[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SOUTHERN CALIFORNIA]

SYNTHETIC ANALOGS OF CORTICAL HORMONES. I. HOMOGENTISIC ACID AND α,2,5-TRIHYDROXYACETOPHENONE DERIVATIVES FROM 2,5-DIACETOXY-α-DIAZOACETOPHENONE[1]

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Reactions of 2,5-diacetoxy-α-diazoacetophenone (IV) might be expected to yield a variety of compounds of biological interest. For example, homogentisic acid derivatives should be directly available through the Wolff rearrangement of the diazo ketone. The diazo ketone side chain should also be capable of conversion to the α-ketol group, an important structural feature of the adrenal cortex steroids. In view of the growing recognition of biological similarities between cortisone and salicylates (1), and the report (2) that sodium gentisate had an antirheumatic effect equal to that of salicylate, there appeared the possibility that α,2,5-trihydroxyacetophenone (XII) or its derivatives might possess interesting physiological activity.

Exploration of the reactions of 2,5-diacetoxy-α-diazoacetophenone was facilitated by the ease with which this diazo ketone could be synthesized, in 80% over-all yield, starting from commercially available[3] gentisic acid (I). Acetylation of gentisic acid, essentially by the method of Klemenc (3), gave 2,5-diacetoxybenzoic acid (II) in 90% yield. The reaction of the corresponding acid chloride (III) with diazomethane under the general conditions described by Newman and Beal (4) afforded the diazo ketone (IV) in 89% yield.

The Wolff rearrangement (5) of 2,5-diacetoxy-α-diazoacetophenone (IV) proceeded smoothly in methanol and ethanol to give methyl 2,5-diacetoxyphenylacetate (VIII) and ethyl 2,5-diacetoxyphenylacetate (IX) respectively. These new derivatives of homogentisic acid readily afforded the corresponding esters (X and XI) of homogentisic acid itself upon deacetylation with anhydrous hydrogen chloride in the appropriate alcohol (6). Hydrolysis of ester VIII with dilute hydrochloric acid yielded homogentisic acid.

2,5-Diacetoxy-α-diazoacetophenone reacted with anhydrous hydrogen bromide and hydrogen chloride in ether or acetic acid. In ether, the reactions were essentially quantitative, to yield 2,5-diacetoxy-α-bromoacetophenone (VI) and its chloro analog (XVIII) respectively. When the reactions were effected in acetic acid, the formation of by-products rendered the isolation of VI and its chloro analog impractical. Instead, α-bromo-2,5-dihydroxyacetophenone (V) and its chloro analog (XIV) were isolated after the crude reaction products had been treated with methanolic hydrogen halide. When applied to a pure sample of 2,5-diacetoxy-α-chloroacetophenone (XVIII), these alcoholysis conditions were shown to produce a good yield of α-chloro-2,5-dihydroxyacetophenone (XIV).

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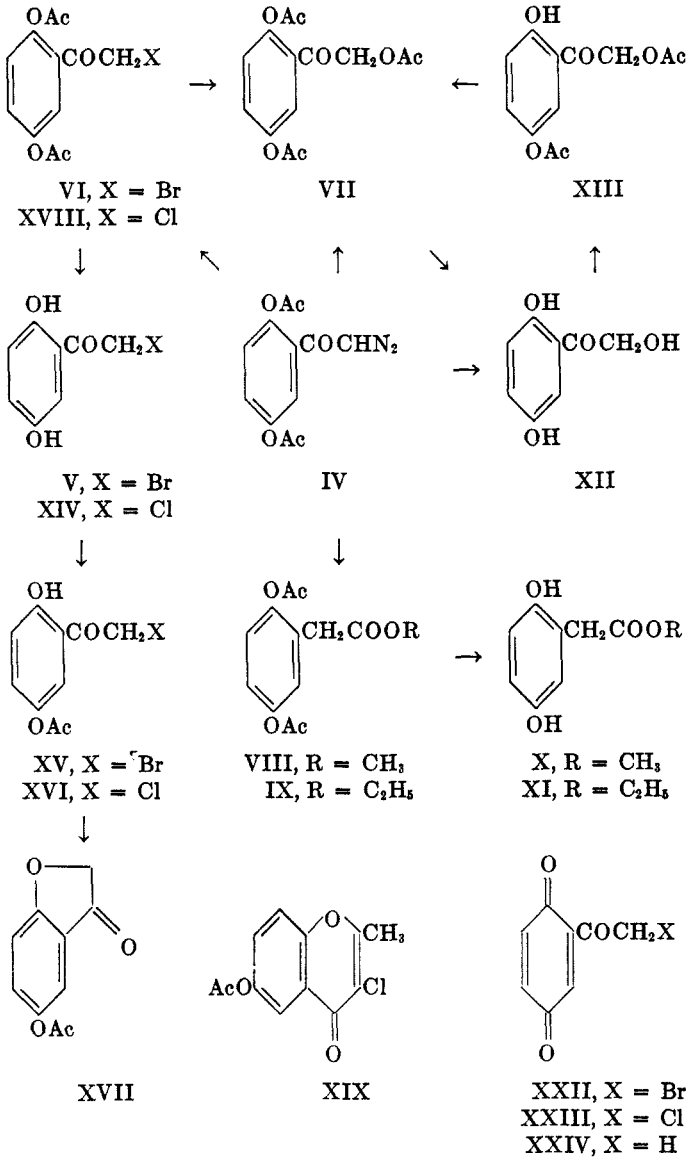

Both V and XIV were converted quantitatively to the corresponding diacetates by means of acetic anhydride and sulfuric acid. Brief treatment with acetyl bromide or acetyl chloride, however, yielded a monoacetate (XV and XVI) in each instance.

When 2,5-diacetoxy-α-bromoacetophenone (VI) was heated with silver acetate in ether or, better, dry acetic acid, the bromine atom was displaced and α,2,5-triacetoxyacetophenone (VII) was obtained in yields up to 69%. Under similar conditions, 5-acetoxy-α-bromo-2-hydroxyacetophenone (XV) was cyclized and yielded 5-acetoxycoumaranone (XVII) as the only crystalline product.

5-Acetoxy-α-chloro-2-hydroxyacetophenone (XVI) also yielded 5-acetoxycoumaranone upon treatment with sodium acetate in boiling ethanol. Under similar conditions, both V and XIV yielded 5-hydroxycoumaranone, which was characterized by conversion to 3,5-diacetoxycoumarone with acetic anhydride[4] and to 5-methoxycoumaranone with diazomethane. It is of interest that V did not react with anhydrous sodium acetate in boiling acetic acid.

When an attempt was made to prepare α,2,5-triacetoxyacetophenone (VII) by heating 2,5-diacetoxy-α-chloroacetophenone (XVIII) with anhydrous sodium acetate in a mixture of acetic acid and acetic anhydride,[5] the only crystalline products were α,5-diacetoxy-2-hydroxyacetophenone (XIII), 5-acetoxy-α-chloro-2-hydroxyacetophenone (XVI), and a compound believed to be 6-acetoxy-3-chloro-2-methylchromone (XIX). The structure of the latter compound is postulated on the basis of analytical data and the report (11) that a similar reaction occurs with 2,5-diacetoxyacetophenone and with α-chloro-2-hydroxy-5-methylacetophenone.[6]

In view of the somewhat disappointing yield of triacetate (VII) from bromo ketone (VI), we turned our attention to the direct preparation of this ester (VII) and its parent triol (XII) from diazo ketone IV. While the decomposition of certain diazo ketones by glacial acetic acid has been reported to give α-acetoxy ketones in good yield (13), such reactions usually involve diazo ketone groups which are isolated from other functional groups capable of taking part in a cyclization reaction. When a substituent such as nitro (14) or hydroxyl (15) is present in the *ortho* position, the formation of a cyclic compound (an isatin or a coumaranone) frequently occurs readily, particularly in the presence of a trace of sulfuric or formic acid, even when the hydroxyl group is protected by acetylation (16, 17) or ether formation (18, 19). This difficulty may also be reflected in the report (20) that no crystalline product could be obtained from the reaction of glacial acetic acid with 3,4-diacetoxy-α-diazo-2-acetonaphthone, but that hydrolysis of the reaction product with dilute sulfuric acid finally gave a poor yield of α,3,4-trihydroxy-2-acetonaphthone. However, Langenbeck and Baehren (21) reported the isolation (although in only 18% yield) of α,3-diacetoxy-2-acetonaphthone from the reaction of 3-acetoxy-α-diazo-2-acetonaphthone with acetic acid.

When 2,5-diacetoxy-α-diazoacetophenone (IV) was treated with cold acetic acid containing a small amount of sulfuric acid and acetic anhydride, the expected 5-acetoxycoumaranone (XVII) was obtained in 37% yield. However, when the diazo ketone was allowed to react at 56° for 15 hours with acetic acid in the absence of sulfuric acid, triacetate (VII) was obtained in 55% yield. In view of these results, it is of particular interest that treatment of the diazo ketone (IV) with boiling 15% sulfuric acid afforded α,2,5-trihydroxyacetophenone (XII) in 62% yield. The same triol was obtained in nearly quanti-

[4] The ready acetylation of the enolic forms of coumaranones is well known (7–9).

[5] Voswinkel (10) successfully prepared α,3,4-triacetoxyacetophenone in this manner.

[6] Contrast Nierenstein, Wang, and Warr (12), who did not observe any chromone formation when 2,4-diacetoxy-α-chloroacetophenone was treated with sodium acetate in boiling acetic anhydride.

tative yield when the triacetate (VII) was hydrolyzed by means of boiling dilute hydrochloric acid containing a small amount of hydriodic acid.

Triol XII readily formed an osazone and, upon brief treatment with hot acetyl chloride, a diacetate. The diacetate readily reverts to the triol (XII) upon hydrolysis and can be converted to triacetate (VII) by long treatment with acetyl chloride. The diacetate has a free phenolic hydroxyl group, for it gives an intense red-brown color with 1% ferric chloride solution. Neither triacetate (VII) nor benzoylcarbinol gives this color test. Since both V and XIV can be monoacetylated readily to leave a free hydroxyl group *ortho* to the ketone side chain, it is most probable that the aforedescribed diacetate of triol XII also has a free hydroxyl in position 2 and the compound accordingly has been designated α,5-diacetoxy-2-hydroxyacetophenone (XIII).

Although α-bromo-2,5-dihydroxyacetophenone (V) was accessible from the diazo ketone (IV), it appeared that the reaction of bromoacetyl bromide with 1,4-dimethoxybenzene and anhydrous aluminum bromide might provide a larger scale source of this key bromo ketone. The major products of this reaction proved to be α-bromo-2-hydroxy-5-methoxyacetophenone (XX) and a monobromoacetate of α-bromo-2,5-dihydroxyacetophenone, together with a small quantity of α-bromo-2,5-dihydroxyacetophenone itself. However, both XX and the monobromoacetate could be converted to α-bromo-2,5-dihydroxyacetophenone; the former in 87% yield by demethylation with aluminum bromide at room temperature, and the latter also in 87% yield by treatment with a methanol solution of hydrogen bromide. Compound XX was identified by its conversion to 5-methoxycoumaranone.

The reaction of 1,4-dimethoxybenzene with chloroacetyl chloride, catalyzed by aluminum chloride (23–26), yielded α-chloro-2,5-dimethoxyacetophenone (XXI). This α-chloro ketone was demethylated by anhydrous aluminum bromide at room temperature, to give a 72% yield of α-chloro-2,5-dihydroxyacetophenone (XIV), but suffered halogen exchange when demethylation was attempted with aluminum bromide in boiling benzene (22).

Halo ketones V and XIV, as well as 2,5-dihydroxyacetophenone (prepared by demethylation of 2,5-dimethoxyacetophenone with aluminum bromide) were oxidized to the corresponding benzoquinones, XXII–XXIV respectively, when they were shaken with freshly prepared silver oxide in anhydrous benzene. Quinone XXIII was reduced to the corresponding hydroquinone (XIV) with an aqueous solution of sulfur dioxide, and XXIV regenerated 2,5-dihydroxyacetophenone when treated with aqueous sodium hydrosulfite.

α,2,5-Trihydroxyacetophenone (XII) gave a negative Venning liver glycogen deposition test and produced no lowering of the eosinophil count in adrenalectomized mice at dose levels up to 500 mg./kg. α,2,5-Triacetoxyacetophenone (VII) and α,5-diacetoxy-2-hydroxyacetophenone (XIII) likewise failed to produce a lowering of the eosinophil count in adrenalectomized mice at dose levels up to 500 mg./kg.

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EXPERIMENTAL[7]

2,5-Diacetoxybenzoyl chloride (III). 2,5-Diacetoxybenzoic acid (27) was prepared in 90% yield by acetylation of gentisic acid[3] with acetic anhydride and sulfuric acid; colorless platelets, from a mixture of benzene and ligroin, m.p. 119–121°. A mixture of 10 g. of 2,5-diacetoxybenzoic acid, 10 cc. of thionyl chloride, 100 cc. of anhydrous ether, and 50 cc. of anhydrous benzene was refluxed for 5 hours, allowed to stand at room temperature for 15 hours, and was finally evaporated to dryness under reduced pressure. The residual solid was broken up and mixed with 10 cc. of anhydrous benzene and the solvent was again evaporated under reduced pressure. The acid chloride obtained in this manner was employed for preparation of the diazo ketone without further purification.

Recrystallization of the acid chloride from a mixture of benzene and *n*-heptane yielded colorless prisms, m.p. 93–94.5°.

Anal. Calc'd for $C_{11}H_9ClO_5$: C, 51.48; H, 3.54.
Found: C, 51.54; H, 3.32.

2,5-Diacetoxy-α-diazoacetophenone (IV). The acid chloride from 23.8 g. of 2,5-diacetoxybenzoic acid, dissolved in 200 cc. of benzene and 600 cc. of ether, was treated with diazomethane according to the directions of Newman and Beal (4). After standing for 3.25 hours, the reaction mixture was filtered and the solid residue was washed with water to remove triethylamine hydrochloride. There remained 11.6 g. of solid diazo ketone. An equal quantity of diazoketone was obtained by evaporation of the filtered reaction mixture; total yield, 23.2 g. (89%), m.p. 88–90.5°. Recrystallization from ether gave square yellow tablets, m.p. 90–91°.

Anal. Calc'd for $C_{12}H_{10}N_2O_5$: C, 54.96; H, 3.84.
Found: C, 55.10; H, 3.83.

Methyl 2,5-diacetoxyphenylacetate (VIII). To a suspension of silver oxide, from 0.75 cc. of 10% silver nitrate, in 10 cc. of absolute methanol at 60–65° was added in small portions a total of 1.0 g. of diazo ketone IV. When gas evolution was complete the filtered solution was evaporated and the residue was distilled at 1 mm. pressure; yield, 835 mg. (82%) of colorless solid, m.p. 62–64°. Three crystallizations from aqueous methanol yielded colorless plates, m.p. 65.5–66.5°.

Anal. Calc'd for $C_{13}H_{14}O_6$: C, 58.64; H, 5.30; CH_3CO, 33.08.
Found: C, 58.61; H, 5.06; CH_3CO, 33.11.

Methyl homogentisate (X), was obtained when 440 mg. of the aforementioned ester was dissolved in 4 cc. of absolute methanol, 0.2 cc. of a saturated solution of anhydrous hydrogen chloride in methanol was added, and the mixture was allowed to stand at room temperature for 65 hours. Evaporation under reduced pressure yielded 265 mg. (94%) of pink solid, m.p. 118–119°. Three crystallizations (decolorization with Nuchar the first time) from water gave colorless prisms, m.p. 119.5–120.5°. McElvain and Cohen (28) reported the m.p. to be 116–117°.

Anal. Calc'd for $C_9H_{10}O_4$: C, 59.32; H, 5.53.
Found: C, 59.28; H, 5.31.

Ester VIII (8 g.) was heated under reflux for 12 hours with 30 cc. of concentrated hydrochloric acid and 30 cc. of water and the mixture then was extracted with ether. Evaporation of the ether left a brown residue of *homogentisic acid*, which crystallized in needles from a

[7] Melting points are uncorrected. Analyses are by Dr. Adalbert Elek, Elek Microanalytical Laboratories, Los Angeles, and by Mr. Joseph Pirie, University of Southern California.

mixture of ethyl acetate and hexane; yield, 2.4 g. (48%), m.p. 142–144°. McElvain and Cohen (28) reported a m.p. of 144–146°.

Ethyl 2,5-diacetoxyphenylacetate (IX) was prepared by employing a procedure similar to that described for the methyl ester; yield 84% of distilled material, m. p. 38–40°. Crystallization from aqueous ethanol yielded colorless rods, m.p. 42.5–44°.

Anal. Calc'd for $C_{14}H_{16}O_6$: C, 59.97; H, 5.75; CH_3CO, 30.71.
Found: C, 59.64; H, 5.87; CH_3CO, 30.76.

Ethyl homogentisate (XI) was prepared from ester IX as described for the preparation of methyl homogentisate. The crude product in ether solution was decolorized with Nuchar and triturated with ether to give a 50% yield of tan solid, m.p. 114–116.5°. Evaporative distillation in a vacuum and recrystallization from water yielded colorless prisms, m.p. 117–117.5°, which showed no depression of m.p. upon admixture with a sample of the ester prepared from alcaptonuric urine (29).

α-Bromo-2,5-dihydroxyacetophenone (V). When 2.5 g. of diazo ketone (IV) was added slowly at room temperature to 15 cc. of acetic acid saturated with anhydrous hydrogen bromide, a vigorous reaction occurred. After 10 minutes the acetic acid was removed under reduced pressure and the residue was dissolved in a mixture of 10 cc. of absolute methanol and 5 cc. of a saturated methanolic solution of hydrogen bromide. After 18 hours the solution was decolorized and upon evaporation under reduced pressure yielded 1.30 g. (59%) of yellow-brown crystalline solid, m.p. 115–117°. The bromo ketone separated from benzene in yellow platelets, m.p. 117.5–119°, which produced an evanescent green color with 1% ferric chloride solution.

Anal. Calc'd for $C_8H_7BrO_3$: C, 41.58; H, 3.05.
Found: C, 41.89; H, 3.15.

A solution of 3 g. of bromo ketone (V) in 23 cc. of acetyl bromide was allowed to stand at room temperature for 10 minutes, was warmed gently for 1 minute, and was finally poured onto ice. As soon as the ice had melted the mixture was filtered to give 3.45 g. of cream-colored solid, m.p. 136–139° with decomposition. Recrystallization from ether or benzene yielded 2.18 g. (61.5%) of pure *5-acetoxy-α-bromo-2-hydroxyacetophenone* (XV), m.p. 143.5–144°, which produced a brown color with ferric chloride solution.

Anal. Calc'd for $C_{10}H_9BrO_4$: C, 43.98; H, 3.32; CH_3CO, 15.76.
Found: C, 44.22; H, 3.21; CH_3CO, 15.83.

When a mixture of 400 mg. of compound XV, 245 mg. of silver acetate, and 10 cc. of anhydrous toluene or acetic acid was heated under reflux, a heavy, dark precipitate separated rapidly. After being heated for 1 hour, the solution was filtered hot (decolorizing charcoal) and evaporated under reduced pressure. The crystalline residue was washed with a mixture of ether and petroleum ether (20–30°) and finally was recrystallized from a mixture of these solvents; yield, 151 mg. (54%) of *5-acetoxycoumaranone* (XVII) which separated as diamond-shaped plates, m.p. 95–96°. No other crystalline substance could be isolated. The compound gave no color with ferric chloride solution.

Anal. Calc'd for $C_{10}H_8O_4$: C, 62.49; H, 4.19; Mol. Wt., 192.
Found: C, 62.72; H, 4.27; 186 (cryoscopic, in camphor).

A solution of 230 mg. of α-bromo-2,5-dihydroxyacetophenone (V), 100 mg. of anhydrous sodium acetate, and 6 cc. of acetic acid was heated under reflux for 2 hours. The solution was poured into water and extracted with ether. Evaporation of the neutralized (sodium bicarbonate) and dried extract yielded 210 mg. of unchanged bromo ketone (V).

α-Bromo-2,5-dihydroxyacetophenone (V) was converted to *5-hydroxycoumaranone* with sodium acetate in methanol, essentially by the procedure described by von Auwers and Pohl (30). Recrystallization from isopropyl ether yielded yellow prisms, m.p. 152–153°.

Anal. Calc'd for $C_8H_6O_3$: C, 64.00; H, 4.03.
Found: C, 64.44; H, 4.14.

A sample of the 5-hydroxycoumaranone (103 mg.) dissolved in benzene (10 cc.) was added to a solution of diazomethane (from 500 mg. of N-nitrosomethylurea) in benzene (10 cc.). After 70 hours at room temperature the solvent was removed under reduced pressure and the

oily residue was extracted with hot *n*-hexane. The decanted extract yielded 55 mg. (50%) of yellow *5-methoxycoumaranone*, m.p. 88.5–90°. Sublimation of this material in a vacuum yielded a product which separated from methanol in colorless needles, m.p. 92.5–93.5° as reported previously (30).

Another sample of 5-hydroxycoumaranone (150 mg.) was dissolved in 0.5 cc. of acetic anhydride containing a trace of concentrated sulfuric acid, and allowed to stand at room temperature for 6 minutes. Filtration of the diluted (water) mixture yielded 214 mg. of cream-colored 3,5-diacetoxycoumarone, m.p. 83–85°, which was distilled at 1 mm. pressure to give 202 mg. (90%) of colorless solid. The compound separated from absolute ethanol in colorless rectangular prisms, m.p. 85.5–86.5°.

Anal. Calc'd for $C_{12}H_{10}O_5$: C, 61.54; H, 4.30; CH_3CO, 36.75.
Found: C, 61.76; H, 4.42; CH_3CO, 35.81.

α-Chloro-2,5-dihydroxyacetophenone (XIV). This chloro ketone was prepared in 53% yield from diazo ketone IV and hydrogen chloride by a method similar to that previously described for the bromo analog and separated from benzene in yellow platelets, m.p. 132–133°. The compound gave an evanescent blue-green color with ferric chloride solution.

Anal. Calc'd for $C_8H_7ClO_3$: C, 51.49; H, 3.78.
Found: C, 51.36; H, 3.90.

When a solution of 1 g. of compound XIV in 8 cc. of acetyl chloride was heated under reflux, separation of crystalline material began in 15 minutes. The mixture then was cooled and poured into 180 cc. of water. Recrystallization of the solid precipitate from absolute ethanol yielded 890 mg. (72.5%) of *5-acetoxy-α-chloro-2-hydroxyacetophenone* (XVI) in colorless needles, m.p. 149–150.5°. One further crystallization from ether gave rectangular platelets, m.p. 151–152°. The compound produces a brown-red color with ferric chloride solution.

Anal. Calc'd for $C_{10}H_9ClO_4$: C, 52.53; H, 3.97.
Found: C, 52.33; H, 4.02.

A mixture of 890 mg. of acetate XVI, 1.57 g. of sodium acetate trihydrate, and 20 cc. of ethanol was heated under reflux for 15 minutes, was evaporated to half its volume under reduced pressure, and finally was poured into water. Filtration yielded 370 mg. of crude *5-acetoxycoumaranone* (XVII) which, upon purification as previously described, proved to be identical with that obtained from compound XV.

α-Chloro-2,5-dihydroxyacetophenone (XIV) was converted to *5-hydroxycoumaranone* with sodium acetate in methanol as previously described for the bromo analog; yield, 72% of yellow prisms, m.p. 151–153°.

2,5-Diacetoxy-α-chloroacetophenone (XVIII). (*a*) *From 2,5-diacetoxy-α-diazoacetophenone* (IV). Dry hydrogen chloride was passed over a solution of 1.0 g. of the diazo ketone in 50 cc. of anhydrous ether until evolution of nitrogen ceased. Evaporation of the yellow solution left a yellow oil which solidified after standing for 18 hours; yield, 1.02 g. (98%) of 2,5-diacetoxy-α-chloroacetophenone (XVIII), m.p. 65–67°. Recrystallization from absolute ethanol raised the m.p. to 67–68°.

Anal. Calc'd for $C_{12}H_{11}ClO_5$: C, 53.25; H, 4.10.
Found: C, 53.18; H, 3.99.

(*b*) *From α-chloro-2,5-dihydroxyacetophenone* (XIV). One gram of compound XIV, warmed to 80–90° for 2 hours with 4 cc. of acetic anhydride and a drop of concentrated sulfuric acid, yielded 1.40 g. (97%) of the diacetate (XVIII), m.p. 61.5–67.5°. Two crystallizations from absolute ethanol yielded colorless material, m.p. 67–68°, which did not depress the m.p. of diacetate prepared from diazo ketone (IV).

A sample of diacetate (1.02 g.) was dissolved in 30 cc. of methanol containing hydrogen chloride, allowed to stand at room temperature for 41 hours, and then evaporated under reduced pressure. An ethereal solution of the residue was treated briefly with sodium bicarbonate solution and upon evaporation left 597 mg. of α-chloro-2,5-dihydroxyacetophenone (XIV) identical with that previously described.

Reaction of 2,5-diacetoxy-α-chloroacetophenone with sodium acetate. A solution of 1.0 g.

of α-chloro-2,5-dihydroxyacetophenone (XIV) in 4 cc. of acetic anhydride containing 1 drop of concentrated sulfuric acid was warmed on the steam-bath for 2 hours. Then 600 mg. of fused sodium acetate was added and the mixture was heated for an additional period of 2 hours. After standing for 22 hours at room temperature, the resulting mixture was poured into water and allowed to stand for 6 hours. Decantation from precipitated oil gave an aqueous solution which eventually deposited 100 mg. of colorless leaflets, m.p. 90–95°, which, when crystallized from a mixture of benzene and petroleum ether (62–69°), melted at 97.5–99° and did not depress the m.p. of *α,5-diacetoxy-2-hydroxyacetophenone* (XIII; preparation described later).

The oily residue from which the aqueous solution had been decanted was dissolved in ether and washed with sodium bicarbonate solution. Evaporation of the dried solution left a residue which crystallized from absolute ethanol in long colorless prisms, m.p. 163–163.5°; yield 166 mg., presumably *6-acetoxy-3-chloro-2-methylchromone* (XIX). The compound gave a positive test for halogen.

Anal. Calc'd for $C_{12}H_9ClO_4$: C, 57.04; H, 3.59; CH_3CO, 17.07.
Found: C, 57.07; H, 3.84; CH_3CO, 17.22.

The alcoholic mother liquor from which the chromone originally separated was warmed and diluted with an equal volume of water. Upon prolonged standing at 8° the solution deposited 104 mg. of colorless crystals, m.p. 146–150°. Recrystallization from absolute ethanol yielded 88 mg. of *5-acetoxy-α-chloro-2-hydroxyacetophenone* (XVI), m.p. 151–151.5° and showing no m.p. depression when mixed with the ester prepared as previously described.

2,5-Diacetoxy-α-bromoacetophenone (VI). (*a*) *From 2,5-diacetoxy-α-diazoacetophenone* (IV). Bromo ketone VI was obtained in quantitative yield from diazo ketone IV and hydrogen bromide in a manner similar to that already described for preparation of the chloro analog; m.p. 67–69.5°. Three crystallizations from absolute ethanol gave colorless rods, m.p. 72–73°.

Anal. Calc'd for $C_{12}H_{11}BrO_5$: C, 45.74; H, 3.52; CH_3CO, 27.32.
Found: C, 45.83; H, 3.87; CH_3CO, 26.54.

(*b*) *From α-bromo-2,5-dihydroxyacetophenone* (V). A solution of 1.3 g. of V in 10 cc. of acetic anhydride containing a drop of sulfuric acid was warmed for 20 minutes. In the manner previously described for the chloro analog, there was obtained a quantitative yield of diacetate (VI).

α,2,5-Triacetoxyacetophenone (VII). (*a*) *From 2,5-diacetoxy-α-bromoacetophenone* (VI). A mixture of 500 mg. of bromo ketone (VI), 270 mg. of silver acetate, and 25 cc. of anhydrous acetic acid was heated under reflux for 1 hour and the filtered solution then was evaporated under reduced pressure. The residue crystallized from ether to yield 320 mg. (69%) of triacetate (VII), m.p. 76–77°. Two crystallizations from methanol gave colorless prisms, m.p. 77.5–78°. The ester produced no color with ferric chloride solution.

Anal. Calc'd for $C_{14}H_{14}O_7$: C, 57.14; H, 4.79; CH_3CO, 43.88.
Found: C, 57.15; H, 5.22; CH_3CO, 43.85.

(*b*) *From 2,5-diacetoxy-α-diazoacetophenone* (IV) *and acetic acid.* The diazo ketone (400 mg.) was added slowly to 5 cc. of glacial acetic acid at 56° and this temperature was maintained for 15 hours. Evaporation of the solution under reduced pressure left a gummy residue which yielded 100 mg. of triacetate (VII), m.p. 76–77°. The mother liquor was evaporated and the residue was evaporatively distilled in a vacuum to give a colorless distillate which yielded 150 mg. more of triacetate; total yield of triacetate (VII), 250 mg. (55%), which did not depress the m.p. of a sample prepared from bromo ketone (VI). The nonvolatile residue remaining after the vacuum distillation was recrystallized from acetic acid to yield 50 mg. of an unidentified yellow solid, m.p. 235–240°.

Another sample of diazo ketone (IV, 800 mg.) was added in small portions to 8 cc. of acetic acid containing 3 drops each of acetic anhydride and sulfuric acid, cooled in an ice-bath. The solution then was diluted with 60 cc. of benzene and extracted once with cold water and once with dilute sodium bicarbonate solution. The dried benzene extract was evaporated and the residue was evaporatively distilled at 1 mm. pressure to yield 219 mg.

(37%) of *5-acetoxycoumaranone* (XVII) identical with a sample prepared as described earlier.

α,2,5-Trihydroxyacetophenone (XII). (*a*) *From α,2,5-triacetoxyacetophenone* (VII). A mixture of 200 mg. of the triacetate (VII), 2.6 cc. of water, 0.4 cc. of 36% hydrochloric acid, and 0.1 cc. of 47% hydriodic acid was heated under reflux for 5 minutes and then cooled to 5°. α,2,5-Trihydroxyacetophenone (84 mg.; 74%) crystallized in yellow needles, m.p. 150–155.5°. Concentration of the mother liquor in a vacuum yielded 20 mg. more of the triol (total yield, 91%). Recrystallization from water gave long yellow needles, or from ether rod-shaped prisms, m.p. 154–156°. A final crystallization from ether raised the m.p. to 157–158°. The triol produced an evanescent blue-green color with ferric chloride solution.

Anal. Calc'd for $C_8H_8O_4$: C, 57.14; H, 4.79; CH_3CO, 0.

Found: C, 57.43; H, 5.04; CH_3CO, 0.

(*b*) *From 2,5-diacetoxy-α-diazoacetophenone* (IV). A mixture of 250 mg. of the diazo ketone, 1 cc. of ethanol, and 10 cc. of 15% sulfuric acid was heated under reflux for 35 minutes, then cooled and extracted with ether. Evaporation of the dried extract yielded 100 mg. (62%) of triol (XII), m.p. 154–155°. A recrystallized sample did not depress the m.p. upon admixture with triol prepared by hydrolysis of triacetate (VII).

The *osazone of α,2,5-trihydroxyacetophenone* formed readily when a hot solution of 0.4 cc. of phenylhydrazine in 2 cc. of 40% acetic acid was added to a hot solution of 117 mg. of the triol (XII) in 0.5 cc. of water (31). Three crystallizations from aqueous ethanol yielded a yellow crystalline product, m.p. 191–192°.

Anal. Calc'd for $C_{20}H_{18}N_4O_2$: N, 16.17. Found: N, 16.23.

α,5-Diacetoxy-2-hydroxyacetophenone (XIII) was formed when a mixture of 500 mg. of triol (XII), 4.3 cc. of acetyl chloride, and 4 cc. of anhydrous benzene was heated under reflux. Hydrogen chloride was evolved and the triol gradually went into solution over a period of 50 minutes. After being heated for 15 minutes more, the solution became nearly colorless and then was cooled and poured onto 30 g. of ice. As the ice melted, the benzene was evaporated in a current of air and the crystalline product was finally filtered and washed with water; yield, 703 mg. (94%) of diacetate, m.p. 94–96°. One crystallization from dry ether yielded an analytical sample separating in thin colorless plates, m.p. 97.5–99°. The substance produced a red-brown color with ferric chloride solution.

Anal. Calc'd for $C_{12}H_{12}O_6$: C, 57.14; H, 4.79; CH_3CO, 34.13.

Found: C, 57.32; H, 5.02; CH_3CO, 34.23.

When a solution of 73 mg. of diacetate (XIII) in 2 cc. of acetyl chloride was heated under reflux for 19 hours, then allowed to stand at room temperature for 154 hours, and finally evaporated under reduced pressure, there was obtained 76 mg. (89%) of *α,2,5-triacetoxyacetophenone* (VII), m.p. 76.5–77.5° after one crystallization from ether.

Hydrolysis of diacetate XIII, effected exactly as described for triacetate VII, produced α,2,5-trihydroxyacetophenone (XII) in 92% yield.

Reaction of 1,4-dimethoxybenzene with bromoacetyl bromide. To a solution of 27.6 g. of 1,4-dimethoxybenzene in 28 cc. of bromoacetyl bromide cooled in an ice-bath, there was added gradually, with mechanical stirring, 53.4 g. of anhydrous aluminum bromide. After standing at room temperature for 73 hours the dark red reaction mixture was hydrolyzed with ice and hydrobromic acid. An ether extract of the hydrolyzed mixture, after being washed with aqueous sodium bicarbonate and dried, was evaporated and left a solid residue which was crystallized from ethanol; yield, 9.05 g. of yellow crystals, m.p. 102.5–104.5°. Three crystallizations from ethanol and one from dilute methanol gave an analytical sample of *a monobromoacetate of α-bromo-2,5-dihydroxyacetophenone*, separating in colorless nacreous needles, m.p. 106–107°.

Anal. Calc'd for $C_{10}H_8Br_2O_4$: C, 34.11; H, 2.20.

Found: C, 34.40; H, 2.12.

The mother liquor from which the aforementioned ester had separated was concentrated, whereupon 13.0 g. of yellow *α-bromo-2-hydroxy-5-methoxyacetophenone* (XX) separated, m.p. 54–58°. Recrystallization from petroleum ether (32–35°) yielded 9.1 g. of XX melting

above 61°. Finally, recrystallization from a mixture of ether and petroleum ether (32–35°) gave yellow leaflets, m.p. 65–66°. This compound gave a qualitative test for halogen, produced a green color with ferric chloride, and dissolved in aqueous potassium hydroxide to give a red solution.

Anal. Calc'd for $C_9H_9BrO_3$: C, 44.10; H, 3.70.

Found: C, 44.47; H, 3.83.

The alcoholic mother liquor from separation of bromo ketone (XX) was evaporated and extracted with carbon tetrachloride to leave a brown solid which was treated in ether solution with Nuchar C. The residue from evaporation of the ether was extracted with benzene. Concentration of the benzene extract yielded 800 mg. of *α-bromo-2,5-dihydroxyacetophenone* (V), m.p. 117–119°.

The benzene-insoluble residue (1.55 g.) was recrystallized from acetic acid and yielded an unidentified yellow compound, m.p. 165–166° with decomposition.

The aforedescribed monobromoacetate of α-bromo-2,5-dihydroxyacetophenone was acetylated by the method of Klemenc (3) to give a *monoacetate* in 94% yield. The ester separated from a mixture of ethyl acetate and petroleum ether (32–35°), or from absolute ethanol, in colorless needles, m.p. 79–81°.

Anal. Calc'd for $C_{12}H_{10}Br_2O_5$: C, 36.58; H, 2.56.

Found: C, 36.88; H, 2.69.

When the monobromoacetate of α-bromo-2,5-dihydroxyacetophenone was treated with a methanol solution of anhydrous hydrogen bromide in the manner previously described for deacetylation of acetates, there was obtained an 87% yield of α-bromo-2,5-dihydroxyacetophenone (V).

α-Bromo-2,5-dihydroxyacetophenone (V) was also obtained when a solution of 3.67 g. of α-bromo-2-hydroxy-5-methoxyacetophenone (XX) in 120 cc. of carbon disulfide was added to a solution of 8.5 g. of anhydrous aluminum bromide in 80 cc. of carbon disulfide. After standing at room temperature for 18 days, the solution was evaporated and the residue was hydrolyzed with 140 g. of ice and 25 cc. of 48% hydrobromic acid. Extraction with ether yielded compound V, m.p. 114–117° after one crystallization from a mixture of benzene and Skellysolve B; yield 3.0 g. (87%). The purified compound did not depress the m.p. of a sample of V obtained from diazo ketone (IV).

α-Bromo-2-hydroxy-5-methoxyacetophenone (XX) was converted to 5-methoxy-coumaranone in 69% yield by the general method of von Auwers and Pohl (30). The product did not depress the m.p. of a sample prepared as previously described from 5-hydroxycoumaranone.

α-Chloro-2,5-dimethoxyacetophenone (XXI) was demethylated by treatment with aluminum bromide in carbon disulfide for 160 hours at room temperature, as previously described for demethylation of XX. Crystallization from benzene yielded 72% of α-chloro-2,5-dihydroxyacetophenone (XIV), m.p. 129–131°. When the reaction was effected in boiling carbon disulfide for 6 hours and the reaction product was extracted with petroleum ether, there remained are insoluble residue (350 mg. from 1.15 g. of XXI) which melted at 115–116.5° after crystallization from benzene and did not depress the m.p. of α-bromo-2,5-dihydroxyacetophenone (V). The compounds also gave a positive test for bromine (32).

2,5-Dihydroxyacetophenone. To a solution of 208 g. of anhydrous aluminum bromide in 1 l. of dry carbon disulfide was added, over a period of 90 minutes with continuous stirring, 66 g. of 2,5-dimethoxyacetophenone. Sufficient heat was liberated to cause gentle refluxing of the solvent. After standing for 1 week at room temperature, the precipitated orange-brown complex was hydrolyzed with ice and 100 cc. of 36% hydrochloric acid. There was obtained 53.2 g. (96%) of 2,5-dihydroxyacetophenone, m.p. 192–197°. Recrystallization from ethanol yielded 45.3 g. (81.5%) melting at 201–202°.

Preparation of benzoquinones. A mixture of 1.0 g. of 2,5-dihydroxyacetophenone, 1.5 g. of anhydrous magnesium sulfate, 10 cc. of dry benzene, and the dried silver oxide from 5.5 g. of silver nitrate, was shaken for 30 minutes and then filtered through a sintered glass filter. The solid was washed with benzene and the combined solutions were evaporated

under reduced pressure to yield 894 mg. (91%) of *2-acetyl-1,4-benzoquinone* (XXIV), m.p. 60–64.5°. Sublimation at 1 mm. pressure (bath temperature 40–75°) yielded 796 mg. (81%) of orange crystals, m.p. 65.5–66.5°.

Anal. Calc'd for $C_8H_6O_3$: C, 64.00; H, 4.03.
Found: C, 64.20; H, 4.14.

When an ethereal solution of the quinone was shaken with aqueous sodium hydrosulfite and the ether layer was evaporated, the residual 2,5-dihydroxyacetophenone melted at 200–201°.

Oxidation of 1.0 g. of α-chloro-2,5-dihydroxyacetophenone (XIV) as described for 2,5-dihydroxyacetophenone yielded 600 mg. (61%) of sublimed *2-chloroacetyl-1,4-benzoquinone* (XXIII), m.p. 61–62°.

Anal. Calc'd for $C_8H_5ClO_3$: C, 52.05; H, 2.73.
Found: C, 51.81; H, 3.15.

2-Chloroacetyl-1,4-benzoquinone was reduced to the corresponding hydroquinone (XIV) by passing sulfur dioxide through an aqueous solution of the quinone until the solution was pale yellow and then extracting the hydroquinone with ether.

Oxidation of α-bromo-2,5-dihydroxyacetophenone (V) as described for 2,5-dihydroxyacetophenone yielded 17% of sublimed yellow-orange *2-bromoacetyl-1,4-benzoquinone* (XXII), m.p. 60–61°.

Anal. Calc'd for $C_8H_5BrO_3$: C, 41.95, 2.20.
Found: C, 42.12; H, 2.31.

SUMMARY

The synthesis and some reactions of 2,5-diacetoxy-α-diazoacetophenone have been described. The Wolff rearrangement yielded derivatives of homogentisic acid. Reactions with hydrogen halides yielded α-halo ketones. With hot acetic acid the diazo ketone yielded α,2,5-triacetoxyacetophenone, although when sulfuric acid was also present, cyclization to a coumaranone was observed. α,2,5-Trihydroxyacetophenone was obtained from the reaction of the diazo ketone with aqueous sulfuric acid and from acidic hydrolysis of the triacetoxyacetophenone.

2,5-Diacetoxy-α-bromoacetophenone reacted with silver acetate in hot acetic acid to give α,2,5-triacetoxyacetophenone. α-Halo ketones with a free phenolic hydroxyl *ortho* to the halo ketone side chain were cyclized to coumaranones by silver acetate in acetic acid or by sodium acetate in ethanol.

The preparation of α-bromo-2,5-dihydroxyacetophenone *via* the reaction of 1,4-dimethoxybenzene with bromoacetyl bromide and aluminum bromide has been described. This halo ketone, its chloro analog, and 2,5-dihydroxyacetophenone itself, have been oxidized to the corresponding 1,4-benzoquinones by means of silver oxide.

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