Summary

1. The following barbituric acid derivatives have been prepared: diallyl, ethyl-allyl, *n*-propyl-allyl, *iso*propyl-allyl, *n*-butyl-allyl, *iso*butyl-allyl, *sec*.-butyl-allyl, *iso*-amyl-allyl. Their physiological actions have been compared with those of known dialkyl-barbituric acids.
2. Tests on white rats show that the alkyl-allyl-barbituric acids fall in the following order of decreasing desirability as hypnotics, based upon their efficiency and toxicity: *n*-butyl-allyl, *iso*butyl-allyl, diallyl, *n*-propyl-allyl, *iso*propyl-allyl or *sec*.-butyl-allyl, *iso*-amyl-allyl, ethyl-allyl.
3. The replacement of an alkyl group in 5,5-dialkyl-barbituric acids by an allyl group frequently leads to an increase in effectiveness, together with a lower degree of increase in toxicity.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

BENZOYLHYDROPEROXIDE: PREPARATION AND APPLICATION TO ORGANIC SYNTHESIS[1,2]

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The use of benzoylhydroperoxide for the synthesis of organic oxides and glycols[3] from unsaturated derivatives offers many advantages over that of permanganates, hypochlorous acid, halogens, etc., due to the fact that the oxide formation is carried out in the absence of water and in a neutral, organic medium from which the reaction products can be easily isolated.

For these reasons it is particularly applicable to syntheses relating to studies on carbohydrates and polysaccharides.[3b] Unfortunately there is no detailed description available in the literature regarding the preparation of benzoylhydroperoxide from benzoylperoxide[4] and this has proved to

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[1] This paper is constructed from part of a dissertation presented by C. Pauline Burt in June, 1925, to the Faculty of the Graduate School of Yale University in candidacy for the degree of Doctor of Philosophy.

[2] Communicated to the Organic Division of the American Chemical Society at Baltimore, April, 1925.

[3] (a) Prileschajew, *Ber.*, **42**, 4811 (1909); *J. Russ. Phys.-Chem. Soc.*, **42**, 1387 (1910); **43**, 609 (1911); **44**, 613 (1912). (b) Bergmann and others, *Ber.*, **54**, 440 (1921); **56**, 2255 (1923); *Ann.*, **432**, 333 (1923). (c) Derx, *Rec. trav. chim.*, **40**, 524 (1921); **41**, 332 (1922). (d) Böeseken and Blumberger, *ibid.*, **44**, 90 (1925).

[4] Baeyer and Villiger, *Ber.*, **33**, 1569 (1900). Ref. 3 a. Also in the work of Derx (Ref. 3 c) and in the recent paper of Böeseken and Blumberger (Ref. 3 d), published after the completion of the present investigation, the details are still lacking. The last-named authors find that benzoylhydroperoxide, as prepared by them, shows a somewhat "capricious behavior" towards unsaturated hydrocarbons, the "rate of oxide formation" being greatly influenced by the presence of small traces of other products. A freshly-prepared solution of the hydroperoxide is stated to be less active than one that has stood for 24 hours at 15°; and the latter is more active than one kept at 0°.

be a considerable handicap in the attempts by various chemists[5] to utilize it for synthetic purposes.

The method of Baeyer and Villiger[4] was found to give only a poor yield. These authors make no mention of the quantity of solvent to be used, the concentration of the sodium ethylate solution or the manner of carrying out the acidification. Each of these factors has an important bearing on the success of the operation.

Quantity of Solvent.—This can be decreased much below that needed for the complete solution of the benzoylperoxide at —5°, provided good agitation is employed. If the quantity of ether used is reduced still further, it renders effective stirring of the precipitated sodium benzoylperoxide impossible, and thus reduces the yield. Thus, in two experiments using 12 g. of benzoylperoxide and 200 cc. and 100 cc. of ether, respectively, the yield was lowered from 90 to 70%.

Concentration of Sodium Ethylate Solution.—The presence of a considerable quantity of free alcohol in the sodium ethylate solution is to be avoided on account of its influence in increasing the tendency towards emulsification during the extraction of the hydroperoxide with ether. A 10% solution of the ethylate in absolute alcohol was found to be satisfactory.

Effect of Altering the Mode of Acidification.—Benzoylhydroperoxide is very unstable in the presence of alkali and its preparation must, therefore, be carried out in such a manner that there is no trace of sodium peroxide in solution when the free hydroperoxide is liberated. This is practically impossible when the separation is effected by adding the acid to the aqueous solution of the sodium benzoylperoxide. When the latter is precipitated in ether solution by the action of sodium ethylate on the benzoylperoxide, the sodium salt always carries down with it a small amount of the ethylate, and the latter during the acidification process yields sufficient free alkali to bring about a decomposition of the hydroperoxide as fast as it is formed. The reverse process of addition is therefore employed, in that the benzoylhydroperoxide is liberated by adding the aqueous solution of the sodium salt of benzoylperoxide to a slight excess of sulfuric acid. Under these conditions the benzoylhydroperoxide is stable.

Determination of Purity of Benzoylperoxide and Hydroperoxide

Method.—A weighed portion (0.5 g.) of benzoylperoxide is suspended in ether solution, approximately 0.5 cc. of 10% sodium ethylate solution added, and the precipitated sodium salt dissolved in water. The mixture is added to twice the calculated quantity of 20% sulfuric acid. Two cc. of a 5% solution of potassium iodide is then added, and the iodine liberated is titrated with 0.1 *N* sodium thiosulfate solution.[6]

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[5] Private communications from American colleagues.

[6] This corresponds with the method used by Derx and by Böeseken and Blumberger (Ref. 3).

Estimation of the Benzoylhydroperoxide.—In order to obtain benzoylhydroperoxide free from the reagents used in its preparation, it is necessary to extract the product with chloroform, such extraction resulting in a loss of about 10%. The chloroform extract is analyzed by mixing with an excess of acidified potassium iodide solution and titrating with thiosulfate.

Revised Method for the Preparation of Benzoylhydroperoxide

The experiment is best carried out in a three-necked, 3-liter flask equipped with a mechanical stirrer and thermometer, the third opening being reserved for the addition of the sodium ethylate. One hundred and twenty-one g. (0.5 mole) of benzoylperoxide (Eastman Kodak Company's C. P. product) and 1.5 liters of ether are introduced into the flask, the mixture is vigorously agitated, and cooled to —5° by an ice-salt mixture. The calculated quantity of an approximately 10% solution of sodium ethylate (prepared from 11.5 g. of sodium and 110 cc. of absolute alcohol) is then slowly added in several portions over a period of 15 minutes, with the temperature of the mixture carefully maintained at —5°. The stirring is continued for about 15 minutes after the last addition, to insure thorough mixing and complete formation of the sodium salt. About 300 cc. of ice water is now added to the mixture, whereupon the sodium salt dissolves completely, leaving the ethyl benzoate dissolved in the ether layer. The mixture is transferred to a separatory funnel and the lower aqueous layer containing the sodium benzoylperoxide dropped slowly into a cooled solution of 240 cc. of 20% sulfuric acid (that is, nearly twice the calculated quantity). The temperature is maintained at 0° and the mixture stirred vigorously. The oily layer of benzoylhydroperoxide formed is extracted thrice with chloroform, using 150 to 160 g. for each extraction, and the combined extracts are dried with fused sodium sulfate; yield, 90%.

Properties of Benzoylhydroperoxide

Benzoylhydroperoxide is decomposed readily by alkalies. Evaporation of a chloroform solution under reduced pressure yields a paste containing 20–30% of hydroperoxide. On further evaporation this decomposes into benzoic acid. A chloroform solution of benzoylhydroperoxide when carefully dried over anhydrous sodium sulfate at 0° may be kept exposed to light at room temperature for a number of days without appreciable decomposition.

Addition of Benzoylhydroperoxide to Unsaturated Derivatives

Formation of Styrol Oxide

The styrol was obtained by the thermolysis of phenylethyl phenylacetate.

Preparation of Phenylethyl Phenylacetate.—Ten cc. of concd. sulfuric acid was added to a mixture of 170 g. (1 mole) of phenylethyl alcohol and 250 g. (1.33 moles) of phenylacetic acid. The product was heated on the steam-bath for three hours and the lower aqueous acid layer that separated was removed. After adding 10 cc. more of concd. sulfuric acid, the heating was continued for a further four hours. The lower acid layer was removed, the product dissolved in ether, washed with 10% sodium hydroxide solution, then with water and dried with fused calcium chloride. After removal of the ether, fractionation under reduced pressure of the residual oil gave 295 g. of a colorless product; b. p., 177–178° (4–5 mm.); yield, 88%.

Preparation of Styrol.—At a temperature of approximately 320°, that is, just below its boiling point, phenylethyl phenylacetate is decomposed into phenylacetic acid and styrol.

$$C_6H_5CH_2COOCH_2CH_2C_6H_5 = C_6H_5CH{=}CH_2 + C_6H_5CH_2COOH.$$

One hundred and twenty g. of phenylethyl phenylacetate was heated in a distilling flask at 315–320° under atmospheric pressure for 11 hours, at the end of which period there remained only a small amount of brown polymerized residue. This was not investigated.

The distillate was dissolved in ether and the phenylacetic acid removed by washing with 20% sodium hydroxide solution. The ether solution was washed with water, dried with fused calcium chloride and the ether removed. Fractionation of the remaining product yielded 31 g. of styrol; b. p., 144–145°; yield, 60%. The alkaline extract on acidification with sulfuric acid gave 40 g. of phenylacetic acid, indicating that the styrol and acid are formed in approximately equivalent quantities.

Preparation of Styrol Oxide.[7]—Twenty-two g. of styrol (b. p., 141–143°) was added to 34 g. of benzoylhydroperoxide (10% excess), dissolved in 400 g. of chloroform. The solution was kept at 0° for the first hour and vigorously agitated. It was then allowed to stand at 0° for 24 hours. The rate of reaction was followed by titration of a small sample at intervals. It was found that about 6–7% of the addition took place within the first hour. At the end of 12 hours the reaction was half completed and at the end of 24 hours only the excess of benzoylhydroperoxide was left. A control experiment carried out under the same conditions showed no decomposition of benzoylhydroperoxide during this period. The titrations thus indicated a quantitative addition to the styrol with oxide formation.

The benzoic acid produced in the reaction was removed from the chloroform solution by washing with 10% sodium hydroxide solution, the alkali was removed by washing with water and the chloroform solution dried with sodium sulfate. It was then fractionated at atmospheric pressure through a column of beads. Removal of the chloroform left a practically colorless liquid which distilled without change at 192–194° (the boiling-point of styrol oxide); yield, 75%.

Summary

1. A detailed account is given of the preparation of benzoylhydroperoxide (with a yield of 90%) and of its application to the synthesis of styrol oxide.

2. A new method is described for the synthesis of styrol by the thermolysis of phenylethyl phenylacetate.

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[7] This preparation is referred to briefly in the article by Böeseken and Blumberger (Ref. 3).