and the filtrate was diluted with ether and extracted with 10% hydrochloric acid. The acid extract was diluted with water and neutralized with sodium carbonate, after which the resulting mixture was extracted with ether. The ether extract was washed, dried, and evaporated under reduced pressure. Acidification of an acetone solution of the residue with ethereal hydrogen chloride yielded 0.3 g. of a hydrochloride which melted at 217–221° and was shown by a mixture melting point to be 2,5-diphenyl-3-(morpholinomethyl)-furan (XIII) hydrochloride.[2]

Catalytic dehalogenation of **3-(chloromethyl)-2,5-diphenylfuran** (XII) (1 g. in 50 ml. of ethanol) using 1 g. of palladium–barium sulfate proceeded at a steady rate until one equivalent of hydrogen had been absorbed. At this point the rate of absorption decreased greatly and for this reason the reaction was stopped. The reaction mixture was filtered and evaporated to a low volume under an air blast, after which the resulting mixture was cooled and filtered. Thus was obtained 0.4 g. of material which melted at 54–57° and gave a large mixture melting point depression with starting material. It was shown to be 2,5-diphenyl-3-methylfuran (XIV) by a mixture melting point with an authentic sample.[13]

Summary

Catalytic reduction of *cis*-dibenzoyl-(morpholinomethyl)-ethylene in ethanol solution is found to involve saturation of the double bond and deamination, yielding dibenzoylmethylethane; in contrast reductions in acetic acid solution involve retention of the morpholino group and yield dibenzoyl-(morpholinomethyl)-ethane.

cis - Dibenzoyl - (morpholinomethyl) - ethylene furanizes in two different ways, one spontaneously to the known 3-benzoyl-5-phenylfuran, and the other under the influence of methanolic hydrogen chloride to 2,5-diphenyl-3-formylfuran. The structure of the latter compound is demonstrated. Possible mechanisms for these reactions are suggested.

CHARLOTTESVILLE, VIRGINIA

RECEIVED SEPTEMBER 28, 1945

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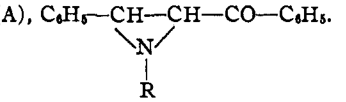
[13] Lutz and McGinn, THIS JOURNAL, 64, 2585 (1942).

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

Ethylene Imine Ketones

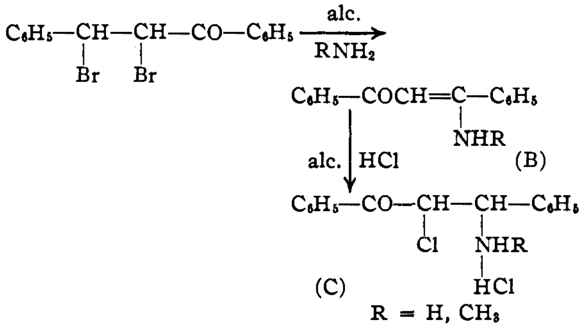
BY NORMAN H. CROMWELL AND JOHN A. CAUGHLAN

In a previous communication[1] the reactions of primary amines with α-bromobenzalacetophenone and with α,β-dibromobenzylacetophenone were shown to produce ethylene imine ketones of the type (A),



$$C_6H_5-\underbrace{CH-CH}_{\underset{R}{\underset{|}{N}}}-CO-C_6H_5.$$

Algar, Hickey and Sherry[2] have published an article in which they describe some interesting experiments involving the reactions of ammonia and methylamine with α,β-dibromobenzylacetophenone. These investigators did not attempt to isolate the immediate products from these reactions, but treated the resulting crude products with alcoholic hydrogen chloride to obtain, as isolable products, dichlorides for which they wrote the structure (C). The mechanisms of the reactions were described as indicated.



$$C_6H_5-\underset{Br}{CH}-\underset{Br}{CH}-CO-C_6H_5 \xrightarrow[RNH_2]{alc.} C_6H_5-COCH{=}\underset{NHR}{C}-C_6H_5 \quad (B)$$

$$\xrightarrow[alc.]{HCl} C_6H_5-CO-\underset{Cl}{CH}-\underset{\underset{HCl}{NHR}}{CH}-C_6H_5 \quad (C)$$

$R = H, CH_3$

The Irish workers refer to the early work of Ruhemann and Watson[3] in assigning the structures for their intermediate products (B). The structure of the intermediate bromobenzalacetophenone has long been known to be α-bromobenzalacetophenone[4] and not β-bromobenzalacetophenone as Ruhemann and Watson wrote it. Moreover, the work of Dufraisse and Moureu[5] has since shown that the product from the reaction of ammonia with α,β-dibromobenzylacetophenone cannot have the β-aminobenzalacetophenone structure (B). By analogy with the behavior of secondary amines in such reactions the French investigators wrote the structure for this product as α-aminobenzalacetophenone. Our recent investigations[1,6] indicate the true structures for the products of the reactions of ammonia and primary amines with these dibromo ketones to be ethylene imine ketones of type (A).

It seemed important to reinvestigate some of the reactions described by the Irish workers and attempt to isolate the intermediate ethylene imine ketone which we expected resulted from the reaction of methylamine with α,β-dibromobenzylacetophenone. Also, a more careful study of the structures of the dihalides of type (C), which we also had reported as resulting from the

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[1] Cromwell, Babson and Harris, THIS JOURNAL, 65, 312 (1943).

[2] Algar, Hickey and Sherry, *Proc. Roy. Irish Acad.*, 49B, 109–119 (1943). A communication to the Editor from Professor Algar points out that their paper was read before the Royal Irish Academy on Feb. 22, 1943, and published on June 11, 1943, and that the paper by us (ref. 1), published in March, 1943, was not available to them until sometime later because of difficult overseas communication.

[3] Ruhemann and Watson, *J. Chem. Soc.*, 85, 1181 (1904).

[4] Kohler, *Am. Chem. J.*, 33, 36 (1905); Dufraisse, *Compt. rend.*, 171, 1062 (1920).

[5] Dufraisse and Moureu, *Bull. soc. chim.*, (4) 41, 861 (1927).

[6] Cromwell and Johnson, THIS JOURNAL, 65, 316 (1943).

reactions of ethylene imine ketones and hydrohalides, seemed necessary.

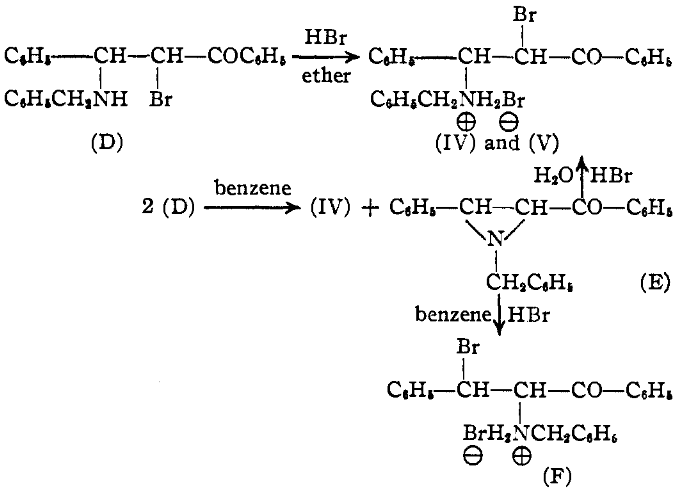
From the reaction of α,β-dibromobenzylacetophenone with methylamine in aqueous alcohol solution, a colorless product (I) was obtained in 26% yields, melting at 88–89°. A residual oil which could not be crystallized was treated with alcoholic hydrogen chloride according to the method used by the Irish workers[2] with their entire reaction product. From this latter reaction we obtained the dihalide (II) melting at 170–171°, as described by Algar, *et al.*[2]

A dihalide (III) similar to (II), but melting at 151–153°, was prepared by treating an ether solution of (I) with alcoholic hydrogen chloride. Both of these dichlorides (II) and (III) were found to have the same chemical composition, $C_{16}H_{17}NOCl_2$.

The colorless product (I) undoubtedly has the ethylene imine structure assigned to it. In all respects it is quite similar to the previously prepared ethylene imine ketones.[1] The absorption spectra in the range of 3100–7000 Å. for (I) is almost identical with those of 1-benzyl and 1-cyclohexyl-2-phenyl-3-benzoylethylenimines.[6] The reactions of these compounds with two molecules of a hydrogen halide are characteristic of ethylene imines in general.

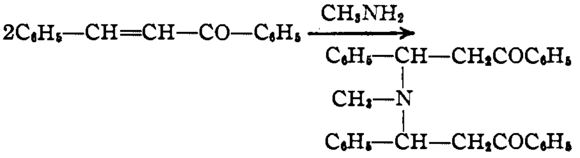
α-Bromo-β-benzylaminobenzylacetophenone hydrobromide (IV), was prepared from α-bromo-β-benzylaminobenzylacetophenone (D) and dry hydrogen bromide. This same dibromide (V) resulted from the reaction of 1-benzyl-2-phenyl-3-benzoylethylenimine (E) with aqueous hydrogen bromide. In the previous investigation[1] we also reported this dihalide as resulting when 1-benzyl-2-phenyl-3-benzoylethylenimine (E) was treated with dry hydrogen bromide in dry benzene solution. The melting points of these products, which are really decomposition points, are all very nearly the same. This latter product, however, did depress the melting points of both (IV) and (V) a few degrees, and so it seemed possible that this product was actually the isomeric α-benzylamino-β-bromobenzylacetophenone hydrobromide (F).

Since α-halogenated ketones could be expected to release iodine from acidified potassium iodide solutions at a more rapid rate than the β-isomers, a series of controlled experiments was devised to reveal the location of the aliphatic halogen in such halogenated amino ketones. In Table I are given the results which show conclusively that both products (IV) and (V) have a bromine atom in the α-position. It is also now shown that the product resulting[1] from the decomposition of α-bromo-β-benzylaminobenzylacetophenone (D) has the bromine in the α-position, while the product (F) resulting[1] from the reaction of 1-benzyl-2-phenyl-3-benzoylethylenimine (E) with dry hydrogen bromide in benzene solution has the bromine in the β-position. These reactions may be portrayed graphically as follows



It seems surprising that hydrogen bromide under aqueous conditions opens the ethylene imine ring one way to give (V) while under anhydrous conditions (F) is formed.

Algar, *et al.*,[2] reported that the reduction of their dihalide, $C_{16}H_{17}NOCl_2$, m. p. 169°, resulted in the formation of β-methylaminobenzylacetophenone hydrochloride hydrate, m. p. 191°. We hoped that the addition of methylamine to benzalacetophenone would produce this β-amino ketone by an independent synthesis. Instead only the bis-product (VI) could be isolated.



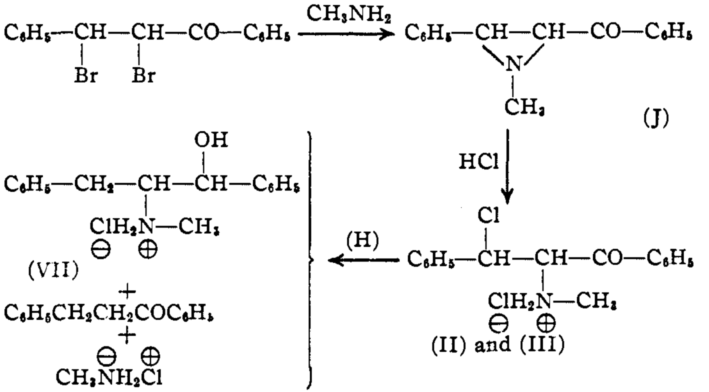
(VI)

The dichlorides (II) and (III) did not release iodine rapidly from acidified potassium iodide solutions. This was also true for the dichlorides which had been prepared in the previous investigation from 1-benzyl-2-phenyl-3-benzoylethylenimine. Although these experiments indicate all of these dichlorides to have the chlorine in the β-position and not the α-position, they are not conclusive as in the case of the dibromides. No authentic α-chloro-β-amino ketone was available for comparison. Since Algar, *et al.*,[2] and Cromwell, *et al.*,[1] had written the structures for such dichlorides as α-chloro-β-aminobenzylacetophenone hydrochlorides it seemed necessary to reinvestigate the reduction of these compounds as reported by the Irish workers.[2]

Reduction of either (II) or (III) with hydrogen using a noble metal as a catalyst resulted in the formation of an impure hydrochloride which melted in the range described by Algar, *et al.*[2]

From this mixed product methylamine hydrochloride and a very small amount of α,γ-diphenyl-β-methylaminopropanol hydrochloride[7] (VII) were isolated. We were not able to isolate a hydrochloride which would seem to be β-methylaminobenzylacetophenone hydrochloride, or its hydrate. Some benzylacetophenone was produced in all of these experiments. Reduction experiments were also carried out with the dibromides (IV) and (F) and were equally inconclusive. We believe, however, that these dichlorides are probably mixtures of the α-chloro and the β-chloro-amino ketone hydrochlorides, consisting mainly of the β-chloro-α-amino isomer.

The reactions described by Algar, *et al.*, should now be written as follows



It seems likely that the difference in melting points of the two dichlorides (II) and (III) is the result of a difference in racemic mixture composition, rather than a difference in α-chloro and β-chloro isomer composition.

The chemistry of these ethylene imine ketones requires further study and other investigations are in progress in this Laboratory.

Experimental[8]

Reaction of Methylamine with α,β-Dibromobenzylacetophenone.—The dibromide (30 g.) was suspended in 90 ml. of absolute alcohol and 40 g. of 33% aqueous methylamine (5 molar equiv. of CH_3NH_2) added to the mixture at room temperature. After standing at room temperature for twelve hours, all of the starting dibromide had dissolved to form a clear, red solution. The reaction mixture was then allowed to stand in the ice chest for five days before distilling off the solvent under vacuum to leave an oil. The resulting oil was mixed with ether and shaken several times with water. After drying, the ether solution was evaporated and petroleum ether (b. p. 40–45°) was added to bring about the crystallization of colorless needles, wt. 5 g., m. p. 85–87°. Recrystallization of this product (I) from hot 85% ethyl alcohol gave colorless needles, m. p. 88–89°.

Anal. Calcd. for $C_{16}H_{15}NO$: C, 80.98; H, 6.37. Found: C, 80.95; H, 6.38.

Spectrographic analysis[9] with a Coleman Universal Spectrophotometer, using a 0.01 *M* solution gave the following result for (I): max. abs. band in range from 3100–7000 Å., in benzene λ Å., 3325; $\epsilon \times 10^{-3}$, 0.0564.

This ethylene imine ketone (I), as well as the 1-benzyl- and 1-cyclohexyl-2-phenyl-3-benzoylethylenimines[1] previously reported, all develop a slight pink tinge of color on standing in the solid form at room temperature, especially in direct sun light. All three of these substances, especially when on the skin, possess a characteristic nauseating odor, similar to that of an isocyanide.

The filtrate from (I) was poured into a 95% alcohol solution of hydrogen chloride to give a colorless, crystalline product which formed slowly, wt. 7.1 g., m. p. 168–170°. Recrystallization of this product from a mixture of alcohol and ether gave colorless crystals (II), m. p. 170–171°, dec.[2]

Anal. Calcd. for $C_{16}H_{17}NOCl_2$: C, 61.93; H, 5.53. Found: C, 61.95; H, 5.64.

Reaction of 1-Methyl-2-phenyl-3-benzoylethylenimine (I) with Hydrogen Chloride.—The ethylenimine (I) (1.5 g.) was dissolved in dry ether and alcoholic hydrogen chloride added until the white precipitate, which came down immediately, had dissolved. After standing in the ice chest for three hours all of the solvent was evaporated and the resulting oil was redissolved in the minimum amount of hot absolute alcohol and dry ether added. A colorless product crystallized slowly, wt. 1.57 g., m. p. 150–153°, dec. Recrystallization of this product from a mixture of alcohol and ether gave colorless crystals (III), m. p. 151–153° dec., mixed with (II), m. p. 151–164° dec. This product (III) is more soluble in 95% alcohol than is (II). Both of these products were soluble in water.

Anal. Calcd. for $C_{16}H_{17}NOCl_2$: C, 61.93; H, 5.53. Found: C, 61.81; H, 5.50.

α-Bromo-β-benzylaminobenzylacetophenone Hydrobromide (IV).—α-Bromo-β-benzylaminobenzylacetophenone[1] (m. p. 76°, 6.0 g.) was dissolved in cold, dry benzene and an equivalent amount of a solution of hydrogen bromide in cold, dry ether immediately added. The precipitated product was rapidly filtered, washed with dry ether and dried under vacuum, wt. 6.5 g., m. p. 155–157°, dec.

Anal. Calcd. for $C_{22}H_{21}NOBr_2$: C, 55.59; H, 4.45. Found: C, 55.50; H, 4.60.

If this procedure is not completed rapidly the resulting product seems to contain some of the isomeric α-benzylamino-β-bromobenzylacetophenone hydrobromide.

Reaction of 1-Benzyl-2-phenyl-3-benzoylethylenimine with Hydrogen Bromide.—A pure sample (5.0 g.) of the ethylene imine ketone[1] was heated at 85° for thirty minutes with 50 ml. of 6 *N* hydrobromic acid. The reaction mixture was then cooled in the ice chest for two days. A brown, water insoluble mass was removed and suspended in ether to give colorless crystals, wt. 3.2 g. Recrystallization from methyl alcohol and ether gave a colorless product (V), m. p. 155–157°, dec.; mixed with (IV), m. p. 153–157°, dec.

Anal. Calcd. for $C_{22}H_{21}NOBr_2$: C, 55.59; H, 4.45. Found: C, 55.73; H, 4.49.

When (IV) or (V) was mixed with the dibromide (F) previously prepared by treating 1-benzyl-2-phenyl-3-benzoylethylenimine with hydrogen bromide in dry benzene–ether solution,[1] a m. p. range of 146–151°, dec., was obtained. However, when (IV) or (V) was mixed with the dibromide previously reported from allowing α-bromo-β-benzylaminobenzylacetophenone to stand in benzene solution,[1] no depression of melting point was experienced.

When (IV) or (V) was treated with excess benzylamine in alcohol solution, 1-benzyl-2-phenyl-3-benzoylethylenimine (m. p. 105–107°) was obtained in 40–50% yields.

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(7) Wilson and Ling-hsien Sun, *J. Chinese Soc.*, **2**, 243 (1934).

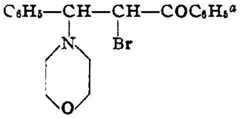
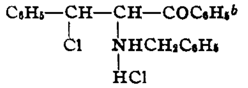
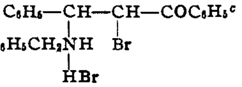
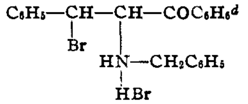
(8) All m. p.'s were observed using a strong glass and obtained by placing the sample in the bath about 10° below the m. p. and heating at the rate of 3° per minute. Some of the semi-micro carbon–hydrogen analyses are by K. Murai, graduate student, Department of Chemistry, University of Nebraska.

Similar treatment of dibromide (F) prepared from the ethylene imine ketone using dry hydrogen bromide,[1] regenerated only traces of the ethylene imine ketone.

Reaction of Halogenated Ketones with Potassium Iodide.—A small sample of the halogenated ketone was dissolved in 10 ml. of a dry solution of 50% acetone and absolute alcohol. To this solution was added 16 ml. of 0.2 *N* potassium iodide in 50% dry acetone and absolute alcohol, followed by the addition of 0.6 ml. of 3 *N* hydrochloric acid in absolute alcohol. After standing at room temperature for thirty minutes, 50 ml. of water and 2 ml. of a 2% starch solution were added to the solutions. The blue solutions were immediately titrated with 0.0300 *N* sodium thiosulfate until the blue color was destroyed to leave colorless, clear solutions. The results are recorded in Table I.

TABLE I

RELEASE OF IODINE BY HALOGENATED KETONES IN THIRTY MINUTES

Halogenated ketone	Sample, g.	0.0300 *N* $Na_2S_2O_3$ ml. used	0.0300 *N* $Na_2S_2O_3$ ml. required	Per cent. reaction
$C_6H_5CH_2CHBrCOC_6H_5$	0.200	12.68	46.07	27.60
 [a]	.100	14.10	17.80	79.12
 $C_6H_5-CH(Cl)-CH(NHCH_2C_6H_5\cdot HCl)-COC_6H_5$ [b]	.100	0.00	17.25	0
(II)	.200	1.30	42.80	3.00
(III)	.200	0.40	42.80	0.93
(IV)	.100	12.60	14.03	90.03
(V)	.200	27.20	28.07	97.00
 $C_6H_5-CH(NHCH_2C_6H_5\cdot HBr)-CH(Br)-COC_6H_5$ [c]	.114	15.50	16.00	97.00
 $C_6H_5-CH(Br)-CH(HN(HBr)-CH_2C_6H_5)-COC_6H_5$ [d]	.164	0.20	23.00	0.87

[a] Cromwell, THIS JOURNAL, **62**, 2897 (1940). [b] Prepared in aqueous hydrochloric or hydrochloric acid–benzene, and the structures apparently are as indicated here instead of as given by Cromwell, Babson and Harris, THIS JOURNAL, **65**, 312 (1943). [c] Product resulting from self reaction of α-bromo-β-benzylaminobenzylacetophenone in benzene solution, see reference under (b). [d] Product prepared from 1-benzyl-2-phenyl-3-benzoylethylenimine and hydrogen bromide–benzene apparently should have the structure (F) given here instead of as given in reference under (b).

Reaction of Methylamine with Benzalacetophenone.—A solution of 20 g. of benzalacetophenone and 13.5 g. of a 33% aqueous solution of methylamine (1.5 equiv. of CH_3NH_2) in 70 ml. of absolute alcohol was allowed to stand at room temperature for twelve hours and in the ice chest for four days. All of the solvent was removed at 30° under vacuum and the resulting oil dissolved in ether. The ether solution was washed several times with water, dried over anhydrous calcium sulfate and dry, gaseous hydrogen chloride passed into the solution. The resulting hygroscopic product was recrystallized once from 95% alcohol and ether, m. p. 222–225°, wt. 2.0 g. This hydrochloride analyzed low in chlorine for $C_{31}H_{30}NO_2Cl$. The impure hydrochloride (1.5 g.) was shaken with dilute sodium hydroxide in the presence of ether. The ether solution was washed with water, dried and evaporated. The white solid residue was recrystallized from dry ether and petroleum ether (b. p. 60–70°) to give 1.1 g. of colorless crystals (VI), m. p. 167°.

Anal. Calcd. for $C_{31}H_{29}NO_2$: C, 83.19; H, 6.53. Found: C, 83.08; H, 6.62.

Bis-(α-phenacyl-benzyl)-methylamine (VI) was not soluble in dilute mineral acids.

Reduction of α-Methylamino-β-chlorobenzylacetophenone Hydrochloride.—(a) With platinum oxide (0.1 g.) in 95% alcohol and hydrogen at 30 lb./sq. in., 2.0 g. of (II) gave an impure hydrochloride, m. p. 186–191°, wt. 0.10 g. The only sharp melting product separated from this crude product was methylamine hydrochloride, m. p. 230–233°. The reaction mixture residue on concentration gave 0.0050 g. of benzylacetophenone, m. p. 71–73°.

(b) With 30% palladium on charcoal (0.5 g.) in 95% alcohol and hydrogen at 30 lb./sq. in., 3.02 g. of (III) was shaken for one hour. Evaporation of the solvent and addition of dry ether gave 1.2 g. of colorless crystals, m. p. 186–225°. Continued fractional crystallization of this product from alcohol and ether gave 0.5 g. of a product identical with methylamine hydrochloride, m. p. 230–233°, and 0.005 g. of a product identical with α,γ-diphenyl-β-methylaminopropanol hydrochloride, m. p. 204–206°.[7] The remainder of the hydrochloride product was a mixture, m. p. 189–192°. The residual ether solution from the hydrochloride product, on concentration, gave 0.010 g. of a product identical with benzylacetophenone, m. p. 71–73°.

Reduction of Benzylaminobromobenzylacetophenone Hydrobromides.—Using palladium on charcoal, as outlined above, 2.0-g. samples of (IV) and (F) were reduced with hydrogen in absolute alcohol solutions. The only pure product obtained from these reactions was benzylacetophenone. (IV) gave 0.14 g., while (F) gave 0.020 g. From both reaction mixtures almost half of the unchanged starting material was recovered.

Summary

1. Methylamine has been found to react with α,β-dibromobenzylacetophenone to form 1-methyl-2-phenyl-3-benzoylethylenimine, and with benzalacetophenone to give bis-(α-phenacyl-benzyl)-methylamine.

2. Ethylene imine ketones react with two molecules of hydrogen halides to produce the hydrohalides of either α-halo-β-amino ketones or β-halo-α-amino ketones, depending on the conditions.

LINCOLN, NEBRASKA RECEIVED JUNE 19, 1945