5–10° in a similar fashion gave a 61% yield of the methyl ester, yellow crystals, m. p. 171–172° cor., after recrystallization from a mixture of benzene and hexane.

Anal. Calcd. for $C_{11}H_8O_4$: C, 64.7; H, 3.92. Found: C, 64.78; H, 4.12.

***n*-Hexyl Phthalideneacetate.**—Seventy grams of crude phthalideneacetyl chloride was treated with 250 cc. of *n*-hexanol at room temperature and warmed to 60° with stirring. The resultant oil was distilled twice to give 54 g. (59%) of a pale yellow oil, b. p. 208–210° (3 mm.).

Anal. Calcd. for $C_{16}H_{18}O_4$: C, 70.2; H, 6.58. Found: C, 69.92; H, 6.96.

Summary

The preparation of 3-ethylidenephthalide from phthalic anhydride and propionic anhydride in the presence of sodium acetate has been studied and 2-methyl-1,3-indanedione has been isolated as a by-product. The formation of a second by-product, 3-ethyl-3-propionoxyphthalide, is inferred since an analogous compound has been isolated from a similar reaction using tetrachlorophthalic anhydride. 3-Propylidenephthalide, 3-*n*-hexylidenephthalide, 3-ethylidenethiophthalide, 3-ethylidene- and 3-benzal-4,5,6,7-tetrachlorophthalides, and the methyl, ethyl and hexyl esters of phthalideneacetic acid have been prepared and characterized.

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[13] Weiss, "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1943, p. 61.

[14] Gabriel and Newman, *Ber.*, **26**, 951 (1893).

[15] Karslake and Huston, THIS JOURNAL, **31**, 479 (1909).

[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY, THE UNIVERSITY OF CHICAGO]

Reduction of Aldehydes, Ketones and Acid Chlorides by Sodium Borohydride

BY SAUL W. CHAIKIN AND WELDON G. BROWN

The successful use of lithium aluminum hydride as a reducing agent for organic compounds[1] has prompted the investigation of the reducing properties of other complex hydrides. The borohydrides of aluminum,[2] gallium,[3] beryllium,[4] lithium[5] and sodium[6] have been described. Of these, the sodium compound appeared to be of the greatest practical interest because it is potentially a cheaper material than lithium aluminum hydride and because a convenient preparative method is available.[6]

The reduction of various inorganic substrates by sodium trimethoxyborohydride, $NaBH(OCH_3)_3$, in aqueous solution has been studied by Sheft,[7] who also effected the reduction of carbon dioxide to formate. Previous studies on sodium borohydride, $NaBH_4$, as a reducing agent by Schlesinger, Schaeffer and collaborators[8] have been concerned with applications in the fields of inorganic and analytical chemistry, but have nevertheless served to indicate the potential value of the reagent in organic synthesis.

We find that the reduction of aldehydes and ketones by sodium borohydride follows the same pattern as with lithium aluminum hydride. The reactions occur rapidly at room temperature in most cases, although occasionally heating is required, and the corresponding alcohols are formed in comparable yields. Unsaturated aldehydes and ketones, in three examples studied, furnish the unsaturated alcohols.

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[1] Nystrom and Brown, THIS JOURNAL, **69**, 1197, 2548 (1947).

[2] Schlesinger, Sanderson and Burg, *ibid.*, **62**, 3421 (1940).

[3] Schlesinger, H. C. Brown and Schaeffer, *ibid.*, **65**, 1786 (1943).

[4] Burg and Schlesinger, *ibid.*, **62**, 3425 (1940).

[5] Schlesinger and H. C. Brown, *ibid.*, **62**, 3429 (1940).

[6] (a) Albert E. Finholt, Ph.D. Dissertation, The University of Chicago, June, 1946; (b) Schlesinger, "Final Report on Contract W.3434-SC-174," Official Publications Board, PB 6331, Department of Commerce, Washington, 1946.

[7] Irving Sheft, M.S. Dissertation, The University of Chicago, March, 1944.

[8] (a) Henry R. Hoekstra, Ph.D. Dissertation, The University of Chicago, August, 1946; (b) Albert C. Stewart, M.S. Dissertation, The University of Chicago, March, 1948; (c) Schaeffer and Frank, unpublished work.