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SYNTHESIS OF ARYLMALEIC ANHYDRIDES

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In connection with a study of the mechanism of the reaction of dienophiles with olefins (1), the need arose for convenient syntheses of phenyl-, *p*-nitrophenyl-, and *p*-methoxyphenyl-maleic anhydrides. Only the first compound has been described in the printed literature. Early workers obtained phenylmaleic anhydride in low or unspecified yields from a variety of reactions (2–6). Recently, Miller described its preparation by the N-bromosuccinimide dehydrogenation of phenylsuccinic anhydride (7). He prepared the *p*-nitro derivative similarly, by dehydrogenation of *p*-nitrophenylsuccinic anhydride, but ring bromination predominated with *p*-methoxyphenylsuccinic anhydride (8).

In many trials, the latter method furnished low yields of bromine-contaminated phenylmaleic anhydride, so new syntheses of phenyl- and *p*-nitrophenylmaleic anhydrides were devised.[2] The new synthesis described below are thought to be as convenient as those employing an N-bromosuccinimide dehydrogenation.

Alexander (2) and Almstrom (3, 4) found that α-phenylmalic acid was dehydrated thermally to phenylmaleic anhydride. Torrey, Kuck, and Elderfield (6) performed the Reformatsky reaction of ethyl bromoacetate on phenylglyoxal diethyl acetal; by way of structure proof, the product was hydrolyzed and oxidized to α-phenylmalic acid. We effected the Reformatsky reaction directly upon ethyl phenylglyoxylate in 60 % yield. Hydrolysis of the diester with alkali at room temperature proceeded smoothly in 90 % yield, and dehydration with refluxing acetic anhydride produced pure phenylmaleic anhydride in 72 % yield. The over-all yield from commercially available starting materials was 33 %, and none of the reactions was difficult or time-consuming. It appears that anhydride formation *precedes* double bond formation, and this fact may be responsible for the gratifying yield in the last step. In alternate syntheses (see below) where the double bond is formed first, the fumaric acid isomer is isomerized only at the cost of considerably decomposition.

Other synthetic methods were explored, but less thoroughly. Cyanoacetic ester was condensed with ethyl phenylglyoxylate in 59 % yield, and the product was hydrolyzed in 64 % yield to a mixture of the maleic and fumaric acids. However, anhydride formation proceeded in poor yield (see above), so that the over-all yield by this route was much lower (13 %). Furthermore, malonic ester would not condense with zinc chloride catalysis, and ammonium acetate caused the production of higher-boiling material. Ethyl glyoxylate hemiacetal (VI) failed

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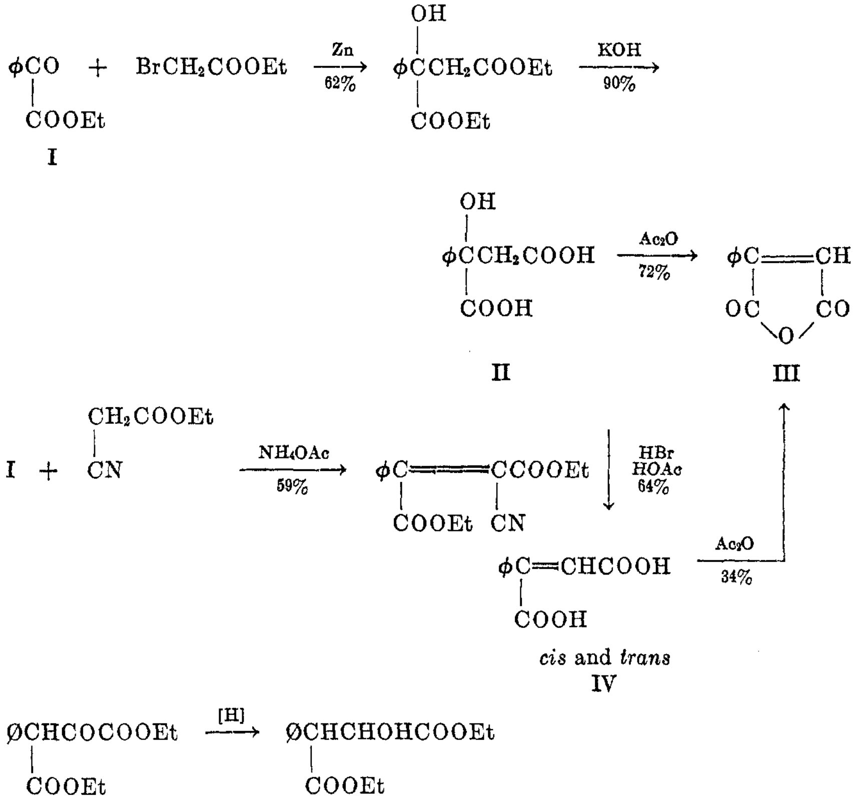
[1] Abstracted from a portion of the Ph.D. Dissertation of Allen H. Filbey, University of Michigan, 1953. Present address, Ethyl Corporation, Detroit, Michigan.

[2] After this work was substantially complete, we learned from Dr. Miller that it was essential to use a Nichrome wire stirrer for the dehydrogenation step, not a glass paddle, in order to obtain satisfactory yields. We confirmed this point.

to condense with ethyl phenylacetate in refluxing acetic anhydride, evidently because the α-hydrogens are insufficiently reactive; ethyl *p*-nitrophenylacetate will condense (see below).

It was hoped that oxalphenylacetic ester could be reduced to α′-phenylmalic ester, but the former compound was too unstable (9, 10). An attempt was made to add hydrogen cyanide to ethyl benzoylacetate, similar to the addition to ethyl γ-chloroacetoacetate (11), but an intractable tar was obtained.



p-Nitrophenylmaleic anhydride. The successful preparation of phenylmaleic anhydride through the Reformatsky reaction did not appear to be extensible to nitro compounds, since Reformatsky conditions would prove fatal to the nitro group. Furthermore, the lengthy synthesis of ethyl *p*-nitrophenylglyoxylate from the expensive *p*-nitrobenzaldehyde was not attractive, and selenium dioxide oxidation of ethyl *p*-nitrophenylacetate failed; the condensation with cyanoacetic ester employed above was therefore ruled out.

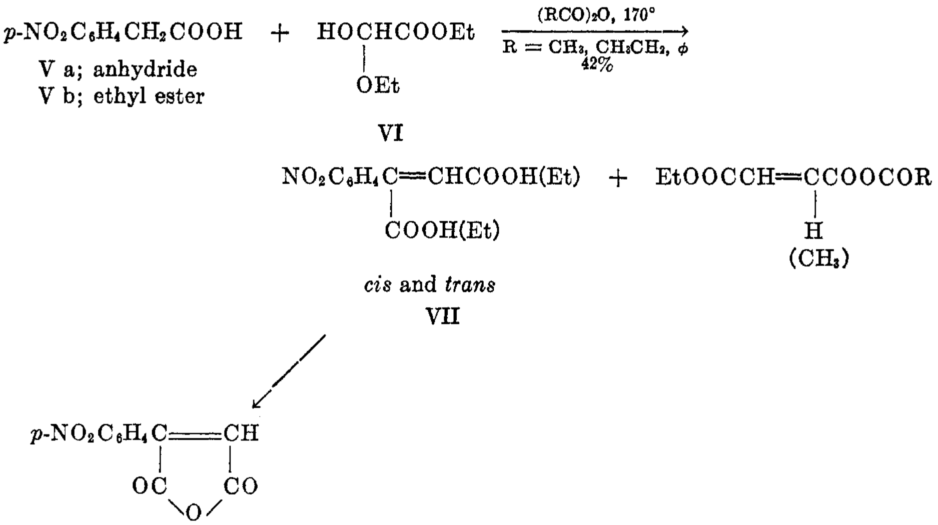
Even though ethyl glyoxylate hemiacetal did not condense with ethyl phenylacetate, the additional activation provided by the nitro group promised greater success with *p*-nitrophenylacetic acid derivatives. It was known that *p*-nitrophenylacetic anhydride (Va) would condense with aldehydes under basic catalysis (12). Moreover, in hot acetic anhydride, ethyl glyoxylate will condense with ethyl propionylacetate (13) and even with singly-activated hydrogens as in acetone, cyclohexanone, and tetrahydro-γ-pyrone (14).

The simplest experimental procedure appeared to be like that of Traube (13) — heating Va and VI in acetic anhydride. At temperatures up to 150°, there was no reaction. At 180°, using an excess of VI, a 25 % yield of condensation product was obtained. Use of propionic anhydride did not improve the yield. With either anhydride, there appeared variable amounts of a by-product thought to arise from condensation of ethyl glyoxylate with α-hydrogens of the anhydride, in competition with V. This side reaction was effectively suppressed by using benzoic anhydride as the condensing agent. In the best experiments, yields of 42 % (based on Va) were obtained in eight hours at 170°. It was also found that ethyl *p*-nitrophenylacetate would react similarly.

An alternate method gave higher yields of nitrophenylmaleic (fumaric) acid, but excessive experimental labor was required to isolate the product. In this, Va was condensed with VI in a typical Perkin reaction catalyzed by sodium acetate (12). The former method is preferred for its greater simplicity.

Either method gave rise to a mixture of *p*-nitrophenylmaleic and fumaric acids. Extensive decomposition occurred during many attempts to dehydrate this mixture with acetyl chloride or acetic anhydride. It was better, though more tedious, to separate the mixture by extracting the *cis* form with hot benzene, then dehydrating it by slow sublimation at 145°. No satisfactory method was developed for cyclodehydrating the *trans* acid.

The over-all yield of *p*-nitrophenylmaleic anhydride by the procedures developed here is not high (20 %, based on V charged), but readily-available starting materials are employed and the reactions are simple to carry out.



$$p\text{-}\mathrm{NO_2C_6H_4CH_2COOH} + \underset{\displaystyle \mathrm{OEt}}{\mathrm{HO\underset{|}{C}HCOOEt}} \xrightarrow[\mathrm{R\,=\,CH_3,\ CH_3CH_2,\ \phi}\ \ 42\%]{\mathrm{(RCO)_2O,\ 170^{\circ}}}$$

V a; anhydride
V b; ethyl ester

VI

$$\mathrm{NO_2C_6H_4\underset{\displaystyle COOH(Et)}{C}{=}CHCOOH(Et)} + \mathrm{EtOOCCH{=}\underset{\displaystyle H\ (CH_3)}{C}COOCOR}$$

cis and *trans*

VII

$$p\text{-}\mathrm{NO_2C_6H_4\underset{\displaystyle OC}{C}{=}\underset{\displaystyle CO}{CH}}\quad \mathrm{(OC\!-\!O\!-\!CO)}$$

p-Methoxyphenylmaleic anhydride. An obvious method for preparing this compound is by a Reformatsky reaction on *p*-methoxyphenylglyoxylic ester. Contrary to expectations, this keto ester refused to react with ethyl bromoacetate,

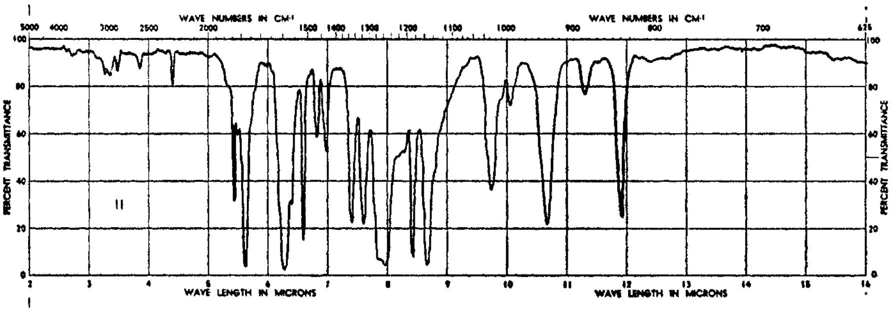


FIG. 1. INFRARED SPECTRUM OF α-*p*-METHOXYPHENYL-α′-CYANOMALEIC ANHYDRIDE. [In chloroform (5%) on a Baird double-beam spectrophotometer; 0.116 mm. cell].

even in boiling xylene. Theory predicts that electron release from the methoxyl group would somewhat decrease the positive character of the carbonyl carbon and reduce its reactivity toward nucleophilic reagents like $BrZnCH_2COOEt$. The complete failure of the reaction is surprising.[3]

Some of the alternate methods above for phenylmaleic anhydride appeared feasible. Trial experiments showed that malonic acid and malonic ester would not condense with ethyl *p*-methoxyphenylglyoxylate; cyanoacetic ester gave the expected Knoevenagel product (IX). However, the usually facile hydrolysis and decarboxylation of the product by a number of standard methods was unsuccessful. Hydrobromic-acetic acid mixture also cleaved the ether linkage. With other acidic reagents, side reactions occurred, including cleavage of the new double bond (retrograde aldol). The same difficulty was experienced during hydrolysis by hot aqueous base. Our experience is paralleled by that of others (16). Cold alcoholic alkali converted IX slowly to a salt of a compound believed to be the unstable hydroxy acid X, which was readily dehydrated to α-*p*-methoxyphenyl-α′-cyanomaleic anhydride (XI). The assigned structure was corroborated by the infrared spectrum (Fig. 1). The peaks at 5.42 and 5.62μ are characteristic of a cyclic anhydride; the weak but sharp peak at 4.40μ is assigned to the cyano group. The aromatic ring accounts for the band at 6.60μ, while that at 10.67μ is due to the C—O—C linkage.

Unfortunately, attempted further hydrolysis of XI again caused retrograde aldol degradation, so the synthesis was abandoned.

Free-radical arylation of maleic acid derivatives was looked into briefly. Meerwein (17) was able to prepare *p*-chlorophenylmaleic anhydride from a sequence of reactions beginning with the cupric chloride-catalyzed reaction of *p*-chlorobenzenediazonium chloride with dimethyl fumarate. It is not possible to repeat Meerwein's reaction from his published directions,[4] and it appeared even

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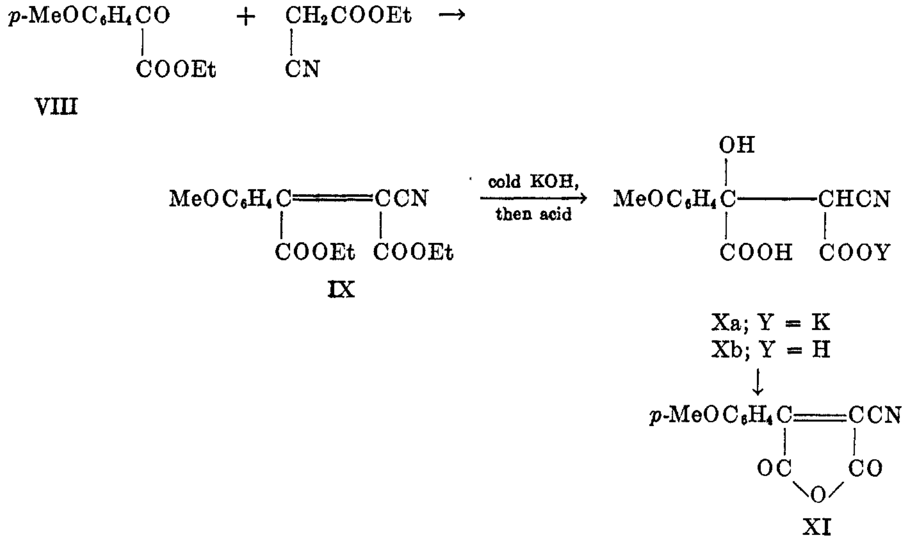
[3] Since the completion of this work, a paper by Hauser and Puterbaugh (15) was published. It appears that condensation of *tert*-butyl lithioacetate with ethyl (or *tert*-butyl) *p*-methoxyphenylglyoxylate might be susceptible to forcing. This possibility is being explored, as is the related use of *tert*-butyl esters of bromoacetic and *p*-methoxyphenylglyoxylic acids with a more active metal such as magnesium.

[4] Peter A. S. Smith and Masao Yoshimine, private communication.

less likely that success would be obtained with anisyldiazonium salts, for Mathur (18) found that anisyl radicals were singularly unreactive toward unsaturated systems.

One attempt to perform a Friedel-Crafts reaction upon anisole with diethyl chloromaleate was unsuccessful.



$$\underset{\text{COOEt}}{p\text{-MeOC}_6\text{H}_4\text{CO}} + \underset{\text{CN}}{\text{CH}_2\text{COOEt}} \rightarrow$$

VIII

$$\underset{\text{COOEt}}{\text{MeOC}_6\text{H}_4\text{C}}=\underset{\text{COOEt}}{\text{CCN}} \xrightarrow[\text{then acid}]{\text{cold KOH,}} \text{MeOC}_6\text{H}_4\overset{\text{OH}}{\underset{\text{COOH}}{\text{C}}}-\underset{\text{COOY}}{\text{CHCN}}$$

IX

Xa; Y = K
Xb; Y = H

$$\downarrow$$

$$p\text{-MeOC}_6\text{H}_4\underset{\text{OC}}{\text{C}}=\underset{\text{CO}}{\text{CCN}},\quad \text{OC}-\text{O}-\text{CO}$$

XI

EXPERIMENTAL

Diethyl α-phenylmalate. A mixture of 55.4 g. (0.31 mole) of ethyl phenylglyoxylate (19), 30.3 g. (0.46 mole) of granulated zinc, 52.0 g. (0.31 mole) of ethyl bromoacetate, a pinch of zinc dust, and an iodine crystal in 220 ml. of sodium-dried benzene was warmed gently with a micro-burner. On this scale, the reaction is not vigorous; using 1.2 moles, there is spontaneous refluxing. After three hours, the zinc cake was broken up with stirring and the solution was refluxed an additional two hours. The cooled reaction mixture was poured onto 370 ml. of 20% hydrochloric acid. The organic layer was washed with dilute acid, sodium bicarbonate solution, and water, and dried with magnesium sulfate. After removing the benzene, the residue was distilled at reduced pressure, b.p. 124–130°/0.3 mm. On redistillation, there was obtained 52.5 g. (60%) of diethyl α-phenylmalate, b.p. 119–121°/0.2 mm.

α-Phenylmalic acid (II). To a solution of 141 g. (0.53 mole) of diethyl phenylmalate in 250 ml. of ethyl alcohol was added 300 ml. of 20% aqueous potassium hydroxide. The mixture was cooled under the tap during the addition. After standing at room temperature for 24 hours, the alcohol was evaporated on the water-pump. To the residue was added 300 ml. of water, and the resulting solution was acidified with hydrochloric acid. Continuous ether extraction of the clear acidic solution for 24 hours and evaporation of the ether gave 100 g. (90%) of the crude yellow solid acid. Recrystallization from ether-petroleum ether gave white needles, m.p. 186.5–188.0° [reported (2), 187–188°].

Phenylmaleic anhydride (III). A mixture of 52 g. (0.25 mole) of recrystallized II and 330 g. of acetic anhydride was refluxed for one hour. On cooling to 0°, 18 g. of a yellow solid separated. Concentration of the filtrate on the water-pump gave an additional 8 g. of solid. Distillation of the filtrate gave 12 g. of solidifying liquid, b.p. 122–125°/0.2 mm. [reported (7), b.p. 120–145°/1 mm.]; total 38 g. (80%). The crude solid was dissolved in dry acetone, treated with decolorizing charcoal, and diluted with petroleum ether (60–75°). After two recrystallizations, a total of 34 g. (72%) of light yellow needles, m.p. 119–120° [reported

(7) 119.0–119.5°], was obtained; the melting point of a mixture with pure III from Miller's procedure was not depressed.

1-Phenyl-2-cyano-1,2-dicarbethoxyethene. According to Cragoe, *et al.* (20), a solution of 44.5 g. (0.25 mole) of ethyl phenylglyoxylate, 56.5 g. (0.50 mole) of ethyl cyanoacetate, 24 g. of glacial acetic acid, and 3 g. of ammonium acetate in 100 ml. of benzene was refluxed under a water separator. After two hours, 1 g. of ammonium acetate was again added and the solution was refluxed for six more hours. The solution was then washed with water and distilled. The fraction distilling at 110–130°/0.1 mm. weighed 40 g. (59%). No further purification was attempted.

A mixture of 36 g. (0.13 mole) of crude 1-phenyl-2-cyano-1,2-dicarbethoxyethene, 150 ml. of 48% hydrobromic acid, and 75 ml. of glacial acetic acid was refluxed for five hours. The ethyl acetate formed then was distilled off, and refluxing was continued for 12 hours. Then 400 ml. of water was added, and the clear solution was washed twice with benzene. The aqueous layer was evaporated to dryness at 100°/30 mm. The residue was boiled with 400 ml. of benzene, filtered hot, and the insoluble inorganic salts were washed with an additional 100 ml. of hot benzene. The benzene was evaporated on the steam-bath with a water-pump vacuum. The solid residue (16 g., 64%, m.p. 110–130°) was presumably a mixture of phenylfumaric acid (m.p. 128–129°), phenylmaleic acid, and III.

The crude mixture was refluxed for 45 minutes with acetic anhydride. Vacuum distillation gave 5 g. (22%, based on crude 1-phenyl-2-cyano-1,2-dicarbethoxyethene) of III, b.p. 125–135°/0.5 mm. There was a large amount of residue which distilled above 200°/0.5 mm. as a red oil. The recrystallized anhydride melted at 119–120°, mixture m.p. 118.5–119.5°.

Diethyl p-nitrophenylfumarate (-maleate). Method I. In a three-liter, three-necked flask equipped with a stirrer, a reflux condenser with a drying tube, and a large dropping-funnel, was placed 37 g. (0.45 mole) of anhydrous sodium acetate, 78 g. (0.255 mole) of Va (12), 62 g. (0.42 mole) of VI (21), 150 ml. of acetic anhydride, and 225 ml. of dry dioxane (12). The stirred solution was maintained at 55–60° for 16 hours in an oil-bath. The solution was cooled to room temperature and the calcium chloride tube was replaced with a hydrogen chloride trap. To the stirred solution was *cautiously* added 1200 ml. of absolute ethyl alcohol saturated with dry hydrogen chloride. Vigorous refluxing began immediately, and sodium chloride began to separate. The ethyl acetate and excess ethyl alcohol were then removed by distillation of the stirred mixture at atmospheric pressure. The residue was taken up in ether, washed with water and dilute sodium bicarbonate, dried, and distilled. Ethyl *p*-nitrophenylacetate (19 g.) was collected at 125–145°/0.1 mm., then 34 g. of viscous product at 170–180°/0.2 mm. The yield was 28% based on Va charged and 43% based on unrecovered Va (recovered as the ethyl ester). With $\frac{1}{20}$ of the above amounts, the yield was 40% based on material charged. The product gave a positive permanganate test for unsaturation. A portion was redistilled at 161°/0.15 mm.

Anal. Calc'd for $C_{14}H_{15}NO_6$: C, 57.32; H, 5.16.
Found (K):[5] C, 57.25; H, 5.32.

Method II. A number of runs were made using the procedure of Traube (13). Although the yields were somewhat lower than in *Method I*, the experimental procedure was much shorter and easier to carry out. In a typical run, a solution of 12.5 g. (0.06 mole) of Vb and 8.9 g. (0.06 mole) of VI in 32 g. (0.25 mole) of propionic anhydride was vigorously refluxed for eight hours. The orange solution was distilled directly, and the ethyl propionate and propionic anhydride were removed below 90°/0.1 mm. At 90–100°/0.1 mm., 11 g. of colorless liquid was isolated.[6] At 120–140°/0.1 mm., 7.5 g. of unreacted Vb was collected, then 3.5 g. of diethyl *p*-nitrophenylfumarate (-maleate) at 170–180°/0.2 mm. (20% yield based on material charged, or 50% based on unrecovered Vb).

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[5] Microanalyses by Goji Kodama (K) and W. J. Byrd (B) of this Laboratory, and by the Clark Microanalytical Laboratory, Urbana, Illinois (C).

[6] Tentatively identified as $EtOOCCH{=}C(CH_3)COOCOCH_2CH_3$, sapn. equiv. 67, calc'd 68. Aqueous solutions of this material formed propionic acid rapidly.

Method III. The side reaction between VI and the aliphatic anhydride in *Method II* was eliminated by using benzoic anhydride as the condensing agent. A mixture of 0.06 mole each of Vb and VI and 0.25 mole of benzoic anhydride was heated for 36 hours at 150°. The warm reaction mixture was poured into 100 ml. of vigorously stirred water, and 20 g. of solid sodium bicarbonate was cautiously added. After one hour of stirring, the two-phase system was extracted with ether and the ether layer was dried. Vacuum-distillation gave diethyl *p*-nitrophenylfumarate (-maleate) in yields of 31% based on material charged, or 65% based on unrecovered ethyl *p*-nitrophenylacetate.[7]

With a higher reaction temperature (170° for eight hours) and vigorous stirring, yields of 42% (based on material charged) were realized.

p-Nitrophenylfumaric (-maleic) acid (VII). A solution of 14 g. (0.048 mole) of diethyl *p*-nitrophenylfumarate (-maleate) in 250 ml. of 20% hydrochloric acid was stirred at 100° for eight hours. The homogeneous solution was then extracted continuously with ether for 48 hours. Removal of ether left 10.5 g. (93%) of a mixture of solid and oil. The solid (3.5 g.) remained undissolved when the mixture was washed three times with hot benzene. Recrystallization from the minimum amount of acetonitrile gave a white solid, m.p. 229° (dec.); Neut. Equiv. 117; Neut. Equiv. calc'd for *p*-nitrophenylfumaric acid, 118.5.

Anal. Calc'd for $C_{10}H_7NO_6$: C, 50.62; H, 2.98.
Found (K): C, 50.80; H, 3.16.

The cooled benzene washings deposited a small amount of gummy solid, m.p. 150–190°, which was presumed to be a mixture of the *cis* and *trans* dibasic acids. The clear benzene solution was evaporated on the steam-bath, leaving 6.5 g. of residual oil which failed to solidify.

p-Nitrophenylmaleic anhydride. The oily *cis* acid (2 g., 0.0085 mole) was heated in a sublimation apparatus. After eight hours, 1.5 g. (81%) of pure *p*-nitrophenylmaleic anhydride had sublimed at 145°/0.3 mm., leaving a tarry residue of 0.2 g. Recrystallization of the anhydride from acetone-petroleum ether (60–75°) gave fine needles, m.p. 126.5–128.0°; the melting point of a mixture with an authentic sample[8] gave no depression.

With 6 g., the yield was only 65%.

ATTEMPTED CONDENSATIONS OF ETHYL GLYOXYLATE HEMIACETAL

A. With p-nitrophenylacetonitrile. Using Traube's (13) procedure, a solution of equimolar amounts of *p*-nitrophenylacetonitrile and VI in four moles of propionic anhydride was vigorously refluxed for eight hours. On vacuum distillation, 83% of the nitrile was recovered.

B. With sodium p-nitrophenylacetate. Following the procedure of Haffcke and Becker (12), a solution of 6.1 g. (0.03 mole) of sodium *p*-nitrophenylacetate, 5.3 g. (0.036 mole) of VI, 30 ml. of acetic anhydride, and 100 ml. of isopropyl ether was stirred for three days at 35–40°. A small amount of oil was obtained at 190–215°/1 mm., and a dark residue (4 g.) remained. In a similar experiment, the reaction mixture was esterified with absolute alcohol saturated with dry hydrogen chloride. Vacuum distillation after removal of solvent gave 2.9 g. (45% recovery) of Vb, b.p. 125–150°/0.1 mm., m.p. 63–64°. At 164–172°/0.1 mm., 2.1 g. (25%) of crude VII (ester) was collected.

According to the directions of Thielcke and Becker (12), a solution of 24 g. (0.07 mole) of Va, 22.2 g. (0.15 mole) of VI, 12.3 g. (0.15 mole) of anhydrous sodium acetate, 50 ml. of acetic anhydride, and 80 ml. of dioxane was stirred at 55–60° for 17 hours. Excess water was added and the solution was partially distilled on the water-pump. The residue was refluxed

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[7] Isolation of the diester was not necessary when benzoic anhydride was the condensing agent. In one run, the entire reaction mixture was stirred at 100° for 12 hours in 20% hydrochloric acid. Filtration of the chilled mixture removed unreacted Vb (as the acid) and most of the benzoic acid. A single ether extraction removed the last traces of benzoic acid; the aqueous phase, containing the very water-soluble product, was then continuously extracted with ether and worked up as described in the next section.

[8] Kindly furnished by Dr. L. E. Miller.

for six hours with 60 ml. of 20% hydrochloric acid. The aqueous acid layer was continuously extracted with ether for three days. Removal of solvent and vacuum-distillation yielded 3.3 g. (11%) of crude *p*-nitrophenylmaleic anhydride, b.p. 195–197°/0.8 mm., m.p. 123–126° [from acetone-petroleum ether (60–75°)]. A large amount of decomposition accompanied the distillation.

Selenium dioxide oxidation of p-nitrophenylacetic acid. Equimolar quantities of *p*-nitrophenylacetic acid and selenium dioxide were refluxed for eight hours in dry xylene; some selenium was produced.[9] After filtration pyridine was added and the mixture was heated at 105–110° for 24 hours while a two-mole excess of malonic acid was added in portions. Only *p*-nitrophenylacetic acid (44%) could be isolated.

Ethyl p-methoxyphenylglyoxylate (VIII) (23) *and ethyl bromoacetate.* The Reformatsky reaction in benzene as described above returned more than 90% of VIII. In boiling toluene or xylene, an average of 87% unreacted VIII was isolated.

Allen's procedure (24) led to the recovery of 90% of VIII. Similar results were observed with ammonium acetate-acetic acid catalyst. A solution of VIII in pyridine with a small amount of piperidine was maintained at 85–95° and a 150% excess of malonic acid was added in portions over a 24 hour period. Only a small amount of acid, m.p. 171–190°, was obtained, and it was not characterized.

Condensation of VIII with ethyl cyanoacetate. Following the general procedure of Cragoe (20), a solution of 104 g. (0.5 mole) of VIII, 114 g. (1 mole) of ethyl cyanoacetate, 48 g. (0.8 mole) of glacial acetic acid, and 1.5 g. of ammonium acetate in 200 ml. of benzene was refluxed for 18 hours, using a continuous water separator. At three-hour intervals, 1.5 g. of ammonium acetate was added to the refluxing solution. After washing with water, the reaction mixture was vacuum-distilled. At 165–168°/0.1 mm., 106 g. (70%) of diethyl 1-(*p*-methoxyphenyl)-2-cyanoethene-1,2-dicarboxylate (IX) was obtained. The distillate solidified, and recrystallization from aqueous alcohol gave needles, m.p. 59–60°. A slow positive test for unsaturation (permanganate) was observed.

Anal. Calc'd for $C_{16}H_{17}NO_5$: C, 63,35; H, 5.65; N, 4.62.
Found (C): C, 62.71; H, 5.71; N, 4.82.

The yield was only 46% when the reaction time was three hours; refluxing for three days did not materially increase the yield beyond 70%.

Hydrolyses of diethyl 1-(p-methoxyphenyl)-2-cyanoethene-1,2-dicarboxylate. (*A*). When a mixture of IX and 10% sodium hydroxide was refluxed for one hour, the odor of ammonia was detected; 77% of malonic acid was isolated. When IX was refluxed for five hours with a mixture of acetic acid and 48% hydrobromic acid, the material isolated gave a ferric chloride test, indicating ether cleavage. When IX was refluxed with an acetic acid-50% sulfuric acid mixture, there was obtained an oil which, after refluxing with acetyl chloride, yielded 97% of glycolic acid [m.p. 73–76°, N.E. 78; *p*-toluidide, m.p. 140–142° (25)]. When IX was refluxed for 24 hours with concentrated hydrochloric acid, and the oily material was boiled with acetyl chloride and distilled, there was isolated 28% of *p*-methoxyphenylglyoxylic acid (26), m.p. 84–87°, N.E. 178. When IX was refluxed for five hours with 95% alcohol saturated with hydrogen chloride, 90% of unreacted IX precipitated on cooling.

(*B*). To a solution of 3 g. (0.01 mole) of IX in 60 ml. of absolute alcohol, 30 ml. of 10% alcoholic potassium hydroxide was added. Within ten minutes, a precipitate began to form. After standing at room temperature at least overnight, it was filtered and the solid (3.15 g.) was washed with a small amount of absolute alcohol. The solid was dissolved in 25 ml. of water and acidified with concentrated hydrochloric acid. White needles (Xa) precipitated from the green acidic solution and were removed; 2.5 g., m.p. 216–219°. The green filtrate was continuously extracted with ether; solvent removal gave 0.5 g. of a solid, (Xb), m.p. 140–142°.

The relative amounts of the two solids varied considerably. When the salt which was

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[9] The extreme instability of $p\text{-}NO_2C_6H_4COCN$ (22) indicated that an attempt to isolate the keto acid would be unwise.

filtered from the alcoholic solution was dissolved in the minimum quantity of water and then acidified, the main product was the precipitate of high-melting solid. On the other hand, dissolving the salt in excess dilute hydrochloric acid gave predominantly the water-soluble, lower-melting product.

The water-soluble green solid lost water so easily that it was impossible to obtain consistent analytical data. Its neutral equivalent indicated it to be 1-(*p*-methoxyphenyl)-1-hydroxy-2-cyanoethane-1,2-dicarboxylic acid (Xb). It was recrystallized from benzene and then sublimed with some decomposition at 120°/0.2 mm. The orange sublimate dissolved in water or dilute base very slowly. It melted at 145°, and its infrared spectrum (Fig. 1) indicated the presence of an anhydride linkage and a cyano group. The sublimate is considered to be α-(*p*-methoxyphenyl)-α'-cyanomaleic anhydride (XI).

Anal. Calc'd for $C_{12}H_7NO_4$: C, 62.90; H, 3.08; N.E., 114.5.

Found (K): C, 62.90; H, 3.14; N.E., 111.0.

The high-melting solid, sparingly soluble in water (green-colored solution), was insoluble in ethyl ether and absolute ethanol. Recrystallization from dilute alcohol or the minimum amount of water gave fine white needles, m.p. 223°. No reaction occurred with nitrous acid, indicating the absence of an amide group. The solid when allowed to stand in dilute hydrochloric acid slowly dissolved to give an intensely green solution. Extraction with ether and solvent removal gave a green solid, m.p. 144° after sublimation, mixture m.p. with XI not depressed. The compound appears to be the mono potassium salt of 1-(*p*-methoxyphenyl)-1-hydroxy-2-cyanoethane-1,2-dicarboxylic acid, Xa.

Anal. Calc'd for $C_{12}H_{10}KNO_6$: C, 47.62; H, 3.32; K, 12.89; N.E., 303.

Found (K): C, 46.51, 46.18; H, 2.81, 3.16; K, 13.01; N.E., 298.

Attempted hydrolysis and decarboxylation of Xa and XI. (A). When Xa was dried in a vacuum or in a drying oven, a color change of white to yellow was observed. When Xa or XI was heated in diphenyl ether at 150–250°, it lost water and became yellow-orange; no carbon dioxide was evolved. Neutral equivalent determinations varied considerably, but were always significantly lower than 303.

When Xa was refluxed with 20% hydrochloric acid for eight hours, the mixture frothed and became green; no carbon dioxide was evolved. There was isolated 64% of malonic acid and 65% of *p*-methoxyphenylglyoxylic acid. When Xa or XI was boiled for 45 minutes with 10% sodium hydroxide, ammonia was evolved, and 96% of malonic acid was recovered. When XI was heated for two hours at 100°, 90% was recovered on cooling.

Attempted Friedel-Crafts synthesis. When anisole and ethyl chloromaleate were stirred with an excess of aluminum chloride at room temperature in a mixture of tetrachloroethane and nitrobenzene, 90% of the unreacted ester was recovered. Only a little tar remained.

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SUMMARY

1. Ethyl phenylglyoxylate undergoes a Reformatsky reaction with ethyl bromoacetate. The product can be hydrolyzed and dehydrated to phenylmaleic anhydride; over-all yield 33 %. Ethyl *p*-methoxyphenylglyoxylate does not react with ethyl bromoacetate, even in boiling xylene.

2. *p*-Nitrophenylacetic anhydride and ethyl *p*-nitrophenylacetate will condense with ethyl glyoxylate hemiacetal; phenylacetic anhydride (or ester) fails to react. The *cis* product can be converted to *p*-nitrophenylmaleic anhydride in good yield; the *trans* isomer is anhydridized only with extensive decomposition.

3. Ethyl phenylglyoxylate and ethyl *p*-methoxyphenylglyoxylate undergo Knoevenagel condensations with cyanoacetic ester. The product from the former

keto ester can be converted to phenylmaleic anhydride. The product from the latter readily undergoes a retrograde aldol degradation with conventional hydrolytic procedures. Mild hydrolysis does not affect the cyano group, and *p*-methoxyphenylcyanomaleic anhydride can be prepared.

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