[Contribution from the Chemical Laboratories of the Polytechnic Institute of Brooklyn]

THE CONDENSATION OF *p*-NITROPHENYLACETIC ACID WITH ACYCLIC ALDEHYDES. I. ACROLEIN

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INTRODUCTION

p-Nitrophenylacetic acid has been condensed with a wide variety of aromatic aldehydes: benzaldehyde (1, 2), *p*-tolylaldehyde (3), *p*-isopropylbenzaldehyde (1), salicylaldehyde (1), *m*-hydroxy- (4) and *p*-hydroxybenzaldehydes (5), *o*-methoxy- (3), *m*-methoxy- (3), and *p*-methoxy-benzaldehydes (1, 5), 2,4-, 3,4-, and 2,5-dimethoxybenzaldehydes (6), *m*-dimethylamino- and *m*-di-*n*-propylamino-benzaldehydes (7), *p*-dimethylaminobenzaldehyde (3), *m*-nitro- (4, 8) and *p*-nitro-benzaldehyde (4, 9, 10), and 1-naphthaldehyde (11). The products of these reactions were α-*p*-nitrophenylcinnamic acids or the corresponding stilbenes resulting from their decarboxylation. One exception is the condensation with salicylaldehyde which leads to 3-(4′-nitrophenyl)coumarin. However, only three non-aromatic aldehydes have been employed: cinnamaldehyde (11), formaldehyde which, in the presence of primary and secondary amines, gives Mannich bases (12), and glyoxal which forms only polymers (13). The present paper is the first to report on the condensation of *p*-nitrophenylacetic acid with acyclic aldehydes.

RESULTS AND DISCUSSION

The condensation of acrolein with *p*-nitrophenylacetic acid was first tried in aqueous solution. An aqueous suspension of the acrolein-potassium bisulfite addition product was refluxed with *p*-nitrophenylacetic acid for two hours. Only *p*-nitrophenylacetic acid was recovered.

Conditions for the Doebner reaction were next tried, but when acrolein and *p*-nitrophenylacetic acid were refluxed in pyridine no acidic product was recovered. *p*-Nitrotoluene was obtained in almost quantitative yield. It was later observed that this decarboxylation of *p*-nitrophenylacetic acid takes place even at steam-bath temperatures. This reaction is to be studied further.

The Kuhn-Winterstein procedure was studied next (14, 15). Acrolein and *p*-nitrophenylacetic acid were heated to reflux in acetic anhydride with litharge as a catalyst. From the resinous-appearing reaction product, about 4–7% of an acidic material was obtained which melted at 170–175°.

Several other metals, in the form of their acetates, were tried in place of lead. These included calcium, cadmium, zinc, and tin. Alumina was also tried in place of litharge. None of the desired product was obtained in any of these experiments; considerable *p*-nitrophenylacetic acid was recovered in all cases. It appears that these metallic acetates are too insoluble in acetic anhydride to achieve much, if any, catalytic effect.

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Sodium acetate, in varying amounts, was also tried as a catalyst under the same conditions. With large amounts of this catalyst, only resinous materials were obtained, while with small amounts, a mixture of resinous material and unreacted *p*-nitrophenylacetic acid resulted.

The next attempted method employed the Oglialoro modification of the Perkin reaction in which the sodium salt of the arylacetic acid, acetic anhydride, and the aldehyde are heated at 180° (16). At this temperature only an ether-insoluble resinous material could be obtained, but when the reaction was carried out at room temperature a 12% yield of the same new acid as obtained previously was recovered. At 35° and 45° the yield was further raised to 21 and 28%, respectively.

The final variation adopted was the application of the Perkin reaction itself; the condensation of *p*-nitrophenylacetic anhydride with acrolein in the presence of anhydrous sodium acetate as the catalyst in a mixture of dioxane and acetic anhydride as the solvent. This procedure gave the same new compound in slightly impure form in 38% yield.

The acid was isolated as a light yellow microcrystalline solid, m.p. 174–176°. Analyses for carbon, hydrogen, and nitrogen were in accord with the values expected for 2-(4′-nitrophenyl)-2,4-pentadienoic acid. It absorbed five moles of hydrogen, indicating the presence of two double bonds and one nitro group. The resulting colorless compound was amphoteric and its analysis for nitrogen corresponded with the expected value for α-(4′-aminophenyl)valeric acid. Both the dienic acid and its reduction product gave the expected neutral equivalents.

The dienic acid did not form an adduct with maleic anhydride, either at room temperature in benzene or in refluxing nitrobenzene. This is taken to confirm the structure, since 1,1-disubstituted butadienes characteristically do not undergo the Diels-Alder reaction. For example, 1,1-dimethyl-1,3-butadiene gives no adduct, but polymerizes when heated with maleic anhydride (17).

The above series of reactions, combined with the analytical work, indicated that the new product is the expected 2-(4′-nitrophenyl)-2,4-pentadienoic acid.

An attempt to decarboxylate 2-(4′-nitrophenyl)-2,4-pentadienoic acid in quinoline at 180–200° using Adkins-Connor catalyst (15, 18) gave a neutral red residue which could not be induced to crystallize.

EXPERIMENTAL

All temperatures are uncorrected.

Starting materials. *p*-Nitrophenylacetic acid was prepared from benzyl chloride in the following series of reactions (19, 20):

$$C_6H_5CH_2Cl \rightarrow C_6H_5CH_2CN \rightarrow p\text{-}NO_2C_6H_4CH_2CN \rightarrow p\text{-}NO_2C_6H_4CH_2CO_2H$$

The *p*-nitrobenzyl cyanide and the *p*-nitrophenylacetic acid were crystallized several times to remove all traces of the *ortho*-acid. The final product had m.p. 152–153°.

Acrolein was a commercial product furnished by the Shell Chemical Corporation. It contained 0.01 per cent of hydroquinone and was used as such without further purification.

Aqueous procedure. Acrolein (2 ml., 0.03 mole) was added dropwise with shaking and cooling to a suspension of 3.54 g. (0.016 mole) of potassium metabisulfite in 10 ml. of water.

To this was added 2.71 g. (0.015 mole) of *p*-nitrophenylacetic acid. The mixture was refluxed for two hours, cooled, made alkaline with dilute sodium hydroxide, filtered, and acidified with dilute hydrochloric acid. After crystallizing the solid (2.3 g.) from water, a mixture melting point (m.m.p.) with *p*-nitrophenylacetic acid gave no depression.

Doebner procedure. A mixture of 2 ml. (0.03 mole) of acrolein, 2.71 g. (0.015 mole) of *p*-nitrophenylacetic acid, and 10 ml. of pyridine was heated for one hour on the steam-bath and then refluxed for an additional hour. The reaction mixture was poured into 100 ml. of water containing 10 ml. of concentrated hydrochloric acid, cooled, and extracted with 100 ml. of ether. The ether solution was washed successively with dilute hydrochloric acid, twice with dilute sodium hydroxide solution, twice with water, dried over calcium chloride, and evaporated. A red oil remained with solidified on cooling and weighed 2.06 g. Recrystallization from dilute ethanol gave m.p. 52–53° (m.m.p. with authentic *p*-nitrotoluene, 53–54°).

Kuhn-Winterstein procedure. A mixture of 2.71 g. (0.015 mole) of *p*-nitrophenylacetic acid, 1.11 g. (5 mmole) of litharge, and 20 ml. of acetic anhydride was refluxed under a stillhead equipped with a condensate take-off. Ten milliliters of condensate were collected to remove acetic acid presumably formed during conversion of the *p*-nitrophenylacetic acid to its anhydride. After cooling to room temperature, which precipitated most of the lead salt, 1.0 ml. (0.015 mole) of acrolein was added. The flask was loosely stoppered and heated on the steam-bath for four hours. Water (25 ml.) was added and heating continued for a short time to hydrolyze the anhydride.

After cooling, ether (50 ml.) was added followed by 1:1 hydrochloric acid (15 ml.) to precipitate the lead, and the ether and water layers were decanted into a separatory-funnel. The residue in the flask was washed with 50 ml. of ether and the washings added to the separatory-funnel. The ether layer was washed twice with water to remove acetic acid and then extracted with 10% sodium carbonate solution. Acidification of the extract gave a yellow solid (1.83 g.). Four crystallizations from dilute alcohol gave 0.22 g. (1.0 mmole; 7%) of a light yellow product, m.p. 172–174° (dec.).

Oglialoro procedure. *p*-Nitrophenylacetic acid (10.8 g., 0.06 mole) was dissolved in a solution of 3.18 g. (0.03 mole) of anhydrous sodium carbonate in 50 ml. of water. The water was distilled and the residual salt partially dried by the addition of three 50-ml. portions of absolute alcohol, which were removed by distillation at atmospheric pressure and then at reduced pressure. Acrolein (4 ml., 0.06 mole) and acetic anhydride (10 ml.) were added and the flask was stoppered and shaken. Heat was evolved and the temperature rose to 35°, which was maintained for three hours by external warming, with occasional shaking. Most of the salt dissolved after one hour and then the mixture became a semi-solid, yellow mass.

A mixture of hydrochloric acid (10 ml.) and water (50 ml.) was added and the solution heated on the water-bath for one hour. The reaction mixture was cooled, taken up in 150 ml. of ether, washed twice with water, and extracted with three portions (100 ml. total) of 10% sodium carbonate solution. Acidification gave 7.1 g. of crude acid, m.p. 135–155° (dec.). After washing with hot water the residue weighed 4.7 g. and melted at 158–164° (dec.). Crystallization from petroleum ether (b.p. 125–135°) gave 2.75 g. of light yellow needles, m.p. 168–172°. Recrystallization raised the melting point to 172–174°.

The extracted ether solution was evaporated leaving 3.0 g. of a neutral red oil which solidified on cooling. Crystallization from dilute alcohol and petroleum ether gave a light yellow product, m.p. 64–65°. This compound proved to be *ethyl p-nitrophenylacetate* [reported m.p. 62.8–63.3° (21), 65–66° (22), 65–67° (23), 65.5–66° (24)]. A mixed melting point with ethyl *p*-nitrophenylacetate prepared from the acid according to Maxwell (24) showed no depression.

Anal. of compound m.p. 64–65°. Calc'd for $C_{18}H_{11}NO_4$: C, 57.41; H, 5.31; N, 6.69; Mol. wt., 209. Found: C, 57.12; H, 4.95; N, 6.69; Mol. wt. (cryoscopic, benzene), 196, 203.

The adjusted yield of recrystallized acid, m.p. 168–176°, was thus 28% based on *p*-nitrophenylacetic acid.

Perkin procedure. A number of experiments were performed to determine optimum conditions for the synthesis of *p*-nitrophenylacetic anhydride [previously prepared by refluxing a suspension of sodium *p*-nitrophenylacetate with *p*-nitrophenylacetyl chloride in benzene (25)].

p-Nitrophenylacetic acid (100 g., 0.55 mole) and 400 ml. of acetic anhydride (b.p. 138–139.5°) were heated to reflux (this took 10 minutes) and maintained at reflux for 20 minutes. The acetic acid and excess anhydride were distilled at reduced pressure until the residue solidified. Crystallization from chlorobenzene followed by washing with petroleum ether and drying gave 71.5 g. (0.21 mole; 77%) of a pale yellow solid, m.p. 148–149° [reported m.p. 153° (25)].

One gram of the anhydride refluxed with 10 ml. of aniline for one hour gave 0.55 g. (74%) of yellow anilide, m.p. 209–212°. Crystallization from ethyl acetate—isopropanol (1:3) raised the melting point to 211–212° [reported 198° (26), 211.7–213.2° (21)].

Acrolein (1 ml., 0.015 mole) was added to a mixture of *p*-nitrophenylacetic anhydride (2.4 g., 0.007 mole), 1.23 g. (0.015 mole) of anhydrous sodium acetate, 8 ml. of dioxane, and 5 ml. of acetic anhydride. The anhydride dissolved slowly with a slight evolution of heat. After heating the mixture at 55° for 16 hours, the product was isolated as in other experiments and crystallized from dilute alcohol to give 1.17 g. (38%) of a crude acid, m.p. 165–175° (dec.).

Characterization of the product. After recrystallization from petroleum ether (b.p. 125–135°), the acid melted 172–174° (dec.). It was unsaturated towards bromine in carbon tetrachloride and potassium permanganate in acetone.

Anal. Calc'd for $C_{11}H_9NO_4$: C, 60.27; H, 4.14; N, 6.39; Neut. equiv., 219.

Found: C, 60.45, 59.77; H, 4.26, 4.58; N, 6.36, 6.21; Neut. equiv., 221.

The acid (6.3 g., 0.029 mole) was hydrogenated at 731 mm. in acetic acid solution over a 5% palladium-on-charcoal catalyst. It absorbed 96.5% of the calculated volume of hydrogen (assuming saturation of two double bonds and reduction of the nitro-group to an amino group). The filtered solution was poured into 300 ml. of ice-water, taken up in ether, filtered, and then extracted with dilute hydrochloric acid. Upon neutralizing the solution to *p*H 5 (optimum) 1.20 g. of a colorless compound separated, which after two crystallizations from dilute ethanol had m.p. 137–138°. Concentration and extraction of the mother liquors gave an additional 1.23 g. (total yield 2.43 g., 44%).

Anal. Calc'd for $C_{11}H_{15}NO_2$: N, 7.25; Neutral equivalent, 193.

Found: N, 7.26, 7.22; Neutral equivalent, 195.

Extraction of the ether solution with dilute sodium hydroxide gave, after neutralization, 0.1 g. of an acid, m.p. 170–171°. This proved to be the acetyl derivative as verified by acetylating 0.46 g. (2.4 mmole) of α-(*p*-aminophenyl)valeric acid in 5 ml. of acetic anhydride followed by dilution with water, concentration at reduced pressure, and recrystallization twice from ethanol, m.p. 172–173°, showing no depression in a mixed melting point with the previous product.

Anal. of compound m.p. 172–173°. Calc'd for $C_{13}H_{17}NO_3$: N, 5.95; Neut. equiv., 235.

Found: N, 5.94, 5.93; Neut. equiv., 238.

The acid (11 g., 0.05 mole) in acetic acid (100 ml.) was treated portionwise with bromine (8 g., 0.05 mole) in 40 ml. of acetic acid. The color was discharged rapidly until near the end of the addition. The solution was diluted with 75 ml. of water, allowed to stand in an ice-chest for 24 hours, filtered, and the solid crystallized six times from 50–55% ethanol to give 1.52 g. of dibromide, m.p. 162–162.5°. The filtrate gave an additional 2.20 g., m.p. 159–161°.

Anal. Calc'd for $C_{11}H_9Br_2NO_4$: N, 3.70; Neutral equivalent, 379.

Found: N, 3.72; Neutral equivalent, 390, 389.

When 0.55 g. (2.5 mmole) of the acid was treated with 0.8 g. (5 mmole) of bromine, the color was not discharged on heating for one-half hour at 70°. The same product was isolated.

Attempted decarboxylation. Ten grams of 2-(4′-nitrophenyl)-2,4-pentadienoic acid and 1 g. of Adkins-Connor catalyst were heated to 180–200° in 50 ml. of quinoline with mechanical stirring for 15 minutes. Evolution of carbon dioxide began at 180° and ended after 12 minutes. The reaction mass was diluted with ether, filtered (most of the material was insoluble in ether), washed with dilute sodium hydroxide, water, and then evaporated to dryness. Neither the ether-insoluble material nor the ether-soluble material could be induced to crystallize. The alkaline extracts were acidified, but no acid precipitated.

SUMMARY

A number of procedures were investigated for effecting the condensation of acrolein with *p*-nitrophenylacetic acid. The best yield (38%) of 2-(4′-nitrophenyl) -2,4-pentadienoic acid was obtained by a low-temperature modification of the Perkin reaction. Several derivatives of this acid were prepared.

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