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3,702,854

SYNTHESIS OF 2-PHENYL BENZOFURANS

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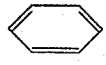
No Drawing. Filed Mar. 27, 1970, Ser. No. 23,517
Int. Cl. C07d 5/42
U.S. Cl. 260—346.2 R 3 Claims

ABSTRACT OF THE DISCLOSURE

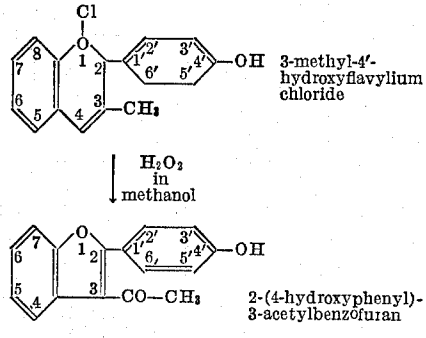
Flavylium salts are converted into benzofuran derivatives which are unsubstituted at the 3 position. The key item of the synthesis is that intermediates are not isolated: Steps of oxidation, alkali treatment, and acid treatment are applied in sequence without isolating any of the intermediates whereby the desired end product is obtained directly and in high yield.

A non-exclusive, irrevocable, royalty-free license in the invention herein described, throughout the world for all purposes of the United States Government, with the power to grant sublicenses for such purposes, is hereby granted to the Government of the United States of America.

This invention relates to and has among its objects the provision of novel procedures for preparing benzofuran derivatives from flavylium salts. Further objects of the invention will be evident from the following description wherein parts and percentages are by weight unless otherwise specified. The abbreviation p.p.m. used herein refers to parts per million. Temperatures are given in degrees centigrade. The symbol Ph is used to represent



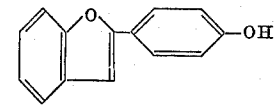
Previously I have shown in U.S. Pat. 3,165,537 that when a flavylium salt, dissolved in methanol, is oxidized with hydrogen peroxide there results an addition of a carbonyl group to the substituent in the 3 position, together with conversion of the flavylium ring into a benzofuran ring. For example, where the starting compound contains a methyl group at position 3, the product is a benzofuran containing a —CO—CH_3 group at the corresponding position. The reaction as applied to 3-methyl-4'-hydroxyflavylium chloride, by way of example, is graphically represented as follows:



It is further shown in the aforesaid patent that this same result of introduction of a carbonyl group into the side chain at position 3 takes place with many different types of substituents and is not limited to the methyl group.

In accordance with the present invention, the oxidation of flavylium salts is carried out under conditions whereby the end product is unsubstituted at the 3 position. For

example, where the reaction is applied to the same starting compound as above (3-methyl-4'-hydroxyflavylium chloride), the end product is 2-(4-hydroxyphenyl) benzofuran



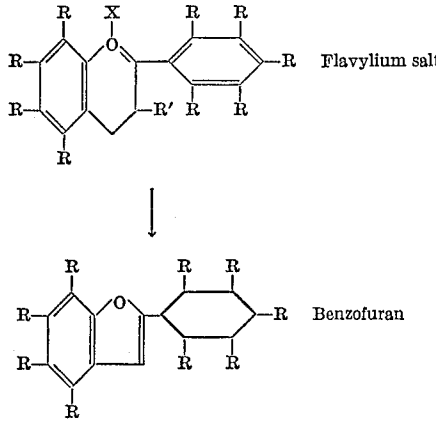
Special attention is called to the fact that the product is unsubstituted at the 3 position.

In a practice of the invention a flavylium salt is first subjected to oxidation in a medium of aqueous acetic acid. The proportion of glacial acetic acid in the medium may be varied, but in any case should be high enough to maintain the flavylium salt and the oxidation product in solution during the reaction. In general, the medium will contain about 40–60% glacial acetic acid. Preferably, the medium also contains a small proportion—about 5–10%—of sulphuric acid or perchloric acid. It may be observed that the alcoholic medium of Pat. 3,165,537 cannot be used. With such a medium one could not achieve as a major product the desired product unsubstituted at position 3. The temperature at which the oxidation of this invention is carried out is not critical, and may range from about 100° down to room temperature or even below room temperature, although it is obvious that the speed of reaction will be slower at the lower temperatures. A convenient plan of operation is to dissolve the flavylium salt in the medium warmed to about 40–60°, then add the oxidizing agent and allow the system to react without applying any more heating. The reaction proceeds quite rapidly under such conditions and the desired effect is attained in a matter of a few minutes to about an hour at the outside. The oxidizing agent is generally added in excess of the stoichiometrical amount. Thus, it is preferred to use about 10 to 60 moles of peroxide per mole of flavylium salt. Hydrogen peroxide is the preferred oxydizing agent, but one can use other agents which contain peroxide groups, such compounds being commonly referred to as peroxygen oxidizing agents. Typical of these are hydrogen peroxide, acetyl peroxide, benzoyl peroxide, tertiary butyl hydroperoxide, alkali metal salts of tert butyl peroxide, ascaridole, urea peroxide, persulphuric acid, alkali metal salts of per-acids such as peracetic, persulphuric, perbenzoic, and the like. The flavylium salts are generally strongly-colored compounds, and the completion of the oxidation can be discerned by a fading or de-coloration of the reaction mixture.

After the oxidation reaction has been carried out, the reaction mixture is diluted with water and extracted with ether or other essentially water-immiscible solvent such as benzene, toluene, xylene, chloroform, carbon tetrachloride, or the like. The resulting solvent phase is washed with water to remove any residual acetic acid, and is then extracted with water containing a strongly-alkaline material such as an alkali metal hydroxide or carbonate. The resulting aqueous alkaline extract is collected and acidified with a strong mineral acid such as hydrochloric or sulphuric, yielding the desired benzofuran product. Generally, this will crystallize out of the acidified aqueous liquor and can be purified by crystallization from conventional solvents such as aqueous methanol.

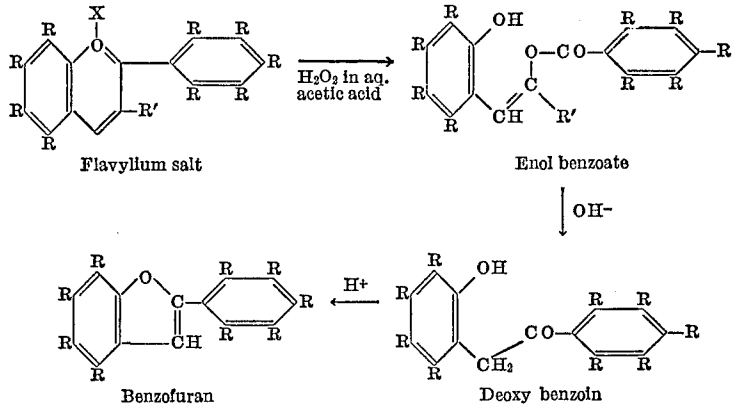
The process of the invention is by no means limited to the example given above but can be employed to prepare benzofurans of all kinds by selection of the appropriate

flavylium salt as the starting material. Thus generically, the synthesis may be represented by the formulas



wherein each R represents a radical selected from the group consisting of hydrogen, hydroxy, lower alkyl, and lower alkoxy, R' is a lower alkyl group, and X is an anion. The radical represented by X is usually the chloride ion but may be the anion of other acids, e.g., the bromide, sulphate, bisulphate, benzenesulphonate, paratoluenesulphonate, etc. ion.

It is evident from the above formulas that the process of the invention has the end result of rearranging the benzopyrylium ring into a benzofuran ring with elimination of one ring carbon atom plus the original side chain on position 3. The ring substituents represented by R carry through to the end product without change in identity or position. My investigations have suggested that the end product is reached through a sequence of chemical changes. This sequence is outlined below merely to explain the end result—which has been definitely determined—but without limiting the invention to the particular mechanisms shown.



The complex mechanisms postulated above are in sharp contrast with the simplicity of actually achieving the end product. Thus, a particularly important aspect of the invention is that none of the intermediates are isolated. The three critical steps of oxidation, alkali treatment, and acid treatment are simply applied in sequence without isolating any of the intermediates, whereby the desired end product is produced directly.

Among the compounds which may be synthesized in accordance with the invention are benzofurans containing one or more hydroxy groups. These compounds are generally useful as antioxidants to be added to organic materials which are subject to deterioration in the presence of air or oxygen, and as rust inhibitors. The invention may be utilized for the preparation of 2-(4-hydroxyphenyl) benzo-furan which exhibits anti-microbial activity and may be used to preserve substances which are normally subject to microbial growth, for example, foods, animal glues and mucilages, starch pastes and solutions, animal feeds and tankage, etc. The use of 2-(4-hydroxyphenyl) benzofuran for such purposes is disclosed and claimed in the copending application of Leonard Jurd and Alfred Douglas King, Jr., Ser. No. 15,302, filed Feb. 27, 1970, and the following material taken from said application is illustrative. The compound, at a concentration of 500 p.p.m., was found to inhibit growth of the following yeasts: *Zygosaccharomyces japonica* var. *soya, Z. arkeri, Hanseniaspora melligeri, Pichia chodati* var. *fermentans, Candida chalmersi, C. tropicalis, Saccharomyces rouxii, S. mallis;* the following bacteria: *Achromobacter hartlebii, Bacillus cadaveris, B. cereus, B. megatherium, Micrococcus lysodeikticus, Proteus vulgaris, Staphylococcus aureus,* and *Streptococcus mitis;* and the molds *Aspergillus glaucus* and Sclerothinia sp. (brown rot mold). Its ability to prevent fermentation of a juice is illustrated by the following.

A lot of grape juice was divided into two 100-ml. samples. Into one sample was incorporated 2-(4-hydroxyphenyl)-benzofuran in a concentration of 500 p.p.m. Both samples were inoculated with wine yeast (*Saccharomyces cerevisiae*) at a concentration of about 2.5×10^4 cells per sample. The samples were then stored at 28° C. for several days.

On the third day it was observed that the control juice was foamy—indicating that active fermentation was taking place. The treated juice was not foaming at all.

On the fourth day the two samples were assayed for yeast cell count. The following results were obtained:

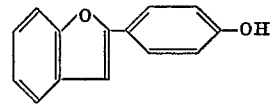
Treated juice: <10 yeast cells/ml.
Control juice: 7×10^7 yeast cells/ml.

The flavylium salts used as starting materials in the present synthesis may be prepared by the Robinson method. Many illustrative examples thereof are presented in my Pat. 3,266,903.

The invention is further demonstrated by the following illustrative examples.

EXAMPLE 1

Preparation of 2-(4-hydroxyphenyl)benzofuran



(A) A solution of salicylaldehyde (12.2 g.) and 4-hydroxybutyrophenone (16.4 g.) in ethyl acetate (100 ml.) and ethanol (20 ml.) was saturated with HCl gas during ten minutes and allowed to stand overnight. The flavylium salt separated as orange crystals (24 g.). Recrystallized from 5% aqueous hydrochloric acid, 3-ethyl-4'-hydroxyflavylium chloride was obtained as orange crystals, M.P. 218–220° (dec.).

Analysis.—Calc. for $C_{17}H_{15}O_2Cl$ (percent): C, 71.1; H, 5.30. Found (percent): C, 71.3; H, 5.30.

(B) 30% hydrogen peroxide (10 ml.) was added to a solution of 3-ethyl-4'-hydroxyflavylium chloride (5 g.) in glacial acetic acid (50 ml.) and 10% aqueous sulphuric acid (50 ml.) at 30–35°. The reaction mixture became slightly warm (about 50°) and after 45 min. considerable decoloration had occurred. Water (400 ml.) was added and the mixture extracted with ether (2×100 ml.). The ether extract was washed with water (3×50 ml.) to remove acetic acid, and then with 10% aqueous sodium hydroxide solution (2 × 50 ml.), the aqueous alkaline phase being collected for further use. After 5 min., this alkaline aqueous phase was warmed to expel dissolved ether, and acidified while hot with concentrated hydrochloric acid (40 ml.). The benzofuran product rapidly crystallized. After cooling, it was collected and recrystallized from aqueous methanol. The crude product was obtained as cream-colored needles, M.P. 187–189° (2.24–2.40 g., 60–65% theory). Recrystallized from benzene, pure 2-(4-hydroxyphenyl) benzofuran was obtained as colorless crystals, M.P. 192°,

$\lambda_{max.}^{EtOH}$ 308 mμ (lit. M.P. 193–194°, $\lambda_{max.}^{EtOH}$ 308mμ)

Analysis.—Calc. for $C_{14}H_{10}O_2$ (percent): C, 80.0; H, 4.80. Found (percent): C, 80.1; H, 4.83.

For identification purposes several derivatives of the product were made as follows:

The benzyl ether of the above product, prepared by heating it (0.1 g.) under reflux with benzyl chloride (1.0 ml.), potassium iodide (0.5 g.), potassium carbonate (3.0 g.) and acetone (20.0 ml.) for 1.5 hours, crystallized from acetone-methanol as colored needles, M.P. 179–180°,

$\lambda_{max.}^{EtOH}$ 307, 246 mμ (lit. (4), M.P. 180–180.5°)

Analysis.—Calc. for $C_{21}H_{16}O_2$ (percent): C, 84.0; H, 5.37. Found (percent): C, 84.1; H, 5.42.

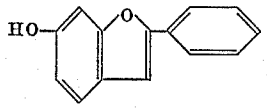
The methyl ether of the product was prepared by refluxing it with dimethyl sulfate, potassium carbonate and acetone. It separated from methanol as colorless, prismatic needles,

$\lambda_{max.}^{EtOH}$ 307, 246 mμ, M.P. 148–149°

undepressed with authentic (6) 2-(4-methoxyphenyl)benzofuran.

EXAMPLE 2

Preparation of 2-phenyl-6-hydroxybenzofuran



30% hydrogen peroxide (2 ml.) was added to a solution of 7-hydroxy-3-methylflavylium chloride (1 g.) in warm (about 50 to 60° glacial acetic acid (10 ml.) and 10% aqueous sulphuric acid (10 ml.). After 30 minutes, water was added to the reaction mixture and it was then extracted with ether (50 ml.). The ether extract was washed with water and with 5% aqueous sodium bicarbonate, and then extracted with 10% aqueous sodium

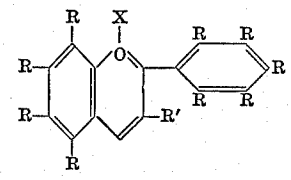
hydroxide (20 ml.). After 5 min. the sodium hydroxide extract was warmed and acidified with dilute hydrochloric acid. Sufficient methanol was added to the hot mixture to dissolve the oil which separated. On cooling, crystals separated. These were collected and purified by recrystallization from aqueous methanol. 2-phenyl-6-hydroxybenzofuran was obtained as slightly colored needles, M.P. 172–173°.

Analysis.—Calc. for $C_{14}H_{10}O_2$ (percent): C, 79.98; H, 4.79. Found (percent): C, 79.8; H, 4.78.

Having thus described the invention, what is claimed is:

1. A process for synthesizing a benzofuran which comprises

(a) reacting a flavylium salt of the formula



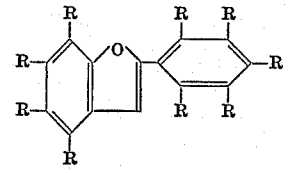
wherein each R represents a radical selected from the group consisting of hydrogen, hydroxyl, lower alkyl, and lower alkoxy, R' is a lower alkyl group, and X is an anion,

(b) with a peroxygen oxidizing agent in an aqueous acetic acid medium,

(c) extracting the reaction mixture with an essentially water-immiscible organic solvent,

(d) extracting the resulting organic extract with water containing a strongly-alkaline substance, and

(e) acidifying the resulting aqueous alkaline extract, thus to produce a benzofuran of the formula



wherein the R's are as above defined.

2. The process of claim **1** wherein the flavylium salt is 3-ethyl-4'-hydroxyflavylium chloride, and the product is 2-(4-hydroxyphenyl)benzofuran.

3. The process of claim **1** wherein the flavylium salt is 7-hydroxy-3-methylflavylium chloride, and the product is 2-phenyl-6-hydroxybenzofuran.

References Cited

Jurd, Tetrahedron (1966), vol. 22, pp. 2913–2921.

ALEX MAZEL, Primary Examiner

B. DENTZ, Assistant Examiner

U.S. Cl. X.R.

260—999

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UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

Patent No. 3,702,854 Dated November 14, 1972

Inventor(s) Leonard Jurd

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

The following statement should appear in the heading in col. 1:

Assignee: The United States of America, as represented by the Secretary of Agriculture.

Signed and sealed this 13th day of November 1973.

(SEAL)
Attest:

EDWARD M.FLETCHER,JR.
Attesting Officer

RENE D. TEGTMEYER
Acting Commissioner of Patents