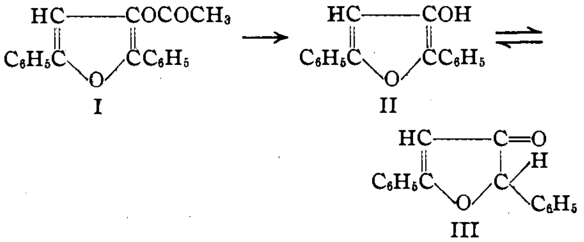
[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

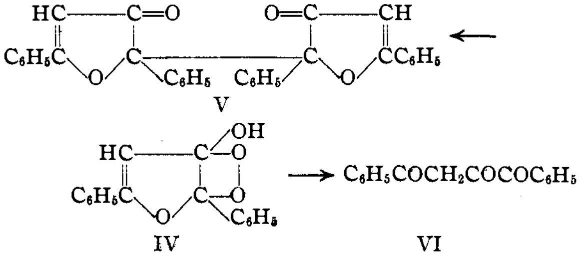
Hydroxy Furans. II. Beta Hydroxy Diphenylfuran

BY E. P. KOHLER AND D. W. WOODWARD

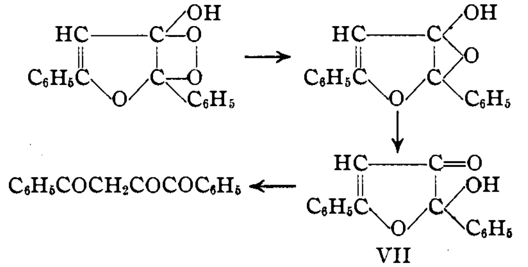
In accordance with the plan set forth in the first paper of this series[1] we have studied the properties of a β-hydroxy furan which has one phenyl group less than the one employed in the earlier work. Solutions of the new hydroxy compound were obtained by hydrolyzing the corresponding acetate[2] in the manner that was found to be best in the case of the triphenyl compound. The hydroxyl compound itself could not be isolated because it ketonizes rapidly and the less soluble ketonic modification crystallizes from the solutions.


I II III

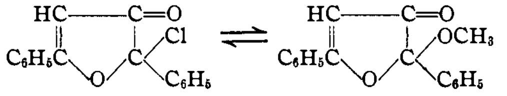
Solutions containing the enolic form, like those containing the corresponding triphenyl derivative, develop a color reaction with ferric chloride and absorb oxygen. The oxidation product is a crystalline peroxide which is unstable at the ordinary temperature and which explodes at about 100°. Like other peroxides that are formed from enols it readily gives up one atom of oxygen to mild reducing agents. Depending largely upon the medium in which it is reduced, the stable reduction product is either a dimolecular furan derivative or an open-chained triketone.


V IV VI

In accordance with the mechanism which has been established in more favorable cases in which all the intermediates were isolated, the triketone, doubtless, is the final product in a series of transformations which can be represented as follows


VII

The hydroxy furanone VII could not be isolated in this series but its ethers and esters were obtained without difficulty. Thus, when the acetate is treated either with chlorine or with phosphorus pentachloride, it is converted into a chloro furanone which passes into the ethers when it is dissolved in alcohols


VIII IX

For reasons which were enumerated in the discussion of the corresponding triphenyl derivatives, we had no doubt about the structure of these compounds, but inasmuch as others had previously obtained them by alkylating the triketone and had regarded them as open-chained compounds we decided to establish their formulas with certainty.

To this end we first prepared the two isomeric triketones, represented by formulas X and XI, and established their structure with alkaline hydrogen peroxide—the substance represented by X being oxidized to *p*-bromobenzoic acid and acetophenone while the isomer was oxidized to benzoic acid and *p*-bromoacetophenone.

$C_6H_5COCH_2COCOC_6H_4Br$ X $\quad$ $BrC_6H_4COCH_2COCOC_6H_5$ XI

Each of these triketones was then methylated by means of methyl alcohol and hydrochloric acid and the structure of the resulting ethers was established by ozonization. The ozonization products of the ether derived from X were benzoic acid and methyl *p*-bromobenzoate, and those from XI were *p*-bromobenzoic acid and methyl benzoate. These are the degradation products to be expected from the cyclic ethers; they could not be formed from any open-chained ethers.

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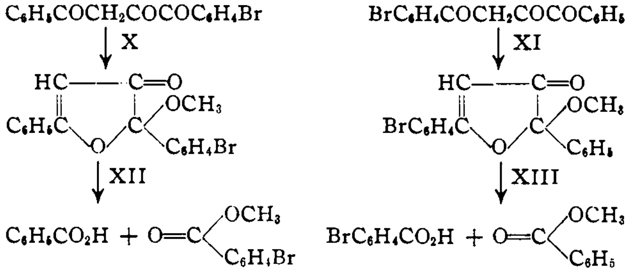
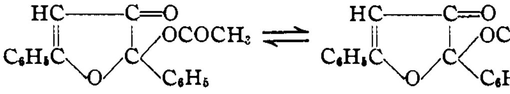
(1) Kohler, Westheimer and Tishler, THIS JOURNAL, **58**, 264 (1936).

(2) Lutz, *ibid.*, **48**, 2918 (1926).



With the cyclic character of the ethers established in this manner, the cyclic structure of substances related in origin and similar in properties can be accepted with confidence. Thus the acetate which is formed by the action of acetic anhydride on the triketone must be a furanone derivative because it passes into the ethers when it is dissolved in boiling alcohols.



XIV

This acetate was first obtained by Lutz and his collaborators who, misled by a faulty analysis, described it as the diacetate—"2,5-diphenyl-3,4-diacetoxy furan."[3] Both our analyses and our acetyl determination show that it is a monoacetate.

The chloro compound VIII which is related to the ethers in the same manner as the acetate must likewise have the cyclic structure with which we represent it. This chloro compound was first described by Lutz, Parrish and Wilder who obtained it by heating their supposed diacetate with acetyl chloride and sulfuric acid and therefore regarded it as a chloro acetate. It was later described again by Lutz and Wilder who obtained it from the triketone and the methyl ether and who, failing to recognize its identity with the previous preparation, now regarded it as the open-chained compound—$C_6H_5C(Cl){=}CHCOCOC_6H_5$. We repeated these reactions and found that the product in all cases is the cyclic chloro compound VIII. The simple and direct relations between the chloro compound, the ethers and the triketone nullify the elaborate mechanisms devised by Lutz and his collaborators.

A comparison of the reactions of β-hydroxy diphenylfuran with those of the triphenyl compound described in the earlier paper shows that the elimination of the phenyl group in the 4 position has virtually no effect on the chemical properties. Like the more highly phenylated analog, the new β-hydroxy furan behaves like an exceedingly reactive enolic form of a ketone.

Experimental

The acetate of β-hydroxy diphenylfuran[2] I was hydrolyzed by the same two methods that were employed with the triphenyl compound, namely, digestion with sulfuric acid in aqueous acetic acid and treatment with methylmagnesium iodide followed by acidification. The first method was employed for the purpose of isolating the keto furan and the second for preparing the peroxide.

Hydrolysis and Preparation of the Keto Furan.—A suspension of 10 g. of the acetate in a solution composed of 250 cc. of acetic acid, 250 cc. of water and 4 cc. of sulfuric acid was boiled in an atmosphere of nitrogen until all of the acetate had dissolved—about half an hour. The solution was made slightly alkaline with sodium carbonate and extracted with ether. The ethereal solution, washed and dried in the usual manner, was evaporated in a current of nitrogen. It deposited a solid product which after recrystallization from ether melted at 93°. The yield was 40–60%.

Anal. Calcd. for $C_{16}H_{12}O_2$: C, 81.3; H, 5.1. Found: C, 80.9; H, 5.3.

2,5-Diphenyl Furanone-3, III.—The furanone is unstable in the air both as solid and in solution. It is not extracted from its ethereal solutions by sodium carbonate but its solutions give a feeble color reaction with alcoholic ferric chloride.

Hydrolysis and Preparation of the Peroxide.—To a solution of methylmagnesium iodide containing three equivalents of the reagent was added 10 g. of the finely powdered acetate. The mixture was boiled for fifteen minutes and then decomposed with ice and acid in the usual manner. The ethereal layer, which gave a strong reaction with ferric chloride, was washed thoroughly with ice water and shaken with air. It soon deposited the peroxide in crystalline form. The yield was about 50%.

3-Hydroxy-2,5-diphenylfuran Peroxide, IV.—The peroxide crystallizes from ether with a molecule of ether. It can be obtained free from solvent by adding hexane to its ethereal solution and boiling off the ether. Both forms decompose in the air and explode at about 100°.

Anal. Calcd. for $C_{16}H_{12}O_4$: C, 71.6; H, 4.5. Found: C, 71.2; H, 4.7. Calcd. for $C_6H_{12}O_4 \cdot (C_2H_5)_2O$: C, 70.2; H, 6.4. Found: C, 70.5; H, 6.3.

Reduction: The Dimolecular Product, V.—When the peroxide was reduced with potassium iodide and acetic acid it was in part converted into a dimolecular product which was also formed in variable quantities when the acetate was treated with halogens. It crystallized in minute needles and melted at 255°.

Anal. Calcd. for $C_{32}H_{22}O_4$: C, 81.7; H, 4.7. Found: C, 81.5; H, 4.9.

Reduction: β-Benzoyl Methylphenyl Diketone, VI.—Solutions of the peroxide in ethyl acetate or methyl alcohol rapidly absorbed one mole of hydrogen. The colorless solutions left after the removal of the catalyst, doubtless, contained the hydroxy furanone VII but they gradually

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(3) Lutz, Wilder and Parrish, This Journal, **56**, 1986 (1934).

developed a yellow color and when they were concentrated they deposited oils. When the ethereal solutions were shaken with aqueous copper acetate they deposited a copper derivative from which acids liberated the triketone. Our examination of the two forms of the triketone which were reported by Lutz, Wilder and Parrish[3] (p. 1984) indicates that the yellow form is the triketone and the colorless form one of its enols. In the very pale yellow alcoholic solutions, equilibrated at the ordinary temperature, Kurt Meyer titrations showed 96.4% enol. In the distinctly yellow ethereal solutions the percentage of enol dropped to 71 and in bright yellow solutions in chloroform it is only 24. From these yellow solutions hexane precipitated the yellow form which has the characteristic color of α diketones.

2-Chloro-2,5-diphenyl Furanone-3, VIII.—A stream of chlorine was passed into a solution of 10 g. of the acetate of the hydroxy furan until the gain in weight was 3.2 g. The solution was washed with sodium bicarbonate, dried and evaporated. It deposited the chloro compound in colorless needles melting at 133°. The yield was 92%. The same chloro compound was formed when the acetate was treated with phosphorus pentachloride and also when the magnesium halide derivative of the hydroxy furan was treated with chlorine.

Anal. Calcd. for $C_{16}H_{11}O_2Cl$: C, 71.0; H, 4.1; Cl, 13.1. Found: C, 70.9; H, 4.3; Cl, 13.6.

2-Bromo-2,5-diphenyl Furanone-3.—The bromo compound was obtained in the same manner as the chloro compound. It crystallized in nearly colorless needles and melted at 135°.

Anal. Calcd. for $C_{16}H_{11}O_2Br$: C, 61.0; H, 3.5; Br, 25.4. Found: C, 61.0; H, 3.7; Br, 25.7.

These halogen compounds are active substances; in boiling alcohols they are transformed into ethers, methyl magnesium chloride reduces them to the magnesium derivative of the hydroxy furan, and when they are boiled with dioxane and water they are hydrolyzed to the triketone.

2-Methoxy-2,5-diphenyl furanone-3, IX, and the corresponding ethoxy compound are obtained when the halogen compounds are dissolved in boiling alcohols. They have been adequately described by Lutz, Wilder and Parrish who formulated them as open-chained compounds.

***p*-Bromobenzoyl Acrylic Acid,** $BrC_6H_4COCH{=}CHCOOH$.—The acid, which was needed for the preparation of the bromo triketones, was made by dissolving one mole of bromobenzene in a liter of purified tetrabromoethane, adding 2.1 moles of aluminum bromide and then, with constant stirring and as rapidly as possible without raising the temperature above 50°, one mole of maleic anhydride. The mixture was stirred for three hours and then decomposed in the usual manner. A part of the acid separated from the acidified mixture, the remainder was recovered after distillation with steam. By recrystallization from acetone or benzene it was obtained in small, pale yellow prisms melting at 161°. The yield was 185 g.

Anal. Calcd. for $C_{10}H_7O_3Br$: C, 47.1; H, 2.8; Br, 31.4. Found: C, 47.1; H, 3.0; Br, 31.4.

The acid was converted into its chloride by heating it to 45° with an equivalent quantity of phosphorus pentachloride, removing the phosphorus oxychloride under diminished pressure and crystallizing the residue from benzene. The product crystallized in yellow needles which turned bright red on exposure to light and which melted at 103°.

***p*-Bromodibenzoyl Ethylene,** $BrC_6H_4COCH{=}CHCOC_6H_5$.—To a solution of one mole of the acid chloride in 2 l. of benzene 1.2 moles of aluminum chloride was added while the solution was stirred and kept as free from hydrogen chloride as possible by sweeping it with a rapid current of nitrogen. The mixture was stirred and heated on a steam-bath for three hours, then decomposed in the usual manner. The product crystallized from benzene and chloroform in light yellow needles and melted at 127°. The yield was 62%. The same product was obtained in a yield of 50–60% by heating equivalent quantities of phenyl glyoxal and *p*-bromoacetophenone with two equivalents of acetic anhydride for an hour on a steam-bath.

Anal. Calcd. for $C_{16}H_{11}O_2Br$: C, 61.0; H, 3.5; Br, 25.4. Found: C, 60.9; H, 3.7; Br, 25.8.

Dibromides, $BrC_6H_4COCHBrCHBrCOC_6H_5$.—Addition of bromine to the unsaturated diketone in chloroform resulted, as usual, in the formation of two stereoisomeric dibromides. One of these dibromides separated from the chloroform in needles melting, with decomposition, at 170–175°; the other was obtained by evaporating the solution and recrystallizing the residue from ether. It melted at 116–119°.

Anal. Calcd. for $C_{16}H_{11}O_2Br_3$: Br, 50.6. Found: (I) Br, 50.5; (II) Br, 50.5.

2-Methoxy-2-phenyl-5-bromophenyl Furanone-3.—In order to convert the dibromide into the triketone a solution of 11 g. of potassium hydroxide in 100 cc. of methyl alcohol was gradually stirred into a solution of 27 g. of the dibromides in the same solvent. The solution was boiled for ten minutes, then acidified and boiled for fifteen minutes longer. The result was a mixture of triketones which were readily isolated by means of their copper derivatives but which were extremely difficult to separate by fractional crystallization. The mixture was therefore converted into ethers.

For this purpose a solution of 10 g. of the mixture in 30 cc. of methyl alcohol was saturated with gaseous hydrogen chloride. As the solution cooled it deposited 4.6 g. of an ether which separated in nearly colorless prisms and which melted at 158° after recrystallization from methyl alcohol.

Anal. Calcd. for $C_{17}H_{13}O_3Br$: C, 59.1; H, 3.8. Found: C, 59.1; H, 3.8.

Ozonization of the Ether.—A solution obtained by ozonizing 3 g. of the ether in carbon tetrachloride was evaporated under reduced pressure in a current of air. The residue was dissolved in ether and the solution was extracted with sodium bicarbonate. It removed *p*-bromo benzoic acid in 80% of the calculated quantity. The ethereal layer was evaporated and the residue was distilled under diminished pressure. The result was 0.8 g. of methyl benzoate boiling at 91° (15 mm.)—identified by the odor and hydrolysis to benzoic acid.

***p*-Bromobenzoyl Methylphenyl Diketone, XI.**—The methyl ether melting at 158° was hydrolyzed in the usual way with methyl alcoholic potassium hydroxide and the product was isolated by means of the copper derivative. It crystallized from ether–petroleum ether in long yellow needles and it melted at 100–101°.

Anal. Calcd. for $C_{16}H_{11}O_3Br$: C, 58.0; H, 3.3. Found: C, 58.0; H, 3.7.

Proof of Structure.—A methyl alcoholic solution containing 4 g. of the triketone and 1.5 g. of 30% hydrogen peroxide was cooled to 0° and treated gradually with 1 g. of potassium hydroxide in the same solvent. The resulting red solution was left to itself until most of the color had disappeared, then acidified and extracted with ether. The oily residue left after the ether had been evaporated was digested for a short time on a steam-bath with sulfuric acid in order to decompose intermediate products, then subjected to the usual treatment for the separation of the acid and the neutral products. The neutral fraction contained only *p*-bromoacetophenone—identified as benzal *p*-bromoacetophenone. The acid fraction contained *p*-bromobenzoic acid and benzoic acid—separated by crystallization and identified by melting points. The yields were: 30% of the possible quantity of bromoacetophenone, 60% of bromobenzoic acid and 92% of benzoic acid.

2-Methoxy-2-*p*-bromophenyl-5-phenyl Furanone-3.—The second ether that was formed when the mixture of the triketones was alkylated, was obtained by concentrating the solution under diminished pressure. It crystallized from methyl alcohol in fine needles melting at 102°.

Anal. Calcd. for $C_{17}H_{13}O_3Br$: C, 59.1; H, 3.8. Found: C, 59.0; H, 4.0.

Ozonization.—The same procedure that was employed in the case of the isomeric ether resulted in methyl *p*-bromobenzoate melting at 80° and identified by comparison with a sample on hand—and benzoic acid. The yields were, respectively, 60 and 75%.

Benzoyl Methyl-*p*-bromophenyl Diketone, X.—The triketone was obtained without difficulty by hydrolyzing the ether and isolating the product by means of the copper derivative. It crystallized in yellow plates melting at 88–90°.

Anal. Calcd. for $C_{16}H_{11}O_3Br$: C, 58.0; H, 3.5. Found: C, 57.8; H, 3.5.

Proof of Structure.—Oxidation with alkaline hydrogen peroxide in the manner described under the isomeric triketone gave *p*-bromobenzoic acid—85% of the possible quantity—benzoic acid and acetophenone (50%) which was identified as *m*-nitrobenzal acetophenone.

2-Acetoxy-2,5-diphenyl Furanone-3.—All methods of preparation—from the chloro compound, the ether or the triketone—gave the same product melting at 140°.

Anal. Calcd. for $C_{16}H_{10}O_3(COCH_3)$: C, 73.5; H, 4.9; $COCH_3$, 14.6. Found: C, 73.4; H, 4.8; $COCH_3$, 14.3.

Summary

The properties of β-hydroxyl derivative of 2,5-diphenylfuran are compared with those of the hydroxyl derivative of 2,4,5-triphenylfuran. The removal of the phenyl group in the 4-position does not affect the properties of the hydroxyl compound but it diminishes the stability of the furanone into which the hydroxyl compound passes by spontaneous ketonization.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

Researches on Pyrimidines. CLIV. Pyrimidine Side Chain Reactions Useful for the Synthesis of 1,3-Diazines Related Structurally to Vitamin B_1[1]

BY ANNE LITZINGER[2] AND TREAT B. JOHNSON

In two previous publications from this Laboratory,[3] the authors have emphasized the importance of increasing our present knowledge of aliphatic chemistry as applied to the pyrimidine cycle, and the bearing of such research developments on the determination of the correct constitution of vitamin B_1. In our preliminary paper entitled "Synthesis of Uracil-5-methylamine," we wrote as follows: "We believe that constructions of this type will prove to be of immediate interest in connection with the development of the newer chemistry of vitamin B_1."

The object of this paper is to present and describe a series of new reactions which have been applied successfully in our pyrimidine investigations, and which have opened up a practical method for synthesizing this interesting pyrimidine amine.[4] The chemistry of this amine will be discussed in the next paper of this series.[5]

The starting point of our new program of synthesis was the ethyl ester of 2-ethylmercapto-6-oxypyrimidine-5-acetic acid I which was first described by Johnson and Speh.[6] Applying suc-

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[1] This research was partially supported by a special grant from the Research Committee of the American Medical Association.

[2] This paper was constructed from a thesis presented by Dr. Anne Litzinger in June, 1936, to the Graduate Faculty of Yale University in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[3] Pyrimidine paper CXLVI, Johnson and Litzinger, THIS JOURNAL, **57**, 1139 (1935); CLIII, Johnson and Litzinger, *Science*, **84**, 25 (1936).

[4] Nomenclature: Uracil-5-methylamine or thyminylamine. The last name is coined to emphasize its aliphatic nature and to indicate its relationship to the naturally occurring pyrimidine-*thymine*.

[5] CLV, THIS JOURNAL, **58**, 1940 (1936).

[6] Johnson and Speh, *Am. Chem. J.*, **38**, 602 (1907).