

anhydrous potassium carbonate, and fractionally distilled. The nearly constant boiling fraction was then condensed with methyl iodide in a toluene solution. This condensation took place rapidly, the onium compounds being recrystallized from alcohol or acetone. Further data for these compounds are listed in Table I.

The corresponding compounds derived from diethylamine were prepared in the same way, except that an equivalent quantity of pure diethylamine was used instead of the aqueous dimethylamine. The yields of the redistilled products were about 10% higher than those in the dimethyl series, the highest being 72% for diethylaminomethyl-*n*-propyl sulfide, and 64% for dimethylaminomethylisobutyl sulfide.

The onium compounds of the diethyl series were prepared by condensation of ethyl iodide with the tertiary amine sulfide, without any solvent. This reaction proceeded very slowly. Table I gives the data for the compounds prepared.

The sulfones were prepared from formocholine thioethers after converting the iodides into sulfates by oxidizing with 5% permanganate in a neutral solution. The slightly acidified filtrates from these oxidations were evaporated on a steam-bath to dryness. The residues were extracted with hot 95% alcohol and the extracted sulfones were purified by recrystallization from that solvent. These products are soluble in water and hot alcohols, and insoluble in acetone and ether.

TABLE II

Sulfones	Dec. point, °C.	Sulfate sulfur, %		
		Calcd.	Found	
$[(\text{CH}_3)_2\text{NCH}_2\text{SO}_2\text{CH}_2\text{CH}_3]_2\text{SO}_4$	178	7.49	7.50	7.47
$[(\text{CH}_3)_2\text{NCH}_2\text{SO}_2\text{CH}_2\text{CH}_2\text{CH}_3]_2\text{SO}_4$	190	7.02	7.04	7.05
$[(\text{CH}_3)_2\text{NCH}_2\text{SO}_2\text{CH}(\text{CH}_3)_2]_2\text{SO}_4$	190	7.02	7.64	
$[(\text{CH}_3)_2\text{NCH}_2\text{SO}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3]_2\text{SO}_4$	190	6.61	6.51	6.55
$(\text{CH}_3)_2\text{NCH}_2\text{SO}_2\text{CH}_2\text{CH}(\text{CH}_3)_2]_2\text{SO}_4$	197	6.61	6.62	6.66

The pharmacological properties have been

investigated by Hunt.<sup>7</sup> These thioethers of formocholine have pronounced acetylcholine and stimulating nicotine actions, being possibly slightly more active than the corresponding oxygen compounds. However, the methyl and *n*-propyl derivatives are definitely less toxic to mice. The maximum acetylcholine action was reached in the ethyl and *n*-propyl compounds, while the stimulating nicotine action increased from the methyl to the *n*-butyl derivatives.

The thioethyl analogs of formocholine ethers, like the oxygen ethers, have neither acetylcholine action nor the stimulating nicotine action. They have, however, a paralyzing nicotine action, being somewhat more active in this respect than the oxygen compounds. The most active was the isobutyl thioether. It had a powerful but brief curare action. The oxidation of the thioether sulfur to the sulfonyl group brought about great reduction in the toxicity of the compounds and a marked diminution in the acetylcholine action.

### Summary

1. A number of thioethers of formocholine and their triethyl analogs have been prepared and their pharmacological properties investigated.

2. The thioethers were oxidized to the corresponding sulfones. This change of structure reduced markedly the physiological activity of the compounds.

(7) Hunt and Renshaw, *J. Pharmacol.*, **44**, 151 (1932).

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[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

## Phenylbenzyl Ketimine and Derivatives<sup>1</sup>

BY KENNETH N. CAMPBELL<sup>2</sup>

In the course of other work, it became necessary to prepare and study the properties of phenylbenzyl ketimine and some of its derivatives.

Phenylbenzyl ketimine hydrochloride was first reported by Moureu and Mignonac,<sup>3</sup> who did not obtain it in pure form. Ectors<sup>4</sup> later prepared a

(1) This paper presents a portion of the dissertation submitted by the author in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the University of Chicago in 1932. The investigation was carried out under the direction of the late Professor Julius Stieglitz.

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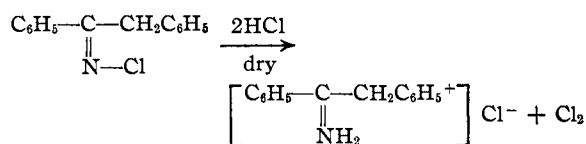
(3) Moureu and Mignonac, *Ann. chim.*, [9] **14**, 322-59 (1920).

(4) Ectors [*Bull. acad. roy. Belg., Classes des Sciences*, [5] **10**, 347-52 (1924)] prepared a crude hydrochloride (m. p. 213°) which

compound by an indirect method which he called phenylbenzyl ketimine hydrochloride, but which did not have the physical constants of the substance obtained by us.

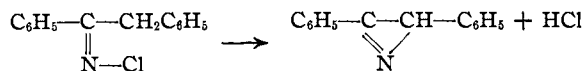
he believed was a mixture of phenylbenzyl ketimine hydrochloride (m. p. 137°) and 3,4,5-triphenylpyrazoline hydrochloride (m. p. 221°). His evidence for this belief was the fact that the free base, liberated from this hydrochloride, gave, on distillation under reduced pressure, desoxybenzoin and triphenylpyrazoline. He prepared a compound (m. p. 137°), from *N*-acetylphenylbenzyl ketimine, which he called phenylbenzyl ketimine hydrochloride, and which he believed was formed according to the equation  $\text{C}_6\text{H}_5-\text{C}(=\text{N}-\text{CO}-\text{CH}_3)\text{CH}_2\text{C}_6\text{H}_5 + \text{HCl} + \text{C}_2\text{H}_5\text{OH} \longrightarrow \text{CH}_3-\text{C}(=\text{O})-\text{OC}_2\text{H}_5 + [\text{C}_6\text{H}_5-\text{C}(\text{NH}_2)-\text{CH}_2\text{C}_6\text{H}_5]^+ + \text{Cl}^-$ . He liberated a free base from this hydrochloride, and it melted at 92-93°. It is possible that the phenylbenzyl ketimine and its hydrochloride obtained by Ectors are geometrical isomers of the ones prepared in our study.

The phenylbenzyl ketimine obtained in our study hydrolyzed very rapidly in the presence of moisture or dilute acid to desoxybenzoin and ammonia. The N-bromo- and N-chloroketimines were prepared by treating the ketimine hydrochloride with sodium hypobromite and sodium hypochlorite, respectively. The N-bromoketimine decomposes extremely easily. Although the N-chloroketimine is more stable than the N-bromo derivative, it could not be obtained pure. It was converted back to phenylbenzyl ketimine hydrochloride as shown by the equation



The phenylbenzyl ketimine hydrochloride regenerated thus was in every way identical with the original material. This reaction<sup>5</sup> established both the structure of the N-chloroketimine and the purity of the original phenylbenzyl ketimine hydrochloride.

Attempts were made to remove hydrogen chloride from the N-chloroketimine to produce a cyclic ketimine



This reaction would resemble the formation of nitriles from aldochlorimines, as noted by Raschig<sup>6</sup> and by Hauser.<sup>7</sup> However, when the N-chloroketimine was heated for six hours with dry silver oxide suspended in dry benzene, or with dry potassium hydroxide suspended in anhydrous ether, no reaction occurred.

When the N-chloroketimine was heated with a 3% aqueous-alcoholic solution of potassium hydroxide, decomposition occurred and a sticky yellow gum was formed, which was not identified. It might have been a polymer or a ketisoketimine.<sup>8</sup> When the N-chloroketimine was heated with a 10% aqueous-alcoholic solution of

(5) Stieglitz and Peterson, *Ber.*, **43**, 786 (1910).

(6) Raschig, "Schwefel und Stickstoff Studien," Verlag Chemie G. m. b. H., Berlin, 1924, p. 80.

(7) Hauser, *et al.*, *THIS JOURNAL*, **52**, 4157, 4163 (1930); **55**, 4526 (1933).

(8) Moureu and Mignonac, *Ann. chim.*, [9] **14**, 322 (1920). Diphenylbenzyl-benzylidene ketisoketimine,  $\text{C}_6\text{H}_5\text{CH}_2\text{C}(\text{C}_6\text{H}_5)=\text{N}-\text{C}(\text{C}_6\text{H}_5)=\text{CHC}_6\text{H}_5$ , is described as a very viscous yellow oil of b. p. 248–250° at 2 mm. pressure. It hydrolyzes to desoxybenzoin and ammonium chloride. Similar yellow substances were obtained from the decomposition of phenylbenzyl ketimine when it stood in air, from the N-bromoketimine, which decomposed almost instantly, and from the N-chloroketimine as noted above.

potassium hydroxide, the solution developed a transient blue-violet coloration, and benzoic acid was formed in addition to the yellow gum. The formation of benzoic acid may be explained upon the assumption that the N-chloroketimine was hydrolyzed to desoxybenzoin and potassium hypochlorite.<sup>9</sup> The desoxybenzoin then would be oxidized by the hypochlorite to benzoin or benzil, which in the presence of alkali, is converted readily to benzoic acid.<sup>10</sup>

### Experimental Part

**Phenylbenzyl Ketimine Hydrochloride.**—Benzylmagnesium chloride was prepared from 19 g. of magnesium turnings (0.8 mole) and 110 cc. of benzyl chloride (0.88 mole) in 400 cc. of dry ether. To the Grignard reagent 24 cc. of benzonitrile (0.23 mole<sup>11</sup>) was added slowly. A yellowish-white solid precipitated out and the ether boiled vigorously. When this reaction ceased, the flask was heated and the mixture allowed to reflux for at least four hours. The Grignard complex was then cooled in an ice-salt bath and hydrolyzed with ice and ammonium chloride. The mixture was extracted immediately with cold ether. The ether extract was dried over sodium sulfate for one hour at 0°. It was then saturated with dry hydrogen chloride gas. The crude yellow hydrochloride which precipitated was collected on a filter and stored immediately *in vacuo* over phosphorus pentoxide. The yield was about 30 g.

The crude hydrochloride was extracted, in small portions, several times with dry chloroform. The pure hydrochloride was precipitated from this chloroform extract with anhydrous ligroin (b. p. 35–60°). A very light yellow hydrochloride was obtained, which melted with decomposition at 210–211°. This substance was very sensitive to moisture and hydrolyzed with extreme ease.

*Anal.* Calcd. for  $\text{C}_{14}\text{H}_{14}\text{NCl}$ : N, 6.05; Cl, 15.31. Found: N, 5.96, 5.95; Cl, 15.23, 15.25.

**Hydrolysis of Phenylbenzyl Ketimine Hydrochloride.**—The ketimine hydrochloride was suspended in warm water. It hydrolyzed instantly to give a white precipitate which melted at 56°. This was identified as desoxybenzoin, for it did not depress the melting point of a known sample (m. p. 56°). When the aqueous filtrate was evaporated to dryness on the steam-bath it gave white crystals which proved to be ammonium chloride.

**Preparation of Phenylbenzyl Ketimine (Free Base).**—The pure ketimine hydrochloride was suspended in dry benzene, the mixture cooled in an ice-bath and saturated with dry ammonia gas (this required about one-half hour). The precipitated ammonium chloride was removed by

(9) Hauser, *THIS JOURNAL*, **57**, 1056 (1935); *cf.* also, Stieglitz and Slosson, *Am. Chem. J.*, **29**, 289 (1903).

(10) Porter, "Molecular Rearrangements," American Chemical Society Monograph, 1928, pp. 100–108. A blue-violet color generally appears during the course of the benzoic acid rearrangement. Klinger [*Ber.*, **19**, 1868 (1886)] reported that benzoin, when heated in a 5% aqueous solution of potassium hydroxide and a stream of oxygen, was converted to benzoic acid.

(11) Ectors (Ref. 4) used equimolar quantities of Grignard reagent and benzonitrile. He found considerable amounts of condensation products formed from the ketimine and the unused nitrile.

filtration, and the filtrate evaporated under reduced pressure at 0° until the base began to crystallize out. The ketimine was then precipitated by the addition of three volumes of dry ligroin (b. p. 35–60°). The ketimine was collected immediately on a filter and sealed in small glass tubes. It was obtained as a fine white powder, melting at 57°,<sup>12</sup> with a nitrile odor. It decomposes rapidly in air to a sticky yellow gum, and hydrolyzes rapidly in moist air to ammonia and desoxybenzoin. The ketimine is slightly soluble in low-boiling ligroin, soluble in ether and very soluble in benzene.

*Anal.* Calcd. for C<sub>14</sub>H<sub>13</sub>N: C, 86.11; H, 6.72; N, 7.18. Found: C, 86.02, 86.09; H, 6.93, 6.71; N, 7.00, 7.07.

**N-Bromophenylbenzyl Ketimine.**—This was synthesized by a modification of the method of Young.<sup>13</sup> Potassium hypobromite solution was prepared by the slow addition of 11.2 g. of bromine to a 10% solution of potassium hydroxide made from 8.1 g. of the base in 80 cc. of water, cooled to –10°. The solution was shaken continuously during this process. It was then saturated with borax at –5°. A solution of 4 g. of phenylbenzyl ketimine hydrochloride in cold chloroform was shaken with the hypobromite solution in a cooled separatory funnel for about two minutes. The chloroform layer was drawn off, dried quickly at 0° with sodium sulfate, and filtered. The filtrate was kept cold in an ice-salt bath while the chloroform was removed by suction until the bromimine began to crystallize. The bromimine was precipitated by the addition of three volumes of dry ligroin (b. p. 40–60°, free from unsaturated compounds). The bromimine was collected on a filter and immediately sealed up in small glass tubes. It could be kept for about six hours in this way. It was too unstable for further purification. The yield was about 2 g.

N-Bromophenylbenzyl ketimine is a cream-white solid, melting at about 55°. It is very soluble in chloroform and slightly soluble in low-boiling ligroin. It decomposes exceedingly rapidly in air to a sticky yellow gum.

*Anal.* Calcd. for C<sub>14</sub>H<sub>12</sub>NBr: Br, 29.17. Found: Br, 26.72.

**N-Chlorophenylbenzyl Ketimine.**—This was prepared by a modification of the method of Peterson.<sup>14</sup> A sodium hypochlorite solution was made by the addition of 11.5 g. of chlorine to a solution of 17 g. of sodium carbonate in 250 cc. of water, which had been cooled to 4°. The solution was then treated with 4 g. of potassium carbonate, and after the reaction was over, a solution of 6 g. of phenylbenzyl ketimine in cold chloroform was added, and the flask shaken constantly in an ice-bath for ten minutes. The chloroform layer was separated, the aqueous layer extracted once with chloroform, and the combined chloroform solutions dried over sodium sulfate at 0° for thirty minutes. The chloroform was removed by suction until the chlorimine started to crystallize. Three volumes of dry ligroin, free from unsaturated substances, was then added to precipitate the chlorimine. The product so

obtained was a white solid, melting at 78°. The yield was about 3 g. The compound decomposes in air, acquiring a yellow color and the odor of hypochlorous acid. It is slightly soluble in ligroin and may be recrystallized from this solvent. Because of its instability the chlorimine was never obtained pure.

*Anal.* Calcd. for C<sub>14</sub>H<sub>13</sub>NCl: Cl, 15.44. Found: Cl, 13.99.<sup>15</sup>

**Proof of Structure of N-Chlorophenylbenzyl Ketimine.**—Some of the purest chlorimine was dissolved in dry ligroin and dry hydrogen chloride passed into the solution. A white precipitate was formed, which melted at 210°, and proved to be phenylbenzyl ketimine hydrochloride. It did not depress the melting point of an authentic sample. When some of the phenylbenzyl ketimine hydrochloride obtained in this way from the chlorimine was hydrolyzed with water, desoxybenzoin (m. p. 56°) was produced. This was converted to the oxime (m. p. 97°) which did not depress the melting point of a known sample of desoxybenzoin oxime (m. p. 98°).

**Attempts to Prepare the Cyclic Ketimine from N-Chlorophenylbenzyl Ketimine.**—Some of the chlorimine was heated under a reflux condenser for six hours with silver oxide suspended in dry benzene. No reaction occurred. The solid which was recovered was the original chlorimine. It gave a strong test for "active" chlorine, melted at 79°, and did not depress the melting point of a known sample of the chlorimine (m. p. 79–80°).

Some of the chlorimine was heated under a reflux condenser for six hours with dry, powdered potassium hydroxide suspended in dry ether. No reaction took place, and the solid recovered was identical with the original N-chlorophenylbenzyl ketimine.

**Alkaline Hydrolysis of N-Chlorophenylbenzyl Ketimine.**—The chlorimine was dissolved in 50% alcohol containing about 3% of potassium hydroxide. The solution was boiled for one hour and then evaporated on the steam-bath. A yellow gum was obtained, together with a white solid which gave the red sulfuric acid test for benzoic acid.<sup>16</sup>

Another portion of the chlorimine was boiled with 50% alcohol containing about 10% potassium hydroxide for two hours. When the solution was evaporated on the steam-bath, a potassium salt was obtained. The acid liberated from this salt melted at 150°, and did not depress the melting point of benzoic acid (m. p. 150°). The yield was approximately 50%. The chlorimine evidently was decomposed by alkali to some compound which, on further treatment with alkali, formed benzoic acid.

### Summary

1. A method is described for the preparation of pure phenylbenzyl ketimine hydrochloride.
2. Methods are given for the preparation of phenylbenzyl ketimine, and its N-chloro and N-bromo derivatives.
3. N-Chlorophenylbenzyl ketimine was treated

(12) This is in agreement with the melting point recorded by Moureu and Mignonac, *Compt. rend.*, **159**, 149–52 (1914).

(13) H. D. Young, Doctorate Dissertation, University of Chicago, 1926. Abstracts of Theses, University of Chicago, Science Series, IV (1925–1926), pp. 203–211.

(14) Peterson, *Am. Chem. J.*, **46**, 325 (1911).

(15) This analysis might indicate that N-chloro- $\alpha$ -chlorophenylbenzyl ketimine, C<sub>6</sub>H<sub>5</sub>C(=NCl)CH(Cl)C<sub>6</sub>H<sub>5</sub> (theoretical Cl, 13.33%), was formed. This, however, is not the case, because the chlorimine was decomposed into desoxybenzoin.

(16) Mulliken, "Identification of Pure Organic Compounds," John Wiley and Sons, Inc., New York, 1904, Vol. I, p. 35.

with various reagents, such as silver oxide in benzene, potassium hydroxide in ether, aqueous potassium hydroxide, in an attempt to eliminate hydrogen chloride and form a cyclic ketimine.

No reaction occurred in anhydrous media, and aqueous alkali decomposed the compound to give benzilic acid.

NOTRE DAME, INDIANA

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF IDAHO]

## Thermal Transitions in Ammonium Compounds<sup>1</sup>

BY HAROLD P. KLUG<sup>2</sup> AND WAYNE W. JOHNSON<sup>3</sup>

The phenomenon of molecular rotation in crystalline solids has been treated theoretically by several investigators.<sup>4</sup> Systematic investigations of those groups of compounds in which molecular rotation might be expected to occur have not as yet been made. In fact most of the experimental data on this phenomenon thus far have come as more or less incidental findings of studies with other ends in view. An exception would be the dielectric constant studies on solids.<sup>5</sup> We have been interested in the systematic investigation of these compounds for the purpose of locating the transitions where molecular rotation sets in. The purpose of this paper is to report some results of the investigation of a series of ammonium compounds for thermal transitions which might be interpreted as molecular rotation transitions.

By means of the method of differential temperatures we have investigated the warming curves of these substances over the temperature range from  $-70$  to  $+40^{\circ}$ . The ammonium halides had been observed to show such transitions in the temperature range between  $-45$  and  $-30^{\circ}$ .<sup>6</sup> As pointed out by Pauling,<sup>4a</sup> the temperature at which rotation sets in may be expected to decrease with increase in the size of the anion. Other hindrances to rotation, however, may be present and exert their influence, thus preventing the inception of rotation until a somewhat higher tem-

perature if at all. At the beginning of this study it was anticipated that crystals of most ammonium compounds would show such rotational transitions, and at temperatures below  $-30^{\circ}$ . The studies in this paper were limited on the low temperature side by the refrigerant available, solid carbon dioxide. Further studies in the future will take these investigations down to liquid air temperatures.

### Experimental

The experimental procedure and equipment were similar to those used in the studies of thermal transitions in hydrates.<sup>7</sup> The copper block for the sample and neutral body was gold plated so that the materials might be placed directly in it without glass protecting tubes. Both single and triple junction copper-constantan differential thermocouples were used. The temperature thermocouples (of same material) were calibrated at the melting points of sodium sulfate decahydrate, carbon tetrachloride, mercury, and chloroform. They were used with a deviation curve and the standard calibration table of the "I. C. T."<sup>8</sup> A photographic recording device<sup>9</sup> was available, during the latter part of the investigation, for the automatic and continuous recording of the differential curves. Using the triple junction differential thermocouple with this device, a temperature difference of  $0.01^{\circ}$  between its junctions gave a deflection of approximately 7.25 cm. on the photographic paper.

The ammonium compounds used were Mallinckrodt "Analytical Reagent" or Baker "C. P. Analyzed" salts. No further purification was deemed necessary for this study. Where possible they were ground to pass through a 100-mesh sieve, otherwise they were ground as fine as could readily be attained. The neutral body was sodium chloride, Baker "C. P. Analyzed Special Crystals," ground to 100 mesh.

Since ammonium chloride and bromide had had the most work done on them in the past, they were chosen for investigation as a check on our method. Other ammonium compounds which had been studied previously were investigated to obtain a more accurate value for their transition temperatures. In the above cases the entire tem-

(1) In part abstracted from a thesis presented by Wayne W. Johnson to the Graduate Faculty of the University of Idaho in partial fulfillment of the requirements for the degree of Master of Science, June, 1937.

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(4) (a) Pauling, *Phys. Rev.*, **36**, 430 (1930); (b) Stern, *Proc. Roy. Soc. (London)*, **A130**, 551 (1931); (c) Nielsen, *J. Chem. Phys.*, **3**, 189 (1935); (d) Frenkel, Tode and Ismailow, *Acta. Phys. U. R. S. S.*, **1**, 97 (1934); (e) Frenkel, *ibid.*, **3**, 23 (1935); (f) Fowler, *Proc. Roy. Soc. (London)*, **A149**, 1 and **A151**, 1 (1935); (g) Devonshire, *ibid.*, **A153**, 601 (1936).

(5) Smyth, *Chem. Rev.*, **19**, 329 (1936). A large list of references on the subject accompanies this article.

(6) Crenshaw and Ritter, *Z. physik. Chem.*, **B16**, 143 (1932).

(7) Taylor and Klug, *J. Chem. Phys.*, **4**, 601 (1936).

(8) "International Critical Tables," McGraw-Hill Book Co., Inc., New York, Vol. I, 1926, p. 58.

(9) Klug, *Northwest Science*, **11**, 36 (1937).