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HARCOURT BUTLER TECHNOLOGICAL INSTITUTE]

# Chalcones. Condensation of Aromatic Aldehydes with Resacetophenone. II

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Using resacetophenone as starting material, some chalcones and flavanones have been synthesized for the first time.

Since so many plant pigments have been recognized as polyhydroxychalcones, it was of some interest to synthesize compounds of this type. The present paper records the syntheses of the polyhydroxychalcones derived by the Claisen-Schmidt reaction of resacetophenone with *o*-,*m*-,*p*-tolualdehydes, 2,3-dimethoxybenzaldehyde, and vanillin in the presence of aqueous-alcoholic potassium hydroxide by either the cold or hot condensation procedure, outlined by Geissman and Clinton.[1] In all the cases reported except vanillin, it was found that some quantity of the flavanone accompanied the corresponding chalcone. The chalcones prepared above were then cyclized to flavanones with 4% aqueous-alcoholic sulfuric acid.

High temperature condensation of resacetophenone with the isomeric tolualdehydes is advantageous over the cold condensation, as the former leads to increased yield of chalcones and decreased resin formation. The quantity of 2′,4′-dihydroxy-2,3-dimethoxychalcone recovered is more when the reaction is carried out at room temperature for 48 hours than at the end of a reaction time of 7 days. The longer reaction period increases the quantity of a slowly crystallizable oil formed along with the chalcone, and from which it is readily separated owing to its greater solubility in alcohol. This oil slowly solidifies on ageing and was found to chiefly consist of the corresponding flavanone. This observation leads to the conclusion that when the reaction time is increased, the reaction does not stop with the formation of chalcone, but the latter partly undergoes gradual cyclization into flavanone. This conclusion is in agreement with that reported by Shah and his co-workers.[2]

2′,4,4′-Trihydroxy-3-methoxychalcone has previously been obtained by Russell and Todd[3] by condensation of resacetophenone dibenzoate with vanillin benzoate in the presence of dry hydrogen chloride, and saponification of the resulting 2′,4,4′-tribenzoyloxy-3-methoxychalcone into the required chalcone. We have, however, succeeded in effecting a direct synthesis of 2′,4,4′-trihydroxy-3-methoxychalcone by condensing resacetophenone with vanillin in the presence of strong alkali, in the cold, but the yield of chalcone was small (about 5%).

Owing to the reversible[4] nature of the Claisen-Schmidt reaction, it is apparent that by taking the reactants in excess of the stoichiometric proportion, the yield of the $\alpha,\beta$-unsaturated ketone can be increased. An excess of the aldehyde component is desirable as against that of resacetophenone, since with the excess of the latter the reaction takes other than the desired course.[5] In the case of all the above condensations by taking an excess of aldehyde the yield of chalcone was found to increase.

2′,4′-Dihydroxychalcone was synthesized by the interaction of resacetophenone and benzaldehyde in the presence of 40% aqueous-ethanolic potassium hydroxide solution, at room temperature, for seven days. Besides the expected $\alpha,\beta$-unsaturated ketone small quantities of 7-hydroxyflavanone, benzyl alcohol, and benzoic acid were identified. The isolation of the last two products indicates that some of the benzaldehyde undergoes the Cannizzaro reaction.

## EXPERIMENTAL

All melting points are uncorrected. Resacetophenone,[6] *o*-tolualdehyde,[7] and *p*-tolualdehyde[8] were prepared as described previously. *m*-Tolualdehyde was prepared from *m*-tolunitrile[9] *via* the Stephen's reaction.[10] The aldehydes were characterized through their phenylhydrazones.

*2′,4′-Dihydroxy-2,3-dimethoxychalcone.* Resacetophenone (6.0 g.), 2,3-dimethoxybenzaldehyde (6.5 g.), and ethanol (40 cc.) were mixed at 0° and to the mixture 40% aqueous potassium hydroxide (176 cc.) was added with shaking at room temperature. The mixture was allowed to stand, out of contact with air, for 47 hr. with shaking at intervals, during which it acquired a dark red color. After dilution with cold water, it was acidified with $6N$ hydrochloric acid and the voluminous yellow precipitate was separated, filtered, washed with warm water, dissolved in about 400 cc. ether and extracted thrice with 5% aqueous sodium bicar-

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(1) T. A. Geissman and R. O. Clinton, *J. Am. Chem. Soc.*, **68**, 697 (1946).

(2) G. N. Vyas and N. M. Shah, *J. Indian Chem. Soc.*, **28**, 75 (1951); C. C. Patel and N. M. Shah, *J. Indian Chem. Soc.*, **31**, 867 (1954).

(3) A. Russell and J. Todd, *J. Chem. Soc.*, 422 (1937).

(4) R. L. Schriner and T. Kurosawa, *J. Am. Chem. Soc.*, **52**, 2538 (1930).

(5) A. Cornelson and S. von Kostanecki, *Ber.*, **29**, 240 (1896).

(6) S. R. Cooper, *Org. Syntheses*, **21**, 103 (1941).

(7) J. W. Williams, C. H. Witten, and J. A. Krynitsky, *Org. Syntheses*, **Coll. Vol. III**, 818 (1955).

(8) G. H. Coleman and D. Craig, *Org. Syntheses*, **Coll. Vol. II**, 583 (1943).

(9) H. T. Clarke and R. R. Read, *Org. Syntheses*, **Coll. Vol. I**, 500 (1932).

(10) H. Stephen, *J. Chem. Soc.*, 1874 (1925).

bonate solution (75 cc., 75 cc., and 50 cc.). The bicarbonate washings on neutralization gave 2,3-dimethoxybenzoic acid (0.12 g.). The ethereal layer was washed with water and extracted with four 50-cc. portions of 10% aqueous potassium hydroxide solution. The alkaline solution on neutralization gave flocks of yellow mass together with an oil which crystallized during the course of several months and was identified as 7-hydroxy-2′,3′-dimethoxyflavanone, m.p. 170°. From the yellow mass the chalcone crystallized in yellow stellate aggregates of squat prisms from ethanol and then from benzene in flat needles, yield, 4.9 g. (41.7% based on the resacetophenone used), m.p. 188–189°.

*Anal.* Calcd. for $C_{17}H_{16}O_5$: C, 67.98; H, 5.37. Found: C, 68.07; H, 5.30.

The chalcone is very soluble in acetone, ethyl acetate and pyridine, moderately soluble in other common organic solvents, and sparingly soluble in petroleum ether and water.

*7-Hydroxy-2′,3′-dimethoxyflavanone.* The above chalcone (1.0 g.) in ethanol (60 cc.) water (35 cc.) and concentrated hydrochloric acid (3 cc.) was refluxed for 61 hr. on a water bath. The residue obtained after the removal of alcohol under reduced pressure was treated with water (300 cc.). The oily mass thus obtained solidified and crumbled to powder in contact with alcohol, which on repeated crystallization from alcohol and finally from benzene gave the flavanone as colorless, shiny plates with tapering ends; yield, 0.2 g., m.p. 170°.

*Anal.* Calcd. for $C_{17}H_{16}O_5$: C, 67.98; H, 5.37. Found: C, 67.60; H, 5.21.

*2′,4′-Dihydroxy-2,3-dimethoxychalcone 2,4-dinitrophenylhydrazone.* A solution of 2,4-dinitrophenylhydrazine (0.2 g.) in concentrated sulfuric acid (2.0 cc.) and ethanol (7 cc.) was refluxed with 2′,4′-dihydroxy-2,3-dimethoxychalcone (0.6 g.) in alcohol (25 cc.) for 10 hr., when the 2,4-dinitrophenylhydrazone separated as dark red microcrystalline needles; yield, 0.13 g., which on recrystallization from acetone-alcohol melted at 251–252°.

*Anal.* Calcd. for $C_{23}H_{20}O_8N_4$: N, 11.66. Found: N, 11.80.

*Acetylation of 2′,4′-dihydroxy-2,3-dimethoxychalcone.* Acetylation by acetic anhydride, and fused sodium acetate at 125–130° for 5 hr. gave an oil, which partially solidified after about 2 months and the solidified mass, on crystallization from ethanol and finally from benzene, gave the monoacetate in yellow short slender needles, m.p. 123.5°. Acetylation with acetic anhydride and pyridine in the cold gave the monoacetate in good yield.

*Anal.* Calcd. for $C_{19}H_{18}O_6$: C, 66.65; H, 5.30. Found: C, 66.52; H, 5.35.

Schotten-Baumann benzoylation of 2′,4′-dihydroxy-2,3-dimethoxychalcone gave an oily product which failed to crystallize.

*2′,4,4′-Trihydroxy-3-methoxychalcone.* Aqueous potassium hydroxide (88 cc., 40%) was gradually added with shaking to a solution of resacetophenone (3.0 g.) and vanillin (3.0 g.) in ethanol (20 cc.) at 0°. The reaction mixture was then kept in a closed container at room temperature for 7 days, with occasional shaking, and on being worked up as before, gave the crude chalcone as an oil. The oil was desiccated and repeatedly washed with hot petroleum ether (b.p. 40–60°) and finally with hot benzene in order to remove most of the associated vanillin. It was finally purified by precipitation from aqueous alkaline solution. The chalcone crystallized from 40% aqueous ethanol as yellow microcrystalline powder and then from boiling benzene (sparingly soluble) in glistening yellow flakes. The yield was 0.3 g., m.p. 210° (Russell and Todd[3] record m.p. 210°).

*Anal.* Calcd. for $C_{16}H_{14}O_5$: C, 67.12; H, 4.92. Found: C, 67.11; H, 4.84.

This chalcone was also prepared by using different solvents as reaction medium, *viz.*, water, ethylene glycol. The use of ethanol as solvent, sometimes, produces the chalcone as an oily-resinous mass, difficult to crystallize. Attempts to prepare the chalcone by the hot condensation procedure, however, failed.

When the condensation was carried out, in the presence of aqueous-alcoholic potassium hydroxide, for a period of 6 months or 1 year, a black resinous mass was obtained.

*4′,7-Dihydroxy-3′-methoxyflavanone.* The above chalcone was isomerized by dilute aqueous ethanolic sulfuric acid and worked up as in the previous case. The flavanone crystallized from ethanol (animal charcoal) in glistening plates, m.p. 191°.

*Anal.* Calcd. for $C_{16}H_{14}O_5$: C, 67.12; H, 4.92. Found: C, 67.32; H, 4.91.

*2′,4,4′-Trihydroxy-3-methoxychalcone 2,4-dinitrophenylhydrazone.* This derivative was prepared from the above chalcone in the usual way. It separated from ethyl acetate in dark red micro-needles, m.p. 235°.

*Anal.* Calcd. for $C_{22}H_{18}O_8N_4$: N, 12.02. Found: N, 11.74.

*2′,4,4′ - Triacetoxy - 3 - methoxychalcone.* Acetylation of 2′,4,4′-trihydroxy-3-methoxychalcone (0.3 g.) by acetic anhydride (6.1 cc.) and fused sodium acetate (0.7 g.) at 125–130° for 6 hr. gave the required compound as an oil which gradually solidified and crystallized from 95% ethanol in glistening pale yellow plates, m.p. 133°, yield, 0.35 g.

*Anal.* Calcd. for $C_{22}H_{20}O_8$: C, 64.07; H, 4.88. Material dried at 62° in a high vacuum. Found: C, 63.92; H, 4.81.

It is less soluble in organic solvents than the parent chalcone and gives a negative ferric chloride reaction.

*2′,4′-Dihydroxy-2-methylchalcone.* Resacetophenone (3.0 g.) in ethanol (12 cc.) was condensed with *o*-tolualdehyde (2.28 cc.; $d_4^{19}$ 1.0386) in presence of 40% aqueous potassium hydroxide (88 cc.) by keeping in a closed container for 7 days at room temperature and worked up as before. The crude chalcone (1.1 g.) was purified by several recrystallizations from aqueous ethanol (animal charcoal) and finally from benzene when it separated as yellow needle-like crystals, m.p. 180–181°.

*Anal.* Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.54. Found: C, 75.57; H, 5.86.

The mother liquor left after crystallization of the chalcone gave 7-hydroxy-2′-methylflavanone in small amount as colorless plates, m.p. 212°.

*7-Hydroxy-2′-methylflavanone.* 2′,4′-Dihydroxy-2-methylchalcone was isomerized to the flavanone as previously described. It was obtained from ethyl alcohol in mica-like plates, m.p. 212°.

*Anal.* Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.54. Found: 75.81; H, 5.60.

*2′,4′-Dihydroxy-3-methylchalcone.* A mixture of resacetophenone (3.0 g.), *m*-tolualdehyde (2.31 cc., $d_4^{21.4}$ 1.0189), ethanol (25 cc.) and potassium hydroxide pellets of 85% purity (15 g. dissolved in 15 cc. water) was heated in a water bath at about 60° for 2 hr. It was worked up as usual. The crude chalcone obtained as an oil (2.1 g.) was washed with warm water, dried, and dissolved in chloroform. A little petroleum ether (b.p. 40–60°) was added to the solution. After some time a resinous deposit had formed on the sides of the container. The clear liquid was decanted and a little more petroleum ether was added, this process being repeated until no more resin precipitated. Further addition of petroleum ether brought about the separation of the chalcone as an oil. The oil was nucleated with a few seed crystals of 2′,4′-dihydroxy-3-methylchalcone obtained from a previous preparation and chilled. The entire mass solidified after some time. For further purification the solid mass was dissolved in benzene and fractionally precipitated by the addition of light petroleum ether and the various fractions thus obtained were left overnight in a refrigerator; the last fraction had solidified. The supernatant layer of benzene–petroleum ether mixture was decanted, and to this solid a small quantity of ethanol was added to dissolve the associated oily impurity and the solvent was decanted from the solid immediately. The solid was then crystallized from aqueous-methanol (animal charcoal) in yellow needles, m.p. 135°.

*Anal.* Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.54. Found: C, 75.42; H, 5.90.

*7-Hydroxy-3′-methylflavanone.* The above chalcone was isomerized to flavanone in the usual way. The reaction product, after the removal of alcohol under reduced pressure, on standing in contact with glacial acetic acid in a refrigerator for 12 hr. partially solidified. The adherent oily portion was centrifuged and the solid thus recovered was dissolved in ethanol and precipitated by the addition of water, filtered, and dried. The product on repeated dissolution in benzene and precipitation by light petroleum ether gave the flavanone as pinkish white microcrystalline powder, m.p. 146–147°.

*Anal.* Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.54. Found: C, 75.74; H, 5.82.

*2′,4′-Dihydroxy-4-methylchalcone.* A solution of resacetophenone (3.0 g.), *p*-tolualdehyde (2.36 cc., $d_4^{16.7}$ 1.0194) in ethanol (25 cc.) was treated with potassium hydroxide pellets of 85% purity (15 g. dissolved in 15 cc. water), and heated in a water bath at about 60° for 2 hr. It was worked up as before. The crude chalcone (2.6 g.) separated as a yellow oil. It was washed several times with warm water (about 70°) and dried. On nucleation with the crystals of isomeric 2′,4′-dihydroxy-2-methylchalcone and cooling in a freezing mixture, with stirring, the oil suddenly solidified. An alcoholic solution of this solidified mass on standing deposited the 2′,4′-dihydroxy-4-methylchalcone in needles, but the compound was not pure since the crystals occluded an appreciable quantity of resinous matter from the solution. The crystalline magma was filtered at a pump, washed with a little ethanol, and then crystallized from aqueous ethanol in yellow needles and finally from benzene in yellow, well shaped prisms, m.p. 153–154°.

*Anal.* Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.54. Found: C, 75.41; H, 5.80.

The resulting aqueous alcoholic mother liquor deposited 7-hydroxy-4′-methylflavanone in irregular plates, m.p. 170°.

*7-Hydroxy-4′-methylflavanone.* The ring closure of the above chalcone (crude) by refluxing it with aqueous-alcoholic sulfuric acid gave an oily product which crystallized slowly (80 days) in contact with acetic acid. Recrystallization from alcohol (animal charcoal) furnished the flavanone in colorless rectangular plates, m.p. 170–171°.

*Anal.* Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.54. Found: C, 75.22; H, 5.62.

The chalcones described in this paper give a yellow coloration with concentrated sulfuric acid (except 2′,4,4′-trihydroxy-3-methoxychalcone-red, 2′,4′-dihydroxy-2,3-dimethoxychalcone-orange), dissolve in alkali with the production of an orange color which changes to yellow, and give a dark brown coloration with ethanolic ferric chloride.

All the flavanones, described herein, on reduction with magnesium and ethanolic hydrochloric acid give a pink color, whereas 4′,7-dihydroxy-3′-methoxyflavanone, gives various transitory shades of color, *viz.* bluish violet, violet, rose-violet, and finally pink.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

# Organometallic Compounds from Aryl Halides Containing Ether Functions[1]

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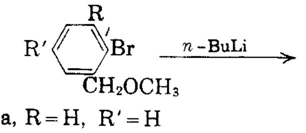
A number of *o*-methoxymethylaryl halides have been synthesized, and a study has been made of the synthesis and properties of the corresponding aryllithium and arylmagnesium compounds.

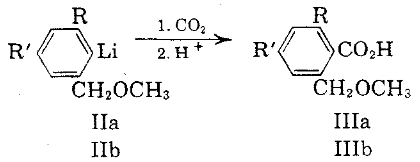
Although aryl methyl ethers which contain lithium in the nucleus have been synthesized previously, a careful study of the preparation and properties of *o*-methoxymethylphenyllithium compounds has apparently not been made. In the present study a method for the preparation of such compounds has been developed which consists of allowing an *o*-bromobenzyl methyl ether to react with *n*-butyllithium for a limited time. In this way *o*-methoxymethylbromobenzene (Ia), 4-*t*-butyl-2-methoxymethyl-6-methylbromobenzene (Ib), and 4-*t*-butyl-2,6-di(methoxymethyl)bromobenzene (Ic) were converted to the corresponding lithium derivatives, IIa, IIb, and IIc. Carbonation of these lithium compounds afforded the acids, IIIa, IIIb, and IIIc in yields of 34, 65, and 91%, respectively. In comparison, 4-*t*-butyl-2,6-dimethylbromobenzene, when treated similarly, gave the corresponding acid in a 51% yield.



Ia, R = H, R′ = H

Ib, R = $CH_3$, R′ = $C(CH_3)_3$

Ic, R = $CH_2OCH_3$, R′ = $C(CH_3)_3$



| | |
|---|---|
| IIa | IIIa |
| IIb | IIIb |
| IIc | IIIc |

Coupling of the aryllithium with the aryl bromide may be responsible for the variation in the yields of acids; the aryllithium compound least hindered

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