CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF MICHIGAN

THE *o*-FORMYL- AND *o*-ACETYL-PHENYLACETIC ACIDS

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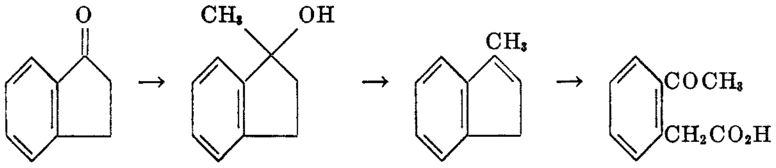
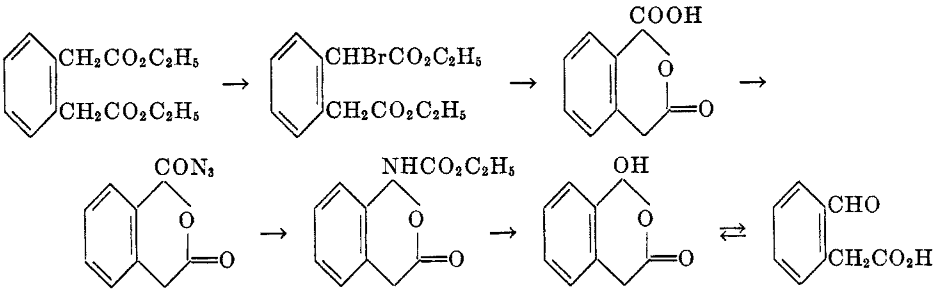
o-Acetylphenylacetic acid has been synthesized from 1-indanone by a route which should be generally applicable to the *o*-acylphenylacetic acids, as follows:



I

No difficulty was encountered in controlling the dichromate oxidation of the known 3-methylindene to give the keto acid in 58% yield. Apparently the product has escaped previous preparation only because no occasion has arisen to attempt its synthesis.

This is not true, however, for the *o*-formylphenylacetic acid, for which one unsuccessful attempt at synthesis has been reported. The method used here for the *o*-acetyl compound is not applicable because of the susceptibility of the aldehyde group to oxidation. Three more proposed syntheses failed before a usable one was found, namely, the hydrolysis of 1-(carbethoxyamino)isochroman-3-one, prepared from ethyl *o*-phenylene diacetate by bromination, hydrolysis to isochroman-3-one-1-carboxylic acid, conversion through the acid chloride to the acid azide, and reaction of the azide with ethyl alcohol:



II III

A brief statement about each of the unsuccessful proposed syntheses follows:

1. Fieser and Pechet (1) wished to subject the acid chloride of methyl *o*-carboxyphenylacetate to Rosenmund reduction, but their attempt to prepare the acid chloride led to the formation of a chloroisocoumarin.

2. In the present work, *o*-(carboxymethyl)phenylglyoxylic acid was synthesized in fair yield from isochroman-3-one-1-carboxylic acid by alkaline per-

manganate oxidation, but the subsequent proposed decarboxylations as the bisulfite addition product and the anilino derivative were not successful (2).

3. *o*-Cyanophenylacetic acid was synthesized from the known barium *o*-aminophenylacetate by an adaptation of the Sandmeyer reaction. When methyl *o*-cyanophenylacetate was treated with stannous chloride in ether (3), a rapid complex reaction occurred and none of the expected imine of the aldehyde acid was obtained.

4. Another attempt started with the further bromination of *o*-xylylene bromide to ω,ω,ω'-tribromo-*o*-xylene. The melting point, 40°, was far from the 97° reported by Atkinson and Thorpe (4) for a tribromoxylene of poor analysis isolated as a by-product of the bromination of *o*-xylene. The structure of the tribromoxylene prepared here is supported by its ready conversion in alcohol to a derivative with the correct analysis for the 2,4-dinitrophenylhydrazone of *o*-(ethoxymethyl)benzaldehyde. The bromine compound reacts readily with sodium iodide in acetone to replace one bromine rapidly, the other two more slowly. It was therefore proposed that ω,ω-dibromo-ω'-cyano-*o*-xylene might be prepared and subsequently hydrolyzed to *o*-formylphenylacetic acid, but the required reactions were not successfully carried out.

Descriptions of the several new compounds produced as intermediates in the proposed syntheses are included in the experimental part.

In the formulation of *o*-formylphenylacetic acid, two representations, II and III, are shown in tautomeric equilibrium, and the successful synthesis is the one which deliberately sets out to produce structure II. The reactions, however, of both the formyl and the acetyl derivate are those expected of structure III, including hydrazone formation and salt formation with sodium bicarbonate. This evidence does not give any information about the distribution between the two structures, since either one readily accounts for the observations. The possibility of an appreciable stability of the cyclic form (II) suggests a study of hemiacetal formation, which will be looked into at a later date.

EXPERIMENTAL

o-Acetylphenylacetic acid. 3-Methylindene was prepared by dehydrating (5) the carbinol resulting from the reaction of 1-indanone with methylmagnesium iodide (6). To a vigorously stirred solution of 87 g. of sodium dichromate hydrate, 5 g. of sodium benzene sulfonate, and 240 ml. of sulfuric acid in 1330 ml. of water, at 55°, 35.4 g. of 3-methylindene was added dropwise in 60 minutes. Solid separated during the addition. The temperature was held at 55 ± 2° for an additional 25 minutes, when the dichromate had been consumed. The mixture was filtered after chilling for 3 hours at 0°, and the resulting gummy solid was washed successively with several small portions each of cold dilute sulfuric acid, cold water and cold benzene. Recrystallization from water, with Norit, and with rapid cooling, gave nearly colorless fine needles of *o*-acetylphenylacetic acid, m.p. 165–166°, yield 58%. A colorless analytical sample of the same melting point was obtained by recrystallization from acetic acid and from benzene. Hot aqueous solutions of the acid slowly developed turbidity.

Anal. Calc'd for $C_{10}H_{10}O_3$: C, 67.4; H, 5.66; Mol. wt., 178.2.

Found: C, 67.7; H, 5.90; Neut. equiv., 179.6.

The *phenylhydrazone* was formed by adding phenylhydrazine hydrochloride to a hot aqueous solution of the acid containing sodium acetate. After one recrystallization, it was pale yellow, m.p. 176–177° dec. The analytical sample, m.p. 177–178°, was colorless when filtered but turned slightly yellow before it could be vacuum-dried. The compound was readily soluble in aqueous sodium bicarbonate solution.

Anal. Calc'd for $C_{16}H_{16}N_2O_2$: N, 10.44. Found: N, 10.82.

The *semicarbazone*, also soluble in sodium bicarbonate solution, was formed by reaction of the acid with semicarbazide hydrochloride and sodium acetate in hot aqueous solution, and was recrystallized from ethanol, m.p. 187.5° with yellow coloration and gas evolution.

Anal. Calc'd for $C_{11}H_{13}N_3O_3$: N, 17.86. Found: N, 17.73.

Ethyl o-phenylene diacetate was prepared from *o*-phenylene diacetonitrile and sulfuric acid in ethanol (7) in 75–83% yield, n_D^{25} 1.497; b.p. 151–154°/3 mm.; reported (8) 173–174°/10 mm.

Isochroman-3-one-1-carboxylic acid. A mixture of 138 g. of ethyl *o*-phenylene diacetate, 98 g. of N-bromosuccinimide, and 0.5 g. of benzoyl peroxide in 500 ml. of carbon tetrachloride was refluxed for 3 hours. After filtering the succinimide from the chilled mixture, the solvent was removed from the filtrate under reduced pressure, the last traces at steam-bath temperature, leaving 185 g. of orange-colored oil. A mixture of 177 g. of this oil with 600 ml. of propionic acid and 60 ml. of 48% aq. hydrobromic acid was heated in a distilling-flask equipped with a six-inch Vigreux column at such a rate that 430 ml. of distillate was collected in 100 minutes. More propionic acid was removed under reduced pressure at the steam-bath temperature. Except for a small tarry residue, the viscous brown material was dissolved by refluxing overnight with 775 ml. of water. The hot aqueous solution was treated with Norit and, after cooling and partial crystallization, was kept for several days in the refrigerator. The resulting solid was recrystallized from acetic acid to give 51 g. (51%) of slightly yellow isochroman-3-one-1-carboxylic acid, m.p. 149–150°, which was used in further reactions. An additional 10 g. of lower purity was recovered. The purified lactone acid melted at 151–152° and was apparently dimorphic, since earlier purified material had melted at 144–145° and a mixture of the two forms had the higher melting point. Reported (9) m.p. 140°. Crystallization from water gave a hydrate, m.p. 81°, reported 85°. Lower yields of the lactone acid were obtained with several other hydrolytic agents.

Isochroman-3-one-1-carbonyl chloride was obtained from 0.96 g. of the acid, refluxed with 3 ml. of thionyl chloride for 30 minutes. Excess thionyl chloride was removed under reduced pressure at 50°, and the last traces were taken out by reduced pressure distillation with three successive 2-ml. additions of benzene. The residual acid chloride was a viscous oil of light orange color, yield 100%.

Anal. Calc'd for $C_{10}H_7ClO_3$: Cl, 16.84. Found: Cl, 16.92.

Reaction with excess aniline in acetone gave the *anilide*, which was recrystallized from ethanol as colorless plates, m.p. 173–174°.

Anal. Calc'd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90.
Found: C, 71.94; H, 5.11.

The *amide*, from the acid chloride and ammonia in benzene, was recrystallized from ethanol, m.p. 206–207°.

Anal. Calc'd for $C_{10}H_9NO_3$: N, 7.30. Found: N, 7.06.

1-(Carbethoxyamino)isochroman-3-one. To the acid chloride from 1.92 g. of isochroman-3-one-1-carboxylic acid, dissolved in 25 ml. of acetone, at 0°, was added in 3 minutes, with stirring, a solution of 1 g. of sodium azide (10) in 3 ml. of water. After 10 minutes more stirring, 75 ml. of ice-water was added and crystallization was induced by seeding and scratching. The crude tan azide, washed with water and rapidly dried at 0.1 mm., weighed 1.03 g. (48%) and melted with gas evolution at about 69°. It decomposed slowly at room temperature but could be kept in the refrigerator for several weeks. The yield depended on the rapidity with which crystallization could be induced. On a larger scale the yield was lower.

The above azide, in 10 ml. of abs. ethanol, when rapidly heated, evolved nitrogen below the boiling point. After refluxing for 1 hour, the ethanol was removed under reduced pressure to leave an amber syrup which was crystallized from chloroform and petroleum ether with the aid of seed crystals obtained by slow evaporation of an alcohol solution. Yield of the urethan: first crop, 0.65 g. (58%) m.p. 122–123°; second crop, 0.17 g. (15%). M.p. after further purification, 123–124°. The compound was very soluble in ethanol, soluble in chloroform, benzene or ether, insoluble in petroleum ether, cold water, and cold sodium bicarbonate solution, and dissolved in hot water with decomposition.

Anal. Calc'd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57.
Found: C, 61.32; H, 5.37.

An attempted Hofmann degradation of isochroman-3-one-1-carboxamide with one molar quantity of bromine and two of sodium methoxide in dry methanol (11) was not successful.

o-Formylphenylacetic acid. A stirred suspension of 0.75 g. of 1-(carbethoxyamino)isochroman-3-one in 3 ml. of water was heated for 5 minutes on the steam-bath. The solid rapidly changed to an oil which subsequently dissolved. The *o*-formylphenylacetic acid separated as an oil from the cooled solution and crystallized with scratching to a cream-colored solid, yield 0.44 g. (84%), m.p. 107–108°. Colorless flat needles of the same melting point were obtained by recrystallization from benzene. The acid was soluble in hot benzene, hot water, or ether and slightly soluble in cold benzene or cold water.

Anal. Calc'd for $C_9H_8O_3$: C, 65.85; H, 4.91; Mol. wt., 164.15.
Found: C, 65.70; H, 4.94; Neut. equiv., 164.6.

A further small quantity of the acid was recovered as the *semicarbazone*. Ethyl carbamate, m.p. 48–49°, was recovered in 72% yield from the aqueous mother liquor by ether extraction.

A slight excess of semicarbazide hydrochloride added to a dilute aqueous solution of the *o*-formylphenylacetic acid, precipitated the *semicarbazone*, m.p. 220° with yellow coloration and gas evolution. The same derivative was formed directly when 1-(carbethoxyamino)isochroman-3-one was warmed with semicarbazide hydrochloride in aqueous ethanol.

Anal. Calc'd for $C_{10}H_{11}N_3O_3$: C, 54.29; H, 5.01.
Found: C, 54.70; H, 5.02.

The *phenylhydrazone* was rapidly precipitated when the calculated quantity of phenylhydrazine hydrochloride was added to a nearly saturated aqueous solution of the aldehyde acid containing a trace of hydrochloric acid. Colorless needles, m.p. 147–148°, were obtained by recrystallization from aqueous ethanol under carbon dioxide.

Anal. Calc'd for $C_{15}H_{14}N_2O_2$: N, 11.02. Found: N, 11.24.

Both the phenylhydrazone and the semicarbazone dissolved readily in aqueous sodium bicarbonate at room temperature.

o-(Carboxymethyl)phenylglyoxylic acid. Isochroman-3-one-1-carboxylic acid (1.92 g.) was dissolved in 4.1 ml. of 5.0 *M* sodium hydroxide by warming for 15 minutes on the steam-bath. The solution was diluted to 20 ml. and stirred in a water-bath at 45° while 1.05 g. of dissolved potassium permanganate was added dropwise in 50 minutes (12). Stirring and heating were continued for 40 minutes, excess permanganate was destroyed by adding a little ethanol, and the manganese dioxide was filtered off. Thorough ether extraction of the filtrate and washings, concentrated to small volume, led to a syrup when the ether was evaporated. Yield, by recrystallization from benzene, 0.58 g., m.p. after repeated recrystallization, 147–148°, soluble in cold water or warm ethyl acetate.

Anal. Calc'd for $C_{10}H_8O_5$: Equiv. wt., 104.1. Found: Neut. equiv. 104.8.

The *phenylhydrazone,* m.p. 181° with carbon dioxide evolution, formed from a solution of the acid and phenylhydrazine hydrochloride after standing several hours, and recrystallized from ethanol, was a yellow powder.

Anal. Calc'd for $C_{16}H_{14}N_2O_4$: Equiv. wt., 149.2. Found: Neut. equiv., 149.9.

Treatment of the acid with aniline (13) gave an orange-colored oil which was not successfully crystallized. An attempted decarboxylation with sodium bisulfite (14) was likewise unsuccessful.

o-Cyanophenylacetic acid. *o*-Nitrophenylacetic acid was prepared from *o*-nitrotoluene according to Reissert (15) and was converted to the hydrated barium salt of *o*-aminophenylacetic acid (16). The barium salt was converted to the sodium salt (0.12 mole) in aqueous solution and diazotization was conducted with 0.12 mole of sodium nitrite and 0.49 mole of hydrochloric acid in a total volume of about 300 ml. at 2–3°. Excess acid was removed with chilled sodium carbonate solution (0.06 mole). The diazonium salt was added to a potassium cuprocyanide solution with rapid stirring below 3°. The mixture stood at 0° for 30 minutes, was warmed slowly thereafter to 15°, and was finally heated to 50° for an hour and allowed to stand overnight. After dilution to one liter and filtering, the aqueous solution was extracted with ether which was in turn extracted with sodium bicarbonate solution. The resulting aqueous extract was decolorized, chilled, and acidified with conc'd hydrochloric acid to precipitate *o*-cyanophenylacetic acid as tan needles in 51% yield, m.p. 122–123°. Colorless material obtained by vacuum sublimation and recrystallization from benzene had the same melting point.

Anal. Calc'd for $C_9H_7NO_2$: Mol. wt., 161.2; N, 8.69.

Found: Neut. equiv., 160.9; N, 8.84.

Methyl o-cyanophenylacetate, obtained by reaction of the acid with diazomethane, boiled at 107°/1 mm., n_D^{25} 1.5253, d_4^{25} 1.1328.

Anal. Calc'd for $C_{10}H_9NO_2$: C, 68.56; H, 5.19.

Found: C, 68.65; H, 5.52.

An ether solution of methyl *o*-cyanophenylacetate was added to a stirred two-phase mixture of stannous chloride in ether, prepared from 17.7 g. of tin, 140 ml. of ether, and excess hydrogen chloride. A voluminous yellow precipitate separated over a 30-minute period. After 5 hours of stirring, the filtered yellow material, washed with dry ether, gave a negative test with dinitrophenylhydrazine reagent. Treatment with sodium potassium tartrate and sodium bicarbonate produced an oily yellow solid which appeared to contain at least four crystalline components.

ω,ω,ω'-Tribromo-o-xylene. *o*-Xylylene bromide (80 g.) was placed in a 100-ml. flask fitted with a high efficiency reflux condenser and a dropping-funnel with its outlet near the bottom of the flask. The flask was illuminated by a "Photoflood" lamp and heated by an oil-bath maintained at 160° while 27 g. of bromine was added in 50 minutes. After cooling, the brown reaction mixture, seeded with *o*-xylylene bromide, deposited a solid which, upon recrystallization, proved to be *o*-xylylene bromide, 31 g., m.p. 95–96°. The residual liquid of the reaction mixture, diluted with 25 ml. of 90–100° petroleum ether and 5 ml. of ether, and seeded with crystals obtained at the Dry Ice temperature, deposited a solid at refrigerator temperatures. Recrystallization from ether gave colorless plates, 12 g., m.p. 39–40°, and a second crop, 12 g., m.p. 34–36°. The analytical sample melted at 40–41°.

Anal. Calc'd for $C_8H_7Br_3$: Br, 69.92. Found: Br, 69.6.

A preliminary experiment indicated that substantial quantities of this tribromo compound could be obtained by direct bromination of *o*-xylene.

A 1.0-g. sample of the tribromo derivative was refluxed for 22 hours with 0.9 g. of potassium oxalate hydrate in 20 ml. of aqueous ethanol. Most of the alcohol was distilled off on the steam-bath, crystalline material was dissolved with a little sodium bicarbonate, and the remaining brown oil was extracted with ether. Distillation of the dried extract gave 0.18 g. of colorless oil, 80–105°/0.2 mm. A sample of this oil, with 2,4-dinitrophenylhydrazine and alcoholic hydrogen chloride, gave an orange-colored solid of wide melting range which, upon repeated recrystallization, yielded the *2,4-dinitrophenylhydrazone of o-(ethoxymethyl)-benzaldehyde*, m.p. 186–187°, slightly soluble in hot ethanol.

Anal. Calc'd for $C_{16}H_{16}N_4O_5$: C, 61.27; H, 5.57.

Found: C, 61.32; H, 5.37.

When the tribromide was treated with 2 *M* sodium iodide in acetone, sodium bromide (atom-equivalents) was precipitated as follows: 1.06 in 10 minutes, 1.10 in 25 minutes, 2.3 in 10 hours.

SUMMARY

Syntheses are reported as follows: *o*-Formyl- and *o*-acetyl-phenylacetic acids and their phenylhydrazones and semicarbazones; isochroman-3-one-1-carbonyl

chloride and the corresponding amide and anilide; 1-(carbethoxyamino)isochroman-3-one; *o*-(carboxymethyl)phenylglyoxylic acid and its phenylhydrazone; *o*-cyanophenylacetic acid and its methyl ester; ω,ω,ω'-tribromo-*o*-xylene which is incorrectly described in the literature; the 2,4-dinitrophenylhydrazone of *o*-(ethoxymethyl)benzaldehyde.

A satisfactory preparation of isochroman-3-one-1-carboxylic acid is described.

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