I. MECHANISMS FOR LIQUID PHASE HYDROLYSES OF CHLOROBENZENE AND HALOTOLUENES

II. THE PRODUCTS FROM THE REACTION OF N-(2-BROMOALLYL)-ETHYLAMINE WITH SODIUM AMIDE

III. THE NITROGEN INVERSION FREQUENCY IN CYCLIC IMINES

IV. THE NUCLEAR MAGNETIC RESONANCE SPECTRUM OF FEIST'S ACID

Thesis by

Albert Thomas Bottini

In Partial Fulfillment of the Requirements

for the Degree of

Doctor of Philosophy

California Institute of Technology

Pasadena, California

1957

ACKNOWLEDGMENTS

I wish to express my deepest thanks to my research director, Professor John D. Roberts, for his unlimited aid, inspiration and understanding.

My thanks also go to the National Science Foundation for providing me with fellowships throughout my tenure at the California Institute of Technology.

Parts of the research reported here were supported by grants from the National Science Foundation and the American Petroleum Institute.

To Marilyn

ABSTRACT

Part I. A study of the rearrangements which occur during the high temperature liquid phase hydrolyses of the halotoluenes has shown that the extent of rearrangement is a sensitive of temperature, base strength and the nature of the halogen. These hydrolyses involve either a benzyne (elimination-addition) mechanism, which gives both rearranged and unrearranged products, or an S_N2-type mechanism. The S_N2-type mechanism was found to be favored att lower temperatures, in the presence of weaker bases and with the more easily ionizable halogens. By suitable choice of conditions, one or the other reaction could be made to occur almost exclusively. Chlorobenzene-1-^{14}C, with 4 M sodium hydroxide solution at 340°, gave 58 ± 1% phenol-1-^{14}C and 42 ± 1% phenol-2-^{14}C, which indicates that under these conditions the benzyne mechanism predominates but is not the exclusive reaction path.

Part II. The principal product obtained from N-(2-bromoallyl)-ethylamine and sodium amide in liquid ammonia has been shown to be N-ethylallenimine as proposed by Ettlinger and Kennedy rather than N-ethylallylideneamine. N-Ethylpropargylamine was also isolated in small yield from this reaction. N-Ethylpropargylamine was obtained in 71% yield by treatment of N-(2-chloroallyl)-ethylamine with potassium amide in liquid ammonia.

Part III. The nuclear magnetic resonance spectra of derivatives of cyclic imines ranging in ring size from three to six were examined. The temperature dependent spectra of aziridine (ethylenimine) derivatives allowed an evaluation of the factors which affect the nitrogen inversion frequency. Conjugation with nitrogen and, generally to a lesser degree, bulkiness of the group attached to nitrogen increase the inversion frequency. Two groups attached to carbon on opposite sides of the imine ring also increase the inversion frequency. One, or two substituents attached to the ring carbons in a cis manner essentially fix the configuration about nitrogen with the N-substituent trans to the other group (s). The inversion frequency is decreased in hydroxylic solvents due to stabilization of configuration by hydrogen bonding with nitrogen. The data obtained indicate that theoretically resolvable aziridines in which the asymmetric center is trivalent nitrogen are resolvable only at temperatures below -50°. The nitrogen inversion frequency in N-substituted azetidines (trimethylenimines) and larger-ring imines is too great to measure from nuclear magnetic resonance data at temperatures above -77°.

Part IV. The nuclear magnetic resonance spectrum of

Feist's acid, as the sodium salt in a basic solution of deuterium oxide, was found to be consistent with the structure 3-methylene-1,2-trans-cyclopropanecarboxylic acid (I). It was discovered that the ring hydrogens undergo exchange with the solvent whereas the methylene hydrogens do not appear to exchange. These facts cast serious doubt on the possibility of a facile equilibration of I and 3-methyl-1,2-cyclopropenedicarboxylic acid (II). Structure II has been considered elsewhere to account for the ozonization product of esters of I. A mechanism that accounts for the formation of ethyl acetoxaloacetate in the ozonization of the diethyl ester of I has been developed.

The nuclear magnetic resonance spectrum of the reduction product of I was also studied. The ring hydrogens did not appear to undergo exchange with the solvent in a deuterium oxide solution of sodium deuteroxide.

TABLE OF CONTENTS

FIGURES

TABLES

Page

PART I

MECHANISMS FOR LIQUID-PHASE HYDROLYSES OF CHLOROBENZENE AND HALOTOLUENES

This section is copied from a manuscript published in the Journal of the American Chemical Society, Vol. 79, pp. 1458-1462 (1957).

[Contribution No. 2131 from the Gates and Crellin Laboratories of Chemistry, California Institute of Technology]

Mechanisms for Liquid-Phase Hydrolyses of Chlorobenzene and Halotoluenes[1]

(1) Presented in part at the National Academy of Science Meeting in Pasadena, California, November 4, 1955; J. D. Roberts, A. T. Bottini and D. A. Semenow, Science, 122, 881 (1955).

By Albert T. Bottini[2] and John D. Roberts

(2) National Science Foundation Predoctoral Fellow, 1954-1957.

Abstract

A study of the rearrangements which occur during the high-temperature liquid-phase hydrolyses of the halotoluenes has shown that the extent of rearrangement is a sensitive function of temperature, base strength and the nature of the halogen. These hydrolyses involve either a benzyne (elimination-addition) mechanism, which gives both rearranged and unrearranged products, or an S_N2-type mechanism. The S_N2-type mechanism was found to be favored at lower temperatures, in the presence of weaker bases and with the more easily ionizable halogens. By suitable choice of conditions, one or the

other reaction could be made to occur almost exclusively. Chlorobenzene-1-^{14}C, with 4 M sodium hydroxide solution at 340°, gave 58±1% phenol-1-^{14}C and 42±1% phenol-2-^{14}C, which indicates that under these conditions the benzyne mechanism predominates but is not the exclusive reaction path.

* * * * * * * * * * *

It has been known for many years that the individual chlorotoluenes are hydrolyzed with sodium hydroxide solution at temperatures above 300° to yield mixtures of cresols.[3,4]

- -

(3) V. E. Meharg and I. Allen, Jr., This Journal, 54, 2920 (1932).

(4) R. A. Shreve and C. J. Marsel, Ind. Eng. Chem., 38, 254 (1946).

- -

The extent and character of these rearrangements bear a marked similarity to what would be expected if a "benzyne" (elimination-addition) mechanism[5] were operative. Thus, the

- -

(5) (a) J. D. Roberts, H. E. Simmons, Jr., L. A. Carlsmith and C. W. Vaughan, This Journal, 75, 3290 (1953); (b) J. D. Roberts, D. A. Semenow, H. E. Simmons, Jr., and L. A. Carlsmith, ibid., 78, 601 (1956); (c) J. D. Roberts, C. W. Vaughan, L. A. Carlsmith and D. A. Semenow, ibid., 78, 611 (1956).

- -

entering hydroxyl group has never been found farther than one carbon away from the leaving chlorine, and the chlorotoluenes

and cresols (as sodium cresolates) are apparently not isomerized under the reaction conditions.[6,7] In the present

- -

(6) R. Huisgen and H. Rist, Ann., 594, 137 (1955), have also noted this similarity.

(7) A. Lüttringhaus and D. Ambros, Ber., 89, 463 (1956), have used the benzyne mechanism to account for the formation of the several side products obtained from the hydrolysis of chlorobenzene.

- -

research, it has been found that the compositions of the cresol mixtures obtained from hydrolyses of the halotoluenes under various conditions are best understood in terms of concurrent operation of the benzyne mechanism and a nonrearranging S_N2-type mechanism. The proportion of reaction proceeding by either path is easily correlated with the factors which govern the ratio of elimination (E2) to direct substitution (S_N2) in reactions of alkyl halides. As expected, direct substitution is favored at lower temperatures, with weaker bases and with the more easily ionizable halogens, *i.e.*, I > Br > Cl. Some indication has been obtained that a non-rearranging displacement is catalyzed by a manganese steel surface at lower temperatures, and that use of potassium hydroxide in place of sodium hydroxide increases the amount of rearrangement at lower temperatures. These last two findings were not thoroughly investigated.

Earlier research with chlorobenzene[8,9] and chlorotoluenes[4]

- -

(8) K. H. Meyer and F. Bergius, ibid., 47, 3155 (1914).

(9) W. J. Hale and E. C. Britton, Ind. Eng. Chem., 20, 114 (1928).

- -

indicates 4 M sodium hydroxide solution to be the optimum medium for aryl halide hydrolyses. Most of our results were obtained with this medium although a number of experiments were conducted with 1-8 M sodium hydroxide solution. The hydrolysis yields were found to vary considerably with hydroxide concentration but no significant differences in product composition were observed over the range of concentrations employed, provided the conditions were otherwise identical. Approximately 20 g. of halotoluene and 250 ml. of sodium hydroxide solution were heated to the desired temperature in 1.5 - 2.5 hours, shaken for two hours, and allowed to cool. The reaction mixtures were shaken only at the reaction temperature. Usually the reactions were conducted in a monel liner enclosed in a manganese steel bomb. The resulting cresols were isolated, purified by distillation and analyzed by means of their infrared spectra. The results are presented in Table I. The cresol analyses are considered to be accurate to ± 1-2%, since no deviations greater than this were observed when known cresol mixtures were carried through the isolation procedure. However, since the results of five runs similar to those in Table I showed differences in product com-

composition as large as ± 4%, no greater accuracy than this is claimed for the reaction product compositions. The figures for % conversion to cresols may be taken as a rough indication of the reaction rate within the limitations imposed by the fact that the reaction times were not exactly the same, variations were noted in the extent of formation of secondary products and in all cases, heterogeneous mixtures were employed.

Table I

Orientations in Hydrolyses of Halotoluenes with Sodium Hydroxide Solutions[a]

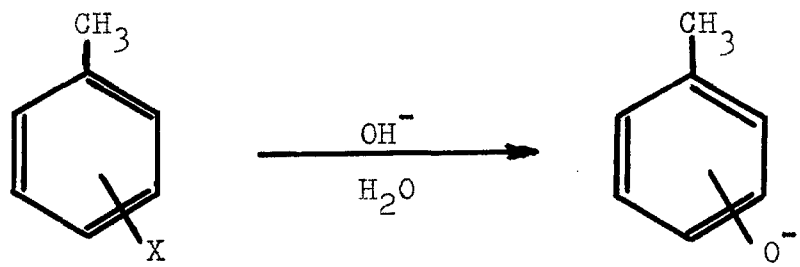


Table I, Cont.

X[b]	Temp., °C[c]	NaOH, M[d]	Conversion,[e] %	Product Composition[f] Ortho, %	Meta, %	Para, %
o-Cl[g]	340	4	68	48.2	51.8	-
m-Cl	300	4	25	18.0	68.0	14.0
m-Cl[h,i]	300	4	27	18.4	69.0	12.6
m-Cl	340	4	56	21.4	63.6	15.0
p-Cl[h,i]	250	1	3.6	-	9	91
p-Cl[h]	250	4	1.2	-	14.4	85.6
p-Cl[j]	250	4	~0.3	-	~40-50	~50-60
p-Cl	300	4	17	-	47.7	52.3
p-Cl	340	1	23	-	48.6	51.4
p-Cl	340	2	39	-	49.3	50.7
p-Cl	340	4	59	-	50.4	49.6
p-Cl	340	8	50	-	50.0	50.0
p-Cl[k]	360	4	54	-	50.0	50.0
o-Br	250	4	15	53.6	47.4	-
o-Br	340	4	63	45.4	54.6	-
m-Br	250	4	15	12.6	79.8	7.6
m-Br	340	4	60	23.9	60.2	15.9
p-Br	250	1	26	-	21.5	78.5
p-Br	250	4	17	-	25.8	74.2
p-Br	340	1	38	-	50.0	50.0
p-Br	340	4	55	-	54.6	45.4
o-I	250	4	22	63.4	36.6	-
o-I	340	4	50	41.7	58.3	-
m-I	250	4	38	5.7	88.9	5.4
m-I	340	4	47	19.8	66.1	14.1
p-I	250	1	45	-	<3	~97
p-I	250	4	45	-	<3	~97
p-I	340	1	44	-	49.2	50.8
p-I	340	4	43	-	48.7	51.3

[a] Unless otherwise stated, all reactions were carried out in a monel liner in a manganese steel bomb for 2 hours. [b] Approximately 20 g. [c] Deviations are ± 4° at 250° and 300° and ± 5° at 340° and 360°. [d] In all cases, 250 ml. [e] Percentage of halide converted to cresols, not corrected for recovered starting material. [f] Better than ± 4%. [g] This result may be several percent in error. E. C. Britton, U. S. Pat. 1,996,744, C. Zentr. 1935, II, 1962 (1935), reported that 59% m-cresol is formed from o-chlorotoluene on hydrolysis with sodium hydroxide solution. [h] No liner was used. [i] Reaction time was 6 hours. [j] Two runs of 2.5 and 6 hours. The products were contaminated with phenol. [k] Reaction time was 0.5 hour.

The cresol mixtures obtained from the hydrolyses of p-halotoluenes were spectrophotometrically free of o-cresol. Furthermore, no p-cresol was detected in hydrolyses of o-halotoluenes. These results establish that the cresols (as cresolate ions) and halotoluenes are not isomerized under the reaction conditions. At 340°, the various o-halotoluenes gave essentially identical mixtures of o- and m-cresols. The p-halotoluenes behaved similarly and gave essentially identical mixtures of m- and p-cresols. These results are easily accounted for by the benzyne mechanism.[10] Thus, the o- and p-

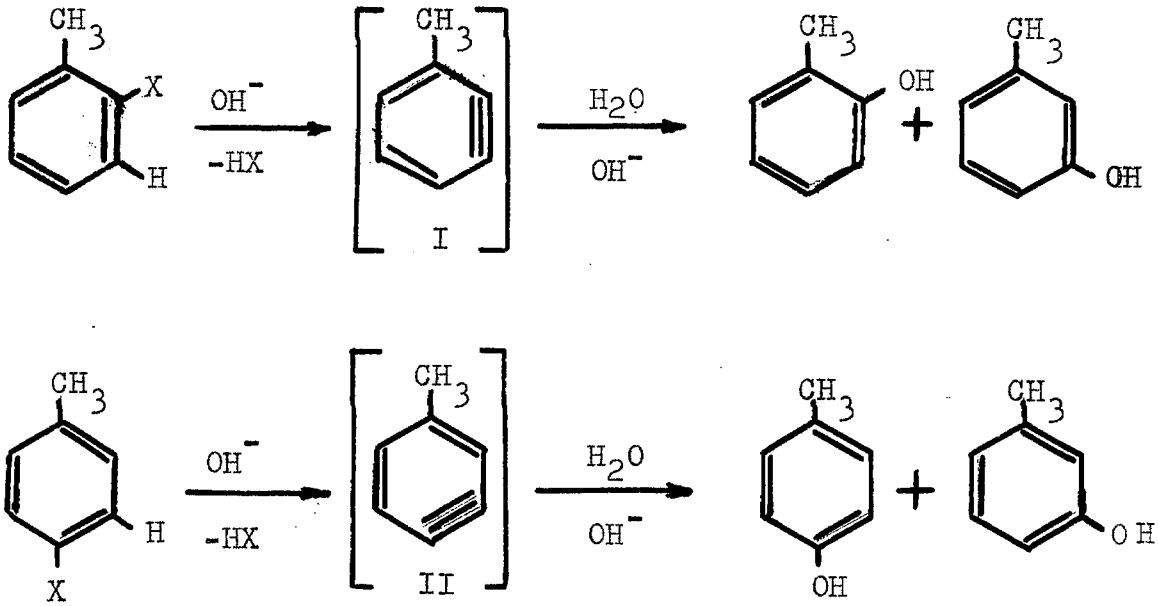
- -

(10) Arguments previously given[5b] against other possible intermediates in the amination reaction also apply here.

The alternative amination mechanisms presented by A. A. Morton, J. Org. Chem., 21, 593 (1956) are too vague to merit serious consideration. It should be noted that the intermediate proposed by Morton to account for the rearrangement with ^{14}C-labeled chlorobenzene is, in effect, o-phenylenediamine with a hydride ion coordinated between the 1- and 2-positions. Such an arrangement, with four electrons shared among three mutually overlapping orbitals, is predicted to be highly unfavorable on quantum mechanical grounds.

- -

halotoluenes are dehydrohalogenated to form 3-methylbenzyne (I) and 4-methylbenzyne (II), respectively, which react with hydroxide ion to form mixtures of cresols (as cresolate ions).



The orientations observed in amination reactions of halotoluenes[5c] have been rationalized on the basis of a slow addition of amide ion to the benzyne intermediate followed by a fast abstraction of a proton from the solvent or an intramolecular proton shift. The direction of addition to a substituted benzyne is predicted on this basis to lead to the more favorable location of the negative charge in consideration of the inductive effect of the substituent. By analogy, II might be expected to add hydroxide ion preferentially at the meta-position while I should prefer to react at the ortho-position (assuming steric hindrance to be unimportant).

Actually, in halotoluene hydrolyses, the methyl group appears to have considerably less net directing power than in aminations because o- and p-halotoluenes at 340° with 4 M sodium hydroxide give roughly equal amounts of normal and rearranged products. Nonetheless, the cresol compositions resulting from hydrolysis are quite similar to the toluidine composition from amination and this is all the more striking when the differences in reaction conditions, particularly the temperature (~370°), are considered.

A small amount of direct substitution may be occurring in hydrolyses of p-halotoluenes at 340°. However, such processes probably cannot account for more than 2-3% of the cresols formed because p-chlorotoluene gave the same product composition at 360° with 4 M sodium hydroxide and at 340° with 4 M potassium hydroxide. The latter result is especially significant since 4 M potassium hydroxide gave almost double the amount of rearrangement as 4 M sodium hydroxide at 250°. If not more than 3% of the cresols obtained from the p-halotoluenes (and o-halotoluenes) at 340° are formed by direct substitution, then from 5-25% of the m-cresol formed from the m-halotoluenes at 340° must be formed by direct substitution. This follows from the fact that 3-methyl- and 4-methylbenzynes give approximately equimolal mixtures of o- and m-cresols and m- and p-cresols, respectively. If all of the reaction were to proceed by elimination-addition with m-halotoluenes, the products would be expected in each case to contain about 50% of m-cresol. As will be shown later, some direct substitution

seems to occur when chlorobenzene is hydrolyzed with 4 M sodium hydroxide solution at 340°.

Considerable direct substitution was observed for the hydrolyses of halotoluenes at 250°. The iodotoluenes gave consistently more direct substitution than the corresponding bromotoluenes. p-Chlorotoluene gave only a 0.3% yield of cresol when hydrolyzed under identical conditions. The cresol mixtures from two similar runs contained a considerable amount of m-cresol (40-50%) as well as a small amount of phenol which made quantitative analysis of the cresols difficult. When p-chlorotoluene was hydrolyzed in a manganese steel reaction vessel, the yield was raised to 1.2% and 3.6% for reaction times of two and six hours, respectively. In the first experiment, 4 M sodium hydroxide gave 14.4% rearrangement, while in the second, 1 M sodium hydroxide gave 9% rearrangement. No similar change in product composition was observed when m-chlorotoluene was hydrolyzed similarly at 300°.

Direct substitution was found to be the main reaction path at 340° with 4 M sodium acetate solution as the hydrolytic medium. p-Bromotoluene gave a 33% yield of spectrophotometrically pure p-cresol and p-chlorotoluene gave a 6% yield of a mixture of 95% p- and 5% o-cresols.

The amount of rearrangement at 250° for the three bromotoluenes and the three iodotoluenes decreases with increasing distance of the halogen from the methyl group. Thus the proportion of reaction occurring via the benzyne mechanism is

85, ~51, and 47% for o- m- and p-bromotoluene, respectively; and 63, <33 and <6% for o- m and p-iodotoluene, respectively. This behavior indicates that the direct substitution reaction proceeds by an S_N2-type mechanism. The inductive effect (+I) of the methyl group would be expected to retard an S_N2 reaction, the effect falling off with the distance between the groups. The methyl group might also be expected to retard S_N2-type attack at the ortho-position through its steric effect.

The possibility of an S_N1-type mechanism for the direct reaction would seem ruled out by the fact that p-iodotoluene failed to yield any cresols with 4 M sodium iodide solution at 340°. In an earlier experiment, no cresols were obtained when p-iodotoluene was treated with 4 M sodium chloride solution at the same temperature. However, Dr. J. F. Bunnett has suggested that the iodo-compound could have been converted to p-chlorotoluene which would be expected to be much less readily hydrolyzed. This direct displacement of iodide by chloride does in fact occur since the recovered neutral fraction contained p-chlorotoluene. However the failure of cresols to be formed in the presence of sodium iodide argues against the S_N1-type reaction path unless one is willing to allow operation of a very large common ion rate depression. It is interesting to note that the reactivity order I > Br > Cl found for the direct displacement reaction shows that breaking of the carbon-halogen bond is well under way in the transition

state.[11]

- -

(11) G. S. Hammond and L. R. Parks, This Journal, 77, 340 (1955).

- -

Chlorobenzene-1-$^{14}C^{12}$ was found to hydrolyze at 340° with

- -

(12) M. Fields, M. A. Leaffer and J. Rohan, Science, 109, 35 (1949); obtained from Tracerlab, Inc., on allocation by the U. S. Atomic Energy Commission.

- -

4 M sodium hydroxide solution to yield 58 ± 1% phenol-1-^{14}C and 42 ± 1% phenol-2-^{14}C. If only the benzyne mechanism were operative, equal quantities of the two phenols should have been formed in the absence of a ^{12}C-^{14}C kinetic isotope effect which might tend to favor formation of phenol-2-^{14}C. The discrepancy is undoubtedly due to occurrence of the S_N2-type reaction which was shown earlier to be of importance in the hydrolysis of m-halotoluenes. The contribution to the extent of rearrangement resulting from the hydrolysis of diphenyl ether[9] is not known. Diphenyl ether might be formed by a direct displacement between phenolate ion and chlorobenzene or from a combination of phenolate ion and benzyne.[7] The diphenyl ether could hydrolyze by either rearranging or non-rearranging reactions. The fact that the ditolyl ethers are more difficultly hydrolyzed than diphenyl ether under the reaction conditions[4] makes it unlikely that the 5-25% direct displacement postulated for the m-halotoluenes at 340° is due

to a non-rearranging formation and hydrolysis of ditolyl ethers. The mechanisms of diaryl ether formation and cleavage during the hydrolyses of aryl halides awaits further study.

The variation of the product composition with reaction temperature indicates the direct and elimination-addition reactions have quite different temperature coefficients. It is not known to what extent the profound temperature effects can be associated with the fact that the reactions are very likely to be heterogeneous. Shreve and Marsel[4] observed no change in reaction velocity in the presence of emulsifying agents and felt that the reactions might be homogeneous. However, it was allowed that the emulsifying agents may have been ineffective in the presence of hot concentrated alkali.

The variation of product composition with temperature satisfactorily accounts for the small differences between our results and those reported by Shreve and Marsel[4] for experiments in which the reaction mixtures were shaken during the heating and cooling periods. The character of the effect associated with this seemingly minor difference in procedure may be illustrated as follows. Chlorobenzene-1-^{14}C was hydrolyzed with 6 M sodium hydroxide solution in a stainless steel bomb at 330° for 2.5 hours, the reaction mixture being shaken during the heating and cooling periods as well as at the reaction temperature. Only 7% rearrangement was observed. However, p-chlorotoluene, when hydrolyzed in a stainless steel bomb with shaking only at 320 ± 15° with 6 M sodium hydroxide solution for two hours, gave the customary 50% of rearrange-

ment product.

The dual mechanism here postulated for the hydrolysis of the halotoluenes and chlorobenzene satisfactorily explains the behavior of the chlorobiphenyls on hydrolysis with different bases. When sodium carbonate solution was used, no rearrangement was observed,[13] while sodium hydroxide solution gave re-

(13) E. C. Britton, U. S. Pat. 1,959,283; C. Zentr., 1934, II, 1688 (1934).

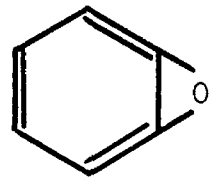
arranged products.[14] Exceptional behavior is observed during

(14) J. E. Moose, U. S. Pat. 1,979,116; C. A., 29, 182 (1935).

the hydrolysis of o-chlorophenolate ion[15] with sodium hydroxide

(15) A. I. Kipriyanov and E. D. Suich, Ukrain. Khem. Zhur., 7, 94 (1932); C. A., 27, 3824 (1933); S. C. Burroughs, U. S. Pat. 2,041,592; C. A. 30, 4513 (1936).

solution and/or strontium hydroxide solution in that only pyrocatechol is formed. The negatively charged oxygen atom ortho to the leaving chlorine could very well retard both the benzyne and the S_N2-type reactions. A possible alternative would be frontside displacement of the chloride by the oxygen to give "benzyne oxide" (III). Such an intermediate could account for the exclusive formation of pyrocatechol as the hydrolysis product.



III

Experimental

The halotoluenes were redistilled Eastman or Matheson, Coleman and Bell products. As far as could be judged from their infrared spectra each contained none of its isomers. The chlorobenzene-1-^{14}C was the same material used previously.[5a] The cresols employed as standards for infrared analyses were center cuts of redistilled Eastman products. The infrared spectrum of each cresol was identical with those published elsewhere.[16]

- -

(16) R. A. Friedel, This Journal, 73, 2881 (1951); "American Petroleum Institute Research Project 44," Carnegie Institute of Technology, Pittsburgh, Pa., 1952, No. 1433-1435.

- -

The radioactive analyses were made using the vibrating-reed electrometer method of Neville.[17] The infrared spectra

- -

(17) O. K. Neville, This Journal, 70, 3499 (1948).

- -

were taken with a Perkin-Elmer (Model 21) double-beam spectrophotometer.

Analysis of Cresol Mixtures. - The cresol mixtures were analyzed by means of their infrared spectra in carbon disulfide solution.[18] Measurements were made at 9.04, 10.77 and

- -

(18) J. J. Heigl, M. F. Bell and J. U. White, Anal. Chem., 19, 293 (1947).

- -

11.84 μ for mixtures of o- and m-cresols and at 10.77, 12.23 and 12.88 μ for mixtures of m- and p-cresols. The optical density was found to be linear with mole fraction at each of the above wavelengths. Mixtures of the three cresols were analyzed with the aid of measurements at 10.77, 12.23 and 12.88 μ.

Halotoluene Hydrolyses. A. Sodium Hydroxide Solutions. - The following procedure is typical. A mixture of 20.1 g. of p-chlorotoluene and 250 ml. of 4 M sodium hydroxide solution contained in a monel liner was sealed in a manganese steel hydrogenation bomb. The bomb was heated to 340° in 2 hours in a conventional electrically heated jacket with the temperature controlled by a Leeds-Northrup Micromax regulator and a calibrated iron-constantan thermocouple. The reaction mixture was then shaken at 340 ± 4° for 2 hours and allowed to cool overnight.[19] The contents of the liner (245 ml.) were

- -

(19) Considerable residual pressure was noted only for the iodotoluenes and bromotoluenes when hydrolyzed at 340°.

- -

extracted three times with 50-ml. portions of ether, cooled in an ice bath and cautiously acidified with concentrated hydrochloric acid. The resulting mixture was extracted three times with 50-ml. portions of ether. The combined extracts were dried, the ether was removed and the residual cresol mixture was distilled through a semimicro column.[20] The distil-

- -

(20) C. A. Gould, Jr., G. Holzman and C. Niemann, Anal. Chem., 20, 361 (1948).

- -

late, b.p. 72-74° (5 mm.) amounted to 10.1 g. (59%) and was shown by its infrared spectrum to contain 50.5% m-cresol and 49.5% p-cresol.

The distillation residues were usually less than 0.25 g. except with iodotoluenes which gave residues of 0.5-0.7 g. These fractions and the non-phenolic reaction products were not investigated. Where effort was made to recover the unreacted starting material, material balances of about 90% were obtained. Several mixtures of cresols were prepared and carried through the isolation procedure, one being subjected to the reaction conditions. Between 85 and 90% of each cresol mixture was recovered. The compositions of these mixtures agreed to within 2% of the compositions of the original mixtures.

B. Sodium Acetate Solution. - A description of a typical experiment follows. A mixture of 20.1 g. of p-chlorotoluene and 250 ml. of 4 M sodium acetate solution was shaken for

2 hours at 340°. The reaction mixture remaining in the liner (233 ml.) was extracted three times with 50-ml. portions of ether. The combined extracts were extracted three times with 30-ml. portions of 1 N sodium bicarbonate solution, washed with 30 ml. of water and extracted three times with 30-ml. portions of 1 M sodium hydroxide solution. The sodium hydroxide solution was acidified with 6 M hydrochloric acid and extracted three times with 30-ml. portions of ether. The combined extracts were dried, the ether was removed and the residual cresol mixture was distilled through a semimicro column.[20] The distillate, b.p. 56-62° (2 mm.), weighed 0.98 g. (6.1%) and was found to consist of 5% m-cresol and 95% p-cresol. A mixture of 15.7% m-cresol and 84.3% p-cresol was carried through the reaction conditions and isolated as above. The infrared spectrum of the product indicated it to contain 11.8% m-cresol.

Attempted Hydrolysis of p-Iodotoluene with 4 M Sodium Iodide and 4 M Sodium Chloride Solutions. - A mixture of 20.0 g. of p-iodotoluene and 250 ml. of 4 M sodium iodide solution was shaken at 340° for 10 hours. A tarry acidic fraction of 45 mg. was obtained. The infrared spectrum of this fraction in carbon disulfide solution failed to indicate the presence of cresols. Similar treatment of 20.1 g. of iodotoluene with 4 M sodium chloride solution for 2 hours also yielded no cresols. The infrared spectrum of the crude recovered neutral material showed all the bands with the same relative intensities possessed by p-chlorotoluene but no

band at 12.57μ as is characteristic of p-iodotoluene. Considerable decomposition occurred during both attempted hydrolyses.

Hydrolysis of Chlorobenzene-1-^{14}C. - The labeled chlorobenzene[12] (19.7 g.) was hydrolyzed with 250 ml. of 4 M sodium hydroxide solution at 340°. The reaction mixture remaining in the liner (233 ml.) was treated in the usual manner. The neutral fraction consisted of 0.15 g. of starting material, 0.30 g. of diphenyl ether, b.p. 74-95° (0.7 mm.), and about 10 mg. of a dark residue. The crude acidic fraction amounted to 13.0 g. (79%), 0.2 g. of which was probably a mixture of hydroxybiphenyls.[9] The crude phenol-X-^{14}C was hydrogenated in absolute alcohol over platinic oxide and yielded 8.9 g. (66%) of cyclohexanol-X-^{14}C; b.p. 159.0-159.4° (741 mm.), $n^{25}D$ 1.4629. The cyclohexanol was degraded[5b] to 1,5-diaminopentane which was isolated as the dibenzenesulfonamide, m.p. 118.2-118.7 (lit.[21] m.p. 119°) after 5 recrystallizations from

(21) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 3rd Ed., 1948, p. 234.

ethanol, and carbon dioxide (collected as barium carbonate). The specific activity of the phenol-X-^{14}C was taken as equal to the activity of the 2,4-dinitrophenylhydrazone of cyclohexanone-X-^{14}C, m.p. 160.6-161.1° (lit.[22] m.p. 162°) after 4

(22) Ref. 21, p. 262.

recrystallizations from ethanol. The ^{14}C results are summarized in Table II.

1,5-Diaminopentane (0.28 g.) was oxidized[5b] in 19% yield to glutaric acid with potassium permanganate; unlabeled glutaric acid was added to the reaction mixture as a carrier. The glutaric acid-X-^{14}C was assayed as the di-p-bromophenacyl ester, m.p. 136.7-137.4° (lit.[23] m.p. 136.8°) after 3 recrystal-

- -

(23) C. H. Huntress and S. P. Mulliken, "Identification of Pure Organic Compounds," John Wiley and Sons, Inc., New York, N.Y., 1941, p. 98.

- -

lizations from ethanol. The glutaric acid was degraded[5b] to 1,3-diaminopropane, isolated as the dibenzamide, m.p. 147.6-149.0° (lit.[5b] m.p. 150.0-150.5°) after one recrystallization from cyclohexane.

Table II

Radioactivity Determinations of Degradation Products of Phenol-X-^{14}C from Hydrolysis of Chlorobenzene-1-^{14}C

Compound	Activity[a]	% Total act.
Phenol-X-^{14}C	0.2908 ± 1.1%	(100)
1,5-Diaminopentane	.1207 ± 1.5%	41.5 ± 0.8
Carbon dioxide	.1644 ± 0.9%	56.5 ± 0.8[b]
Glutaric acid	.0227 ± 1.3%	(41.5)[d]
1,3-Diaminopropane	.00028 ± 100%	0.6 ± 0.6

[a] μc./mmole. [b] Possibly low by 0.4-2.0%.[5b] [c] The 1,5-diaminopentane was substantially diluted during the oxidation. [d] Assumed to be the same as the 1,5-diaminopentane.

Pasadena, California

PART II

THE PRODUCTS FROM THE REACTION OF N-(2-BROMOALLYL)-ETHYLAMINE WITH SODIUM AMIDE

This section is copied from a manuscript published in the Journal of the American Chemical Society, Vol. 79, pp. 1462-1464 (1957).

[Contribution No. 2130 from the Gates and Crellin Laboratories of Chemistry, California Institute of Technology]

The Products from the Reaction of N-(2-Bromoallyl)-ethylamine with Sodium Amide[1]

(1) Supported in part by a grant from the National Science Foundation.

By Albert T. Bottini[2] and John D. Roberts

(2) National Science Foundation Predoctoral Fellow, 1954-1957.

Abstract

The principal product obtained from N-(2-bromoallyl)-ethylamine and sodium amide in liquid ammonia has been shown to be N-ethylallenimine (I) as proposed by Ettlinger and Kennedy rather than N-ethylallylideneamine (II). N-Ethylpropargylamine (III) was also isolated in small yield from this reaction. III was obtained in 71% yield by treatment of N-(2-chloroallyl)-ethylamine with potassium amide in liquid ammonia.

* * * * * * * * *

Pollard and Parcell,[3] in an attempt to extend their synthesis of N,N-dialkylpropargylamines[4] to N-alkylpropargylamines, treated N-(2-bromoallyl)-ethylamine with sodium amide in liquid ammonia. The main product was shown by its infrared spectrum not to be the expected N-ethylpropargylamine (III) and the isomeric N-ethylallylideneamine structure (II) was assigned.[5] This compound rapidly took up two moles of hydrogen to yield N-ethyl-n-propylamine. With hydrochloric acid, the compound was hydrolyzed to ethylamine and a chlorine-containing "aldehyde" which reduced Fehling solution, formed a silver mirror with Tollens reagent but could not be isolated in pure form. When hydrolyzed with dilute hydrochloric acid in the presence of 2,4-dinitrophenylhydrazine, the compound yielded a derivative which melted at 124-125° and was reported to con-

(3) C. B. Pollard and R. F. Parcell, THIS JOURNAL, 73, 2925 (1951).

(4) R. F. Parcell and C. B. Pollard, ibid., 72, 2385, 3312 (1950).

(5) The absence of N-ethylaminoallene was indicated by the lack of nitrogen-hydrogen stretching absorption at about 3230 cm.$^{-1}$. V. A. Engelhardt, ibid., 78, 107 (1956) has recently observed rapid base-catalyzed isomerizations of allenic amines to acetylenic amines and concluded that these reactions probably proceed by way of carbanion intermediates as postulated by T. L. Jacobs, R. Akawie, and R. G. Cooper, ibid., 73, 1273 (1951).

tain 50.89% C, 3.85% H and 12.03% Cl. Treatment of other N-(2-bromoallyl)-alkylamines in the same manner yielded related compounds as shown by similarities in their ultraviolet and infrared absorption spectra as well as formation of the same hydrazone derivative and the respective amine when hydrolyzed with dilute hydrochloric acid in the presence of 2,4-dinitrophenylhydrazine. Pollard and Parcell[3] pointed out that the strong band near 1770 cm.$^{-1}$ in the infrared spectra of these compounds was of too high frequency to be considered as a fundamental stretching vibration of either the carbon-carbon or carbon-nitrogen double bond and was "therefore probably a harmonic or combination frequency." Ettlinger and Kennedy[6] have noted that this unusual band

- -

(6) M. G. Ettlinger and F. Kennedy, Chem. and Ind., 166 (1956).

- -

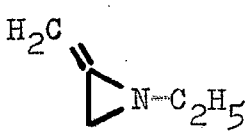
corresponds to the double bond stretching frequency of methylenecyclopropane[7] and have assigned these compounds

- -

(7) J. T. Gragson, K. W. Greenlee, J. M. Derfer and C. E. Boord, THIS JOURNAL, 75, 3344 (1953).

- -

the N-alkylallenimine structure.



I

$CH_2=CH-CH=N-C_2H_5$

II

At the suggestion of Dr. Ettlinger, we have repeated the preparation of the reported N-ethylallylideneamine and have examined its nuclear magnetic resonance (n-m-r) spectrum (Fig. I). The spectrum is in complete agreement with the N-ethylallenimine structure (I) proposed by Ettlinger and Kennedy. Besides the characteristic and undistorted bands of the methylene- and methyl-hydrogens of the N-ethyl group (B and D, respectively) the n-m-r spectrum possesses two other unsplit bands of equal intensity at lower (A) and higher (C) field strengths than resonance B. The positions of A and C correspond respectively to expected resonances of vinylic hydrogens[8] and the cyclic methylene hydrogens of ethylenimine.[9]

- -

(8) L. H. Meyer, A. Saika and H. S. Gutowsky, ibid., 75, 4567 (1953).

(9) H. S. Gutowsky, R. L. Rutledge, M. Tamres and S. Searles, ibid., 76, 4242 (1954).

- -

II would be expected to possess an n-m-r spectrum having, together with the absorptions of the N ethyl group, three or four principal bands split into extensive fine structure characteristic of the grouping CH_2=CH-CHR_2. These resonances would appear at lower field strengths than that of the methylene-hydrogens of the N-ethyl group.

Although the n-m-r spectrum of I leaves little doubt as to the correctness of the structure, some of the results of Pollard and Parcell might appear to contradict this assignment. On hydrolysis with dilute hydrochloric acid, I would

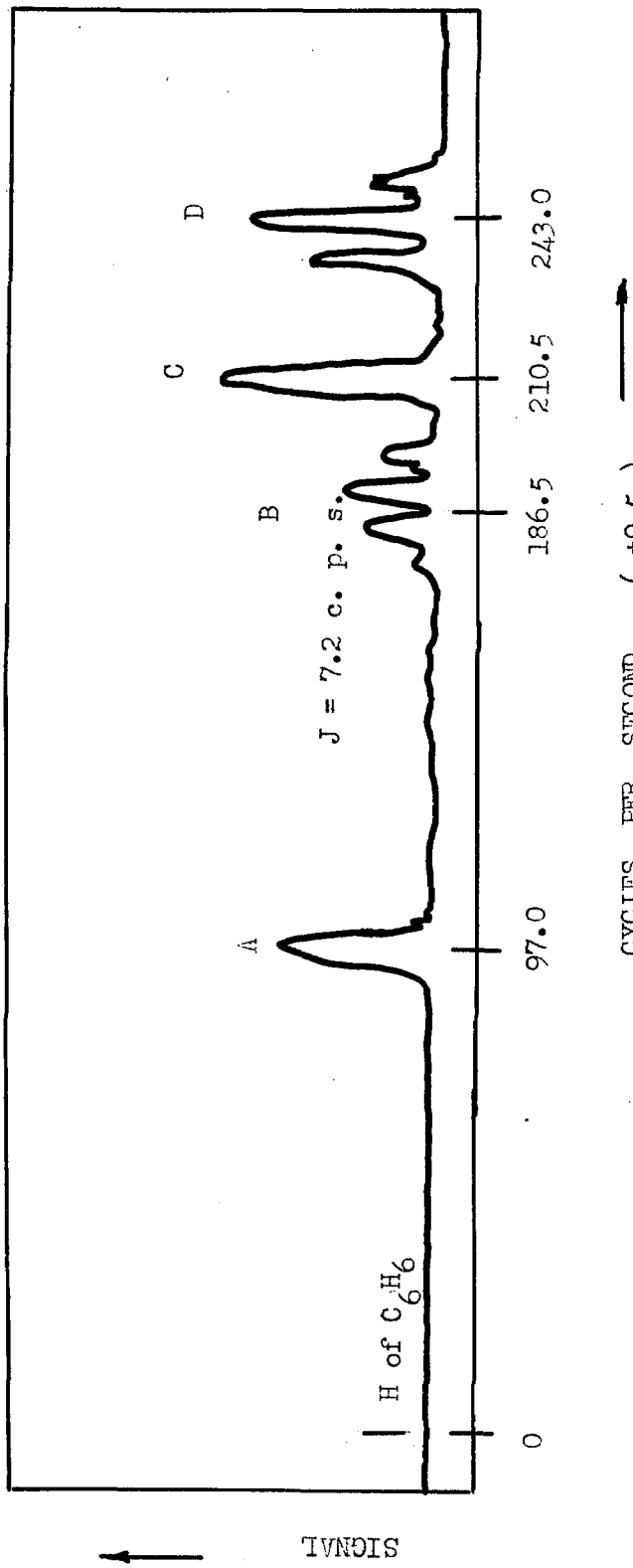


Fig. 1.- Nuclear magnetic resonance spectrum of protons of N-ethylallenimine taken with Varian Associates high resolution nuclear magnetic resonance spectrometer (V-4300B) with 12-in. magnet equipped with a flux stabilizing unit (super stabilizer) at 40 mc. using a spinning 5 mm. sample: A, the protons of the double bond methylene group; B, the methylene protons of the N-ethyl group; C, the ring methylene protons; D, the methyl protons of the N-ethyl group.

be expected to yield chloroacetone rather than an aldehyde. The tests employed on the hydrolysis product,[3] however, failed to distinguish between chloroacetone and an aldehyde since chloroacetone is oxidized by silver oxide[10] and is

(10) E. Linnemann, Ann., 134, 170 (1865).

capable of reducing Fehling solution through preliminary formation of acetol with excess alkali.[11] The melting point

(11) E. H. Huntress, "Organic Chlorine Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 683.

(124-125°) of the 2,4-dinitrophenylhydrazone obtained from the hydrolysis products of I is the same as that reported for chloroacetone 2,4-dinitrophenylhydrazone[12] and the

(12) C. Bulow and F. Seidel, Ann., 439, 48 (1924).

identity of these compounds has now been established by comparison of their infrared spectra. Hydrolysis of I with sulfuric acid in the presence of 2,4-dinitrophenylhydrazine was reported to yield a derivative which contained organic sulfur and melted above 200°. We found this reaction to yield two substances, separable by solubility differences, which melted at 134-135° and 302-304°. The higher melting compound was shown to be methylglyoxal bis-(2,4-dinitrophenyl)-

osazone by its melting point and infrared spectrum. The lower melting compound has not been identified.

In two separate preparations of I from N-(2-bromoallyl)-ethylamine, a small amount of material boiling at about 100° was obtained. The infrared spectrum of this fraction, which contained some I, had a weak band at 2100 cm.$^{-1}$, the characteristic stretching frequency of mono-substituted carbon-carbon triple bonds.[13] The main constituent was shown to be

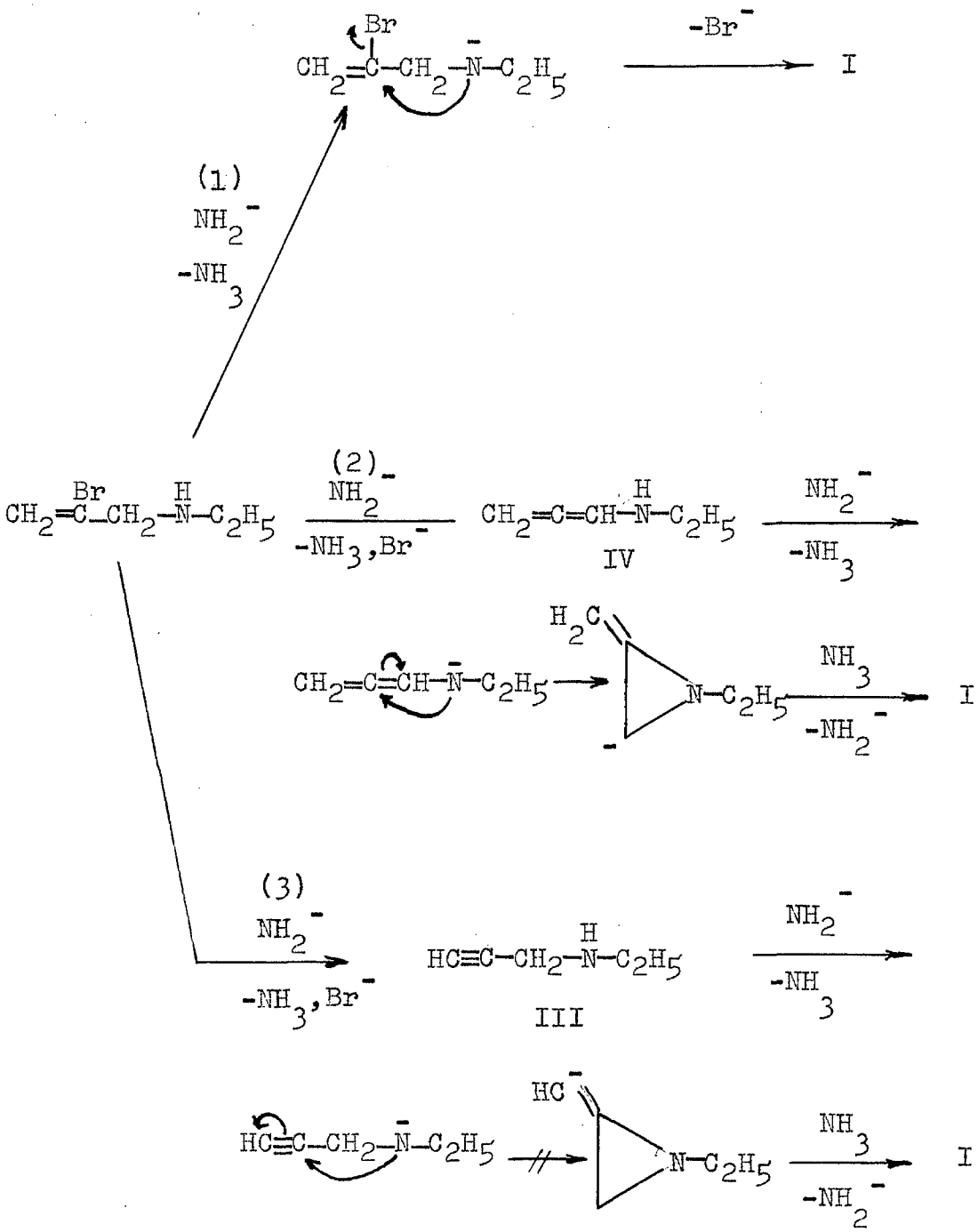
- -

(13) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N.Y., 1954, p. 49.

- -

N-ethylpropargylamine (III) by comparison of its infrared and n-m-r spectra with those of authentic III prepared in 71% yield by treatment of N-(2-chloroallyl)-ethylamine with potassium amide in liquid ammonia. III slowly took up 98% of the theoretical amount of hydrogen over platinum oxide in ethanol at atmospheric pressure to yield N-ethyl-n-propylamine which was identified as its hydrochloride.

The formation of I from N-(2-bromoallyl)-ethylamine and sodium amide can occur by either an internal displacement of bromide ion (1) or by an elimination-addition mechanism (2) involving an allenic amine intermediate (IV). The possibility of an analogous elimination-addition mechanism (3) involving N-ethylpropargylamine (III) is precluded by the high yield of III from the reaction of N-(2-chloroallyl)-ethylamine with


Br
CH2=C-CH2-N-C2H5
-Br⁻
I
(1)
NH2⁻
-NH3
CH2=C-CH2-N-C2H5
Br
H
(2)
NH2⁻
-NH3,Br⁻
CH2=C=CH-N-C2H5
H
IV
NH2⁻
-NH3
CH2=C=CH-N-C2H5
H2C
N-C2H5
NH3
-NH2⁻
I
(3)
NH2⁻
-NH3,Br⁻
HC≡C-CH2-N-C2H5
H
III
NH2⁻
-NH3
HC≡C-CH2-N-C2H5
HC⁻
N-C2H5
NH3
-NH2⁻
I

potassium amide. A choice between paths (1) and (2) might be made by employing N-(2-bromoallyl-1,1-d_2)-ethylamine and determining the amount of deuterium in the resulting I.

Acknowledgment.--We are indebted to Dr. Martin Ettlinger for drawing this problem to our attention in advance of publication[6] and suggesting the use of n-m-r spectra in its solution.

Experimental[14]

(14) Boiling points are uncorrected. Infrared spectra were obtained with a Model 21 Perkin-Elmer spectrophotometer. Microanalyses were performed by Dr. A. Elek.

N-Ethylallenimine, b.p. 77.0-78.2° (745 mm.), $n^{25}D$ 1.4283, was prepared by the method of Pollard and Parcell.[3] A fraction collected at 95-101° (745 mm.) representing 6% of the theoretical yield was shown by its infrared spectrum to be mainly N-ethylpropargylamine.

Hydrolysis of N-Ethylallenimine in the Presence of 2,4-Dinitrophenylhydrazine.--To a warm solution prepared from 0.25 g. of 2,4-dinitrophenylhydrazine, concentrated hydrochloric acid and ethanol[15] was added 0.1 g. of N-ethylallenimine. The mixture was allowed to stand overnight at room temperature and the yellow-brown needles were collected.

(15) S. M. McElvain, "The Characterization of Organic Compounds," The Macmillan Co., New York, N. Y., 1949, p. 199.

After two recrystallizations from ethanol, the product had m.p. 123.6-124.6° (lit.[3] m.p. 124-125°).

Anal. Calcd. for $C_9H_9N_4O_4Cl$: C, 39.65; H, 3.32. Found: C, 39.58; H, 3.34.

The infrared spectrum of the compound was identical with that of chloroacetone 2,4-dinitrophenylhydrazone, m.p. 122-124° (lit.[12] m.p. 124-125.5°).

To a warm solution prepared from 0.25 g. of 2,4-dinitrophenylhydrazine, sulfuric acid, water and ethanol[16] was added

- -

(16) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," Third Edition, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 171.

- -

0.1 g. of N-ethylallenimine. The mixture was allowed to stand overnight at room temperature and the orange platelets (52 mg.) were collected. The product was heated with 10 ml. of ethanol and 3 ml. of ethyl acetate on a steam bath for 10 min. and filtered hot. The insoluble material (13 mg.) had m.p. 302-304° (uncorr.) and an infrared spectrum identical with that of methylglyoxal bis-(2,4-dinitrophenyl)-osazone, m.p. 302-304° (uncorr.; lit.[17] m.p. 300-302°). The filtrate was allowed

- -

(17) W. Swoboda, Monatsh., 82, 388 (1951).

- -

to cool to room temperature and yielded 34 mg. of fine yellow needles which contained no sulfur and had m.p. 134-135°.

N-(2-Chloroallyl)-ethylamine.--To 88 ml. of a 70% aqueous solution of ethylamine was added 34 g. of 2,3-dichloropropene. The mixture was cautiously warmed on a steam bath to start the reaction and then allowed to boil gently under reflux for 15 min. When the spontaneous ebullition ceased, the mixture was heated under reflux for an additional 35 min. The two-phase mixture was cooled in an ice bath and 15 g. of solid sodium hydroxide was added cautiously. The upper layer (31.8 g.) was separated, dried over solid sodium hydroxide and distilled rapidly from a 50-ml. Claisen flask. The colorless N-(2-chloroallyl)-ethylamine (18.9 g., 52%) had b.p. 127-131°, $n^{25}D$ 1.4470.

Anal. Calcd. for $C_5H_{10}NCl$: C, 50.20; H, 8.43; N, 11.71. Found: C, 50.21; H, 8.54; N, 11.73.

N-Ethylpropargylamine.--To a stirred solution of potassium amide prepared from 6.9 g. of potassium and 350 ml. of anhydrous liquid ammonia in a three-necked flask equipped with a Dry Ice reflux condenser, stirrer and a dropping funnel was added 18.7 g. of N-(2-chloroallyl)-ethylamine over 10 min. Stirring was continued for eight hours, after which time, the ammonia was allowed to evaporate until a volume of about 75 ml. remained in the flask. Water (100 ml.) was cautiously added while stirring was continued. The mixture was then extracted with ether and the ether extracts were combined, dried over solid sodium hydroxide and most of the ether was removed by flash distillation. The residual N-ethylpropargylamine (9.23 g., 71%) was distilled through a 60-cm. Podbielniak

column, b.p. 100.2-101° (742 mm.), $n^{25}D$ 1.4315.

Anal. Calcd. for C_5H_9N: C, 72.24; H, 10.91; N, 16.85. Found: C, 72.01; H, 11.18; N, 16.82.

N-Ethylpropargylamine hydrochloride had m.p. 181.2-182.5° while the hydrobromide had m.p. 164.1-165.1° after crystallization from absolute ethanol-ether.

Anal. Calcd. for $C_5H_{10}NBr$: C, 36.61; H, 6.14; Br, 48.71. Found: C, 36.56; H, 6.24; Br. 48.87.

N-Ethylpropargylamine, when hydrogenated in absolute ethanol over platinum oxide at atmospheric pressure, took up 98% of the theoretical amount of hydrogen in 20 hours. The hydrochloride of the resulting N-ethyl-n-propylamine had m.p. 225.4-227.9° (lit.[18] m.p. 225°).

- -

(18) K. N. Campbell, A. H. Sommers and B. K. Campbell, THIS JOURNAL, 66, 82 (1944).

- -

The infrared spectrum of N-ethylpropargylamine had a strong, sharp band at 3300 $cm.^{-1}$, the characteristic stretching frequency of acetylenic carbon-hydrogen bonds,[13] and a weak band at 2100 $cm.^{-1}$, the characteristic stretching frequency of carbon-carbon triple bonds.[13] The n-m-r spectrum was in complete agreement with the assigned structure.

Pasadena, California

PART III

THE NITROGEN INVERSION FREQUENCY IN CYCLIC IMINES

Part of the work reported in this section was published as a Communication to the Editor in the Journal of the American Chemical Society, Vol. 78, p. 5126 (1956).

INTRODUCTION

Considerable effort has been expended in attempts to resolve substances into optical isomers which would owe their asymmetry solely to non-planar trivalent nitrogen.[1,2] Suitably substituted aziridines (ethylenimines) have been postulated to be particularly well constituted to permit existence of stable, optically active antipodes.[3-7] All attempts to resolve such imines have failed.

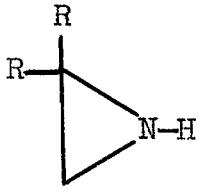
In this section, nuclear magnetic resonance (NMR) data are presented which indicate that resolution of aziridines in which the asymmetric center is trivalent nitrogen is unlikely except at rather low temperatures. Various factors that affect the nitrogen inversion frequency, and thus the rate of racemization, are discussed. The NMR spectra of larger-ring imines were also examined.

Attempts to Resolve Aziridine Derivatives

Failure to obtain optically active compounds in which the center of asymmetry is non-planar trivalent nitrogen is generally explained as being due to the ease with which molecules of the type NR'R''R''' undergo optical inversion. The existence of isolable syn- and anti-forms of oximes is attributed to the stability of the planar configuration about nitrogen in these compounds. The possibility that the strain of the carbon-nitrogen double bond in oximes is responsible for this stability of configuration prompted

several workers to investigate the possibility of resolving compounds in which asymmetric nitrogen was incorporated in the highly strained aziridine ring. In 1939, several investigators reported independent and unsuccessful efforts to resolve such compounds.

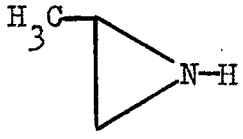
Meisenheimer and Chou[3] attempted to prepare 2,2-dimethyl-, 2,2-diethyl- and 2,2-dibenzylaziridine (I) from the corresponding disubstituted ethanolamines (II) via the chlorides.



I

$R_2C(OH)CH_2NH_2$

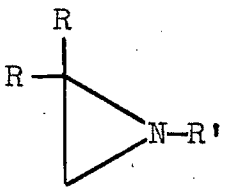
II



III

Replacement of the hydroxyl group with chlorine proved difficult and only unsaturated substances or oils were obtained. They successfully prepared 2-methylaziridine (III) which contains an asymmetric carbon atom. III was allowed to react with several optically active acids in the hope of obtaining two sets of racemates. Only one crystalline product was obtained, that from d-camphoric acid, from which III could not be regenerated.

Adams and Cairns[4] successfully prepared the theoretically resolvable 1-p-bromobenzenesulfonyl-2,2-dimethylaziridine (IV; R = CH_3, R' = p-$BrC_6H_4SO_2$) from the p-bromobenzenesulfonyl derivative of 1-amino-2-methyl-2-propanol via the



IV

$R_2C(NH_2)CH_2OH$

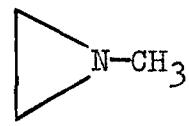
V

chloride. Attempts to prepare the d-camphorsulfonyl and the d-bromocamphorsulfonyl derivatives of the precursor alcohol gave only impure oils. The corresponding diphenyl alcohol, 1,1-diphenyl-2-aminoethanol gave a crystalline derivative with p-bromobenzenesulfonyl chloride, but not with d-α-bromocamphorsulfonyl chloride. The p-bromobenzenesulfonamide could not be converted to an aziridine derivative.

Mole and Turner[5] investigated compounds of type IV wherein R' contained a salt forming group remote from the nitrogen atom. They also examined other aziridine derivatives containing one or two asymmetric ring carbon atoms. Unfortunately, they gave no experimental details, although they referred to the unexpected difficulties encountered in synthesizing suitable compounds.

Adams and Cairns,[4] and Maitland,[6] suggested that the difficulty in obtaining suitable aziridine derivatives for resolution might be overcome by using aminoalcohols of type V as precursors. With such aminoalcohols, the possibility of dehydration to form allylamine or vinylamine derivatives is unlikely.

In the year following the appearance of these papers, Kincaid and Henriques[7] reported the results of a calculation of the energy barrier for optical inversion in 1-methylaziridine (VI).



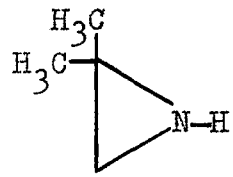
VI

Using Wall and Glocker's expression for the potential energy of ammonia,[8] they estimated an activation energy (E) of 38 kcal./mole for the nitrogen inversion. Since the approximations used in their calculation led to a value of 11 kcal./mole for the barrier height in ammonia, as compared to what they considered a more reasonable value of 8 kcal, Kincaid and Henriques corrected their E for VI to 25 kcal./mole. They noted that the necessary condition for resolution is an intramolecular first order rate constant for racemization of less than 10^{-5} sec.$^{-1}$ From the Arrhenius equation (Eq.1), and a "normal" preexponential factor of 10^{13}, it is easy to show that E must be greater than 25 kcal./mole if resolution

$$k' \approx 10^{13} e^{-E/RT} \qquad \text{(Eq.1)}$$

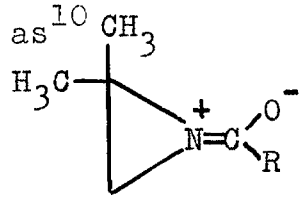
at room temperature is to be possible.

In 1941, Cairns[9] synthesized 2,2-dimethylaziridine (VII) from 2-amino-2-methylpropanol (V; R = CH_3) via the sulfonate ester. He prepared a crystalline derivative from VII and

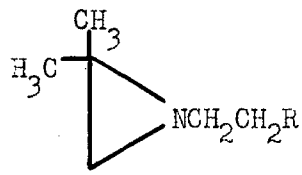


VII

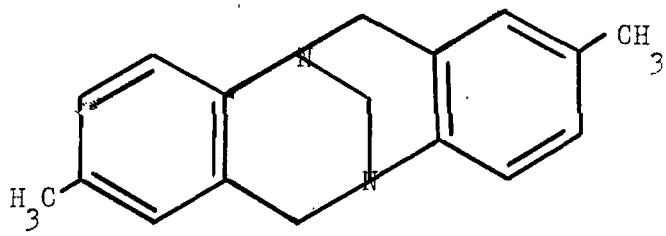
l-α-phenylethyl isocyanate and subjected it to repeated fractional crystallization. No evidence of separation into diastereoisomers was obtained. The urea derivative exhibited mutarotation in boiling benzene, but this was found to be due to decomposition. Cairns pointed out that the carbonyl group on the imine nitrogen would be expected to increase the nitrogen inversion frequency through contributions from resonance forms such as[10]



The next and last detailed account of attempts to resolve aziridine derivatives appeared in 1952. Kissman and Tarbell[11] prepared a colored urethan from 3-(2,2-dimethyl-1-aziridinyl)-propanol (VIIIa; R = CH_2OH) and p-phenylazophenyl isocyanate and chromatographed it on d-lactose. This elegant method, employed successfully by Prelog and Wieland[2] for the resolution of Troeger's base (IX), in which trivalent nitrogen is the asymmetric center, failed to effect a separation "due probably to lack of proper surface activity of the lactose." VIIIa and the corresponding amine (VIIIb;



VIII



IX

R = CH_2NH_2) were treated with optically active reagents with the object of separating the resulting diastereoisomers by crystallization or chromatography. However, the urethan and urea derivatives from VIIIa and VIIIb and l-α-phenylethyl isocyanate were non-crystalline as were those prepared from the isocyanate derived from l-menthyl-p-aminobenzoate. Kissman and Tarbell made note of the difficulty in obtaining crystalline derivatives of VIIIa and VIIIb from optically active reagents as compared to the ease with which crystalline products were formed with inactive reagents.

Applications of NMR Spectroscopy to the Measurement of Reaction Rates

In the NMR spectra of compounds containing non-equivalent protons, the proton resonance lines usually appear at frequencies corresponding to the different magnetic environments of each individual species.[12,13] Under ideal circumstances, the relative intensities of the resonance lines are given by

the relative numbers of chemically individual protons.[14] Gutowsky and co-workers,[15-17] through applications of the equations derived by Bloch[18] to describe the shape of the absorption lines, have shown that when exchange of nuclei between two individual chemical environments occurs at a rate such that the average lifetime ($\underline{t}$) in each environment is of the order of 10^{-4} sec., such exchange is capable of collapsing a complex NMR pattern into a simpler one. As $\underline{t}$ decreases, the observed separation, $d\underline{w}_e$, decreases from $d\underline{w}$ to 0. If the line widths at half-maximum intensity for the absorption lines in the complex spectrum are small with respect to $d\underline{w}$, a particularly simple expression (Eq. 2) results.[17]

$$d\underline{w}_e = (1 - 2/\underline{t}^2 d\underline{w}^2)^{\frac{1}{2}} d\underline{w} \text{ if } \underline{t}d\underline{w} > 2^{\frac{1}{2}} \qquad \text{(Eq. 2)}$$

$$d\underline{w}_e = 0 \text{ if } \underline{t}d\underline{w} \leq 2^{\frac{1}{2}}$$

As the chemical shift is proportional to the applied field, the temperature at which $d\underline{w}_e$ becomes 0 (T_T) will change with the applied field, thus allowing determination of the activation energy.[16]

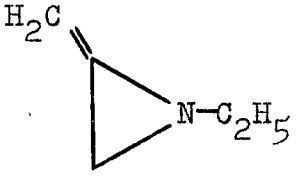
This method of measuring rates of chemical change is particularly valuable because it is applicable to reaction rates too rapid to be followed by conventional methods. NMR measurements of fast reaction rates of interest to organic chemists include studies of the kinetics of proton exchange between water and amine hydrochlorides,[19] the rates and activation energies of rotation about carbon-

nitrogen bonds of amides[17,20] and carbon-carbon bonds of rotationally hindered ethanes.[21] For other applications, see refs. 16, 22 and 23.

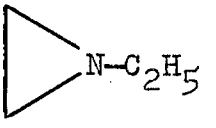
RESULTS AND DISCUSSION

Measurements of the Nitrogen Inversion Frequency

The NMR spectra of 1-ethylaziridine (X) and 1-ethyl-2-methyleneaziridine (XI) were found to be markedly temp-



XI



X

erature dependent (Fig. 1). At room temperature, X shows the characteristic bands of the ethyl group[24] and two triplet band systems separated by 27 c. p. s. at 40 mc. The latter band systems are best interpreted as being due to the two groups of ring hydrogens which are either *cis* or *trans* to the 1-ethyl group. In such event, the mean lifetime of a given imine molecule must be much greater than 0.052 sec. On heating to 120 - 130°, the ring hydrogens appear to lose their identity with respect to the position of the ethyl group and the mean lifetime before nitrogen inversion must be substantially less than 0.052 sec. The intermediate temperature, *i. e.* T_T, at which $t = 0.052$ sec. is $108^\circ \pm 5^\circ$.

XI shows only one band for the ring methylene group at room temperature. However, at and below -77°, this band is split into two components separated by about 30 c. p. s.

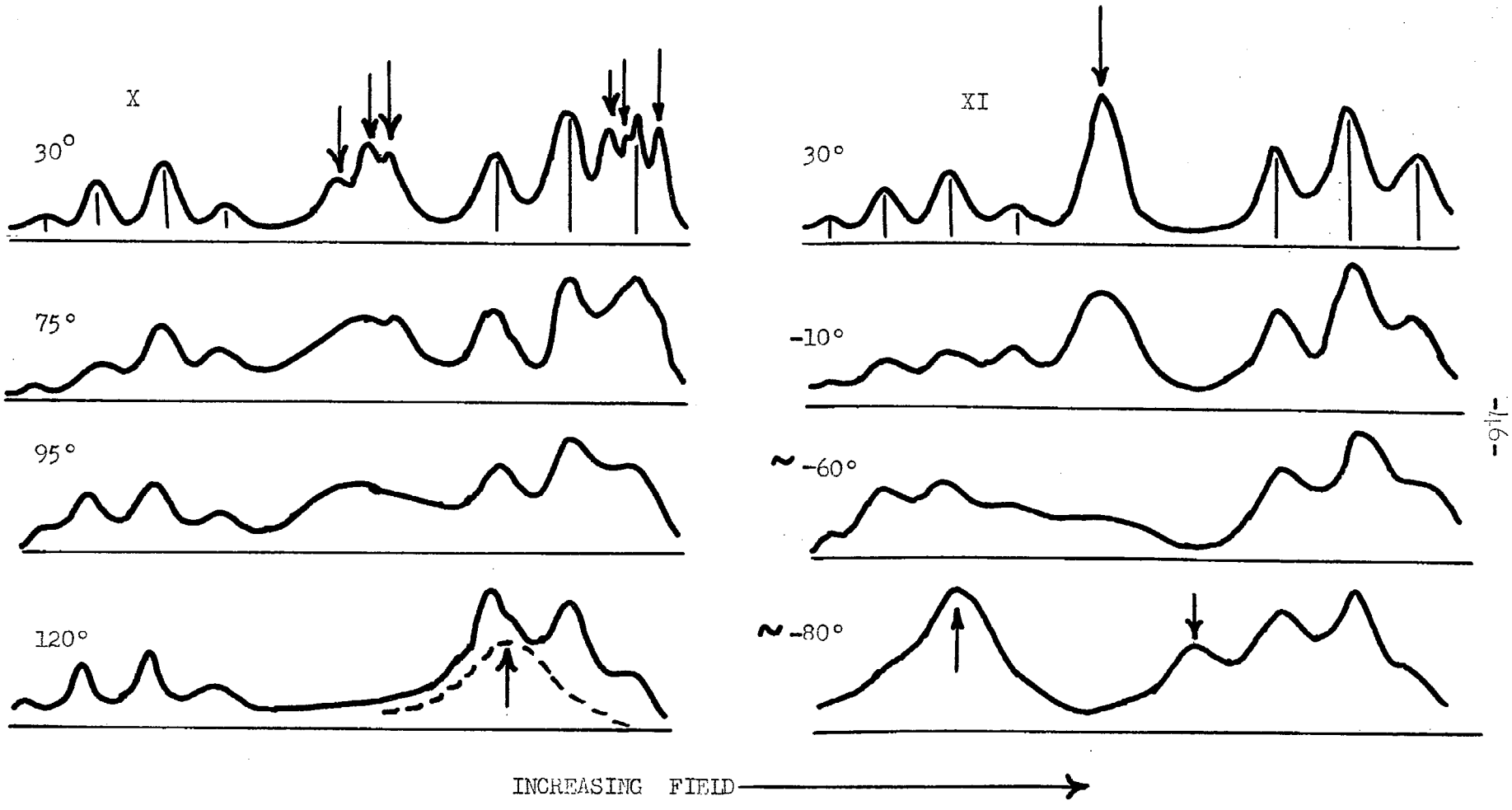
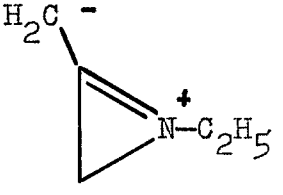

X
30°
75°
95°
120°
XI
30°
-10°
~ -60°
~ -80°
INCREASING FIELD

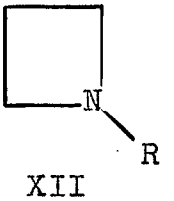
Fig. 1.-- Nuclear magnetic resonance spectra of protons of 1-ethylaziridine (X) and 1-ethyl-2-methyleneaziridine (XI) as a function of temperature with samples in 5.0-mm. o. d. tubes. Spectra were taken with the Varian Associates High Resolution Spectrometer (V-4300B) at 40 mc. with a vacuum-jacketed probe insert and 12-in. magnet equipped with Super Stabilizer. Heavy vertical lines mark characteristic bands of the ethyl group while vertical arrows indicate absorption of ring hydrogens. The temperature-invariant absorption of the double-bond methylene protons of XI is off scale on the left (see Part II, Fig. 1).

T_T is estimated to be about -65°, at which point the mean lifetime before inversion of the nitrogen is about 0.04 sec.

The tremendously faster inversion rate of XI compared to X is expected on the basis of contribution of electron delocalization involving the nitrogen and double bond as indicated by structure XIa. Such delocalization would markedly aid attainment of a planar inversion transition state.



XIa



XII

A number of suitably substituted aziridines and azetidines (XII) were prepared or obtained and their NMR spectra were examined at various temperatures. For each, T_T was determined with samples in either a vacuum-jacketed probe insert or a probe insert so constructed that the temperature of the sample was controlled by a flow of preheated air.[57] At T_T, $\underline{t}$ was taken as equal to $2^{\frac{1}{2}}/d\underline{w}$ (Eq. 2), and the first order rate constant, k', for the nitrogen inversion was obtained from the equality $k' = 1/\underline{t}$.[17] The activation energy, $\underline{E}$, was calculated from Eq. 3 derived

$$k' = \chi(kT/h)e^{-\underline{E}/RT} \qquad \text{(Eq. 3)}$$

from the theory of absolute reaction rates.[25] In Eq. 3, k is Boltzmann's constant, h is Planck's constant, T is the absolute temperature, R is the universal gas constant and κ, the transmission coefficient, was estimated as unity.

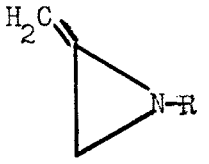
For a great many reactions κ is equal to unity,[58] which means that every activated complex becomes a product. As the nitrogen inversion is not expected to involve transitions between states of different multiplicities, for which values of κ are considerably less than unity, the assumed value for κ seems reasonable. It must be emphasized, however, that the calculated activation energies might be significantly in error since Gutowsky and Holm[17] found surprisingly low values of κ for rotation about the carbon-nitrogen bond of amides, transformations which would not seem to involve any considerable electronic change in state. Knowledge of actual values of the activation energies for nitrogen inversion await determinations of T_T at 10 mc.

For purposes of comparison, values of $\underline{t}$ at 25° were calculated from the observed $\underline{t}$ and the calculated values of $\underline{E}$. The results are summarized in Table I.

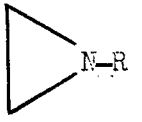
The results in Table I show that conjugation with nitrogen is a very important rate enhancing factor. At present, it is impossible to decide whether the decrease in energy brought about by electron delocalization is

Table I

The Nitrogen Inversion Frequencies in Substituted Aziridines and Azetidines



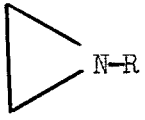
XI



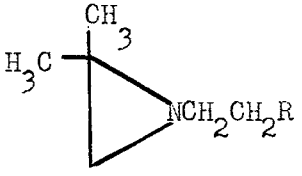
XIII

Compound	R	Solvent	T_T, °C	t, sec.	k, $sec.^{-1}$	E, kcal. per mole	t at 25°C, sec.
XI	C_2H_5	-	-65[a]	0.047	21.3	10.8	2×10^{-5}
XI	C_2H_5	CH_3OH	-25[a]	0.047	21.3	13.0	6×10^{-4}
XIIIa	C_2H_5	-	108[b]	0.052	19.2	20.4	90
XIIIa	C_2H_5	D_2O	>145	>0.052[c]	<19.2	>22.4	>2500
XIIIb	t-C_4H_9	-	<-70	<0.05[c]	>20	<11.1	$<10^{-5}$
XIIIb	t-C_4H_9	CH_3OH	<-70	<0.05[c]	>20	<11.1	$<10^{-5}$
XIIIc	C_6H_{11}	-	95[a]	0.061	16.4	19.8	34
XIIId	C_6H_5	-	<-77	<0.075[c]	>13.3	<10.3	$<10^{-5}$
XIIId	C_6H_5	CH_3OH	-60[a]	0.075	13.3	11.3	4×10^{-5}
XIIId	C_6H_5	$C_6H_5CH_3$	<-77	<0.075[c]	>13.3	<10.3	$<10^{-5}$
XIIIe	1-C_2H_4N	-	>120	>0.04[c]	<25	>20.8	>180

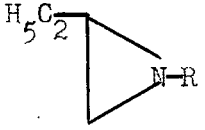
Table I - continued



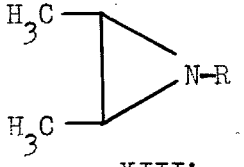
XIII



VIII



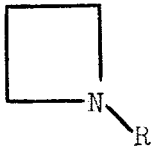
XIIIh



XIIIi

Compound	R	Solvent	T_T, °C	t, sec.	k', sec^{-1}	E, kcal. per mole	t at 25°C, sec.
XIIIf	$C_6H_5CH_2$	-	105[b]	0.052	19.2	20.2	67
XIIIg	$C_6H_5CH_2CH_2$	-	96[b]	0.045	22.2	19.6	25
VIIIa	CH_2OH	-	55[b]	0.32	3.1	18.6	5.5
VIIIc	$CO_2C_2H_5$	-	55[b]	0.24	4.2	18.4	4.0
XIIIh	C_2H_5	-	>140	>0.24[d]	<4.2	>23.4	>13000
XIIIi cis	C_2H_5	-	>140	>0.18[c]	<5.6	>23.2	>9000
XIIIi trans	C_2H_5	-	58[b]	0.18	5.6	18.4	3.9

Table I - continued

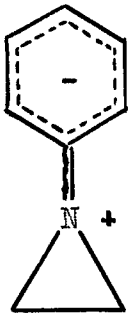


XII

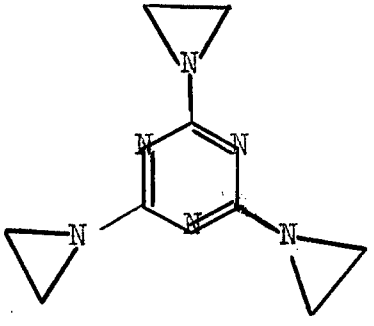
Compound	R	Solvent	T_T, °C	t sec.	k', sec^{-1}	E, kcal. per mole	t at 25°, sec.
XIIa	C_2H_5	-	<-90	<0.04[d]	>25	<9.1	$<10^{-6}$
XIIa	C_2H_5	CH_3OH	<-90	<0.04[d]	>25	<9.1	$<10^{-6}$
XIIb	n-C_4H_9	-	<-90	<0.04[d]	>25	<9.1	$<10^{-6}$
XIIc	t-C_4H_9	-	<-90	<0.04[d]	>25	<9.1	$<10^{-6}$

[a] ±10°. [b] ±5°. [c] Estimated by analogies to t's observed for compounds of a similar type. [d] Estimated.

greater in XI or the transition state of XIIId (XIIId'). This is because the net increase in energy due to bond angle strain in going from the ground state to the transition state is expected to be greater for XI than for XIIId.



XIIId'



XIV

Triethylenemelamine (XIV) was also prepared and its spectra in chloroform and in water were examined. At -40° and at -10°, where XIV began to crystallize from chloroform and water, respectively, there was no indication that T_T was approached.

In general, the effect of bulk of the substituent on nitrogen was found to be less than conjugation. 1-Benzyl-aziridine (XIIIf) and 1-(β-phenethyl)-aziridine (XIIIg) exhibited only slightly greater rates of nitrogen inversion than the 1-ethyl derivative (XIIIa). The character of the spectrum of the cyclohexyl derivative (XIIIc) in which one of the two ring-hydrogen bands overlaps with the broad cyclohexyl-hydrogen resonance, made exact determination

of T_T difficult. Disappearence of fine structure was not noted until above 80° and T_T was estimated at 95°±10° on this basis.

The greatest effect of bulk in increasing the nitrogen inversion frequency was observed with 1-t-butylaziridine (XIIIb). Examination of a model of XIIIb reveals that no conformation of the molecule exists with a tetrahedral configuration about nitrogen wherin the steric interactions of the t-butyl-hydrogens and the ring-hydrogens are greatly minimized. If one allows that the potential energy contribution of the substituent is the same in the ground and transition states, it follows that the lower barrier for inversion in XIIIb as compared to XIIIa results from the greater hydrogen-hydrogen repulsions in the ground state of XIIIb.

The argument just given explains why two groups attached to carbon on opposite sides of the imine ring of 1-substituted aziridines increase the inversion frequency. This increase was approximately the same when the groups were on the same or different carbon atoms.

The observed rates for nitrogen inversion in theoretically resolvable aziridines (VIIIa and VIIIc) were far too great to permit resolution at room temperature even if E were above 30 kcal. per mole. The problem can be shown more clearly with the aid of Table II. First order rate constants at different temperatures were calculated

for different values of E and the observed inversion frequency in VIIIa. Rate constants given below the dotted

Table II

Estimates of the Nitrogen Inversion Frequency in 3-(2,2-Dimethyl-1-aziridinyl)-propanol

Temp., °C	Frequency, sec.$^{-1}$, E = 15 kcal. per mole	20 kcal. per mole	25 kcal. per mole	30 kcal. per mole
20	1.9×10^{-1}	7.5×10^{-2}	3.0×10^{-2}	1.3×10^{-2}
0	2.9×10^{-2}	6.3×10^{-3}	1.4×10^{-3}	2.9×10^{-4}
-20	3.3×10^{-3}	3.5×10^{-4}	3.7×10^{-5}	3.8×10^{-6}
-40	2.6×10^{-4}	1.2×10^{-5}	5.2×10^{-7}	2.3×10^{-9}
-60	1.3×10^{-5}	2.0×10^{-7}	3.3×10^{-9}	5.1×10^{-11}
-80	3.2×10^{-7}	1.6×10^{-9}	7.4×10^{-12}	3.5×10^{-14}

lines in Table II are less than 10^{-5} and are considered small enough to permit resolution.[7] If the transmission coefficient (Eq. 3) for inversion of VIIIa is unity, and E is 18.4 kcal. per mole as calculated, the temperature required for successful resolution is below -50°.

The NMR spectra of the aziridine derivatives with one, or two substituents attached to the ring carbon atoms in a cis manner, XIIIh and XIIIi (cis) respectively, were found to be temperature independent even up to 140°. This is probably because the molecules have preferred orientations with the N-substituent trans to the other group(s).

Several imine inversion frequencies were substantially decreased in hydroxylic solvents undoubtedly because of stabilization of configuration through hydrogen bonding of the solvent with the imino nitrogen. For example, 1-ethylaziridine (XIIIa) in the pure liquid exhibits an inversion frequency of 19.2 $sec.^{-1}$ at $108^{\circ}\pm5^{\circ}$. This frequency is not reached in deuterium oxide solution even up to 145°. The effect of this stabilization, which is calculated to be at least 2.1 kcal. per mole, can be best shown by comparing the calculated values for $\underline{t}$ at 25°. In deuterium oxide solution, the average lifetime of configuration is at least 25 times longer than in the pure liquid at 25°. 1-Ethyl-2-methyleneaziridine (XI) has an inversion frequency of about 21.4 $sec.^{-1}$ at $-65^{\circ}\pm10^{\circ}$ in the pure liquid, but in 0.01 $\underline{N}$ methanolic sodium hydroxide solution, this inversion frequency is not reached until $-25^{\circ}\pm10^{\circ}$. The calculated energy of stabilization due to hydrogen bonding was 2.2 ± 0.2 kcal. per mole.

The NMR spectra of pure 1-phenylaziridine (XIIId) and pure 1-$\underline{t}$-butylaziridine (XIIIb) at -77° possessed only single sharp lines for the ring hydrogens indicating that inversion was occurring too rapidly for measurement. In 0.01 $\underline{N}$ methanolic sodium hydroxide solution, the inversion frequency in XIIId was decreased sufficiently to produce two ring-hydrogen bands in the spectrum and allow measure-

ment of a frequency of 13.4 sec.$^{-1}$ at -60°±10°. Dissolution of XIIIb in alkaline methanol did not change the shape of the spectrum at -77°.

No evidence was obtained for significant stabilization of configuration in 3-(2,2-dimethyl-1-aziridinyl)-propanol (VIIIa) from hydrogen bonding in the pure liquid. The absence of such an effect might be due to steric repulsion by the gem-dimethyl group.

The spectrum of 1-aziridinylaziridine (XIIIe) was independent of temperature from -70° in alkaline methanol solution to 120° as the pure liquid. The spectrum consisted of one absorption band, a sextet with J = 2.9. The presence of fine structure at 120° can be interpreted in two ways. It may indicate that the inversion rate is not rapid as might otherwise have been expected from the appearance of a single band system. However, this requires that there be no chemical shift for the cis and trans hydrogens. On the other hand, the inversion frequency may be too rapid to measure and the fine structure might be due to spin-spin splitting interraction from the ^{14}N to the hydrogens. Use of the so-called "double resonance" technique,[59] in which splitting due to ^{14}N is eliminated, should allow a choice of the proper interpretation.

The azetidine derivatives had T_T values considerably below -77°. Examination of the changing spectrum of a methanol solution of 1-ethylazetidine (XIIa) which had been

cooled to -196° revealed that on warming to room temperature the fine structure due to spin-spin coupling of the ring-hydrogen bands appeared later than that of the bands of the ethyl group. However, no reasonably accurate estimate of T_T could be made.

Kincaid and Henriques[7] have also calculated an upper limit of 15 kcal. per mole for the activation energy of inversion for trimethylamine. From simple considerations of strain, it is evident that five- or six-membered ring imines will be only slightly more stable than analogous open chain compounds. It was not surprising, therefore, when the NMR spectra of a number of N-substituted five- and six-membered ring imines were found to be temperature independent.

The NMR Spectra of Cyclic Imines

The resonance frequencies of the various bands in the spectra of a large number of cyclic imines were determined with respect to the benzene resonance at 40 mc. These results are summarized in Tables III-V. It was difficult to determine the resonance frequencies of some bands in complex spectra and these bands are so noted in the tables.

The aziridine-hydrogen bands in spectra of compounds undergoing slow nitrogen inversion, i.e. $t \gg 2^{\frac{1}{2}}/d_W$, were generally split into triplets with J, the separation due to spin-spin coupling, equal to 1.8 c.p.s. In the spectra of aziridine derivatives undergoing rapid nitrogen inversion, i.e. $t \ll 2^{\frac{1}{2}}/d_W$, the aziridine-hydrogen resonance was a sharp singlet. The spectrum of 1-aziridinylaziridine (XIIIe) was unusual. It was a sextet with $J = 2.9$.

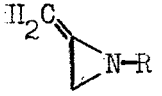
The splitting due to spin-spin coupling in the azitidine derivatives was more pronounced. The α- and β-hydrogen bands were triplets and quintets, respectively, with $J = 7.4$. Less well defined fine structure was present in the bands of the ring-hydrogens of pyrrolidine and morpholine derivatives and their hydrochlorides. The ring-hydrogen bands of piperidine derivatives and hydrochlorides were broad with no fine structure.

The resonance frequencies of the various ring-hydrogen bands in cyclic imines are shifted to lower fields compared to the corresponding bands in the respective hydrochlorides.

As expected, the shift is more pronounced in the bands of hydrogens closest to the nitrogen. The positions of the bands in the spectra of the hydrochlorides, with the exception of the water band, were found to be independent of the concentration of acid. The splitting of the exocyclic α-hydrogen bands observed in the spectra of the hydrochlorides in excess acid and the broadening of the water band observed in the spectra of some hydrochlorides is accounted for by the slowness of proton exchange between amine hydrochlorides and water.[19]

Table III

Resonance Frequencies in NMR Spectra of Aziridines and Azetidines[a]

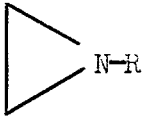


XI

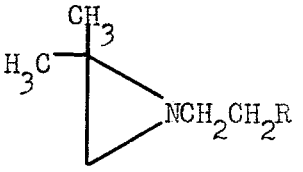
XIII

Sample	R	Solvent	Ring Hydrogens	Other Hydrogens
XI	C_2H_5	-	210	97 (CH_2) 186[b] (CH_2) 243[b](CH_2)
XI	C_2H_5	CH_3OH	206	94 (CH_2) 185[b] (CH_2) 243[b](CH_2)
XIII	H	-	218 238(N-H)	
XIII	H	H_2O	205	
XIII	H	D_2O	205	
XIIIa	C_2H_5	-	224[c] 251[c]	199[b](CH_2) 244[b](CH_3)
XIIIa	C_2H_5	D_2O	210[c] 237[c]	188[b](CH_2) 244[b](CH_3)
XIIIb	t-C_4H_9	-	222	239
XIIIb	t-C_4H_9	CH_3OH	217	239
XIIIc	C_6H_{11}	-	213[c] 236[c]	210[d]
XIIId	C_6H_5	-	215	-2

Table III - continued



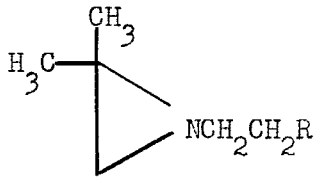
XIII



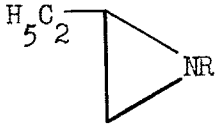
VIII

Sample	R	Solvent	Ring Hydrogens	Other Hydrogens
XIIId	C_6H_5	CH_3OH	209	- 2
XIIId	C_6H_5	$C_6H_5CH_3$	224	0
XIIIe	1-C_2H_4N	-	218[e]	
XIIIe	1-C_2H_4N	CH_3OH	211	
XIIIf	$C_6H_5CH_2$	-	223[c] 250[c]	-15(C_6H_5) 156(CH_2)
XIIIg	$C_6H_5CH_2CH_2$	-	234[c] 265[c]	- 9(C_6H_5) 185[d] 192[d]
VIIIa	CH_2OH	-	220 - 225 (?)	11(OH) 120($\underline{CH_2}OH$) 168($\underline{CH_2}N$) 204(2-CH_2) 219(CH_3) 223(CH_3)

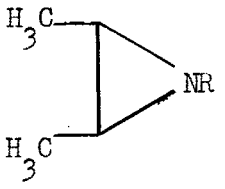
Table III - continued



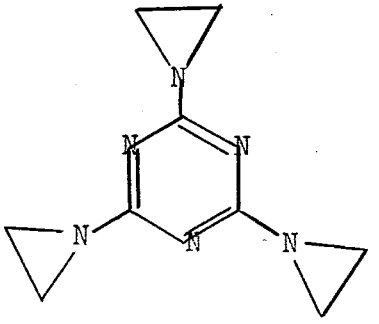
VIII



XIIIh



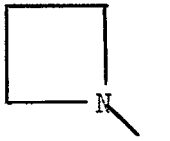
XIIIi



XIV

Sample	R	Solvent	Ring Hydrogens	Other Hydrogens
VIIIc	$CO_2C_2H_5$	-	210 - 240 (?)	$108^b(OCH_2)$ $176(CH_2CH_2)$ $226^b(CH_2\underline{CH_3})$ $234(CH_3)$ $240(CH_3)$
VIIIc	$CO_2C_2H_5$	CH_3OH	$209 - 225^f$	$108^b(OCH_2)$ $176(CH_2CH_2)$ $226^b(CH_2\underline{CH_3})$ $224(CH_3)$ $230(CH_3)$
XIIIh	C_2H_5	-	225 - 240 (?)	$189^f(CH_2)$ $233^f(CH_3)$
XIIIi <u>cis</u>	C_2H_5	-	235^f	$190(CH_2)$ $237(CH_3)_2$ $238^f(CH_2\underline{CH_3})$
XIIIi <u>trans</u>	C_2H_5	-	228 - 247 (?)	$185(CH_2)$ $237(CH_2\underline{CH_3})$ $230(CH_3)$ $237(CH_3)$
XIV	-	$HCCl_3$	136	

Table III - continued



XII

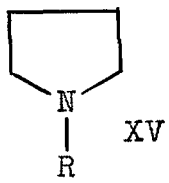
Sample	R	Solvent	Ring Hydrogens	Other Hydrogens
XIV	-	CH_3OH	167	
XIIa	C_2H_5	-	157^g($-CH_2$) 200^f($-CH_2$)	$188^f(CH_2)$ $249^b(CH_3)$
XIIa	C_2H_5	CH_3OH	155^g($-CH_2$) 200^f($-CH_2$)	$190^f(CH_2)$ $250^b(CH_3)$
XIIb	$\underline{n}$-C_4H_9	-	153^g($-CH_2$) 200^f($-CH_2$)	$185^f(NCH_2)$ 210 - 242 (several
XIIc	$\underline{t}$-C_4H_9	-	152^g($-CH_2$) 203^h($-CH_2$)	245

[a]Resonance frequencies in c.p.s. with respect to the benzene resonance at 40 mc.; ±3 unless otherwise indicated. [b]J = 7.2. [c]J = 1.8. [d]±5. [e]J = 2.8, sextet. [f]±10. [g]J = 7.4, quintet. [h]J = 7.4, triplet.

Table IV

Resonance Frequencies in NMR Spectra of

Pyrrolidine Derivatives[a]



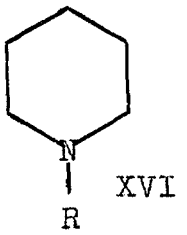
XV

Sample	Ring Hydrogens (2,5)	(3,4)	Other Hydrogens
XVa; R = H	163	212	180
XVa•HCl	125	180	59 (H_2O)
XVa•HCl with excess XVa	125	180	48 (H_2O)
XVa•HCl with excess acid	125	180	[b]
XVb; R = CH_3	189	218	194
XVb•HCl	113	172	73 (H_2O) 140
XVb•HCl with excess acid	113	173	140[c]
XVc; R = t-C_4H_9	170	210	237
XVc•HCl	125	180	67 (H_2O) 204
XVc•HCl with excess acid	123	174	199[d]
XVd; R = CHO	141	205	-64

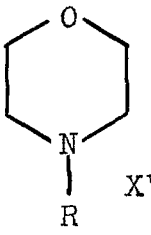
[a]Resonance frequencies in c. p. s. with respect to the benzene resonance at 40 mc.; ±5. [b]Six different acid concentrations; H_2O band at -42 to 43. [c]Methyl resonance; doublet, J = 5.5; six different acid concentrations; H_2O band at -36 to -1. [d]One acid concentration; H_2O band at 11.

Table V

Resonance Frequencies in NMR Spectra of Piperidine and Morpholine Derivatives[a]



XVI



XVII

Sample	Ring Hydrogens (2,6)	Ring Hydrogens (3,4,5)	Other Hydrogens
XVIa; R = H	167	219	204
XVIa·HCl	130	191	55 (H_2O)
XVIa·HCl with excess acid	130	192	[b]
XVIb; R = CH_3	191	224	196
XVIb·HCl with excess acid	120	187	65 (H_2O) 143[c]
XVIc; R = CHO	137	213	-57
XVId; R = C_2H_5	189	220	189[c] 240
XVId·HCl	127	192	75 (H_2O) 135[c] 211
XVId·HCl with excess acid	125	190	135[d] 210 [e]
XVIe; R = t-C_4H_9	171	214	235
XVIe·HCl	?	199	62 (H_2O) 215
XVIe·HCl with excess acid	124	197	215 [f]
XVIIa; R = H	168	132	192
XVIIa·HCl	127	99	62 (H_2O)
XVIIa·HCl with excess acid	125	95	[g]

Table V - continued

Sample	Ring Hydrogens (2,6)	Ring Hydrogens (3,4,5)	Other Hydrogens	
XVIIb; R = CH_3	183	130	189	
XVIIb·HCl	121	97	63 (H_2O)	142
XVIIb·HCl with excess acid	120	97	142[h]	i

[a]Resonance frequencies in c. p. s. with respect to the benzene resonance at 40 mc.; ±5. [b]Six different acid concentrations; H_2O band at -31 to 33. [c]Doublet, J = 5.3. [d]Methylene resonance, J = 7.4. [e]Six different acid concentrations, H_2O band at -52 to -27. [f]One sample; H_2O band at 47. [g]Six different acid concentrations; H_2O band at -38 to -2. [h]Doublet, J = 5.4. [i]Six different acid concentrations; H_2O band at -40 to -3.

Synthesis of Cyclic Imines

Most of the simple N-substituted aziridines and all the azetidines were prepared from the corresponding amino-alcohols via the sulfonate ester by the method of Elderfield and Hageman.[26] Other aziridine derivatives were prepared following literature procedures or their modifications, purchased, or generously provided by Drs. R. Ghirardelli and H. J. Lucas.[27]

The alkylaminoethanols were prepared most satisfactorily from either the alkylamine and ethylene oxide[28] or the alkylamine and ethylene chlorohydrin.[29] A satisfactory synthesis for 3-alkylaminopropanols from the alkylamines and trimethylene chlorohydrin was worked out. It is noteworthy that synthesis of these aminoalcohols from oxetane (trimethylene oxide) is impractical.[30] 3-t-Butylaminopropanol was obtained in fair yield from lithium aluminum hydride reduction of ethyl 3-t-butylaminopropionate. Similar reduction of the 3-ethylaminopropionate gave a low yield of alcohol.

1-Formylpyrrolidine (XVd) was prepared from chloral and pyrrolidine (XVa).[31] 1-Formylpiperidine (XVIc) was prepared by heating an ethyl formate solution of piperidine (xVIa) and distilling the mixture. 1-t-Butylpyrrolidine (XVc) and 1-t-butylpiperidine (XVIe) were prepared by boiling ethanolic mixtures of t-butylamine, sodium carbonate and the proper α,ω-dichloroalkane.

An attempt to N-formylate 2,2-dimethylaziridine with ethyl formate yielded only starting materials and polymers.

EXPERIMENTAL

Melting points are corrected unless stated otherwise. Boiling points are uncorrected. NMR spectra were obtained at 40 mc. with the Varian Associates High Resolution Spectrometer (V-4300B) with 12-in. magnet equipped with Super Stabilizer using samples contained in 5-mm. o. d. tubes. Infrared spectra were obtained with a model 21 Perkin-Elmer spectrophotometer. Microanalyses were performed by Dr. A. Elek.

2-t-Butylaminoethanol.-- The procedure is a modification of Biel's synthesis of the isopropylamino analog.[28] To a cooled, stirred mixture of 219 g. (3.0 moles) of t-butylamine, 5.0 g. of concentrated hydrochloric acid and 10.4 g. of water in a one-liter, three necked flask equipped with a stirrer, dropping funnel and reflux condenser was added 44 g. (1.0 mole) of ethylene oxide in five-ml. portions in one hour. The mixture was allowed to warm to room temperature and a mild exothermic reaction took place which maintained the mixture at gentle reflux for 30 min. The stirred mixture was then heated gently under reflux for 10 hours. Most of the t-butylamine was removed by distillation through a 500-ml. Claisen flask modified so that the distilling arm carried a 25 x 250-mm. section packed with glass helices. The remainder of the t-butylamine and the water were removed by distillation at aspirator pressure through an 8 x 600-mm. Podbielniak column[32] packed with a tantalum wire coil. 2-t-Butylaminoethanol was

collected at 74-76° (8 mm.); lit.[33] b.p. 84° (20 mm.). The colorless product solidified in the receiver when cooled in an ice bath, m.p. 44-46° (uncor.); lit.[33] m.p. 43-45°.

2-Cyclohexylaminoethanol.-- The modification of Biel's procedure[28] was used. From 200 g. (2.02 moles) of cyclohexylamine and 30 g. (0.68 mole) of ethylene oxide was obtained 95.6 g. (79%) of 2-cyclohexylaminoethanol, b.p. 87-89° (1 mm.), m.p. 37-39° (uncor.); lit.[36] b.p. 122-123.5° (13 mm.), m.p. 40-41°.

2-Benzylaminoethanol. A. From Benzylamine and Ethylene Chlorohydrin.-- The following is a modification of the procedure of Wedekind and Bruck.[29] A mixture of 214 g. (2.0 moles) of benzylamine, 80 g. (1.0 mole) of ethylene chlorohydrin and 30 g. (1.67 moles) of water was heated on a steam bath for five hours. Sixty grams (1.5 moles) of sodium hydroxide was added to the cooled solution and the resulting mixture was heated on a steam bath for 30 min. Water (400 ml.) was added to dissolve the inorganic salts and the two-phase mixture was extracted twice with 200- and 100-ml. portions of benzene. The extracts were combined and the water was removed by co-distillation with benzene through the modified Claisen flask. The residual benzene was removed by distillation through the modified Claisen flask at atmospheric pressure and by distillation through the Podbielniak column at 24-33° (77-96 mm.). Benzylamine (100.2 g.) was collected at 89° (40 mm.). 2-Benzylaminoethanol (86.1 g., 57%) was

collected at 112-114° (1 mm.) $n^{25.2}D$ 1.5418; lit.[35] b.p. 148-149° (13 mm.).

B. From Benzaldehyde and Ethanolamine.-- The general procedure of Cope and Hancock[36] for the preparation of 2-alkylaminoethanols was used. 2-Benzylaminoethanol, b.p. 113-114° (1 mm.), was obtained in 15% yield from 61 g. (1.0 mole) of ethanolamine and 122 g. (1.15 mole) of benzaldehyde.

3-n-Butylaminopropanol.-- The following procedure was found to be the most satisfactory. Trimethylene chlorohydrin (142 g., 1.5 moles) was added to a solution of 385 g. (5.0 moles) of n-butylamine and 165 ml. (9.1 moles) of water. The reaction mixture was allowed to stand at room temperature for 18 hours and was then heated at reflux on a steam bath for four hours. The mixture was cooled in an ice bath and 80 g. of solid sodium hydroxide was added cautiously. About 200 ml. of water was added to dissolve the inorganic salts and the mixture was extracted three times with 300-ml. portions of ether, the extracts combined, dried over sodium carbonate and the ether and most of the n-butylamine were removed by flash distillation through a Claisen head. The residue was distilled through the Podbielniak column. 3-n-Butylaminopropanol (121 g., 61%) was collected at 83-86° (1.5 mm.), $n^{22}D$ 1.4488; lit.,[30] b.p. 106-108 (16 mm.), $n^{25}D$ 1.4474. The product had the same b.p., $n^{22}D$, infrared spectrum and NMR spectrum as a sample prepared in 13% yield from 1.4 moles of trimethylene bromohydrin and 1.4 moles of n-butylamine.[37]

3-Ethylaminopropanol.-- Following the above method for the preparation of 3-n-butylaminopropanol, 3-ethylaminopropanol was prepared in 29% yield from 2.0 moles of trimethylene chlorohydrin and 600 ml. of 70% aqueous ethylamine solution. The product had b.p. 90-91° (12 mm.), $n^{25}D$ 1.4463; lit.[37] b.p. 181°, n 1.4550 (no temperature or wave length given). The infrared and NMR spectra of the product were dissimilar from those of trimethylene chlorohydrin and in agreement with the 3-ethylaminopropanol structure. Elemental analysis indicated that the product contained 5% trimethylene chlorohydrin.

Anal. Calcd. for $C_5H_{13}ON$: C, 58.21; H, 12.70. Found: C, 57.00; H, 12.41.

Ethyl 3-Ethylaminopropionate.-- The procedure is a modification of that used by Morsch[38] for the preparation of methyl 3-methylaminopropionate. Ethyl acrylate (180 g., 1.8 moles) was added with cooling to 330 ml. of a stirred 6 M solution of ethylamine in absolute ethanol. The mixture was allowed to stand at room temperature for two days. Most of the ethanol was removed by distillation and the residue was allowed to stand for two days and distilled. Ethyl 3-ethylaminopropionate (232 g., 87%) was collected at 74-76° (30 mm.), $n^{31.4}D$ 1.4231.

Anal. Calcd. for $C_7H_{15}O_2N$: C, 57.90; H, 10.41; N, 9.65. Found: C, 58.13; H, 10.30; N, 9.99.

The Reaction of Ethyl 3-Ethylaminopropionate with Lithium Aluminum Hydride.-- To a stirred suspension of 11.0 g. (0.29 mole) of lithium aluminum hydride and 500 ml. of ether in a one-liter, three-necked flask equipped with a reflux condenser, dropping funnel and sealed mechanical stirrer was added dropwise in two hours a solution of 52 g. (0.36 mole) of ethyl 3-ethylaminopropionate in 100 ml. of dry ether. The mixture was stirred for an additional hour and allowed to stand overnight. The complexes were destroyed by the cautious dropwise addition of 22 g. of water to the stirred mixture, the mixture was filtered and the filtrate was dried over potassium carbonate. The drying agent was removed by filtration and most of the ether was removed by distillation through the modified Claisen flask. The remainder of the ether was removed by distillation through the Podbielniak column, the last traces at aspirator pressure. The residue was distilled at reduced pressure and two fractions were taken. The fraction with b.p. 96-99° (34 mm.) weighed 6.0 g. and was primarily the aminoalcohol with a small amount of unreacted ester as shown by its infrared spectrum. The other fraction (4.6 g.) had b.p. 136-145° (6 mm.).

Ethyl 3-t-Butylaminopropionate.-- Following the modified procedure of Morsch, ethyl 3-t-butylaminopropionate, b.p. 91-93° (6 mm.), $n^{23}D$ 1.4244, was prepared in 84% yield from 1.8 moles of ethyl acrylate and 2.0 moles of t-butylamine.

Anal. Calcd. for $C_9H_{19}O_2N$: C, 62.39; H, 11.05; N, 8.09. Found: C, 62.31; H, 11.02; N, 8.40.

3-t-Butylaminopropanol. A. From the Reaction of Ethyl 3-t-Butylaminopropionate and Lithium Aluminum Hydride.-- Using essentially the same procedure as described for the reduction of ethyl 3-ethylaminopropionate, 240 g. (1.4 moles) of ethyl 3-t-butylaminopropionate and 42 g. (1.1 moles) of lithium aluminum hydride yielded 44.3 g. (24%) of crude 3-t-butylaminopropanol, m.p. 69-73°; lit.[39] m.p. 67-69°. A second crop of 35.9 g. with m.p. 71-88° was also taken. Only the first crop was converted to 1-t-butylazetidine.

B.-- From Trimethylene Chlorohydrin and t-Butylamine.-- The procedure described for the preparation of 3-n-butylaminopropanol was used. After most of the ether had been removed, the residue was allowed to cool to room temperature. Long, white needles of 3-t-butylaminopropanol separated and they were collected by suction filtration. The needles weighed 53.2 g. and had m.p. 73.5-75.3°. A second crop of 20.2 g., m.p. 66-71°, was taken from the filtrate and the mother liquor was distilled. The aminoalcohol (19.2 g.), which solidified in the receiver, was collected at 85-87° (3 mm.); m.p. 64-70°. The overall yield was 48%.

Synthesis of Cyclic Imines from Aminoalcohols.-- The method employed by Elderfield and Hageman[26] for the synthesis of 1-n-butylaziridine was used. The following is a typical procedure. 2-t-Butylaminoethanol (72.5 g., 0.62 mole) was dissolved in 400 ml. of absolute ethanol and the solution was made acidic to methyl orange with concentrated hydrochloric acid. Most of the ethanol was removed on a lyophilizer[40] at aspirator pressure and the remainder was removed at 1 mm. The crude, dry hydrochloride, contained in a one-liter flask, was converted to the sulfonate ester by the cautious, portion-wise addition of 120 g. (1.03 moles) of chlorosulfonic acid. The reaction mixture was shaken vigorously after each addition until the vigorous reaction subsided. The reaction mixture, protected with a calcium chloride tube, was heated on a steam bath for 40 min. and in an oil bath first at 80° under water pump pressure and finally at 140-145° for 1.5 hours. The crude sulfonate was taken up in 190 ml. of cold water and added in portions in 40 min. to a vigorously stirred solution of 225 g. (3.5 moles) of 85% potassium hydroxide and 250 ml. of water in a two-liter, three-necked flask equipped with a stirrer and reflux condenser. The temperature of the reaction mixture was maintained below 70° by occasional cooling in an ice bath. The mixture was stirred for two hours and allowed to stand overnight. Propylene glycol (5 ml.) was added and the mixture was indirectly steam distilled through a foam-trap. The condenser and receiver had both been rinsed twice with 100-ml. portions of 3 N sodium

hydroxide solution. Potassium hydroxide (85%; 30 g.) was dissolved in the cooled homogeneous distillate (500 ml.) and the resulting mixture was extracted three times with 200-ml. portions of ether. The extracts were combined and dried over potassium carbonate. The drying agent was removed by filtration and the filtrate was concentrated to a volume of 90 ml. by distillation through an 18 x 1000-mm. column packed with glass helices and equipped with a total reflux head. The residue was distilled through the Podbielniak column. The yield and physical properties are given in Table VI together with those of other aziridines and azetidines. The elemental analyses of new compounds are given in Table VII.

1-Phenylaziridine (XIIId).-- Following the procedure of Heine, Kapur and Mitch,[43] 40 g. (0.11 mole) of 2-anilinoethyl bromide hydrobromide,[44] m.p. 137-139° (lit.[44] m.p. 138-139°) was converted in 60% yield to XIIId, b.p. 73-74° (18 mm.), $n^{23}D$ 1.5518; lit.[43] b.p. 70° (13 mm.), $n^{25}D$ 1.5498.

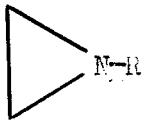
1-(β-Phenethyl)-aziridine (XIIIg).-- Following Bestian's procedure,[45] 17.2 g. (0.40 mole) of aziridine and 20.8 g. (0.20 mole) of styrene were converted in 94% yield to XIIIg, b.p. 78-79° (3 mm.), $n^{21.8}D$ 1.5220; lit.[45] b.p. 89° (8 mm.).

Triethylenemelamine (XIV).-- Cyanuric chloride (18.4 g., 0.10 mole) and 14.0 g. (0.32 mole) of aziridine were converted to XIV in 78% yield by the method of Wystrach, Kaiser and Schaefer,[46] dec. pt. 138°; lit.[46] dec. pt. 139°.

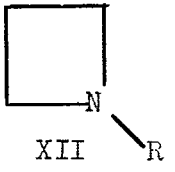
Table VI

Yields and Physical Properties of 1-Substituted Aziridines (XIII)

and Azetidines (XII)



XIII



XII

Compound	R	Yield, %	b.p. (mm.)	$n^T D$	T
XIIIb	t-C_4H_9	27	91-92° (745)	1.4110	22
XIIIc	C_6H_{11}	32	89-90° (66)	1.4592	26
XIIIf	$C_6H_5CH_2$ [a]	65	86-88° (12)	1.5298	22
XIIa	C_2H_5	13	74-75° (743)	1.4090	25.5
XIIb	n-C_4H_9 [b,c]	24	128-129° (748)	1.4241	25.6
XIIc	t-C_4H_9 [d]	47	116.5-117.3° (747)	1.4241	25.6

[a]The sulfonate ester was prepared with sulfuric acid by the method of Leighton, Perkins and Renquist[41] and isolated and reacted by the method described; lit.[42] b.p. 84-87° (8 mm.), $n^{20}D$ 1.5300. [b]Lit.[26] b.p. 127-128°. [c]The methiodide deriva-

Table VI - Continued

tive had dec. pt. 150°. Anal. Calcd. for $C_8H_{18}NI$: C, 37.66; H, 7.11. Found: C, 38.19; H, 7.12 [d]The methiodide derivative had dec. pt. 227°. Anal. Found: C, 37.84; H, 7.05.

Table VII

Elemental Analyses of New 1-Substituted Aziridines and Azetidines

		Calcd.			Found		
Compound	R	C	H	N	C	H	N
XIIIc	$\underline{t}$-C_4H_9	72.67	13.21	14.12	72.84	13.22	14.26
XIIIf	C_6H_{11}	76.74	12.08	11.18	76.91	12.18	10.944
XIIa	C_2H_5	70.53	13.03	16.44	70.65	13.14	16.56
XIIc	$\underline{t}$-C_4H_9	74.27	13.36	12.37	74.56	13.30	12.46

Ethyl 3-(2,2-Dimethyl-1-aziridinyl)-propionate (VIIIc).-- The modification of Morsch's procedure was followed. VIIIc was obtained in 71% yield from 0.56 mole of 2,2-dimethyl-aziridine and 0.54 mole of ethyl acrylate. The colorless oil had b.p. 95-97° (11 mm.), $n^{25}D$ 1.4312.

Anal. Calcd. for $C_9H_{17}O_2N$: C, 63.13; H, 10.01; N, 8.18. Found: C, 63.10; H, 9.93; N, 8.14.

3-(2,2-Dimethyl-1-aziridinyl)-propanol (VIIIa).-- Following the procedure described by Kissman and Tarbell[12] for the reduction of the methyl ester, 0.12 mole of VIIIc was reduced with 0.077 mole of lithium aluminum hydride to VIIIa in 68% yield. The product had b.p. 101-102° (20 mm.), $n^{22}D$ 1.4547; lit.[12] b.p. 110° (24 mm.), $n^{25}D$ 1.4535.

Other Aziridine Derivatives.-- 1-Ethylaziridine (XIIIa) (Matheson, Coleman and Bell) was distilled through the Podbielniak column at 51.7-52.3° (746 mm.), $n^{25}D$ 1.3920 (lit.[47] b.p. 48.5-49.0° at 690 mm.). The preparations of the samples of other derivatives have been described elsewhere.[27,47]

1-Formylpyrrolidine (XVd).-- Following the procedure of Blicke and Lu,[31] XVd was prepared in 93% yield from 0.50 mole of chloral. The product had b.p. 82-85° (10 mm.), $n^{25.5}D$ 1.4774; lit.[31] b.p. 87-89° (16 mm.).

1-Methylpyrrolidine (XVb).-- Following the general procedure of Blicke and Lu[31] for the reduction of N-formylamines, 0.42 mole of XVd was reduced with 0.42 mole of lithium aluminum hydride to XVb in 53% yield; b.p. 79.0° (742 mm.), $n^{28}D$ 1.4195; lit.[49] b.p. 77-78°.

1-Formylpiperidine (XVIc).-- A mixture of 30 g. (0.35 mole) of piperidine and 165 g. (2.75 moles) of ethyl formate was heated at reflux on a steam bath for three hours and allowed to stand overnight. Most of the methanol and methyl formate were removed by distillation through a 30-cm Vigreux column and the residue was distilled from a 50-ml. Claisen flask. XVIc (37.4 g., 94%) had b.p. 73-75° (2 mm.), $n^{25}D$ 1.4770; lit.[31] b.p. 104-105 (16 mm.).

1-t-Butylpyrrolidine (XVc).-- The procedure is essentially that used by Elderfield and Hageman[26] for the preparation of 1-n-butylpyrrolidine. To a 500-ml. three-necked flask equipped with a stirrer and reflux condenser was added 60 ml. of absolute ethanol, 63.6 g. (0.60 mole) of sodium carbonate, 66 g (0.90 mole) of t-butylamine and 76.2 g. (0.60 mole) of 1,4-dichlorobutane. The mixture was heated under reflux with stirring for 40 hours over a period of six days. During the heating periods, a white solid formed in the condenser. The reaction mixture was cooled and the inorganic salts were removed by suction filtration. The unreacted amine and most of the ethanol were removed by distillation through the modified Claisen flask and 300 ml. of

water was added to the cooled residue in order to dissolve the precipitated salts. The resulting two-phase mixture was separated and the aqueous solution was extracted with 200 ml. of ether. The ethereal solution was combined with the organic phase and extracted three times with 100-ml. portions of 2 N hydrochloric acid. The acidic extracts were combined, washed with 50 ml. of ether, made alkaline with 3 N sodium hydroxide solution and extracted twice with 150-ml. portions of ether. The extracts were combined and dried over sodium carbonate. The drying agent was removed by filtration and most of the ether was removed by flash distillation through the Podbielniak column. The residue was distilled and 30.2 g (40%) of XVc was collected at 146-147° (747 mm.), $n^{20.6}D$ 1.4429.

Anal. Calcd. for $C_8H_{17}N$: C, 75.52; H, 13.47; N, 11.01. Found: C, 75.50; H, 13.51; N, 11.05.

The methiodide had dec. pt. 249°.

Anal. Calcd. for $C_9H_{20}NI$: C, 40.16; H, 7.49. Found: C, 40.76; H, 7.62.

1-t-Butylpiperidine (XVIe).-- Following the procedure described for the preparation of XVc, XVIe was obtained in 25% yield from 0.60 mole of 1,5-dichloropentane. XVIe had b.p. 165-166° (745 mm.), $n^{20.6}D$ 1.4525.

Anal. Calcd. for $C_9H_{19}N$: C, 76.53; H, 13.56; N, 9.92. Found: C, 76.40; H, 13.49; N, 9.85.

The methiodide had dec. pt. 225°.

Anal. Calcd. for $C_{10}H_{22}NI$: C, 42.42; H, 7.83. Found: C, 42.51; H, 7.86.

Other Cyclic Imines.-- 1-Methylpiperidine was prepared by Mr. P. Jordan from 1-formylpiperidine.[31] The other cyclic imines were redistilled commercial products. Physical properties of these imines are given in Table VIII.

Hydrochlorides of Several Cyclic Imines.-- Several hydrochlorides were prepared as follows: one milliliter of the imine was dissolved in 20 ml. of dry ether and dry hydrogen chloride was passed into the cooled solution. The hygroscopic hydrochlorides were collected on sintered glass funnels and dried in a vacuum desiccator. Samples of the dry hydrochlorides were sealed in capillary tubes and their m.p.'s were determined. The results are summarized in Table IX.

Attempted N-Formylation of 2,2-Dimethylaziridine.-- A mixture of 160 ml. (2.0 moles) and 11.3 g (0.16 mole) of 2,2-dimethylaziridine was heated under reflux on a steam bath for three hours, cooled in an ice bath and allowed to stand overnight. Most of the ethyl formate was removed by flash distillation through the Podbielniak column. Distillation of the residue yielded only the remaining ester and

3.6 g. (32%) of the starting imine, b.p. 71-72°. The residue was an unguent, colorless mass which did not distill at 2 mm. with a bath temperature of 170°.

Table VIII

Physical Properties of Some Five- and Six-membered Ring Imines

Compound	b.p. (mm.)	Lit. b.p. (mm.)	Ref.	$n^{T}D$	T	Lit. $n^{20}D$	Ref.
Pyrrolidine	86-87° (743)	86-87°	50	1.4390	25.8	1.4424	50
Piperidine	105.0-105.7° (742)	106.3°	51	1.4522	25	1.4534	51
1-Methylpiperidine	101-102°	107°	52	1.4348	25	1.4378[a]	55
1-Ethylpiperidine	128-129 (745)	130.8°	51	1.4414	25.6	1.4440	51
Morpholine	126.5-127°	128.9°	53	1.4500	25	1.4545	53
N-Methylmorpholine	115.0-115.8° (743)	116-117°	54	1.4352	23.6	1.4332	54

[a] Taken at 21.6°

Table IX

Melting Points of Some Cyclic Imine Hydrochlorides

Hydrochloride	m.p., °C	Lit. m.p., °C	Ref.
Pyrrolidine	151-153	--	--
1-Methylpyrrolidine	172-176	--	--
Morpholine	174-177	176	56
1-Methylmorpholine	195-200	205	54
Piperidine	246-249	246-247	51
1-Ethylpiperidine	234-236	233	51

REFERENCES

1. R. L. Shriner, R. Adams and C. S. Marvel in H. Gilman, "Organic Chemistry, An Advanced Treatise," John Wiley and Sons, Inc., New York, N.Y., Second Edition, 1943, Vol. I, pp. 402-413.
2. V. Prelog and P. Wieland, Helv. Chim. Acta, 27, 1127-1134 (1944).
3. J. Meisenheimer and L.-H. Chou, Ann., 539, 70-77 (1939).
4. R. Adams and T. L. Cairns, J. Am. Chem. Soc., 61, 2464-2467 (1939).
5. J. D. C. Mole and E. E. Turner, Chem. and Ind., 17, 582 (1939).
6. P. Maitland, Ann. Rept. Chem. Soc. London, 36, 239-246 (1939).
7. J. F. Kincaid and F. C. Henriques, Jr., J. Am. Chem. Soc., 62, 1474-1477 (1940).
8. F. T. Wall and G. Glocker, J. Chem. Phys., 5, 314-315 (1937).
9. T. L. Cairns, J. Am. Chem. Soc., 63, 871 (1941).
10. L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, New York, 1948, 2nd Edition, p. 207.
11. H. M. Kissman and D. S. Tarbell, J. Am. Chem. Soc., 74, 4317-4319 (1952).
12. H. S. Gutowsky and C. J. Hoffman, Phys. Rev., 80, 110-111 (1950).

13. E. L. Hahn, ibid., 80, 580-594 (1950).

14. H. S. Gutowsky, D. W. McCall, B. R. McGarvey and L. H. Meyer, J. Am. Chem. Soc., 74, 4809-4817 (1952).

15. H. S. Gutowsky, D. W. McCall and C. P. Slichter, J. Chem. Phys., 21, 279-292 (1953).

16. H. S. Gutowsky and A. Saika, ibid., 21, 1688-1694 (1953).

17. H. S. Gutowsky and C. H. Holm, ibid., 25, 1228-1234 (1956).

18. F. Bloch, Phys. Rev., 70, 460-474 (1946).

19. E. Grunwald, A. Lowenstein and S. Meiboom, J. Chem. Phys., 25, 382-383 (1956).

20. W. D. Phillips, ibid., 23, 1363-1364 (1955).

21. J. J. Drysdale and W. D. Phillips, J. Am. Chem. Soc., 79, 319-322 (1957).

22. E. R. Andrew, "Nuclear Magnetic Resonance," Cambridge University Press, Glasgow, U. K., 1955, p. 147.

23. H. M. McConnell and H. E. Weaver, Jr., J. Chem. Phys., 26, 307-311 (1956).

24. B. P. Dailey and J. N. Shoolery, J. Am. Chem. Soc., 77, 3977-3981 (1955).

25. S. Glasstone, K. J. Laidler and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N.Y., 1941, p. 295.

26. R. C. Elderfield and H. A. Hageman, J. Org. Chem., 14, 605-637 (1949).

27. R. Ghirardelli and H. J. Lucas, J. Am. Chem. Soc., 79, 734-741 (1957).

28. J. H. Biel, ibid., 71, 1306-1309 (1949).

29. E. Wedekind and E. Bruck, Ann., 471, 73-112 (1929).

30. S. Searles and V. P. Gregory, J. Am. Chem. Soc., 76, 2789-2790 (1954).

31. F. F. Blicke and C.-J. Wu, ibid., 74, 3933-3934 (1952).

32. J. Cason and H. Rapoport, "Laboratory Text in Organic Chemistry", Prentice Hall, Inc., New York, N. Y., 1950, pp. 237-243.

33. R. E. Holmen and D. D. Carroll, J. Am. Chem. Soc., 73, 1859-1860 (1951).

34. W. H. Carothers and G. A. Jones, ibid., 47, 3051-3057 (1925).

35. H. Schotte, D. R. P. 442, 413 (1927); C. Zentr., 1929, II, 636.

36. A. C. Cope and E. M. Hancock, J. Am. Chem. Soc., 64, 1503-1506 (1942).

37. S. D. Goldberg and W. F. Whitmore, ibid., 59, 2280-2282 (1939).

38. K. Morsch, Monatsh., 63, 220-235 (1933).

39. F. Wille and L. Saffer, Ann., 568, 34-46 (1950).

40. M. E. Volk, Anal. Chem., 27, 1207 (1955).

41. P. A. Leighton, W. A. Perkins and M. L. Renquist, J. Am. Chem. Soc., 69, 1540 (1947).

42. W. S. Gump and E. J. Nikawitz, ibid., 72, 1309-1312 (1950).

43. H. W. Heine, B. L. Kapur and C. S. Mitch, ibid., 76, 1173 (1954).

44. W. J. Pearlman, ibid., 70, 871 (1948).

45. H. Bestian, Ann., 566, 210-244 (1950).

46. V. P. Wystrack, D. W. Kaiser and F. C. Schaefer, J. Am. Chem. Soc., 77, 5915-5918 (1955).

47. P. A. Laselle and S. A. Sundit, ibid., 63, 2374-2376 (1941).

48. A. T. Bottini and J. D. Roberts, ibid., 79, 1462-1464 (1957).

49. L. C. Craig and R. M. Hixon, ibid., 53, 187-190 (1931).

50. Y. K. Yur'ev, I. K. Korobitsyna, R. D. Ben Yakii, L. A. Savina and P. A. Akishin, Vestrick Moskov. Univ., 6, No. 2, Ser. Fig.-Mat. i Estestven. Nauk No. 1, 37-46 (1951); C. A., 47, 124 (1953).

51. H. W. Magnusson and E. R. Schiery, Univ. Wyoming Pub., 7, 1-11 (1940); C. A., 34, 6867 (1940).

52. H. T. Clarke, J. Chem. Soc., 101, 1788-1809 (1912).

53. V. H. Dermer and O. C. Dermer, J. Am. Chem. Soc., 59, 1148-1149 (1937).

54. J. W. Bruhl, Z. physik. Chem., 16, 193-241 (1895).

55. L. Knorr, Ann., 301, 1-18 (1898).

56. S. M. McElvain, "The Characterization of Organic Compounds," Macmillan Co., New York, N.Y., 1949, p. 133.

57. J. N. Shoolery and J. D. Roberts, Rev. of Sci. Instruments, 28, 61-62 (1957).

58. K. J. Laidler, "Chemical Kinetics," McGraw-Hill Book Company, Inc., New York, N. Y., 1950, pp. 69-70.

59. A. L. Bloom and J. N. Shoolery, Phys. Rev., 97, 1261-1267 (1955).

PART IV

THE NUCLEAR MAGNETIC RESONANCE SPECTRUM OF FEIST'S ACID

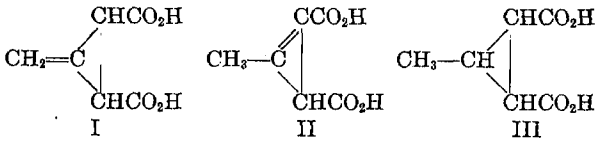
[Reprinted from the Journal of Organic Chemistry, **21**, 1169 (1956).]

The Nuclear Magnetic Resonance Spectrum of Feist's Acid[1]

ALBERT T. BOTTINI[2] AND JOHN D. ROBERTS

Received January 6, 1956

Feist's acid[3] is generally accepted to be either I



or II. Cogent evidence in favor of I has been obtained by Ettlinger[4] and his structural assignment has been confirmed by x-ray diffraction analysis.[5] Unequivocal evidence that Feist's acid is I and not II has now been obtained from its nuclear magnetic resonance (NMR) spectrum (Fig. 1) in a solution of excess sodium deuteroxide in heavy water. Three peaks of almost equal area were obtained (see Curve A) corresponding from left to right to the two methylene hydrogens, the two carboxyl hydrogens (present as water) and the 1,2-ring hydrogens respectively. The center peak was clearly due to H_2O because it increased markedly on addition of a drop of ordinary water to the solution (compare Curve B). If the acid actually had Structure II, the C—H peaks would be in the ratio of one (the ring hydrogen) to three (the methyl hydrogens).[6] The NMR spectrum (Curve C) of the hydrogenation product of Feist's acid (III) is in satisfactory agreement with the assigned structure although, in this case, the three varieties of hydrogen attached to carbon absorb too closely together to permit clear resolution.

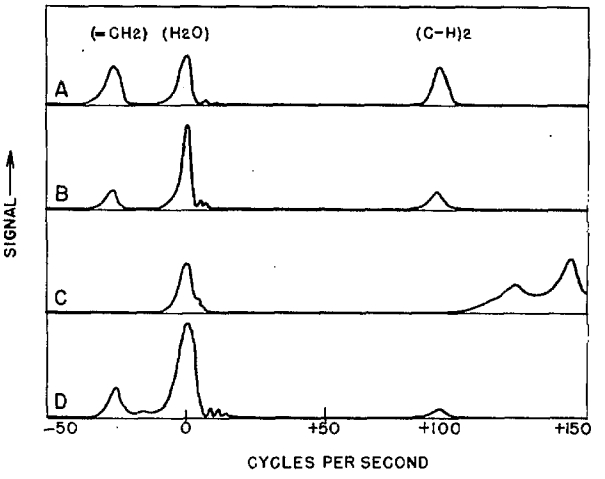


FIG. 1.—NUCLEAR MAGNETIC RESONANCE SPECTRA OF 5-MM. SAMPLES at 40 mc. and 9400 gauss (12-sec. sweep) with Varian Associates Model V-4300B High Resolution Spectrometer. A, 0.19 g. of I dissolved in 0.46 g. of a solution prepared from 0.12 g. of sodium and 0.8 g. of deuterium oxide; B, same solution plus one drop of ordinary water; C, 0.14 g. of III dissolved in 0.36 g. of a solution prepared from 0.10 g. of sodium and 0.8 g. of deuterium oxide; D, solution as for B after five days at room temperature.

After five days at room temperature, the NMR absorption of the 1,2-ring hydrogens of I decreased about 75% relative to the methylene hydrogens showing that the 1,2-hydrogens were exchanging with the solvent. No additional bands were noted in the spectrum after 60 days at room temperature. Removal of the solvent under reduced pressure, dissolution of the residue in fresh deuterium oxide, and equilibration reduced the absorption of the 1,2-hydrogens to negligible proportions without effect on the absorption of the methylene hydrogens. The occurrence of hydrogen-deuterium exchange was confirmed by examination of the infrared spectrum (potassium bromide pellet) of the deuterated acid and regeneration of I by equilibration of a sample of the deuterated acid with a solution of sodium hydroxide. The strong absorption band at 910 cm.$^{-1}$ characteristic of the protated acid was absent from the infrared spectrum of the deuterated material. The specificity of the exchange (*i.e.*, no exchange of the methylene hydrogens) precludes any possibility of a facile base-induced equilibration between forms I and II under these conditions. The spectrum of the deuterium oxide solution of III did not appear to change over 60 days at room temperature.

The recent reassertion that Feist's acid is II[7] because of its infrared spectrum, has been controverted by Ettlinger and Kennedy.[6] Ozonization of the diethyl ester of Feist's acid is reported to

(1) Supported in part by the Petroleum Research Fund of the American Chemical Society.

(2) National Science Foundation Predoctoral Fellow, 1954–1957.

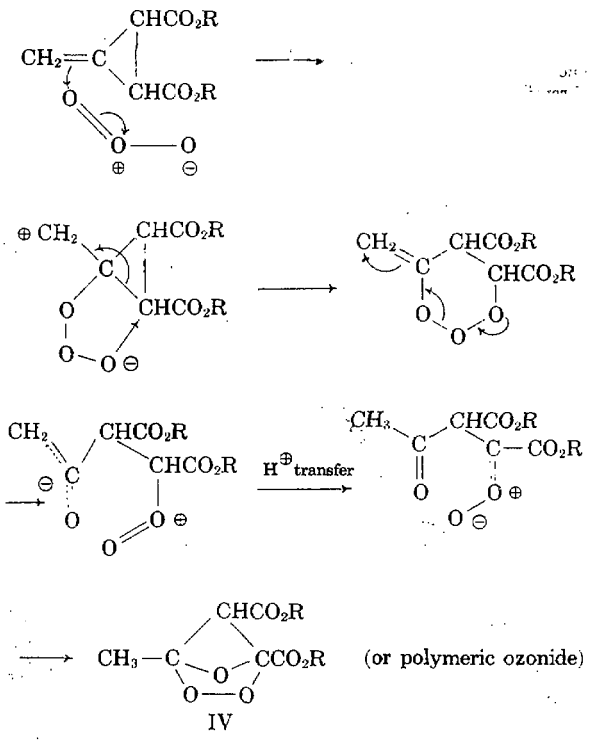
(3) F. Feist, *Ber.*, **26**, 747 (1893); *Ann.*, **436**, 125 (1924).

(4) M. G. Ettlinger, *J. Am. Chem. Soc.*, **74**, 5805 (1952).

(5) Unpublished work by J. H. Sturdivant and D. R. Petersen; D. R. Petersen, Ph.D. Thesis, California Institute of Technology, 1955. A less complete analysis has been reported by D. Lloyd, T. C. Downie, and J. C. Speakman, *Chemistry & Industry*, 222, 492 (1954).

(6) Similar conclusions have been reached from NMR spectra of dimethyl and diethyl esters of Feist's acid by M. G. Ettlinger and F. Kennedy, *Chemistry & Industry*, 166 (1956). We are grateful to Dr. Ettlinger for information regarding these results in advance of publication.

(7) G. R. Boreham, F. R. Goss, and G. J. Minkoff, *Chemistry & Industry*, 1354 (1955).



(or polymeric ozonide)

IV

yield ethyl acetoxaloacetate and no formaldehyde as expected of esters of *II*.[8] However, it should be noted that methylenecyclopropane yields but 2% of formaldehyde on ozonization.[9] Furthermore, if attack of ozone is electrophilic in character, esters of I might afford acetoxaloacetates by a sequence of reasonable reactions like the following (here presented in condensed form), which involves a rather common type of ring-opening process as the key step. IV can be regarded as the normal ozonide of II.

We are indebted to Dr. Martin G. Ettlinger for helpful discussions and generous samples of I and III.

CONTRIBUTION NO. 2110
GATES AND CRELLIN LABORATORIES
CALIFORNIA INSTITUTE OF TECHNOLOGY
PASADENA, CALIFORNIA

---

(8) F. R. Goss, C. K. Ingold, and J. F. Thorpe, *J. Chem. Soc.*, 123, 327 (1923).

(9) J. T. Gragson, K. W. Greenlee, J. M. Derfer, and C. E. Boord, *J. Am. Chem. Soc.*, 75, 3344 (1953).

PROPOSITIONS

1. A method to determine the mechanism of formation of the diaryl side products formed during the hydrolysis of aryl halides is proposed.

2. It is proposed that the products from reactions of N-(2-haloallyl)-alkylamines with metal amides be investigated.

3. A synthesis for N-substituted azetines is proposed.

4. It is proposed that rates of proton exchange of N-substituted allenimines and N-(2-bromoallyl)-alkylamines with solvent in sodium amide solutions of ammonia be determined. If the exchange rates are slow, knowledge of the amount and position of deuterium incorporated in the N-alkylallenimine obtained from the reaction of N-(2-bromoallyl)-alkylamine with sodium amide-$\underline{d}_2$ in ammonia-$\underline{d}_3$ should allow a choice of the possible mechanisms for the reaction.

5. Cram[1] has suggested that N-substituted 1-azaspiropentanes should be the most easily resolvable aziridine derivatives wherein the sole source of asymmetry is trivalent nitrogen. A synthesis for these interesting compounds is proposed.

6. Possible syntheses of trimethylenecyclopropane from Feist's acid are proposed.

7. It is proposed that the controversy over the structure of sterculic acid[2] be settled by determination of its NMR spectrum.

8. It is proposed that the NMR spectra of the vinyl amines reported by Reppe[3] be determined. If these compounds are vinylamines rather than aziridines, it is further proposed that 1-vinylaziridine be prepared and its nitrogen inversion frequency determined. This would allow a comparison of the effects of intracyclic and exocyclic conjugation on the nitrogen inversion frequency in aziridines.

9. The conversion of trans-1-chloro-2-(p-tolylmercapto)-ethene (I) to cis-1,2-bis-p-tolylmercaptoethene[4] takes place by either a cis elimination followed by addition of p-toluenethiol, or by addition of the thiol followed by elimination of the elements of hydrogen chloride. It is proposed that a choice between these two mechanisms be made by using I labeled with deuterium.

10. It is proposed that derivatives of the two forms of 9-azatricyclo(4.2.1.$1^{2,5}$)deca-10-one analogous to tropane alkaloids[5,6] be prepared and their biological activity determined.

11. It is proposed that the fate of tritium in bean plants treated with 2,4-dichlorophenoxyacetic acid-α-t and -6-t be determined in order to determine the mechanism of the action of that auxin.

REFERENCES TO PROPOSITIONS

1. Private communication from D. J. Cram to J. D. Roberts.

2. V. V. Narayan and B. C. L. Weedon, Chem. and Ind., 1957, 394.

3. W. Reppe et al, Ann., 601, 128-138 (1956)

4. W. E. Truce and M. M. Boudakian, J. Am. Chem. Soc., 78, 2748-2751 (1956).

5. H. L. Holmes in R. H. F. Manske and H. L. Holmes, "The Alkaloids," Academic Press, Inc., New York, N. Y., 1950, Vol. I, pp. 272-374.

6. G. Fodor and K. Nador, J. Chem. Soc., 1953, 721-723.