A STEREOCHEMICAL STUDY OF CYCLOPROPYLCARBINYL DERIVATIVES IN CARBONIUM-ION REACTIONS

Thesis by

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ABSTRACT

Cyclopropylmethylcarbinylamine and cyclopropylmethylcarbinol were resolved and their configurations related. The former was deaminated with aqueous nitrous acid to give the latter with 0-4% net inversion of configuration. The solvolyses of several N-methyl-4-alkoxypyridinium salts were investigated. Solvolysis rates for N-methyl-4-(cyclopropylcarbinyloxy)-pyridinium iodide and perchlorate in water and in 80% ethanol and of N-methyl-4-(cyclopropylmethylcarbinyloxy)-pyridinium iodide in water were measured. The first-order rate constant for the hydrolysis of N-methyl-4-(cyclopropylmethylcarbinyloxy)-pyridinium iodide at 30° was calculated to be 6×10^5 times that of N-methyl-4-(cyclopropylcarbinyloxy)-pyridinium iodide. The hydrolysis of optically active N-methyl-4-(cyclopropylmethylcarbinyloxy)-pyridinium iodide produced cyclopropylmethylcarbinol with $4.4 \pm 1.5\%$ inversion of configuration.

The stereochemistry of the deamination of cyclopropylmethylcarbinylamine and of the hydrolysis of N-methyl-4-(cyclopropylmethylcarbinyloxy)-pyridinium iodide and the ratio of rate constants for the cyclopropylmethylcarbinyl and cyclopropylcarbinyl pyridinium salts are discussed with respect to the possible intervention of non-classical carbonium-ion intermediates in these reactions.

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I. INTRODUCTION

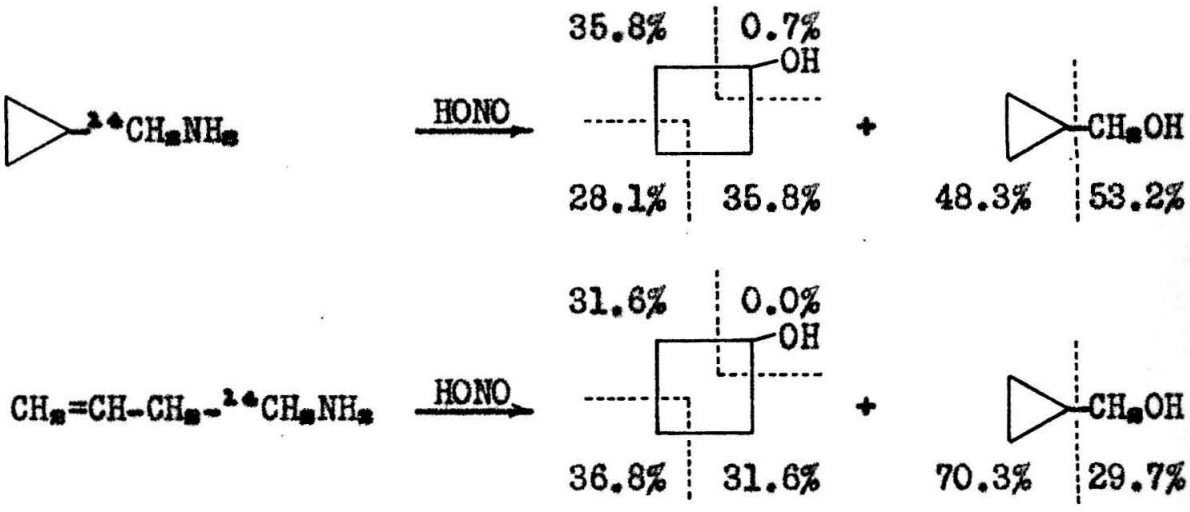
Considerable interest attends the nature of the intermediates in carbonium ion-type interconversion reactions of cyclopropylcarbinyl, cyclobutyl and allylcarbinyl derivatives. Evidence regarding these intermediates has come principally from two sources, namely studies of solvolysis rates and product distributions in such interconversion reactions. The purpose of this thesis was to gain additional information from the viewpoint of stereochemistry.

A wide variety of carbonium ion-type reactions of both cyclopropylcarbinyl and cyclobutyl derivatives gives similar relative amounts of products with the cyclopropylcarbinyl, cyclobutyl and allylcarbinyl structures, almost independently of which of the two starting structures is employed. Such reactions include the reaction of cyclopropylcarbinylamine and cyclobutylamine with nitrous acid (1, 2), the solvolysis of cyclopropylcarbinyl and cyclobutyl derivatives (1, 3), and the reactions of cyclopropylcarbinol and cyclobutanol with thionyl chloride (1, 4) and of cyclopropylcarbinol with hydrogen bromide or phosphorous tribromide (1). This behavior suggests that all the above reactions go through common cationic intermediates; small variations in product

composition may be accounted by specific effects of each reaction and do not require postulation of a drastic change in mechanism.

The solvolyses of cyclopropylcarbinyl and cyclobutyl derivatives are unusually fast. For instance, in 50% aqueous ethanol at 50°, cyclopropylcarbinyl chloride is 40 times more reactive than β-methylallyl chloride and cyclobutyl chloride is 15 times more reactive than isopropyl chloride (1). Unusually high solvolysis rates are often indicative of non-classical cationic intermediates (5). The weight of the evidence is such, therefore, that the common intermediate(s) in the solvolyses of cyclopropylcarbinyl and cyclobutyl derivatives have been inferred to be non-classical in nature (6).

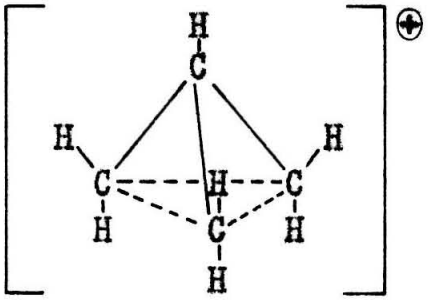
More detailed information as to the common non-classical intermediate(s) may be obtained from isotopic labeling experiments. Both cyclopropylcarbinylamine-α-^{14}C (6) and allylcarbinylamine-α-^{14}C (2) have been deaminated with aqueous nitrous acid and the cyclobutanol and cyclopropylcarbinol produced by the reactions were degraded in each case with the results shown below.



The isotopic carbon of the cyclopropylcarbinol derived from the corresponding amine is less extensively scrambled than that of the other products examined. About 16% of this cyclopropylcarbinol appears to arise from a non-rearranging path as shown by the ratios of cyclopropylcarbinol to cyclobutanol obtained from the deaminations of cyclopropylcarbinylamine and of allylcarbinylamine (1.39 and 1.17, respectively (2)). If a correction for the non-rearranging path is made, the cyclopropylcarbinol derived from cyclopropylcarbinylamine-α-^{14}C via the non-classical intermediate(s) contains 42% of the label in the α-position and 58% in the ring positions, in line with the results of the other degradations.

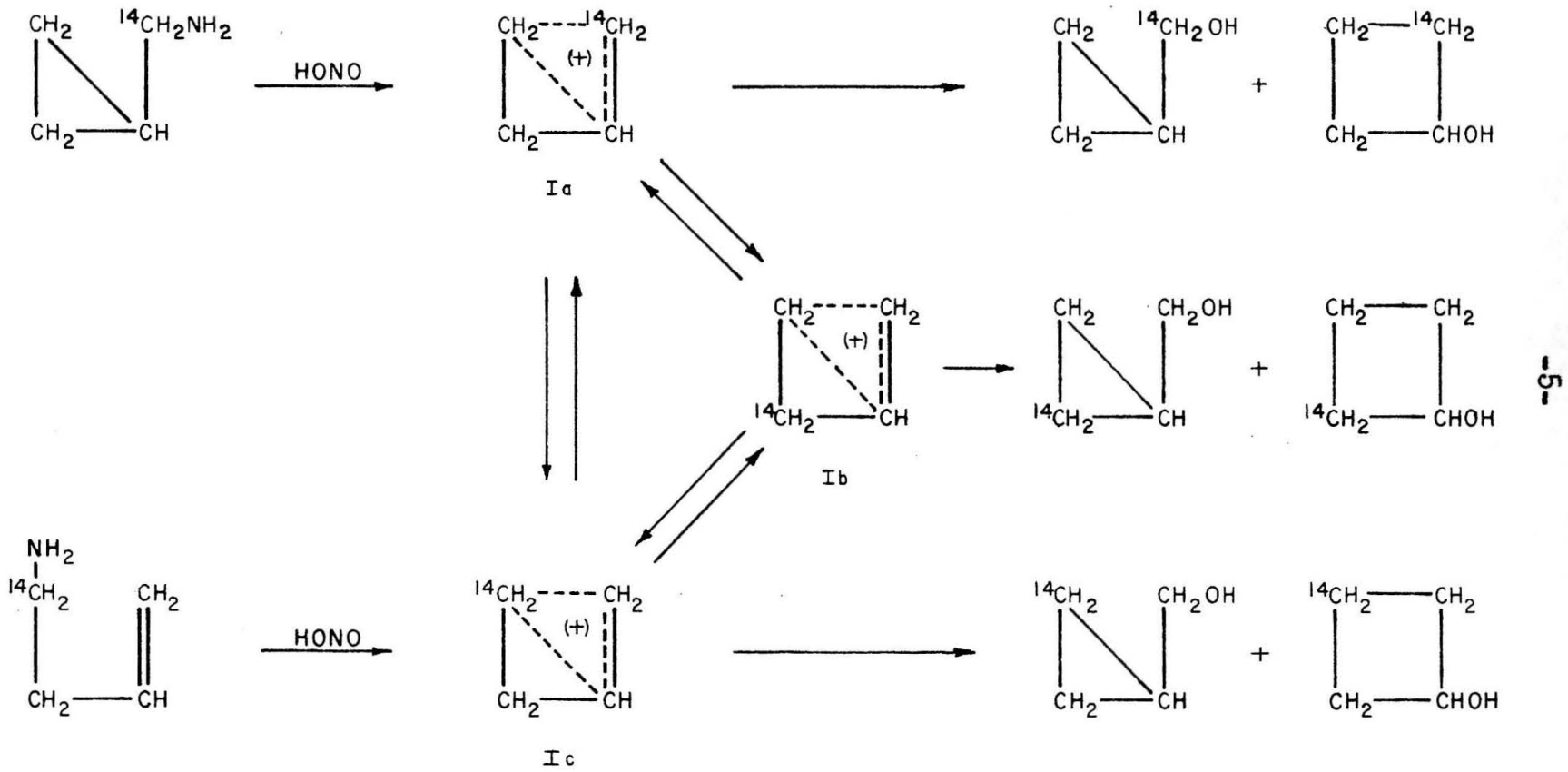
The isotopic label of the cyclopropylcarbinol and cyclobutanol approaches but does not attain a random

distribution among the three methylene groups. These results have been correlated with a scheme (p. 5) having the three non-classical "bicyclobutonium" ions (Ia-c) approaching but not quite attaining equilibrium with one another. Other systems of non-classical intermediates can account for the available experimental data but the scheme presented here is the most attractive from a theoretical viewpoint. A possible intermediate stage for the interconversion of ions Ia-c is the symmetrical "tricyclobutonium" ion (II). The plane determined by the carbon and



II

the two hydrogen atoms of each methylene group of II is perpendicular to the plane of the three methylene carbon atoms. The ion II cannot be the sole intermediate in these reactions because II predicts complete scrambling of the isotopic label between the methylene groups of the cyclopropylcarbinol and cyclobutanol formed from


HONO
Ia
Ib
Ic
HONO

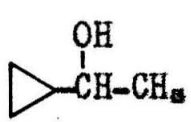
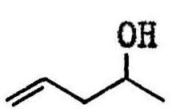
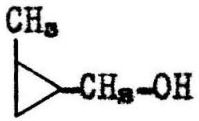
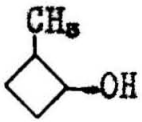
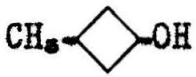
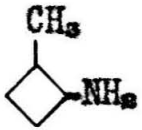
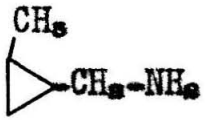
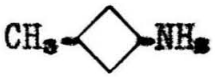
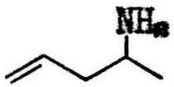
allylcarbinylamine-α-^{14}C and in the cyclobutanol from cyclopropylcarbinylamine-α-^{14}C.

The effect of methyl substitution at the methylene groups of the bicyclobutonium ions Ia-c has been investigated by Silver (7) by means of a product study of the deamination of appropriate amines with aqueous nitrous acid. Silver's results, summarized in Table I, fit rather well into a scheme similar to that presented for the unmethylated amines with some understandable differences due to the presence of the added methyl group. The methyl-substituted ions IIIa-c are no longer equal in stability (in contrast to the unsubstituted ions Ia-c) and their order appears to be IIIa > IIIc ≫ IIIb. Two of the amines, 2-methylcyclobutylamine and 2-methylcyclopropylcarbinylamine, can form directly either of two non-classical ions but only the more stable of the possible ions actually appears to be formed.

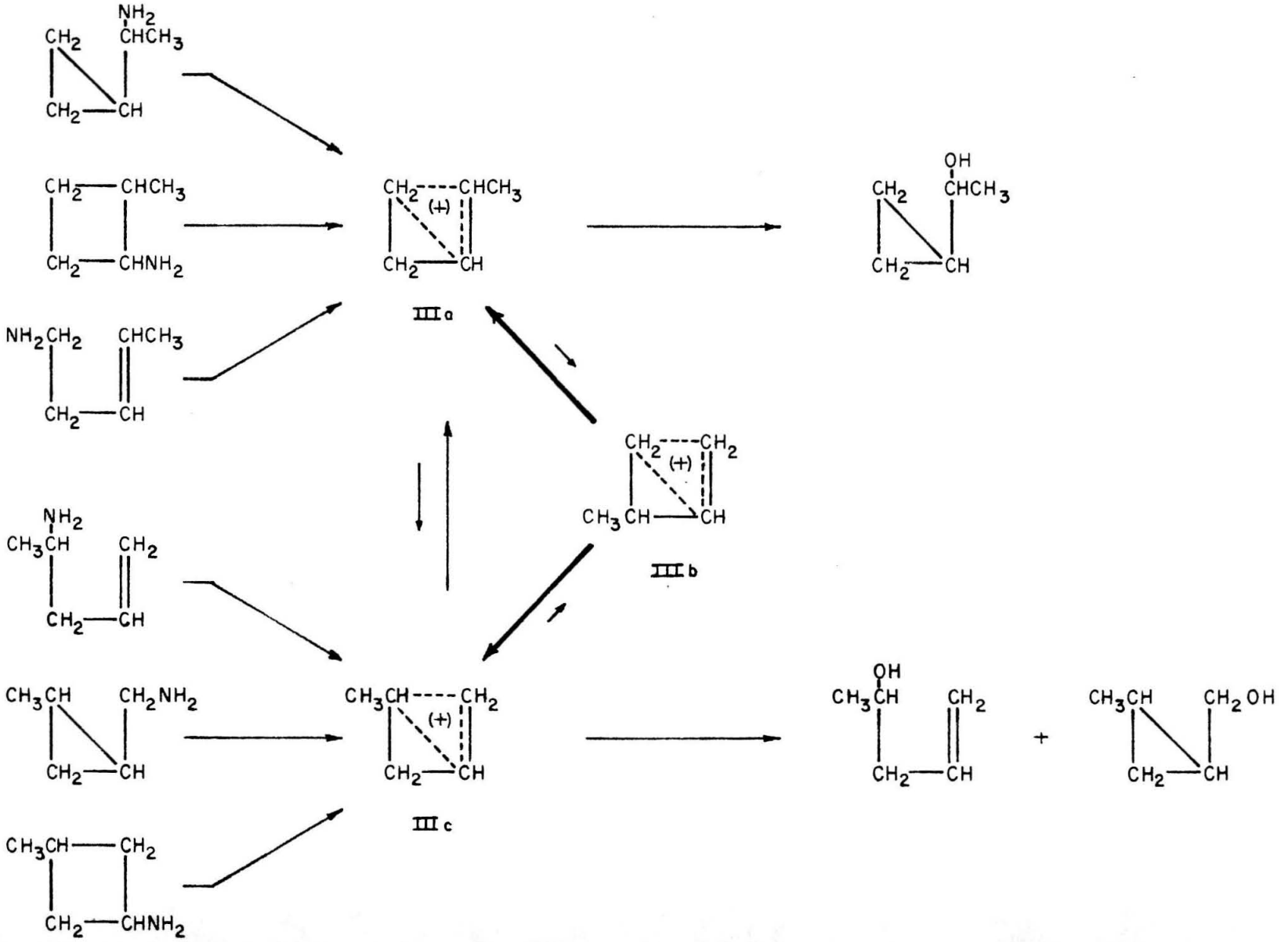
The success of a scheme of non-classical ions in accounting for Silver's results suggested that the added methyl group has not drastically altered the nature of the intermediates in the deaminations of the methyl-substituted compounds. Consequently, we chose to study the stereochemistry of the carbonium ion-type reactions of optically active cyclopropylmethylcarbinyl derivatives with a

TABLE I

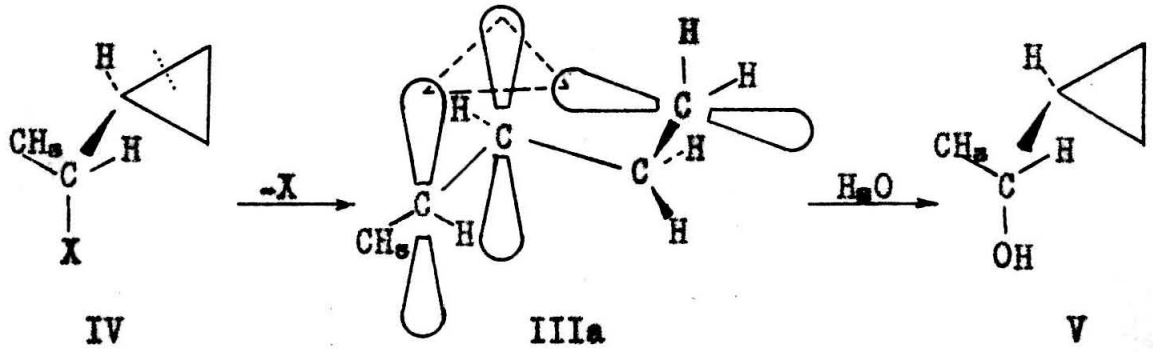
PERCENTAGES OF ISOMERIC ALCOHOLS FROM AMINE-NITROUS ACID EXPERIMENTS (7)

					
	100	0	0	0	0
	100	0	0	0	0
	74[a]	0	0	0	0
	51	35	13	0	0
	47	39	9	0	5
	17[a]	49[a]	3?[a]	0	0

[a] Plus isomeric (allylic) alcohols <u>via</u> hydride shifts.


NH2
CH2
CHCH3
CH2
CH
CH2
CHCH3
CH2
CHNH2
CH2
CHCH3
(+)
CH2
CH
IIIa
OH
CH2
CHCH3
CH2
CH
NH2CH2
CHCH3
CH2
CH
CH2
CH2
(+)
CH3CH
CH
IIIb
NH2
CH3CH
CH2
CH2
CH
CH3CH
CH2NH2
CH2
CH
CH3CH
CH2
(+)
CH2
CH
IIIc
CH3CH
CH2
CH2
CHNH2
OH
CH3CH
CH2
CH2
CH
+
CH3CH
CH2OH
CH2
CH

reasonable hope of obtaining evidence for a non-classical intermediate such as IIIa. We shall now examine the possible consequences of non-classical intermediates upon the stereochemistry of carbonium ion-type reactions of cyclopropylmethylcarbinyl derivatives using water as the solvent.

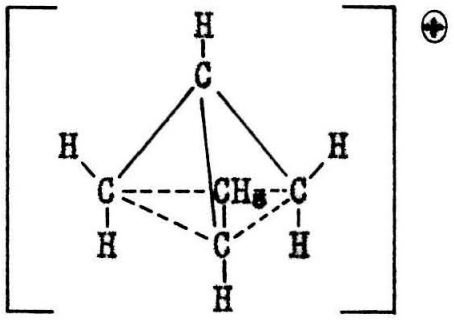


IV IIIa V

The formation of the non-classical ion IIIa (shown here in an atomic orbital representation) from an optically active cyclopropylmethylcarbinyl derivative IV should proceed preferentially in the depicted sense, with the ring bond farthest from the leaving group (X) breaking to provide p-orbital overlap on the rear side of the developing p-orbital on the α-carbon atom. Only the preferred conformation of the α-carbon atom relative to the cyclopropane ring of the substrate IV is discussed here. However, consideration of the other possible conformation with the methyl group nearest the cyclopropane ring does not alter the

stereochemical predictions. Water should attack ion IIIa predominantly from below, leading to cyclopropylmethylcarbinol, V, with the same configuration as the starting material IV. Thus, if the non-classical ion IIIa is the sole ionic intermediate, the transformation of the substrate IV to the alcohol V should occur with predominant retention of configuration.

The asymmetric non-classical ion IIIa may have time to equilibrate with other ionic species, including its mirror image, before reacting with water. However, the isomeric ions IIIb and IIIc do not appear to form to a significant extent in water because no products derived from these ions are observed when the initially formed species is IIIa. The methyl-substituted tricyclobutonium ion VI



VI

may approach equilibrium with IIIa. (Reaction of VI with water could reasonably give only cyclopropylmethylcarbinol.)

To the extent that this equilibrium occurs, the product, cyclopropylmethylcarbinol, will be racemized since ion VI has a plane of symmetry. VI could alternatively serve as the transition state for the facile conversion of the asymmetric ion IIIa to its mirror image, also leading to racemized product.

While still further structures can be visualized for the carbonium ion-type reactions of cyclopropylmethylcarbinyl derivatives, the preceding discussion suffices to illustrate the general stereochemical conclusion: That portion of the reaction proceeding through non-classical intermediates might reasonably lead to products with anywhere from nearly complete retention of configuration to complete racemization.

The reactions chosen for this stereochemical study were not the customary solvolytic reactions of alkyl halides and esters for several reasons. The cyclopropylmethylcarbinyl halides have never been obtained in a pure form because of their ready rearrangement to isomeric structures (7). Likewise, attempts to prepare cyclopropylmethylcarbinyl brosylate have not been successful (7). The solvolysis of carboxylic esters always involves the question of acyl-oxygen vs. alkyl-oxygen fission. In addition, the solvolyses of

halides and esters are complicated by the problem of internal return from intimate ion-pairs (5).

The reactions actually employed were the deamination of cyclopropylmethylcarbinylamine with aqueous nitrous acid and the hydrolysis of N-methyl-4-(cyclopropylmethylcarbinyloxy)-pyridinium iodide, giving in both cases cyclopropylmethylcarbinol as the product. Both of the cyclopropylmethylcarbinyl starting materials are stable and easily handled. In addition, both generate the ion(s) of interest by means of a neutral leaving group which should obviate the complication of internal return. Goering (8) has shown that the solvolysis of 5-methyl-2-cyclohexenyl p-nitrobenzoate in 80% acetone is accompanied by internal return but the acid-catalyzed solvolysis of the same substrate is not. Presumably, the uncatalyzed solvolysis proceeds through an ion-pair, held together largely by electrostatic forces, from which internal return occurs (9). The acid-catalyzed reaction, where the leaving group is a neutral p-nitrobenzoic acid molecule, cannot form an ion-pair and the leaving group escapes before internal return can occur.

The first reaction of interest, the deamination of primary aliphatic amines with nitrous acid, is generally

considered to proceed through a carbonium-ion intermediate although some of the more detailed aspects of the reaction are a matter of active controversy (10).

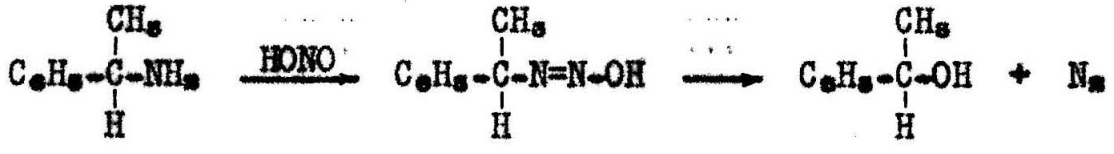
$$RNH_2 \xrightarrow{HONO} RNH\text{-}NO \longrightarrow RN{=}NOH \xrightarrow[-H_2O]{+H^{\oplus}} RN{\equiv}N^{\oplus} \longrightarrow R^{\oplus} + N_2$$

The stereochemistry of the amine-nitrous acid reaction, in general, is typical of S_Ni processes (11). The deamination in excess aqueous acid of 2-butyl-, 2-octyl-, and 1-phenylethylamines is reported to give racemization and inversion of configuration; alanine gives retention and phenylglycine gives retention and racemization (12). Wiberg found 22% net inversion of configuration in the deamination of 2-butylamine in excess aqueous sulfuric acid and 26% inversion in glacial acetic acid (13). The deamination of 1-butylamine-1-^{2}H in glacial acetic acid gives 69% net inversion of configuration (14). Optically active α-methylallylamine is deaminated in glacial acetic acid to give a mixture of α- and γ-methylallyl acetates. The α-acetate showed 16% net inversion and neither the ratio of α- to γ-acetates nor the optical activity of the α-acetate was affected by the addition of acetate ion (15). However, less rearrangement to the γ-acetate was observed than in the

silver-catalyzed acetolysis of α-methylallyl chloride. To account for the smaller amount of rearrangement in the deamination reaction, Young (15) proposed the intermediacy of a "hot" carbonium ion (without the proper spatial orientation for allylic delocalization of the positive charge) which gives unrearranged and predominantly inverted acetate in competition with the normal delocalized ion which gives racemic product with the same isomer distribution observed in the solvolytic reaction.

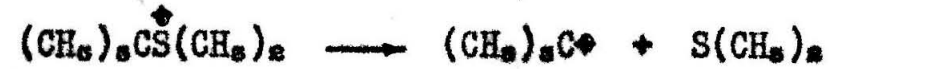
Unfortunately, the amine-nitrous acid reaction has only rarely been used to provide stereochemical evidence for non-classical ions. An example of its use is the deamination of either endo- or exo-2-norbornylamine to give exclusively products of the exo configuration (16-18) which has been cited (18) as evidence in support of the non-classical nature of the cationic intermediates derived from this system; this non-classical nature is well documented by other data (18-20). It should be noted that there are examples in the literature of deamination reactions, uncomplicated by neighboring group or unusual structural effects, leading to products of retained configuration, apparently by an S_Ni mechanism. A particularly interesting example is the deamination of optically active 1-phenylethylamine,

VII, in carefully dried acetic acid (21). The major product was the corresponding acetate, formed with 8% net retention of configuration. However, a small amount of 1-phenylethanol, VIII, was also formed and with 37% retention. The formation of VIII was explained by an S_Ni decomposition of the intermediate diazoacid IX (21).



VII IX VIII

The second reaction used in this work, the hydrolysis of N-methyl-4-(cyclopropylmethylcarbinyloxy)-pyridinium iodide, is a new example of the solvolysis of a cationic substrate. Similar reactions that have been studied previously are the solvolyses of sulfonium salts and of quaternary ammonium salts. Swain has shown that while the decomposition of trimethyl- and tribenzyl-sulfonium salts in solution are bimolecular processes (22), the decomposition of t-butyldimethylsulfonium salts is a unimolecular solvolysis (23).

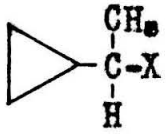


The decomposition of benzhydryltrimethylammonium hydroxide is reported to give benzhydrol by a first-order process and methanol by a second-order process (24). The hydrolysis of isobornyltrimethylammonium hydroxide or iodide gives camphene and tricyclene, undoubtedly through a carbonium ion intermediate (25).

The stereochemistry of the solvolysis of cationic substrates is poorly documented. The decomposition of optically active 1-phenylethyltrimethylammonium iodide in methanol, ethanol and n-butanol gives the respective ethers of 1-phenylethanol with complete racemization (26). The starting material and the products were shown to be optically stable under the reaction conditions. Although no kinetic evidence is given, the racemized products are taken as proof of a unimolecular mechanism (26). The reaction of 2-benzamidoalkyldimethylsulfonium salts with water gives the products typical of a solvolysis with participation of a neighboring benzamido group, except when such participation is sterically prohibited (27). The second-order reaction of optically active 1-phenylethyldimethylsulfonium iodide with azide ion proceeds with complete inversion of configuration (28).

II. RESULTS AND DISCUSSION

Cyclopropylmethylcarbinylamine, X, was resolved by means of its tartrate salt and the maximum rotation obtained was $\alpha^{25}D$ +21.80° (neat). That the resolution was complete or nearly complete was indicated by the conversion of the amine X of maximum rotation to the benzamide XI in 93% yield with $[\alpha]^{25}D$ +33.7° (absolute ethanol, c = 5.0); the melting point of the optically active benzamide XI could not be improved by recrystallization.



V, X = OH

X, X = NH_2

XI, X = $-NHCOC_6H_5$

XII, X = $-O_2CC_6H_4CO_2H$

XIII, X = $-O_2CC_6H_5$

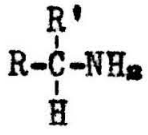
Cyclopropylmethylcarbinyl hydrogen phthalate, XII, was resolved with brucine. The almost constant melting point and specific rotation of the resolved phthalate XII upon fractional recrystallization speak for its optical purity. The reduction of optically pure phthalate XII with lithium aluminum hydride gave cyclopropylmethylcarbinol, V, containing impurities but a value of αD +20.1° (neat) could

be calculated for pure V.

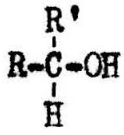
The alkoxide ion corresponding to the optically pure alcohol V reacted with benzoyl chloride to give the optically pure benzoate XIII with $\alpha^{27}D$ +33.82° (neat).

The transformation of amine X to benzamide XI and the transformation of alcohol V to benzoate XIII do not disturb any of the bonds attached to the asymmetric carbon atom so that amine X and benzamide IX of the same sign of rotation have the same configuration and alcohol V and benzoate XIII of the same sign of rotation have the same configuration. It remains to establish the relative configurations of the alcohol and amine derivatives.

There are at least 13 pairs of compounds with structures XIV and XV whose relative configurations have been established (29).



XIV



XV

For each pair, with no exceptions, the amine and alcohol of the same configuration have the same sign of rotation. It would not be unreasonable to conclude that cyclopropylmethylcarbinylamine, X, and cyclopropylmethylcarbinol, V,

of the same sign of rotation also have the same configuration, especially because the optical rotations of X and V are both comparatively large.

Additional information on the relative configurations of amine X and alcohol V was sought from the thermal decomposition of N-nitroso-N-(cyclopropylmethylcarbinyl)-benzamide, XVI, to benzoate XIII. In a variety of polar and non-polar solvents, N-(1-arylethyl)-nitrosamides

XVI XIII

decompose with predominant retention of configuration (21, 30, 31). White (30) has found that N-nitroso-N-(2-butyl)-benzamide decomposes with retention in polar solvents such as dioxane. On the other hand, a bimolecular inversion reaction (with benzoic acid released into the solution by an olefin-forming side reaction) competes in non-polar solvents such as pentane, leading to a slight net inversion of configuration. In general, however, the decomposition of N-alkylnitrosamides occurs with retention of configuration and this reaction has been used to relate the configurations of at least one amine and alcohol (32).

When nitrosamide XVI, prepared by the nitrosation of amide (+)-XI, was decomposed in dioxane and in pentane, benzoate (+)-XIII was obtained with 21.2% and 16.8% retention of optical activity, respectively. It appears safe to conclude that the transformation of (+)-XI to (+)-XIII, especially in dioxane, represents retention of configuration and therefore alcohol (+)-V and amine (+)-X have the same configuration, in agreement with the conclusion reached above by consideration of the signs of rotation. Note, however, that the per cent retention of configuration observed here is small compared to the 40-94% (polar solvents) observed in other cases (21, 30, 31).

When optically active amine X was deaminated with aqueous nitrous acid at high pH, nearly racemic alcohol V was obtained with a small (up to 4%) but definite excess of V of the opposite sign and hence opposite configuration to the starting amine X. The largest observed rotation of the product was $\alpha^{25}D$ +0.27° (neat), starting with amine X with $\alpha^{25}D$ -9.67°; 1% of the amine was in the product. If the contributions of amine and alcohol to the observed rotation are additive, then the alcohol would have αD +0.37° when free of amine. This corrected rotation corresponds to 4% net inversion using the maximum rotations for amine

and alcohol given above. The product of one deamination experiment had the same sign of rotation as the starting amine but a similar correction for amine in the product reversed the sign. Significant amounts of methyl cyclopropyl ketone were also found in the products. The alcohol V was shown to racemize only slightly (16%) under the reaction conditions. For one deamination experiment, the major product was bis-(cyclopropylmethylcarbinyl) ether; the formation of ethers under mild conditions is indicative of a highly stable carbonium-ion intermediate (33).

The observed stereochemical result of the deamination of amine X might be due in part to any of the following effects: (1) The racemization of the product V by means of a base-catalyzed hydride-transfer mechanism with methyl cyclopropyl ketone; (2) an "abnormal" S_Ni deamination mechanism; (3) a "normal" deamination reaction proceeding through a diazonium-ion intermediate. The first effect can be largely discounted. Optically active 1-phenylethanol racemizes to the extent of 50% in the presence of potassium t-butoxide and fluorenone in t-butanol solvent at 100° after 17 hours, presumably by a base-catalyzed hydride-transfer mechanism (34). Under the much milder conditions (particularly the much less basic conditions) employed for the

deamination of cyclopropylmethylcarbinylamine, cyclopropylmethylcarbinol should racemize little if any due to this mechanism. (Assumptions that corresponding derivatives of the 1-phenylethyl and cyclopropylmethylcarbinyl structures behave similarly will be made often in this discussion. Justification for this assumption may be found in the fact that both structures are secondary carbinyl systems with comparable steric requirements and both have the same order of solvolytic reactivity.)

The second effect, the S_Ni mechanism, is a more serious problem and can be discussed in terms of the following description of the amine-nitrous acid reaction. The "normal" deamination, leading to inverted products, is pictured as

$$R\text{-}N{=}N\text{-}OH \xrightarrow[-H_2O]{+H^{\oplus}} R\text{-}N{\equiv}N^{\oplus} \longrightarrow R^{\bullet} + N_2 \xrightarrow[-H^{\oplus}]{+H_2O} ROH \quad (1)$$

$$S_Ni \longrightarrow R^{\oplus}....OH^{\ominus} + N_2 \longrightarrow ROH \quad (2)$$

an acid-catalyzed decomposition of the intermediate diazoacid (path 1). However, an uncatalyzed S_Ni mechanism, <u>via</u> an ion-pair, may also be visualized (path 2). Evidence for the occurrence of path 2 in glacial acetic acid has already been presented (p. 14) but this path may also be

available for deaminations in water, especially under the basic conditions employed for the deamination of cyclopropylmethylcarbinylamine which should discourage the acid-catalyzed path 1. Evidence for the occurrence of path 2 in an aqueous deamination reaction was obtained in this work from a study of the deamination of optically active 1-phenylethylamine to 1-phenylethanol under various pH conditions; the results of the study are summarized in Table II. Examination of Table II shows a definite change in the stereochemical result with pH, with high pH leading to more nearly racemic product. Experiment H is exceptional in that it gave racemic alcohol, undoubtedly due to the acid-catalyzed racemization of the same. The product should be optically stable under the reaction conditions of at least experiments B and C because cyclopropylmethylcarbinol was shown to be reasonably stable under conditions closely approximating those of these two experiments. The most reasonable explanation for the more nearly racemic 1-phenylethanol obtained in experiments B and C (and probably A) is the competition of an S_Ni mechanism (path 2) with the normal mechanism (path 1) at high pH.

The stereochemical result of path 1 for the deamination of cyclopropylmethylcarbinylamine may be due to contributions

TABLE II

DEAMINATION OF OPTICALLY ACTIVE 1-PHENYLETHYLAMINE IN WATER

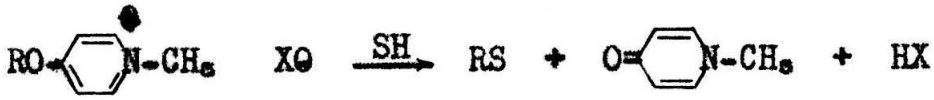
Expt.	Moles of $HClO_4$/ Moles of Amine	pH	% Net Inversion	Reaction Conditions
A	0.80	8.4 -8.9	5.5	20 hr. at reflux
B	0.90	--------	5.2	----------
C	1.07	--------	4.3	4 hr. at reflux
D	1.20	--------	7.4	overnight at room temperature
E	phosphate buffer	5.9 -6.0	11.6	3 hr. at reflux
F	phosphate buffer	6.05-6.07	13.2	2 hr. at reflux; 3 hr. at room temperature
G	phosphate buffer	6.2 -6.2	13.6	2 hr. at reflux; 12 hr. at room temperature
H	phosphate buffer	3.95-4.20	0	4 hr. at reflux

from (1) an S_N2 displacement by water of nitrogen from the intermediate diazonium ion or (2) a "hot" classical carbonium ion which can give products directly or go over to (3) the more stable "cold" (solvolytic), presumably non-classical ion(s) such as discussed in the Introduction. Evidence for either of the first two possibilities may be found in the non-rearranging path which is important in the deamination of cyclopropylcarbinylamine-α-^{14}C (see p. 3). Young (15) found that 43% of the acetate formed in the deamination of α-methylallylamine in acetic acid appears to come from a non-rearranging mechanism (and the rest from a solvolytic carbonium ion). He concluded from the calculated stereochemistry of the non-rearranging process (40% net inversion if the solvolytic carbonium ion gives racemic product) that a "hot" carbonium ion is most likely to be involved rather than an S_Ni or S_N2 process (see p. 13).

Because of the unknown relative contributions of the S_Ni mechanism and a "hot" carbonium-ion intermediate to the observed stereochemical result of the deamination of cyclopropylmethylcarbinylamine, it is impossible to determine the contribution of the solvolytic intermediate(s). However, it appears reasonable that the stereochemical consequence of the solvolytic intermediate(s) is not a high

degree (>50%) of retention of configuration although some retention of configuration cannot be excluded.

The next approach to the general problem was to find a method of generating carbonium ions from the solvolysis of a positively charged cyclopropylmethylcarbinyl derivative. Thus, the disadvantages of the amine-nitrous acid reaction might be avoided and the advantages retained: The carbonium ion would no longer be formed in an exothermic step, obviating the problem of "hot" carbonium ions; the formation of the carbonium ion would be the slow step of the reaction and consequently accessible to kinetic investigation; internal return might still be avoided. Desirable properties of the cationic substrate would be ease of preparation and purification, ability to be rendered optically active and to be configurationally related to the solvolysis products, ability to be followed kinetically during solvolysis, and freedom from side reactions during solvolysis. A class of compounds was found which generally met these qualifications, namely N-methyl-4-alkoxypyridinium salts (XVII).

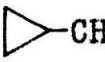


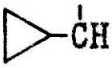
XVII

XVIIa, R = $C_6H_5CH_2$-, X = I

XVIIb, R = $C_6H_5CH_2$-, X = ClO_4

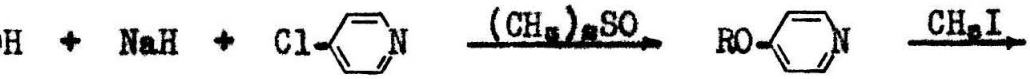
XVIIc, R =  , X = I

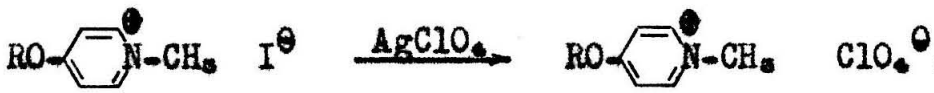
XVIId, R =  , X = ClO_4

XVIIe, R =  , X = I

XVIIf, R = $C_6H_5\dot{C}H(CH_3)$, X = I

The synthesis of XVII was accomplished by the following route:





The yields were 86-89% for the first step, 68-100% for the second step and 51-72% for the third step. All of the pyridinium salts were readily purified solids except for XVIIe and f which were viscous liquids. The former liquid was purified by low-temperature crystallization but the purification of the latter was not attempted.

The products of the solvolyses of the pyridinium salts in various solvents were determined mainly by means of

vapor-phase chromatography. Thus, the reaction of N-methyl-4-benzyloxypyridinium iodide, XVIIa, with glacial acetic acid at 109° gave a quantitative yield of benzyl acetate after 92 hours; the half-life of the reaction was 2-3 hours. In contrast, the corresponding perchlorate salt XVIIb was completely unreactive under the same conditions, indicating that the anion must be involved in the rate-determining step of the reaction of the iodide salt XVIIa. The solvolysis of N-methyl-4-(cyclopropylcarbinyloxy)-pyridinium iodide, XVIIc, in 80% ethanol at 120° gave cyclopropylcarbinol, cyclobutanol and allylcarbinol but predominantly the corresponding ethyl ethers as products. The ratio of the three ethers was cyclopropylcarbinyl:cyclobutyl:allylcarbinyl = 3.6:1.5:1.0; this ratio may be compared to the ratio observed for the ether products of the solvolysis of cyclopropylcarbinyl chloride in 80% ethanol at 97° of 5.7:2.5:1.0 (4). The hydrolysis of the cyclopropylcarbinyl derivative XVIIc at 98.6° in the presence of lithium carbonate gave a 99% yield of cyclopropylcarbinol, cyclobutanol and allylcarbinol; 8% of the alcohol mixture was allylcarbinol and the remaining 92% was cyclopropylcarbinol and cyclobutanol in the ratio of 1.2-1.5 to 1. The aqueous deamination of allylcarbinylamine, where cyclopropylcarbinol

and cyclobutanol can arise presumably only from non-classical ions, gives a ratio of these alcohols of 1.17 to 1 (2). The ethanolysis of N-methyl-4-(cyclopropylmethylcarbinyloxy)-pyridinium iodide, XVIIe, at 98.4° gave cyclopropylmethylcarbinyl ethyl ether with no isomeric ethers; hydrolysis at room temperature in the presence of lithium carbonate gave only cyclopropylmethylcarbinol. On the other hand, the acetolysis of the same substrate at 87° gave a host of products, including cyclopropylmethylcarbinyl acetate; the product mixture observed at 125° contained no cyclopropylmethylcarbinyl acetate, undoubtedly due to the isomerization of this substance under the conditions of the reaction. Acetolysis of the 1-phenylethyl derivative XVIIf gave 1-phenylethyl acetate.

The fate of the heterocyclic ring during the solvolysis reactions was not rigorously determined. From the solvolyses of the cyclopropylmethylcarbinyl derivative XVIIe in acetic acid and in ethanol and the solvolysis of the 1-phenylethyl derivative XVIIf in acetic acid were isolated what appeared to be the same yellow crystalline solid. The solid could not be obtained in a pure state but contained carbon, hydrogen, nitrogen and ionizable iodine, was very soluble in hydroxylic solvents and insoluble in non-polar

solvents, and was very acidic. The available evidence indicates that this material was the impure hydroiodide of N-methyl-γ-pyridone, as expected. When a solution of N-methyl-γ-pyridone in aqueous hydrogen iodide was evaporated to dryness, a yellow solid remained with a wide melting-point range that appeared to be similar to the solids obtained from the solvolytic reactions.

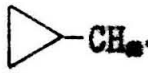
The kinetics of the solvolyses of N-methyl-4-(cyclopropylcarbinyloxy)-pyridinium iodide, XVIIc, and perchlorate, XVIId, in water and in 80% ethanol and of N-methyl-4-(cyclopropylmethylcarbinyloxy)-pyridinium iodide, XVIIe, in water were measured. The reactions were followed by titration of the evolved acid and the data are summarized in Table III. The first-order rate constants stayed relatively constant through the first or second half-life of each reaction but decreased significantly in value thereafter (see Tables IV-IX). From experiments 2 and 3, an activation energy, $\Delta E^{\ddagger} = 31.2 \pm 0.9$ kcal./mole, and an activation entropy, $\Delta S^{\ddagger} = 3.6 \pm 2.5$ e.u., may be calculated (5) for the hydrolysis of the cyclopropylcarbinyl derivative XVIIc. The rate constant for this compound, extrapolated to 30°, is $\underline{k}_1 = 2.65 \times 10^{-5}$ hr.$^{-1}$; therefore, the cyclopropylmethylcarbinyl derivative XVIIe

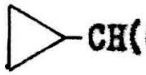
TABLE III

SOLVOLYSIS OF N-METHYL-4-ALKOXYPYRIDINIUM SALTS (XVII)

Expt.	Substrate	Solvent	Temp., °C.	k_1 ($hr.^{-1}$)	Infinity Titer (% of Theory)
1	XVIIc	80% ethanol	98.4	0.013	89.4
2	XVIIc	water	98.6	0.20	90.7, 91.9
3	XVIIc	water	70.7	0.0065	89.4
4	XVIId	80% ethanol	98.4	0.010	84.0
5	XVIId	water	98.6	0.19	90.7
6	XVIIe	water	30.0	0.16	84.5, 84.7, 86.1

XVIIc, R =  , X = I

XVIId, R =  , X = ClO_4

XVIIe, R =  , X = I

(k_1 = 0.16 hr.$^{-1}$) is 6 x 10^5 more reactive than the cyclopropylcarbinyl derivative XVIIc in water at 30°.

The alcohols (or esters) obtained from the solvolyses of the pyridinium salts may arise by means of three reasonable mechanisms: (1) A direct solvolysis reaction (S_N1); (2) an S_N2 displacement by iodide to give unrearranged alkyl iodide which then solvolyzes to give the final products; and (3) the displacement of the alkoxy group from the pyridine ring by an aromatic nucleophilic substitution mechanism. The solvolyses of N-methyl-4-(cyclopropylcarbinyloxy)-pyridinium iodide in 80% ethanol and in water cannot be S_N2 because the rates are virtually the same as those of the corresponding perchlorate (see Table III). The very weak nucleophilicity of perchlorate ion compared to iodide ion (35) would demand a large difference in rate between the iodide and the perchlorate salts if the S_N2 mechanism were operative. Furthermore, the large rate enhancement (6 x 10^5) produced by α-methyl substitution on the cyclopropylcarbinyl substrate is consistent only with the direct solvolysis reaction (5). The aromatic nucleophilic substitution may compete successfully in some of the investigated solvolyses. However, the hydrolysis of the cyclopropylcarbinyl derivative must be proceeding

mostly by the direct solvolysis reaction because the alcoholic products were a mixture of isomers typical (within the wide limits of experimental error) of carbonium ion-type reactions of cyclopropylcarbinyl systems (see p. 28) whereas the nucleophilic displacement mechanism predicts no isomerization. The enhanced solvolytic reactivity of the cyclopropylmethylcarbinyl derivative should completely overwhelm any tendency to react by the aromatic substitution mechanism so the product, cyclopropylmethylcarbinol, undoubtedly is formed exclusively by a direct solvolysis mechanism.

The observed infinity titers of the kinetic experiments presented in Table III (84-92% of theory) were disturbingly low and the factors responsible for this phenomenon are very likely related to those causing the decrease of rate constants in the later stages of the reactions. A possible explanation is the formation of isomeric unreactive pyridinium salts by internal return. Streitwieser (5) has explained the acid-catalyzed allylic rearrangements of 2-hexen-4-ol to 3-hexen-2-ol (36) and of 1-phenyl-2-buten-1-ol to 1-phenyl-1-buten-3-ol (37) with partial net retention of configuration on the basis of internal return from an "ion-pair" with water playing the role of the anion part of a true ion-pair. Thus, there is some evidence for

internal return with neutral leaving groups. Cyclopropylcarbinyl chloride shows a remarkable propensity to rearrange by internal return; the acetolysis of the chloride appears to give 70% of rearranged chlorides (1) and even the hydrolysis gives a 10% isolated yield of rearranged chlorides (1). However, internal return should certainly be much less important with a neutral rather than an anionic leaving group (see p. 12). In addition, the fact that the cyclopropylcarbinyl derivative XVIIc gave a 99% yield of alcohols (admittedly under different conditions than those of the kinetic experiments) indicates that internal return is unimportant for this substrate. Another possible explanation is the consumption of the evolved acid by a side reaction. When hydrogen iodide was dissolved in 80% ethanol under conditions approximating those of experiment 1, 15% of the initial acid titer disappeared after 17 hours, due, probably, to the formation of ethyl iodide or molecular iodine (the spent solution was brown-colored). Thus, this factor is undoubtedly important in experiment 1 but its importance in the other kinetic experiments is not known. Still further side reactions may be occurring. A careful investigation of the solvolysis products should shed considerable light on the source of the low infinity titers and diminishing rate constants.

The ratio of rate constants for the solvolyses of N-methyl-4-(cyclopropylmethylcarbinyloxy)-pyridinium iodide and of N-methyl-4-(cyclopropylcarbinyloxy)-pyridinium iodide in water at 30° (6×10^6) is the first reliable measurement of the effect of an α-methyl group upon the solvolysis rate of a cyclopropylcarbinyl derivative. Silver (7) found that the acid-catalyzed solvolysis of cyclopropylmethylcarbinyl p-nitrobenzoate is 40 times faster than that of cyclopropylcarbinyl p-nitrobenzoate but there is good reason to believe that the slower of the two compounds is reacting by acyl-oxygen fission. From the solvolysis in 50% ethanol of a mixture of bromides that probably contained about 10% of cyclopropylmethylcarbinyl bromide, Silver (7) calculated a minimum rate constant for cyclopropylmethylcarbinyl bromide which was about twice that of cyclopropylcarbinyl bromide.

If the solvolysis of a cyclopropylcarbinyl derivative proceeds through the classical carbonium ion, one would expect a rate enhancement due to α-methyl substitution of greater than 10^6. The formolysis of t-butyl bromide is about 10^6 times faster than that of isopropyl bromide (38). Since the solvolysis of isopropyl bromide is far from limiting (39), the formolysis of isopropyl bromide is being

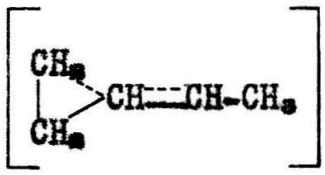
assisted to some extent by nucleophilic attack and the rate enhancement due to α-methyl substitution would be still greater if the solvolysis of isopropyl bromide were limiting. Available rate data (1, 40) indicate that the solvolysis of cyclopropylcarbinyl chloride is nearly limiting (m = 0.9) so that one would predict for this case a rate enhancement of greater than 10^6 upon α-methyl substitution if a classical cation were formed in the transition state. In addition, one might expect the effect of methyl substitution upon a primary carbonium ion (cyclopropylcarbinyl) to be greater than upon a secondary carbonium ion (isopropyl) because the positive charge of the secondary carbonium ion would be more delocalized over the additional alkyl group.

The observed rate enhancement due to α-methyl substitution of the hydrolysis rate of N-methyl-4-(cyclopropylcarbinyloxy)-pyridinium iodide of 6×10^3 is considerably less than 10^6 and does not speak for the classical intermediate. However, the factor of 6×10^3 is large enough to raise the question of whether the intermediates in the solvolyses of cyclopropylcarbinyl and cyclobutyl derivatives are better formulated as classical cyclopropylcarbinyl and cyclobutyl ions, respectively, rather than a common "bicyclobutonium" ion. For a classical cyclopropylcarbinyl

intermediate, one would expect very little rate enhancement due to β-methyl substitution on cyclopropylcarbinyl chloride [(1-methylcyclopropyl)-carbinyl chloride], whereas a factor of about 10^4 is actually observed (41). Also, for a classical cyclobutyl intermediate, one would expect a solvolysis rate enhancement due to α-methyl substitution on cyclobutyl chloride (1-methylcyclobutyl chloride) approaching 10^6 but the observed effect is a factor of only 10^2 (41). These results indicate that the positive charge of the intermediates in the solvolyses of cyclopropylcarbinyl chloride and cyclobutyl chloride is highly delocalized and are inconsistent with rate-determining formation of classical cyclopropylcarbinyl and cyclobutyl ions. In this connection, it would be useful to have rates on some 2-methylcyclobutyl derivatives. These substances should be quite reactive (perhaps 10^2-10^3 faster than cyclobutyl) because they should ionize to the most stable of the three methyl-substituted "bicyclobutonium" ions (IIIa) as should cyclopropylmethylcarbinyl derivatives; a classical intermediate would predict essentially no rate enhancement. The rather large effect (6×10^4) upon the solvolysis rate of N-methyl-4-(cyclopropylcarbinyloxy)-pyridinium iodide due to α-methyl substitution suggests that the intermediate in the

methyl-substituted case may be better formulated as a more classical (less delocalized) structure such as the "hyperconjugated" ion XVIII or possibly as a true homoallylic cation XIX (42).

XVIII



XIX

In the foregoing discussion of the effect of methyl substitution on solvolysis rates, no mention has been made of ground-state free energies. This is a potentially dangerous oversight because solvolysis rates are a reflection of both the transition-state (essentially the carbonium ion) and the ground-state stabilities (42). However, the approach taken here should minimize this peril because the effect of methyl substitution on ground-state stabilities should be approximately constant for the various substrates and consequently introduce a constant factor into the observed rate enhancements. Thus, the relative values of the rate enhancements due to methyl substitution can be attributed to carbonium-ion stabilities even if their absolute values cannot.

Both N-methyl-4-(cyclopropylcarbinyloxy)-pyridinium iodide and perchlorate are about two times more reactive in water than in 80% ethanol. This small dependence of rate on solvent is surprising when compared to the 3110 times greater reactivity of t-butyl chloride at 25° in water than in 80% ethanol (43). However, Swain (23), in a study of the S_N1 solvolysis of t-butyldimethylsulfonium chloride in a wide range of solvents and solvent mixtures, found less than a four-fold variation in the first-order rate constants; in general, the better solvating media gave the slowest rates (the solvolysis in 80% ethanol was about twice as fast as that in water). This behavior was attributed to an important role played by the cation-solvating power of the solvent; the better solvating media stabilize the sulfonium ion with its localized charge relative to the transition state where the charge is distributed over sulfur, carbon and nine hydrogens (23). It is reasonable, then, that the pyridinium salts, where the charge of the substrate is already delocalized over the pyridine ring and oxygen, should show behaviors intermediate between those of t-butyl chloride and t-butyldimethylsulfonium chloride.

When N-methyl-4-(cyclopropylmethylcarbinyloxy)-pyridinium iodide was synthesized, starting with optically active cyclopropylmethylcarbinol (V), and hydrolyzed in the presence of lithium carbonate, the product, V, was of the opposite configuration and had 4.4 ± 1.5% of the original activity. We have already shown that the cyclopropylmethylcarbinol is undoubtedly formed exclusively by an S_Ni-type mechanism. However, the interpretation of this stereochemical result is complicated by the possible competition between neighboring cyclopropyl and solvent participation. To illustrate this point we may consider the solvolysis of 1-phenyl-2-propyl tosylate which gives ca. 85% net inversion in ethanol (44), 29% net inversion in acetic acid (45) and up to 70% retention in formic acid (45). These results are explained in terms of a competition between a classical ion intermediate and a non-classical phenonium ion with the latter being important only in formic acid (45). Even though the cyclopropyl group appears to make a very large contribution to the hydrolysis of N-methyl-4-(cyclopropylmethylcarbinyloxy)-pyridinium iodide, an appreciable part of the reaction may be proceeding through a classical ion and the contributions of the classical and non-classical intermediates to the product cannot

be evaluated. The acetolysis or formolysis of this pyridinium salt would minimize the possibility of solvent participation. Consequently, the acetolysis of the pyridinium salt was investigated but unfortunately no satisfactory method of following the kinetics of the reaction could be found and considerable amounts of rearranged products appeared to be formed (see p. 29). This approach is worthy of further experimentation.

It is interesting that the decomposition of N-nitroso-N-(cyclopropylmethylcarbinyl)-benzamide, the deamination of cyclopropylmethylcarbinylamine and the hydrolysis of N-methyl-4-(cyclopropylmethylcarbinyloxy)-pyridinium iodide all give unusually racemic products for their respective types of reaction. Taken together, these results suggest the existence of a mechanism for facile racemization of the common cationic intermediates in these reactions such as the one proposed in the Introduction.

III. EXPERIMENTAL

All melting points and boiling points are uncorrected. Elemental analyses were performed by Dr. Adalbert Elek, Elek Microanalytical Laboratories, Los Angeles, California. Infrared absorption spectra were obtained using a Perkin-Elmer double-beam recording infrared spectrophotometer, Model 21, or a Beckman infrared spectrophotometer, Model IR-7. All vapor chromatographs were obtained with a Perkin-Elmer Vapor Fractometer, Model 154-C, using diisodecyl phthalate (Column A) as the stationary phase, unless otherwise indicated. All optical rotations were observed with a Winkel-Zeiss Polarimeter relative to air or the appropriate solvent in the cases of neat liquids and solutions, respectively; the rotations were observed with a 1-dm. tube and are accurate to $\pm$ 0.02° unless otherwise noted. Appendix I gives detailed descriptions of some of the fractional-distillation columns used in this work.

Cyclopropylmethylcarbinylamine.--In a 2-l. three-necked flask, equipped with a pressure-equalizing addition funnel, a mechanical stirrer, a nitrogen inlet and a reflux condenser fitted with a calcium chloride drying tube, were placed 77 g. (2.0 moles) of lithium aluminum hydride and

750 ml. of anhydrous ether. To the stirred mixture in a nitrogen atmosphere was added dropwise 105 g. (1.06 moles) of methyl cyclopropyl ketoxime dissolved in 450 ml. of dry ether so as to maintain a moderate rate of reflux. The first half of the oxime solution was added over a period of 1.5 hr.; the flask was cooled with an ice-water mixture and the remaining oxime was added over a 1-hr. period. The mixture was stirred at room temperature for 18 hr. and then under reflux for 34 hr. The condenser was replaced by a Dry-Ice condenser; the flask was immersed in an ice-water bath and the reaction mixture was hydrolyzed with 500 ml. of 10% aqueous sodium hydroxide. Ether (250 ml.) and water (250 ml.) were then added. The flask was equipped for downward distillation, and distillation was conducted until a second, aqueous phase formed in the receiver. The aqueous phase was saturated with potassium carbonate and the ethereal phase was removed and dried over potassium carbonate. The solvent was stripped through Column 1 and the residue was distilled through a 30-cm. Vigreux column, yielding 70.0 g. (78%) of material, b.p. 91-94° (740 mm.), $\underline{n}^{25}$D 1.4243 (lit. b.p. 94.2-94.8° (745 mm.), $\underline{n}^{25}$D 1.4265 (46)).

Resolution of Cyclopropylmethylcarbinylamine.--From a solution of 108 g. (1.27 moles) of amine and 190 g. (1.27 moles) of d-tartaric acid in 300 ml. of water was obtained 121 g. (41%) of the amine tartrate salt. Six recrystallizations from 93% ethanol gave 69 g. of salt, m.p. 161.8-163.0°. A 15-g. sample of the tartrate and 30 g. of potassium hydroxide were added to 20 ml. of water. The organic layer was withdrawn and repeatedly shaken with sodium hydroxide pellets until an aqueous layer no longer formed. The recovered amine was dried over barium oxide and distilled through Column 2, yielding 3.6 g. with b.p. 88-92°. The amine was redistilled through Column 3, giving 1.15 g., b.p. 92-94°, $\alpha^{25}D$ +21.30° (neat). Since analysis by vapor-phase chromatography (VPC) showed the sample to contain about 5% of impurities, it was purified by preparative VPC. The material which collected had $\alpha^{24}D$ +21.14° (neat) and contained about 5% water as determined by VPC.

The remaining amine tartrate, 54 g., was crystallized twice from 93% ethanol giving 46 g., m.p. 161.0-162.0°.

Anal. Calcd. for $C_8H_{17}NO_6$: C, 45.95; H, 7.29; N, 5.96. Found: C, 46.19; H, 7.23; N, 6.11.

A 15-g. sample of the analytically pure tartrate was decomposed as above and the crude amine was purified by

preparative VPC and dried over barium oxide, yielding material with $\alpha^{24}D$ +21.29° (neat). The sample contained 5% water (VPC).

The remaining tartrate salt (31 g.), after two more recrystallizations, gave 26.3 g., m.p. 162.6-164.2°, which was dissolved with 60 g. of potassium hydroxide in 45 ml. of water. The solution was continuously extracted with ether and the extracts were dried over potassium carbonate. The ether was removed through Column 1 and the residue was distilled from barium oxide through Column 2, giving 8.0 g. (83%) of amine, b.p. 92-93°, $\alpha^{25}D$ +21.80° (neat), 99% pure by VPC.

The combined ethanolic mother liquors from all the crystallizations were evaporated to 700 ml., and, on cooling, 30 g. of tartrate was obtained. Decomposition of the salt with aqueous base, continuous extraction of the resulting solution with ether, drying of the extracts over potassium carbonate and then barium oxide, stripping of the solvent and finally distillation of the residue through Column 3 gave 5.4 g. (50%) of amine, b.p. 93°, $\alpha^{25}D$ +21.45° (neat).

The amine tartrate remaining in the original aqueous mother liquor was decomposed with 150 g. of potassium

hydroxide. The solution was saturated with sodium chloride and the organic phase was removed, dried with potassium hydroxide and then with barium oxide and distilled through Column 2, yielding 38.2 g. of amine, b.p. 88-93°, $\alpha^{25}D$ -11.14° (neat).

d-N-(Cyclopropylmethylcarbinyl)-benzamide.--A mixture of 5.7 g. (0.067 mole, $\alpha^{25}D$ +21.80°) of d-cyclopropylmethylcarbinylamine, 8.3 g. of sodium hydroxide, 12 g. (0.085 mole) of benzoyl chloride and 60 ml. of water was stirred magnetically for 10 hr. The white precipitate which separated was collected by vacuum filtration and was recrystallized from 50% ethanol-water and then from 50% benzene-hexane. The yield of purified benzamide was 11.0 g. (93%), m.p. 123.4-124.0°, $[\alpha]^{25}D$ +33.7 ± 0.2° (absolute ethanol, c = 5.0). Further recrystallization failed to raise the melting point of the product. The infrared spectrum of the optically active benzamide was identical to that of a sample of racemic benzamide with m.p. 96.0-97.0° (lit. m.p. 96.8-97.6° (7)).

Cyclopropylmethylcarbinol was prepared in 62% yield by the reduction of methyl cyclopropyl ketone (62.7 g., 0.746 mole) with lithium aluminum hydride (11.9 g., 0.31 mole) in ether solution and had b.p. 119°, $n^{25}D$ 1.4299 (lit. b.p. 123.5°, $n^{20}D$ 1.4316 (47)).

Resolution of Cyclopropylmethylcarbinol. A. d,l-Cyclopropylmethylcarbinyl Hydrogen Phthalate.--In a 100-ml., round-bottomed flask was placed 75 ml. of reagent-grade toluene and one-third was distilled to remove any moisture that may have been present. The remaining toluene was allowed to cool (protected from moist air with a calcium chloride drying tube) and 10.8 g. (0.125 mole) of d,l-cyclopropylmethylcarbinol and 18.5 g. (0.125 mole) of phthalic anhydride were added. The mixture was stirred magnetically and heated in an oil bath at 85-90° for 12 hr.; it was then cooled and poured into a solution of 18 g. of sodium carbonate in 900 ml. of water. The aqueous phase was filtered and acidified with conc. hydrochloric acid. The oil that separated solidified upon standing and was collected and vacuum-dried to give 20.2 g. (69%) of white crystals, m.p. 67.8-69.4°. An analytical sample, m.p. 68.4-69.8°, was obtained by recrystallization from acetic acid-water.

Anal. Calcd. for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found: C, 66.66; H, 5.94.

B. Resolution of Cyclopropylmethylcarbinyl Hydrogen Phthalate.--To 800 ml. of reagent-grade acetone were added 81 g. (0.345 mole) of racemic cyclopropylmethylcarbinyl phthalate and 136 g. (0.345 mole) of anhydrous brucine.

When the mixture was heated to reflux, the reactants dissolved but a precipitate of crude brucine cyclopropylmethylcarbinyl hydrogen phthalate soon formed. The hot acetone solution was vacuum-filtered from the precipitate and the filtrate, upon cooling, deposited crystals of the brucine salt. The yield of crystals was 52 g. The mother liquor was used to dissolve more of the crude brucine salt. Filtration and cooling of the solution gave 88 g. of crystals. Repetition of the process dissolved the remaining crude brucine and afforded 16 g. of crystals.

The three crops of crystallized brucine salt (156 g.) were dissolved in the minimum amount (350 ml.) of boiling reagent-grade methanol and the solution was refrigerated, affording 81 g. of salt, m.p. 166-170°. Seven additional recrystallizations gave 38 g. of brucine d-cyclopropylmethylcarbinyl phthalate, m.p. 175.0-177.6°. From previous experiments, it was known that this melting point could not be raised by repeated recrystallizations from methanol.

Anal. Calcd. for $C_{36}H_{40}N_2O_8$: C, 68.77; H, 6.41. Found: C, 68.18; H, 6.35.

The pure salt was decomposed by dissolving it in the minimum amount of boiling 95% ethanol and pouring the resulting solution into 240 ml. of water and 16 ml. of

conc. hydrochloric acid in a separatory funnel. An oil separated at the bottom of the funnel. It was known from preliminary experiments that the oil could not be induced to crystallize directly; consequently, it was dissolved in five volumes of glacial acetic acid; then, water was added to the cloud point. The solution was frozen solid in a Dry-Ice acetone bath and scratched as the solid warmed and melted. At about 15° a finely divided precipitate remained but turned to oil at room temperature. When the solution was cooled before it reached room temperature, oiling was prevented. The first crop, A, of optically pure phthalate was collected and dried in a vacuum desiccator over phosphorous pentoxide, 2.3 g., m.p. 57.8-59.8°, $[\alpha]^{25}D$ +33.1 ± 0.2° (carbon tetrachloride, c = 10.2); the infrared spectrum was identical to that of the d,l-phthalate. Water was added to the mother liquor to the cloud point. Freezing, scratching while warming, and refrigeration of the solution gave a second crop, B, 1.6 g., m.p. 58.2-59.8°, $[\alpha]^{25}D$ +33.7 ± 0.2° (c = 10.2). A third crop, C, was obtained in a similar manner, 1.0 g., m.p. 57.4-59.0°, $[\alpha]^{25}D$ +32.9 ± 0.2° (c = 10.1). A fourth crop could not be realized.

Crop B was recrystallized from acetic acid-water by the above procedure into three fractions: B-1, 0.15 g., m.p. 57.8-59.6°; B-2, 0.50 g., m.p. 57.8-59.2°, $[\alpha]^{27}D$ +33.1 ± 0.2° (*c* = 9.7); B-3, 0.3 g., m.p. 57.6-59.2°.

C. Reduction of d-Cyclopropylmethylcarbinyl Hydrogen Phthalate.--The combined crops A, B-1,2,3, and C of the d-phthalate (4.0 g., 0.017 mole, including all the samples used for measuring optical rotations, which had been evaporated to dryness under an air stream and dried) were dissolved in 75 ml. of dry ether. The solution was added over a 0.5-hr. period to 2.3 g. (0.060 mole) of lithium aluminum hydride suspended in 75 ml. of ether in a 500-ml., three-necked flask equipped with a mechanical stirrer, a reflux condenser, a pressure-equalizing addition funnel and a nitrogen inlet. A nitrogen atmosphere and stirring were maintained throughout the reaction. The mixture was held at reflux for 1 hr. and then 7.7 ml. of ethyl acetate was added to decompose excess hydride. The mixture was stirred for an additional 15 min., the condenser was replaced by a Dry-Ice condenser and 10 ml. of water was added. The mixture was then stirred and heated under reflux for 1 hr. and at room temperature for 4 hr., and was then allowed to stand for 3 hr. until all the grey salts had disappeared,

leaving only a white precipitate. The ether was decanted and the precipitate was washed twice with 50-ml. portions of ether. The combined ethereal solutions were dried over potassium carbonate. The ether was removed through Column 1 and the residue was distilled through Column 2. Low-boiling materials (b.p. < 76°) were removed at atmospheric pressure and the rest of the distillation was carried out under reduced pressure. After 0.26 g. of forerun, 1.17 g. of a mixture, containing 82.6% of cyclopropylmethylcarbinol and 17.4% of ethanol and water (VPC), was obtained with b.p. 70-72° (96 mm.), $\alpha^{25}D$ +18.25° (neat). The main fraction was redistilled through the same column giving 0.19 g. of forerun and 0.68 g. of a mixture, containing 93.7% of carbinol and 6.3% of ethanol and water with b.p. 70° (90 mm.), $\alpha^{25}D$ +19.45° (neat). Linear extrapolation of the two observed rotations to 100% carbinol gave αD +20.1°.

d-Cyclopropylmethylcarbinyl Benzoate.--In a 100-ml., round-bottomed flask, equipped with a magnetic stirrer, a reflux condenser and a calcium chloride drying tube were placed 50 ml. of dry ether, 0.30 g. (0.012 mole) of sodium hydride and 0.54 g. (0.006 mole, $\alpha^{25}D$ +19.45°) of d-cyclopropylmethylcarbinol. The mixture was stirred under reflux for 4 hr. The white sodium alcoholate precipitated. The

mixture was cooled to room temperature and 1.0 ml. (0.009 mole) of benzoyl chloride was added. The mixture was stirred at reflux for 1.5 hr. and at room temperature for 12 hr. After 24 more hr., 5 ml. of water was added to decompose the remaining hydride and to dissolve the sodium salts. The ethereal phase was separated, extracted twice with 2-ml. portions of water and dried over magnesium sulfate. After removal of the solvent, the residue was distilled through Column 2. After 0.05 g. of forerun, 0.52 g. (44%) of benzoate was obtained with b.p. 47-49° (1 mm.), $\alpha^{27}D$ +33.82° (neat), $n^{25}D$ 1.5064; the infrared spectrum was identical to that of an analytically pure sample obtained from the decomposition of N-nitroso-N-(cyclopropylmethylcarbinyl)-benzamide (below).

Preparation and Decomposition of Optically Active N-Nitroso-N-(cyclopropylmethylcarbinyl)-benzamide.--For each of the two experiments, the nitrosamide was prepared from a mixture of 100 ml. of a 0.5M solution of nitrogen tetroxide (Matheson) in reagent-grade carbon tetrachloride, 8.3 g. (0.10 mole) of sodium acetate and 4.7 g. (0.025 mole) of the above d-N-(cyclopropylmethylcarbinyl)-benzamide, stirred magnetically for 30 min. at 5°. The mixture was poured onto 100 g. of ice and the organic layer was removed

and extracted with water and with 5% aqueous sodium bicarbonate and then dried over sodium sulfate; all operations were carried out at 0-5°. The solution was decanted and evaporated to dryness under vacuum at 0°, leaving the crude nitrosamide as a yellow oil. The per cent retention of optical activity in the product (cyclopropylmethylcarbinyl benzoate) of the decomposition of the nitrosamide was calculated on the basis that the starting benzamide was optically pure and the rotation of optically pure product is αD 33.82°.

A. Decomposition in Pentane.--The crude nitrosamide was stirred overnight in 125 ml. of reagent-grade pentane at room temperature. The solution was then stirred with sodium hydroxide pellets to precipitate the benzoic acid formed during the decomposition. After filtration and distillation of the solvent, the residue was distilled through Column 2, yielding 2.00 g. (50%) of cyclopropylmethylcarbinyl benzoate, b.p. 55-58° (1 mm.), $\alpha^{25}D$ +5.25° (neat). A broad absorption band at 3200 $cm.^{-1}$ in the infrared spectrum of the product suggested the presence of benzoic acid as an impurity. Consequently, the product was dissolved in 50 ml. of ether and the ethereal solution was extracted with 50% aqueous potassium carbonate and

dried over sodium sulfate. Removal of the solvent and distillation of the residue through Column 2 gave 1.25 g. of benzoate, b.p. 56-58° (1 mm.), $\alpha^{25}D$ +5.68° (neat, 16.8% retention of optical activity), $n^{25}D$ 1.5066; the 3200 $cm.^{-1}$ band had disappeared. The nuclear magnetic resonance (NMR) spectrum (see p. 78) and the infrared spectrum were consistent with the assigned structure.

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 76.11; H, 7.39.

B. Decomposition in Dioxane.--The crude nitrosamide was stirred magnetically in 100 ml. of purified (48) dioxane at room temperature for 18 hr. The solution was then stirred with a sodium hydroxide pellet and decanted. The solvent was stripped and the residue was distilled through Column 2, yielding 1.40 g. (35%) of liquid with b.p. 67-72° (1 mm.). Because of the presence of an infrared absorption band at 3200 $cm.^{-1}$, the product was purified by dissolving it in 40 ml. of ether and treating the solution as in Part A; yield 0.71 g., b.p. 65° (1 mm.), $\alpha^{25}D$ +7.18° (neat, 21.2% retention of optical activity), $n^{25}D$ 1.5065; the infrared spectrum was now identical to that of the analytically pure sample of Part A.

Deamination of Optically Active Cyclopropylmethylcarbinylamine with Nitrous Acid.--For all but the last experiment, the reaction vessel was a 100-ml., round-bottomed flask, equipped with a magnetic stirrer, a reflux condenser and a gas exit tube. The evolved gases were collected by displacing water from an inverted graduate cylinder. The pH measurements were made with a Beckman Glass Electrode pH Meter, Model H, on the entire reaction mixture cooled to room temperature. The pH of the reaction mixture was deliberately kept high to avoid acid-catalyzed racemization of the product, cyclopropylmethylcarbinol. The deaminations were conducted at reflux but were still very slow, as indicated by the rate of gas evolution, and virtually ceased as the reaction proceeded and the solution became more basic. Consequently, the reaction was periodically interrupted and more acid was added to lower the pH and speed up the reaction. The pH of the solution was measured before and after the reaction and before and after each addition of acid but only the extremes of the pH readings are reported. The total period of time under reflux and the total amount of acid used are given for each experiment. The products were isolated by continuous extraction of the reaction mixture (saturated with sodium chloride) with

ether. The ethereal solution was dried over sodium sulfate and decanted. The ether was removed through Column 1 and the residue was distilled through Column 2. All optical rotations were measured with neat samples.

A. The reactants were 50 ml. of water, 8.7 g. (0.052 mole) of 60% aqueous perchloric acid, 4.3 g. (0.050 mole, $\alpha^{22}D$ +9.18°) of amine and 10 g. (0.14 mole) of sodium nitrite and 870 ml. of gas was evolved after 9.5 hr. of heating. The pH range was 8.2-9.2. The isolation procedure gave 0.25 g. of forerun which was mostly methyl cyclopropyl ketone as determined by infrared analysis and VPC. The main fraction, 0.78 g., b.p. 69-72° (99 mm.), $\alpha^{24}D$ +0.04°, had an infrared spectrum identical to that of cyclopropylmethylcarbinol with the exception of additional bands at 1600, 1660 and 1695 $cm.^{-1}$. The 1695 $cm.^{-1}$ band corresponded to the carbonyl absorption band of methyl cyclopropyl ketone and the 1600 and 1660 $cm.^{-1}$ bands were attributed to the N-H deformation mode of cyclopropylmethylcarbinylamine. No satisfactory method of analyzing for small amounts (1-2%) of the amine (or the ketone) in the presence of the carbinol by VPC could be developed. However, the concentration of the amine in the product was estimated as 2% by comparing the infrared spectrum of the

product with those of mixtures of amine and alcohol of known concentrations.

B. The reactants were 8.6 g. (0.052 mole) of perchloric acid, 4.3 g. (0.050 mole, $\alpha^{25}D$ +9.18°) of amine and 5 g. (0.07 mole) of sodium nitrite in 40 ml. of water and 980 ml. of gas was collected over 11 hr. of heating. The pH range was 8.3-8.9. The products isolated were 0.19 g. of forerun, mostly alcohol with some ketone (VPC), and 0.67 g. of alcohol containing 1% of amine (infrared), b.p. 70-72° (98 mm.), $\alpha^{27}D$ -0.04°.

C. The reactants were 50 ml. of water, 8.9 g. (0.053 mole) of perchloric acid, 4.3 g. (0.050 mole, $\alpha^{25}D$ -9.67°) of amine and 10 g. (0.14 mole) of sodium nitrite and 1050 ml. of gas was evolved over 21.5 hr. of heating. The pH range was 7.6-9.4. The usual isolation procedure (with the exception that the ether was removed through a 50-cm. Helipak-packed column) gave 0.24 g. of forerun, mostly ketone (VPC), and 1.39 g., b.p. 70° (95.5 mm.). The main fraction was redistilled from 0.5 g. of adipic acid (to remove amine) through Column 2, giving 0.19 g. of forerun and 1.01 g. of alcohol containing 1% of amine (infrared), b.p. 70° (95 mm.), $\alpha^{25}D$ +0.27°.

D. The apparatus was a 100-ml., three-necked flask equipped with pH electrodes, a magnetic stirrer, a reflux condenser, a thermometer and a gas-collecting system. To the flask were added 40 ml. of water, 8.0 g. (0.048 mole) of acid, 4.3 g. (0.050 mole, $\alpha^{26}D$ +9.18°) of amine and 5 g. (0.07 mole) of sodium nitrite. The electrodes and the thermometer were adjusted so that they were well below the surface of the solution but did not interfere with the magnetic stirring bar. Stirring was maintained throughout the reaction. At 26°, the pH was 8.0. The solution was heated to 80° with an oil bath over a 10-min. period, during which time 45 ml. of gas was collected. The pH meter now read 7.8 without adjusting the temperature compensating control. The solution was held at 80° and additional acid was added periodically, through the condenser, closing the system as soon as possible thereafter. By this method, the reading of the pH meter was maintained between 6.0 and 7.8. After 10 hr., 1200 ml. of gas had been collected and the meter read 6.4 (5.5 after cooling the solution to room temperature). Isolation of the products gave 0.50 g. of forerun, 1.61 g., b.p. 72-101° (98-81 mm.) and 0.28 g., b.p. 56° (11 mm.). The main fraction contained 14% of cyclopropylmethylcarbinol and 75% of an unknown compound,

A (VPC). The last fraction contained 3% of the alcohol and 91% of A (VPC) and its infrared spectrum showed no prominent absorption in the region of 1500-5000 cm.$^{-1}$ except for bands in the C-H stretching region (2800-3100 cm.$^{-1}$). On the basis of the NMR (fig. 1) and infrared spectra of the last fraction, A was assigned the structure bis-(cyclopropylmethylcarbinyl) ether.

Racemization of Cyclopropylmethylcarbinol under the Conditions of the Amine-Nitrous Acid Reaction.--To 50 ml. of water were added 6.4 g. (0.038 mole) of 60% perchloric acid, 5.0 ml. (0.039 mole) of d,l-1-phenylethylamine, 7 g. (0.11 mole) of sodium nitrite and 1.21 g. of cyclopropylmethylcarbinol, $\alpha^{25}D$ -1.36° (neat). The initial pH was 7.0. The solution was heated under reflux for 5 hr. and evolved 965 ml. of gas. The cooled solution was now pH 8.9. The usual isolation procedure gave 0.08 g. of forerun and then 0.75 g. of cyclopropylmethylcarbinol, b.p. 70-71° (101 mm.), $\alpha^{25}D$ -1.14° (neat), corresponding to 84% retention of optical activity. The still residue contained 4.6 g. of a red liquid.

Deamination of Optically Active 1-Phenylethylamine with Nitrous Acid.--The amine was resolved by the method of Theilacker and Winkler (49). The products were isolated

by continuous extraction of the reaction mixture with ether; the ethereal solution was then dried, stripped of solvent through Column 1, and the residue was distilled through Column 2. It was found that 1% of the starting amine in the product could easily be detected by VPC by examining mixtures of amine and alcohol of known composition. Some of the products contained appreciable amounts of amine which could be removed by redistillation from adipic acid through Column 2. The final samples of 1-phenylethanol contained much less than 1% of amine unless otherwise indicated. All pH measurements were made at room temperature with a Beckman pH Meter. All optical rotations were measured with neat liquids. The stereochemical results were calculated using a value of $\alpha^{25}D$ 38.30° for the optically pure amine (49); $\alpha^{20}D$ 43.44° was used (50) for the alcohol. Amine and alcohol of the same sign of rotation have the same configuration (51).

A. To 50 ml. of water were added 5.2 g. (0.031 mole) of 60% perchloric acid, 5.0 ml. (0.039 mole, $\alpha^{25}D$ +25.46°) of amine and 7 g. (0.11 mole) of sodium nitrite; the pH was 8.4. The solution was stirred magnetically at reflux for 20 hr. raising the pH to 8.9. The isolation procedure gave 0.13 g. of forerun and 2.84 g., b.p. 68-72° (4.5 mm.),

$\alpha^{27}D$ +3.15°. Redistillation from 1 g. of adipic acid gave 0.17 g. of forerun and 1.11 g. of pure 1-phenylethanol, b.p. 63° (2.8 mm.), $\underline{n}^{25}D$ 1.5253, $\alpha^{25}D$ -1.57° (5.5% net inversion of configuration). The reported values are b.p. 100° (18 mm.), $\underline{n}^{20}D$ 1.5211 (50).

B. The reaction mixture was 35 ml. of water, 5.9 g. (0.035 mole) of perchloric acid and 5.0 ml. (0.039 mole, $\alpha^{25}D$ -22.18°) of amine and 7 g. (0.11 mole) of sodium nitrite. After 0.07 g. of forerun, 3.43 g., b.p. 77-83° (6 mm.), $\alpha^{25}D$ -1.42°, was obtained. Redistillation from adipic acid gave 0.04 g. of forerun and 1.75 g. of pure alcohol, b.p. 61-62° (2.4-2.8 mm.), $\underline{n}^{25}D$ 1.5250, $\alpha^{20}D$ +1.30° (5.2% inversion).

C. The reaction mixture contained 35 ml. of water, 7.0 g. (0.042 mole) of acid, 5.0 ml. (0.039 mole, $\alpha^{25}D$ -22.18°) of amine and 7 g. (0.11 mole) of sodium nitrite and was stirred magnetically at reflux for 4 hr. After 0.24 g. of forerun, 3.34 g., b.p. 89° (11.5 mm.), $\alpha^{20}D$ +1.04°, was obtained. Redistillation of the main fraction from adipic acid gave 0.04 g. of forerun and 2.42 g. of pure alcohol, b.p. 63° (3.0 mm.), $\underline{n}^{25}D$ 1.5250, $\alpha^{25}D$ +1.08° (4.3% inversion).

D. To 50 ml. of water were added 7.84 g. (0.047 mole) of acid, 5.0 ml. (0.039 mole, $\alpha^{28}D$ +25.46°) of amine and 7 g. (0.11 mole) of sodium nitrite. The solution was stirred for 15 min. and allowed to stand overnight. The isolation procedure gave 0.17 g. of forerun and 3.20 g. of pure alcohol, b.p. 72-76° (4.5 mm.), $\alpha^{31}D$ -2.11° (7.4% inversion).

E. In 100 ml. of water were dissolved 3.1 g. (0.026 mole, $\alpha^{28}D$ -22.18°) of amine, 69 g. (0.5 mole) of sodium dihydrogen phosphate monohydrate and 8.0 g. (0.2 mole) of sodium hydroxide; the solution had pH 5.9. A solution of 6.0 g. (0.087 mole) of sodium nitrite in 15 ml. of water was added. The solution had pH 6.0 after 3 hr. at reflux. After 1.07 g. of forerun, 1.44 g. of pure alcohol, b.p. 75-78° (6.5 mm.), $\alpha^{28}D$ +2.92° (11.6% inversion) was obtained.

F. To 150 ml. of water were added 104 g. (0.76 mole) of sodium dihydrogen phosphate monohydrate, 12.4 g. (0.31 mole) of sodium hydroxide, 5.0 ml. (0.039 mole, $\alpha^{28}D$ -19.24°) of amine and 7 g. (0.11 mole) of sodium nitrite; the pH was 6.05. The solution was heated to reflux for 2 hr. and after cooling the same over a 3-hr. period, had pH 6.07. After 0.15 g. of forerun, 3.33 g. of pure alcohol, b.p. 71-75° (5.5 mm.), $\alpha^{28}D$ +2.87° (13.2% inversion of configuration), was obtained.

G. The reaction mixture consisted of 150 ml. of water, 52 g. (0.38 mole) of sodium dihydrogen phosphate monohydrate, 6.0 g. (0.15 mole) of sodium hydroxide, 5.0 ml. (0.039 mole, $\alpha^{25}D$ +25.46°) of amine and 7.0 g. (0.11 mole) of sodium nitrite and had pH 6.2. The solution was heated under reflux for 2 hr. and allowed to stand at room temperature for 12 hr.; the pH was unchanged. After 0.36 g. of forerun, 3.33 g., b.p. 73-77° (5.5 mm.), $\alpha^{25}D$ -3.88°, was obtained. Redistillation of the main fraction from adipic acid gave 0.53 g. of forerun and 1.80 g. of pure alcohol, b.p. 56° (2.0 mm.), $n^{25}D$ 1.5256, $\alpha^{25}D$ -3.91° (13.6% inversion).

H. The reaction mixture was the same as that of experiment F (except that the sodium hydroxide was omitted) and had pH 3.95. After heating the solution under reflux for 4 hr., the pH was 4.20. The isolation routine gave 0.58 g. of forerun and 2.32 g., b.p. 65-70° (4 mm.), $\alpha^{25}D$ -0.23°, of alcohol containing 1% of amine (VPC).

4-Pyridylpyridinium Dichloride was prepared by the method of Bowden and Green (52). From 1000 g. of technical-grade thionyl chloride and 340 ml. of pyridine was obtained 293 g. of a golden-brown powder, m.p. 160-166° (lit. m.p. 158-160° (52)).

4-Hydroxypyridine was prepared by the method of Koenigs and Greiner (53). From 120 g. of 4-pyridylpyridinium dichloride was obtained 34.3 g. (69%) of tan crystals.

4-Chloropyridine was prepared by the method of Leis and Curran (54). From 38 g. of phosphorous pentachloride, 38 g. of phosphorous oxychloride and 33 g. of 4-hydroxypyridine was obtained 24 g. (61%) of product, $n^{25}D$ 1.5290 (lit. $n^{25}D$ 1.5280 (54)), which was stored at -5° to prevent polymerization.

4-Benzyloxypyridine was prepared after the method of Shaw (55) and had m.p. 51.6-54.8° (lit. m.p. 55-56° (55)).

N-Methyl-4-benzyloxypyridinium Iodide.--On a steam bath were heated 0.50 g. of 4-benzyloxypyridine and 0.50 g. of methyl iodide. The solution solidified after a few minutes. The solid was crystallized from ethanol-ethyl acetate giving 0.70 g. (79%), m.p. 146.8-149.8°. Two recrystallizations from absolute ethanol gave 0.6 g. of light-tan crystals, m.p. 149.4-150.8° after vacuum drying.

Anal. Calcd. for $C_{13}H_{14}INO$: C, 47.72; H, 4.31; I, 38.79. Found: C, 47.34; H, 4.49; I, 39.09.

N-Methyl-4-benzyloxypyridinium Perchlorate was prepared from 88 mg. of N-methyl-4-benzyloxypyridinium iodide dissolved in 6 ml. of 80% ethanol to which was added a solution

of silver perchlorate in ethanol until no more yellow precipitate would form. The solution was filtered from the precipitate and evaporated to dryness under vacuum. The residue was dissolved in 10 ml. of methylene chloride, filtered, and ether was added to the cloud point. Cooling gave 41 mg. (51%) of white crystals, m.p. 141.4-142.2° after vacuum drying over phosphorous pentoxide.

Anal. Calcd. for $C_{15}H_{14}ClNO_3$: C, 52.09; H, 4.71; Cl, 11.83; N, 4.67. Found: C, 51.66; H, 4.69; Cl, 11.96; N, 4.89.

4-(Cyclopropylcarbinyloxy)-pyridine.--In a 50-ml., round-bottomed flask, protected by a calcium chloride drying tube, were placed 2.4 g. (0.032 mole) of cyclopropylcarbinol, 0.76 g. (0.032 mole) of sodium hydride and 10 ml. of purified (56) dimethyl sulfoxide. The mixture was stirred magnetically for 1 hr., when 3.2 g. (0.028 mole) of 4-chloropyridine was added, and stirring was continued for 8 hr. The red solution was filtered and the precipitate was washed with hot benzene. The dimethyl sulfoxide solution and benzene washings were combined, the benzene was removed under vacuum and the residue was distilled through Column 2 at 1 mm. After the dimethyl sulfoxide (b.p. 31°) was distilled, 3.73 g. (89%) of a colorless

liquid, b.p. 57° (1 mm.), was obtained which was redistilled through the same column giving three fractions, b.p. 85° (3 mm.), $n^{25}D$ 1.5214-1.5260. The third fraction, $n^{25}D$ 1.5258, was analyzed.

Anal. Calcd. for $C_8H_{11}NO$: C, 72.45; H, 7.43; N, 9.39. Found: C, 72.83; H, 7.82; N, 9.29.

The NMR spectrum of the third fraction was consistent with the assigned structure (see p. 78).

N-Methyl-4-(cyclopropylcarbinyloxy)-pyridinium Iodide was prepared from 1.5 g. of 4-(cyclopropylcarbinyloxy)-pyridine and 2 ml. of methyl iodide in a tightly stoppered test tube. The exothermic reaction was moderated by periodically cooling the tube in ice water. The mixture became thick and then crystallized. Recrystallization from methylene chloride-ether gave 2.00 g. (68%) of yellow crystals, m.p. 110.4-111.1° after vacuum drying. The NMR spectrum was consistent with the assigned structure (see p. 78).

Anal. Calcd. for $C_{10}H_{14}INO$: C, 41.25; H, 4.85; I, 43.59; N, 4.81. Found: C, 41.40; H, 4.85; I, 44.79; N, 5.04.

N-Methyl-4-(cyclopropylcarbinyloxy)-pyridinium Perchlorate was prepared from 0.40 g. of N-methyl-4-(cyclopropylcarbinyloxy)-pyridinium iodide dissolved in 10 ml.

of absolute ethanol to which a solution of silver perchlorate in ethanol was added until no more yellow precipitate would form. The mixture was boiled and filtered and the precipitate was washed with 10 ml. of hot ethanol. The combined ethanolic filtrates were evaporated to 10 ml. under vacuum whereupon a white precipitate separated. Subsequent boiling and cooling gave 0.28 g. of white crystals, which, after vacuum drying, had m.p. 87.0-87.6° (cloudy). The product was taken up in 2 ml. of methylene chloride and filtered from a small amount of grey insoluble material. Addition of ether to the filtrate and cooling gave 0.26 g. (72%) of material having m.p. 87.6-88.0° after vacuum drying.

Anal. Calcd. for $C_{10}H_{14}ClNO_3$: C, 45.55; H, 5.35; Cl, 13.45; N, 5.31. Found: C, 45.80; H, 5.52; Cl, 13.50; N, 5.80.

4-(Cyclopropylmethylcarbinyloxy)-pyridine was prepared in a similar manner to 4-(cyclopropylcarbinyloxy)-pyridine. From 5.6 g. (0.065 mole) of cyclopropylmethylcarbinol, 1.56 g. (0.065 mole) of sodium hydride, 20 ml. of purified dimethyl sulfoxide and 7.4 g. (0.065 mole) of 4-chloropyridine was obtained 9.1 g. (86%) of a colorless liquid, b.p. 72° (1 mm.). Redistillation gave three fractions, b.p. 77° (2 mm.), $n^{25}D$ 1.5130-1.5160. The third fraction, $n^{25}D$ 1.5160, was redistilled from barium oxide and analyzed.

Anal. Calcd. for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.91; H, 8.02; N, 9.03.

The NMR spectrum of the product was consistent with the assigned structure (see p. 78).

N-Methyl-4-(cyclopropylmethylcarbinyloxy)-pyridinium Iodide.--In a stoppered flask were placed 2.94 g. of 4-(cyclopropylmethylcarbinyloxy)-pyridine and 3 ml. of methyl iodide. The exothermic reaction was moderated by cooling the flask under a stream of water. The excess methyl iodide was removed under vacuum leaving 5.74 g. (104%) of a viscous orange oil. It was known from preliminary experiments that this oil could not be induced to crystallize from methylene chloride-ether; however, its NMR spectrum was consistent with the assigned structure (see p. 78). The oil was dissolved in 15 ml. of reagent-grade acetone and filtered. Crystallization was induced by cooling the solution in a Dry Ice-acetone bath with vigorous scratching. Just after the first crystal appeared, the solution was cooled at 0°, and crystallization slowly continued. The white crystals were collected in a 2-ml., sintered-glass Beuchner funnel. The funnel was quickly transferred to a stoppered, 15-ml. centrifuge tube and was centrifuged for 5 min. in a centrifuge cooled by placing

Dry Ice in the guard bowl. The centrifuged crystals, 1.8 g., were quickly placed in a vacuum desiccator where they began to fuse. Before fusion was complete, the product was cooled and 1.2 g. of acetone was added. The mixture was stirred until solution was almost complete and cooled again. The precipitate that formed was collected as before and was placed in a vacuum desiccator where it melted to a slightly yellow oil weighing 0.90 g. Two more crystallizations from acetone gave 0.40 g. of a nearly colorless oil which was dissolved in methylene chloride and filtered to remove a few particles of foreign material. The methylene chloride solution was placed in a vacuum desiccator over phosphorous pentoxide for four days, leaving 0.41 g. of oil which was analyzed.

Anal. Calcd. for $C_{11}H_{16}INO$: C, 43.29; H, 5.29; I, 41.59; N, 4.59. Found: C, 43.49; H, 5.53; I, 41.23; N, 4.52.

Metathesis of samples of the methiodide with silver perchlorate and with silver trifluoroacetate produced colorless oils which could not be induced to crystallize.

4-(1-Phenylethoxy)-pyridine was prepared in a similar manner to 4-(cyclopropylcarbinyloxy)-pyridine. From 5.1 g. (0.042 mole) of 1-phenylethanol, 1.0 g. (0.042 mole) of sodium hydride, 10 ml. of purified dimethyl sulfoxide and

5.1 g. (0.045 mole) of 4-chloropyridine was obtained 7.2 g. (86%) of a viscous yellow liquid, b.p. 120° (1 mm.). The product was refractionated and a nearly colorless central cut, 5.0 g., had b.p. 94° (1 mm.), $n^{25}D$ 1.5644.

Anal. Calcd. for $C_{15}H_{15}NO$: C, 78.36; H, 6.57; N, 7.03. Found: C, 78.02; H, 6.79; N, 7.04.

The analytical sample darkened upon standing unless sealed under nitrogen. The NMR spectrum of the product was consistent with the assigned structure (see p. 78).

The reaction of the alkoxypyridine with methyl iodide produced a viscous orange oil which could not be induced to crystallize although its NMR spectrum (see p. 78) was consistent with the structure N-methyl-4-(1-phenylethoxy)-pyridinium iodide. From 1.00 g. of the alkoxypyridine was obtained 1.73 g. (101%) of an orange oil after removing the excess methyl iodide under vacuum. The oil was dissolved in 1.90 g. of glacial acetic acid and heated on a steam bath for 4 hr., at which time two phases formed. The lower phase solidified upon cooling the system to room temperature. The precipitate was collected and washed with ether and had m.p. 129-137°. Recrystallization from acetone gave 0.14 g. of yellow crystals, m.p. 125-137°. The liquid phase of the reaction mixture was distilled through a

simple head at 1 mm., the receiver being cooled in Dry Ice-acetone. Examination of the distillate by VPC showed acetic acid and one other peak. The unknown peak was collected on a preparative scale giving 182 mg. of a yellow liquid. Repurification by preparative VPC failed to remove the yellow color. The unknown material was assigned the structure 1-phenylethyl acetate on the basis of its NMR spectrum (see p. 78).

Optically Active 4-(Cyclopropylmethylcarbinyloxy)-pyridine was prepared in a similar fashion to the racemic compound. From 3.0 g. (0.035 mole, $\alpha^{27}D$ -3.39°) of cyclopropylmethylcarbinol, 0.84 g. (0.035 mole) of sodium hydride, 15 ml. of purified dimethyl sulfoxide and 4.0 g. (0.035 mole) of 4-chloropyridine was obtained 4.1 g. (72%) of product, b.p. 65-66° (1 mm.). Redistillation of the product gave 0.57 g. of forerun and 3.40 g., b.p. 106-107° (6.5 mm.), $n^{28}D$ 1.5156, $\alpha^{28}D$ -0.87° (neat).

Preparation and Hydrolysis of Optically Active N-Methyl-4-(cyclopropylmethylcarbinyloxy)-pyridine.--The reaction of 2.37 g. of the above optically active 4-(cyclopropylmethylcarbinyloxy)-pyridine with excess methyl iodide gave 4.36 g. (98%) of a viscous orange oil, $[\alpha]^{28}D$ +0.3° (chloroform, c = 6.8), after removal of the excess methyl

iodide in a vacuum desiccator over phosphorous pentoxide for five days. The infrared spectrum (neat) of the oil was similar to but not superimposable with that of the racemic methiodide. The variations were minor except for a broad band at 3440 cm.$^{-1}$ which was much stronger in the spectrum of the racemic methiodide.

The optically active methiodide (3.85 g.) was dissolved in 50 ml. of triply distilled water and 2 g. of reagent-grade lithium carbonate was added to buffer the solution. The mixture was stirred magnetically at room temperature for 36 hr. and was then continuously extracted with ether. The ethereal extracts (75 ml.) were dried over sodium sulfate and then magnesium sulfate, stripped of solvent through Column 1 and the residue was distilled through Column 2, giving 0.57 g. (53%) of product with b.p. 70° (98 mm.), $n^{25}D$ 1.4373, $\alpha^{25}D$ +0.15 ± 0.05° (neat). The infrared spectrum of the product was identical to that of an authentic sample of cyclopropylmethylcarbinol except for the presence of additional, weak absorption bands at 965, 1170, 1240, 1645, and 1715 cm.$^{-1}$. The latter two bands were broad and highly suggestive of an amine.

Solvolysis of N-Methyl-4-(cyclopropylcarbinyloxy)-pyridine in 80% Ethanol.--A mixture of 51.8 mg. of the

methiodide, 0.73 ml. of absolute ethanol and 0.15 ml. of water was sealed in a glass tube and heated at 120° (bath temperature); the solid dissolved. After the solution was heated for 18 hr., it was analyzed by VPC under the operating conditions used by Graham (4) for the analysis of the products from the solvolysis of cyclopropylcarbinyl chloride. Three major peaks appeared in the chromatogram, corresponding in retention times to the ethyl ethers of cyclopropylcarbinol, cyclobutanol and allylcarbinol. The cyclobutyl and cyclopropylcarbinyl ethers were poorly resolved, but could be separated under different operating conditions. The peaks were cut out of the chromatograph and weighed; the ratio of the weights of the three ethers was cyclopropylcarbinyl:cyclobutyl:allylcarbinyl = 3.6:1.5:1.0. Peaks with retention times equal to those of cyclobutanol, cyclopropylcarbinol, and allylcarbinol were also detectable but were too small to measure.

Reaction of N-Methyl-4-benzyloxypyridinium Iodide and Perchlorate with Glacial Acetic Acid.--In 0.98 g. of glacial acetic acid was dissolved 96 mg. of the methiodide by warming the mixture on a steam bath. In capillary tubes were sealed approximately 30 μl. samples and the tubes were heated in an oil bath at 109°. Capillaries were

periodically withdrawn and their contents analyzed with a F and M Programmed Temperature Gas Chromatograph, Model 202, using a silicone rubber column. The appearance of benzyl acetate was measured by comparing the chromatographs to that of a solution of benzyl acetate in acetic acid of known concentration. By this method the half-life of the reaction was estimated as 2-3 hr.

A 34-mg. sample of the perchlorate was treated in the same way. Little or no benzyl acetate could be detected after 36 hr. of heating.

For comparison, benzyl chloride was found to be unreactive under the same conditions.

Reaction of N-Methyl-4-(cyclopropylmethylcarbinyloxy)-pyridinium Iodide with Ethanol.--The methiodide (0.69 g.) was a sample of unknown purity that had been recrystallized from acetone and dried under vacuum. A solution of the methiodide in 0.69 g. of absolute ethanol was sealed in a glass tube and heated for 80 min. at 98.4°. The resulting orange solution deposited a yellow precipitate when cooled to room temperature. The volatiles were removed under vacuum and collected in a Dry Ice-acetone trap. The residue was crystallized from ethanol giving 0.18 g. of yellow crystals, m.p. 141.5-149.5°. Recrystallization from ethanol

gave 0.10 g., m.p. 145-149°, which was triturated with boiling acetone in which it was insoluble. The vacuum-dried yellow crystals, m.p. 148.0-149.7°, were soluble in ethanol and the solution gave an immediate yellow precipitate with alcoholic silver perchlorate. A solution of the crystals in water, in which it was very soluble, turned pH paper red (pH 2).

Anal. Found: C, 35.51; H, 3.54.

The volatiles from the original reaction (0.73 g.) were examined by VPC and were found to contain one product besides ethanol. The product was separated by preparative VPC, giving 66 mg. of a colorless liquid which was assigned the structure cyclopropylmethylcarbinyl ethyl ether on the basis of its NMR spectrum (fig. 1).

Reaction of N-Methyl-4-(cyclopropylmethylcarbinyloxy)-pyridinium Iodide with Glacial Acetic Acid.--A sample of the methiodide of unknown purity was dissolved in glacial acetic acid and was heated at 125° (bath temperature) for 8 hr. The solution became dark red. The volatiles were transferred to a Dry-Ice trap under vacuum. The dark-orange crystalline residue was crystallized from ethanol giving yellow crystals, m.p. 147.4-149.8°. A mixed melting point with the crystalline product from the reaction of the methiodide with ethanol (above) was 147.8-149.7°.

Anal. Found: I, 48.18; N, 7.72.

The volatiles were examined by VPC and were found to contain, besides acetic acid, four major products, none of which corresponded in retention time to cyclopropylmethylcarbinyl acetate.

The reaction was repeated with 0.28 g. of methiodide and 0.32 g. of glacial acetic acid at 87° for 12 hr. The nonvolatile portion of the product was 0.15 g. of a dark-red, partially crystalline oil. The volatiles (0.32 g.) were examined by VPC. Three of the four peaks of the chromatograph from the 125° reaction were present but in different ratios. A new peak appeared which had the same retention time as cyclopropylmethylcarbinyl acetate.

Hydrolysis of N-Methyl-4-(cyclopropylcarbinyloxy)-pyridinium Iodide.--A solution of 25.0 mg. of the iodide in 83.2 mg. of triply distilled water was sealed in a glass tube and heated in an oil bath at 98.6° for two days. The reaction mixture was examined by VPC and was shown to contain, besides water, allylcarbinol, cyclobutanol, and cyclopropylcarbinol, although the latter two alcohols were poorly resolved from each other. The peaks of the chromatogram were weighed giving a ratio of cyclobutanol and cyclopropylcarbinol to allylcarbinol of 3.8 to 1. The ratio

of cyclobutanol to cyclopropylcarbinol was judged, visually, to be 10 to 1. That this ratio of alcohols resulted from rearrangement of the initially produced alcohols was indicated by adding 1 μl. of cyclopropylcarbinol to about one-third of the spent reaction mixture, sealing in glass, and heating for two days at 98.6°. The ratio of alcohols was essentially unchanged.

Consequently, a mixture of 12.2 mg. of iodide, 7.3 mg. of lithium carbonate and 48.0 mg. of water was sealed in glass and heated for two days at 98.6°. The concentrations of the alcoholic products were estimated by VPC and a solution of the alcohols in water of the estimated concentrations was made. Comparison of the ratios of peak areas of the chromatograms of the reaction products and of the solution of known concentrations gave a more refined estimate. The total yield of alcohols was 99%; the ratio of cyclobutanol and cyclopropylcarbinol to allylcarbinol was 12.0 to 1; the ratio of cyclopropylcarbinol to cyclobutanol was 1.2-1.5 to 1.

N-Methyl-γ-pyridone was prepared by the method of Toomey and Riegel (57). The extremely hygroscopic solid had m.p. 96.2-98.4° (sealed capillary), lit. m.p. 92-94° (58).

In an attempt to prepare the hydroiodide, 0.10 g. of the pyridone and 0.69 g. of 48% aqueous hydrogen iodide were mixed and the water and excess hydrogen iodide were removed in a vacuum desiccator over phosphorous pentoxide. The yellow crystalline residue had m.p. 131-140°.

NMR spectra were observed at 60 Mc. with a Varian Model V4300B spectrometer equipped with a Super Stabilizer. The samples were either neat liquids or solutions in methylene chloride with tetramethylsilane as an internal standard. The chemical shift between two prominent peaks in each spectrum was measured by the audio side-band superposition method and other chemical shifts were obtained by interpolation or extrapolation, assuming a linear sweep-rate.

The proton resonances of the following compounds were observed: 4-(cyclopropylcarbinyloxy)-pyridine and methiodide, 4-(cyclopropylmethylcarbinyloxy)-pyridine and methiodide, 4-(1-phenylethoxy)-pyridine and methiodide, cyclopropylmethylcarbinyl ethyl ether, bis-(cyclopropylmethylcarbinyl) ether, cyclopropylmethylcarbinyl benzoate, 1-phenylethyl acetate and 1-phenylethanol (containing one drop of conc. hydrochloric acid). For the two compounds containing the cyclopropylcarbinyloxy structure, the

secondary ring protons appeared as a highly split pattern centered at 9.4 and 9.6 τ*; the tertiary ring proton appeared as a quartet, each peak of which was split again, at 8.7 and 8.8 τ; at 6.3 and 5.7 τ appeared a doublet for the methylene group. In the case of the five cyclopropylmethylcarbinyloxy structures, the secondary ring protons were at 9.4-9.7 τ; the tertiary ring multiplet was at 8.8-9.3 τ, partially obscured by the methyl doublet at 8.5-8.9 τ; the tertiary proton was a quintet at 5.5-7.1 τ. The four 1-phenylethoxy structures had phenyl multiplets at 2.4-2.8 τ, tertiary proton quartets at 3.9-4.7 τ and methyl doublets at 8.1-8.3 τ. The aromatic protons of the three alkoxypyridines appeared as a doublet at 1.6-1.7 τ and a doublet at 3.2-3.3 τ; in two of the cases, each peak of the doublets was resolvable into two lines. In the case of the three methiodides, the protons of the pyridine ring appeared as doublets at 0.8-0.9 and 2.4-2.5 τ; the N-methyl group was a singlet at 5.5-5.6 τ.

Two spectra are worthy of special comment. The tertiary proton of bis-(cyclopropylmethylcarbinyl) ether (fig. 1) was observed to be a quintet at 7.0 τ with each peak of the quintet split into two lines by about 3 c.p.s. This

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* τ (in p.p.m.) = 10.0 - 10^6(ν_{obs} - ν_{Me_4Si})/ν_{Me_4Si}.

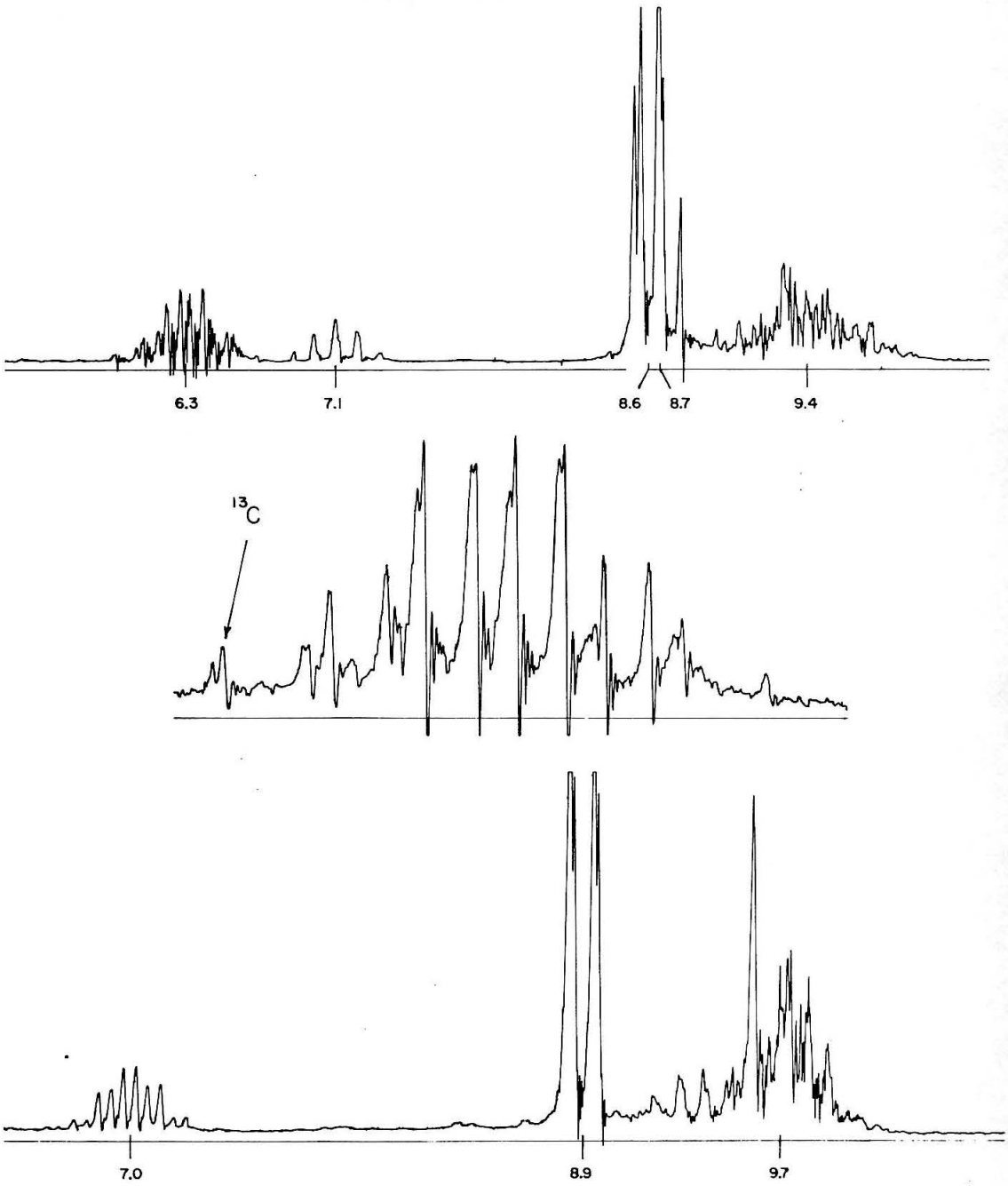

Fig. 1. - Proton nuclear magnetic resonance spectra at 60 Mc. Chemical shifts are in p.p.m. relative to tetramethylsilane = 10.0 as internal standard (not shown). Top: cyclopropylmethylcarbinyl ethyl ether in methylene chloride (not shown). Middle: region of top spectrum near 6.3 τ at slower sweep. A satellite resonance produced by ^{13}C in the solvent is indicated. Bottom: bis-(cyclopropylmethylcarbinyl) ether (neat).

additional splitting is understandable if the ether is an approximately equal molar mixture of the meso and d,l forms and the tertiary protons of the two forms have slightly different chemical shifts. The ten-line pattern is then a superposition of the five lines of each diastereomer. The methyl protons of the ether, farther removed from the center of asymmetry, show the same effect but to a smaller extent; both peaks of the methyl doublet at 8.9 τ are split by about 1 c.p.s. While the methyl protons of the ethyl group of cyclopropylmethylcarbinyl ethyl ether (fig. 1) are unexceptional (triplet at 8.7 τ), the methylene group at 6.3 τ is a very complicated pattern which can be explained if the two methylene protons are unequivalent due to the proximity of an asymmetric center (59). The observed spectrum agrees well with that calculated for an ABC_3 system with J_{AB} = 9.4 c.p.s., J_{AC} = 7.35 c.p.s., J_{BC} = 6.68 c.p.s., and δ_{AB} = 9.0 c.p.s. We are indebted to Mr. Donald R. Davis for recording the spectra in fig. 1 and to Dr. Stanley L. Manatt and the Computing Center of the Jet Propulsion Laboratory for IBM 704 calculations of comparison spectra to check the chemical-shift and spin-coupling parameters for cyclopropylmethylcarbinyl ethyl ether.

Kinetics of the Solvolyses of the N-Methyl-4-alkoxypyridinium Salts.--A stock solution of 80% ethanol was made up from 400 ml. of purified absolute ethanol (kindly supplied by Mr. E. F. Kiefer (60)) and 100 ml. of freshly boiled distilled water. For solvolyses in purely aqueous solvent, triply distilled water was used. The reactions were followed titrimetrically with 0.026M aqueous sodium hydroxide, made from the appropriate amount of 50% aqueous sodium hydroxide filtered into freshly boiled distilled water. The base was standardized against potassium acid phthalate before and after the two-month period during which the rate measurements were made. The titer decreased by 1.5% during this period and the base concentration at intermediate times was determined by a linear interpolation of concentration with time. All titrations were performed in a rubber-stoppered beaker protected from atmospheric carbon dioxide by an Ascarite tube and fitted with pH electrodes, a magnetic stirrer, and a 1-ml. Koch burette with a capillary tip extending below the surface of the solution being titrated; a Leeds and Northrop pH Indicator was used. The temperatures of the constant-temperature baths were measured with a National Bureau of Standards standardized thermometer. The temperature variation during

a single run was no more than ±0.04° as observed with a Beckmann thermometer.

For the experiments at 71 and 96°, a weighed sample of salt was transferred to a volumetric flask and diluted to the mark with the appropriate solvent. Approximately 5.5-ml. samples were sealed in freshly cleaned and dried glass ampoules. After the ampoules were placed in the bath, a "zero time" sample was withdrawn when the bath re-attained equilibrium (about 5 min.). Ampoules were periodically withdrawn, quenched in ice water, brought to room temperature and a 5-ml. aliquot of the contents was added to 20 ml. of carbon dioxide-free distilled water. The endpoint of the titrations was taken as the pH corresponding to the point of maximum slope in a plot of pH *vs.* volume of base, determined for a few of the points in each run. Although the endpoint ranged from pH 7.0 to 7.4 during the various runs, the variation during a single run was no more than 0.2 pH units. Solvent "blanks" were treated in the same manner as the kinetic samples; the blank corrections were negligible in all cases. Solutions of the iodide salts turned noticeably brown during the kinetic runs; the perchlorate salt solutions remained colorless.

For all the experiments, the data were treated by calculating a first-order rate constant for each sample relative to the "zero time" sample. The "constants" determined in this fashion fell off seriously after the first or second half-life. Consequently, the samples where this decrease was noticeable were ignored, and the remaining constants were averaged to give the final rate-constant. The kinetic data are presented in Tables IV-IX and the individual experiments are discussed below.

N-Methyl-4-(cyclopropylcarbinyloxy)-pyridinium Iodide in 80% ethanol at 98.4° gave an infinity titer of 89.4% after 72 hr. at 119-121°; in water at 98.6° gave infinity titers of 90.7 and 91.9% after 49 hr. at 98.6°; in water at 70.7° gave an infinity titer of 89.4% after 54 hr. at 100°.

N-Methyl-4-(cyclopropylcarbinyloxy)-pyridinium Perchlorate in 80% ethanol at 98.4° gave an infinity titer of 84.0% after four days at 119-121°; in water at 98.6° gave an infinity titer of 90.7% after 49 hr. at 98.6°.

N-Methyl-4-(cyclopropylmethylcarbinyloxy)-pyridinium Iodide.--A sample of the analytically pure iodide was placed in a vacuum desiccator over phosphorous pentoxide for six days to insure dryness. The sample did not reach a constant

weight during this time but lost about 2% of its weight each day. After dissolution of the sample with thorough mixing in triply distilled water (previously equilibrated in the thermostat) to the mark of a volumetric flask, the "zero time" aliquot was withdrawn immediately. The aliquots were quenched by pipetting them into 20 ml. of 95% ethanol, precooled in the titration vessel in an ice-water bath; the time was recorded when the pipetting was complete. The potentiometric titration was carried out immediately, keeping the titration vessel in an ice-water bath. The effectiveness of the quenching technique was indicated by the complete absence of drift in the pH reading at the endpoint. The titration curves were unusual in that the pH rose rapidly at pH 6.1-6.3, leveled off at around pH 7.5 and then rose rapidly again. The point of maximum slope (pH 6.1-6.3) was taken rather arbitrarily as the endpoint. A solvent blank, treated by the quenching technique, had pH 7.6. The infinity titer was determined after 50-51 hr.; using the quenching technique, the titers were 80.1 and 80.7%; however, the titration method employed for the rest of the kinetic experiments (described above) gave infinity titers of 84.5, 84.7 and 86.1% with an endpoint at pH 7.2.

Reaction of 80% Ethanol with Hydrogen Iodide.--

A 3.1×10^{-5} M solution of hydrogen iodide in 80% ethanol was titrated using the technique described for the kinetic experiments in the same solvent. Samples were sealed in ampoules and heated at 99.2°. After 13 hr., titers of 88.2 and 97.5% of the original titer were observed; after 17 hr., the titer was 84.8%. The sample with the titer of 97.5% was nearly colorless while the other two were brown-colored.

TABLE IV

SOLVOLYSIS OF 6.77×10^{-5} M N-METHYL-4-(CYCLOPROPYLCARBINYLOXY)-PYRIDINIUM IODIDE IN 80% ETHANOL-WATER AT 98.4°

Time (hr.)	% Unreacted	k_1 ($hr.^{-1}$)
0.0	100.0	
5.5	92.4	0.0146
11.6	86.5	0.0126
23.1	73.2	0.0135
38.5	62.0	0.0124
49.7	50.8	0.0136
73.8	38.6	0.0129
148.6	19.9	0.0109
196.8	17.0	0.0090
264.6	13.7	0.0075

$k_1 = 0.013\ hr.^{-1}$

TABLE V

SOLVOLYSIS OF 7.06×10^{-3}M N-METHYL-4-(CYCLOPROPYLCARBINYLOXY)-PYRIDINIUM IODIDE IN WATER AT 98.6°

Time (hr.)	% Unreacted	k_1 (hr.$^{-1}$)
0.00	98.0	
0.52	88.5	0.198
1.00	79.0	0.215
1.52	71.9	0.204
2.00	64.2	0.211
2.50	59.6	0.199
3.02	53.4	0.201
3.50	49.4	0.196
4.00	43.8	0.201
5.05	36.1	0.198
6.07	30.4	0.193
7.00	26.3	0.188
8.02	22.5	0.184
9.00	19.0	0.182
12.00	12.3	0.173

$k_1 = 0.20$ hr.$^{-1}$

TABLE VI

SOLVOLYSIS OF 6.94×10^{-3} M N-METHYL-4-(CYCLOPROPYLCARBINYLOXY)-PYRIDINIUM IODIDE IN WATER AT 70.7°

Time (hr.)	% Unreacted	k_1 (hr.$^{-1}$)
0.0	99.7	
9.3	92.7	0.00778
23.8	85.1	0.00665
32.9	80.5	0.00653
44.7	74.5	0.00652
56.8	68.7	0.00657
71.3	63.1	0.00643
80.9	60.0	0.00627

$k_1 = 0.0065$ hr.$^{-1}$

TABLE VII

SOLVOLYSIS OF 6.69×10^{-5} M N-METHYL-4-(CYCLOPROPYLCARBINYLOXY)-PYRIDINIUM PERCHLORATE IN 80% ETHANOL-WATER AT 98.4°

Time (hr.)	% Unreacted	k_1 ($hr.^{-1}$)
0.0	99.0	
7.7	90.7	0.0113
18.3	82.5	0.0110
24.2	78.2	0.0097
32.8	70.7	0.0102
43.0	65.7	0.0095
95.9	45.0	0.0082
142.3	37.1	0.0069

$k_1 = 0.010\ hr.^{-1}$

TABLE VIII

SOLVOLYSIS OF 7.14×10^{-3}M N-METHYL-4-(CYCLOPROPYLCARBINYLOXY)-PYRIDINIUM PERCHLORATE IN WATER AT 98.6°

Time (hr.)	% Unreacted	k_1 ($hr.^{-1}$)
0.00	95.0	
0.76	84.1	0.161
1.50	71.4	0.190
2.25	62.0	0.189
3.01	53.7	0.190
3.75	45.4	0.197
8.00	22.7	0.179
12.00	14.2	0.158

$k_1 = 0.19\ hr.^{-1}$

TABLE IX

SOLVOLYSIS OF 2.95×10^{-3}M N-METHYL-4-(CYCLOPROPYLMETHYLCARBINYLOXY)-PYRIDINIUM IODIDE IN WATER AT 30.0°

Time (hr.)	% Unreacted	k_1 ($hr.^{-1}$)
0.00	89.9	
1.03	77.0	0.151
1.30	74.2	0.148
2.08	64.4	0.161
2.50	60.0	0.163
3.20	54.0	0.159
3.67	49.2	0.165
4.24	46.0	0.158
9.52	24.7	0.136
10.61	23.9	0.125
11.53	23.3	0.117

$k_1 = 0.16\ hr.^{-1}$

APPENDIX I

DESCRIPTION OF FRACTIONATING COLUMNS

Column No. 1. - A 1.3 x 80-cm. column packed with glass helices and equipped with an electrically heated air jacket and a total reflux head.

Column No. 2. - A 0.6 x 30-cm. column packed with a tantalum wire coil and carrying a partial reflux head (61).

Column No. 3. - A 0.8 x 35-cm. spinning-band column equipped with an electrically heated air jacket and a total reflux head. The band was a stainless-steel, wire-gauze spiral and was operated at about 1100 r.p.m.

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PROPOSITIONS

1. The pyrolysis of an ester and the pyrolysis of the corresponding amine oxide usually give very similar mixtures of isomeric olefins (1). In contrast, the pyrolysis of 1-methylcyclohexyl acetate yields an olefin mixture containing about 75% of the endocyclic isomer (2) while pyrolysis of the corresponding dimethylamine oxide gives almost exclusively the exocyclic isomer (3). This apparent anomaly has been explained (2) in terms of the transition states for the two elimination reactions, that of the acetate being a six-membered ring and that of the amine oxide a five-membered ring. The carbonyl oxygen of 1-methylcyclohexyl acetate can reach one of the gauche hydrogens in the cyclohexane ring while the ring is in the chair form and eliminate to form the more stable endo-olefin. In contrast, the oxygen of the corresponding amine oxide cannot reach a gauche hydrogen without considerable strain and consequently eliminates an eclipsed hydrogen in the methyl group to form the exo-olefin.

It would be of interest to determine the isomer distribution of the olefins produced by the pyrolysis of the acetates of exo- and endo-2-methylnorborneol and the

corresponding dimethylamine oxides. Elimination into the cyclohexane ring would occur by removal of a proton constrained to an eclipsed configuration by the bicyclic structure and consequently any difference in the isomer distributions of the olefins from the acetates and from the corresponding amine oxides would have to be ascribed to factors other than those believed to be responsible for the behavior of the 1-methylcyclohexyl system. Also, the known instability of the norbornene structure (4) might have an interesting effect on the ratio of exocyclic to endocyclic olefins.

2. Cis and trans isomers of vinyl lithium compounds (5) and cis and trans isomers of vinyl Grignard reagents (6) have been prepared. The vinyl lithium compounds prepared from cis- and trans-1-bromo-2-(p-chlorophenyl)-1,2-diphenylethylene are slowly interconverted at elevated temperatures (7).

It is proposed to measure the rates of isomerization of cis and trans vinyl lithiums and of the corresponding Grignard reagents to elucidate the mechanism of the isomerization reaction.

3. Whitmore (8) has thoroughly investigated the reaction of methylamine with aqueous nitrous acid and although as little as 25% of the starting amine was

recoverable in some cases, no products (methanol, dimethyl ether, methyl chloride or methyl nitrite) could be detected. This puzzling observation should be reinvestigated with the aid of recently developed analytical tools such as vapor-phase chromatography and nuclear magnetic resonance (NMR). It is suggested that diazomethane may have been evolved and have escaped detection by Whitmore. If so, this reaction would be an extremely convenient preparation of diazomethane.

4. Divalent carbon intermediates are probably involved in the Arndt-Eistert synthesis (9).

$$RCOCl + CH_2N_2 \longrightarrow RCOCHN_2 \longrightarrow RCOCH: + N_2 \longrightarrow RCH=C=O$$

In view of the recent successes in generating carbenes by α-elimination of hydrogen halide from alkyl halides (10), it is suggested that α-haloketones may be capable of eliminating the elements of hydrogen halide and rearranging to ketenes. The loss of halide ion may not occur

$$C_6H_5\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_2Cl + NaH \longrightarrow C_6H_5\text{-}\overset{O}{\overset{\|}{C}}\text{-}\overset{\ominus}{C}HCl \longrightarrow C_6H_5\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH: + Cl^{\ominus}$$

$$\longrightarrow \quad C_6H_5\text{-}CH=C=O$$

spontaneously but might take place in the presence of

silver ion. Acylcarbenes may add to olefins, providing a useful synthesis of acylcyclopropanes.

5. The NMR spectra of compounds of structure $R_1R_2R_3COCH_2CH_3$ exhibit ABX_3-type spectra (11) for the ethyl protons (12). While the non-equivalence of the methylene hydrogens is clearly due to the presence of the asymmetric center in the molecule, the detailed manner in which this center exerts its influence is debatable. It (a) undoubtedly makes the two methylene hydrogens unequivalent in any one of the possible rotational conformations about the carbon-oxygen bonds and (b) may make the populations of the various conformations unequal. The relative contributions of effects (a) and (b) to the observed chemical shift between the methylene hydrogens are difficult to assess. Examination of the NMR spectra as a function of temperature of a series of compounds $R_1R_2R_3COCH_2CH_3$ where R_1 = H, R_2 = CH_3 or Cl, and R_3 is variable should allow an evaluation of the relative importance of effects (a) and (b) and also provide information about the enthalpies of the rotational conformations about the carbon-oxygen bonds.

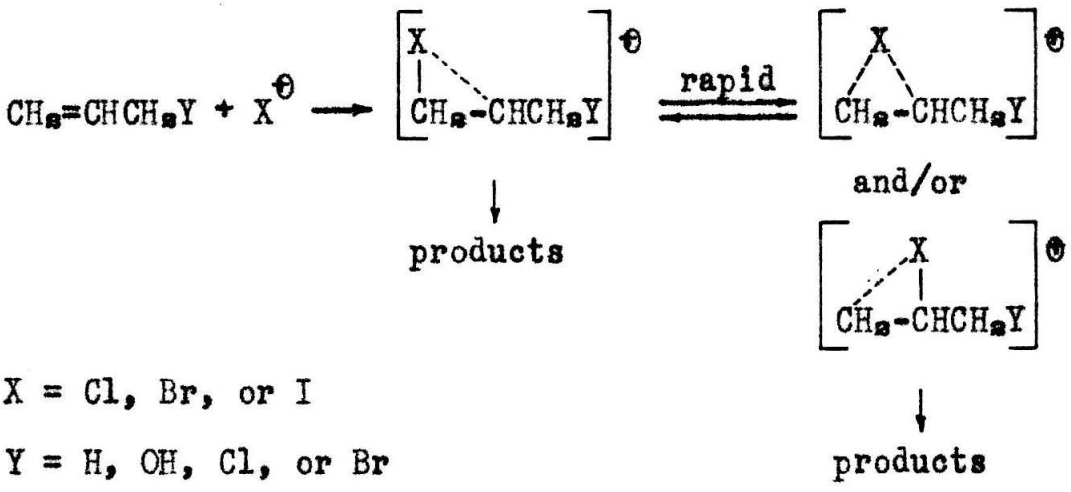
6. Swain (13) has suggested that "participation of acetic acid as a nucleophilic reagent in the rate-determining step may be the general rule for solvolyses in acetic

acid." In particular, t-butyldimethylsulfonium perchlorate is believed to behave in this way (14). It is proposed to determine the rho (15) values for the solvolyses of a series of p-substituted phenyldimethylcarbinyldimethylsulfonium perchlorates in different solvents. The rho value for acetolysis should be quite anomalous if Swain's suggestion is correct.

7. Dipole moment, infrared, ultraviolet, and optical rotatory dispersion studies have been used to differentiate between an axial halogen and an equatorial halogen in α-halocyclohexanones (16). We propose that NMR may prove effective toward the same end. The NMR spectra of cis- and trans-2-chloro-4-t-butylcyclohexanone should show the feasibility of the method. In particular the splitting pattern of the hydrogen alpha to the halogen atom should be characteristic of an axial or an equatorial conformation.

8. Recent work by Dessy (17) indicates that the Grignard reagent has the formula $R_2Mg \cdot MgX_2$ and not RMgX. The NMR spectrum of the Grignard reagent prepared from 1-phenylethyl bromide may show the presence of a meso and a d,l form which would be compatible with the $R_2Mg \cdot MgX_2$ structure but not with the RMgX structure.

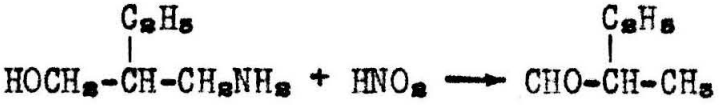
9. To account for the direction of addition of reagents such as iodine nonochloride, bromine chloride, hypochlorous acid, and hypobromous acid to allylic double bonds, de la Mare has considered it necessary to postulate a rapid equilibrium between more than one carbonium-ion intermediate (18).



The same results can be accommodated by one bridged intermediate which is distorted one way or the other depending on the nature of X and Y. It is proposed to study the products from hydrolysis of 2-chloro-2-methyl-3-butyl brosylate and the isomeric 3-chloro-2-methyl-2-butyl brosylate and the products from addition of hypochlorous acid to 2-methyl-2-butene. All three reactions should proceed through the same carbonium-ion

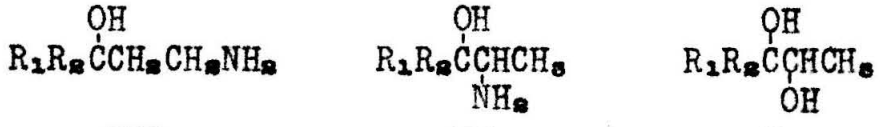
intermediate(s). This would be a very favorable case in which to detect the presence of more than one carbonium-ion intermediate if there is any validity to the idea. If there is more than one intermediate and equilibration between the intermediates is slow compared to the rate of product formation, different product mixtures should be obtained from the isomeric brosylates.

10. It is proposed to study the stereochemistry of double 1,2-carbonium ion shifts. For instance, the deamination of optically active I could reasonably be expected to give II after two 1,2-hydride shifts and it would be interesting to determine whether or not II has the same



I II

configuration as I. Also, a study of the migratory aptitudes of R_1 and R_2 in the deamination of III and IV and the pinacolic rearrangement of V should illuminate the nature of the carbonium-ion intermediates involved in these reactions.



III IV V

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