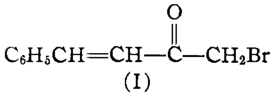
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CARNEGIE INSTITUTE OF TECHNOLOGY]

The Action of N-Bromosuccinimide on β-Phenyl-α,β-unsaturated Ketones. I.

BY PHILIP L. SOUTHWICK, L. A. PURSGLOVE[1] AND PAUL NUMEROF[2,3]

The present investigation is an outgrowth of experiments directed toward the preparation of bromomethyl styryl ketone (I), a compound which would have a combination of functional groups which might make it useful in a variety of syntheses.[4] The preparation of this compound



$$C_6H_5CH{=}CH{-}\overset{\overset{O}{\|}}{C}{-}CH_2Br$$

(I)

was attempted by means of the action of N-bromosuccinimide on benzalacetone. It seemed reasonable to expect that if a reaction occurred between these substances, the result would be substitution of bromine into the methyl group of benzalacetone, as desired. Although no report had appeared concerning the action of N-bromosuccinimide on an α,β-unsaturated ketone such as benzalacetone, which has no allyl position available for bromination, but in which the moiety on the other side of the carbonyl group contains α-hydrogen atoms,[5] the bromination of saturated ketones in the α-position had previously been accomplished by the use of N-bromosuccinimide in a number of instances.[6] Moreover, a variety of α,β-unsaturated ketones had been brominated in an allyl position by use of this reagent without appreciable concomitant reaction at the double bond.[6,7]

When a solution of freshly distilled benzalacetone in dry carbon tetrachloride was heated with N-bromosuccinimide at the reflux temperature of the solution, very little reaction occurred during a period of forty-eight hours. The addition of 5 mole per cent. of benzoyl peroxide to an otherwise identical mixture caused the bromination to proceed slowly, and the N-bromosuccinimide was consumed in a period of about eighteen hours. During the course of the reaction the solution acquired a deep red color and a red-brown solid separated. A 67.5% yield of succinimide was isolated from this material, the remainder of which consisted of a brown resin. This resin, rather than free bromine, was responsible for the color developed in the reaction mixture; the vapors and condensate in the condenser were colorless throughout the reaction period and did not affect starch–iodide paper. The product obtained from the benzalacetone, however, was not the desired bromomethyl styryl ketone (I), but benzalacetone dibromide. The yield of the purified dibromide was 46%, based on N-bromosuccinimide, and no additional pure product except unchanged benzalacetone was isolated from the mixture. The bromo ketone I, if formed at all, must have been present only in small amount.

This result, in addition to demonstrating a limitation of the reagent, raised a number of questions concerning the mode of action of N-bromosuccinimide. It was, of course, not possible to write a balanced equation for the formation of benzalacetone dibromide and succinimide as chief products without discovering the source of the hydrogen required to replace the bromine of N-bromosuccinimide. Moreover, the fact that the reaction must be initiated by a small amount of benzoyl peroxide strongly suggested that the addition of bromine had occurred by means of a free radical chain mechanism,[8] although it appeared difficult to formulate a self-sustaining chain mechanism which would lead to the observed products in the amounts obtained.

The formation of benzalacetone dibromide as one product of the reaction could be explained if N-bromosuccinimide could be shown to decompose with the release of free bromine under the conditions of the experiment. The failure to discover free bromine during the course of the reaction does not eliminate this possibility; if bromine were released slowly, its immediate absorption by the unsaturated ketone might prevent its detection above the reaction mixture. Although prolonged heating of carbon tetrachloride solutions of N-bromosuccinimide in the presence of benzoyl peroxide does liberate small amounts of bromine, the disappearance of N-bromosuccinimide is extremely slow unless there is present another substance which acquires bromine by substitution or addition. There-

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(1) Institute Fellow in Organic Chemistry, 1948–1949.

(2) Institute Fellow in Organic Chemistry, 1948.

(3) Present address: Squibb Institute for Medical Research, New Brunswick, New Jersey.

(4) The reactions of halomethyl vinyl ketones, the class of substances of which the bromo ketone I would be representative, have been very little investigated, and should prove to be of considerable interest. The preparation of the simplest substance of this type, chloromethyl vinyl ketone, has been reported since this work was initiated; see Bissinger, Fredenburg, Kadesch, Kung, Langston, Stevens and Strain, THIS JOURNAL, **69**, 2955 (1947).

(5) The bromination by N-bromosuccinimide of a cyclic diketone of this description, 2,5-diphenyl-4-cyclopentene-1,3-dione, has been reported by Ruggli and Schmidlin, *Helv. Chim. Acta*, **29**, 383 (1946). In that case the substitution involves the active hydrogen of a β-diketone, however, and is not strictly comparable to the reaction attempted in this investigation.

(6) Djerassi, *Chem. Revs.*, **43**, 271 (1948).

(7) Buu-Hoï, *Experientia*, **2**, 310 (1946), has reported that the bromination of mesityl oxide and ethylideneacetone by N-bromosuccinimide takes place in the methyl group adjacent to the carbonyl group rather than in the allyl position. No complete description of this work has appeared, however. A number of other compounds which could react at two such positions as these have been brominated preferentially in the allyl position; see ref. (6).

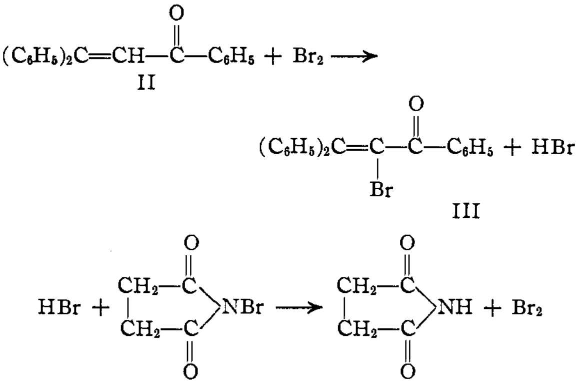
(8) Evidence has been presented that a possibly related addition of bromine by N-bromoacetamide to certain phenyl substituted olefinic compounds proceeds by a free radical chain mechanism; see Buckles, THIS JOURNAL, **71**, 1157 (1949).

fore, unless it is assumed that the liberation of free bromine from N-bromosuccinimide is a reversible process which can be driven to completion by bromine acceptors, it is apparently necessary to conclude that a compound such as benzalacetone participates directly in a reaction with N-bromosuccinimide which leads to dibromide formation.

In order to attempt the elucidation of the reaction mechanism, it was decided to investigate a number of other β-phenyl-α,β-unsaturated ketones in the hope of finding a compound which would give a more clean-cut reaction than did benzalacetone, and yield a mixture from which could be isolated both the bromine adduct and the product resulting from abstraction of hydrogen for the formation of succinimide. This objective has not yet been attained, but a number of observations were made which appear worthy of record, especially in view of the recent interest in other cases of bromine addition by N-bromosuccinimide.[9,10] One consideration which governed the selection of several of the ketones to be studied was the possibility that additional substituents on the double bond might alter the course of the reaction in an illuminating manner.

It was found that benzalacetophenone, like benzalacetone, reacted with N-bromosuccinimide in the presence of benzoyl peroxide, but not in its absence, to give the corresponding dibromide and succinimide in yields based on N-bromosuccinimide of 57 and 65%, respectively. The succinimide which separated was again accompanied by a red-brown resin. Repeated efforts were made to separate pure products from this material, but without success. Analysis showed it to contain both nitrogen and bromine, hydrolysis yielded succinic acid, and oxidation of one sample with sodium dichromate and sulfuric acid yielded a small amount of a water-insoluble halogen-containing acid, but the isolation of this product could not be repeated when subsequently attempted on a larger scale. A careful examination of the carbon tetrachloride-soluble fraction of the reaction mixture revealed the presence of considerable amounts of unchanged benzalacetophenone, as well as the dibromide, but no other pure substance could be isolated. The results of the experiments with benzalacetophenone therefore paralleled those obtained with benzalacetone.

Three other α,β-unsaturated ketones in which the double bond carried additional phenyl groups were subjected to the action of N-bromosuccinimide. One of these, β-phenylbenzalacetophenone (II), reacted with N-bromosuccinimide, even in the absence of added peroxides, to give α-bromo-β-phenylbenzalacetophenone (III) and succinimide in yields of 68 and 69%, respectively. This substitution reaction might be explained by means of the type of chain mechanism which has been suggested for other brominations with N-bromosuccinimide.[6] However, the α-bromo derivative III, not the dibromide, is also obtained when this ketone is treated with bromine in chloroform solutions maintained at the reflux temperature[11]; the dibromide is not known. The same products might therefore result from an alternative process which could be initiated by a trace of bromine formed by the decomposition of N-bromosuccinimide


$$(C_6H_5)_2C{=}CH{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}C_6H_5 + Br_2 \longrightarrow (C_6H_5)_2C{=}\underset{\displaystyle Br}{\underset{|}{C}}{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}C_6H_5 + HBr$$
II

III

Although in this case a trace of bromine was actually observed above the reaction mixture, it did not appear until the reaction was nearly finished, and cannot be regarded as important evidence in favor of the above mechanism. It is perhaps noteworthy, however, that only β-phenylbenzalacetophenone yielded an α-bromo-α,β-unsaturated ketone; no products of this kind could be discovered from benzalacetone and benzalacetophenone, the dibromides of which are stable.

The result was quite different when α-phenylbenzalacetophenone (benzaldesoxybenzoin) was used. With this ketone most of the N-bromosuccinimide was recovered unchanged after a heating period of forty-eight hours in the presence of 7 mole per cent. of benzoyl peroxide, although the compound reacts with bromine to give a dibromide.[12] However, only a small portion of the original ketone was recovered, and in its place a 62% yield of its geometrical isomer, the so-called isobenzaldesoxybenzoin, was isolated. This isomerization required the presence of both N-bromosuccinimide and benzoyl peroxide; neither reagent alone in the amount previously used accomplished it.[13] The interconversion of these isomers had previously been achieved by heating in the presence of iodine or hydrogen chloride.[12] The effect of N-bromosuccinimide upon α,β-diphenylbenzalacetophenone was also examined, but reaction did not occur at an appreciable rate even in the presence of benzoyl peroxide, and both the

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(9) Buchman and Howton, THIS JOURNAL, **70**, 2517, 3510 (1948); Howton, *ibid.*, **69**, 2060 (1947).

(10) English and Gregory, *ibid.*, **71**, 1115 (1949).

(11) Barré and Kohler, *ibid.*, **50**, 2036 (1928).

(12) Stobbe and Niedenzu, *Ber.*, **34**, 3897 (1901).

(13) A similar isomerization of *cis*-stilbene by N-bromoacetamide was observed by Buckles, ref. (8), and Kharasch, Mansfield and Mayo, THIS JOURNAL, **59**, 1155 (1937), have isomerized *cis*-stilbene by use of hydrogen bromide in combination with benzoyl peroxide.

ketone and the N-bromosuccinimide were recovered unchanged after forty-eight hours. The recovery of most of the N-bromosuccinimide after a forty-eight hour reaction period, which was the result in the case of these two α-phenyl-α,β-unsaturated ketones, was also observed in a subsequent experiment with α-bromobenzalacetophenone, so that α-substitution can be stated to have been effective in preventing reaction in the three cases so far examined. Whether this was due to the blocking of some such process as hydrogen bromide elimination, or to changes in reactivity at the double bond, is not clear, however.

The study of the reactions of N-bromosuccinimide with α,β-unsaturated ketones is being continued.

Experimental[14]

Reactions of Unsaturated Ketones with N-Bromosuccinimide.—All experiments were conducted at the reflux temperature of the reaction mixtures in an apparatus protected from moisture by a calcium chloride tube. The carbon tetrachloride which was used as the solvent in all cases had been dried over phosphorus pentoxide and distilled. The N-bromosuccinimide was purified by the method of Ziegler, *et al.*[15] The benzoyl peroxide was of the "white label" grade supplied by the Eastman Kodak Company.

(A) **Benzalacetone.**—A mixture of 50 g. (0.34 mole) of freshly-distilled benzalacetone,[16] 57 g. (0.32 mole) of N-bromosuccinimide, 4 g. of benzoyl peroxide and 250 ml. of carbon tetrachloride was heated for eighteen hours, at the end of which time the N-bromosuccinimide had been consumed, as indicated by a negative test with acidified potassium iodide solution. The solution became red-brown in color during this period, but the vapors above the refluxing solution were colorless and did not affect starch-iodide paper. A crust of red-brown solid was formed on the sides of the flask at the surface of the liquid.

The mixture was allowed to cool and the solution was separated from the solid by decantation and filtration, then concentrated under reduced pressure until a viscous oil remained. This material was dissolved in 15 ml. of warm absolute ethanol, and the solution was stored overnight in a refrigerator. The crystals which separated were recrystallized from aqueous ethanol to yield 22.6 g. (46% based on N-bromosuccinimide) of benzalacetone dibromide, m. p. 125–126°. The identity of the product was established by the mixed melting point test and by conversion to α,β-dimorpholinobenzalacetone, m. p. 159–160°.[17]

The solvents were removed from the solution from which the benzalacetone dibromide had separated, and an attempt was made to distill the residual oil under reduced pressure. Unchanged benzalacetone was distilled from the mixture, but after it had been removed, the residue decomposed when the distillation of higher boiling components was attempted.

The solids (33.5 g.) which separated during the heating period were extracted twice with 100-ml. portions of boiling water. Evaporation of the aqueous extracts, and recrystallization of the residue from ethanol yielded 21.5 g. (67.5%) of succinimide, m. p. 125°. There remained after the water extraction a red-brown sticky substance which hardened when it was cooled and dried. Attempts at purification were unsuccessful; the substance remained amorphous and continued to melt over the range 183–205°.

(B) **Benzalacetophenone.**—A mixture prepared from 62.4 g. (0.3 mole) of benzalacetophenone,[18] 53.4 g. (0.3 mole) of N-bromosuccinimide, 5.0 g. of benzoyl peroxide and 200 ml. of carbon tetrachloride was heated for forty-eight hours. This heating period was found to be sufficient to consume all but a trace of the N-bromosuccinimide. The appearance of the reaction mixture was similar to that obtained with benzalacetone.

After the solution had been separated from the solids by decantation and filtration, it was concentrated at reduced pressure to a thick red oil. This oil was dissolved in 50 ml. of warm absolute ethanol, and the solution was stored in a refrigerator overnight. The crystals which separated were purified by crystallization from ethanol to give 23.5 g. of benzalacetophenone dibromide, m. p. 159–160°. This quantity of dibromide, together with an additional 8 g. isolated from the original insoluble fraction (see below) comprised a yield of 57% based on N-bromosuccinimide. A mixed melting point test demonstrated the identity of the product with an authentic sample of benzalacetophenone dibromide.

An attempt was made to separate additional products from the alcoholic filtrate after the recovery of the dibromide. Concentration of the solution under reduced pressure left a thick red oil which was extracted repeatedly with boiling petroleum ether (b. p. 65–110°). Concentration of the petroleum ether extracts and crystallization of the residue from ethanol yielded 25 g. of unchanged benzalacetophenone. The residue which remained undissolved by petroleum ether extraction was a black tarry mass (20 g.) from which no additional pure product could be separated.

The solid which separated from the carbon tetrachloride solution during the reaction period was extracted with 250 ml. of boiling water in two portions. Concentration of the aqueous extracts left a residue which yielded 19.5 g. (a 65% yield) of succinimide, m. p. 124°, following crystallization from ethanol. The water-insoluble residue from the extraction was extracted with two 100-ml. portions of boiling benzene. Concentration of the benzene extracts and recrystallization of the residue from ethanol yielded an additional 8 g. of benzalacetophenone dibromide.

There remained after the water and benzene extractions 13 g. of a brown amorphous solid which softened at about 240°, but failed to melt completely at 350°. Efforts to separate pure products from this material by crystallization from a wide variety of solvents were unsuccessful. It was found to be soluble in hot ethanol, but separated upon cooling the solution without significant change in properties. A sample reprecipitated in this manner was found to contain both nitrogen and bromine. Oxidation of a 3-g. sample with sodium dichromate and sulfuric acid[19] yielded a minute quantity of a water-insoluble halogen-containing acid melting at 141–150° in the partly-purified condition. An attempt to repeat this experiment on a larger scale with material from another batch failed to yield any water-insoluble acid.

A 3-g. sample of the amorphous solid was hydrolyzed by suspending it in 25 ml. of 20% aqueous sodium hydroxide solution and boiling the mixture under reflux for two hours. The undissolved solids, now dark and tarry, were removed by filtration. Acidification of the filtrate with concentrated hydrochloric acid precipitated 0.4 g. of an acid, m. p. 189°, after crystallization from water. The melting point of a mixture of this product with an authentic sample of succinic acid was not depressed.

(C) **β-Phenylbenzalacetophenone.**—A solution of 5 g. of β-phenylbenzalacetophenone,[20] m. p. 86–87°, in 25 ml.

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[14] Melting points are corrected.

[15] Ziegler, *et al.*, *Ann.*, **551**, 89 (1942).

[16] Drake and Allen, "Organic Syntheses," Coll. Vol. I, 77 (1941). An old sample of benzalacetone which had not been purified before use reacted with N-bromosuccinimide in the absence of benzoyl peroxide.

[17] Cromwell, THIS JOURNAL, **62**, 3470 (1940).

[18] Kohler and Chadwell, "Organic Syntheses," Coll. Vol. I, 78 (1941).

[19] The procedure was taken from Shriner and Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 3rd edition, 1948, p. 140.

[20] Prepared according to the method of Clemo, Raper and Robeson, *J. Chem. Soc.*, 431 (1939), from β-hydroxyl-β,β-diphenylpropiophenone, which was obtained from phenylmagnesium bromide and ethyl malonate as described by Vorlander, Osterburg and Meye, *Ber.*, **56**, 1136 (1923).

of dry carbon tetrachloride was heated for forty-eight hours at the reflux temperature with 3.1 g. of N-bromosuccinimide. Near the end of the reaction period a faint red color was noticeable in the vapors above the mixture and the starch-iodide test also indicated the presence of bromine.

The suspended solid consisted almost entirely of succinimide, 1.2 g. (a 69% yield) of which was obtained in the pure state after crystallization from ethanol. Concentration of the filtered reaction mixture at reduced pressure and crystallization of the solid residue from ethanol yielded 4.4 g. (a 68% yield) of α-bromo-β-phenylbenzalacetophenone, m. p. 88-89° in a preheated bath, which was shown to be identical with an authentic sample[11] by the mixed melting point test.

(D) **α-Phenylbenzalacetophenone (Benzaldesoxybenzoin).**—A mixture containing 5 g. of benzaldesoxybenzoin,[21] m. p. 100-101°, 3.1 g. of N-bromosuccinimide, 0.3 g. of benzoyl peroxide and 30 ml. of carbon tetrachloride was heated for forty-eight hours. The solution had developed a red-brown color during this period.

The undissolved solids were removed by filtration, washed with carbon tetrachloride, then extracted with two 15-ml. portions of boiling water. The aqueous extract was cooled quickly, and after it had been allowed to stand in a refrigerator for two hours, 2 g. (64%) of unchanged N-bromosuccinimide was removed by filtration. Concentration of the filtrate to dryness left 0.3 g. of succinimide.

The filtrate from the reaction mixture was diluted with 100 ml. of additional carbon tetrachloride and passed through a column of alumina (15 × 3 cm.). The column then was eluted with 25-ml. portions of solvent, using in turn 8 portions of carbon tetrachloride, 12 portions of a mixture of carbon tetrachloride and ether (1:1 by volume) and 8 portions of ether. From the first 12 eluate fractions there was obtained, following evaporation of the solvents, a mixture of benzaldesoxybenzoin and isobenzaldesoxybenzoin which was separated by fractional crystallization from methanol. The yield of isobenzaldesoxybenzoin, m. p. 88-89°,[12] was 3.1 g., representing a 62% conversion of benzaldesoxybenzoin, the recovery of which was 0.98 g. (20%), m. p. 100-101°. The identity of the isobenzaldesoxybenzoin was demonstrated by its conversion to benzaldesoxybenzoin dibromide by addition of bromine.[12] The dibromide prepared both from the isomerized compound and from the original benzaldesoxybenzoin melted at 134-135° and the melting point of a mixture of the products from the two sources was not depressed. Upon evaporation of eluate fractions 16 to 25 inclusive, there was obtained 20 mg. of a compound melting at 190-192° after recrystallization. There was too little of the purified sample to make possible its identification.

From experiments in which benzaldesoxybenzoin was heated in carbon tetrachloride solution with N-bromosuccinimide alone and with benzoyl peroxide alone, using the same proportions as in the experiment above, the higher-melting form (m. p. 100-101°) was recovered unchanged.

(E) **α,β-Diphenylbenzalacetophenone.**—A mixture of 3.6 g. of α,β-diphenylbenzalacetophenone,[11] m. p. 148°, 1.8 g. of N-bromosuccinimide, 0.1 g. of benzoyl peroxide and 15 ml. of carbon tetrachloride was heated at the reflux temperature for forty-eight hours. The mixture turned brown during this period. By filtering the solution and crystallizing the recovered solid from water, 1.6 g. (89%) of unchanged N-bromosuccinimide was obtained. Concentration of the filtrate left a residue from which 3.1 g. (86%) of unchanged α,β-diphenylbenzalacetophenone was recovered following crystallization from methanol.

(F) **α-Bromobenzalacetophenone.**—A mixture containing 2.9 g. of α-bromobenzalacetophenone,[22] 1.8 g. of N-bromosuccinimide, 15 ml. of carbon tetrachloride and 0.1 g. of benzoyl peroxide was heated for forty-eight hours. By filtration of the cooled mixture there was recovered 1.1 g. (61%) of unchanged N-bromosuccinimide. The reaction mixture was not further examined.

Summary

The action of N-bromosuccinimide on six β-phenyl-α,β-unsaturated ketones in boiling carbon tetrachloride solution has been examined. Of the ketones studied, the three which were unsubstituted in the α-position, benzalacetone, benzalacetophenone and β-phenylbenzalacetophenone, reacted to convert most of the N-bromosuccinimide used into succinimide, the former two compounds reacting only with the aid of catalysis by benzoyl peroxide. The chief products obtained from these ketones were benzalacetone dibromide, benzalacetophenone dibromide and α-bromo-β-phenylbenzalacetophenone, respectively. Three additional ketones of this type which carried α-substituents, α-phenylbenzalacetophenone (benzaldesoxybenzoin), α,β-diphenylbenzalacetophenone and α-bromobenzalacetophenone, did not consume N-bromosuccinimide at an appreciable rate even in the presence of benzoyl peroxide. α-Phenylbenzalacetophenone, however, was converted into its geometrical isomer by treatment with N-bromosuccinimide and benzoyl peroxide.

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[21] Kohler and Nygaard, THIS JOURNAL, **52**, 4128 (1930).

[22] Cromwell, Cram and Harris, "Organic Syntheses," **27**, 10 (1947).