[CONTRIBUTION FROM THE RESEARCH LABORATORY, EX-LAX, INC., BROOKLYN 17, N. Y.]

Bis(p-hydroxyphenyl)acetic Acid

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The preparation of bis(p-hydroxyphenyl)acetic acid from phenol and glyoxylic acid is described. As a by-product of this condensation 3-(p-hydroxyphenyl)-2-coumaranone is formed. It is shown that the bis(p-hydroxyphenyl)acetic acid described by Kaufmann and Schierholt is actually 4,4′-dihydroxybenzil.

Recently Kaufmann and Schierholt[1] published a paper on the preparation of the previously unknown bis(p-hydroxyphenyl)acetic acid (I). This same acid was prepared in our laboratory. However, since our acid has properties entirely different from those of the acid described by the two German investigators, it seems appropriate to publish our results.

The acid was prepared for use as an intermediate in the synthesis of compounds having the grouping $(p)\mathrm{HOC_6H_4}{-}\overset{|}{\underset{|}{\mathrm{C}}}{-}\mathrm{C_6H_4OH}(p')$ and was expected to have laxative properties.[2]

First, an attempt was made to synthetize I by the same method which Kaufmann and Schierholt had used with apparent success, namely by heating the 1,1,1-trichloro-2,2-bis(p-hydroxyphenyl)ethane-(II) with aqueous alkali. No acid was isolated from the reaction mixture, only the following three phenols: 4,4′-dihydroxybenzil (III), 1,1-dichloro-2,2-bis(p-hydroxyphenyl)ethylene (IV) and 4,4′-dihydroxytolan (V). In the formation of III and of V, a rearrangement must have taken place similar to that observed by Zincke and Fries[3] who, when reducing the unsymmetrical II, obtained the symmetrical 4,4′-dihydroxystilben. When II was reacted with methanolic potassium hydroxide, then IV was obtained in 72% yield.

From the scant description of their acid which Kaufmann and Schierholt give, having made no derivatives, it is clear that their alleged acid is 4,4′-dihydroxybenzil. The properties of their acid, the melting point of 247°, its light yellow color, its elementary analysis and the solubilities all check with those of 4,4′-dihydroxybenzil (III), a compound having acidic properties. Unfortunately, I could not make a direct comparison because Dr. Kaufmann wrote that he did not have a trace of the acid left.

In the second method tried, the acid I was obtained by demethylating the bis(p-anisyl)acetic acid (VII) with pyridine hydrochloride. However, this method has the drawback that acid VII could be obtained only in small yields, by heating the 1,1-dichloro-2,2-bis(p-anisyl)ethylene (VI) with alcoholic sodium ethylate at higher temperature. No acid was obtained by heating IV under the same conditions.

The third method, which failed in the hands of Kaufmann and Schierholt, was the most successful in our hands. Phenol was condensed with glyoxylic acid, whereby acid I was obtained in yields of 45–58%. As a by-product of this reaction, a phenol was isolated, namely 3-(p-hydroxyphenyl)-2-coumaranone (VIII). This formed by *ortho-para* condensation and lactone formation of the primarily formed (o-hydroxyphenyl)-(p-hydroxyphenyl)acetic acid. The dimethylether of this acid, obtained by methylation of VIII, yielded the 2,4′-dimethoxybenzophenone on oxidation.

EXPERIMENTAL[4]

1,1,1-Trichloro-2,2-bis(p-hydroxyphenyl)ethane (II). This compound was made by the following improved procedure. One dropping funnel was filled with a solution of 37.6 g. of phenol, 33.1 g. of chloral hydrate and 20 ml. acetic acid; the other with 30 ml. concentrated sulfuric acid. The contents of these were added simultaneously, over a period of 1 hr., into a reaction flask, keeping the exothermic reaction at 50–55°. The red mixture was poured into ice water the next day. The crystalline mass was washed free of sulfate and dried at 50°. It was purified by dissolving it in 60 ml. of warm ethanol, adding 240 ml. of benzene and letting the solution stand overnight at room temperature. The crystals contained one mole of solvate benzene, which they lost at 110°. Calcd. for $\mathrm{C_{14}H_{11}O_2Cl_3{\cdot}C_6H_6}$: Benzene: 19.7; loss in weight 19.9 ± 0.5.

The compound, free of solvent, melted at 199–204°.

Reaction of II *with aqueous potassium hydroxide.* A solution of 31.7 g. of II in 200 ml. of 3N potassium hydroxide was refluxed for 30 min., then cooled, 400 ml. water was added and the solution saturated with $\mathrm{CO_2}$. The dried, brown precipitate was extracted by refluxing with 2 portions of 200 ml. each of benzene. The crystals (3.2 g.) consisted of needles as well as granules. The observation that the thin needles dissolve first on reheating with benzene is helpful in their separation.

The needles, recrystallized from 20% ethanol, melted at 211–214° and were proven to be identical with compound IV.

The granular crystals (V) melted at 214.6–215.1°. They did not contain chlorine and gave the red color and the

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(1) H. P. Kaufmann and J. Schierholt, *Pharm. Zentralhalle*, **96**, 443 (1957).

(2) M. H. Hubacher, S. Doernberg, and A. Horner, *J. Am. Pharm. Assoc.*, **42**, 23 (1953).

(3) Th. Zincke and K. Fries, *Ann.*, **325**, 26 (1902).

(4) All melting points are corrected. Molecular weights were determined by the Signer method, as described by E. P. Clark, *Ind. Eng. Chem., Anal. Ed.*, **13**, 820 (1941).

red compound described by Zincke and Münch[5] for 4,4′-dihydroxytolan, and analyzed.

Anal. Calcd. for $C_{14}H_{10}O_2$: C, 79.96; H, 4.79; mol. wt. 210. Found: C, 80.21; H, 5.23; mol. wt. 215.

The acetylderivative of V, crystallized from ethanol, melted at 199.3–201.4°.

4,4′-Dihydroxybenzil (III). The aqueous, alkaline solution from the reaction of II with 3*N* potassium hydroxide, after removal of the phenolic part, yielded a precipitate on acidification (2.8–4.6 g.). This was purified by sublimation at 220° and 10 microns pressure, then the yellowish sublimate was crystallized from 41% ethanol. The pale yellow crystals melted at 250.2–251.4°[6] and proved to be 4,4′-dihydroxybenzil[6] (III).

Anal. Calcd. for $C_{14}H_{10}O_4$: C, 69.42; H, 4.13; mol. wt. 242. Found: C, 69.79; H, 4.63; mol. wt. 240.

The diacetylderivative of III, pale yellow crystals from 41% ethanol, melted at 88.0–89.2°,[7] the dibenzoylderivative at 168.9–169.6°.[8]

When III was reacted with *o*-phenylendiamine, a yellow compound melting at 330.4–331.0° was obtained. This compound, when mixed with 2,3-bis(*p*-hydroxyphenyl)quinoxaline (m.p. 326–328°) kindly furnished by Dr. H. Gilman,[9] melted at 327–330°.

Dipropionylderivative of III. This compound, prepared from above III as well as from authentic 4,4′-dihydroxybenzil, formed pale yellow needles (from ethanol) and melted at 77.1–77.5°.

Anal. Calcd. for $C_{20}H_{18}O_6$: C, 67.77; H, 5.15; mol. wt. 354. Found: C, 67.48; H, 5.36; mol. wt. 363.

1,1-Dichloro-2,2-bis(p-hydroxyphenyl)ethylene (IV). A solution of 15.9 g. of II in 100 ml. 3*N* methanolic potassium hydroxide was refluxed for 30 min. After adding 300 ml. ice water, the purple solution was acidified. The precipitate was crystallized from 500–600 ml. 20% ethanol, yielding 9.8 to 10.4 g. (70–74%) crystals (m.p. 210–213° dec.) of pale yellow color. The pure compound (IV), which may also be crystallized from benzene (1 g. in 70 ml.) formed colorless needles, melting at 214–215° with slight dec., when introduced into the bath at 211°, raising the temperature of the latter 1° a minute. The solution of IV in concentrated sulfuric acid is red.[10]

Anal. Calcd. for $C_{14}H_{10}O_2Cl_2$: C, 59.81; H, 3.59; Cl, 25.23; mol. wt. 281. Found: C, 59.90; H, 3.60; Cl, 24.76; mol. wt. 283.

Diacetyl derivative of IV. Crystallized from a considerable amount of ethanol, it melted at 141.7–142.0°.

Anal. Calcd. for $C_{18}H_{14}O_4Cl_2$: C, 59.18; H, 3.83; Cl, 19.45; mol. wt. 365. Found: C, 59.07; H, 3.96; Cl, 19.24; mol. wt. 382.

This acetyl derivative, when oxidized in acetic acid solution with CrO_3, yielded 4,4′-diacetoxybenzophenone, m.p. 152.1–152.6°.

Dipropionyl derivative of IV. This compound, colorless crystals from ethanol, melted at 82.0–82.6°.

Anal. Calcd. for $C_{20}H_{18}O_4Cl_2$: C, 61.06; H, 4.58; Cl, 18.04. Found: C, 61.16; H, 4.95; Cl, 18.01.

1,1-Dichloro-2,2-bis(p-anisyl)ethylene (VI). Two-tenths mole (69.1 g.) of 1,1,1-trichloro-2,2-bis(*p*-anisyl)ethane (m.p. 83–86°) made by a procedure similar to the one by which II was prepared, was refluxed for 1 hr. with 200 ml. of 3*N* methanolic potassium hydroxide. The resulting compound, crystallized from 600 ml. of ethanol, melted at 110–112° (literature 113°[11a]); yield 48–55 g. (77–89%).

Bis(p-anisyl)acetic acid (VII). A solution of 15.5 g. of VI in 100 ml. of absolute ethanol containing 6.9 g. metallic sodium dissolved (ratio 1 mole to 6 g.-atom) was heated in an all-nickel autoclave for 8 hr. to 180°. Only a small part of VI reacted to the acid VII (2.5 g.). The latter, crystallized from 41% ethanol and then sublimed at 105° and 16 microns pressure, melted at 110.0–110.8°.[11]

Various changes in the experimental conditions did not improve the yield; at higher reaction temperature, tarry matter was formed.

Bis(p-hydroxyphenyl)-acetic acid (I). a. *By demethylation of* VII. Conventional demethylation methods yielded only tars. The Prey method,[12] however, gave good results. A mixture of 1.0 g. of VII and 3.0 g. of pyridine hydrochloride was heated for 40 min. to 210°. The reaction mixture was dissolved in water, acidified, and extracted with ether. The oil, on digestion with a small quantity of benzene, became crystalline. These crystals of the acid I, contained 1 mole of solvate benzene and were found to be identical in every respect to those obtained by method b.

b. *By condensing glyoxylic acid with phenol.* A solution of 37.6 g. (0.2 mole) of phenol and 2 ml. water was placed in a small flask fitted with a stirrer and thermometer. Also added was half of a solution made from 16.1 g. (0.1 mole) of glyoxylic acid (92%; Kay-Fries Chemicals, Inc., West Haverstraw, N. Y.) and 10 ml. 10*N* sulfuric acid. The mixture was heated to 30° and the heat source withdrawn. The exothermic reaction will start slowly, only after 10 to 60 min. The temperature must not go above 50°. When it has fallen to 40°, then the second half of the solution is added.

Experience has shown that when the reaction is done at higher temperature (70°), then it may easily go out of control and heat to its boiling point (110°). In such case, the crude acid is more difficult to purify, since it contains more gummy matter.

The homogeneous, almost colorless reaction mixture becomes turbid and viscous on cooling to 20°. After standing a few days at room temperature, it will usually solidify to a white crystal mass. It may be worked up before crystallization sets in. It is dissolved in 100 ml. water, extracted by ether and the ether extract in turn by 240–280 ml. of 2*N* sodium carbonate.

The phenolic part, an oil, yields 3.5–6.4 g. of phenol on distillation. The oily residue in the distillation flask is refluxed with a small amount of benzene and on cooling, crystals of VIII form (0.6–1.3 g., m.p. 145–165°).

The acid, left after the evaporation of the ether, is a light tan oil which, after shaking with 50 ml. warm benzene, will very slowly yield fine white needles. They are filtered off and washed with benzene, sucked free from oily matter and dried at 50–60°.

The crude acid (39–44 g.) is recrystallized from 3.7–4.4 l. of 1,2-dichloroethane. The acid will crystallize in the form of long, white needles sticking to the walls of the flask. They contain 1 mole of solvent, which they lose at 125°. The yield of solvent free acid (I) is 22.1–28.3 g. (45–58%), m.p. 146.5–151.0°.

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(5) Th. Zincke and S. Münch, *Ann.*, **335**, 184 (1904) give a m.p. of 220–225° for 4,4′-dihydroxytolan and a m.p. of 198° for its acetylderivative.

(6) The melting point of 4,4′-dihydroxybenzil is given in the literature variously from 235–252°.

(7) R. E. Vanderlinde, F. D. Vasington, and W. W. Westerfield, *J. Am. Chem. Soc.*, **77**, 4178 (1955) give a m.p. of 87° for the 4,4′-diacetoxybenzil.

(8) A. Schönberg and O. Krämer, *Ber.*, **55**, 1189 (1922) give a m.p. of 170° for the dibenzoylcompound of 4,4′-dihydroxybenzil.

(9) H. Gilman and H. S. Broadbent, *J. Am. Chem. Soc.*, **70**, 2621 (1948).

(10) After this work was finished, it was found that this compound was mentioned by M. Trojna and J. Hubacek, *Chem. Abstr.*, **51**, 11297d (1957). They obtained it in a yield of 35% by heating II with aqueous sodium hydroxide. Their compound melted at 210°.

(11) (a) P. Fritsch and F. Feldmann, *Ann.*, **306**, 78, 83 (1899). (b) R. Quelet and J. Gavarret, *Chem. Abstr.*, **44**, 5331i (1950). (c) E. Buchta and H. Weidinger, *Chem. Abstr.*, **48**, 3938h (1954), a m.p. of 111°.

(12) V. Prey, *Ber.*, **74**, 1219 (1941); **75**, 445 (1942).

The acid may also be recrystallized by dissolving it in pure ether (1 g. in 2 ml.), then adding 5 ml. benzene; or from chloroform, in which it is scarcely soluble, by extracting it with that solvent in a modified Soxhlet. The crystals thus obtained contain 1 mole of solvent:

Theory for Formula	Solvent Content	Found: Loss in Weight at 110°, %
$C_{14}H_{12}O_4 \cdot CHCl_3$	32.85	31.9
$C_{14}H_{12}O_4 \cdot (ClCH_2)_2$	28.86	27.6 ± 1.0
$C_{14}H_{12}O_4 \cdot C_6H_6$	24.22	23.9 ± 0.4

The pure acid (I) melts at 148–151°, then usually solidifies again and now melts at 157.9–159.1°.

Anal. Calcd. for $C_{14}H_{12}O_4$: C, 68.84; H, 4.95; mol. wt. 244. Found: C, 68.80; H, 4.95; neut. equiv. 245.

This acid is very soluble in water, ethanol, ether, acetone, and acetic acid. By heating a mixture of I with $CaCO_3$ (1 g. and 5 g.) to 250°, a small quantity of 4,4′-dihydroxydiphenylmethane was obtained.

By treatment of I in pyridine with acetic anhydride, a noncrystalline acetylderivative was obtained, which on oxidation with CrO_3 in acetic acid, yielded 4,4′-diacetoxybenzophenone, m.p. 153°.

Methylester of I. By treating I with ethereal diazomethane solution an oil was obtained which, on rubbing with benzene, became crystalline. After crystallizations from benzene (1 g. in 100 ml.), this ester melted at 150.5–152.6°.

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.74; H, 5.50. Found: C, 70.10; H, 5.36.

The monomethyl ether of this ester has only recently been described.[13]

Methyl ester of VII. By treating the acid (I) dissolved in 5*N* sodium hydroxide with an excess of dimethyl sulfate and recrystallizing the insoluble reaction product from methanol, crystals were obtained which melted at 65.0–65.5° (lit. 66–67°[11a]). By hydrolyzing this methylester, acid VII was obtained.

Ethyl ester of I. This ethyl ester, made from 10 g. of I, 50 ml. ethanol and 1 ml. concentrated sulfuric acid, was purified by dissolving it in the minimum amount of warm acetone and then adding benzene; or by crystallization from a considerable quantity of benzene. Colorless crystals, m.p. 163.3–165.7°. They were very soluble in acetone and ethanol.

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.58; H, 5.92. Found: C, 70.81; H, 5.85.

3-(p-Hydroxyphenyl)-2-coumaranone (VIII). This phenol, formed as a by-product in the condensation of phenol with glyoxylic acid, can be purified by sublimation at 150° at 10 microns pressure, followed by crystallizations from benzene (1 g. in 27 ml.); fine needles melting at 168.8–169.5°.[14]

Anal. Calcd. for $C_{14}H_{10}O_3$: C, 74.33; H, 4.42; mol. wt. 226. Found: C, 74.59; H, 4.87; mol. wt. 233.

The initially colorless solution of this phenol in 0.1*N* sodium hydroxide slowly turns to yellow and then to brown.

Acetyl derivative of VIII. The acetylderivative, crystallized from 41% ethanol, melted at 94.6–95.8°.

Anal. Calcd. for $C_{16}H_{12}O_4$: C, 71.64; H, 4.47. Found: C, 71.60; H, 4.59.

(p-Methoxyphenyl)-(o-methoxyphenyl)acetic acid (IX). A solution of 3.0 g. of VIII in 30 ml. 5*N* sodium hydroxide was treated with 3 portions of 5 ml. each of dimethyl sulfate, keeping the mixture alkaline by addition of 40 ml. 5*N* sodium hydroxide. The alkali insoluble oil solidified on cooling (3.0 g.) and is the methyl ester of IX. On acidification of the alkaline solution, an oil fell out, which soon solidified (0.6 g., m.p. 139–140°). This acid, after crystallizations either from 50% acetic acid or benzene, formed white crystals melting at 140.0–141.0° (IX).

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.58; H, 5.89; $—OCH_3$, 22.8; mol. wt. 272. Found: C, 71.17; H, 5.98; $—OCH_3$, 24.4; neut. equiv. 275.

The methyl ester of IX. This ester may be recrystallized from 41% ethanol, or better yet by dissolving it out of a Soxhlet thimble with petroleum ether. It forms colorless crystals, m.p. 70.3–71.0°. On alkaline hydrolysis the acid IX is obtained.

Anal. Calcd. for $C_{17}H_{18}O_4$: C, 71.33; H, 6.29; $—OCH_3$, 32.5; mol. wt. 286. Found: C, 71.95; H, 6.31; $—OCH_3$, 33.3; mol. wt. 281.

Oxidation of IX. To a solution of 0.4 g. of IX in 10 ml. acetic acid was added at 25° 0.2 g. of CrO_3. The colorless crystals were washed with 0.1*N* sodium hydroxide and water (0.18–0.21 g.). After sublimation at 100° and 10 microns pressure, followed by cryst. from 80% ethanol, they melted at 77.2–78.0°. The compound is insoluble in *N* sodium hydroxide.

Anal. Calcd. for $C_{15}H_{14}O_3$: C, 74.37; H, 5.78; $—OCH_3$, 25.6; mol. wt. 242. Found: C, 74.48; H, 5.76; $—OCH_3$, 25.6; mol. wt. 262.

The melting point of 2,4′-dimethoxybenzophenone is given in the literature as 99–100°.[15] When 2,4′-dihydroxybenzophenone (m.p. 146–147°) made by two different methods[16] was methylated with dimethyl sulfate, the resulting 2,4′-dimethoxybenzophenone, crystallized from 80% ethanol, was found to melt at 77.8–78.9°. They had the properties of the oxidation product and the mixture melted at 77.5–78.1°.

Later it was found that this is the dimorphic, less stable form of 2,4′-dimethoxybenzophenone. After several months, samples of the compound of m.p. 78° were found to melt at 97.8–98.1°. A mixture of the latter with a sample of 2,4′-dimethoxybenzophenone (m.p. 97.9–98.2°), kindly sent by Dr. Sunagawa,[15] melted at 98°.

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[13] O. E. Schultz and J. Schnekenburger, *Arch. Pharm.* **291/63**, 361 (1958).

[14] S. Yukawa, *Chem. Abstr.*, **23**, 832^9 (1929) gives a m.p. of 158° for a compound believed to have this structure.

[15] R. Stoermer, *Ber.*, **41**, 323 (1908); P. Pfeiffer, *Ann.*, **398**, 168 (1913); G. Sunagawa, *Pharm. Bull.* (*Japan*), **3**, 123 (1955).

[16] A. Baeyer, *Ann.*, **354**, 177 (1907); W. R. Orndorff and W. R. Barrett, *J. Am. Chem. Soc.*, **46**, 2488 (1924).