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A GRIGNARD REACTION INVOLVING THE FURAN NUCLEUS

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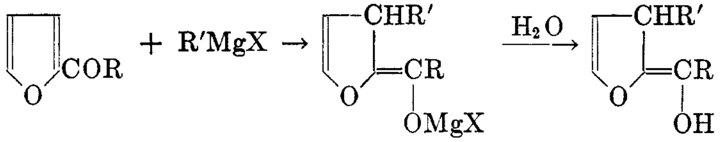
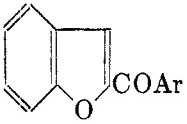
A study of the mode of addition of the Grignard reagent to 2-furyl ketones was initiated in the hope of finding a method of preparing mono ethers of enediols. A compound of the desired type (I) would result if a Grignard reagent could be condensed in the 1,4-manner with a 2-furyl ketone.



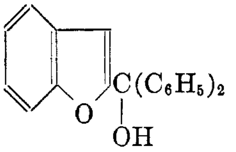
I

The proposed condensation is novel in that it involves a double bond of the furan nucleus.

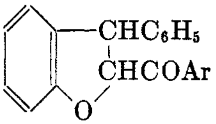
In the present work the action of phenylmagnesium bromide on 2-benzofuryl aryl ketones (II) has been studied. The phenyl ketone (II, Ar = C_6H_5) reacted entirely in the 1,2-manner, yielding the corresponding carbinol (III). The structure of the product was established by oxidative degradation to benzophenone in an 83% yield.



II



III



IV

The mode of addition to the corresponding mesityl and 2,4,6-triisopropylphenyl ketones, however, was 1,4, producing unstable enolic intermediates (V). That from mesityl 2-furyl ketone appeared to form an enol peroxide, which spontaneously decomposed at room temperature to give equimolecular amounts of the known 3-phenylisocoumaranone (VI) and mesitoic acid.

Oxidation of the triisopropylphenyl compound proceeded with more

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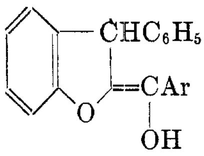
[1] du Pont Post-Doctorate Fellow, 1939–1940.

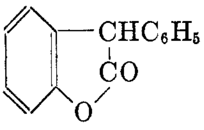
difficulty, and a small amount of triisopropylbenzoic acid was the only product isolated. By analogy with the mesityl ketone, however, it seems safe to conclude that the mode of addition was 1,4.

When the reaction with the two hindered ketones took place in the absence of oxygen, and opportunity was given for the enolic intermediates to rearrange, the products were the corresponding 2-aroyl-3-phenyl-2,3-dihydrofurans (IV).

An attempt was made to synthesize these ketones by an independent method. 3-Phenylcoumarilic acid was reduced by sodium amalgam to yield two isomeric dihydrocoumarilic acids. Attempts to convert these to the desired ketones by condensing the acid chlorides with mesitylene and triisopropylbenzene gave only amorphous products.



V



VI

It is of interest that the mesityl and 2,4,6-triisopropylphenyl-2-benzofuryl ketones were made from coumarilyl chloride by condensation with the aromatic hydrocarbon in the presence of aluminum chloride. The use of the Friedel-Crafts method in the synthesis of aryl 2-furyl ketones appears not to have been reported previously.

EXPERIMENTAL

2-Benzoylbenzofuran was prepared in 69% yield according to the method of Stoermer, Chydenius, and Schinn (1), except that phenacyl chloride was used instead of the bromide.

α-Benzofuryldiphenylcarbinol. Approximately 0.05 mole of phenylmagnesium bromide was added over a period of fifteen minutes to a well-stirred, refluxing solution of 8.12 g. of 2-benzoylbenzofuran in 130 cc. of absolute ether. At first, a tan colored solid separated. On continued refluxing, this solid gradually went into solution and, after refluxing for two hours, a white, finely divided solid separated from the solution. The reaction mixture was poured on a mixture of 150 g. of ice-water and 10 g. of ammonium chloride. The ether solution was washed with 25 cc. of saturated sodium bicarbonate solution containing a few crystals of sodium thiosulfate and dried over anhydrous magnesium sulfate. The solution was concentrated to a small volume, and 200 cc. of petroleum ether (b.p. 30–60°) was added. The solvent was allowed to evaporate on a water-bath until crystallization had started. Cooling gave 8.9 g. of the carbinol—a colorless crystalline solid melting at 129–132°. Recrystallization of the product from benzene-petroleum ether (b.p. 60–110°) and from dilute ethanol gave colorless crystals melting at 133–134°.

Anal. Calc'd for $C_{21}H_{16}O_2$: C, 83.97; H, 5.36.
Found: C, 83.86; H, 5.49.

The carbinol gave no semicarbazone, oxime, acetate, or benzoate.

Oxidation with sodium dichromate. To a solution of 2.1 g. of α-benzofuryldiphenylcarbinol in 55 cc. of glacial acetic acid, 17 g. of technical sodium dichromate was added. The mixture was warmed until a vigorous reaction had begun and, after this initial reaction had subsided, was heated on a water-bath for twelve hours. An additional 3 g. of sodium dichromate was added, and heating was continued another hour. The reaction mixture was poured into 350 cc. of water and was steam distilled until all of the oil was carried over. The benzophenone obtained melted at 47.5–49° and weighed 1.05 g. A mixture with an authentic sample of benzophenone showed no lowering of the melting point.

Coumarin dibromide. The procedure was an adaptation of that used by Karrer, Glattfelder, and Widmer (2) for 5-acetoxycoumarin. A solution of 333 g. of bromine in 270 g. of chloroform was added dropwise over three and one-half hours to a well-stirred solution of 300 g. of coumarin in 650 g. of chloroform at room temperature. After concentration to one-half the volume in a rapid stream of air, the reaction mixture was filtered and the coumarin dibromide was washed with four 80-cc. portions of absolute ether. Further concentration of the filtrate gave additional amounts of product. The colorless crystals weighed 357 g. and melted at 103–107°.

Coumarilic acid. This compound was prepared from coumarin dibromide by a method similar to that of Karrer, Glattfelder, and Widmer (2). The acid, after recrystallization from 50% alcohol, melted at 190–193°; yield 90%.

Coumarilyl chloride. The chloride, boiling at 146–148° (19 mm.), was obtained in 94% yield by the method of Tadeus and Reichstein (3).

2-Mesitoylbenzofuran. A. *From coumarilyl chloride.* A solution of 53 g. of coumarilyl chloride in 140 cc. of carbon disulfide was added over a period of one hour to a suspension of 44 g. of anhydrous aluminum chloride in a mixture of 40 g. of mesitylene and 110 cc. of carbon disulfide at 0°. The reaction mixture was stirred at this temperature for an additional forty minutes after the chloride had been added. The resulting suspension was poured on a mixture of 400 g. of ice and 30 cc. of concentrated hydrochloric acid, and 200 cc. of ether was added. The ether-carbon disulfide layer was removed, and the aqueous layer was extracted with several portions of fresh ether. The combined extracts were washed with three 100-cc. portions of saturated aqueous sodium bicarbonate solution and dried over anhydrous magnesium sulfate. The solvent was distilled; the 2-mesitoylbenzofuran, after recrystallization from 95% ethanol (60 cc.), weighed 57 g. It was white and melted at 74.5–76.5°.

Anal.[2] Calc'd for $C_{18}H_{16}O_2$: C, 81.78; H, 6.11.
Found: C, 81.94; H, 6.12.

B. *From salicylaldehyde.* 2-Mesitoylbenzofuran was also prepared according to the general method of Stoermer, Chydenius, and Schinn (1) for 2-acylbenzofurans. A solution of 9.4 g. of salicylaldehyde in 10 cc. of 95% ethanol was added to a solution of 4.3 g. of potassium hydroxide in 50 cc. of 95% ethanol, and the mixture was warmed until the salt was dissolved. A hot solution of 15 g. of ω-chloroacetomesitylene in 50 cc. of 95% ethanol was added in portions over a period of ten minutes to the warm solution of the aldehyde salt. After being refluxed for two and a quarter hours, the reaction mixture was filtered, and the filtrate diluted with an equal volume of water. The diluted filtrate was then steam-distilled until a distillate of 200 cc. had been collected. The residue was extracted with six 50-cc. portions of ether, and the

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[2] The microanalyses were carried out by Mr. L. G. Fauble, Dr. W. H. Taylor, Miss Mary S. Kreger, and Mr. C. W. Beazley.

combined ethereal extracts, after being washed with 10% sodium hydroxide solution and with water, were dried over anhydrous magnesium sulfate. The ether was then removed by distillation. Addition of petroleum ether (b.p. 30–60°) gave 4.5 g. of a solid which, after repeated recrystallizations from benzene-petroleum ether (b.p. 60–110°), dilute methanol, and dilute ethanol, separated as colorless crystals, melting at 172–173°.

Anal. Calc'd for $C_{18}H_{18}O_4$: C, 72.48; H, 6.08.
Found: C, 71.90; H, 5.86.

This compound was not identified.

Evaporation of the petroleum ether from the filtrate and addition of 95% ethanol gave 3 g. of a colorless solid which, after two recrystallizations from 95% ethanol, melted at 74.5–76.5°. A mixture of this compound with 2-mesitoylbenzofuran prepared by method A melted at 74.5–76.5°.

2-Mesitoyl-3-phenyl-2,3-dihydrobenzofuran. An ether solution containing approximately 0.1 mole of phenylmagnesium bromide, prepared under nitrogen, was added gradually over a period of thirty-five minutes to a refluxing solution of 17.5 g. of 2-mesitoylbenzofuran in 200 cc. of absolute ether. The reaction was carried out in a nitrogen atmosphere and with stirring. When the addition of the Grignard reagent was nearly complete, the color of the mixture changed from red to light green. After being heated under reflux for an additional thirty-five minutes, the mixture was cooled, and 100 cc. of 1.2 *N* hydrochloric acid was added cautiously. The mixture was stirred at reflux temperature for five hours, during which the ether was removed by a stream of nitrogen. The resulting suspension was heated at 75° for thirty-six hours and cooled. The 2-mesitoyl-3-phenyl-2,3-dihydrobenzofuran, after repeated crystallization from 95% alcohol, absolute alcohol and benzene-petroleum ether, melted at 148–154°. A sharp melting point could not be obtained.

Anal. Calc'd for $C_{24}H_{22}O_2$: C, 84.16; H, 6.48.
Found: C, 83.95; H, 6.52.

When this reaction was carried out without using an inert atmosphere, only cleavage products of 2-mesitoyl-3-phenyl-2,3-dihydrobenzofuran were obtained. Approximately 0.1 mole of phenylmagnesium bromide in 75 cc. of absolute ether was added, with stirring, to a refluxing solution of 13.1 g. of 2-mesitoylbenzofuran in 200 cc. of absolute ether over a period of twenty minutes. After an additional thirty-five minutes of refluxing, the reaction mixture was decomposed in the usual manner with ice-ammonium chloride solution. The moist ether solution was condensed to a volume of 75 cc. in a rapid stream of air and was then warmed until the spontaneous evolution of heat had begun. After the mixture was refluxed for an additional thirty minutes and allowed to stand overnight at room temperature, sufficient ether was added to bring the material into solution. Extraction of this solution with three 150-cc. portions of saturated aqueous sodium bicarbonate solution and acidification of the resulting bicarbonate solution with hydrochloric acid, gave 4.6 g. of mesitoic acid melting at 150–152°. The melting point of a mixture of this compound with an authentic sample of mesitoic acid showed no depression.

The ethereal layer, after being dried over anhydrous magnesium sulfate, was concentrated to 50 cc., and an equal volume of petroleum ether (b.p. 60–110°) added. Fractionation of this solution to remove the ether gave a solution which on standing deposited 6 g. of colorless crystals, melting at 98–116°. Recrystallizations of this solid from methanol and from benzene-petroleum ether (b.p. 60–110°) gave colorless needles, melting at 114–115°.

Anal. Calc'd for $C_{14}H_{10}O_2$: C, 79.96; H, 4.81.
Found, C, 79.63; H, 4.96.

A mixture of this compound with a sample of 3-phenylisocoumaranone (m.p. 110–114°), prepared by the method of Bistrzycki and Flatau (4) (from phenol and mandelic acid), melted at 112–115°. Bromination of this compound by the procedure of Bistrzycki and Flatau (4) gave a product melting at 70–72°.[3] Further concentration of the mother liquor from this product gave only a viscous oil which could not be crystallized.

One experiment was carried out in which the reaction mixture was divided into two equal parts. One of these was exposed to air and the other was worked up under nitrogen. The relative amounts of products were the same as when they originated from different reaction mixtures. This shows that the enol is the parent substance of the 2-mesitoyl-3-phenyl-2,3-dihydrobenzofuran as well as of the cleavage products.

2-(2,4,6-Triisopropylbenzoyl)benzofuran. A solution of 33 g. of coumarilyl chloride in 110 cc. of carbon disulfide was added to a well-stirred suspension of 26 g. of anhydrous aluminum chloride in a mixture of 39 g. of 2,4,6-triisopropylbenzene,[4] in 70 cc. of disulfide at 0° over a period of thirty minutes. The ice-bath was removed and the reaction mixture was stirred for four and one-half hours at room temperature. A vigorous evolution of hydrogen chloride took place when the reaction mixture had attained room temperature, and the solid gradually went into solution. The reddish-brown solution was poured on 200 g. of cracked ice and 10 cc. of concentrated hydrochloric acid, and the aqueous layer was extracted with ether (two 75-cc. portions), and after the solution was dried over anhydrous magnesium sulfate, the solvents were distilled. The residue, on treatment with petroleum ether (b.p. 30–60°), gave 45 g. of a colorless, crystalline solid melting at 92–100°. Recrystallization from a benzene-petroleum ether mixture and 95% alcohol gave 2-(2,4,6-triisopropylbenzoyl)benzofuran melting at 103–105°. Evidence was obtained for two crystalline forms of this substance. When these crystals were heated very slowly, they softened and resolidified, finally melting at 117–118°. The higher-melting form when recrystallized from 95% alcohol melted at 103–105°.

Anal. Calc'd for $C_{24}H_{28}O_2$: C, 82.71; H, 8.10.
Found: C, 82.59; H, 7.89.

2-(2,4,6-Triisopropylbenzoyl)-3-phenyl-2,3-dihydrobenzofuran. Approximately 0.1 mole of phenylmagnesium bromide, prepared in the usual manner under nitrogen, was added slowly (forty minutes) to a well-stirred, refluxing solution of 25 g. of 2-(2,4,6-triisopropylbenzoyl)benzofuran in 250 cc. of absolute ether in an atmosphere of nitrogen. After being refluxed for three hours, the reaction mixture was poured on 100 g. of cracked ice and 20 cc. of glacial acetic acid and the aqueous layer removed. The ethereal layer was washed free of acid with saturated sodium bicarbonate solution, containing a few crystals of sodium thiosulfate, and then was washed with water. The ether solution was dried and the solvent distilled. The residue was dissolved in 150 cc. of low-boiling petroleum ether and the solution kept at 0° for several days. The crude 3-phenylcoumaranone (m.p. 107–132°) which separated weighed 21 g. Recrystallization from absolute alcohol gave colorless plates, melting at 140–141°.

Anal. Calc'd for $C_{30}H_{34}O_2$: C, 84.45; H, 8.05.
Found: C, 84.67; H, 8.16.

The foregoing experiment was carried out without rigid exclusion of oxygen, and

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[3] The melting point reported by these authors was 70°.

[4] The 2,4,6-triisopropylbenzene used was Alkazene-13 obtained from the Dow Chemical Company.

through the ether solution of the product (enol) a stream of air was passed for one hour. The product proved to be a mixture; a small amount of 2,4,6-triisopropylbenzoic acid was the only pure compound which could be obtained from it.

3-Phenylcoumarilic acid.[5] To a solution of 4.83 g. of sodium in 75 cc. of absolute alcohol was added 19.7 g. of phenol. The mixture was cooled in an ice-bath and 56 g. of ethyl α-bromobenzoylacetate was added dropwise, with stirring. The ice-bath was removed and the stirring continued for five hours. After standing twelve hours, the mixture, then neutral to litmus, was poured into 800 cc. of cold water. The product was dissolved in ether and the solution washed with 5% sodium bisulfite solution and with water and dried over anhydrous magnesium sulfate.

The oily residue left after the ether had been distilled was added slowly, with shaking, to 100 cc. of concentrated sulfuric acid. The reaction mixture was kept at 0° during the addition and for one hour afterward; it was then allowed to stand at room temperature for three hours. It was finally poured into 800 g. of cracked ice. The product was taken up in ether, washed with water, 5% sodium thiosulfate solution and water, and dried over anhydrous magnesium sulfate.

The impure ester, obtained by evaporating the ether, was saponified by heating on a steam-cone for one and one-half hours with 13 g. of sodium hydroxide and 100 cc. of water. The mixture was filtered and the filtrate acidified with 100 cc. of 6 *N* hydrochloric acid. The 3-phenylcoumarilic acid, after two recrystallizations from dilute ethanol, weighed 9 g. and melted at 228–231°. After several additional crystallizations from dilute ethanol, the acid melted at 232–233°, with decomposition.

Anal. Calc'd for $C_{15}H_{10}O_3$: C, 75.60; H, 4.24; neut. equiv., 238.1.
Found: C, 75.27; H, 4.60; neut. equiv., 240, 245.

Catalytic hydrogenation of 3-phenylcoumarilic acid. A solution of 3.1 g. of 3-phenylcoumarilic acid in 13 cc. of 1 *N* sodium hydroxide solution was hydrogenated under a pressure of 5000 lbs. (340 atm.) at 75°, Raney nickel being used as a catalyst. At the end of four hours the catalyst was removed, and concentrated hydrochloric acid added to precipitate the organic acid. The product weighed 2.8 g. and melted at 130–145°. Repeated recrystallization from benzene and from dilute ethanol gave colorless crystals melting at 160–162°. The compound had the composition of an octahydro derivative of 3-phenylcoumarilic acid; it was not studied further.

Anal. Calc'd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.35.
Found: C, 73.19; H, 7.46.

3-Phenyl-2,3-dihydrocoumarilic acid (m.p. 147°). A. *From 3-phenylcoumarilic acid.* Twenty-five grams of 3% sodium amalgam was added over a period of five hours to a water suspension of 0.5 g. of 3-phenylcoumarilic acid. The temperature was kept at 70° during the addition and for an additional eighteen hours. Ten grams more of the amalgam was added to the filtered solution and the temperature maintained at 70° for another twelve hours. The mixture was allowed to stand for twenty-four hours at room temperature, decanted through a filter and the mercury washed with water. Acidification of the filtrate gave 0.5 g. of crude acid melting at 130–134°. Recrystallization from dilute ethanol and from a benzene-petroleum ether mixture yielded colorless needles of 3-phenyl-2,3-dihydrocoumarilic acid melting at 146–147°.

Anal. Calc'd for $C_{15}H_{12}O_3$: C, 74.97; H, 5.04.
Found: C, 75.17; H, 5.29.

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[5] This procedure is an adaptation of that used by Hantzsch (5) for the preparation of 3-methylcoumarilic acid.

When the reduction was effected at room temperature, the product was an isomeric acid melting at 186–188°. When heated slowly this acid melted partially, resolidified and melted to a clear liquid at 195–196°.

Anal. Calc'd for $C_{15}H_{12}O_3$: C, 74.97; H, 5.04.

Found: C, 75.18; H, 5.13.

B. *From coumarilic acid.* The dihydrocoumarilic acid, melting at 147°, was also prepared by the procedure of King[6] by adding benzene to coumarilic acid in the presence of aluminum chloride. The product melted at 146–148° and proved to be identical with that from method A.

Anal. Calc'd for $C_{15}H_{12}O_3$: C, 74.97; H, 5.04.

Found: C, 75.17; H, 5.29.

SUMMARY

Phenylmagnesium bromide has been found to add in the 1,4-manner to mesityl 2-benzofuryl ketone and to 2,4,6-triisopropylphenyl 2-benzofuryl ketone. The condensation is novel in that it involves a double bond of the furan nucleus.

URBANA, ILL.

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[6] The acid described here is identical with that of King (6) incorrectly reported as 2-phenyl-2,3-dihydrocoumarilic acid.