[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CARNEGIE INSTITUTE OF TECHNOLOGY]

The Action of N-Bromosuccinimide on β-Phenyl-α,β-unsaturated Ketones. II. The Bromination of Benzyl Styryl Ketone

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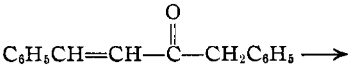
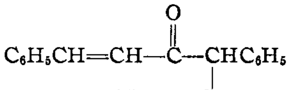
An investigation of the reaction of benzalacetone with N-bromosuccinimide in the presence of a catalytic amount of benzoyl peroxide has shown that the unsaturated ketone reacts predominantly by addition at the double bond to yield benzalacetone dibromide rather than by substitution in the methyl group to give bromomethyl styryl ketone.[4] The latter substance, if formed at all, was present in such a small quantity that it could not be isolated from the reaction mixture. Since the bromination of benzalacetone in the methyl group had apparently failed because of the competition of the addition reaction at the olefinic double bond, it became of interest to discover whether substitution of bromine into an α-methylene group in a similar β-phenyl-α,β-unsaturated ketone could be achieved without bromine addition by somewhat increasing the facility with which substitution could occur.[5]

Experiments with benzyl styryl ketone (I) appear to demonstrate that the course of the reaction can be altered in this way. The reaction of this substance with N-bromosuccinimide required peroxide catalysis, but proceeded more rapidly than the reactions previously described,[4] the N-bromosuccinimide being consumed in seven to twelve hours at the reflux temperature. The solutions, moreover, failed to develop the red-brown color characteristic of the mixtures obtained with benzalacetone and benzalacetophenone,[4] and the succinimide, which was obtained in nearly quantitative yield, separated in pure form unaccompanied by resinous material. The carbon tetrachloride solutions were found to contain a monobromo derivative of benzyl styryl ketone, purified samples of which melted at 82°. None of the previously-known benzyl styryl ketone dibromide, m. p. 93°,[6] was isolated from the mixtures. These observations, as well as others to be described below, indicated that the reaction had produced 1,4-diphenyl-1-bromo-3-butene-2-one (II) by substitution in the α-methylene group

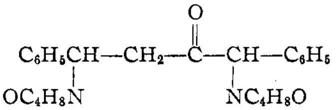

$$C_6H_5CH{=}CH{-}\overset{\overset{O}{\|}}{C}{-}CH_2C_6H_5 \longrightarrow$$

I

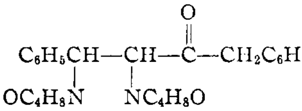

$$C_6H_5CH{=}CH{-}\overset{\overset{O}{\|}}{C}{-}\underset{\underset{Br}{|}}{C}HC_6H_5$$

II

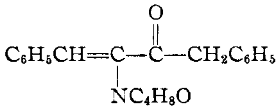
The belief that substitution in benzyl styryl ketone had occurred in the methylene group and not at either of doubly bonded carbon atoms is supported by several additional lines of evidence. The bromo ketone contained an active bromine atom, as shown by the ready precipitation of sodium bromide when it was treated with sodium iodide in acetone solution.[7] α-Bromobenzalacetone fails to give a precipitate under the same conditions. That the bromine was not situated on the α-carbon of the α,β-double bond was also indicated by the result of the reaction of the compound with morpholine. It reacted readily with an excess of this amine to yield a dimorpholino derivative of the parent saturated ketone, apparently 1,4-diphenyl-1,4-dimorpholino-2-butanone (III), melting at 203°. This dimorpholino derivative was not identical with the substance, presumably 1,4-diphenyl-3,4-dimorpholino-2-butanone (IV), m. p. 161°, obtained by the reaction of benzyl styryl ketone dibromide (VI) with an excess of morpholine, as might have been expected if the bromine of the monobromide had been situated on the α-carbon of the α,β-double bond.[8] Although the possibility cannot be excluded that the higher melting isomer is merely the second diastereoisomer of structure (IV), the fact that no trace of it could be detected in the reaction product from benzyl styryl ketone dibromide suggests that such is not the case. A second product was obtained from the reaction of the dibromide (VI) with morpholine, but it


$$\underset{\underset{OC_4H_8N}{|}}{C_6H_5CH}{-}CH_2{-}\overset{\overset{O}{\|}}{C}{-}\underset{\underset{NC_4H_8O}{|}}{CH}{-}C_6H_5$$

III


$$\underset{\underset{OC_4H_8N}{|}}{C_6H_5CH}{-}\underset{\underset{NC_4H_8O}{|}}{CH}{-}\overset{\overset{O}{\|}}{C}{-}CH_2C_6H_5$$

IV


$$C_6H_5CH{=}\underset{\underset{NC_4H_8O}{|}}{C}{-}\overset{\overset{O}{\|}}{C}{-}CH_2C_6H_5$$

V

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[4] Southwick, Pursglove and Numerof, THIS JOURNAL, **72**, 1600 (1950).

[5] The experiments of Ruggli and Schmidlin, *Helv. Chim. Acta*, **29**, 383 (1946), with 2,5-diphenyl-4-cyclopentene-1,3-dione suggest that substitution may be expected to take precedence if the α-hydrogen is highly activated, as in a β-diketone.

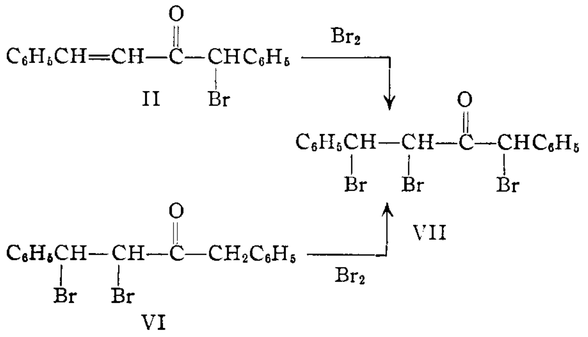
[6] Goldschmiedt and Knöpfer, *Monatsh.*, **19**, 406 (1898); Goldschmiedt and Krczmar, *ibid.*, **22**, 667 (1901).

[7] Shriner and Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., third edition, 1948, p 140.

[8] Cromwell, *Chem. Revs.*, **38**, 83 (1946).

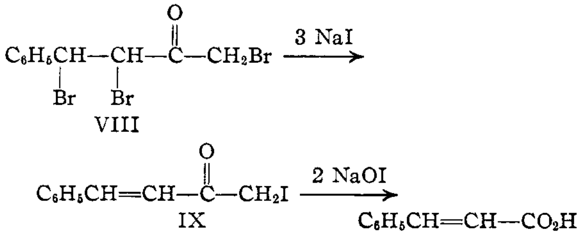
melted at 126° and was found to have the composition $C_{22}H_{21}O_2N$. This formula suggests that the substance is the α-morpholino derivative (V), but the corresponding derivative of benzalacetone is reported to have a light-yellow color,[9] whereas this compound is colorless. The substance is still being investigated.

Other evidence supporting the structure II for the N-bromosuccinimide bromination product was obtained from the investigation of its reaction with bromine. The addition of bromine took place readily to give a tribromo ketone. That this product was 1,4-diphenyl-1,3,4-tribromo-2-butanone (VII) and that the assigned structure II was therefore correct for the monobromo ketone was indicated by the fact that the tribromide could also be prepared by the treatment of 1,4-diphenyl-3,4-dibromo-2-butanone (benzyl styryl ketone dibromide) (VI) with a mole of bromine, or by treatment of benzyl styryl ketone (I) directly with 2 moles of bromine. The substitution reaction took place readily at room temperature, as might have been expected for substitution of the α-hydrogen of a ketone. The considerable activation at carbon 1 of the dibromide (VI) which would be expected to result from the combined influences of the carbonyl group and the phenyl group should favor substitution in that position, certainly over substitution in position 4, and probably over substitution in position 3 as well. These considerations therefore lead to the conclusion that bromination of the dibromide VI should give a tribromide of structure VII, the same diastereoisomeric form of which seems to predominate whether it is prepared from the monobromide II or the dibromide VI.



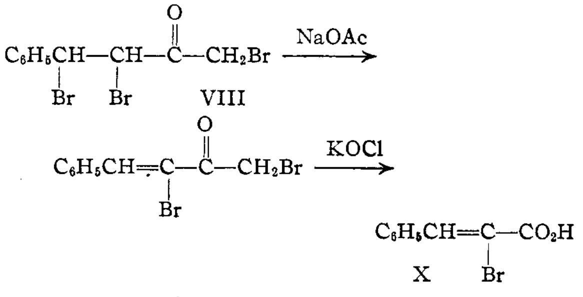
$$C_6H_5CH{=}CH{-}\overset{O}{\overset{\|}{C}}{-}\underset{Br}{CH}C_6H_5 \ (\text{II}) \xrightarrow{Br_2} C_6H_5\underset{Br}{CH}{-}\underset{Br}{CH}{-}\overset{O}{\overset{\|}{C}}{-}\underset{Br}{CH}C_6H_5 \ (\text{VII}) \xleftarrow{Br_2} C_6H_5\underset{Br}{CH}{-}\underset{Br}{CH}{-}\overset{O}{\overset{\|}{C}}{-}CH_2C_6H_5 \ (\text{VI})$$

Comparison of the action of bromine on benzalacetophenone dibromide and benzalacetone dibromide bears out the conclusion that in the case of the dibromide VI preferential substitution would not have been expected on the brominated carbon atoms. Benzalacetophenone dibromide, which has no unbrominated methyl or methylene group, was recovered unchanged after being allowed to stand at room temperature for eighteen hours in a chloroform solution containing a mole of bromine. Benzalacetone dibromide, on the other hand, consumed a mole of bromine in the course of eighteen hours under these conditions to give a product from which a tribromide believed to be 4-phenyl-1,3,4-tribromo-2-butanone (VIII) was obtained in 40% yield after purification. The assignment of the structure VIII to this bromination product is based upon the results of two degradation experiments. In the first of these an excess of sodium iodide in acetone solution was used to convert the tribromide into an unsaturated iodo ketone, which yielded cinnamic acid when treated with sodium hypoiodite. This result is explained most readily by the following reaction sequence, which is based on the formula VIII for the tribromide



$$C_6H_5\underset{Br}{CH}{-}\underset{Br}{CH}{-}\overset{O}{\overset{\|}{C}}{-}CH_2Br \ (\text{VIII}) \xrightarrow{3\ NaI} C_6H_5CH{=}CH{-}\overset{O}{\overset{\|}{C}}{-}CH_2I \ (\text{IX}) \xrightarrow{2\ NaOI} C_6H_5CH{=}CH{-}CO_2H$$

The iodo ketone, apparently iodomethyl styryl ketone (IX), was obtained as a pale-yellow crystalline solid, m. p. 56.5–58.5°. In the second degradation procedure partial dehydrobromination of the tribromide by heating with one mole of sodium acetate in ethanol solution was followed by treatment of the unpurified intermediate with potassium hypochlorite. The product was α-bromocinnamic acid (X), a result which also appears to be best explained on the basis of formula VIII for the tribromide



$$C_6H_5\underset{Br}{CH}{-}\underset{Br}{CH}{-}\overset{O}{\overset{\|}{C}}{-}CH_2Br \ (\text{VIII}) \xrightarrow{NaOAc} C_6H_5CH{=}\underset{Br}{C}{-}\overset{O}{\overset{\|}{C}}{-}CH_2Br \xrightarrow{KOCl} C_6H_5CH{=}\underset{Br}{C}{-}CO_2H \ (\text{X})$$

The study of the reactions of N-bromosuccinimide with β-phenyl-α,β-unsaturated ketones is being continued, and the investigation of the reactions of the bromo ketones II, VII and VIII and of the iodo ketone IX has been undertaken.

Experimental[10,11]

Benzyl Styryl Ketone (I).—Benzyl styryl ketone was prepared by the condensation of benzaldehyde with phenylacetone, using a modification of the method of Goldschmiedt and Knöpfer.[12] A mixture consisting of 15.5 g. (0.146 mole) of benzaldehyde, 12.5 g. (0.093 mole) of

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[9] Cromwell, This Journal, **62**, 3470 (1940).

[10] Microanalyses by Clark Microanalytical Laboratory, Urbana, Illinois.

[11] Melting points are corrected.

[12] Goldschmiedt and Knöpfer, *Monatsh.*, **18**, 437 (1897); Goldschmiedt and Krczmar, *ibid.*, **22**, 667 (1901).

phenylacetone, 800 ml. of water and 2 g. of potassium hydroxide was stirred vigorously for 24 hours in a flask kept in a bath maintained at a constant temperature of 55°. The careful control of the temperature is highly important if the formation of by-products is to be avoided. At the end of the reaction period, the mixture was cooled in a refrigerator, and the solidified product was removed by filtration. After two crystallizations from methanol, 8 g. of benzyl styryl ketone was obtained in white flakes, m. p. 73–74°. The yield can be raised to 10 g. (48%) by reworking the mother liquors from the crystallizations.

1,4-Diphenyl-1-bromo-3-butene-2-one (II).—The reaction of benzyl styryl ketone with N-bromosuccinimide was performed a number of times, the following run being typical. A mixture of 7 g. (0.032 mole) of benzyl styryl ketone, 5.9 g. (0.032 mole) of N-bromosuccinimide,[13] 0.5 g. of benzoyl peroxide, and 75 ml. of dry carbon tetrachloride was boiled for twelve hours. The mixture was cooled and the suspended white solid was removed by filtration and washed with carbon tetrachloride. This was essentially pure succinimide, m. p. 122–123°, and the yield (3.3 g.) was quantitative.

The filtrate, a light-yellow solution, was concentrated at room temperature under reduced pressure until a light-yellow viscous oil was obtained. The bromination product was isolated from this mixture by extraction at room temperature with petroleum ether (boiling range 65–110°), which separated it from a small quantity of less soluble resinous material. Cooling the extract with Dry Ice caused the separation of a layer of oil which crystallized upon continued cooling, and was removed by filtration. The yields of this crude product were usually in the range 8.5–9 g. (89–95%). Although a light-brown (iodine) color was developed when the original liquid crude product was treated with sodium iodide in acetone,[7] no benzyl styryl ketone dibromide could be separated from the mixture.

The recrystallization of the monobromo derivative was accomplished only with considerable difficulty, due to an extremely slow rate of crystal formation and an attendant tendency for the substance to separate as an oil from all solvents which might have been suitable for crystallization. An analytical sample prepared from the product of the run described above was obtained as follows: The extraction was performed with one 10-ml. and three 50-ml. portions of petroleum ether. The first of the 50-ml. extracts was used for the preparation of the sample. It was cooled by the use of Dry Ice until a layer of oil which separated had crystallized, then the precipitate was removed and crystallized from 95% ethanol, again by cooling with Dry Ice. Two more recrystallizations from petroleum ether (b. p. 65–110°) by cooling with Dry Ice were followed by a final recrystallization from petroleum ether at room temperature, achieved by letting a solution concentrate somewhat by evaporation, then keeping it in a stoppered flask for several days. Rosettes of white needles were obtained, m. p. 81–82°.

Anal. Calcd. for $C_{16}H_{13}OBr$: C, 63.78; H, 4.32. Found: C, 63.71; H, 4.19.

The compound gives a precipitate of sodium bromide when treated with sodium iodide in acetone solution at room temperature.[7]

1,4-Diphenyl-1,4-dimorpholino-2-butanone (III).—One gram of the N-bromosuccinimide bromination product of benzyl styryl ketone was dissolved in 6 ml. of morpholine. The solution warmed, developed a yellow color, and deposited crystals of morpholine hydrobromide when allowed to stand. After a period of 24 hours at room temperature, the mixture was filtered to remove the morpholine hydrobromide, and the filtrate was diluted with 50 ml. of water and allowed to stand in a refrigerator overnight. The crystals which were deposited were recrystallized from aqueous ethanol (or from ether) to give 1,4-diphenyl-1,4-dimorpholino-2-butanone as colorless needles, m. p. 202.5–203.5°.

Anal. Calcd. for $C_{24}H_{30}O_3N_2$: C, 73.06; H, 7.67; N, 7.10. Found: C, 72.97; H, 7.43; N, 7.09.

1,4-Diphenyl-3,4-dimorpholino-2-butanone (IV).—To a suspension of 1 g. of benzyl styryl ketone dibromide,[6] m. p. 93°, in 5 ml. of absolute alcohol, 1 ml. of morpholine was added. The mixture warmed, developed a yellow color, and the dibromide dissolved. The mixture was allowed to stand for two days at room temperature. The morpholine hydrobromide which had crystallized from the solution was removed by filtration, and the filtrate was diluted with 50 ml. of ether to complete the precipitation of this product. After filtration the solution was concentrated to a volume of 5 ml., and 15 ml. of petroleum ether (b. p. 65–110°) was added. The resulting solution was distilled on a steam-bath until the temperature of the boiling liquid reached 90°, then 2 ml. of benzene was added and the solution was allowed to cool slowly. The small quantity of crystalline material which separated was removed by filtration. This substance, which was obtained as white needles melting at 124.5–126° following crystallization from ethanol, had the composition of a monomorpholino derivative of benzyl styryl ketone.

Anal. Calcd. for $C_{20}H_{21}O_2N$: C, 78.15; H, 6.89; N, 4.56. Found: C, 78.34; H, 6.81; N, 4.84.

After removal of this substance the filtrate was evaporated, and the somewhat gummy residue was crystallized from aqueous ethanol to yield 1,4-diphenyl-3,4-dimorpholino-2-butanone (IV) as white needles, m. p. 160–161°.

Anal. Calcd. for $C_{24}H_{30}O_3N_2$: C, 73.09; H, 7.61; N, 7.10. Found: C, 72.98; H, 7.79; N, 7.03.

In a repetition of the above experiment it was found that the two products could easily be separated by extraction with dilute hydrochloric acid of an ether solution containing the mixture. The dimorpholino derivative (IV), m. p. 160–161°, passed into the aqueous acid and was precipitated in crystalline form following neutralization, while evaporation of the ether yielded the lower-melting component, also in crystalline condition.

1,4-Diphenyl-1,3,4-tribromo-2-butanone (VII)

(A) From Benzyl Styryl Ketone (I).—A solution prepared from 1 g. of benzyl styryl ketone, 2 ml. of carbon tetrachloride and 1.5 g. of bromine was allowed to stand for a short time at room temperature. Hydrogen bromide was evolved, and nearly all of the bromine was consumed. When the mixture was cooled in an ice-bath, a mass of crystals separated. The cake of crystals was resuspended with the aid of 10 ml. of methanol, then removed by filtration to give 1.65 g. (76%) of crude product, m. p. 138–139°. It was recrystallized several times from aqueous ethanol to give white needles, m. p. 143–144°.

Anal. Calcd. for $C_{16}H_{13}OBr_3$: C, 41.65; H, 2.82. Found: C, 41.74; H, 3.03.

(B) From Benzyl Styryl Ketone Dibromide (VI).—A solution containing 0.4 g. of benzyl styryl ketone dibromide,[6] m. p. 93°, 0.16 g. of bromine and 1 ml. of carbon tetrachloride was stirred until, at the end of ten minutes, crystals began to separate. After the mixture had been allowed to stand for one hour, the crystals were removed by filtration and recrystallized from aqueous ethanol to give white needles, m. p. 141–142°. The melting point of a mixture of this product with that described in (A) above was not depressed.

(C) From 1,4-Diphenyl-1-bromo-3-butene-2-one.—To a solution of 1 g. of the N-bromosuccinimide bromination product of benzyl styryl ketone in 2 ml. of chloroform, a solution of 0.5 g. of bromine in 1 ml. of chloroform was added. The solution was stirred, then placed in an ice-bath until a mass of crystals had separated. Following the addition of 10 ml. of methanol, the cake of crystals was resuspended and removed by filtration to give 1.2 g. (78%) of a crude product, m. p. 135–138°. Recrystalli-

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[13] In order to minimize the formation of colored by-products, it was found advisable to use for this reaction N-bromosuccinimide which had been freshly crystallized from hot water by rapid cooling in an ice-bath, washed thoroughly with ice water, and dried in a desiccator over phosphorus pentoxide. N-Bromosuccinimide which had been allowed to stand for more than a few days after crystallization gave orange-colored reaction mixtures.

zation from aqueous methanol yielded white needles, m. p. 141–142°, which did not depress the melting point of the tribromo derivative obtained by the action of bromine on benzyl styryl ketone, as described in (A) above.

4-Phenyl-1,3,4-tribromo-2-butanone (VIII).—To a solution of 200 g. of benzalacetone dibromide[14] in 1 liter of chloroform, 105 g. of bromine was added, and the mixture was allowed to stand for eighteen hours at room temperature in a loosely stoppered flask. At the end of this period, the bromine had been consumed. The solvent was removed under reduced pressure at room temperature. A 64-g. portion of the crude product (238 g.) so obtained was recrystallized once from methanol to yield 34 g. of white needles, m. p. 111–116.5°. A second recrystallization from methanol of a 15-g. portion of this material yielded 12 g. (representing a 40% yield) of substantially pure 4-phenyl-1,3,4-tribromo-2-butanone, m. p. 114.5–116.5°.[15] Repeated crystallizations from methanol produced an analytical sample of m. p. 116.5–117.5°.

Anal. Calcd. for $C_{10}H_9OBr_3$: C, 31.20; H, 2.36. Found: C, 31.33; H, 2.34.

Under the same conditions, benzalacetophenone dibromide failed to consume the bromine added and was recovered unchanged from the reaction mixture.

Iodomethyl Styryl Ketone (IX)

(A) Preparation.—A solution of 5.3 g. (0.0138 mole) of 4-phenyl-1,3,4-tribromo-2-butanone (VIII), m. p. 115–117°, in 18 ml. of acetone was added to a solution of 8.25 g. (0.0552 mole) of sodium iodide in 55 ml. of acetone. The precipitation of sodium bromide and the liberation of iodine appeared to be nearly complete within a few seconds. The mixture was allowed to stand for three hours at room temperature, then was filtered to remove sodium bromide, placed in a separatory funnel, and diluted with 150 ml. of ether. Following the addition of 500 ml. of water, dilute sodium sulfite solution was added in portions with shaking until the iodine color was discharged in both layers. The ether solution was washed twice with water and concentrated by distillation under reduced pressure from a bath kept at room temperature. The product crystallized during the removal of the solvent and was obtained as a pale-yellow solid, m. p. 50–55°, in a yield of 3.4 g. (90%). After two recrystallizations from methanol, stout pale-yellow needles or prisms were obtained, m. p. 56.5–58.5°.[16]

Anal. Calcd. for $C_{10}H_9OI$: C, 44.14; H, 3.33; I, 46.65. Found: C, 44.79; H, 3.75; I, 43.35.

(B) Degradation to Cinnamic Acid.[17]—To a solution of 2.4 g. of crude iodomethyl styryl ketone, m. p. 50–55°, in 20 ml. of dioxane, 10 g. of iodine was added. A 10% aqueous sodium hydroxide solution was added dropwise with stirring until the iodine had been consumed. The solution was diluted with 300 ml. of water, filtered free of iodoform, and acidified with hydrochloric acid to precipitate the product. The iodine liberated from the iodide-hypoiodite solution by the acidification was removed by the addition of sodium bisulfite, and the product was collected by filtration and dried over phosphorus pentoxide. The yield was 0.9 g. (69%) of nearly white crystals, m. p. 130–132°. The melting point of a mixture of this substance with cinnamic acid was not depressed, and the material was found to be free of halogen after it had been redissolved in sodium bicarbonate solution and precipitated with sulfuric acid.

Degradation of 4-Phenyl-1,3,4-tribromo-2-butanone (VIII) to α-Bromocinnamic Acid.—To a hot solution of 6.2 g. (0.016 mole) of the tribromo ketone, m. p. 115–117°, in 40 ml. of 95% ethanol, 1.4 g. (0.017 mole) of sodium acetate was added and the mixture was boiled under reflux for ninety minutes. The solution was then concentrated under reduced pressure, the residual oil was dissolved in ether, and the ether solution was allowed to evaporate until most of the solvent had been removed. The resulting light-brown oil was dissolved in 30 ml. of dioxane and the solution was placed in a separatory funnel.

A solution of potassium hypochlorite was prepared by adding a solution of 8.75 g. of potassium carbonate and 5.0 g. of potassium hydroxide in 25 ml. of water to a solution of 12.5 g. of calcium hypochlorite in 50 ml. of hot water. The precipitated calcium carbonate was removed by filtration. The hypochlorite solution was added in portions to the dioxane solution of the bromo ketone with shaking and cooling between additions. Following extraction of the resulting mixture with ether, sodium bisulfite was added until the excess hypochlorite was consumed. An acid was precipitated in the form of a yellow oil when the solution was acidified with hydrochloric acid, and was removed by ether extraction, then dissolved in aqueous potassium hydroxide solution. Acidification precipitated 1.6 g. of crystalline solid, m. p. 123–127°. Successive recrystallizations from chloroform–petroleum ether and aqueous ethanol gave white needles, m. p. 128–130°. The acid gave the neutralization equivalent expected for a monobromo derivative of cinnamic acid.

Anal. Calcd. for $C_9H_7O_2Br$: neut. equiv., 227. Found: neut. equiv., 224.

The melting point was not depressed when the compound was mixed with a sample of α-bromocinnamic acid prepared by the hypoiodite degradation of α-bromobenzalacetone.[17]

Acknowledgment.—The authors are indebted to Mr. Walter R. Moore and Mr. Harold L. Dimond for technical assistance.

Summary

1. The action of N-bromosuccinimide on benzyl styryl ketone has been examined in order to compare the results with those previously obtained with benzalacetone. The predominant reaction in this case was bromine substitution to produce 1,4-diphenyl-1-bromo-3-butene-2-one rather than bromine addition to the olefinic double bond such as occurred with benzalacetone.

2. Work performed in order to establish the structure of the bromination product led to the preparation of a number of additional new compounds. Those described include 1,4-diphenyl-1,4-dimorpholino-2-butanone, 1,4-diphenyl-3,4-dimorpholino-2-butanone, 1,4-diphenyl-1,3,4-tribromo-2-butanone, 4-phenyl-1,3,4-tribromo-2-butanone and iodomethyl styryl ketone.

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[14] Cromwell and Benson, "Organic Syntheses," **27**, 5 (1947).

[15] A sample of this m. p. showed slightly high C and H content. Found: C, 31.60; H, 2.50.

[16] Samples purified in this way tend to darken and undergo decomposition upon standing. The decomposition usually proceeds slowly, but may have somewhat affected the analytical results.

[17] This technique for conducting the degradation of methyl ketones by the iodoform reaction is the result of a study of the method with a number of other compounds; unpublished work of Southwick, Numerof and Maddox.