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

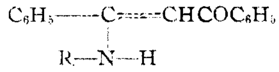
[CONTRIBUTION FROM AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

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]

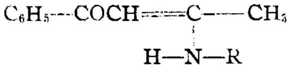
All previous investigations in this series have been concerned with the reactions of secondary amines with bromine derivatives of α,β-unsaturated ketones and with 1,3-diketones. It was of interest to study these same reactions with primary amines.

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.



$$C_6H_5—\underset{\underset{R—N—H}{|}}{C}=CHCOC_6H_5$$

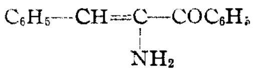
(I), R = $C_6H_5CH_2$
(II), R = C_6H_{11}



$$C_6H_5—COCH=\underset{\underset{H—N—R}{|}}{C}—CH_3$$

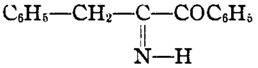
(III), R = $C_6H_5CH_2$
(IV), R = C_6H_{11}

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).



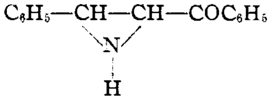
$$C_6H_5—CH=\underset{\underset{NH_2}{|}}{C}—COC_6H_5$$

(A)



$$C_6H_5—CH_2—\underset{\underset{N—H}{\|}}{C}—COC_6H_5$$

(B)



(C)

Since all substances of structure $C_6H_5—CH=\overset{NR_2}{\overset{|}{C}}—COC_6H_5$ 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.

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

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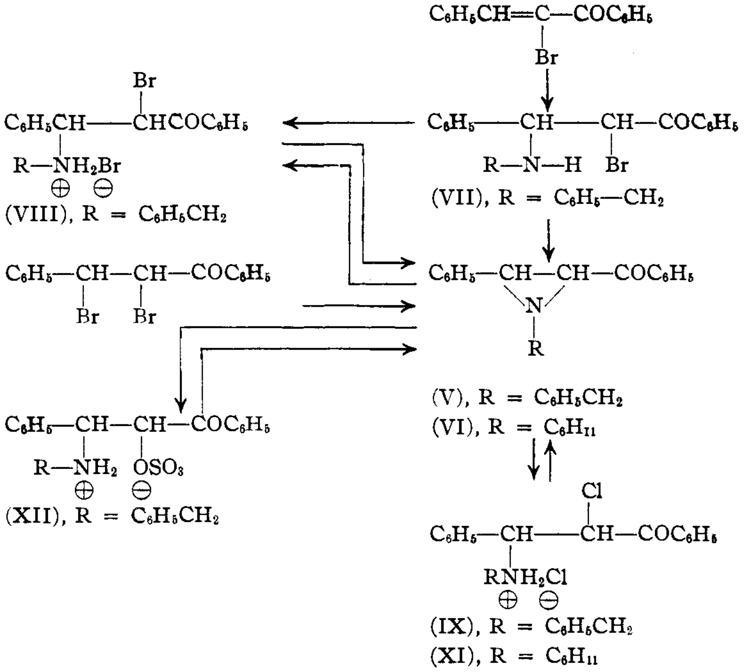
[3] Present address: E. I. du Pont de Nemours and Co., Wilmington, Del.

[4] Cromwell and Johnson, unpublished.

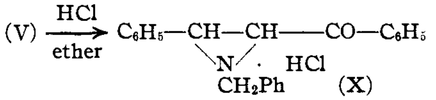
[5] (a) Ruhemann and Watson, *J. Chem. Soc.*, **85**, 1181 (1904); (b) Dufraisse and Moureu, *Bull. soc. chim.*, [4] **41**, 861 (1927); (c) Blatt, THIS JOURNAL, **61**, 3494 (1939).

[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.



Both (V) and (VI) reacted with hydrogen chloride in dry benzene or in water solution to open the imino ring and form the dihalides (IX) and (XI), respectively. Under special conditions with (V), the intermediate hydrochloride (X) was obtained.



$$(V) \xrightarrow[\text{ether}]{\text{HCl}} C_6H_5\text{—CH—CH——CO—}C_6H_5 \quad \underset{\displaystyle CH_2Ph}{\diagdown N \diagup \cdot\ HCl} \quad (X)$$

The imine (V) reacted with dilute sulfuric acid to give ring opening and form a very stable high melting substance (XII). That this substance probably exists as an inner salt of the aminosulfuric acid and not as a simple acid salt of the imine, was demonstrated by its properties. Substance (XII) was not soluble in water or alcohol but dissolved in alcoholic potassium hydroxide and in dilute sodium carbonate to give clear solutions, whence it was recovered unchanged by the addition of some other acid such as hydrochloric. Heating (XII) with potassium hydroxide regenerated (V).[8]

It seems evident that ammonia and primary amines react with α-bromo-α,β-unsaturated ketones to give first an α-bromo-β-amino ketone[6] which then closes the imino ring in the normal way by splitting out hydrogen bromide.[7,9] Blatt[5c] has found that β-methoxyaminobenzylacetophenones react with sodium ethoxide to split out methyl alcohol and form substances which probably have the ethylene imine type of structure (C) and not the vinyl amine structure (A). Dufraisse[5b] has shown that his so-called α-aminobenzalacetophenone (A) reacts with hydrochloric acid to add two moles of hydrogen chloride. It is to be noted that structures (A), (B) and (C) might all be expected to hydrolyze to form varying amounts of 1,2-diketones.

In a following paper[4] spectroscopic evidence will be presented, showing the differences in the spectra of colored α-amino-α,β-unsaturated ketones derived from secondary amines and the colorless ethylene imino ketones derived from primary amines and ammonia.

A method of preparing N-methylbenzylamine which has been used in these studies[1] is described.

Experimental[10]

N-Methylbenzylamine.—The first step in this preparation was the condensation of benzaldehyde with methylamine to give the imine. Benzaldehyde (106 g.) was treated slowly (twenty minutes) with 150 g. of a 33% aqueous solution of methylamine. Considerable heat was evolved during the mixing. This reaction solution was allowed to stand twelve hours at room temperature before adding ether and saturating the solution with salt. The ether layer was dried and evaporated. The residual oil was distilled through an efficient fractionating column to give 83 g. (70% yield) of a colorless liquid, b. p. 183–185°.[11] This product was shown to be free of benzaldehyde by testing with Tollens reagent. Benzalmethylimine (83 g.) was mixed with 100 ml. of absolute alcohol and 7 g. of Raney nickel catalyst. After shaking with hydrogen at room temperature and 45 lb./in.^{2} for two hours the reduction was practically complete. Distillation with an efficient column gave 60 g. of a colorless liquid, b. p. 184–186°,[11] D_{15}^{15} 0.9440.[12] The benzenesulfonamide was prepared,[13] m. p. 94°.

It was not possible to prepare N-methylcyclohexylamine from cyclohexanone by this series of reactions, although various conditions were employed.

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[8] See chemistry of β-aminoethylsulfuric acid, Wenker, THIS JOURNAL, **57**, 2328 (1935).

[9] (a) Taylor, *J. Chem. Soc.*, 206 (1938); (b) Darapsky, *J. prakt. Chem.*, [2] **92**, 295 (1915).

[10] All m. p.'s were obtained by placing the sample in the bath about 10° below the m. p. and heating at the rate of 3° per minute. Micro-Dumas analyses for nitrogen and semi-micro carbon-hydrogen analyses are by the Analytical Laboratory, Department of Chemistry, University of Nebraska, under supervision of H. Armin Pagel.

[11] Zaunschirm, *Ann.*, **246**, 282 (1888).

[12] Heilbron, "Dictionary of Organic Compounds," Eyre and Spottiswoode, London, 1936, Vol. 2, p. 632.

[13] Hinsberg, *Ann.*, **265**, 183 (1891).

TABLE I

PHYSICAL AND ANALYTICAL DATA FOR AMINO KETONES AND DERIVATIVES

Substance	No.	M. p., °C.	Yield, %	Formula	Percentage composition Calcd. C	Calcd. H	Found C	Found H
β-Benzylaminobenzalacetophenone	(I)	101	86	$C_{22}H_{19}NO$	84.31	6.11	84.45	6.27
β-Cyclohexylaminobenzalacetophenone	(II)	78	66	$C_{21}H_{23}NO$	82.59	7.59	82.63	7.88
1-Phenyl-3-benzylaminobutene-2-one-1	(III)	62	66	$C_{17}H_{17}NO$	81.23	6.82	80.99	6.87
1-Phenyl-3-cyclohexylaminobutene-2-one-1[c]	(IV)	54	80	$C_{16}H_{21}NO$	78.97	8.70	78.76	8.51
3-Benzoyl-2-phenyl-			68[a]					
1-benzylethylenimine	(V)	108	52[b]	$C_{22}H_{19}NO$	84.31	6.11	84.01	6.22
1-cyclohexylethylenimine	(VI)	107	50[a] 54[b]	$C_{21}H_{23}NO$	82.59	7.59	82.48	7.62
β-Benzylamino-β-phenyl-								
α-bromopropiophenone[d]	(VII)	76	19	$C_{22}H_{20}NOBr$	67.01	5.11	67.04	5.06
α-bromopropiophenone hydrobromide	(VIII)	158	50	$C_{22}H_{21}NOBr_2$	55.59	4.45	55.27	4.59
α-chloropropiophenone hydrochloride	(IX)	168	100	$C_{22}H_{21}NOCl_2$	68.40	5.45	68.42	5.52
α-sulfatopropiophenone	(XII)	218	84	$C_{22}H_{21}NO_5S$	64.23	5.14	64.41	5.42
β-Cyclohexylamino-β-phenyl-								
α-chloropropiophenone hydrochloride	(XI)	188	80	$C_{21}H_{25}NOCl_2$	66.67	6.65	66.80	6.86

[a] From α-bromobenzalacetophenone. [b] From α,β-dibromobenzylacetophenone. [c] Calcd.: N, 5.74. Found: N, 5.86. [d] Calcd.: N, 3.55. Found: N, 3.52 (Kjeldahl).

β-Benzylaminobenzalacetophenone (I)[14] **and β-Cyclohexylaminobenzalacetophenone** (II).—Dibenzoylmethane (10 g., 0.045 mole) was refluxed from five to eight hours with 0.090 mole of the corresponding primary amine and a drop of concd. hydrochloric acid. The mixtures were then cooled, mixed with ether and washed with water. Evaporation of the ether and addition of low-boiling petroleum ether precipitated the products which were purified by recrystallization from petroleum ether (b. p. 60–70°) and ether solutions to give almost colorless products (I) and (II).

Both of these products, (I) and (II), were moderately soluble in 6 *N* hydrochloric acid, but were readily hydrolyzed by such media to dibenzoylmethane.

β-Benzylaminobenzalacetophenone (I) reacted with dry hydrogen bromide in an ether–benzene solution to give a white product, m. p. 172–174°, which was recrystallized from methanol–ether solutions. This product was not soluble in boiling benzene and not very soluble in absolute alcohol. It was only slightly soluble and readily hydrolyzed in water solution.

Anal. Calcd. for $C_{22}H_{20}NOBr$: C, 67.01; H, 5.11. Found: C, 66.61; H, 5.24.

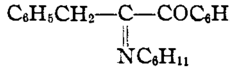
1-Phenyl-3-benzylaminobutene-2-one-1 (III) and 1-Phenyl-3-cyclohexylaminobutene-2-one-1 (IV).—Benzoylacetone[15] (10 g., 0.062 mole) was refluxed for five hours with 0.125 mole of the corresponding primary amine and one drop of concd. hydrochloric acid. These products were isolated in the usual way and purified by recrystallization from petroleum ether (b. p. 45–50°) and ether solutions to give almost colorless products, (III) and (IV).

When the cyclohexylamino ketone (IV) was mixed with benzoylacetone an oil resulted. Both of these amino ketones were soluble in dilute mineral acids but were readily hydrolyzed by such media to give benzoylacetone.

Reaction of α,β-Dibromobenzylacetophenone with Benzylamine and with Cyclohexylamine.—α,β-Dibromobenzylacetophenone (10 g., 0.028 mole) was suspended in 20 ml. of absolute alcohol and cooled to 0°. To these solutions were added 0.112 mole of the corresponding primary amine. After standing in the ice chest for a day the products were obtained by concentrating the solutions and washing the white precipitates with water to remove hydrobromide salts. These products (V) and (VI) were purified by recrystallization from alcohol or benzene and petroleum ether. Along with the 1-cyclohexyl-2-phenyl-3-benzoylethylenimine (VI) was obtained a small amount of a second white crystalline product that analysis showed to be isomeric with (VI). This product, m. p. 85–90°, mixed with (VI), m. p. 80–87°, was not soluble in dilute hydrochloric acid as was (VI). Spectrographic analysis[4] with a Coleman Universal Spectrophotometer using 0.01 *M* solutions gave the following results

Ketone	Max. abs. band in range from 3100–7000 Å., in dry benzene λ Å.	$\Sigma \times 10^{-4}$
(VI) m. p. 107°	3350	0.0745
m. p. 85–90°	3500	.1480

It is probable that this low melting product m. p. 85–90° is a mixture of (VI) and the isomeric form



$$C_6H_5CH_2—\underset{\underset{NC_6H_{11}}{\|}}{C}—COC_6H_5$$

The ethylene imino ketones (V) and (VI) did not decolorize chloroform solutions of bromine as did the corresponding β-aminobenzalacetophenones (I) and (II). Treatment of these products (V) and (VI) with hydrogen and Raney nickel catalyst at 50 lb./sq. in. gave no change.

Reaction of α-Bromobenzalacetophenone with Benzylamine and Cyclohexylamine.—(1) With Two Moles of the Amine.—To a cooled (0°) solution of α-bromobenzalacetophenone (10 g., 0.028 mole) in 30 ml. of dry ether was added 0.056 mole of the corresponding primary amine. These mixtures were allowed to come slowly to room temperature, stand for five hours, and then were cooled in the ice chest for one day. Concentration of these solutions

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[14] This product has been made previously from phenylbenzoylacetylene by Andre, *Compt. rend.*, **152**, 525 (1911).

[15] Benzoylacetone for these experiments was prepared in 70% yields by the method given in Cummings, Hopper and Wheeler, "Systematic Organic Chemistry," D. Van Nostrand Co., 1937, New York, N. Y., 3d ed., p. 97. Eastman Kodak Co. sodium methoxide was used as the condensing agent instead of sodium ethoxide.

and washing of the precipitates with water gave the white ethylene imino ketones (V) and (VI) as the only products that could be isolated. These products were identical with those, (V) and (VI), prepared from α,β-dibromobenzylacetophenone.

(2) **With One Mole of Amine.**—α-Bromobenzalacetophenone (15 g., 0.042 mole) was dissolved in a mixture of 10 ml. of dry ether and 5 ml. of petroleum ether (b. p. 35–40°), and the solution cooled to $-10°$. To this solution over a period of two hours, was slowly added 5.6 g. (0.042 mole) of benzylamine. This mixture was then allowed to stand for three hours at $-5°$. The mixture set solid. The white precipitate was washed with ether, 50% benzene–petroleum ether, 50% alcohol–water, water and finally ether, to give 4.0 g. of a white product (VII), m. p. 75–77°, dec. This bromo amino ketone (VII) gave no reaction with aqueous silver nitrate but reacted readily with the alcoholic reagent. Compound (VII) was only slightly soluble in dilute nitric acid. These dilute nitric acid solutions gave a slow reaction with aqueous silver nitrate.

When 2.0 g. of (VII) was mixed with 4 ml. of absolute alcohol and 1.35 g. of tetrahydroquinoline a slow reaction took place at room temperature which after two days gave 1.4 g. of the ethylene imino ketone (V).

Product (VII) was soluble in benzene but on standing these solutions precipitated a white product (VIII) which after recrystallization from a mixture of benzene, methyl alcohol, ethyl acetate and petroleum ether melted at 157–159°, dec. Some of the ethylene imino ketone (V) was obtained from these filtrates.

Product (VIII) was slightly water soluble and contained ionic bromine. When a sample of it was warmed with two equivalents of pyridine in methyl alcohol solution 1-benzyl-2-phenyl-3-benzoylethylenimine (V) was formed, m. p. 106–107°.

Reaction of 1-Benzyl-2-phenyl-3-benzoylethylenimine (V) with Hydrogen Bromide.—The imine (V) (2.0 g.) was dissolved in 24 ml. of dry benzene and dry hydrogen bromide passed into the cooled solution. At first a precipitate came down but soon went back into solution. Concentration of this clear, colorless solution gave a white precipitate (2.78 g.), m. p. 150–155°. This product was recrystallized from a mixture of methyl alcohol and ether, wt. 2.0 g., m. p. 157–159°, dec. A mixture of this product with (VIII) as described above melted at 154–158°. These products seemed to be identical.

Anal. Calcd. for $C_{22}H_{21}NOBr_2$: C, 55.59; H, 4.45. Found: C, 55.59; H, 4.65.

Reaction of 1-Benzyl-2-phenyl-3-benzoylethylenimine (V) and 1-Cyclohexyl-2-phenyl-3-benzoylethylenimine, (VI) with Hydrogen Chloride.—(1) With Dry Hydrogen Chloride.—The ethylene imino ketone (V) (2.0 g.) in a mixture of 20 ml. of dry benzene and 5 ml. of dry ether reacted at 0° to give a white precipitate which then redissolved. Concentration of this clear colorless solution under vacuum gave white crystals, 2.2 g., m. p. 150–160°, dec. Recrystallization of this product from a mixture of acetone, methanol and ether gave 2.0 g. of a white product (IX), m. p. 167–169°, dec. Product (IX) was only slightly soluble in water but contained ionic chlorine. When a similar experiment was carried out in dry ether alone, a hydrochloride (X) of this ethylene imino ketone (V) was obtained, m. p. 129–131°, dec.

Anal. Calcd. for $C_{22}H_{20}NOCl$: Cl^-, 10.13. Found: Cl^-, 10.18.

(2) **With dilute hydrochloric acid** (50 ml. of 6 *N*) this ethylene imino ketone (V) (3.0 g.) was heated at 85° for five hours. Very little oil was formed (this oil was shown to be a mixture of benzaldehyde and benzyl phenyl diketone). A white precipitate remained (2.94 g.). Recrystallization of this product from a mixture of methyl alcohol, ethyl acetate and dry ether gave white crystals, 2.1 g., m. p. 166–168°. A mixture of this product with (IX) as described above, melted at 166–169°, dec. These two products were identical. A similar experiment with the ethylene imino ketone (VI) gave a white product (XI), m. p. 187–189°, dec. When (IX) was dissolved in methyl alcohol and warmed with an excess of pyridine, 1-benzyl-2-phenyl-3-benzoylethylenimine (V) was formed, m. p. 105–107°.

Reaction of 1-Benzyl-2-phenyl-3-benzoylethylenimine (V) with Sulfuric Acid.—When the ethylene imino ketone (V) (2 g.) was refluxed with 40 ml. of 15% sulfuric acid for one hour a white solid (XII) formed, which was not soluble in dil. sulfuric acid, in water, nor in ether. It was recrystallized from a large amount of boiling methyl alcohol. Only small amounts of the imino ketone (V) were hydrolyzed to benzaldehyde and benzyl phenyl diketone. The main product was the aminosulfuric acid[8] (XII).

This aminosulfuric acid (XII) was not very soluble in 95% alcohol but dissolved readily in alcoholic potassium hydroxide, and in aqueous sodium carbonate. Immediate acidification of these basic solutions with hydrochloric acid reformed the aminosulfuric acid (XII) unchanged. However, when the aminosulfuric acid (XII) was warmed with a dilute 50% alcohol–water solution of potassium hydroxide for five minutes, the mixture cooled and water added, a white precipitate resulted. Recrystallization of this product from 95% alcohol gave 1-benzyl-2-phenyl-3-benzoylethylenimine (V) in 40% yield.[8]

Summary

1. Dibenzoylmethane and benzoylacetone have been found to condense readily with the primary amines benzylamine and cyclohexylamine to give β-amino-α,β-unsaturated ketones.

2. In contradistinction to secondary amines, primary amines have been shown to react with bromine derivatives of benzalacetophenone to give ethylene imino ketones.

LINCOLN, NEBRASKA RECEIVED NOVEMBER 18, 1942