Summary

New 5,5-disubstituted barbituric acids described in this paper are the ethyl-*n*-amyl, the di-*n*-amyl and the ethyltetrahydrofuranmethyl derivatives. The first of these is an effective hypnotic with several times the potency of barbital. *n*-Amylchloromalonamide, prepared from one of the intermediates, is remarkable for its intensely sweet taste, which is estimated to be about 400 times as powerful as that of ordinary sugar.

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THE ACTION OF BROMINE ON BETA-PHENYL BENZALACETOPHENONE

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For reasons that need not be specially considered here, it became desirable to secure an unsaturated ketone which has bromine in the α-position and which is too highly substituted to combine readily with other substances. It was decided, therefore, to study anew the action of bromine on β-phenyl benzalacetophenone.

Dilthey and Last[1] seem to be the first to try the action of bromine on this particular ketone and surprisingly enough they stated that no addition took place. The action of chlorine gave them a substance which they thought was a condensation product between the dichloride of phenyl benzalacetophenone and the unchanged ketone. This substance was not analyzed and was not investigated further.

Vorländer, Osterburg and Meye,[2] studying the action of bromine on this same ketone (obtained by the same method employed by Dilthey and Last), observed an evolution of hydrogen bromide and after repeated crystallizations from alcohol obtained a product which when slowly heated melted at 121° and when heated rapidly melted at 165°. This product gave them a percentage of bromine corresponding to α-bromo-β-phenyl benzalacetophenone. An attempt to remove the bromine atom by potassium hydroxide solutions failed and the substance was not further investigated.

Moureau, Dufraisse and Mackall,[3] who had obtained β-phenyl benzalacetophenone by isomerization of triphenylethinyl carbinol, studied the action of bromine on that ketone in their endeavor to identify it.

They found that, upon exposure to light, the chloroform solution of the ketone gave with bromine a colorless compound which melted at 130–

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[1] Dilthey and Last, *J. prakt. Chem.*, **94**, 50 (1916).

[2] Vorländer, Osterburg and Meye, *Ber.*, **56**, 1136 (1923).

[3] Moureau, Dufraisse and Mackall, *Bull. soc. chim.*, (4) **33**, 937 (1923).

131° and had a bromine percentage corresponding to the mono-bromo derivative. In the dark, they obtained two products: one which melted at 90–96° and which they were unable to obtain in a state of purity sufficient for analysis, and another which melted at 183–184° and which gave a slightly lower percentage of bromine than that required for a mono-bromo derivative (21.2 instead of 22.0).

While they were engaged in that work they learned through a publication of another author that the ketone with which they were working was β-phenyl benzalacetophenone, and then apparently abandoned the study of its bromination.

It became desirable to investigate anew the action of bromine on this highly substituted ketone, which was prepared by the same method employed by Dilthey and Last.[4] The results published in this paper differ materially from the results obtained by the preceding chemists.

The action of bromine on β-phenyl benzalacetophenone gives chiefly two products, the respective amounts of which vary with the conditions of the bromination. If the chloroform solution of the unsaturated ketone is refluxed immediately after the addition of the bromine so that the hydrogen bromide which is formed is removed, the product is α-bromo-β-phenyl benzalacetophenone, which is obtained in a 90% yield.

$$(C_6H_5)_2C{=}CHCOC_6H_5 + Br_2 \longrightarrow (C_6H_5)_2C{=}CBrCOC_6H_5 + HBr$$

This compound is a colorless solid melting at 88–89°. Reduced by acetic acid and zinc, it gives diphenyl propiophenone—identified by mixed melting point with diphenyl propiophenone obtained by the reduction of β-phenyl benzalacetophenone itself.

$$(C_6H_5)_2C{=}CBrCOC_6H_5 + H_2 \longrightarrow (C_6H_5)_2CH{-}CH_2{-}COC_6H_5 + HBr$$

Along with the α-bromo β-benzalacetophenone, a small quantity of material of higher melting point has been obtained but not in a sufficient quantity to determine its structure. This compound gives on microanalysis percentages of carbon and hydrogen close to those required by the α-mono-bromo derivative. The investigation of this substance will be continued.

If the bromination is performed by adding the bromine to a solution of the ketone in chloroform or in ethyl bromide and the reagents are allowed to stand at room temperature for a period of at least fifteen hours, a new product is formed together with α-bromo-β-phenyl benzalacetophenone. This new substance separates from petroleum ether in yellow crystals which melt at 104–105°; it dissolves in hot alcohol forming a solution that on cooling deposits colorless crystals which melt at 130–131°. The compound which melts at 104–105° has the formula $C_{21}H_{14}Br_2$ and the compound which melts at 130–131° the formula $C_{23}H_{19}OBr$; it may be seen immediately by the inspection of these formulas that the compound which

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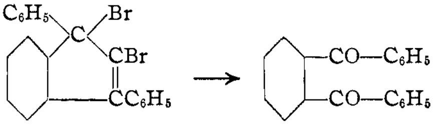
[4] Action of phenyl magnesium bromide on dibenzoyl methane and dehydration of the resulting carbinol.

melts at 130–131° is the ethoxy derivative of the compound which melts at 104–105°, and that this in turn is formed by the loss of a molecule of water from α,β-dibromo-β-diphenyl propiophenone.

$$(C_6H_5)_2C{=}CHCOC_6H_5 + Br_2 \longrightarrow (C_6H_5)_2CBrCBrHCOC_6H_5 \xrightarrow{-H_2O} C_{21}H_{14}Br_2$$

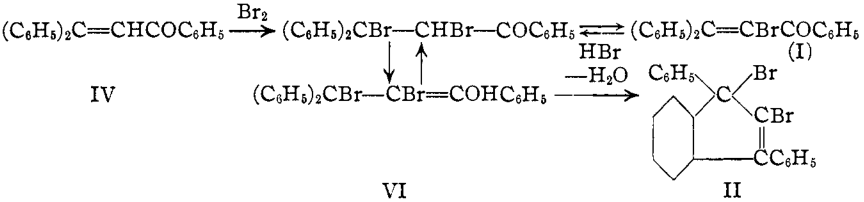
The structure of this particular dibromide was determined by ozonization; the only product obtained was *o*-dibenzoyl benzene, identified by mixed melting point with an authentic sample. The formation of this diketone leaves no doubt that the dibromide is 1,2-dibromo-1,3-diphenyl indene.



II III

That the substance which melts at 130–131° is the ethoxy derivative of the dibromide was confirmed by the fact that *o*-dibenzoyl benzene is also found during its ozonization.

It is also possible to obtain 1,2-dibromo-1,3-diphenyl indene from the α-bromo-β-phenyl benzalacetophenone by the action of hydrogen bromide in glacial acetic acid. The fact that the dibromo indene derivative is formed from both the original ketone and its mono-bromo derivative leads to the following supposition concerning the mechanism of the reaction:



First the unsaturated ketone (IV) would be expected to react with a molecule of bromine to form a dibromide (V). This dibromide (V) which contains a bromine atom linked to a carbon atom which also holds the two phenyl groups is very unstable and loses hydrogen bromide very easily. The loss of hydrogen bromide from the dibromide is reversible as is shown by the fact that the dibromo indene (II) is also obtained from α-bromo-β-phenyl benzalacetophenone by the action of hydrogen bromide. Since hydrogen bromide is also a dehydrating agent, the formation of the indene derivative (II) from the enolic form (VI) of the dibromide (V) is easily explained under the conditions of the reaction.

If hydrogen bromide is removed from the solution as soon as it is formed, the direction of the equilibrium will shift toward the exclusive formation of the α-bromo derivative (I). If hydrogen bromide remains in the solution, its dehydrating effect on the dibromide transforms it into the indene derivative and the equilibrium shifts toward the formation of the dibromide (V), which continues its transformation into the indene derivative (II).

The water formed during the reaction may be seen as a cloud when the bromination is performed in chloroform. In ethyl bromide, the water on standing becomes saturated with hydrogen bromide and collects at the bottom of the flask, then being heavier than the solvent.

The 1,2-dibromo-1,3-diphenyl indene is constituted like 1,2,3-bromo triphenyl indene, which readily forms a free radical.[5] Since it has in addition to the active bromine atom which is common to both these substances a less active bromine in place of the phenyl group on the adjoining carbon atom, its behavior toward metals is peculiarly interesting, and experiments designed to establish this behavior are under way.

Experimental Part

Action of Bromine on β-Phenyl Benzalacetophenone in Boiling Chloroform.—To a solution of 10 g. of β-phenyl benzalacetophenone in chloroform was slowly added 6 g. of bromine. The solution was immediately boiled for five hours. When no more hydrogen bromide was evolved, the chloroform solution, washed with hydrogen sodium sulfite and hydrogen sodium carbonate, was dried and the solvent removed under diminished pressure. The resulting oil was crystallized from petroleum ether after decolorizing with charcoal. The yield of α-bromo-β-phenyl benzalacetophenone was 90%.

α-Bromo-β-Phenyl Benzalacetophenone (I).—This compound forms nearly colorless crystals which melt instantaneously by projection on a mercury bath at 88–89°. Heated before this point, it melts from 80–85°. The substance has a rather inactive bromine atom; it is not ozonized when submitted to a current of 6% ozone for two hours. It is reduced by boiling in moderately dilute acetic acid with zinc dust and forms β,β-diphenyl propiophenone, identified by mixed melting point. It is soluble in ether, chloroform, ethyl bromide, carbon bisulfide and benzene, sparingly soluble in cold alcohol and petroleum ether.

Anal. Calcd. for $C_{21}H_{15}OBr$: C, 69.4; H, 4.1. Found: C, 68.8; H, 4.1. Molecular weight, calcd.: 363. Found (in benzene): 355.

Action of Bromine on β-Phenyl Benzalacetophenone in Chloroform at Room Temperature.—To a solution of 10 g. of β-phenyl benzalacetophenone in chloroform was added rapidly a solution of 6 g. of bromine in the same solvent; the solution became warm and hydrogen bromide was evolved. The reaction mixture was set aside for fifteen to twenty hours. The excess of bromine and hydrogen bromide was removed by shaking with a solution of hydrogen sodium sulfite and hydrogen sodium carbonate. The solution dried and evaporated under diminished pressure leaves a yellow oil which separates from petroleum ether (containing a little ether) in yellow and white crystals. These crystals are easily separated mechanically when the crystals are allowed to grow slowly. When a pure yellow crystal is on hand, a solution of white and yellow crystals in petroleum ether seeded by this pure crystal deposits only yellow crystals. From the white compound, α-bromo-β-phenyl benzalacetophenone, the yellow compound was obtained by dissolving the unsaturated bromo compound in a saturated solution of hydrogen bromide in glacial acetic acid. When heated a few minutes at 100°, this solution de-

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[5] Kohler, *Am. Chem. J.*, 40, 220 (1908).

posited a cloudy precipitate which was redissolved by adding a few drops of glacial acetic acid. The solution, seeded, deposited on standing the dibromo indene derivative.

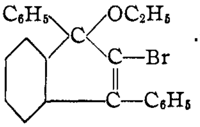
1,2-Dibromo-1,3-diphenyl Indene (II).—This compound separates from petroleum ether in well defined characteristic pyramids which are easily recognized. It melts at 104–105° and is stable. With cold concentrated sulfuric acid, it gives a yellow solution which turns to intense red when heated. It has an active bromine and reacts easily with boiling alcohol, forming the corresponding ethoxy derivative. It is soluble in all organic solvents, less soluble in petroleum ether.

Anal. Calcd. for $C_{21}H_{14}Br_2$: C, 59.1; H, 3.3; Br, 37.6. Found: C, 59.0; H, 3.3; Br, 37.9.

Ozonization of 1,2-Dibromo-1,3-diphenyl Indene.—A solution of 2 g. of the dibromo indene in ethyl bromide was ozonized in a current of ozone for two hours; bromine was evolved and the solution became redder and redder. At the end of this time the solution was treated with cold water and the solvent was removed. The resulting oil was boiled with water to insure the decomposition of the ozonide. The oil was taken up in ether and the ethereal solution, washed with an hydrogen sodium carbonate solution, was dried and evaporated. After decolorizing with charcoal, a colorless, crystalline substance separated from alcohol and melted at 145–146°. The substance is free from bromine.

Anal. Calcd. for $C_{20}H_{14}O_2$: C, 83.9; H, 4.9; molecular weight, 286. Found: C, 83.8; H, 5.2; molecular weight (in benzene), 290.

This compound was found to be *o*-dibenzoyl benzene, which melts at 146° and was identified by mixed melting point.

1-Ethoxy-2-bromo-1,3-diphenyl Indene,  .—When the dibromo indene is boiled with alcohol, the ethoxy compound separates on cooling into colorless crystals which melt at 130–131°.

Anal. Calcd. for $C_{23}H_{19}OBr$: C, 70.8; H, 4.9. Found: C, 70.4, 70.8, 70.6; H, 5.0, 5.1, 5.1.

This compound gives an intensely red coloration with cold concentrated sulfuric acid. By ozonization it gives the same results obtained by the ozonization of the dibromo indene. The insolubility of this compound in cold alcohol makes it a useful derivative for the characterization of 1,2-dibromo-1,3-diphenyl indene.

Summary

It has been shown that the action of bromine on β-phenyl benzalacetophenone gives chiefly two products: α-bromo-β-phenyl benzalacetophenone and 1,2-dibromo-1,3-diphenyl indene. The yield of the two substances depends upon the presence and the concentration of hydrogen bromide which is formed during the bromination. It has also been shown that the action of hydrogen bromide on α-bromo-β-phenyl benzalacetophenone in glacial acetic acid solution gives 1,2-dibromo-1,3-diphenyl indene. This indene derivative offers special interest because it contains two bromine atoms, one of which is very active, and thus should give free radicals. Investigations on this matter are in progress.

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