[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

Halogen Derivatives of 1,4-Diphenyl-1,2,4-butanetrione and 2-Hydroxy-2,5-diphenylfuranone-3

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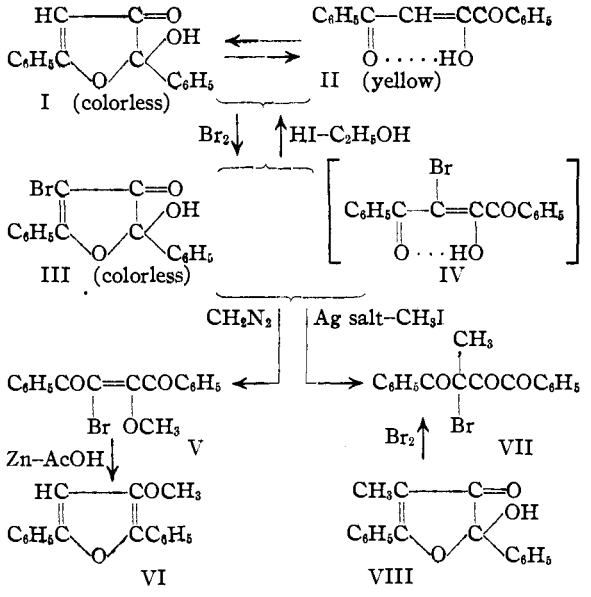
The halogenation of the 1,2,4-triketone enols and the related cyclic tautomers, the hydroxyfuranones, was undertaken because of interest in the effect of substitution of halogen in the chain on the reactions of the systems and on the ring-chain tautomerism involved.

The bromination of either form of diphenylbutanetrione enol (I or II) proceeds very rapidly under a variety of conditions. In chloroform as solvent the reaction stops at the addition of one molecule. The resulting monobromo derivative is

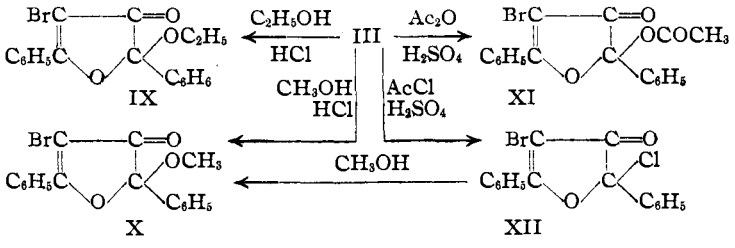


colorless both as a solid and in solution, is readily soluble in aqueous alkali, and is regenerated directly upon acidification. It does not give a ferric chloride color test for an enol, even when freshly precipitated from alkaline solution. It reacts further with a second molecule of bromine in alcohol (but not in chloroform) with a speed which, while great, is definitely less than that in bromination of true enols and intermediate between the speed of bromination of methyldiphenyl- and triphenylhydroxyfuranones. It would appear from these facts that the bromo compound has the hydroxyfuranone structure III.

The bromo compound (like diphenylbutanetrione enol, and in contrast with hydroxymethyldiphenylfuranone, VIII) reacts with diazomethane to give the enol ether, dibenzoylbromomethoxyethylene, V, the structure of which was proved by reduction to methoxydiphenylfuran VI (known).[1] Apparently the isomeric enol ether was formed also but no serious attempt was made to isolate it. No trace of the cyclic ether X could be isolated. From these results it is evident that the change from the hydroxyfuranone form to the more acidic open-chain enol takes place easily.

An alkaline solution of the bromo compound (like that of diphenylbutanetrione enol) does not react with dimethyl sulfate. The bright yellow silver derivative, however, reacts with methyl iodide (like diphenylbutanetrione silver enolate) to give considerable amounts of the carbon alkylation product, bromomethyldiphenylbutanetrione, VII, the structure of which is evident from its synthesis by bromination of hydroxymethyldiphenylfuranone, VIII. Apparently a large amount of oxygen alkylation occurred in the reaction also but no attempt was made to isolate the resulting enol ethers. In view of these results it is evident that the metal derivatives of the bromo compound are true enolates.

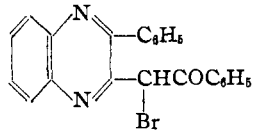
The bromo compound itself, then, appears to have the cyclic structure, but it is capable of reacting with diazomethane or with alkali as an open-chain enol, and shows typical ring-chain tautomerism. It reacts readily in the characteristic way with alcoholic acid to give the alkoxyfuranones, IX and X, with acetyl chloride and sulfuric acid to give the chlorofuranone,



XII, and with acetic anhydride and sulfuric acid to give the acetoxyfuranone, XI.

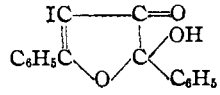
(1) Conant and Lutz, THIS JOURNAL, **47**, 881 (1925).

The bromohydroxyfuranone reacts readily with *o*-phenylenediamine to give the quinoxaline, XIII (this is in contrast with hydroxymethyldiphenylfuranone, VIII, which reacts rather slowly in this way under the usual conditions).



XIII

Reduction of the bromohydroxyfuranone with hydriodic acid in ethanol takes place easily with liberation of the calculated amount of iodine; the diphenylbutanetrione enol is regenerated in the reaction. However, when potassium iodide alone is used, iodine replaces bromine to give an iodo compound which is quite evidently iodohydroxydiphenylfuranone, XIV.



XIV

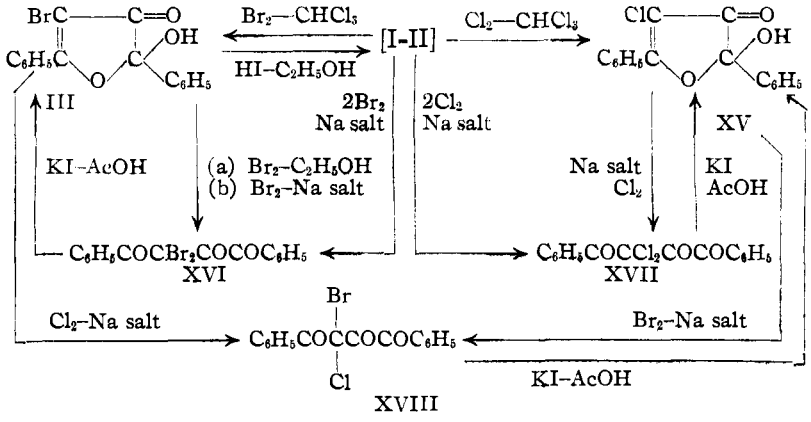
This compound was prepared also directly by the action of iodine on the diphenylbutanetrione sodium enolate, and by the action of iodine and sodium bicarbonate (but not iodine alone) on the free enol. Further reaction with a second molecule of iodine does not occur. The iodohydroxyfuranone is pale yellow, is alkali soluble, but gives no color reaction with ferric chloride.

The analogous chlorohydroxydiphenylfuranone, XV, is obtained by the action of chlorine in chloroform directly on diphenylbutanetrione enol. It is colorless and alkali soluble, but gives no ferric chloride color test as an enol. It reacts readily with methanolic hydrogen chloride to give a typical methyl ether.

Diphenylbutanetrione enol in ethanol reacts rapidly but stepwise with two molecules of bromine. A semi-quantitative study of the rate showed that at −15° the first stage of the reaction was practically instantaneous, but that the rate of addition of the second molecule was easily measurable, 29% being used up in ten seconds, 60% in thirty seconds, with the reaction complete in two minutes. The dibromotriketone, XVI, is the final product under these conditions.

The dihalogeno triketones are very pale yellow or almost colorless solids, but their solutions have the bright yellow color characteristic of α-diketones. They are very easily reduced; in fact the dibromo compound, XVI (like bromomethyldiphenylbutanetrione VII), reacts with *o*-phenylenediamine, losing one of the two bromines, presumably through bromination of excess reagent, and giving the quinoxaline, XIII. When the dibromo triketone is allowed to stand in ethanolic hydrogen chloride, one of the two halogens is lost and the bromoethoxyfuranone, IX, is produced. However, the dibromo ketone does not react very rapidly with boiling ethanol, as does tribromophenyl hypobromite.[2] The stepwise reduction of the dihalogeno triketones can best be controlled to the removal of one halogen by the use of potassium iodide in glacial acetic acid, this reagent being without effect on the monohalogenohydroxyfuranones which are produced.

It is evident from the foregoing discussion that halogen in these brominated triketones has a degree of reactivity which approaches but is not



equal that of halogen in tribromophenyl hypobromite.[2] With the possibility in mind of hypohalite structures of either the open-chain enol or the hydroxyfuranone forms, we made the mixed bromochloro triketone and obtained the same compound (XVIII) from both bromo- and chlorohydroxydiphenylfuranone. This would appear to exclude the hypohalite structures, although of course a single hypohalite might result in both cases if sufficiently mobile halogen were involved. The mixed bromochloro triketone is reduced by means of potassium iodide in acetic acid to the chlorohydroxyfuranone, as would be expected.

(2) (a) Ssuknewitsch and Budnitzky, *J. prakt. Chem.*, **138**, 18 (1933); *cf.* also (b) Howk and McElvain, THIS JOURNAL, **54**, 285 (1932); **55**, 3372 (1933).

Further studies on the bromination of diphenylbutanetrione enol in chloroform were made because Kohler and Woodward in a recent paper[3] reported a value of 24% enolization in this solvent and concluded that the yellow form, dominant at equilibrium, was the triketone. This seemed to us incredible in view of the immediate change from one form to the other in alcohol or chloroform at −15°. Titrations were carried out on the two isomers and also on dimesitylbutanetrione enol and dibenzoylmethane enol (chosen as an example of the better known enols) using the following procedure: an excess of bromine was added to the mixture at −15°, followed immediately by the addition of β-naphthol; the solvent was evaporated under reduced pressure at 30–40° and the residue treated with an excess of alcoholic potassium iodide (acidified); the liberated iodine was titrated in the usual way with thiosulfate. Values below 15–20% were obtained in each instance in spite of the fact that in every case a little more than one molecule of bromine had to be added before there was a visible excess. If, however, instead of evaporating the solvent, the mixtures were diluted with a large volume of ethanol immediately after the addition of β-naphthol, the normal results approximating 100% were obtained. The anomalous results are explained by the fact that in chloroform, with the hydrogen bromide generated during the titration acting as a catalyst, the bromo compounds formed in the reaction themselves very readily brominate excess β-naphthol during the short time when the reaction mixture stands before and during evaporation according to the above described procedure. This was confirmed by an experiment in which a little less than one equivalent of bromine was used in a typical titration of diphenylbutanetrione enol, with subsequent addition of β-naphthol, and isolation at the end of the experiment of bromo-β-naphthol and diphenylbutanetrione enol (as the cyclic ether). Further independent experiments directly on the bromohydroxyfuranone and on the dibromo triketone showed that these bromo compounds are stable in chloroform solutions of β-naphthol, but lose all or most of their bromine in a short time at room temperature when hydrogen bromide is present also.

As was postulated in an earlier paper,[4] the yellow isomer of diphenylbutanetrione very probably is the open-chain chelated enol II and the colorless isomer the cyclic tautomer, the hydroxyfuranone I; and under most conditions in solution these isomers are in very mobile equilibrium with each other. In the light of the new work there appears to be no reason to doubt these conclusions. Furthermore, there is now no reliable evidence for the existence of any keto form among the 1,2,4-triketones[5] or other 1,2,4-tricarbonyl compounds such as hydroxynaphthaquinone, oxalylacetic ester, oxalylacetophenone, and the cyclopentanetriones.[6] The enol forms (or the cyclic tautomers derived therefrom) appear to dominate in this class of compounds.

On the basis of the foregoing results and those described in previous papers, it is now possible to compare the effect on the ring-chain tautomerism of diphenylbutanetrione enol, of substitution of groups on the chain. In the case of the parent compound itself, both open-chain and cyclic forms are in mobile equilibrium and both forms are isolable as solids. The substitution of halogen on the chain appears to stabilize the cyclic form, but does not prevent ready shift to the more acidic open-chain enol in reaction with diazomethane and alkali. In the case of substitution of methyl or phenyl, however, there is no definite evidence for the existence of, or shift to, the open-chain enol form even in alkaline solutions, and the hydroxyfuranone structure, even though presumably the less acidic of the two possible forms, appears to be fixed.

Experimental Part

4-Bromo-2-hydroxy-2,5-diphenylfuranone-3, III.—A 10% solution of bromine in chloroform or carbon tetrachloride was added slowly to a similar solution of diphenylbutanetrione enol (I–II), cooled in an ice-bath, until the color of bromine became distinct and persisted. The solvent was evaporated and the residue crystallized from ethyl acetate–ligroin mixtures; it formed colorless prisms melting at 128–130° (corr.).

Anal. Calcd. for $C_{16}H_{11}O_3Br$: C, 58.0; H, 3.4. Found: C, 57.9; H, 3.5.

The bromo compound did not react with ferric chloride; it is readily soluble in alkali, and is recovered apparently unchanged on acidification. It is not affected by boiling ethanol, and does not react with a dilute dioxane solution saturated with sulfur dioxide. Zinc and acetic acid re-

(3) Kohler and Woodward, THIS JOURNAL, **58**, 1933 (1936). Details of their experiments were omitted.

(4) Lutz and Stuart, *ibid.*, **58**, 1885 (1936).

(5) The supposed dimesitylbutanetrione recently has been shown to be the enol acetate (Lutz and Wood, unpublished results).

(6) A possible exception should be noted in the case of 2-carbethoxy-1,3,4-cyclopentanetrione when an isomeric form has been presumed, without proof, to be the triketone [Wislicenus and Schöllkopf, *J. prakt. Chem.*, **95**, 269 (1917)].

duction gave only oils from which none of the expected reduction products could be isolated. It does not react with more bromine in chloroform over a period of twelve hours but it reacts in ethanol readily with one molecule giving the dibromotriketone, XVI, which crystallizes from the solution directly. The action of bromine on an aqueous suspension of the bromohydroxyfuranone, or on the aqueous solution of the sodium salt, gives the dibromo triketone. Chlorine, bubbled through a solution of the sodium salt, precipitated the bromochloro triketone, XVIII. The bromohydroxyfuranone does not react with potassium iodide in glacial acetic acid but liberates iodine promptly and nearly quantitatively from acidified ethanol solution. In alkaline solution under a variety of conditions no reaction with dimethyl sulfate occurred.

4-Chloro-2-hydroxy-2,5-diphenylfuranone-3, XV, was prepared by passing slightly more than one equivalent of chlorine into a chloroform solution of diphenylbutanetrione enol. The product was isolated by evaporating the solvent and crystallizing from ethyl acetate–ligroin mixtures; m. p. 148° (corr.).

Anal. Calcd. for $C_{16}H_{11}O_3Cl$: C, 67.0; H, 3.9. Found: C, 67.1; H, 4.1.

The properties of this compound are described adequately in the introduction. When dissolved in the correct amount of aqueous alkali and a second molecule of chlorine passed into the solution, the dichlorotriketone, XVII, is precipitated.

4-Iodo-2-hydroxy-2,5-diphenylfuranone-3, XIV, was prepared in the following ways: (a) Solid potassium iodide was added to an ethanol solution of the bromohydroxyfuranone III. A small amount of iodine was liberated. Upon dilution with water and crystallization from ethyl acetate–ligroin mixtures, the iodo compound was obtained in good yield.

(b) Upon addition of iodine directly to an aqueous solution of diphenylbutanetrione sodium enolate, the iodo compound precipitated quickly.

(c) A chloroform solution of diphenylbutanetrione enol was treated with iodine (which does not react directly), and then shaken with aqueous bicarbonate solution until the iodine color disappeared. The iodo compound was obtained by evaporation of the chloroform solution.

The iodo compound was almost colorless after repeated crystallizations from ethyl acetate–ligroin mixtures, and melted at 124° (corr.).

Anal. Calcd. for $C_{16}H_{11}O_3I$: C, 50.8; H, 2.9. Found: C, 51.0; H, 3.2.

Treatment with alcoholic hydrogen chloride gave only intractable products.

4-Bromo-2-methoxy-2,5-diphenylfuranone-3, X, was prepared in the usual way by the action of methanolic hydrogen chloride on the bromohydroxyfuranone, III, or on the ethyl ether, IX, or by short heating of the chlorofuranone, XII, with methanol. It was crystallized from methanol and melted at 78° (corr.).

Anal. Calcd. for $C_{17}H_{13}O_3Br$: C, 59.1; H, 3.8. Found: C, 59.2; H, 3.9.

It was hydrolyzed readily to the bromohydroxyfuranone by sodium methylate.

$C_6H_5C(=O)C(Cl)COC(OCH_3)C_6H_5$, **4-Chloro-2-methoxy-2,5-diphenylfuranone-3,** was prepared in the usual way by the action of methanolic hydrogen chloride on the chlorohydroxyfuranone, XV. It crystallized from methanol as needles melting at 64–65° (corr.).

Anal. Calcd. for $C_{17}H_{13}O_3Cl$: C, 67.9; H, 4.4. Found: C, 67.8; H, 4.7.

4-Bromo-2-ethoxy-2,5-diphenylfuranone-3, IX, was prepared from III in the usual way with ethanolic hydrogen chloride, and crystallized from ethanol; m. p. 95° (corr.).

Anal. Calcd. for $C_{18}H_{15}O_3Br$: C, 60.2; H, 4.2. Found: C, 60.3; H, 4.3.

4-Bromo-2-chloro-2,5-diphenylfuranone-3, XII, was obtained in quantitative yield by the action of acetyl chloride and a few drops of concd. sulfuric acid on the bromohydroxyfuranone, III. It was crystallized from ethyl acetate–petroleum ether mixtures and melted at 106.5° (corr.).

Anal. Calcd. for $C_{16}H_{10}O_2ClBr$: C, 55.0; H, 2.9. Found: C, 55.1; H, 3.2.

2-Acetoxy-4-bromo-2,5-diphenylfuranone-3, XI, was obtained in quantitative yield in the usual way by the action of acetic anhydride and a trace of concd. sulfuric acid on the bromohydroxyfuranone, III. It was crystallized from ethanol or isopropyl ether and melted at 184.5° (corr.).

Anal. Calcd. for $C_{18}H_{13}O_4Br$: C, 57.9; H, 3.5. Found: C, 57.9; H, 3.7.

Hydrolysis to III was effected quickly with sodium methylate.

2-(α-Bromophenacyl)-3-phenylquinoxaline, XIII.—The bromohydroxyfuranone, III, condensed almost immediately in boiling ethanol with *o*-phenylenediamine, and the quinoxaline crystallized from the hot solution. It formed light yellow crystals from ethanol which melted at 191–192° (corr.).

Anal. Calcd. for $C_{22}H_{15}ON_2Br$: C, 65.5; H, 3.8. Found: C, 65.4; H, 4.0.

2-Bromo-1-methoxy-1,2-dibenzoylethylene, V.—Solid bromohydroxydiphenylfuranone (III) was added to an ether solution containing an excess of diazomethane at 0°. Vigorous reaction occurred with evolution of nitrogen. On evaporation of the solvent an oil was obtained which crystallized from methanol giving the methoxy compound in a yield of 50%. It was recrystallized from methanol and melted at 88° (corr.).

Anal. Calcd. for $C_{17}H_{13}O_3Br$: C, 59.1; H, 3.8. Found: C, 59.2; H, 3.9.

Reduction with zinc and glacial acetic acid (boiling for one minute) gave an oil from which 3-methoxy-2,5-diphenylfuran, VI, was isolated and identified by mixed melting point with an authentic sample.

Alkylation of the Silver Salt of Bromohydroxydiphenylfuranone.—The silver salt was obtained as a brilliant yellow solid by the addition of silver nitrate to an aqueous solution of the sodium salt (prepared by treating 0.5 g. of the bromohydroxyfuranone with 3 cc. of methanol

containing 0.04 g. of dissolved sodium, and then diluting with water). It was fairly stable when dry and pure but darkened quickly in contact with solution containing silver nitrate. The sample of dry salt obtained above (0.7 g.) was suspended in 25 cc. of dry ether containing 1 cc. of methyl iodide and the mixture was refluxed for two hours. After filtering and evaporating the solvent a yellow oil was obtained from which 0.1 g. of 3-bromo-3-methyl-1,4-diphenylbutanetrione, VII, was obtained by crystallizing from methanol. When the methanol solution was boiled for a short time and again cooled, 0.35 g. of bromomethoxydiphenylfuranone was obtained, formed presumably by rearrangement of oxygen-alkylation products present (if it had been the primary product it would have crystallized earlier in the experiment).

3,3-Dibromo-1,4-diphenyl-1,2,4-butanetrione, XVI, was prepared most conveniently, and in excellent yield, by the addition of an alcohol solution of two equivalents of bromine to a cooled solution of diphenylbutanetrione enol in ethanol. The product crystallized out directly and was recrystallized from ethanol: m. p. 107.5° (corr.).

Anal. Calcd. for $C_{16}H_{10}O_3Br_2$: C, 46.8; H, 2.5. Found: C, 46.9, 46.7; H, 2.6, 2.8.

In alcohol (acidified) it readily liberated the calculated amount of iodine (two equivalents). In glacial acetic acid, however, the reaction did not go as far as this, and in a typical experiment bromohydroxydiphenylfuranone, III, was isolated. The dibromo triketone reacted with *o*-phenylenediamine in ethanol on boiling for five minutes, giving 2-(α-bromophenacyl)-2-phenylquinoxaline.

3,3-Dichloro-1,4-diphenyl-1,2,4-butanetrione, XVII, was prepared in good yield by passing a slight excess of the calculated amount of chlorine into an aqueous solution of the sodium derivative of either diphenylbutanetrione enol or chlorohydroxydiphenylfuranone, XV. It crystallized as light yellow plates from ethanol and melted at 66.5° (corr.).

Anal. Calcd. for $C_{16}H_{10}O_3Cl_2$: C, 59.8; H, 3.1. Found: C, 59.8; H, 3.4.

When treated with potassium iodide in glacial acetic acid, iodine was liberated and chlorohydroxydiphenylfuranone, XV, was formed.

3-Bromo-3-chloro-1,4-diphenyl-1,2,4-butanetrione, XVIII, was prepared from the sodium derivatives of either bromo- or chlorohydroxydiphenylfuranone using water solution and the calculated amount of the appropriate halogen. It crystallized from ethanol as light yellow plates melting at 96–97° (corr.).

Anal. Calcd. for $C_{16}H_{10}O_3ClBr$: C, 52.5; H, 2.8. Found: C, 52.6; H, 2.8.

When treated with potassium iodide in glacial acetic acid, iodine was liberated and chlorohydroxydiphenylfuranone, XV, was isolated and identified.

Bromine Titrations.—The K. Meyer titrations in ethanol as solvent were carried out in the usual way, adding to the cooled solution a slight excess of bromine followed immediately by β-naphthol and then potassium iodide, with subsequent titration of the liberated iodine with thiosulfate. Both forms of diphenylbutanetrione enol show practically complete enolization (or reaction in that sense) at −17 to −18°. However, in view of the fact that the yellow form added as a solid to alcohol at −15° changes rapidly into the colorless form, little difference between the two isomers, if any at all, would be expected. This holds true equally well with chloroform as solvent when the reverse transformation from the colorless to the yellow form occurs rapidly at −15°. In connection with the numerous titrations made in chloroform as solvent, the difficulties as well as the means to surmount them are adequately discussed in the introduction.

A few experiments were made in petroleum ether as solvent because the two forms of diphenylbutanetrione apparently are stable in this medium, although unfortunately the colorless isomer, as expected of a true hydroxylic compound, is so exceedingly insoluble that significant studies on it could not be made. The same difficulties were encountered using petroleum ether in the titrations, as those described in connection with the experiments in which chloroform was employed, and similar precautions were necessary. The yellow form of diphenylbutanetrione showed approximately 100% enolization in this solvent.

Summary

The stepwise bromination of diphenylbutanetrione enol is described. The properties of the monobromo compound indicate it to be 4-bromo-2-hydroxy-2,5-diphenylfuranone-3. Typical cyclic derivatives, the ethers, acetate and chloride, are obtainable. With diazomethane the open-chain enol ether is produced. The metal derivatives react like open-chain enolates. These results show the reactions of the bromo compound to be intermediate between those of diphenylbutanetrione enol and hydroxymethyldiphenylfuranone.

The dihalogeno derivatives were prepared from and converted into the monohalogenohydroxyfuranones. The ease of reduction and brominating action of the various halogeno compounds is discussed.

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