

[CONTRIBUTION FROM THE WALKER LABORATORY OF THE RENSSELAER POLYTECHNIC INSTITUTE AND THE KENT AND JONES LABORATORIES OF THE UNIVERSITY OF CHICAGO]

The Rates of Reaction of Cyclopropyl Ketimines with Water¹

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Ketimines react normally with water to give the corresponding ketone and ammonia as follows



a reaction which ordinarily is accelerated greatly by the addition of one equivalent of acid. Our original interest in the behavior of the cyclopropyl ketimines with water was aroused by two strikingly different reports: first, that ethyl cyclopropyl ketimmonium chloride



appeared to be unaltered by hot water³; and, second, that the phenyl cyclopropyl analog,⁴ $\text{C}_3\text{H}_5\text{C}(=\text{NH}_2\text{Cl})\text{C}_6\text{H}_5$ (II), is instantly decomposed. The first of these reports became clear when the writer proved that de Booseré's stable compound is in reality the isomeric α -ethylpyrrolinium salt.¹ The present work shows, as was anticipated, that the real cyclopropyl compound (I) is even more readily saponified by water than (II).

Experimental

Phenyl Cyclopropyl Ketimmonium Chloride.—The salt was first prepared in the form of its chloroform compound as already described.¹ This crystalline compound, which was collected on a filter in a special moisture-proof housing, was therefore exposed in a desiccator over phosphorus pentoxide at 50° and under diminished pressure until weighings showed that all chloroform had been removed. Since the compound decomposed very readily, many recrystallizations and several repetitions of the initial preparation were necessary in order to maintain a supply of reasonably pure material.

Ethyl Cyclopropyl Ketimmonium Chloride.—Ethylmagnesium bromide was first prepared in the usual manner from 42.3 g. of ethyl bromide, 9.0 g. of magnesium and 150 cc. of anhydrous ether according to the procedure of Moureu and Mignonac.⁵ To this ethereal solution 10.35 g. of cyclopropyl cyanide⁶ in three times its volume of

ether was added slowly from a dropping funnel. The material was then boiled gently for about twelve hours, when it was transferred to a separatory funnel from which it was added slowly to about 300 cc. of liquid ammonia⁷ in a 500-cc. Dewar flask, which was then connected with a five-foot (1.5-meter) lime tower. From time to time during a twenty-hour period the mixture was agitated gently in order to disintegrate lumps. At this point about 200 cc. of dry ether was added carefully to the mixture, and about half an hour thereafter the solution was filtered through a Büchner in a moisture-proof apparatus. The residue on the filter was well washed with dry ether, and the combined filtrates were refiltered into a suction flask. In order to remove ammonia, a current of very dry air was aspirated through the ketimine solution, which was then diluted somewhat with ether and treated with dry hydrogen chloride.

The hydrogen chloride gave a white crystalline precipitate of the ethyl cyclopropyl ketimmonium chloride and a sticky material,⁸ which collected on the walls of the flask. The entire precipitate was then dissolved in 50–60 cc. of a cold mixture of 100 cc. of glacial acetic acid⁹ and 10 cc. of acetic anhydride, from which it was reprecipitated by the addition of 500 cc. of dry ether. At first a dusky, oily layer was obtained, but eventually this crystallized completely after the flask wall was scratched with a glass rod. Finally, the salt was collected on a suction filter in the absence of moisture, when it was exposed in a vacuum desiccator over sodium hydroxide and calcium chloride for a day, giving 10 g. or a 48.5% yield.

The substance appeared to shrink from 70–80°, but it did not melt until 95–97°, and then it gave a somewhat turbid liquid. Other cyclopropyl ketimmonium salts have behaved similarly, possibly because they pyrolyze to give pyrrolinium salts.

Anal. (micro) Calcd. for $\text{C}_6\text{H}_{12}\text{NCl}$: N, 10.49; Cl, 26.55. Found: N, 10.59, 10.47; Cl, 26.93.

When the salt was redissolved in dry chloroform containing a little acetic anhydride and reprecipitated by ether, neither properties nor composition were changed significantly. However, in a melting point determination begun at 87°, the compound melted at 98.5–100.5°.

Reaction Rate Measurements.—The rates with which the ketimmonium salts react with water were ascertained

(1) The data reported herein have been taken from the second part of a dissertation presented by J. B. Cloke to the University of Chicago in partial fulfillment of the requirements for the degree of Doctor of Philosophy. The first part was published in 1929, *THIS JOURNAL*, **51**, 1174 (1929).

(2) The problem discussed herein was suggested by Dr. Julius Stieglitz, whose inspiration, confidence and fatherly advice will always be treasured by the writer. For various reasons, Mrs. Stieglitz has suggested that her husband's name should be withheld from this second paper, which was his own wish in the case of the first.

(3) de Booseré, *Bull. soc. chim. Belg.*, **32**, 26 (1923).

(4) Bary, *ibid.*, **31**, 404 (1922).

(5) Moureu and Mignonac, *Compt. rend.*, **156**, 1801 (1913); *Ann. chim.*, **19**, **14**, 322 (1920).

(6) Cloke, Anderson, Lachmann and Smith, *THIS JOURNAL*, **53**, 2791 (1931).

(7) The use of liquid ammonia for the decomposition of the bromo-magnesium derivatives of ketimines was developed independently by Cornell, *ibid.*, **50**, 3314 (1928), and by Cloke and Van Wyck, *Thesis*, Rensselaer Polytechnic Institute, 1927. As a rule, the Grignard solution runs quite easily into the ammonia through a tube of precipitate formed at the tip of the funnel. Plugs may be removed with a wire.

(8) The formation of this viscous material, which has often been observed in connection with the precipitation of ketimine hydrochlorides, appears to be the result, in part at least, of the use of an excess of hydrogen chloride.

(9) Later work indicated that chloroform is better than the acetic acid.

by modifications of the method of Stieglitz and Derby¹⁰ for the imido ester hydrochlorides. The method is based upon the fact that a ketimine can be liberated from its salt by the action of sodium hydroxide and that the free base, unlike ammonia, may be extracted from its aqueous solution by carbon tetrachloride. The reaction velocity constant, k , was calculated arithmetically and graphically from the equation for a monomolecular reaction

$$k = \frac{2.303}{t_2 - t_1} \log \frac{v_1}{v_2}$$

where v_1 and v_2 represent the relative concentrations of the ketimmonium salt at times t_1 and t_2 .

Phenyl Salt.—In the work on the phenyl cyclopropyl ketimmonium chloride, special care was taken in order to prepare the aqueous solution rapidly at 0° and to maintain it at this temperature. Furthermore, the transfer pipet used for the removal of the samples was kept cold, when not in use, by allowing it to stand in a long tube, which was clamped in the well-stirred bath of water and cracked ice. Each sample was transferred at a noted time to a Squibb funnel containing a known volume of standard alkali and 30 cc. of purified carbon tetrachloride. At once the mixture was well shaken, the tetrachloride layer was drawn off and the extraction repeated three times with 25, 20 and 15 cc. portions of the immiscible solvent. Finally, the aqueous solution in the funnel was washed into a flask and titrated with standard acid with methyl orange as the indicator. Table I represents a typical run, wherein t is the time in minutes from the moment of preparation of 100 cc. of 0.05 M solution and v_b and v_a designate the volumes used of the 0.1 N sodium hydroxide and hydrochloric acid, respectively; samples of 17.6 cc. were taken.

TABLE I

t	$v_b - v_a$	k , min. ⁻¹
2	8.06
14	5.85	0.02669
33	3.75	.02469
44	2.87	.02460
55	2.13	.02510
70	(1.51)	.02463

Average k 0.02514

The graphical computation of the data in Table I gives a value for k of 0.0246. Table II presents a summary of the constants, computed graphically, for several successive runs on the phenyl salt at 0° in 0.05 M and 0.1 M solutions. The grand averages for the average constants

TABLE II

k , min. ⁻¹ for 0.05 M soln.	k , min. ⁻¹ for 0.1 M soln.
0.0246	0.0242
.0249	.0234
.0249	.0232
.0257	.0217
.0243	
.0250	
Grand av. .0249	.0231

computed arithmetically are 0.0252 and 0.0243 respectively, results for which the first points are generally responsible.

(10) Derby, *Am. Chem. J.*, **39**, 439 (1908).

Ethyl Salt.—Ethyl cyclopropyl ketimine differs from the phenyl analog in that it is decidedly more soluble in water and more reactive by far with water. In addition, it differs from all other ketimines thus far studied in that the base is more sensitive to saponification than the hydrochloride salt. These characteristics made it necessary to adopt the following modification of the analytical method used for the phenyl salt, and, even with the changes indicated, the results are not as accurate as might be desired.

A 100-cc. portion of purified carbon tetrachloride and a suitable volume of 0.5 N sodium hydroxide solution from a microburet were added in order to each of five Squibb funnels, which were suspended in the ice-bath. The ketimmonium salt solution was then prepared in a wide-necked, weighted Erlenmeyer flask, which stood in the bath, by the dropping of the proper weight of compound into the flask, which contained the proper volume of water measured at 0°. At once a definite volume of the well-mixed reacting solution together with a 5-g. portion of finely powdered sodium nitrate were transferred to one of the waiting funnels. The mixture was then shaken vigorously for a few moments, the lower layer was removed and at once the extraction was repeated with a 30-cc. and a 20-cc. portion of ice-cold tetrachloride, when the analysis was finished as in the case of the phenyl salt.

In the foregoing work, the very rapid extraction procedure, which was demanded by the great reactivity of the liberated base, undoubtedly removed some alkali mechanically. However, this error would be offset to some extent, especially in the first analyses, by the rapid decomposition of the base together with its significant solubility in water. The graphical computation of the results of three runs gave the following values of k : 0.0366, 0.0360, (0.0316).

Saponification of Ethyl Cyclopropyl Ketimine Base.—

Since several unsuccessful attempts to prepare pure ethyl cyclopropyl ketimine indicated that this could only be accomplished with much effort, a general idea of its stability to saponification was obtained as follows. In short, the base was liberated from its hydrochloride salt at the moment when it was required by the dropping of the equivalent weight of the salt into a definite volume of 0.05 N sodium hydroxide solution at 0°. Without delay a 10-cc. portion of this solution was pipetted into a Squibb funnel containing 100 cc. of ice-cold tetrachloride and 5 g. of sodium nitrate, when the run was completed as above. The results of two runs, computed graphically, follow: k , min.⁻¹ = 0.46, 0.53.

The foregoing data, which indicate a half time value of about a minute and a half for the ketimine in water at 0°, are only of relative significance: first, on account of the haste necessary in the analytical work¹¹; and, second, because a slight excess of sodium hydroxide, giving a high pH , might greatly accelerate the reaction. The last question may be ascertained in time.

Saponification of Phenyl Cyclopropyl Ketimine Base.—In view of the striking rate with which ethyl cyclopropyl ketimine base reacts with water in comparison with the rate for the salt, the work was extended to the phenyl analog. The procedure followed was analogous to that used for the ethyl compound with the exception that the

(11) In this connection the writer appreciates the aid of Dr. E. C. Knowles, Mr. R. J. Anderson and the Mrs. Sarah and Mary Cloke.

reaction was carried out in a special vessel provided with an efficient stirrer. The results of two runs are given in Table III. It is important to note that the reaction

TABLE III
Successive Values of $k \times 10^3$, min.⁻¹ at 0°

10.1	9.6	9.4	8.6	8.3	7.8	7.3
11.3	10.3	9.7	8.9	8.4	8.0	6.4

mixture was not strictly homogeneous and that the values obtained are therefore not truly comparable with other data in the paper. The drift in the values of k was probably the result chiefly of the reversing action of the ammonia, as in the saponification of diphenyl ketimine.¹²

The Retardation of Ketimmonium Salt Saponification by Acid.—The idea that the presence of an excess of acid would decrease the rate of reaction of ethyl cyclopropyl ketimmonium chloride with water, which was suggested by the foregoing data, has been confirmed for all ketimmonium salts thus far studied. Data on the two cyclopropyl compounds are given in Table IV. A study of these data shows that the rate with which these two

TABLE IV

Cyclopropyl ketimmonium chloride	HCl, <i>N</i>	Av. k , min. ⁻¹ at 0°
Ethyl	0.05	0.00284
Ethyl	.20	.00118
Phenyl	.01	.00747
Phenyl	.05	.00435
Phenyl	.20	.00189

ketimmonium salts react with water decreases remarkably as the hydrogen-ion concentration increases. The imido ester salts are much less sensitive to changes in pH , as shown by the work of Stieglitz and Derby.¹⁰

Discussion

By analogy with ethyl phenyl ketimmonium chloride, $C_2H_5C(=NH_2Cl)C_6H_5$,¹³ and the diphenyl compound, $C_6H_5C(=NH_2Cl)C_6H_5$,^{12,14} the ethyl cyclopropyl ketimmonium chloride (I) is less reactive with water than would be expected. This deduction is also supported by the great reactivity of the ethyl cyclopropyl ketimine base

(12) E. M. Davis, *Thesis* Rensselaer Polytechnic Institute, 1934.

(13) N. B. Tweed, *Thesis*, Rensselaer Polytechnic Institute, 1932.

(14) Culbertson, *et al.*, *Proc. Iowa Acad. Sci.*, **39**, 177 (1932); *ibid.*, **41**, 170, 172 (1934).

with water, for ketimine bases are normally less reactive with water than their salts.⁵ The foregoing considerations are in harmony with the supposition that the salt (I) exists in aqueous solution largely in the form of its enammonium tautomer, presumably $\underline{CH_2CH_2CH}-C(-NH_2Cl)=CHCH_3$.

The reason for suggesting that the tautomerism,¹⁵ if it exists, concerns the ethyl rather than the cyclopropyl group will be considered in a later communication.

Summary

Ketimines are saponified by water to give a ketone and ammonia; similarly, ketimmonium salts give a ketone and an ammonium salt. The measurement of the reaction velocity constants for the saponification of ethyl cyclopropyl ketimmonium chloride and for the phenyl cyclopropyl analog shows, contrary to a previous report, that the former compound is more reactive with water than the latter. More notable is the fact that the free ethyl cyclopropyl ketimine base is still more reactive with water than is its hydrochloride, an anomalous behavior which suggests that the dissolved salt may exist largely in the form of an enammonium tautomer. The work has also shown that the reaction velocity for the decomposition of a ketimmonium salt by water decreases as the hydrogen-ion concentration rises.

Subsequent papers will consider various aspects of ketimine stability.

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(15) In order to get additional evidence for the idea, much effort was expended in the measurement of the hydrolysis constants of the bases corresponding to the salts (I) and (II), and also of the free ethyl cyclopropyl ketimine base. Since these measurements were made a number of years ago by a somewhat involved quinhydrone electrode method, which was subject to several unavoidable errors, the data will not be given until they can be checked by more straightforward methods now available. Nevertheless, the data, as collected, indicated that the base corresponding to the more stable phenyl salt (II) is stronger than that of the less stable ethyl analog (I). The same relationship was found by Stieglitz and his associates in the case of the imido esters.