TABLE III

PHYSICAL PROPERTIES OF PREPARED ESTERS

	B.P./Mm. Index of Refraction		n_D^t		Specific Gravity, d_4^t		Sapon. Equiv.	
Ester	Obs.	Lit.	Obs.	Lit.	Obs.	Lit.	Obs.	Calcd.
Dipropyl maleate[9]	117–119/5.7	102–103/3.0	1.4396^{25}	1.4404^{27}	1.0189_{25}	$1.0305_{18.4}$	100.5	100.1
Dipropyl fumarate[10]	104–106/1.2	None	1.4410^{25}	1.4380^{27}	1.0059_{25}	$1.0213_{20.8}$	100.6	100.1
Diethyl fumarate	90–91/3.7	98–99/14.0[11]	1.4379^{25}	1.4380^{27}[10]	1.0450_{25}	1.0496_{25}[12]	86.1	86.1
Dimethyl fumarate	192–193/760 (m.p. 105°)	192/760[13] (m.p. 102°)	—	—	—	—	—	—

EXPERIMENTAL

Dialkyl fumarates and dialkyl maleates. Fumaric or maleic acid (0.3 mole) and a primary normal alcohol (0.6 mole) with 5 ml. of concd. sulfuric acid was refluxed in a flask fitted with a Dean and Stark distilling receiver and a condenser until 10.8 ml. (0.6 mole) of water was collected in the trap. The contents of the flask were washed first with 10% aqueous sodium hydroxide and then with distilled water. The crude ester was washed, dried, isolated by a previously described method[8] and then distilled. The following esters were prepared in this manner: di-*n*-propyl fumarate, diethyl fumarate, dimethyl fumarate, di-*n*-propyl maleate, and diethyl maleate. All remaining esters were obtained from the Rubber Corporation of America. The properties of the prepared esters are listed in Table III.

Urea inclusion compounds. To 4.5 ml. of urea-methanol solution (0.15 g. urea/ml. of methanol) in a screw cap test tube was added 30 drops of ester. The tube was capped and shaken vigorously for 30 seconds and then allowed to stand for 24 hr. at 4°. The crystals that formed were filtered by suction, washed with 10 ml. of absolute ethanol, cooled to 4°, and vacuum dried at 1 mm. for 24 hr. over anhydrous calcium chloride at 4°.

X-Ray powder diffraction diagrams. The dried urea inclusion compounds were finely ground with a mortar and pestle and applied to the surface of a roughened glass slide. The interplanar spacings and relative intensities were obtained using the North American Philips X-Ray Diffraction Apparatus which was operated at 35,000 volts and 15 milliamperes with a scanning rate of 1° per min. using a CuK α radiation source.

Cross-sectional diameter of maleates and fumarates. Stuart-Briegleb scalar molecular models were arranged in an essentially planar zigzag conformation for the fumarates; the maximum cross section of the molecule was measured between machinists parallel bars. For the maleates a series of conformers were similarly arranged and measured. The conformer with the smallest maximum cross-sectional diameter was chosen.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, RENSSELAER POLYTECHNIC INSTITUTE]

Synthesis of Some Substituted Alkyl Derivatives of Phthalic and Isophthalic Acids

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The utility of the Meerwein reaction in the synthesis of substituted alkyl derivatives of the phthalic acids is illustrated by the synthesis of 3,4-dicarboxycinnamic acid from dimethyl 4-aminophthalate and acrylonitrile. In a reaction similar to the Meerwein reaction, 5-acetylisophthalic acid has been prepared from dimethyl 5-aminoisophthalate and acetaldoxime. New syntheses of dimethyl 4-aminophthalate, dimethyl 5-nitroisophthalate, and dimethyl 5-aminoisophthalate are also reported. 3,4-Dicarboxycinnamic acid has been reduced to 3,4-dicarboxyhydrocinnamic acid and 5-acetylisophthalic acid has been reduced to 1-(3,5-dicarboxyphenyl)ethanol.

The Meerwein reaction was discovered in 1939 by Hans Meerwein[2] and since that time has received considerable attention both from a synthetic viewpoint[3] and from a mechanistic viewpoint.[4] Our interest in the reaction has been a synthetic one, more especially for the synthesis of some substituted alkyl derivatives of the various phthalic acids. There are relatively few examples of substituted alkyl derivatives of phthalic acid in the literature and most of these were obtained by rather involved syntheses. Indeed, there are no general methods available for introducing a substituted alkyl chain into a phthalic acid molecule. It occurred to us that the Meerwein reaction is ideally suited for this purpose. Furthermore, if the starting amines were not contaminated with position isomers, the resulting Meerwein product would also be isomerically pure. The present study is concerned with Meerwein and Meerwein-like

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reactions of the dimethyl esters of 4-aminophthalic acid and 5-aminoisophthalic acid, and of 4-aminophthalimide.

Dimethyl 4-aminophthalate[5] was prepared most satisfactorily from dimethyl 4-nitrophthalate by the catalytic hydrogen transfer method of Braude and co-workers.[6]

The previously unreported nitration of the available dimethyl isophthalate gave dimethyl 5-nitroisophthalate[7,8] of adequate purity in 40% yield. It was converted in good yield by catalytic hydrogen transfer to dimethyl 5-aminoisophthalate, a reduction previously accomplished by ammonium sulfide[8] or zinc and hydrochloric acid.[9]

The only reference to a Meerwein reaction involving a phthalic acid derivative occurs in the German patent literature,[10] which gives inadequate details for the conversion of 4-aminophthalimide to 3,4-dicarboxycinnamic acid through the use of acrylonitrile with diazotized 4-aminophthalimide. We selected dimethyl 4-aminophthalate as the starting material in a successful Meerwein preparation of 3,4-dicarboxycinnamic acid in 40% yield, since a similar procedure could be applied to the isophthalic and terephthalic series. The cinnamic acid was quantitatively reduced to 3,4-dicarboxyhydrocinnamic acid by catalytic hydrogen transfer using acetone[11,12] as a solvent.

Although the reaction of an aromatic diazonium salt with an aldoxime was essentially discovered by Borsche in 1907,[13] it was not until 1954 that Beech[14,15] reported a rather extensive study of this type of reaction with relatively simple aldoximes such as formaldoxime and acetaldoxime. The hydrolysis product of the reaction is an aromatic aldehyde or aryl methyl ketone respectively. 5-Acetylisophthalic acid was prepared in 12% yield by the Beech procedure utilizing dimethyl 5-aminophthalate and acetaldoxime. The identity of the product was not rigorously established, but was based on the melting point and a positive iodoform test. The crude 5-acetylisophthalic acid was reduced to the previously unknown 1-(3,5-dicarboxyphenyl)ethanol using aqueous sodium borohydride.

EXPERIMENTAL[16]

Dimethyl 4-aminophthalate. Palladium black was prepared according to the directions given by Weygand[17] or obtained from the Fisher Scientific Company. It was stored in a vacuum desiccator over magnesium perchlorate and maintained at 0.5 to 1.0 mm. for at least 4 days before removing a sample for weighing. Technical cyclohexene (Matheson, Coleman and Bell) was distilled through a 12-bulb Snyder column and the 83–84° fraction collected and stored in the dark. Commercial absolute ethanol was stored over Drierite and filtered immediately before use.

Thirty-six grams (0.15 mole) of dimethyl 4-nitrophthalate (Eastman White Label), 500 ml. of absolute ethanol, 45.5 ml. (37 g., 0.45 mole) of cyclohexene, and 0.60 g. of palladium black were placed in a 1-l. flask equipped with an efficient reflux condenser and a magnetic stirrer. The reaction mixture was heated at reflux for 18 hr. After slight cooling and filtering, the volatile solvents were distilled until the vapor temperature rose above 80°. The resulting oil was cooled, taken up in about 600 ml. of ether, dried over magnesium sulfate for 2 hr., and filtered. Anhydrous hydrogen chloride was passed through the ether solution to obtain 34.8 g. (94.5%) of the hydrochloride. The free base obtained from the salt had a m.p. of 84.7–86.2° (corr.) (lit.[5] m.p. 84°) after two recrystallizations from aqueous alcohol.

Anal. Calcd. for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.3; N, 6.7; equiv. weight, 245.7. Found: C, 57.53, 57.38; H, 4.90, 5.25; N, 6.52, 6.56; equiv. weight, 245.5.

Dimethyl 5-nitroisophthalate. Dimethyl isophthalate (97 g., 0.5 mole, Hercules Powder Company, Polymer Grade) was added to 133 ml. of concd. sulfuric acid in a 1-l., three-necked flask equipped with a thermometer, an addition funnel, and a reflux condenser. The solution was magnetically stirred and heated to 45° before starting the dropwise addition of a mixture of 43 ml. each of concd. sulfuric and nitric acids. The temperature was kept in the range 55–59° by the dropwise addition of the mixed acids. The reaction mixture was cooled to 45° and then poured onto 650 g. of crushed ice. After 3 hr. the precipitate was collected and washed several times with cold water. Recrystallization from ethanol afforded 50 g. (42%) of dimethyl 5-nitroisophthalate, m.p. 119–121° (lit. m.p. 123°). An analytical sample was prepared by recrystallization from ethanol, m.p. 123.5–124.0° (corr.).

Anal. Calcd. for $C_{10}H_9NO_6$: C, 50.21; H, 3.79; N, 5.86. Found: C, 50.44, 50.41; H, 3.98, 3.81; N, 6.25, 5.93.

Dimethyl 5-aminoisophthalate. In a 1-l. flask were placed 42 g. (0.175 mole) of dimethyl 5-nitroisophthalate, 600 ml. of absolute ethanol, 53 ml. (0.53 mole) of cyclohexene, and 0.72 g. of palladium black. The flask was attached to an efficient reflux condenser, and heated to reflux with stirring. After 22 hr., the solution was filtered hot through a heated fluted filter paper to remove palladium. After chilling the dimethyl 5-aminoisophthalate was collected and dried to give 30.5 g. (83%), m.p. 178.5–179.0° (corr.) (lit.[9] m.p. 176°).

Anal. Calcd. for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.60, 57.31; H, 5.09, 5.20; N, 6.78, 6.76.

3,4-Dicarboxycinnamic acid. To a solution of 17 ml. of concd. hydrochloric acid and 90 ml. of water chilled to 0–5° in an ice bath was added 24.5 g. (0.1 mole) of dimethyl 4-aminophthalate hydrochloride. The resulting suspension was magnetically stirred to dissolve the solid. A solution of 30% sodium nitrite was added dropwise from a buret until the presence of an excess of nitrous acid was indicated, maintaining the temperature at 0–5°. The diazonium salt solution contained a gummy red solid which was removed by filtra-

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tion through a coarse sintered glass Büchner funnel on which a thin layer of Celite filter aid had been deposited.

The *p*H of the clear filtrate was adjusted to 3.0–3.5 with solid sodium acetate. The diazonium salt solution was then added to a solution of 32 ml. (25 g., 0.47 mole) of acrylonitrile in 600 ml. of acetone contained in a 1-l., three-necked flask equipped with a stirrer, thermometer, reflux condenser, and additional funnel. At a temperature of 15–20°, approximately 13 ml. of a 3.5*M* cupric chloride dihydrate solution was added dropwise. Gas evolution was instantaneous and the temperature rose to about 33° in from 15–30 min. As the temperature rose, a reddish oil appeared in the stirred solution. About 1 hr. after the addition of the cupric chloride solution, the acetone was evaporated under reduced pressure, with a maximum pot temperature of 30°. The distillation was continued until the oil layer settled to the bottom when the stirrer was stopped. Five hundred milliliters of ether was added and the reaction mixture stirred for an additional 30 minutes. The layers were separated and the aqueous layer washed with an additional 50 ml. of ether. The combined ether extracts were washed with 100 ml. of water followed by 100-ml., 50-ml., and 50-ml. portions of 5% sodium hydroxide. These were followed by three washings with 100-ml. portions of water. Most of the ether was then distilled and 200 ml. of 10% sodium hydroxide was added to the resulting dark red oil. Any remaining ether was removed and the suspension refluxed until ammonia was no longer evolved. During the reflux the suspended red oil dissolved to yield a clear, dark red solution. After cooling, the solution was acidified with dilute hydrochloric acid and the resulting light tan, finely divided solid collected. If the sample was dried at this point, a melting point of higher than 270° was observed and the compound would not dissolve in any common organic solvents. Therefore, without drying it was recrystallized with the aid of charcoal from about 500 ml. of water containing 15 ml. of concd. hydrochloric acid. A yield of 10 g. (42%) of 3,4-dicarboxycinnamic acid was obtained. The melting point varied considerably and seemed to be dependent on such factors as the size of the sample and the rate of heating. It generally melted over a 1° range in the vicinity of 215°. The analytical sample was given two more recrystallizations from water.

Anal. Calcd. for $C_{11}H_8O_6$: C, 55.94; H, 3.41; neut. equiv., 78.72. Found: C, 56.00, 56.22; H, 3.55, 3.47; neut. equiv. 79.07.

3,4-Dicarboxyhydrocinnamic acid. To 9.2 g. (0.04 mole) of 3,4-dicarboxycinnamic acid and 0.37 g. of palladium black in a 2-l. flask was added 1 l. of acetone containing 16 ml. (12.9 g., 0.157 mole) of cyclohexene. After a 68-hr. stirred reflux the reaction mixture was filtered hot and volatile solvents removed by distillation. A quantitative yield of 3,4-dicarboxyhydrocinnamic acid was thus obtained, m.p. 162–163.5°, neutralization equivalent 82.3. The material dissolved in 5% sodium bicarbonate and gave a negative test with potassium permanganate. An analytical sample was recrystallized from water, m.p. 165–166.5° (corr.).

Anal. Calcd. for $C_{11}H_{10}O_6$: C, 55.46; H, 4.23; neut. equiv., 79.40. Found: C, 55.07, 55.05; H, 4.25, 4.27; neut. equiv., 79.87.

5-Acetylisophthalic acid and 1-(3,5-dicarboxyphenyl) ethanol. A mixture of 21 g. (0.1 mole) of dimethyl 5-aminoisophthalate, 26 ml. of concd. hydrochloric acid, and 75 ml. of water was heated until the amine dissolved. With magnetic stirring, 75 ml. of water was added and the solution chilled rapidly in an ice-salt bath. The amine hydrochloride was titrated with a 30% sodium nitrite solution to a starch-iodide endpoint. The resulting diazonium salt solution was filtered with the aid of Celite through a sintered glass funnel and adjusted to *p*H 3.8 with solid sodium acetate.

In a 1-l., three-necked flask equipped with a stirrer, condenser, thermometer, and an additional funnel with an extension reaching nearly to the bottom of the flask, were placed 66 g. of sodium acetate trihydrate, 100 ml. of acetone, 5 g. of cupric sulfate pentahydrate, and 0.4 g. of anhydrous sodium sulfite. The resulting solution was cooled to 10° and 9.3 ml. (0.15 mole) of acetaldoxime was added. The diazonium salt solution was then added rapidly. Gas evolution and rather pronounced foaming took place at once and the temperature rose 5–10°. After stirring 1 hr. and warming to room temperature, the reaction mixture was acidified to a Congo Red-endpoint with concentrated hydrochloric acid. An additional 100 ml. of acid was added and the reaction mixture heated to boiling. During 3 hr. of boiling, 270 ml. of distillate were collected. On cooling a precipitate formed and the entire reaction mixture was extracted with 400- and 200-ml. portions of ether. The ether extract was dried over magnesium sulfate, filtered through carbon, and the ether removed by distillation. The resulting solid was dissolved in 500 ml. of water and the *p*H adjusted to 6 with 5% sodium bicarbonate. To the resulting solution was added a solution of 10 ml. (0.1 mole) of phenylhydrazine in 100 ml. of water containing 6 ml. of glacial acetic acid. On slight warming a crystalline yellow precipitate appeared. After chilling and collecting the precipitate it was recrystallized from aqueous ethanol with the aid of charcoal to yield 5.7 g. (19%) of the phenylhydrazone of 5-acetylisophthalic acid, m.p. 265° dec. (lit.[18] m.p. 274°).

The phenylhydrazone was added to 50 ml. of dilute hydrochloric acid and refluxed for 3.5 hr. The cooled reaction mixture was extracted several times with ether and the combined ether extracts filtered through charcoal and dried over magnesium sulfate. Removal of the ether left 2.5 g. (65%, 12% over-all yield) of 5-acetylisophthalic acid, m.p. 219–221° dec. lit.[18] m.p. 228°). The product was found to give a positive iodoform test.

To a solution of 1 g. (0.025 mole) of sodium hydroxide in 20 ml. of water was added 2.5 g. (0.012 mole) of 5-acetylisophthalic acid. The resulting solution was added to 0.12 g. (0.0033 mole) of sodium borohydride dissolved in 10 ml. of water containing 1 drop of 5% sodium hydroxide. The reaction mixture was stirred for 1 hr. at 35–40° and then heated to reflux for 1 hr. After cooling, the reaction mixture was acidified with dilute hydrochloric acid. A very small amount of precipitate was collected, dried, but discarded when the melting point was observed to be less than 180°. The acidified filtrate was chilled and the resulting precipitate collected. On drying, 1.28 g. (51%) of 1-(3,5-dicarboxyphenyl)ethanol was obtained, m.p. 241–242° dec. After one recrystallization from water the m.p. was 254.7–255.5° (corr.).

Anal. Calcd. for $C_{10}H_{10}O_5$: C, 57.14; H, 4.80. Found: C, 56.91, 57.11; H, 5.23, 4.91.

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