iodide, it was hoped that in this way these substances might be reduced to β-amino ketones. Unfortunately, only complicated condensation products containing neither halogen nor nitrogen resulted from such experiments.

Reduction of α-Bromo-β-piperidinobenzalacetophenone.[7]—A mixture of 0.1 g. of platinum oxide catalyst and 1 g. (0.0027 mole) of α-bromo-β-piperidinobenzalacetophenone[7] dissolved in 10 ml. of dry benzene was reduced under 1.2 atmospheres of hydrogen at about 28°. The theoretical amount of hydrogen was taken up in about five minutes at the end of which time the reaction mixture was filtered. The filtrate was concentrated and petroleum ether was added and an oil came out which defied attempts at crystallization from either benzene or ether. However, when taken up in alcohol and water a brown solid came out which upon two recrystallizations from alcohol and water gave 0.5 g. (0.00223 mole) of product, m. p. 74–76°. This compound gave a red-violet coloration with ferric chloride and a mixed melting point experiment with dibenzoylmethane gave m. p. 74–76°. The yield amounted to 82.7%.

Addition of Hydrogen Bromide to α-Bromobenzalacetophenone.—α-Bromobenzalacetophenone[2] (4 g.) was dissolved in 15 ml. of ether and dry hydrogen bromide passed into the solution at −5° for twenty minutes. After standing for two hours the white precipitate (5.55 g.) was removed, m. p. 156–158°. A mixture of this product with α,β-di-bromobenzylacetophenone prepared from benzalacetophenone melted at 156–158°.

Addition of Hydrogen Bromide to α-Piperidinobenzalacetophenone.[5]—Dry hydrogen bromide was passed into a dry benzene solution of α-piperidinobenzalacetophenone at 0°. The solution first turned colorless and then red again, indicating decomposition of the addition products. The only product that could be obtained from this reaction was piperidine hydrobromide, which precipitated from the original reaction mixture on standing for two days in the ice-chest.

Summary

1. Tetrahydroisoquinoline, for which a good method of preparation is described, has been found to react with α,β-di-bromobenzylacetone and α-bromobenzalacetone in a manner analogous to that of other strongly basic, heterocyclic, secondary amines.

2. The reactions of tetrahydroisoquinoline, tetrahydroquinoline, morpholine, and piperidine with α-bromo-β-tetrahydroisoquinolinobenzylacetone are discussed.

3. The reactions of tetrahydroisoquinoline with α-bromo-β-piperidinobenzylacetone and with α-bromo-β-morpholinobenzylacetone were investigated.

4. The effects of solvent medium and the relative basic strengths of the secondary amines used in these reactions are discussed with regard to the course of these reactions.

5. Further information is presented with regard to the structure of the addition products from the reaction of α-bromo-α,β-unsaturated ketones and secondary amines. Mechanisms for these reactions have been outlined.

LINCOLN, NEBRASKA RECEIVED SEPTEMBER 29, 1942

[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

α,β-Unsaturated Aminoketones. VII.[1] Reaction of Piperidine and N-Methylbenzylamine with Bromine Derivatives of Benzalacetone and Benzalacetophenone

BY NORMAN H. CROMWELL AND IVAN H. WITT

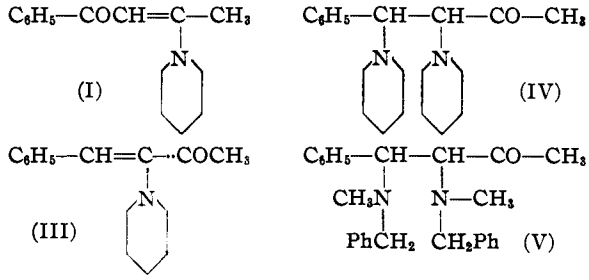
In the first paper[2] in this series, it was reported that diethylamine reacted with α,β-dibromobenzylacetophenone to give only α-N-diethylaminobenzalacetophenone. Subsequent investigations[3] have shown that strong heterocyclic secondary amines such as morpholine, piperidine, pyrrolidine, etc., not only give the unsaturated amino ketone but also an α,β-diamino ketone in these reactions. Also these bases were found to add to the corresponding α-bromo-α,β-unsaturated ketone to give quite active bromo amino ketones. It has not been possible to isolate these addition products using diethylamine.

The present study was carried out in order to check this difference in reaction of open-chain secondary amines as compared with heterocyclic secondary amines.

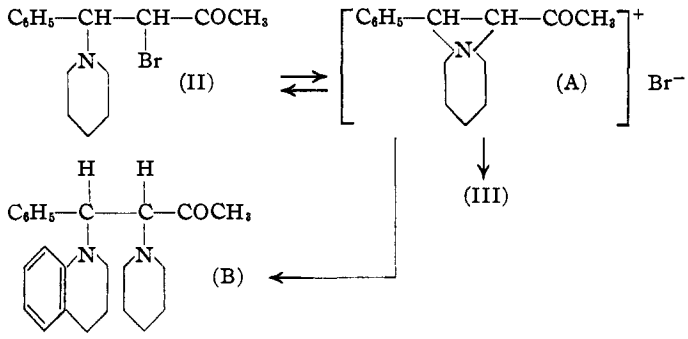
For comparative purposes, 1-phenyl-3-piperidinobutene-2-one-1 (I) was prepared in the usual way from benzoylacetone. Piperidine was found to add readily to α-bromobenzalacetone to give an addition product whose structure has been assigned[1] as α-bromo-β-piperidinobenzylacetone (II). This addition product, which was quite unstable, reacted with sodium ethoxide to give

(1) For paper VI of this series, see Cromwell and Cram, THIS JOURNAL, **65**, 301 (1943).
(2) Cromwell, *ibid.*, **62**, 1672 (1940).
(3) Cromwell, *ibid.*, **62**, 2897, 3470 (1940); **63**, 837, 2984 (1941).

α-piperidinobenzalacetone (III). α,β-Dibromobenzylacetone reacted with piperidine to give α,β-dipiperidinobenzylacetone (IV) which has been reported by Moureu.[4]



This bromo amino ketone (II) could be dissolved in water only by long shaking to give a solution that conducted the electric current.

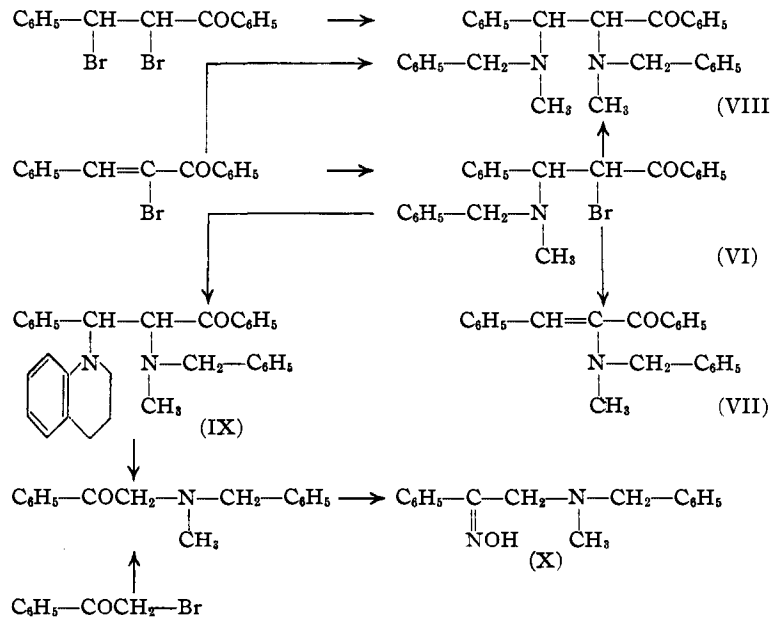


Solution is probably due to the slow rearrangement[1] of the bromo amino ketone (II) into the isomeric quaternary ammonium salt, (A), which would be expected to be water soluble.

These water solutions gave an immediate precipitate of silver bromide on adding silver nitrate, and reacted with sodium hydroxide to precipitate the unsaturated amino ketone (III). This bromo amino ketone (II) gave only a very slow reaction with silver nitrate when dissolved in dilute nitric acid solutions. The presence of the nitric acid prevented the rearrangement to the quaternary ammonium salt (A). When the water solution of (A) was shaken for several hours at room temperature with tetrahydroquinoline, α-piperidino-β-tetrahydroquinolinobenzylacetone[1] (B) resulted.

N-Methylbenzylamine was found to react readily at room temperature with either α,β-dibromobenzylacetone or α-bromobenzalacetone to give only α,β-di-N-methylbenzylaminobenzylacetone (V). Undoubtedly some of the corresponding α-amino-α,β-unsaturated ketone was formed in both of these reactions, but because of its probable low melting point it could not be isolated as a pure compound.

N-Methylbenzylamine added readily at low temperatures to α-bromobenzalacetophenone to give a comparatively stable product whose structure is assigned[1] as α-bromo-β-N-methylbenzylaminobenzylacetophenone (VI). This substance reacted with sodium ethoxide to give the bright-red, α-N-methylbenzylaminobenzalacetophenone (VII). The addition product (VI) reacted with excess N-methylbenzylamine to give mainly (VII) and small amounts of the pale yellow α,β-di-N-methylbenzylaminobenzylacetophenone (VIII). The diamino ketone (VIII) was also obtained directly from the unsaturated bromo ketone, and in smaller amounts from α,β-dibromobenzylacetophenone. The main product from the reaction of the dibromo ketone with N-methylbenzylamine was a substance $C_{31}H_{30}N_2$ whose structure must be established by a difficult synthesis that has not yet been realized.



The bromo amino ketone (VI) reacted with tetrahydroquinoline to give a good yield of α-N-methylbenzylamino-β-tetrahydroquinolino-

(4) Moureu, *Ann. chim.*, [10] **14**, 314 (1930).

benzylacetophenone (IX), whose structure was established by hydrolysis to ω-N-methylbenzylaminoacetophenone, isolated as its oxime (X). This substance was synthesized starting with ω-bromoacetophenone.

These reactions probably proceed by the mechanism previously outlined.[1]

Several investigations involving studies of the bromo amino ketones and the use of primary amines in these reactions are to be reported soon.

Experimental[5]

1-Phenyl-3-piperidinobutene-2-one-1.—A mixture of benzoylacetone (14.2 g., one equiv.), piperidine (14.9 g., two equiv.), and one drop of conc. hydrochloric acid was boiled under reflux for eight hours and then allowed to stand at room temperature for ten hours. The dark red solution was dissolved in ether and washed completely with water. Evaporation of the ether gave white crystals which on recrystallization from benzene and petroleum ether gave white cubes (2.0 g.), m. p. 97–98°.

Anal. Calcd. for $C_{15}H_{19}NO$: C, 78.56; H, 8.36. Found: C, 78.81; H, 8.27.

This compound was soluble in dilute hydrochloric acid, but on standing these solutions gave an almost quantitative precipitation of benzoylacetone.

A similar experiment was attempted to prepare β-piperidinobenzalacetophenone from dibenzoylmethane. This condensation was not realized.

α-Bromo-β-piperidinobenzylacetone.—In 100 ml. of a one–four ether–petroleum ether (b. p. 40°) mixture was dissolved 51 g. (0.226 mole) of α-bromobenzalacetone and the solution cooled to −30°. A cooled mixture of 19 g. (0.226 mole) of piperidine in 50 ml. of one-one ether–petroleum ether solution was added at once and the mixture stirred mechanically for two hours. The white precipitate was filtered and washed with cold petroleum ether, wt. 47 g., m. p. 80–82°. This product was quite soluble in dry benzene.

Anal. Calcd. for $C_{15}H_{20}NOBr$: C, 58.05; H, 6.50. Found: C, 57.97; H, 6.67.

When pure, this bromo amino ketone could be kept *in vacuo*, at low temperatures in the dark for about a week. After shaking 1.0 g. of this substance with 50 ml. of water for two hours, a clear colorless solution was obtained which was quite conductive of the electric current. This solution gave an immediate precipitate of silver bromide on adding silver nitrate. Such water solutions also reacted with dilute sodium hydroxide to precipitate α-piperidinobenzalacetone, m. p. 56–58°, for which another preparation is described below.

If this bromo amino ketone (II) was dissolved in dilute nitric acid, such solutions gave no immediate precipitate of silver bromide on adding silver nitrate, but reacted only after heating or on standing for several hours.

(5) All m. p. are corrected and determined by placing sample in bath 10° below m. p. and heating at the rate of 3° per minute. Micro-Dumas analyses for nitrogen and semi-micro carbon-hydrogen analyses by the Analytical Laboratory, Department of Chemistry, University of Nebraska, under the supervision of H. Armin Pagel

α-Piperidinobenzalacetone.—Freshly prepared α-bromo-β-piperidinobenzylacetone (9.0 g.) was added to a cool solution of sodium ethoxide (1.0 g. sodium in 22 ml. of ethanol). The mixture was heated under reflux for fifteen minutes and then cooled. Addition of water precipitated a brown oil which was crystallized from 95% alcohol to give light yellow crystals (2.5 g.), m. p. 56–58°.

Anal. Calcd. for $C_{15}H_{19}NO$: C, 78.56; H, 8.36. Found: C, 78.63: H, 8.36.

This product was readily hydrolyzed by boiling with dilute sulfuric acid to give benzyl methyl diketone which was identified by preparation of the osazone,[6] m. p. 170–171°.

α-Piperidino-β-tetrahydroquinolinobenzylacetone.[1]—α-Bromo-β-piperidinobenzylacetone (1.27 g.) was dissolved in 50 ml. of water and 1.0 ml. of alcohol by shaking for five hours. To this clear solution was added 1.1 g. (two equiv.) of tetrahydroquinoline and the mixture shaken at room temperature for twenty hours. The crude product was removed and recrystallized from alcohol and chloroform to give 0.90 g. of white crystals, m. p. 126–127°. This product was identical with a sample of α-piperidino-β-tetrahydroquinolinobenzylacetone that has been prepared previously by another method.[1]

α,β-Di-piperidinobenzylacetone.—To a suspension of 30 g. (one equiv.) of α,β-dibromobenzylacetone in 120 ml. of absolute alcohol was added 33.3 g. (four equiv.) of piperidine. The dibromide dissolved and heat was evolved. After standing at room temperature for twelve hours the solvent was evaporated and the residue extracted with ether. The ether solution was washed several times with water and the diamino ketone extracted with dilute sulfuric acid. Neutralization of the acid extract gave a tan precipitate which after several recrystallizations from alcohol gave 5.6 g. of white crystals, m. p. 121–122°.[4]

Anal. Calcd. for $C_{20}H_{30}N_2O$: C, 76.37; H, 9.62. Found: C, 76.46: H, 9.67.

α,β-Di-N-methylbenzylaminobenzylacetone.—This diamino ketone was prepared in two ways.

(1) With **α-Bromobenzalacetone** (10 g., one equiv.) in a mixture of ether and petroleum ether was mixed 10.86 g. (two equiv.) of N-methylbenzylamine at −5°. The solution was allowed to come to room temperature and stand for two days. Although an attempt was made to isolate the desired α-N-methylbenzylaminobenzalacetone, this was not accomplished since this substance seemed to be an oil at ordinary temperatures. The only product isolated was the diamino ketone, which on recrystallization from 95% alcohol gave 2.5 g. of white crystals, m. p. 106–108°.

Anal. Calcd. for $C_{26}H_{30}N_2O$: C, 80.78; H, 7.83; N, 7.25. Found: C, 80.44; H, 7.93; N, 7.33.

(2) From **α,β-dibromobenzylacetone** (10.0 g., one equiv.) and 16.0 g.(four equiv.) of N-methylbenzylamine in 40 ml. of absolute alcohol, 3.5 g. of this diamino ketone was obtained in the usual way, m. p. 106–108°.

α-Bromo-β-N-methylbenzylaminobenzylacetophenone.—α-Bromobenzalacetophenone (10 g., one equiv.) was dissolved in a three–five ether–petroleum ether mixture and cooled to 0°. To this solution was added 4.22 g. (one equiv.) of N-methylbenzylamine. After standing for four

(6) Cromwell, THIS JOURNAL, **62**, 3472 (1940).

hours at 0° the white product was removed and recrystallized from benzene and petroleum ether to give 7.0 g. of white, granular crystals, m. p. 109–110°.

Anal. Calcd. for $C_{23}H_{22}NOBr$: C, 67.63; H, 5.43. Found: C, 67.48; H, 5.70.

This was the most stable of any of the bromo amino ketones yet prepared in these investigations. The product was soluble in alcohol and in ethyl acetate. Alcoholic solutions gave an immediate reaction with silver nitrate and slowly released iodine when acidic, alcoholic potassium iodide solution was added.

α-N-Methylbenzylaminobenzalacetophenone.—α-Bromo-β-N-methylbenzylaminobenzylacetophenone (2.5 g.) was treated with sodium ethoxide in the usual way to give a red product which was recrystallized from absolute alcohol to give 2.0 g. of bright, orange-red crystals, m. p. 73–75°.

Anal. Calcd. for $C_{23}H_{21}NO$: C, 84.35; H, 6.47; N, 4.28. Found: C, 84.42; H, 6.62; N, 4.10.

This product was soluble in 5% hydrochloric acid, but these solutions clouded to precipitate benzyl phenyl diketone.

α,β-Di-N-methylbenzylaminobenzylacetophenone.—This compound was obtained in three different ways.

(1) To 15 ml. of moist ether was added 5 g. (one equiv.) of α-bromobenzalacetophenone and 6.33 g. (three equiv.) of N-methylbenzylamine. After standing at room temperature for three days the precipitate, N-methylbenzylamine hydrobromide, was filtered off and the ether solution washed with water. By fractional crystallization, this reaction mixture gave 2.0 g. of the red crystalline α-N-methylbenzylaminobenzalacetophenone and 1.0 g. of a pale yellow crystalline product (recrystallized from benzene and petroleum ether), m. p. 142–144°.

Anal. Calcd. for $C_{31}H_{32}N_2O$: C, 82.99; H, 7.20; N, 6.25. Found: C, 82.75; H, 7.00; N, 6.37.

This diamino ketone was unchanged after boiling in absolute alcohol with a few drops of N-methylbenzylamine and 0.1 g. of N-methylbenzylamine hydrobromide for one hour.

(2) α-Bromo-β-N-methylbenzylaminobenzylacetophenone (4.0 g., one equiv.) was dissolved in a mixture of 25 ml. of dry ether and 10 ml. of dry benzene and treated with 2.4 g. (two equiv.) of N-methylbenzylamine. Since the reaction appeared to be going slowly the mixture was heated under reflux for ten minutes until all of the starting material had dissolved. After standing at room temperature for five hours the reaction mixture was cooled for two days in the ice-chest. From this was obtained 1.0 g. of α-N-methylbenzylaminobenzalacetophenone, m. p. 72–74° and 0.5 g. of α,β-di-N-methylbenzylaminobenzylacetophenone, m. p. 141–143°.

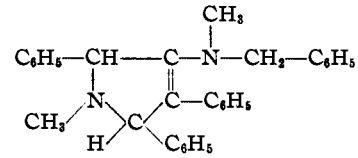
Evaporation of the filtrate also gave a small amount of another light yellow crystalline substance (0.1 g.), m. p. 102–103°. A mixture of this product with the diamino ketone, m. p. 141–143°, melted from 102 to 124°, indicating that these two products are possibly the two racemic mixtures.

Anal. Calcd. for $C_{31}H_{32}N_2O$: C, 82.99; H, 7.20; N, 6.25. Found: C, 83.32; H, 7.35; N, 6.49.

(3) The reaction of N-methylbenzylamine with α,β-dibromobenzylacetophenone was carried out in the usual way, but the reaction took an unexpected course. N-Methylbenzylamine (13.3 g., four equiv.) was added to a suspension of 10 g. (one equiv.) of the dibromo ketone in 20 ml. of absolute alcohol. After standing for twenty-four hours the solvent was evaporated and the free bases extracted by ether from the insoluble N-methylbenzylamine hydrobromide. The ether extract was washed with water, dried and evaporated to give a yellow oil which was crystallized from 95% alcohol to give 5.5 g. of a light-yellow, crystalline product, m. p. 94–106°. Continued recrystallizations of this product from 95% alcohol gave two products. Only 0.5 g. of α,β-di-N-methylbenzylaminobenzylacetophenone was obtained, m. p. 141–142°. The main product from this reaction was a white crystalline substance, 2.6 g., m. p. 118–120°.

Anal. Calcd. for $C_{31}H_{30}N_2$: C, 86.46; H, 7.03; N, 6.51; mol. wt., 430. Found: C, 86.57; H, 6.88; N, 6.81; mol. wt., 424 (Rast).

The molecular formula of this substance differs from that of the diamino ketone by one molecule of water. This compound may be



but it has not been possible to cyclize the diamino ketone by usual methods to give this substance. A long and difficult synthesis of this substance seems necessary. Compound $C_{31}H_{30}N_2$ is soluble in 6 *N* hydrochloric acid and such solutions seem to be stable to heat.

α-N-Methylbenzylamino-β-tetrahydroquinolinobenzylacetophenone.—Tetrahydroquinoline (1.90 g., two equiv.) was added to a suspension of 2.9 g. (one equiv.) of α-bromo-β-N-methylbenzylaminobenzylacetophenone in 5 ml. of absolute alcohol. All of the starting material dissolved in three hours. After standing at room temperature for two more hours, the clear green solution was cooled in the ice-chest for two days. The precipitated pale-green product was water washed and recrystallized from benzene and petroleum ether, 1.75 g., m. p. 150–153°.

Anal. Calcd. for $C_{32}H_{32}N_2O$: C, 83.44; H, 7.01; N, 6.08. Found: C, 83.80; H, 6.92; N, 5.85.

This diamino ketone is only slightly soluble in dilute mineral acids. **Hydrolysis** of this product in the usual way gave a 30% yield of ω-N-methylbenzylaminoacetophenone, isolated as the oxime, m. p. 96–97°. This substance was synthesized in the usual way from the free base which was prepared from ω-bromoacetophenone.

Anal. Calcd. for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.01. Found: C, 75.69; H, 6.87; N, 10.84.

Summary

1. Piperidine has been found to react with bromine derivatives of benzalacetone and with benzoylacetone in a manner analogous to that of morpholine.

2. N-Methylbenzylamine, an open chain type of secondary amine, has been found to react with bromine derivatives of benzalacetone and benzalacetophenone in a manner similar to that of heterocyclic secondary amines.

LINCOLN, NEBRASKA RECEIVED OCTOBER 5, 1942

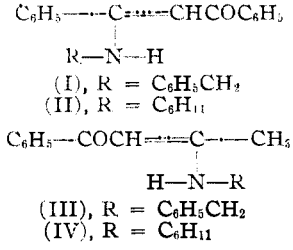
[CONTRIBUTION FROM AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

α,β-Unsaturated Aminoketones. VIII.[1] Reaction of Primary Amines with 1,3-Diketones and Bromine Derivatives of Benzalacetophenone. Ethylene Imines

BY NORMAN H. CROMWELL, ROBERT D. BABSON[2] AND CHARLES E. HARRIS[3]

All previous investigations in this series have been concerned with the reactions of secondary amines with bromine derivatives of α,β-unsaturated ketones and with 1,3-diketones. It was of interest to study these same reactions with primary amines.

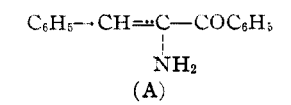
Benzylamine and cyclohexylamine were found to condense readily with dibenzoylmethane to give, respectively, (I) and (II) and with benzoylacetone to give, respectively, (III) and (IV). The reactions of these substances with mineral acids, as well as their absorption spectra, to be reported soon,[4] indicate them to be vinyl amines and not imines.



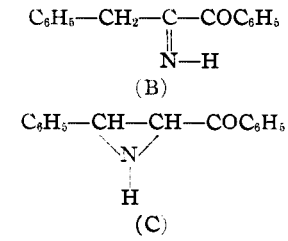
(I), R = $C_6H_5CH_2$
(II), R = C_6H_{11}

(III), R = $C_6H_5CH_2$
(IV), R = C_6H_{11}

The only previously reported reactions of bromine derivatives of α,β-unsaturated ketones with what might be considered as a primary amine are the reactions of α,β-dibromobenzylacetophenone and α-bromobenzalacetophenone with ammonia.[5] These reactions both gave an almost colorless substance whose structure has been assigned as shown by (A).

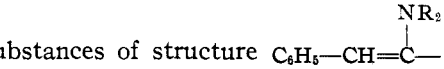


(A)



(B)

(C)

Since all substances of structure  have been found in our series of investigations to be highly colored, it seems doubtful that structure (A) is the true one for these light colored reaction products of ammonia.

In the present investigation two primary amines, benzylamine and cyclohexylamine have been found to react readily with α,β-dibromobenzylacetophenone and with α-bromobenzalacetophenone to give colorless substances which have properties that are consistent only with ethylene imine type of structures, (V) and (VI). When α-bromobenzalacetophenone was treated with one mole of benzylamine under special conditions it was possible to isolate the intermediate, β-benzylamino-α-bromo-β-phenylpropiophenone,[6] (VII). The bromo amino ketone (VII) was unstable and reacted readily in solution with itself to form the ethylene imine (V) and the hydrobromide (VIII). The substance (VIII) was also obtained by treating (V) with dry hydrogen bromide in benzene solution.[7] The dibromide (VIII) reacted with alcoholic potassium hydroxide to reform the ethylene imino ketone (V).

The bromo amino ketone (VII) reacted with tetrahydroquinoline to give the ethylene imino ketone (V). No diamino ketone could be isolated.

(1) For paper VII, see Cromwell and Witt, THIS JOURNAL, **65**, 308 (1943).

(2) Present address: Merck and Co., Inc., Rahway, N. J.

(3) Present address: E. I. du Pont de Nemours and Co., Wilmington, Del.

(4) Cromwell and Johnson, unpublished.

(5) (a) Ruhemann and Watson, *J. Chem. Soc.*, **85**, 1181 (1904); (b) Dufraisse and Moureu, *Bull. soc. chim.*, [4] **41**, 861 (1927); (c) Blatt, THIS JOURNAL, **61**, 3491 (1939).

(6) Cromwell and Cram, *ibid.*, **65**, 301 (1943).

(7) It has been shown by Weissberger, *Ber.*, **64**, 1095 (1931); **65**, 631 (1932), that ethylene imines react readily with hydrogen halides in dry benzene or in water solution to open the imino ring and form the amino halide hydrohalide.