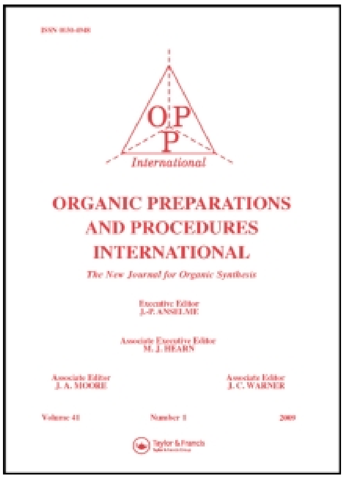

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STUDIES ON DIHYDROISOCOUMARIN (I).
A PRACTICAL SYNTHESIS OF 3-HYDROXYHOMOPHTHALIC ACID

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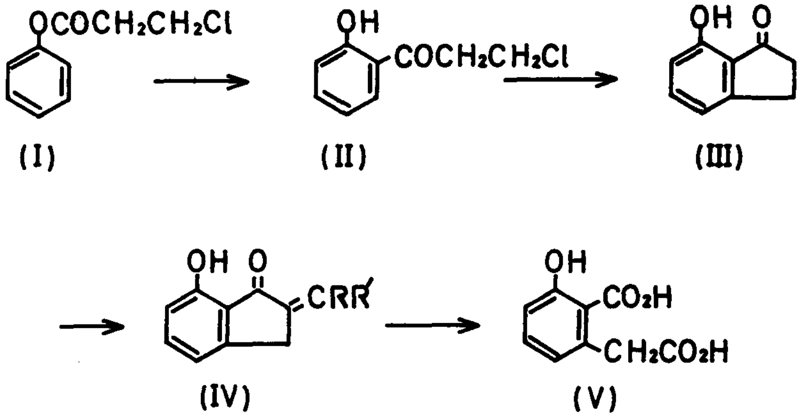
In connection with the synthesis of 8-hydroxy-3-(3'-hydroxy-4'-methoxyphenyl)dihydroisocoumarin (phyllodulcin) and related compounds, a practical preparation of the key precursor, 3-hydroxyhomophthalic acid (V), was needed. Although V had been obtained by oxidative ring cleavage of substituted methylene derivatives of 7-hydroxyindan-1-one (III), which in turn, were prepared by a Fries rearrangement



of phenyl β-chloropropionate (I) followed by a Friedel-Crafts cyclization, the reported overall yield of this sequence and its poor reliability in a large scale preparation were far from satisfactory. Thus, Mayer and van Zutphen reported[1] a two-step synthesis of III from I with an overall yield of 20 %, a one-step modification of this procedure has been reported to be less satisfactory without any experimental detail. Although the reported yields of the ozonolysis of the methylene derivatives IV(R = H, R' = OH) or (R = H, R' = Ph) are high enough[2], some other oxidative methods more suitable to a large scale synthesis were evidently desirable. The most useful would seem to be the hydrogen peroxide oxidation.[3]

Our reexamination revealed that the yield of one-step conversion of I to III is dependent upon the heating process of the reaction. An optimum yield of 50 % was achieved by carefully chosen two-step heating without isolation of intermediate II. The hydrogen peroxide oxidation of IV was examined with three derivatives: (a) R = H, R' = OH, (b) R = H, R' = Ph, (c) R = OH, R' = CO_2Et. While the reaction of IVb gave only trace amount of the acid V, IVa and IVc gave 60 and 80 % yields of V, respectively. The reaction is easily applicable to large scale preparation as is seen in the Experimental Section. The overall yield of V from I was 32 %.

EXPERIMENTAL

Phenyl β-chloropropionate (I).- A solution of 135 g. (1.1 mole) of β-chloropropionyl chloride and 94 g. (1.0 mole) of phenol in 200 ml. of benzene was stirred at 20° until the evolution of hydrogen chloride ceased. The mixture was heated slowly and then finally refluxed for 1 hr. The reaction mixture was cooled and unreacted phenol was extracted several times with 200 ml. of 5% aqueous NaOH. The organic layer was dried and distilled to give 150 g. (80%) of phenyl β-chloropropionate, bp. 120-125°/7mmHg, lit.[1] bp. 132-135°/12mmHg.

7-Hydroxyindan-1-one (III).- One-hundred and sixty five grams (0.84 mole) of phenyl β-chloropropionate and 500 g. (4.2 mole) of aluminum chloride were mixed with an efficient stirring. The mixture was heated carefully at 90-100° for 1 hr. Then the temperature was raised gradually to 160° over a period of 2 hrs. and maintained at this temperature for one additional hour. It was then finally heated at 180° for 1 hr. The cooled reaction mixture was decomposed by the cautious addition of ice followed by 200 ml. of concentrated hydrochloric acid. Steam distillate of the decomposed reaction mixture gave 63 g. (52 %) of 7-hydroxyindan-1-one as white needles, mp. 111°.

2-Hydroxymethylene-7-hydroxyindan-1-one (IVa).- To a mixture of 124 g. (2.3 mole) of sodium methoxide and 1 l. of dry benzene was added over 2 hrs. at room temperature, a solution of 148 g. (1.0 mole) of 7-hydroxyindan-1-one and

111 g. (1.5 mole) of ethyl formate in 1 l. of dry benzene, then the mixture was refluxed gently for 4 hrs. The cooled reaction mixture was extracted twice with 1 l. portions of 10 % aqueous solution of sodium bicarbonate. The aqueous extract was acidified with 18 % hydrochloric acid to give 130 g. (74 %) of 2-hydroxymethylene-7-hydroxyindan-1-one, mp. 136-138°. Recrystallization from methanol-ether gave white plates, mp. 146-147°, lit.[2] mp. 139-142°.

Ethyl 2-(7-hydroxyindan-1-one)glyoxylate (IVc).- To a stirred suspension of 148 g. (1.0 mole) of 7-hydroxyindan-1-one, 162 g. (3.0 mole) of sodium methoxide and 2 l. of dry benzene was added 220 g. (1.5 mole) of diethyl oxalate at room temperature. The mixture was kept at room temperature for 4 hrs. with efficient stirring, and allowed to stand overnight. The resulting canary yellow suspension was poured into 18 % hydrochloric acid and made acidic to litmus. The precipitated cystalline solid was collected, washed twice with water and dried to give 238 g. (96 %) of IVc. Recrystallization from methanol gave light yellow needles, mp. 145-147°.

Anal. Calcd. for $C_{13}H_{12}O_5$: C, 62.90; H, 4.87.
Found: C, 63.18; H, 4.69.

3-Hydroxyhomophthalic acid (V).

a) From 2-hydroxymethylene-7-hydroxyindan-1-one.- To a mixture of 88 g. (0.5 mole) of IVa, 200 g. (3.6 mole) of potassium hydroxide and 4 l. of water was added 800 g. (8.2 mole) of 35 % hydrogen peroxide below 10°. The reaction mixture was kept stirring vigorously for 6 hrs. between 5-10°, by occasional cooling with ice-water. During the course of reaction, the suspended crystalline solid dissolved to give a light brown colored solution. The resulting clear solution was allowed to stand overnight and heated slowly to 60° then cooled. The cold solution was acidified with conc. hydrochloric acid and evaporated to one-fifth of its original volume. The concentrated solution was extracted with 300 ml. portions of isobutyl alcohol. Evaporation the organic layer gave a brown solid which was washed with chloroform to yield 65 g. (66 %) of 3-hydroxyhomophthalic acid as white crystalline powder, mp. 161-163°. Recrystallization from ether gave white needles, mp. 167-168° (dec.), identical with an authentic sample obtained by ozonolysis of 2-benzal-7-hydroxyindan-1-one.[2]

b) From ethyl 2-(7-hydroxyindan-1-one)glyoxylate. - To a mixture of 248 g. (1.0 mole) of IVc, 225 g. (4.0 mole) of potassium hydroxide and 5 l. of water was added 1 Kg. (10.3 mole) of 35 % hydrogen peroxide below 10°. The reaction mixture was kept stirring vigorously at 5-10° for 5 hrs. The resulting light brown opaque solution was then heated to 60° for 1hr. and cooled. The cold solution was acidified with conc. hydrochloric acid, evaporated to one-fifth of its original volume *in vacuo*, and the residual solution was extracted three 500 ml. portions of isobutyl alcohol. Evaporation of the organic extract followed by washing of the resulting brown solid with chloroform gave 143 g. (73 %) of 3-hydroxyhomophthalic acid as slightly yellow crystalline powder, mp. 160-163°. Recystallization from ether gave white needles, mp. 168° (dec.).

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* To whom inquiries should be directed.

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