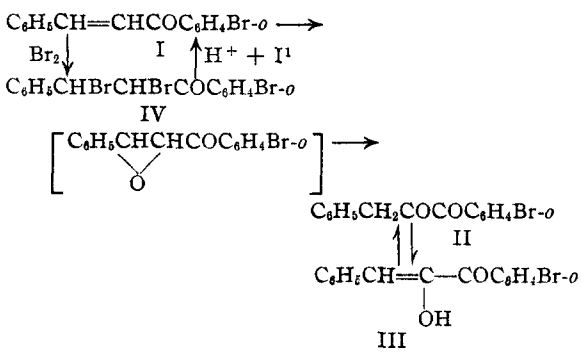
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HOWARD UNIVERSITY]

Preparation and Properties of *o*-Bromophenylbenzylglyoxal—Methylation of Alpha Diketones

BY R. P. BARNES AND NOBLE F. PAYTON[1]

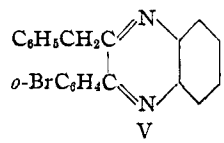
In continuation of the study of the properties of alpha diketones,[2,3,4] it was thought wise to prepare a substituted phenylbenzylglyoxal and study its reactions, since we believe that the glyoxylic acid residue present in the enolic modification of every alpha diketone is intimately related to the methylation reaction. Thus *o*-bromophenylbenzylglyoxal (III) was obtained by the following series of reactions

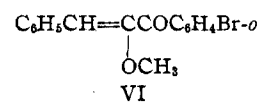


o-Bromoacetophenone was prepared according to the method given by Thorp and Brunskill[5] for *o*-chloroacetophenone. The *o*-bromoacetophenone was condensed with benzaldehyde to benzal-*o*-bromoacetophenone (I), whose constitution was established by converting it into the dibromide (IV) with subsequent reduction to (I). This α,β-unsaturated ketone was in turn oxidized and isomerized to *o*-bromophenylbenzylglyoxal (II). By means of alkali the diketone (II) was converted into the enolic modification (III).

As is the case with the other diketones of this series, *o*-bromophenylbenzylglyoxal differs very markedly from the isomeric series of beta diketones with reference to the extent of O- and C-compound formation.

o-Bromophenylbenzylglyoxal gives a cherry red color with alcoholic ferric chloride, and is 100% enolic in the solid state. It yields a quinoxaline (V) with *o*-phenylenediamine and is quantitatively cleaved to phenylacetic and *o*-bromobenzoic acids by alkaline hydrogen peroxide. Methylation with dimethyl sulfate gives 84.1% of the O-methyl compound (VI), and sufficient unchanged material to indicate that the O-compound is formed exclusively.





Since there was no available information in the literature on the physical constants of *o*-bromophenylglyoxylic acid, it was prepared after the manner described by Russanow,[6] and its ionization constant determined by conductivity measurements. The concentration at which these measurements were made is approximately the same as the upper limit of the range of concentrations on the basis of which the ionization constant for *o*-bromobenzoic acid was determined. Therefore the two ionization constants are excellent criteria for judging the relative strength of the two acids.

The activating effect of carbonyl groups upon alpha hydrogen atoms is common knowledge. A similar effect is observed when one compares the ionization constants[7] of two series of organic acids such as the following.

Acid	K (25°)	Acid	K (25°)
$C_6H_5CO_2H$	5.86×10^{-5}	$C_6H_5COCOOH$	6.00×10^{-2}
o-$BrC_6H_4CO_2H$	1.42×10^{-3}	o-$BrC_6H_4COCOOH$	8.60×10^{-2}[a]
$(CH_3)_3C_6H_2CO_2H$	3.70×10^{-4}	$(CH_3)_3C_6H_2COCOOH$	5.27×10^{-2}[b]

[a] Experimentally determined value reported in this paper.

[b] Breed, Bryn Mawr College Monographs, Vol. I, No. 1, p. 15.

Thus the introduction of the carbonyl tends to increase the extent of ionization.

It is the opinion of the writer that the amount of O-compound formed upon methylation of an alpha diketone in alkaline solution depends very directly upon the acidity of the enol. Every enolic modification of an alpha diketone of the type $RCOCOCH_2R \rightleftarrows R{-}CC{=}CHR$ (O, OH) may easily be considered as a glyoxylic acid in which the double

(1) In part this paper represents a summary of the dissertation presented by Noble F. Payton in partial fulfilment of the requirements for the degree of Master of Arts in 1934.

(2) Kohler and Barnes, THIS JOURNAL, **56**, 211 (1934).

(3) Kohler and Weiner, *ibid.*, **56**, 434 (1934).

(4) R. P. Barnes, *ibid.*, **57**, 937 (1935).

(5) Thorp and Brunskill, *ibid.*, **37**, 1258 (1915).

(6) Russanow, *Ber.*, **25**, 3298 (1892).

(7) "International Critical Tables," Vol. VI, pp. 278, 279, 284.

bonded oxygen has been substituted by a radical. If on the other hand one considers the enolic modification of the isomeric beta diketone of the type $RCOCH_2COR \rightleftarrows RC(OH)=CHCOR$, it is obvious that the acid of which the enol may well be considered a derivative is not a glyoxylic acid. With few exceptions[3] the beta diketones, as well as the beta ketonic esters, yield largely C-methylation products with either methyl iodide or dimethyl sulfate.

Obviously, there are two competing reactions which take place, the relative rates of which determine the extent of O- and C-methylation. One of these reactions is a direct metathesis between the alkali salt of the enol and the alkylating agent, which gives rise to the O-compound—the stronger the acid of which the enol is a conceivable derivative, the greater the amount of O-compound. Whatever the other reaction may involve, it seems to be hindered by substitution on the alpha carbon atom.

The methylation of phenylbenzylglyoxal[2] yields a mixture of O- and C-compounds. Benzhydrylphenyl diketone[3] yields 100% O-compound. Thus it seems that the phenyl group substituted for a hydrogen of phenylbenzylglyoxal offers hindrance to one of the competing reactions with the result that the other reaction preponderates. Mesitylbenzylglyoxal[4] and *o*-bromophenylbenzylglyoxal each yields exclusively the O-compound. As further support of this idea, the alpha ketonic esters of which oxalacetic ester is a good example produce mixtures of O- and C-methylation products.

Experimental Part

Preparation of Benzal-*o*-bromoacetophenone (I).—A solution of 8.4 g. of sodium hydroxide in 65 cc. of water, together with 50 cc. of alcohol, was placed in a 500-cc. wide-mouthed bottle equipped with a stirrer and cooled by an ice-bath. To the reaction chamber was added 30.5 g. of *o*-bromoacetophenone after which stirring was begun. The calculated quantity (17 g.) of benzaldehyde was then introduced. The temperature was maintained between 15 and 20° during three hours of constant stirring. The product was 12.5 g. of a yellow oil distilling at 183–185° (2 mm.).

Anal. Calcd. for $C_{15}H_{11}OBr$: C, 62.7; H, 3.9. Found: C, 62.9; H, 4.0.

Bromination: Dibromobenzal-*o*-bromoacetophenone (IV).—An ethereal solution of 2.0 g. of the α,β-unsaturated ketone was brominated in the usual way, resulting in a quantitative yield of the dibromo product which after crystallization from methyl alcohol melted at 86°.

Anal. Calcd. for $C_{15}H_{11}OBr_3$: C, 40.3; H, 2.5. Found: C, 40.6; H, 2.6.

Reduction: Benzal-*o*-bromoacetophenone (I).—When 1 g. of the dibromoketone was dissolved in 20 cc. of acetone and treated with 10% potassium iodide, a pale yellow color developed. Upon acidification a deep reddish-brown color was produced. Upon dilution a yellow oil separated out. Distillation and analysis of this oil proved that it was identical with the α,β-unsaturated ketone.

Preparation of *o*-Bromophenylbenzylglyoxal (II).—A solution of 7.5 g. of benzal-*o*-bromoacetophenone in 100 cc. of alcohol was treated with 3.5 cc. of 6 *N* sodium hydroxide with stirring. To this mixture was added 7 cc. of 30% hydrogen peroxide. A colorless oil separated out. This oil could not be crystallized. On distilling at 155° (2 mm.) a pale yellow oil was obtained which gave a deep cherry-red color with alcoholic ferric chloride.

Anal. Calcd. for $C_{15}H_{11}O_2Br$: C, 59.4; H, 3.7. Found: C, 59.8; H, 3.6.

Preparation of the Enol of *o*-Bromophenylbenzylglyoxal (III).—To 25 g. of the diketone (II) dissolved in 90 cc. of alcohol, there was added a solution of 14.4 g. of sodium hydroxide dissolved in 30 cc. of water. The mixture generated much heat and boiled on the addition of the sodium hydroxide. The mixture separated into a red upper layer and a colorless alkaline botton layer. The two layers were separated and the red solution was acidified with hydrochloric acid. The solution was largely diluted with water and extracted with ether. The ethereal solution was washed with water, dried over anhydrous sodium sulfate and concentrated. There was obtained a yield of 8 g. of colorless needle-like crystals melting at 107°.

Anal. Calcd. for $C_{15}H_{11}O_2Br$: C, 59.4; H, 3.7. Found: C, 59.2; H, 3.8.

Oxidation.—When 1.0 g. of the alpha diketone was dissolved in 50 cc. of methyl alcohol and treated with an excess of alkaline hydrogen peroxide, cleavage resulted in the production of phenylacetic and *o*-bromobenzoic acids. These products were identified by their melting points and mixed melting points with known pure samples.

Reaction with *o*-Phenylenediamine (V).—A solution of 1.0 g. of the diketone and 1.0 g. of *o*-phenylenediamine in 25 cc. of methyl alcohol was boiled for one hour and allowed to cool. The solution was poured into water, extracted with ether, washed with dilute hydrochloric acid, dried and concentrated. A practically quantitative yield of colorless needles melting sharply at 110° was obtained.

Anal. Calcd. for $C_{21}H_{15}N_2Br$: C, 67.2; H, 4.0. Found: C, 67.5; H, 4.2.

Methylation: Methyl Ether of α-Hydroxybenzal-*o*-bromoacetophenone (VI).—A suspension of 5.0 g. of the powdered enol in 20 cc. of water was treated with 4.2 g. of dimethyl sulfate. To this mixture a 20% solution of potassium hydroxide was added dropwise with vigorous shaking until permanent alkalinity was effected. After extraction with ether, an equal volume of petroleum ether was added to the ethereal layer. This solution was then shaken with successive small portions of 10% potassium hydroxide until the alkaline layer was colorless. The alkaline washings upon acidification gave 0.5 g. of unchanged material. The ethereal solution was dried, filtered

(8) Von Auwers, *Ber.*, **45**, 996 (1912).

and concentrated. There resulted a viscous yellow oil boiling at 280–285° (2 mm.). The yield was 4.4 g. or 84.1%.

Anal. Calcd. for $C_{16}H_{13}O_2Br$: C, 60.5; H, 4.1; —OCH_3, 9.8. Found: C, 60.8; H, 4.0; —OCH_3, 10.0.

o-Bromophenylglyoxylic Acid.—This acid was purified by several crystallizations from methyl alcohol and water. The thin colorless needles melted over a range with decomposition as reported by Russanow. For a concentration of 0.03449, molecular conductivity 266.21, and conductivity at infinite dilution 348, the ionization constant at 25° was calculated to be 8.6×10^{-2}.

Summary

The preparation and properties of a new diketone are herein reported in connection with a discussion of the methylation of alpha diketones.

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The Hydroxylation of the Double Bond[1]

BY NICHOLAS A. MILAS AND SIDNEY SUSSMAN

The use of osmium tetroxide and chlorates for the addition of hydroxyl groups to the double bond[2] is limited to aqueous solutions, and, at times, to specialized conditions. Similarly, organic peracids which have been used for this purpose are not of general applicability.[3] During the past year and a half we have been engaged in the preparation of tertiary alkyl peroxides and hydroperoxides, and found that anhydrous solutions of hydrogen peroxide and tertiary butyl alcohol are stable at room temperature for long periods of time. Such solutions, however, are perfectly inert toward olefinic double bonds, but in the presence of a small amount of osmium tetroxide, likewise dissolved in anhydrous tertiary butyl alcohol, a reaction proceeds smoothly to yield almost invariably a glycol. For example, from ethylene we obtained ethylene glycol; from tetramethylethylene, pinacol; from cyclohexene, adipic acid; from the ethyl esters of crotonic, maleic and fumaric acids, the corresponding dihydroxy esters. Table I shows some of the quantitative results obtained.

TABLE I

Olefinic substance	Main product	% yield
Isobutylene	Isobutylene glycol	37.6
Trimethylethylene	Trimethylethylene glycol	37.8
Allyl alcohol	Glycerol	60.2
Cinnamic acid	Phenylglyceric acid	56.2
Crotonic acid	Dihydroxybutyric acid	53.8
Maleic acid	Mesotartaric acid	30.3
Fumaric acid	Racemic acid	48.3

(1) A preliminary report of this work was presented before the research conference, M. I. T., December 13, 1935.

(2) (a) Milas and Terry, THIS JOURNAL, **47**, 1412 (1925); (b) Terry and Milas, *ibid.*, **48**, 2647 (1926); (c) Milas, *ibid.*, **49**, 2005 (1927).

(3) (a) Milas and Cliff, *ibid.*, **55**, 352 (1933); (b) Milas and McAlevy, *ibid.*, **56**, 1219 (1934).

While our work was under way Criegee[4] published recently some preliminary results using osmium tetroxide and hydrogen peroxide in ethyl ether, and obtained aldehydes as his main products. In the present research, however, all of the unsaturated substances tried yielded glycols, although in certain cases the latter oxidized further to yield small amounts of by-products. We are now actively engaged in this field and hope to publish in the near future a more extended investigation.

Experimental

Preparation of the Reagent.—To 100 cc. of 30% hydrogen peroxide (Albone C) was added 400 cc. of pure tertiary butyl alcohol and the solution treated with small portions of anhydrous sodium sulfate whereby two layers separated out. The alcohol layer, which contained most of the hydrogen peroxide, was removed and dried with anhydrous sodium sulfate and finally with anhydrous calcium sulfate (Drierite). A solution of 6.32% hydrogen peroxide in tertiary butyl alcohol was obtained, giving a recovery of 93.8%. This solution can easily be concentrated by vacuum distillation of the alcohol at room temperature to any desired concentration without any loss of the peroxide provided an all-glass apparatus is employed. When hydrogen peroxide solutions of this sort were allowed to stand at room temperature for over six months, only a small decrease in hydrogen peroxide concentration was noticed.

The Catalyst.—Osmium tetroxide (Merck osmic acid) dissolves readily in tertiary butyl alcohol and the solution is perfectly stable provided no isobutylene is present, otherwise most of the osmium tetroxide is readily reduced into an insoluble black colloidal oxide which is a very active catalyst for the decomposition of hydrogen peroxide. In aqueous solutions osmium tetroxide destroys hydrogen peroxide in a very short time, whereas in anhydrous tertiary butyl alcohol it decomposes the latter to the extent of 20% in one month's time.

(4) Criegee, *Ann.*, **522**, 75 (1936).