

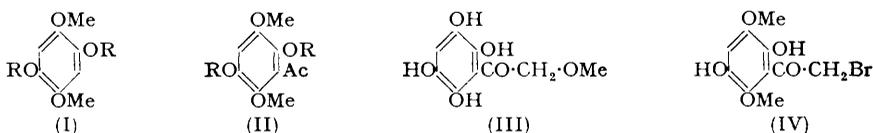
284. 2 : 5-Dihydroxy-3 : 6-dimethoxyacetophenone and Its Degradation by Bromine.

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Attempts to introduce a chloroacetyl or a formyl group into 2 : 5-dimethoxyquinol and its ethers have failed. 2 : 5-Dihydroxy-3 : 6-dimethoxyacetophenone has been obtained, but bromination has resulted in degradation to bromanilic acid (V; R = H).

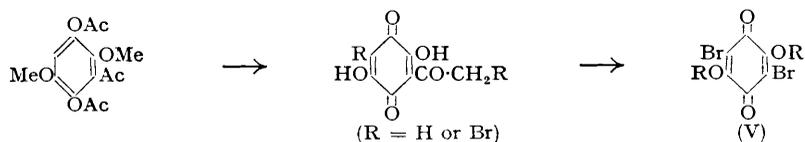
FOR synthesis of a furanochromone isomeric with kellin, 5-hydroxy-4 : 7-dimethoxycoumaran was required. This necessitated the introduction of either a chloroacetyl or a formyl substituent into 2 : 5-dimethoxyquinol (I; R = H), which was obtained by reduction of 2 : 5-dimethoxybenzoquinone with stannous chloride in acid solution (cf. Nietzki and Rechberg, *Ber.*, 1890, **23**, 1211). The quinol, however, did not undergo the Friedel-Crafts, Reimer-Tiemann, Hoesch, or Gattermann reaction. The more readily soluble diethoxyquinol, prepared by ethylation of 2 : 5-dihydroxybenzoquinone and reduction of the resulting 2 : 5-diethoxybenzoquinone as above, also resisted substitution. The dibenzyl ether (I; R = CH₂Ph) and the dicarboxy-derivative (I; R = CO₂Et) showed the same resistance in the Hoesch and the Gattermann reaction. This inertness to nuclear substitution in the 1 : 2 : 4 : 5-tetrahydroxybenzene series is remarkable: similar resistance has also been reported for 1 : 2 : 4 : 5-tetramethoxybenzene (I; R = Me) by Baker (*J.*, 1941, 662), Kuroda and Matsukuma (*Sci. Papers Inst. Phys. Chem. Res., Tokyo*, 1932, **18**, 51), and Oliverio and Lugli (*Gazzetta*, 1948, **78**, 16).

The bischloroacetate (I; R = CO·CH₂Cl), prepared from the quinol and chloroacetic anhydride, failed to rearrange to an identifiable product when treated with aluminium chloride or boron trifluoride. The diacetate (I; R = Ac) gave only amorphous material when treated with aluminium chloride, but when heated with the boron trifluoride-ether complex in acetic acid smoothly rearranged to yield 2 : 5-dihydroxy-3 : 6-dimethoxyacetophenone (II; R = H) in satisfactory yield. Aqueous solutions of this ketone were readily oxidised by air to a dark red solid believed to be 3-acetyl-2 : 5-dimethoxybenzoquinone.



No derivative of 2 : 3 : 5 : 6-tetrahydroxyacetophenone has previously been synthesised, although 2 : 3 : 5 : 6-tetrahydroxy- ω -methoxyacetophenone (III) has been reported as a degradation product of the naturally occurring gardenin by Bose and Nath (*J. Indian Chem. Soc.*, 1938, **15**, 139).

Since the introduction of a chloroacetyl or a formyl group proved impossible, the quinol (II; R = H) was brominated in an attempt to prepare the phenacyl bromide (IV). The quinol or its acetate with bromine in acetic acid gave, however, bromanilic acid (V; R = H) identified by its properties and analysis and by comparison of the di-



acetates (Graebe and Weltner, *Annalen*, 1891, **263**, 31; Jackson and Bolton, *J. Amer. Chem. Soc.*, 1914, **36**, 1473). The yield was influenced by the amount of bromine used, being a maximum with excess. This reaction can be explained as follows. The hydrogen bromide formed during an initial bromination step hydrolyses the acetoxy-groups, and the resultant

quinol is oxidised to a 2 : 5-dimethoxybenzoquinone derivative in which the methoxyl groups are particularly subject to acid hydrolysis. The acetyl group in the ensuing acetylbenzoquinone derivative is incorporated in a β -diketone system and hence is easily replaced by bromine. Bromination in the initially vacant nuclear position yields bromanilic acid. Since the complications owe their origin to the hydrogen bromide produced in the reaction, bromination was next attempted in chloroform in the presence of calcium carbonate; but no reaction then occurred, even under irradiation with ultra-violet light.

EXPERIMENTAL

2 : 5-Dimethoxyquinol (I; R = H) (cf. Nietzki and Rechberg, *loc. cit.*).—Crude 2 : 5-dimethoxybenzoquinone (15 g.) (Knoevenagel and Bückel, *Ber.*, 1901, **34**, 3993) was added to a solution of stannous chloride (25 g.) in concentrated hydrochloric acid (25 c.c.), and the resulting pasty mass refluxed until a clear solution was obtained (*ca.* 15 min.). On cooling, a mass of dark needles appeared which, on recrystallisation from water containing sulphur dioxide, yielded 2 : 5-dimethoxyquinol (9 g., 60%) as colourless needles, m. p. 166°.

2 : 5-Diethoxybenzoquinone.—2 : 5-Dihydroxybenzoquinone (Jones and Shonle, *J. Amer. Chem. Soc.*, 1945, **67**, 1034) was dissolved in ethanolic hydrogen chloride (50 c.c.) under reflux (30 min.). Cooling the brown solution yielded 2 : 5-diethoxybenzoquinone as brown crystals which were filtered off (3 g., 50%) and formed yellow leaflets, m. p. 183°, on recrystallisation from ethanol.

2 : 5-Diethoxyquinol (cf. Nietzki and Rechberg, *loc. cit.*).—Stannous chloride (2.5 g.) was dissolved in concentrated hydrochloric acid (5 c.c.) and the solution added to one of 2 : 5-diethoxybenzoquinone (2 g.) in ethanol (5 c.c.). The mixture was refluxed for 20 min., then cooled, and the resulting brown precipitate crystallised from 30% aqueous ethanol saturated with sulphur dioxide. 2 : 5-Diethoxyquinol (1.1 g., 55%) formed colourless needles, rapidly becoming pink in air, m. p. 138°.

2 : 5-Biscarbethoxyoxy-1 : 4-dimethoxybenzene (I; R = CO₂Et).—2 : 5-Dimethoxyquinol (7.5 g.), anhydrous potassium carbonate (15 g.), ethyl chloroformate (12 c.c.), and anhydrous acetone (100 c.c.) were refluxed for 6 hr. with stirring, then diluted with further acetone (100 c.c.) and filtered hot. Evaporation left a solid which on crystallisation from ethanol yielded 2 : 5-biscarbethoxyoxy-1 : 4-dimethoxybenzene (8.5 g., 66%) as needles, m. p. 162° (Found: C, 53.9; H, 5.8. C₁₄H₁₈O₈ requires C, 53.5; H, 5.8%).

1 : 4-Dibenzoyloxy-2 : 5-dimethoxybenzene (I; R = CH₂Ph).—2 : 5-Dimethoxyquinol (10 g.), acetone (150 c.c.), anhydrous potassium carbonate (11.8 g.), and anhydrous potassium iodide (17.6 g.) were refluxed with stirring. Benzyl chloride (13 c.c.) was added and stirring and refluxing were continued for 20 hr. The hot acetone solution was filtered and the residue washed with hot acetone (100 c.c.), the combined filtrate and washings then being evaporated to 50 c.c. On cooling, crystals appeared which on recrystallisation from acetone yielded 1 : 4-dibenzoyloxy-2 : 5-dimethoxybenzene (12.7 g., 62%) as plates, m. p. 145° (Found: C, 75.4; H, 6.3. C₂₂H₂₂O₄ requires C, 75.4; H, 6.3%).

1 : 4-Bischloroacetoxy-2 : 5-dimethoxybenzene (I; R = CO·CH₂Cl).—2 : 5-Dimethoxyquinol (5 g.) was heated on a water-bath with chloroacetic anhydride (Diels and Okada, *Ber.*, 1911, **44**, 3333) (25 g.) for 1 hr. The solution was then allowed to cool and solidify. Ether (100 c.c.) was added and the insoluble ester filtered off. Crystallisation from chloroform yielded 1 : 4-bischloroacetoxy-2 : 5-dimethoxybenzene (7.5 g., 40%) as plates, m. p. 190° (Found: C, 44.5; H, 3.9. C₁₂H₁₂O₆Cl₂ requires C, 44.6; H, 3.7%).

1 : 4-Diacetoxy-2 : 5-dimethoxybenzene (I; R = Ac).—2 : 5-Dimethoxyquinol (10 g.) was refluxed in acetic anhydride (40 c.c.) for 1 hr. After cooling, the *diacetate* was collected; crystallised from ethanol it formed plates (13.5 g., 90%), m. p. 185° (Found: C, 56.8; H, 5.8. C₁₂H₁₄O₆ requires C, 56.7; H, 5.6%).

2 : 5-Dihydroxy-3 : 6-dimethoxyacetophenone (II; R = H).—1 : 4-Diacetoxy-2 : 5-dimethoxybenzene (2.5 g.) was added to a mixture of the boron trifluoride-ether complex (1.5 g.; 48% of BF₃) and acetic acid (10 c.c.), and the mixture kept at about 75° for 2 hr. The mixture was then cooled, the resulting paste treated with water (12 c.c.) and concentrated hydrochloric acid (3 c.c.), and the mixture refluxed until a clear solution was obtained. On cooling, needles appeared; recrystallisation from water containing sulphur dioxide gave 2 : 5-dihydroxy-3 : 6-dimethoxyacetophenone (1 g., 55%), m. p. 170° (Found: C, 56.3; H, 5.8. C₁₀H₁₂O₅ requires C, 56.6; H, 5.7%). Aqueous solutions of this compound deposited, on exposure to air, red needles, m. p. 301° (decomp.), presumably 3-acetyl-2 : 5-dimethoxybenzoquinone.

The ketone (0.5 g.) was shaken in aqueous sodium hydroxide (10 c.c.; 35%) with methyl sulphate (2.5 c.c.). The resulting 2 : 3 : 5 : 6-tetramethoxyacetophenone (0.4 g., 70%) formed needles, m. p. 101°, from water (Found : C, 60.1; H, 6.9. $C_{12}H_{16}O_5$ requires C, 60.0; H, 6.7%).

The diacetate, prepared by means of hot acetic anhydride (8 c.c.; 1 hr.), formed cubes (95%), m. p. 190°, from ethanol (Found : C, 56.6; H, 5.4. $C_{14}H_{16}O_7$ requires C, 56.8; H, 5.4%).

Bromanilic Acid (V; R = H).—(a) 2 : 5-Dihydroxy-3 : 6-dimethoxyacetophenone (0.5 g.) in acetic acid (8 c.c.) was treated with bromine (0.6 g.) in acetic acid (2 c.c.). The mixture was heated on a steam-bath for 1 hr., then allowed to cool. A yellow solid appeared which was removed and crystallised from acetic acid. Bromanilic acid formed yellow needles drying to a red powder (0.55 g., 75%), subliming at 280—290° (Found : C, 24.9; H, 0.9. Calc. for $C_6H_2O_4Br_2$: C, 24.2; H, 0.7%).

(b) Repetition of this experiment but with 1 : 4-diacetoxy-2 : 5-dimethoxyacetophenone (0.5 g.) yielded bromanilic acid (0.35 g., 69%).

2 : 5-Diacetoxy-3 : 6-dibromobenzoquinone (V; R = Ac), prepared by Jackson and Bolton's method (*loc. cit.*) using bromanilic acid obtained both as above and by Graebe and Weltner's method, had m. p. 204°, admixture producing no depression.

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