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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF DE PAUL UNIVERSITY]

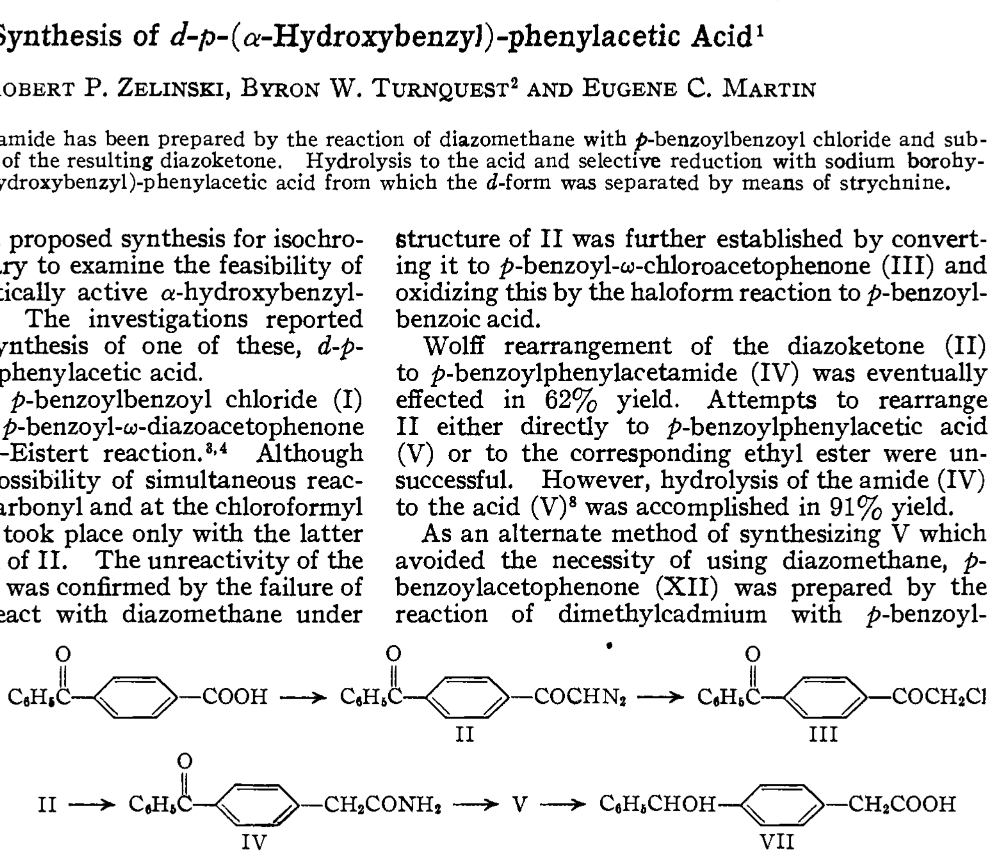
Synthesis of *d-p*-(α-Hydroxybenzyl)-phenylacetic Acid[1]

BY ROBERT P. ZELINSKI, BYRON W. TURNQUEST[2] AND EUGENE C. MARTIN

p-Benzoylphenylacetamide has been prepared by the reaction of diazomethane with *p*-benzoylbenzoyl chloride and subsequent rearrangement of the resulting diazoketone. Hydrolysis to the acid and selective reduction with sodium borohydride yielded *dl-p*-(α-hydroxybenzyl)-phenylacetic acid from which the *d*-form was separated by means of strychnine.

In the course of a proposed synthesis for isochromans it was necessary to examine the feasibility of preparing some optically active α-hydroxybenzylphenylacetic acids. The investigations reported here outline the synthesis of one of these, *d-p*-(α-hydroxybenzyl)-phenylacetic acid.

In the first step *p*-benzoylbenzoyl chloride (I) was converted to *p*-benzoyl-ω-diazoacetophenone (II) by the Arndt–Eistert reaction.[3,4] Although this involved the possibility of simultaneous reaction at the ketone carbonyl and at the chloroformyl group, the reaction took place only with the latter to form a 93% yield of II. The unreactivity of the ketone function in I was confirmed by the failure of benzophenone to react with diazomethane under the conditions employed. This appears to be only the second reported[5] application of the Arndt–Eistert reaction to keto acid chlorides, the other being the conversion of 4-fluorenonecarbonyl chloride to methyl 4-fluorenoneacetic acid.[6,7] The structure of II was further established by converting it to *p*-benzoyl-ω-chloroacetophenone (III) and oxidizing this by the haloform reaction to *p*-benzoylbenzoic acid.



Wolff rearrangement of the diazoketone (II) to *p*-benzoylphenylacetamide (IV) was eventually effected in 62% yield. Attempts to rearrange II either directly to *p*-benzoylphenylacetic acid (V) or to the corresponding ethyl ester were unsuccessful. However, hydrolysis of the amide (IV) to the acid (V)[8] was accomplished in 91% yield.

As an alternate method of synthesizing V which avoided the necessity of using diazomethane, *p*-benzoylacetophenone (XII) was prepared by the reaction of dimethylcadmium with *p*-benzoylbenzoyl chloride. From this the *p*-benzoylphenylacetic acid (V) was obtained by the Kindler modification of the Willgerodt reaction. The over-all yield from *p*-benzoylbenzoyl chloride was 33% compared to the 52% *via* the Arndt–Eistert procedure. However, the alternate method is considerably more rapid.

Selective reduction of the ketone carbonyl in keto esters has been effected by aluminum isopropoxide.[9] Conversion of V to the corresponding

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[1] This investigation was made possible by a grant from the Research Corporation.

[2] Abstracted from the thesis presented by Byron W. Turnquest to the Graduate School of De Paul University in partial fulfillment of the requirements for the degree of Master of Science (1951).

[3] B. Eistert, "Newer Preparative Methods of Organic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1948, p. 513.

[4] W. E. Bachmann and W. S. Struve, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 38.

[5] *Ibid.*, p. 46.

[6] W. E. Bachmann and J. C. Sheehan, THIS JOURNAL, **62**, 2687 (1940).

[7] However, unlike benzophenone, fluorenone reacts with diazomethane; R. F. Schultz, E. D. Schultz and J. Cochran, *ibid.*, **62**, 2902 (1940).

[8] The identity of the only reported acid of this series, *o*-benzoylphenylacetic acid, has not been proved; C. F. Koelsch and R. V. White, *ibid.*, **65**, 1639 (1943).

[9] A. L. Wilds, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 191.

methyl ester (VI) followed by reaction with the isopropoxide and subsequent hydrolysis resulted in only a 9% yield of *dl-p*-(α-hydroxybenzyl)-phenylacetic acid (VII). However, direct reduction of the acid with sodium borohydride[10] produced VII in 91% yield.

The final step, resolution of *dl-p*-(α-hydroxybenzyl)-phenylacetic acid, was accomplished *via* the strychnine salt (VIII). The *l*-α-phenylethylamine salt (IX) and the quinine salt (X) were also solids, but the diastereoisomers could not be separated. Hydrolysis of the strychnine salt yielded *d-p*-(α-hydroxybenzyl)-phenylacetic acid (XI).

Experimental[11]

***p*-Benzoyl-ω-diazoacetophenone** (II).—In one hour a solution of 37.9 g. of *p*-benzoylbenzoyl chloride[12] (I) in 900 ml. of anhydrous ether was added dropwise with stirring to 14.8 g. of diazomethane in 1500 ml. of anhydrous ether held below 8°. After another four hours at this temperature it was then allowed to stand overnight at room temperature. After having been cooled to 0°, 27.2 g. of crystallized product, m.p. 114–116°, was separated. An additional 11.3 g., m.p. 110–114°, was obtained by evaporation of the ether. Recrystallization of this portion from 110 ml. of a solution of equal volumes of benzene and petroleum ether, b.p. 60–70°, yielded 8.7 g., m.p. 114–116°, a total yield of 35.9 g. (93%) of *p*-benzoyl-ω-diazoacetophenone (II).

The diazoketone in this state of purity was suitable for rearrangement to the amide (IV). However, for analytical purposes a sample was purified by chromatography on activated alumina using, as the developing agent, a 9:1 solution of benzene and ethyl acetate. The pure diazoketone melted at 116–117°.

Anal. Calcd. for $C_{15}H_{10}O_2N_2$: C, 71.98; H, 4.03; N, 11.20. Found: C, 72.17; H, 4.11; N, 11.35.

When 1.1 g. of benzophenone and 0.26 g. of diazomethane in 100 ml. of anhydrous ether were mixed at 0–5° and held at room temperature for 24 hours, evaporation of the solvent in a dry air stream yielded only unreacted benzophenone.

***p*-Benzoyl-ω-chloroacetophenone** (III).—To a solution of 0.50 g. of *p*-benzoyl-ω-diazoacetophenone in 7 ml. of dioxane there was added 6 ml. of concentrated hydrochloric acid. After the brisk evolution of nitrogen ceased, the mixture was warmed on a water-bath for ten minutes, diluted with 90 ml. of water and cooled. The 0.51 g. of precipitate was extracted with 20 ml. of petroleum ether, b.p. 60–70°, from which 0.22 g. of solid was obtained by cooling. Two recrystallizations from 15-ml. volumes of petroleum ether yielded 0.04 g., m.p. 86.5–88°. The insoluble residue from the extraction was dissolved in 5 ml. of dioxane and treated with 5 ml. of concentrated hydrochloric acid for 12 hours at 20°. Precipitation with water and recrystallization from 15 ml. of petroleum ether b.p. 60–70°, produced an additional 0.10 g. of product, m.p. 86.5–88°, making the total yield of *p*-benzoyl-ω-chloroacetophenone (III) 0.14 g. (27%).

Anal. Calcd. for $C_{15}H_{11}O_2Cl$: C, 69.63; H, 4.29. Found: C, 69.62; H, 4.36.

One-tenth of a gram of III in 5 ml. of dioxane was oxidized by sodium hypoiodite.[13] Acidification, treatment with Norit and recrystallization from ethanol yielded 0.03 g. of *p*-benzoylbenzoic acid, m.p. 195–196°, mixed m.p. 195–199°. The pure acid melts at 197–200°.[12]

***p*-Benzoylphenylacetamide** (IV).—The general procedure of Arndt and Eistert[14] for the rearrangement of ω-diazoacetophenone was used.

Ten grams of II was heated under reflux for 6.5 hours with 60 ml. of dioxane, 40 ml. of 28% ammonium hydroxide and 22 ml. of 10% silver nitrate solution. The mixture was filtered and the filtrate was diluted with 500 ml. of water and held overnight at 5°. Extraction of the resultant precipitate with a total of 500 ml. of water for 16 hours in a soxhlet extractor, followed by chilling the aqueous solution, yielded 5.8 g. (61%) of *p*-benzoylphenylacetamide (IV), m.p. 134–135°. Recrystallization from water yielded a purer product, m.p. 136–137°.

Anal. Calcd. for $C_{15}H_{13}O_2N$: C, 75.32; H, 5.43; N, 5.84. Found: C, 75.29; H, 5.47; N, 5.86.

An attempt to rearrange II directly to *p*-benzoylphenylacetic acid (V) was made using the procedure employed by Arndt and Eistert[15] for the preparation of 1-naphthylacetic acid. A solution of 1.3 g. of II in 20 ml. of dioxane was added dropwise to 0.60 g. of silver oxide and 0.8 g. of sodium thiosulfate dissolved in 50 ml. of water at 75°. After two hours at 75–80° and 15 minutes at 90–100° the mixture was filtered. Removal of most of the solvent, followed by cooling and filtering, permitted separation of 0.54 g. of starting material. From the remaining solution there was eventually obtained 0.09 g. of impure acid, m.p. 145–160°.

Application of the method of Arndt and Eistert[15] for the rearrangement to the ethyl ester was attempted with a solution of 2.0 g. of II in 50 ml. of anhydrous ethanol and 0.68 g. of silver oxide. After having been heated under reflux for two hours, the alcohol was removed and the residue was boiled with 40 ml. of 20% aqueous potassium hydroxide and 30 ml. of ethanol for 1.5 hours. Most of this alcohol was also removed, the residue was decolorized and then acidified. The only product was a red oil.

***p*-Benzoylphenylacetic Acid** (V).—A mixture of 7.0 g. of *p*-benzoylphenylacetamide (IV) and 250 ml. of 20% aqueous potassium hydroxide was boiled for 1.5 hours, decolorized, cooled and acidified. Filtration yielded 7.0 g. of white solid, m.p. 112–114°. Recrystallization from 180 ml. of an equivolume solution of benzene and petroleum ether, b.p. 60–70°, left 6.4 g. (91%) of *p*-benzoylphenylacetic acid (V), m.p. 112–114°.

Anal. Calcd. for $C_{15}H_{12}O_3$: C, 74.98; H, 5.04; neut. equiv., 240.2. Found: C, 74.91; H, 5.35; neut. equiv., 240.2.

Methyl *p*-Benzoylphenylacetate (VI).—A solution of 2.5 g. of V in 10 ml. of anhydrous ether was added to 0.50 g. of diazomethane in 50 ml. of ether at 0°. After 15 minutes the ether and excess diazomethane were evaporated. The viscous residue solidified after standing overnight at 5°. Recrystallization of the solid, m.p. 56–57°, from petroleum ether, b.p. 60–70°, yielded 2.3 g. (92%) of methyl *p*-benzoylphenylacetate (VI), m.p. 56–58°.

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.46; H, 5.60.

***dl-p*-(α-Hydroxybenzyl)-phenylacetic Acid (VII). Reduction with Aluminum Isopropoxide.**—A solution of 4.0 g. of aluminum isopropoxide in 50 ml. of isopropyl alcohol was boiled with 2.3 g. of VI under conditions described for the reduction of benzophenone.[16] After three hours, the acetone test was negative and most of the isopropyl alcohol was removed by distillation *in vacuo*. The residue was hydrolyzed by treatment with 152 ml. of 1 *M* hydrochloric acid. This solution was concentrated on a steam-bath to 50 ml., and the residue was twice extracted with 100-ml. portions of ether. The residue left by evaporation of the ether was saponified by refluxing for 1.5 hours with 100 ml. of 6 *M* aqueous potassium hydroxide. Decolorization and acidification precipitated 0.40 g. of solid, m.p. 100–101°. Three recrystallizations from benzene left 0.20 g. (9%) of *dl-p*-(α-hydroxybenzyl)-phenylacetic acid (VII), m.p. 108–109°, mixed m.p. 80–85° with *p*-benzoylphenylacetic acid.

Reduction with Sodium Borohydride.—The general directions[10] for use of this reagent were made specific. A solution of 10.8 g. of V and 2.0 g. of sodium hydroxide was added in portions to a mixture of 0.70 g. of sodium borohydride in 10 ml. of water. The mixture was maintained at 60–75° for 40 minutes and then boiled for one-half hour with 6.0 g. of sodium hydroxide. Cooling, acidification and two recrystallizations of the resultant solid from 200-ml. volumes of benzene yielded 9.9 g. (91%) of VII, m.p. 108–109°.

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[10] S. W. Chaikin and W. G. Brown, THIS JOURNAL, **71**, 122 (1949).

[11] Analyses by Micro-Tech Laboratory, Skokie, Illinois, and Clark Microanalytical Laboratory, Urbana, Illinois.

[12] E. Wertheim, THIS JOURNAL, **55**, 2541 (1933); J. F. Norris and V. W. Ware, *ibid.*, **61**, 1418 (1939).

[13] Shriner and Fuson, "The Systematic Identification of Organic Compounds," 3rd ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 138.

[14] F. Arndt and B. Eistert, *Ber.*, **68**, 200 (1935).

[15] *Ibid.*, p. 204.

[16] A. L. Wilds, ref. 9, p. 203.

Anal. Calcd. for $C_{15}H_{14}O_3$: C, 74.37; H, 5.82; neut. equiv., 242.2. Found: C, 74.62; H, 5.79; neut. equiv., 242.3.

***d-p*-(α-Hydroxybenzyl)-phenylacetic Acid (XI).**—A solution of 2.8 g. of strychnine in 70 ml. of hot dioxane was added to 2.0 g. of VII in 10 ml. of dioxane and the whole was evaporated on a steam-bath to a volume of 25 ml. Dilution with 25 ml. of water and chilling overnight yielded 0.05 g. of crystals, m.p. 119–126°. The mother liquor was concentrated to a volume of 30 ml. and, after addition of 5 ml. of water and chilling, produced an additional 0.65 g. of solid. The 0.70 g. of strychnine salts was recrystallized from 50% dioxane to yield 0.24 g. of material, m.p. 120–127°, $[\alpha]^{25}\mathrm{D}$ −26° (methanol, *c* 0.25). Dilution of the mother liquor with another 10 ml. of water precipitated an additional 2.0 g. of salts which, after three recrystallizations, yielded 0.56 g. of strychnine salt having physical constants identical with those of the first two crops. Further dilution of the mother liquor with 25 ml. of water gave 0.34 g. of material, m.p. 112–127°, which was not subsequently employed. After combination of the first three crops, the constants were m.p. 120–127°, $[\alpha]^{25}\mathrm{D}$ −27° (methanol, *c* 0.60). Recrystallization from 8 ml. of 50% dioxane finally yielded 0.66 g. of the pure strychnine salt (VIII) of *d-p*-(α-hydroxybenzyl)-phenylacetic acid, m.p. 120–127°, $[\alpha]^{25}\mathrm{D}$ −27° (methanol, *c* 0.60).

Anal. Calcd. for $C_{36}H_{36}O_5N_2$: C, 74.99; H, 6.28; N, 4.86. Found: C, 74.95; H, 6.40; N, 4.99.

The strychnine salt (VIII) was treated with 10% sodium hydroxide, the mixture was filtered and the mother liquor was acidified. Recrystallization of the acid from 10 ml. of benzene gave 0.18 g. of *d-p*-(α-hydroxybenzyl)-phenylacetic acid (XI), m.p. 121.5–123°, $[\alpha]^{25}\mathrm{D}$ +2.8° (dioxane, *c* 5.9).

Attempted Resolutions with Other Amines. *l*-α-Phenylethylamine Salt (IX).—A solution containing 3.0 g. of VII and 1.6 g. of *l*-α-phenylethylamine in 180 ml. of ethyl acetate slowly deposited 3.8 g. of IX, the *l*-α-phenylethylamine salt of VII. Recrystallization from ethyl acetate, butanone or isopropyl alcohol failed to alter the physical constants of IX, m.p. 140–142°, $[\alpha]^{25}\mathrm{D}$ −5.9° (ethanol, *c* 5).

Anal. Calcd. for $C_{23}H_{25}O_3N$: C, 76.01; H, 6.93; N, 3.85. Found: C, 76.24; H, 7.27; N, 3.74.

When IX was treated with alkali, VII was recovered unchanged.

Quinine Salt (X).—Upon cooling a solution of 1.0 g. of VII and 1.3 g. of quinine in 40 ml. of ethanol, 1.9 g. of X, the quinine salt of VII, crystallized. Three recrystallizations from ethanol failed to change the physical constants, m.p. 204–206°, $[\alpha]^{25}\mathrm{D}$ −114 (methanol, *c* 0.4).

Anal. Calcd. for $C_{35}H_{38}O_5N_2$: C, 74.18; H, 6.76; N, 4.94. Found: C, 74.71; H, 7.06; N, 5.18.

When X was treated with alkali, VII was recovered unchanged.

Attempts to prepare salts of VII with brucine, D-desoxyephedrine, quinidine and cinchonine produced only oils which could not be crystallized.

***p*-Benzoylacetophenone (VII).**—Following the general procedure described by Cason[17] 14.3 g. of methyl bromide was converted to dimethylcadmium in 200 ml. of dry benzene. To this boiling solution 17.3 g. of *p*-benzoylbenzoyl chloride, dissolved in 225 ml. of benzene, was added and the whole was boiled for one hour. After it had been cooled, the mixture was hydrolyzed with ice and dilute sulfuric acid. The benzene layer was washed successively with water, a saturated solution of sodium bicarbonate and then with water. Acidification of the alkaline wash yielded 1.4 g. of *p*-benzoylbenzoic acid.

The 14.4 g. of crude product left by the evaporation of the benzene layer was boiled for one hour with 210 ml. of 50% formic acid and 2 ml. of concentrated sulfuric acid. The solution was then made basic and extracted with three 300-ml. portions of ether. Acidification of the alkaline solution gave 1.6 g. of *p*-benzoylbenzoic acid. Evaporation of the dried ether solution left 10.2 g. (70%) of *p*-benzoylacetophenone, m.p. 82–85°, which was sufficiently pure for use in the Kindler reaction. For analysis a sample was twice chromatographed over 25-g. portions of activated alumina (Merck and Co., Inc., 60–80 mesh) using an eluate containing petroleum ether, b.p. 60–70°, and benzene in a ratio of two to one. This permitted a 42% recovery of pure *p*-benzoylacetophenone, m.p. 83–84°.

Anal. Calcd. for $C_{15}H_{12}O_2$: C, 80.34; H, 5.39. Found: C, 80.06; H, 5.10.

Hypoiodite oxidation[13] of 0.10 g. gave iodoform, m.p. 118–120° and a 20% yield of *p*-benzoylbenzoic acid.

When methyl iodide was substituted for methyl bromide in attempts to prepare XII, a 71% yield of product melting at 106–107° was obtained. The nature of this product is being investigated.

Preparation of *p*-Benzoylphenylacetic Acid by the Kindler Reaction.—The general directions of Schwenk and Block[18] were followed. A mixture of 2.20 g. of *p*-benzoylacetophenone, 0.67 g. of sulfur and 1.48 g. of morpholine was boiled for 2.5 hours. It was then dissolved in 100 ml. of chloroform, washed with water and dilute hydrochloric acid, and dried. Evaporation left an oil which could not be crystallized. It was, therefore, hydrolyzed by boiling it for five hours with 50 ml. of 50% sulfuric acid in 100 ml. of acetic acid. The solution was then cooled and extracted with three 50-ml. portions of ether. The ether solutions were combined and washed with 100 ml. of 12% sodium hydroxide solution. The alkaline wash was then acidified and re-extracted with three 50-ml. portions of ether. Washing the ether phase with aqueous sodium bicarbonate separated the desired acid from a persistent, red impurity, soluble in sodium hydroxide solution, which otherwise was difficult to remove. Acidification of the bicarbonate solution furnished 1.36 g. of acid, m.p. 108–114°, which gave 1.12 g. (48%) of *p*-benzoylphenylacetic acid, m.p. 111–112°.

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[17] J. Cason, THIS JOURNAL, **68**, 2078 (1946).

[18] E. Schwenk and E. Block, *ibid.*, **64**, 3051 (1942).