A NOVEL REARRANGEMENT OF SUBSTITUTED PHENYLHYDROXYLAMINES

A Dissertation

Presented to

the Faculty of the Department of Chemistry

College of Arts and Sciences

University of Houston

In Partial Fulfillment

of the Requirements for the Degree

Doctor of Philosophy

---

by

Robert L. Nolen, Jr.

August 1970

ACKNOWLEDGMENT

There are not enough words to write an acknowledgment to Dr. James R. Cox, Jr. Without his majestic guidance, I could not have proceeded this far. Outside of being a magnificent chemist, he is a man of great character. I thank you, Dr. Cox.

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Thanks are given to Julie and Judy Norris for their part in typing this dissertation.

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ABSTRACT

The rearrangement in different solvents of a number of substituted phenylhydroxylamines has been investigated. Kinetically, the N-acyl-N-phenylhydroxylamines show a great sensitivity to electronic changes in the molecule. Electron withdrawing substituents decrease the rate, and electron donating substituents increase the rate markedly.

In all compounds investigated, O-dichloroacetyl-N-acetyl-N-(4-methylphenyl)hydroxylamine and O-dichloroacetyl-N-acetyl-N-phenylhydroxylamine, two different compounds could be isolated depending on whether or not a base was present. The compound always isolated when no base was present was the kinetically controlled product X or XIII. The second product was the thermodynamically more stable product XI or XIV. The structure of the kinetically controlled product has been shown to be a novel one.

Oxygen-18 tracer studies have shown that the rearrangement of O-dichloroacetyl-^{18}O-N-acetyl-N-(4-methylphenyl)hydroxylamine rearranges in neat solution by an ion pair mechanism, whereby the oxygen-18 strategically placed in the dichloroacetyl carbonyl group was mixed exactly half and half with the phenylhydroxylamine oxygen. The rearrangement of O-dichloroacetyl-^{18}O-N-acetyl-N-phenylhydroxylamine in chloroform solution occurred by transfer of all the labelled oxygen to the ortho position. This result indicates a change in mechanism from that of the 4-methyl compound. In dichloroacetic acid, O-dichloroacetyl-^{18}O-N-acetyl-N-phenylhydroxylamine rearranged by three different pathways; one intermolecular, one cyclic, and the third by an intramolecular process.

Just by changing the ring substituents, two different mechanisms were detected. Also, the change in solvent produced a marked change in mechanism. Therefore, the solvent and electronic effects indicate a very complex and delicate system.

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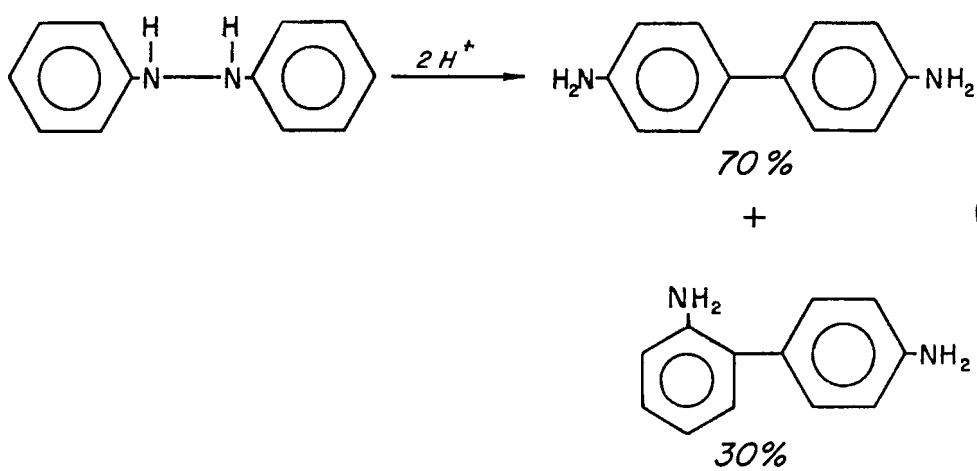
INTRODUCTION

INTRODUCTION

Over the last two decades, many experiments have been performed to test many chemical theories. Much of this effort has been directed at the elucidation of chemical reactions that occur by pathways which involve free radicals, carbanions, carbonium ions, and other discrete intermediates of short lifetime which are formed by fragmentation of the starting compounds and recombination of the resulting fragments. Many intramolecular rearrangements have also been studied; however, in these cases the task of determining the nature of the transition state and/or of the intermediate is frequently much more complex than it is in fragmentation reactions, and controversy may arise among investigators as to the pertinent facts, much less the correct interpretation of them.

One such rearrangement is the complicated acid-catalyzed transformation of hydrazobenzene into benzidine discovered by Hofmann (1) in 1863 (Eq. 1). The literature contains an enormous volume of information concerning the mechanism of the benzidine rearrangement. Since this



(Eq. 1)

material has been extensively reviewed (2), it is not necessary to repeat it here, but the aspects pertinent to the work presented in this thesis will be mentioned briefly.

The fact that the benzidine rearrangement is intramolecular was first hinted at by Jacobson's observation that unsymmetrically substituted hydrazobenzenes give only dissymmetric benzidines as products (3). Later, Wheland, Smith, and Schwarz (4) and Dunn (2) established this point conclusively by isotopic studies.

Kinetic studies (5) of the rearrangement have shown that two protons are transferred to hydrazobenzene in equilibria which precede the rate-determining step. Electron-releasing substituents greatly enhance the rate, in some cases so much as to allow rearrangement of the monoprotonated over the neutral species.

The nature of the bonding along the reaction coordinate during the transformation of the diprotonated hydrazobenzene molecule into benzidine has been the subject of acrimonious debate but is still not resolved. Dewar's ingenious π-complex mechanism (6) is not consistent with the experimentally determined kinetic order. Ingold's heterolytic fragmentation of the symmetric, nitrogen-protonated conjugate acid of hydrazobenzene is without analogy.

Rearrangements of Substituents from Nitrogen of an Aromatic Amine into the Ring

There are many processes during the course of which a substituent migrates from nitrogen into the ring of an aromatic amine. N-Nitroanilines, N-haloanilides, N-phenylsulfamic acids, pyridine-N-oxides, and N-aryl-

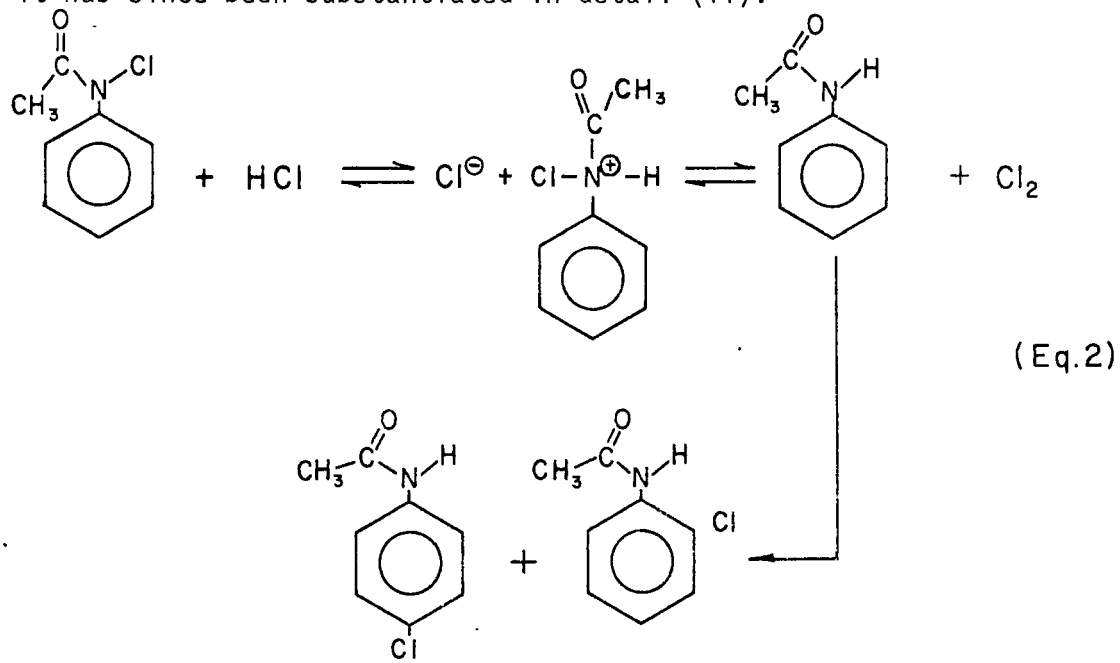
hydroxylamines (7) all undergo acid-catalyzed rearrangements which can be shown to follow a variety of mechanistic pathways.

The chemistry of N-arylhydroxylamines was first reported in 1894 by Bamberger (8) who found that N-phenylhydroxylamine, upon treatment with sulfuric acid, produced o- and p-aminophenols. In alcoholic ethanol or methanol solutions, the main products were the o- and p-ethoxy or methoxyanilines.

Heller, Hughes, and Ingold (9) demonstrated unambiguously the intermolecularity of the N-phenylhydroxylamine rearrangement by carrying out the rearrangement in water enriched in oxygen-18. The results showed a complete exchange of the oxygen in the phenols with the water enriched in oxygen-18. From this labelling study, they suggested a mechanism whereby the oxygen of the hydroxylamine is protonated and water is lost to produce a species which is resonance stabilized ($Ph^{+}NH$). Nucleophiles in solution then react with this species at one of the electrophilic sites (indicated by resonance forms). This unimolecular fragmentation of the conjugate acid need not be the only route. Bimolecular attack of nucleophiles at the ortho or para positions upon the protonated phenylhydroxylamine with simultaneous loss of water cannot be ruled out by such labelling experiments, and no detailed kinetic studies were reported.

A rearrangement which was considered intramolecular until 1909 is the conversion of N-chloroacetanilide into a mixture of o- and p-chloroacetanilides in the presence of hydrochloric acid. During that year, Orton and Jones (10) suggested that a reversible, acid-catalyzed attack

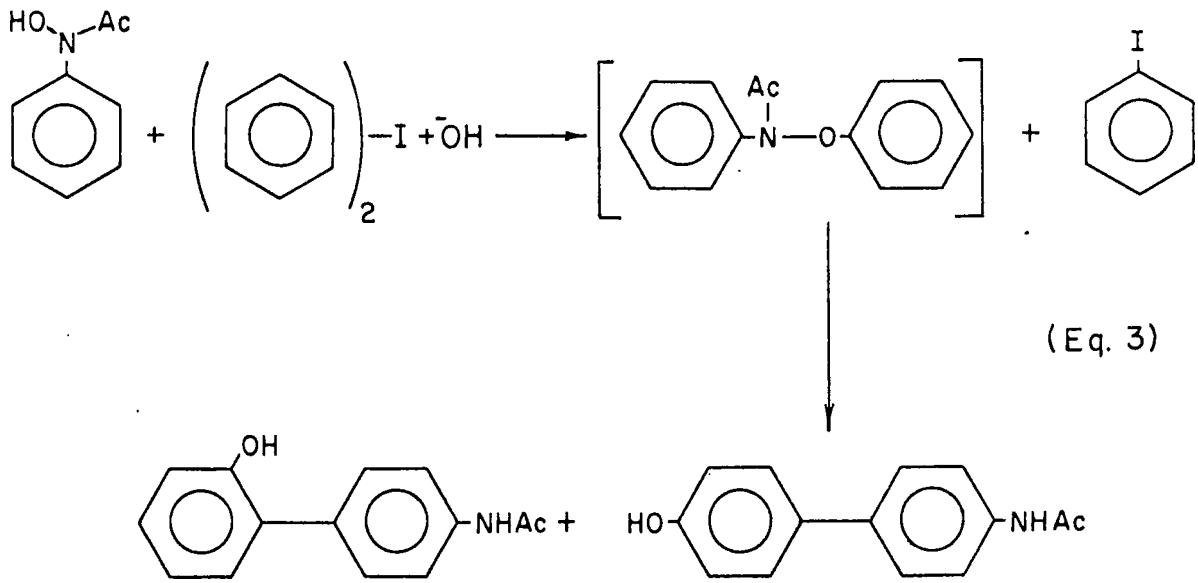
of chloride ion on the electrophilic chlorine of the N-chloro-compound occurs to produce acetanilide and elemental chlorine. Then the latter attacks the former in an ordinary process of aromatic C-chlorination (Eq. 2). Although this process appeared novel when it was first proposed, it has since been substantiated in detail (11).



(Eq.2)

In 1963, Cox and Dunn (12) published an account of the in situ formation of N-acetyl-O,N-diphenylhydroxylamine from the reaction of N-acetyl-N-phenylhydroxylamine with diphenyliodonium hydroxide (Eq. 3). Although the reaction mixture was never acidic, the products isolated were mainly 4'-hydroxy-4-acetamidobiphenyl and a trace of 2'-hydroxy-4-acetamidobiphenyl. Presumably N-acetyl-O-,N-diphenylhydroxylamine was formed and then spontaneously rearranged. This is, if intramolecular, very similar to the benzidine rearrangement.

Dunn demonstrated that the oxygen of the product is derived from that of the starting hydroxamic acid, and not from the solvent or from

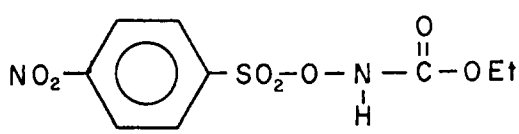


(Eq. 3)

added phenol. Thus, the reaction is intramolecular. Recognizing 1) that the acetyl group serves as an electron-withdrawing (and hence acidic) function, and $\phi\text{-}\overset{\oplus}{N}\text{-}\overset{\oplus}{C}\begin{matrix}\diagup CH_3 \\ \diagdown O^-\end{matrix}$ resembles $Ph\text{-}\overset{\oplus\oplus}{N}H_2$ electronically, and 2) that phenoxide ion is a good leaving group and is isoelectronic with ϕNH_2, Dunn and Cox reasoned that the monoprotonated conjugate acid of acetylhydrazobenzene should rearrange in an intramolecular process analogous to the rearrangement of the diprotonated conjugate acid of hydrazobenzene. This prediction was verified experimentally.

It seemed from the apparent nature of these processes that rearrangement should be facilitated by structural changes that stabilize either the positive fragment or the negative fragment. Acylation of the hydroxyl function of N-acetyl-N-phenylhydroxylamine was, therefore, undertaken in order to make the negative fragment the anion of a strong acid, and therefore, a good leaving group.

Meanwhile, Lwowski and Tisue had approached the same system from an entirely different viewpoint. Nitrenes are species analogous to carbenes in carbon chemistry. These univalent nitrogen species have been implicated in the thermal and photolytic decompositions of carbonyl azides (13-16), as well as in the base-induced elimination of sulfonate esters of N-hydroxyurethane (17). It is this last reaction sequence that suggested to Tisue (18) the possibility of using phenylhydroxylamines as precursors to phenylnitrenes by α-elimination. The α-elimination of p-nitrobenzenesulfonate from O-(p-nitrobenzenesulfonyl)-N-hydroxyurethane (I) generated an intermediate chemically identical to that pro-

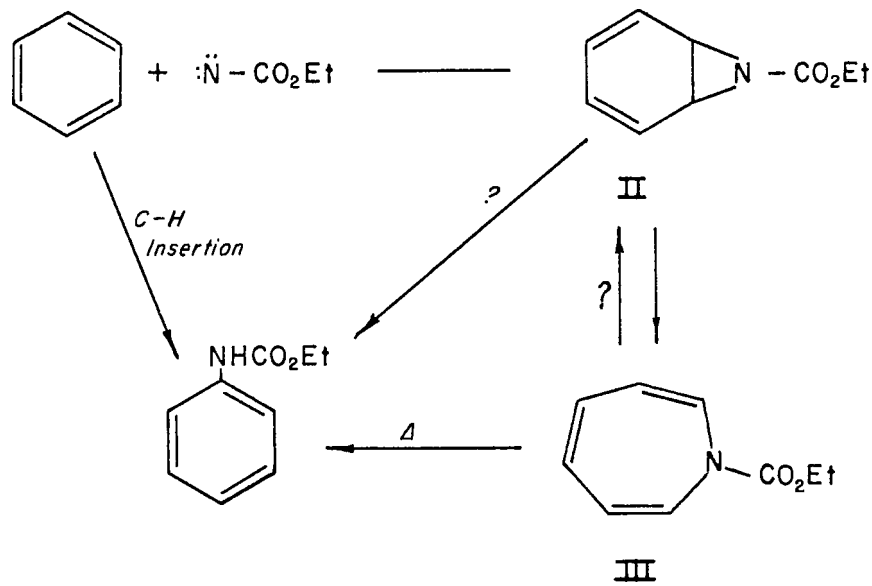


I

duced by the photolysis of ethyl azidoformate (17). The intermediate formed in the presence of benzene in the photolysis of azidoformate is thought to be II (Eq. 4). Products from the reaction are 50 percent yield of N-carbethoxyazepine (III) and traces of phenylurethane and urethane. It was also demonstrated that III readily isomerizes to phenylurethane.

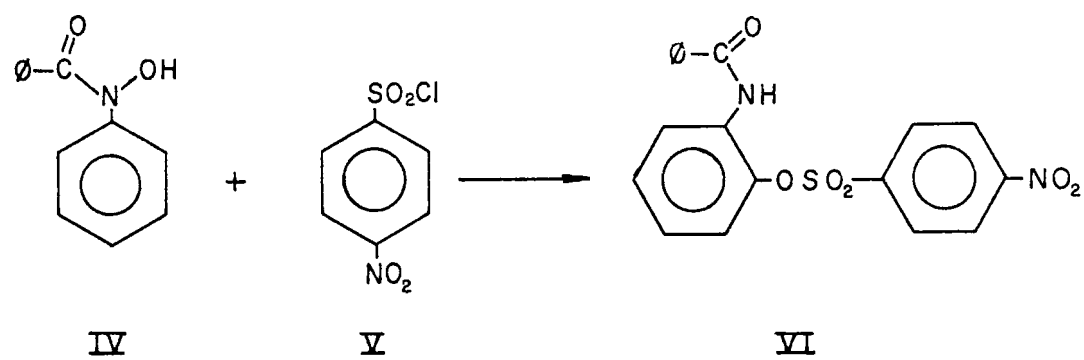
In an effort to extend the scope of this work, aromatic amines substituted with an appropriate leaving group on nitrogen were studied.

Both Cox and Dunn and Lwowski and Tisue found that when phenylhydroxylamine or its N-acyl derivatives (IV) were treated with arylsulfonyl chlorides (V) in dilute ethereal solution at 0°C in the presence



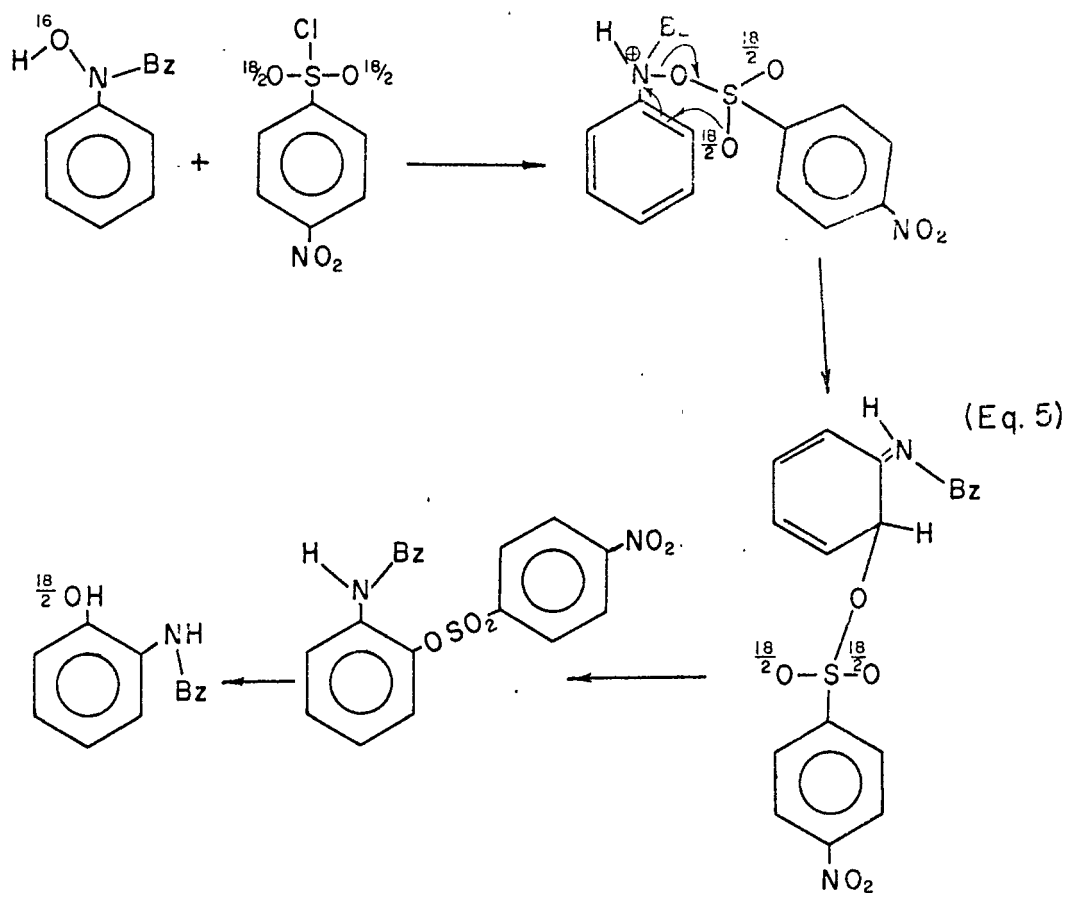
(Eq. 4)

of one equivalent of triethylamine, no products were identified which suggested intervention of a nitrene intermediate. Instead, fair yields of rearranged O-(arylsulfonyl)-2-acylaminophenols (VI) were produced:



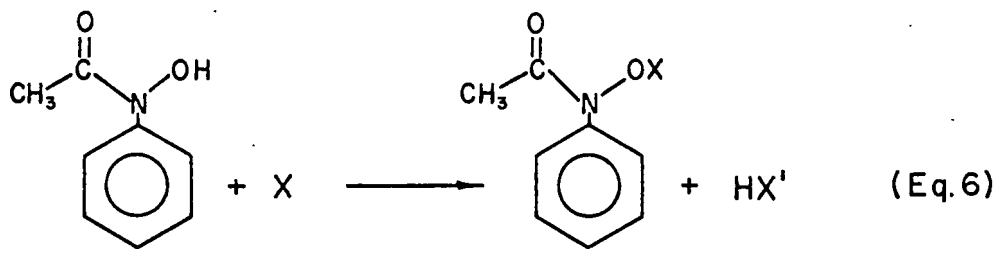
IV V VI

Clearly, this sequence of reactions does not produce nitrenes, but it was interesting from the standpoint of the phenylhydroxylamine rearrangement of Bamberger (8). An apparent discrepancy with a dissociative pathway was that only 1.4 percent of the p-isomer was detected (19). Tisue studied the reaction further by labelling the p-nitrobenzenesulfonyl chloride with oxygen-18. From his results, Tisue and Lwowski interpreted the data as consistent with a concerted, intramolecular rearrangement as indicated in Eq. 5. The same amount of label was found in the hydrolyzed product as was in the starting p-nitrobenzenesulfonyl chloride.



(Eq. 5)

Dunn had isolated about 7 percent of the p-isomer from the rearrangement of N-acetyl-O-tosylphenylhydroxylamine. Realizing that this product is difficult to rationalize on the basis of a concerted pathway and also noting the apparent dependence of the reaction rate upon the leaving group attached to nitrogen, Dunn rearranged a series of acyl derivatives, the leaving groups of which exhibited large differences in electronic effects (Eq. 6). Although all of these rearranged to produce



(Eq. 6)

X = HCl_2CCCl, CH_3-⟨⟩-SO_2Cl, CH_3SO_2Cl, $(CF_3\overset{O}{\overset{\|}{C}}-)_2O$

VII a: X = $-\overset{O}{\overset{\|}{C}}-CCl_2H$ HX' = HCl

b: X = $-SO_2$-⟨⟩-CH_3 HX' = HCl

c: X = $-SO_2CH_3$ HX' = HCl

d: X = $-\overset{O}{\overset{\|}{C}}-CF_3$ HX' = $CF_3\overset{O}{\overset{\|}{C}}-O-H$

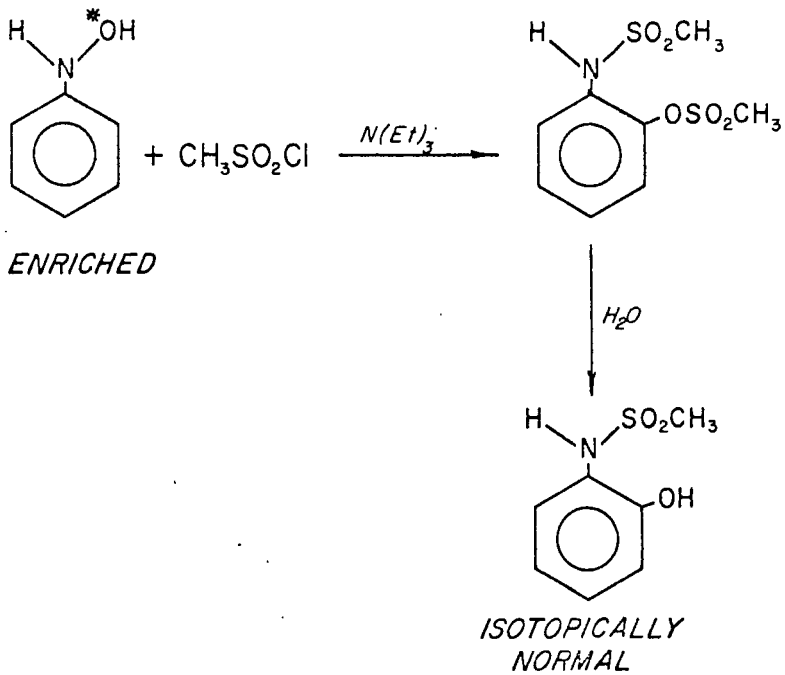
o- and p-isomers, whether in acidic media or not, the rate was influenced drastically by the leaving group present, the order of reactivity being CH_3SO_2-, $CH_3\phi$-SO_2- > CF_3CO- > $CHCl_2CO$- >> ϕCO-, CH_3CO-.

In preliminary experiments, Dunn obtained evidence that the rearrangement of N-acetyl-O-dichloroacetyl-N-phenylhydroxylamine 1) is essentially intramolecular in trifluoroacetic acid solution, 2) produces about 75

percent of the o- and 25 percent of the p-isomer, and 3) results in scrambling of the oxygen atom derived from the hydroxylamine function with that from the carbonyl group in the rearranged carboxyl function of the product.

It appeared, therefore, that substantial discrepancies, certainly of interpretation and possibly of fact, existed between the work of Cox and Dunn and that of Lwowski and Tisue. Reinvestigation of the areas in which these differences occurred was clearly necessary.

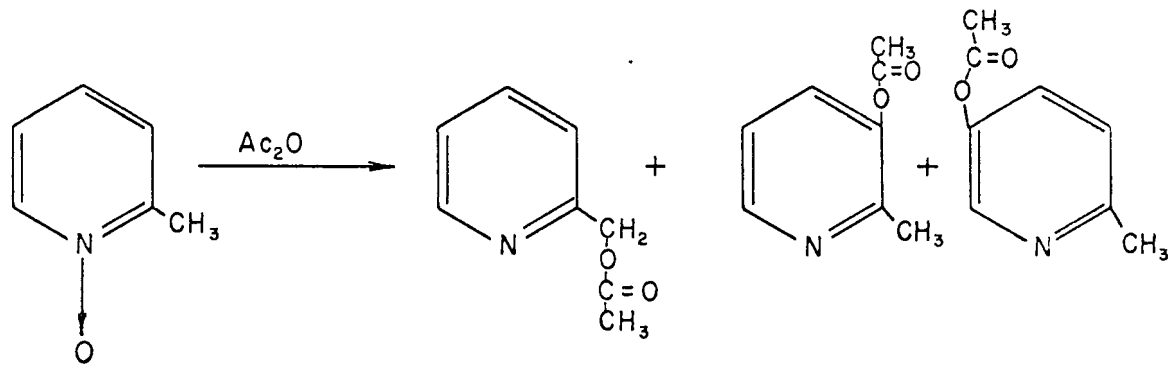
A report by Truce, Fieldhouse, Vrencur, Norell, Campbell, and Brady (20) in 1969, lends some support to the labelling scheme of Tisue, Grassman, and Lwowski (14). In their study of the reaction of diaryl nitrones with alkylsulfonyl chlorides and triethylamine, an analogous reaction was conceived, the reaction of N-phenylhydroxylamine with unsaturated sulfonyl chlorides. While trying to determine a mechanistic pathway for the formation of the benzoxathiazepine systems produced, Truce, et al., labelled N-phenylhydroxylamine with excess oxygen-18. The labelled N-phenylhydroxylamine was then reacted with methanesulfonyl chloride and triethylamine (Eq. 7). The hydrolysis product contained no excess of oxygen-18 over natural abundance. These results tending to support Lwowski's work were mentioned in Truce's account; however, no experimental details were reported. If the rearrangement had passed through an ion pair loose enough for the methanesulfonate ion to rotate, a third of the label would have been deposited in the phenol oxygen, since the oxygen from the hydroxylamine would thereby have been mixed



(Eq. 7)

with the two oxygens of the sulfonyl moiety. Since Truce, et al., found there was no oxygen-18 excess in the hydrolyzed product, it could be concluded that the rearrangement was a concerted one and passed through a cyclic intermediate.

Another reaction sequence which may be considered to bear some relationship to the N-acetyl-N-phenylhydroxylamine rearrangement is the reaction of acetic anhydride with the 2-, 3-, and 4-picoline-N-oxides, which yields products in which the acetoxy moiety has migrated to the methyl carbon and the 3- and 5-positions of the ring (Eq. 8). This reaction was first discovered by Kobayashi and Furukawa in 1953 (21) and Boekelheide and Linn in 1954 (22). In 1962, Oae, Kitao, and Kitaoka published work on reaction of two picoline oxides, 2-picoline-N-oxide

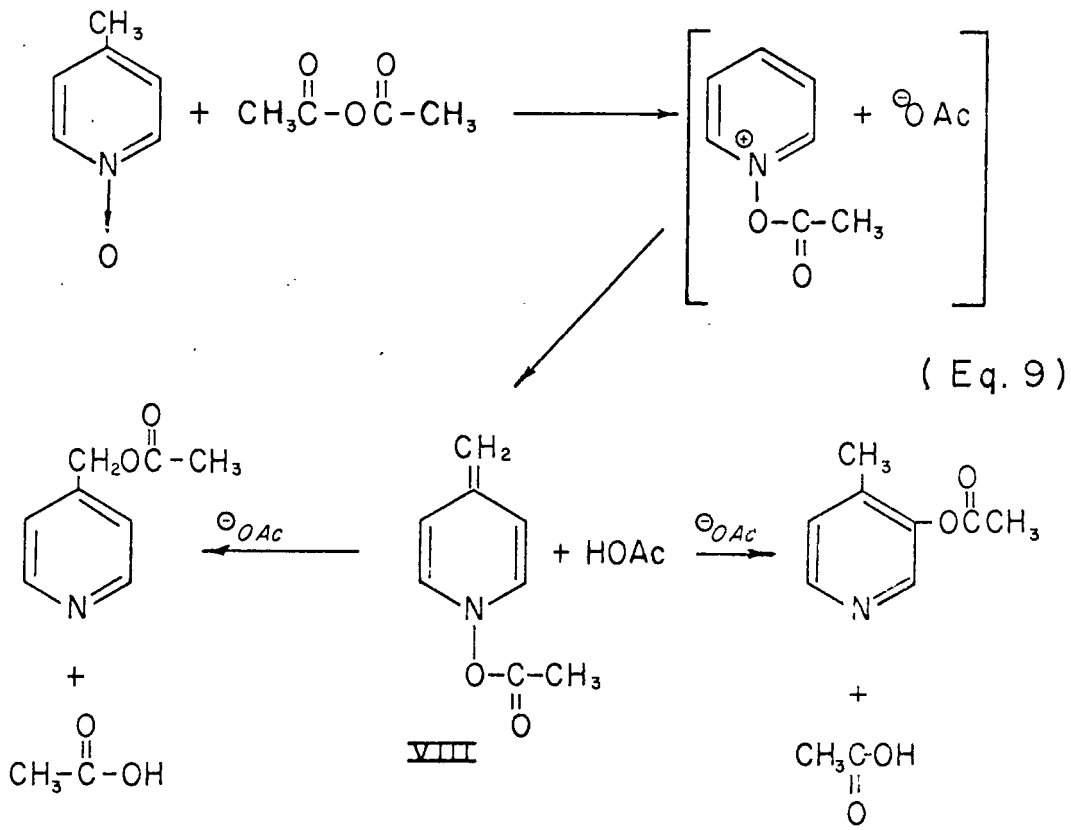


(Eq. 8)

with acetic anhydride enriched with oxygen-18 (23). A concerted mechanism had been accepted up to this time, but Oae's work showed that in the product, 2-pyridylmethanol, the label was scrambled half and half between the acetyl oxygen and the oxygen attached to the "benzylic" carbon. Also, he showed that in three different solvents, the rearrangement displayed no change in the isotopic content of the product, a result which was interpreted as in accord with an intramolecular ion pair or radical pair (24).

When the 3- or 4-picoline-N-oxides reacted with less than one molecular equivalent of labelled acetic anhydride (25), all the oxygen atoms became equivalent; that is, one isotopically normal oxygen had been mixed with three atoms of oxygen-18. It is to be emphasized that this result is true only for the special cases of mole ratios $PyOx/Ac_2O \geq 1$. These results were explained as an ionic chain process in which an

intermolecular attack of acetate ion occurs on the initial intermediate, VIII (Eq. 9). After the first molecular event is over, there is then an



(Eq. 9)

isotopically normal oxygen available in the acetate ion for the next molecular event. By the end of the reaction, all of the isotopically normal oxygen has become scrambled in with the oxygen-18. When ^{18}O-labelled acetic anhydride was used in excess, the ^{18}O value of both the etherial and carbonyl oxygens of the ester attained an average value of all the oxygens of the reaction mixture. These results strongly suggest an intermolecular ionic process (25).

When the reaction in Eq. 9 was run in three different solvents, there was a small decrease in the amount of label introduced from the acetic anhydride as compared to the reaction without solvent. This was interpreted as indicating a transition from an intermolecular to an intramolecular pathway.

EXPERIMENTAL

EXPERIMENTAL

Instrumentation and Equipment

Analytical results were obtained from M. H. W. Laboratories and Alfred Bernhardt Laboratories.

All melting points and boiling points are uncorrected. All melting points were taken on a modified Hershberg melting point apparatus equipped with a motor driven stirrer and Anschütz thermometers if the melting points were below 209°C. Melting points higher than 209°C were taken on a Fisher-Johns hot stage.

NMR spectra were measured on a Varian-100 MHz instrument using tetramethylsilane as an internal standard.

Infrared spectra were measured on a Beckman IR-10 spectrophotometer using the 3.3026μ band of polystyrene film as a calibration for the spectrophotometer.

The isotope ratios were determined using a 60° McKinney-Nier mass spectrometer which is outlined in Figure 1*. The standard carbon dioxide used each time was tank carbon dioxide purchased from Matheson Chemical Company (Highly Purified Grade). There was a negligible difference between the isotopic content of the tank carbon dioxide and that of the carbon dioxide prepared from the unlabelled materials in control experiments.

A standard carbon dioxide sample is first directed into the mass spectrometer. The mass 44 ion beam composed of $^{12}C^{16}O_2$ is separated

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*The mass spectrometer was constructed in the Biophysical Sciences Department at the University of Houston by W. Updegrove, D. Flory, and R. Wilkin.

Figure 1. Outline of Isotope Ratio Mass Spectrometer

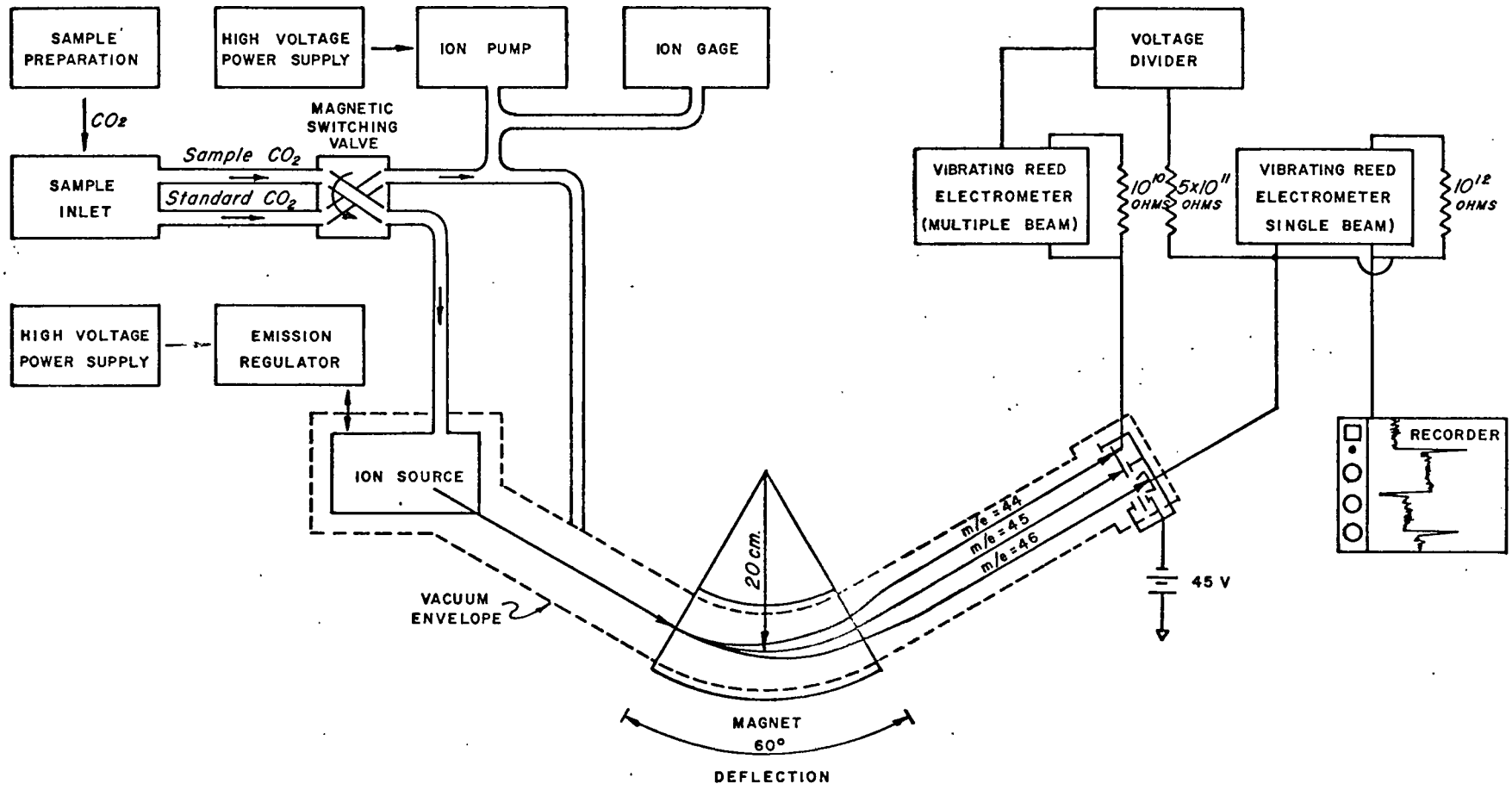

SAMPLE PREPARATION
HIGH VOLTAGE POWER SUPPLY
ION PUMP
ION GAGE
VOLTAGE DIVIDER
CO_2
MAGNETIC SWITCHING VALVE
Sample CO_2
Standard CO_2
SAMPLE INLET
VIBRATING REED ELECTROMETER (MULTIPLE BEAM)
10^{10} OHMS
5×10^{11} OHMS
VIBRATING REED ELECTROMETER SINGLE BEAM)
10^{12} OHMS
HIGH VOLTAGE POWER SUPPLY
EMISSION REGULATOR
ION SOURCE
RECORDER
m/e = 44
m/e = 45
m/e = 46
20 cm.
45 V
VACUUM ENVELOPE
MAGNET
60°
DEFLECTION

FIGURE 1

from the mass 45 beam ($^{12}C^{16}O^{17}O$) mass 46 beam which consists mostly of $^{12}C^{18}O^{16}O$. A dual collector simultaneously collects the 44 and 45 beams separately from the 46 beam. The ion current from the more intense beam corresponding to masses 44 and 45 of the standard gas is divided by a calibrated, precision, decade voltage divider until the minor ion current of the mass 46 is nulled out. This null position is recorded on a potentiometric recorder. The sample of unknown isotopic composition is then directed into the ion source by actuating a gas switch valve. Any difference in isotope ratio will cause a deviation from the previously established null settings. This difference is determined by returning the system to a null position using the voltage divider and recording the new settings required to rebalance the system. This measurement is directly related to the difference in isotope ratios of a standard and an unknown gas. Comparisons of isotopic content to 5 ppm precision are possible, provided that the isotopic composition of the sample is relatively close to that of the standard.

The following mathematical expression expresses the number as a percent difference:

$$\delta = \frac{(R_s - R_{std})}{R_{std}} \times 100$$

R_s = Resistance required to null sample ion beam

R_{std} = Resistance required to null standard ion beam

To obtain atom percent excess, one multiplies the natural abundance of ^{18}O in a standard sample of carbon dioxide by δ. The natural abundance has been well demonstrated as 0.204 atom percent. The quantity δ is expressed in percent difference for work reported here.

All samples were run in duplicate with the exception of the 2-methylbenzoxazole and the hydrolysis product of XIV. Some samples were run from two different reactions which are indicated in the tables. Most samples are within experimental error ±0.010 relative percent.

Sample Preparation, Combustion, and Collection of Carbon Dioxide-O^{18} for Labelling Studies

Each compound that was a solid was recrystallized to a constant melting point and sublimed, if possible. If some of the samples were still colored, the color was either removed by washing the crystals with an appropriate solvent or recrystallizing the solids.

The overall procedure for decomposing the enriched compounds to carbon dioxide, representatively, was the procedure used by Rittenberg and Ponticorvo (26), who employed mercuric chloride as an oxidant. When heated above 350°C, mercuric chloride partially dissociates into chlorine gas. At high temperatures, the chlorine presumably oxidized the organic compound, and at least a representative portion of the oxygen is converted to carbon dioxide. A typical procedure was as follows: From 11 mm Pyrex tubing, break seal tubes were made with the dimensions as shown in Figure 2. These tubes were annealed in an annealing oven and immediately placed in a dessicator. A sample of the compound to be decomposed (8-25 mg gave enough carbon dioxide for analysis) and $HgCl_2$ (approximately 100 mg-175 mg) were placed in a break seal tube, attached to a vacuum line and evacuated to 10^{-4} mm Hg. The break seal tube was then immersed in liquid nitrogen and sealed with the vacuum being maintained on the sample. The break seal tube was then placed in a pre-

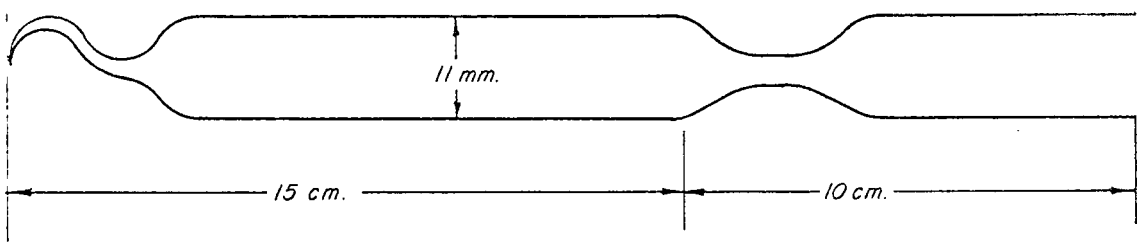


FIGURE 2

heated oven with a stable temperature (~530°C). All samples were then pyrolyzed for 3 hours at 530-560°C. A timer was employed to allow the same time for pyrolysis of each sample. Rittenberg and Ponticorvo (26) demonstrated that if temperatures of 530°C or higher were not used on phenols with excess oxygen-18, the isotopic numbers were very low in comparison to the theoretical number. After the tube was sealed, it was placed in an apparatus like that shown in Figure 3. A plug of glass wool was placed at the end of the tube containing the break seal tube, then 15 drops of distilled quinoline, the break seal tube, and a magnetic stirring bar were added, respectively. The trap F was immersed in a liquid nitrogen-methylcyclopentane slush (-135°C) (27). All stopcocks were opened to the vacuum line; after a pressure of 25 x 10^{-3} mm Hg had been attained, stopcock A was closed, and the break seal tube was broken with a magnet and the stirring bar inside the tube. After the quinoline had been allowed to react with the hydrogen chloride for 5-10 minutes, stopcock B was closed, and stopcock A was opened. The carbon dioxide

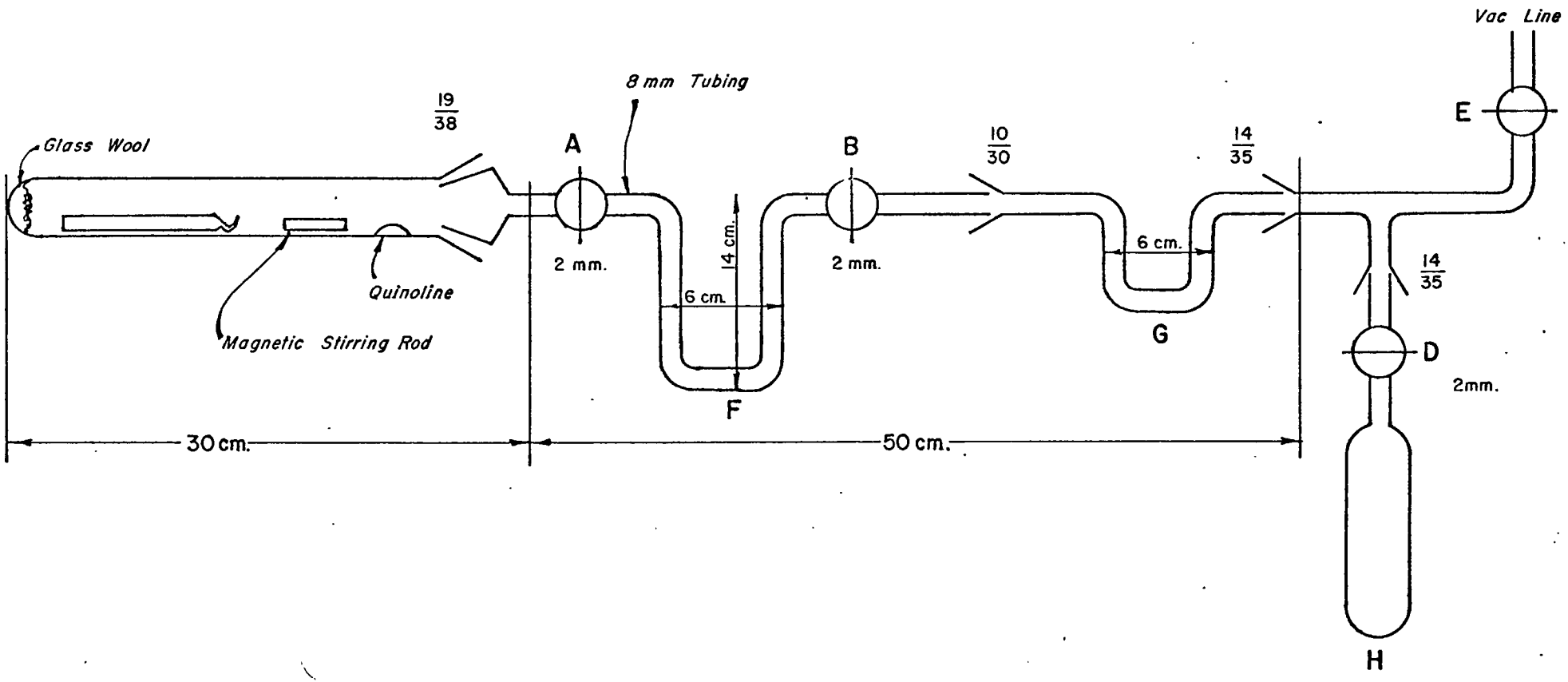


FIGURE 3 : Apparatus For Collection of CO_2.

was trapped for about 5 minutes in trap F at -135°C. Stopcock B was opened three or four times to the vacuum line for 2-3 seconds at a time to remove the non-condensable gases. After the pressure had reached 10^{-4} mm in the vacuum line, stopcocks A and E were closed. Trap G was then immersed in liquid nitrogen, the stopcock B was opened, and the carbon dioxide sublimed into trap G. The gas bulb H was then immersed in liquid nitrogen, and trap G was allowed to warm. The carbon dioxide then sublimed into the gas bulb, ready to be attached through its ground joint to the inlet system of the mass spectrometer.

Preparation of Dichloroacetic Acid-^{18}O

Hydrogen chloride gas was bubbled into deuterium oxide, 11.1 ml (0.61 mole), enriched in isotopic oxygen-18 content (1.51 atom percent oxygen-18 concent, purchased from YEDA Research and Development Co., Ltd.) for 15 minutes while the water-hydrogen chloride solution was stirred. The slow addition of 16.10 g (0.134 mole) of dichloroacetonitrile (28) was found to give a less violent reaction when the hydrolysis occurred than had been reported by Dunn (29). A continuous saturation of the water with hydrogen chloride was necessary before reaction occurred (which took about 15 minutes). At this time, a violent boiling of the water occurred which lasted only a few seconds, and the precipitation of ammonium chloride followed immediately. Hydrogen chloride was bubbled into the solution for a period of 15 minutes more. The mixture was then stirred at room temperature for 48 hours. Using a fritted glass filter, the ammonium chloride, 6.65 g, was removed and washed with 2 ml of the

deuterium oxide enriched in oxygen-18 content. The solution was then subjected to vacuum distillation through a 20 cm Vigreaux column. The deuterium oxide and dichloroacetonitrile distilled into a Dry Ice-acetone trap at room temperature and 0.2 mm vacuum. The dichloroacetic acid distilled at 67°C (0.2 mm) to yield 11.76 g (67 percent of theory); [lit. (29) bp 46-55° (0.05 mm)].

Preparation of N-(4-Methylphenyl)hydroxylamine

The preparation of N-(4-methylphenyl)hydroxylamine was primarily that of Rising (30), but addition of chloroform to the reaction mixture as a solvent increased the reaction's yield to 74 percent. The reaction was sensitive to the amount of chloroform used. The volume of chloroform needed for a 0.1 molar scale appeared to be between 15 and 20 ml.

Under a nitrogen atmosphere, a mixture of 150 ml (technical) chloroform, 600 ml (technical) methanol, 137.1 g (1.00 mole) p-nitrotoluene, and 20 g ammonium chloride in 600 ml of distilled water was stirred in a 3-neck, 3-liter, round bottom flask fitted with a mechanical stirrer and reflux condenser. One hundred fifty g (2.3 moles) of "purified" zinc dust was added to this mixture over a period of approximately 2 minutes. The temperature rose to 50-59°C after the addition of the zinc. The mixture was stirred until the temperature dropped to 40°C, at which time 200 ml chloroform was added. The mixture was then filtered, and the precipitate was washed with 3 x 100 ml portions of chloroform. The solution was then diluted with 500 ml of water while nitrogen was being bubbled through the solution. The aqueous layer was separated and

discarded. The chloroform layer was dried over anhydrous calcium chloride, and the chloroform was removed by means of a flash evaporator. The residue amounted to 123.0 g or 74 percent of the theoretical amount. After two recrystallizations from benzene, the melting point was 85-96°C when measured on a Fisher-Johns melting point apparatus; but in a modified Hirschberg melting point apparatus, it was 92.0-93.5°C [lit. (31) 98°C]. The nmr spectrum showed absorptions in benzene-d_6 at 2.04δ (s, 3), 5.56δ (broad s, 1), 6.72δ (q, AA'BB', 4), 7.05δ (s, 1).

Preparation of N-Acetyl-N-(4-Methylphenyl)hydroxylamine

Freshly distilled acetic anhydride, 16.32 g (0.10 mole, was added dropwise under nitrogen atmosphere to a stirred solution of N-(4-methylphenyl)hydroxylamine, 19.90 g (0.10 mole), dissolved in 220 ml of anhydrous ethyl ether, which was cooled in a salt-ice slurry during the addition. The addition was carried out at a rate which would maintain the temperature of the reaction mixture at 0°C. The reaction mixture was stirred for an additional 3 hours at 0°C and then evaporated to a purple, viscous residue at ambient temperature under aspirator vacuum. This residue was further evaporated under a vacuum of 0.05 mm at room temperature to a semi-crystalline state. When opened to the air, it turned brown. The syrup-solid mixture was dissolved in benzene and crystallized with low boiling petroleum ether, 30°-60°, and benzene, 75:25, to yield 14.00 g (52.6 percent of theoretical amount) of N-acetyl-N-(4-methylphenyl)hydroxylamine with a melting point of 71.5-73°C. The nmr spectrum showed absorptions in carbon tetrachloride at 1.97δ (s, 3), 2.27δ (s, 3), 7.11δ (q, AA'BB', 4), 9.70δ (broad s, 1).

Reaction of Dichloroacetyl Chloride and N-Acetyl-N-(4-Methylphenyl)hydroxylamine

To a solution in 15 ml of ether of 0.660 g (0.004 mole) of N-acetyl-N-(4-methylphenyl)hydroxylamine there was added 386 µl (0.004 mole) of freshly distilled dichloroacetyl chloride from a 500 µl syringe at such a rate as to keep the temperature at 0°C or below; meanwhile, the solution was cooled externally with salt-ice. If the solution was kept at 0°C or below, the hydroxylamine precipitated but dissolved again after a few minutes. The ether and hydrogen chloride were immediately removed by a vacuum pump. If the flask was kept cold during these operations, a white to light yellow solid formed. The nmr spectrum of this solid in deuterochloroform showed absorptions at 2.02δ (s, 3), 2.36δ (s, 3), 6.12δ (s, 1), 7.23δ (q, AA'BB', 4). This agreed well with the expected O-dichloroacetyl-N-acetyl-N-(4-methylphenyl)hydroxylamine. The nmr spectrum of the product from the reaction of N-acetyl-N-(4-methylphenyl)hydroxylamine with dichloroacetic anhydride was exactly the same as the nmr spectrum from the reaction between the hydroxylamine and dichloroacetyl chloride. This solid was not stable to heat or acid. As was demonstrated in the kinetics experiment, the solid rearranged at 38°C in about an hour to form a new compound. A great amount of heat was emitted when the reaction mixture was allowed to rearrange by warming on a water bath for a minute. After the rearrangement mixture was cooled, a brown solid formed which was washed with carbon tetrachloride, treated with charcoal and recrystallized from carbon tetrachloride to give 0.85 g (77 percent of theoretical) of fluffy white needles, melting point 118.4-120.0°C.

The nmr spectrum (Figure 4) of the product in deuterochloroform showed absorptions at 2.065δ (s, 3), 2.30δ (s, 3), 6.17δ (s, 1), 6.95δ-7.04δ (m, 2), 7.55δ (broad s, 1), 7.79δ (d, 1); ir in $CDCl_3$ 1703, 1790, and 3440 cm^{-1}. Analysis: Calc'd. for $C_{11}H_{11}Cl_{12}NO_3$: C, 47.85; H, 4.01; Cl, 25.68. Found: C, 47.79; H, 3.97; Cl, 26.20.

Hydrolysis of X

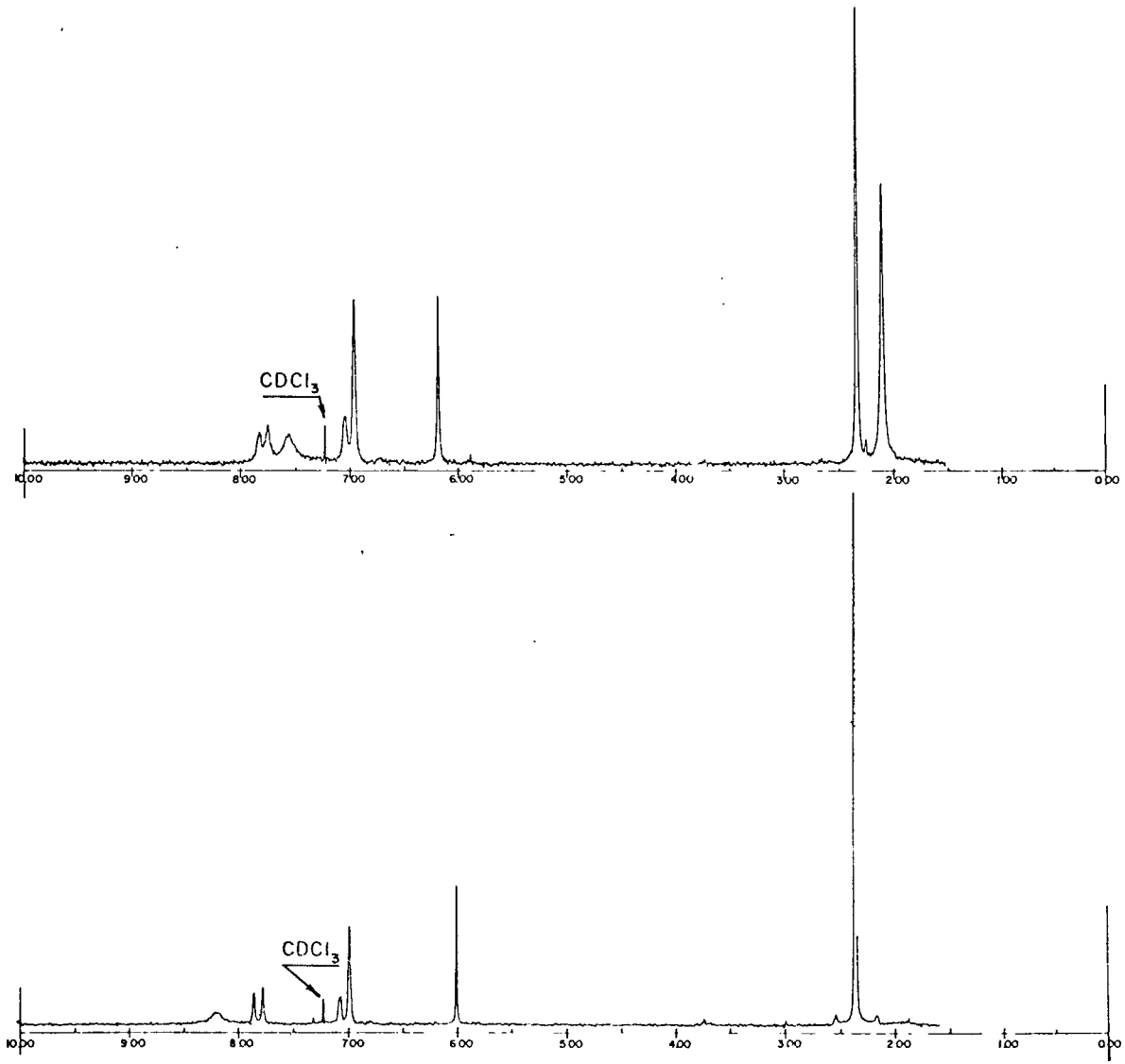
X, 0.40 g, was dissolved in acetone and water. Immediately, a precipitate formed which was stirred in the solution for 0.25 hour. The solid was collected by filtration and recrystallized from 50 percent ethanol to afford white needles melting at 167.4-168.6°C. An authentic sample of N-(4-methyl-2-hydroxyphenyl)ethanamide was prepared by reduction of 5-methyl-2-nitrophenol following the method of Proskouriakoff and Titherington (32), who reported a melting point of 170°C from 50 percent ethanol. The nmr spectra of the authentic compound and of the hydrolyzed rearrangement product were superimposable.

Reaction of Dichloroacetyl Chloride with N-Acetyl-N-(4-methylphenyl)-hydroxylamine in the Presence of Triethylamine

To a stirred solution of 0.660 g (0.004 mole), N-acetyl-N-(4-methylphenyl)hydroxylamine and 0.70 ml (0.005 mole) freshly distilled triethylamine in 15 ml of dry ether, there was added 385 µl (0.004 mole) dichloroacetyl chloride at such a rate as to keep the temperature at 0°C. Immediately, triethylamine hydrochloride precipitated and was filtered from the solution after the addition of the dichloroacetyl chloride. All the precipitate dissolved in water; hence, it was all triethylamine hydro-

Figure 4. NMR Spectrum ($CDCl_3$) of X, the Product of Rearrangement of IX in a Neat Solution.

Figure 5. NMR Spectrum ($CDCl_3$) of XI, the Product of Rearrangement of IX in the Presence of a Trace of Triethylamine.


CDCl3
CDCl3

chloride. The ether solution, hydrogen chloride, and excess triethylamine were removed under 0.005 mm vacuum. After evaporation of the solvent, an amber syrup was left which showed the same nmr spectrum as the solid product obtained in the reaction without triethylamine present which was previously assigned the structure N-acetyl-O-dichloroacetyl-N-(4-methylphenyl)hydroxylamine. Upon warming on a water bath, the syrup reacted as the evolution of heat indicated. After cooling, the syrup crystallized into a light brown solid. Carbon tetrachloride, 15 ml, was added, and the solid was filtered off. The brown solid was recrystallized twice with charcoal and carbon tetrachloride. A white, microcrystalline solid, melting at 127.2-128.2°C, was recovered to give 1.00 g (90 percent of theoretical) (XI). The nmr spectrum (Figure 5) showed absorptions at 2.32δ (s, 6), 6.00δ (s, 1), 6.97δ-7.06δ (m, 2), 7.82δ (d, 1), 8.19δ (broad s, 1). The ir spectrum showed characteristic absorptions at 1718, 1783, and 3410 cm^{-1}. This experiment was repeated three times, and each time the same compound was isolated as was shown by the nmr and ir spectra. This compound was definitely not the same as the one obtained in the reaction from which triethylamine was absent.

Elemental analysis: Calc'd. for $C_{11}H_{11}Cl_2NO_3$: C, 47.85; H, 4.01; Cl, 25.68. Found: C, 47.70; H. 4.01; Cl, 26.19.

Hydrolysis of XI

XI, 0.50 g, was dissolved in acetone and water. The complete hydrolysis took about 2 to 3 hours at room temperature, significantly longer than that of X under the same conditions. The solution was filtered, and the

light yellow solid was then recrystallized from 50 percent ethanol solution, affording white needles which melted at 169.0-170.2°C. This hydrolysis product has the identical nmr and ir spectra as authentic N-(4-methyl-2-hydroxyphenyl)ethanamide.

Influence of Triethylamine on X

Since two different products, X and XI, were obtained from the reaction of dichloroacetyl chloride and N-acetyl-N-(4-methylphenyl)hydroxylamine, depending on whether triethylamine was present or not, the next step was to attempt the conversion of X to XI in the presence of triethylamine. X, 0.85 g, was recrystallized from carbon tetrachloride which contained a few drops of triethylamine. The nmr spectrum and melting point of the recovered solid were identical with those of XI. The carbon tetrachloride was evaporated, and the nmr spectrum of the solid residue showed a trace of triethylamine; the remaining spectrum was that of XI.

Influence of Hydrogen Chloride on XI

XI was dissolved in 15 ml of ether, and anhydrous hydrogen chloride was bubbled into the ether solution for 10 seconds. The ether and hydrogen chloride were removed in vacuo. The nmr spectrum in deuterochloroform showed that no change had occurred.

Kinetics of Rearrangement of O-Dichloroacetyl-N-Acetyl-N-(4-Methylphenyl)-hydroxylamine

The preparation of O-dichloroacetyl-N-acetyl-N-(4-methylphenyl)-hydroxylamine for kinetic runs was exactly like that already described in the method without triethylamine. The rate of the rearrangement was

conveniently followed by nmr techniques. The methyl regions (2.22δ and 2.36δ) and the dichloroacetyl region (6.12δ) of the starting material were sufficiently separated from those of the single product (methyl absorptions, 2.06δ and 2.30δ; dichloroacetyl absorption, 6.17δ) that integration could be performed in order to measure the rate of disappearance of the starting material and the rate of appearance of the product. The integration was carried out by two methods: one by using a planimeter and reducing the areas to percentages, and the other by using the integrator system built into the HA-100. The absorptions were observed at 100 Hz sweep width and integrated with a 10 Hz per second sweep time which allowed consistent integrals. Solutions were 20-25 percent W/W in deuterochloroform. No thermostated bath was used because the rearrangement was too fast to allow moving the sample to a bath and then back again. Therefore, the sample was left in the probe which operated at about 38°C. The rate of disappearance of the starting material was consistent no matter which integration method was employed. The rate constant ($k = 3.6 \times 10^{-4}$ sec^{-1}, $t_{1/2}$ = 32.0 min) was obtained from plots.

Reaction of Dichloroacetic Anhydride with N-(4-Methyl-2-Hydroxyphenyl)-ethanamide

N-(4-methyl-2-hydroxyphenyl)ethanamide, 1.00 g (0.006 mole), was dissolved in 40 ml of p-dioxane (reagent), and 0.92 ml (0.006 mole) dichloroacetic anhydride was added. The solution was stirred for 24 hours, after which the p-dioxane was removed in vacuo. The dichloroacetic acid was not removed easily; therefore, the solution was dissolved in 25 ml of ethyl ether, and low boiling petroleum ether (30°-60°) was added until

the solution turned cloudy. The solution was placed in the freezer for 24 hours after which a white, crystalline precipitate was removed by filtration. Yield, 0.8283 g (30 percent theoretical). When the compound was recrystallized from carbon tetrachloride, its melting point was 118.4-120.2°C.

The nmr and ir spectra showed were identical with those of X.

When this solid was recrystallized from carbon tetrachloride in the presence of triethylamine, XI was isolated.

Thermal Stability of X and XI

X, 0.1 g, was heated while under vacuum to melting. The nmr spectrum of the cooled product showed 27 percent 2,6-dimethylbenzoxazole, 40 percent of XI, and the remainder unreacted starting material.

A 0.1 g sample of XI was also heated to melting under vacuum. The nmr spectrum showed no change whatsoever.

Reaction of N-(4-Methyl-2-Hydroxyphenyl)ethanamide-d_3 with Dichloroacetic Anhydride

The reaction conditions, quantities of reactants, and work up of this reaction was the same as those in the reaction using the protio acetic anhydride. The melting point of the product was 116.0-118.0°C ($X\text{-}d_3$).

Investigation of the nmr spectrum showed only one methyl group absorption at 2.30δ and the rest of the spectrum was the same as that of the product of the protio compound.

If the solid was recrystallized from carbon tetrachloride in the presence of triethylamine, there also was only one methyl absorption in the nmr spectrum which was at 2.32δ (melting point 122.7-125°C, impure since the compound was not recrystallized from fresh carbon tetrachloride) (XI-d_3). In the protio compound this absorption integrated for six protons but here integrated for only three protons.

Preparation of 2,6-Dimethylbenzoxazole

The 2,6-dimethylbenzoxazole was prepared by the procedure of Hewitt and King (33) who prepared 2-methylbenzoxazole by heating 1 mole of the o-aminophenol with 3 moles of acetic anhydride and isolated the product by distillation.

To a round bottom flask was added 0.1000 g (0.0005 mole) of N-(4-methyl-2-hydroxyphenyl)ethanamide and 0.17 ml (0.018 mole) of 99.9 percent acetic anhydride. The flask was fitted with a Claisen head and condenser. The first fraction removed was acetic acid, and the second fraction was acetic anhydride. After the removal of the second fraction, the temperature dropped. As the pot temperature was raised, the temperature of the distillate rose to 235°C. After cooling, the inside of the apparatus was washed with 3 ml of ether. The ether wash was combined with the fraction boiling at 235°C. The ether was washed with 2 x 5 ml portions of 20 percent sodium hydroxide, then 2 x 5 ml portions of water; the last water wash was made acidic with one drop of hydrochloric acid (pH-2). The ether was dried with sodium sulfate and evaporated to produce a light yellow oil. A short path distillation afforded a color-

less liquid which had turned yellow after 48 hours, 50 mg (55 percent of theoretical amount); nmr ($CDCl_3$) 2.37δ (s, 3), 2.51δ (s, 3), 6.96δ-7.155δ (3 broad s, 2), 7.55δ (d, 1); ir (thin film), 1557 and 1593 cm^{-1}.

Attempted Reaction of 2,6-Dimethylbenzoxazole with Dichloroacetic Acid

A 100 μl sample of 2,6-dimethylbenzoxazole was dissolved in 100 μl of dichloroacetic acid and 50 μl of carbon tetrachloride and placed in an nmr tube. The sepctrum showed absorptions just like those of the benzoxazole in deuterochloroform. The spectrum was scanned at time intervals over a two-day period, and no change was observed. Even after remaining at room temperature for 2 weeks, there was no change. The nmr tube and solution were heated to 60°C for 15 minutes, and the absorptions at 2.51δ and the aromatic region broadened. They shifted some, but essentially the overall spectrum looked the same. Even after hydrogen chloride gas had been bubbled into the mixture, the nmr spectrum did not change.

Preparation of O-Dichloroacetyl-^{18}O-N-Acetyl-N-(4-Methylphenyl)hydroxylamine and Rearrangement

The procedure that was followed for this preparation was exactly that of the isotopically normal compound already described. O-dichloroacetyl-^{18}O-N-acetyl-N-(4-methylphenyl)hydroxylamine, 1.104 g (0.004 mole, 100 percent of theoretical by nmr), was isolated after evaporation of solvent and hydrogen chloride. This syrup, as has already been stated, was heated over a hot water bath until rearrangement occurred. After the syrup had been cooled, the solid formed was recrystallized twice from

carbon tetrachloride and charcoal to a constant melting point of 118.4-120.0°C. The fluffy white solid was hydrolyzed with a water-acetone solution. The ester and amidophenol were sublimed at 97°/0.25 mm and then recrystallized from 50 percent ethanol. The atom percent excess ^{18}O is listed in Table I.

The Rearrangement of O-Dichloroacetyl-^{18}O-N-Acetyl-N-Phenylhydroxylamine in Dichloroacetic Acid

The procedure that was followed for the rearrangement was the same as that of Dunn in most all cases. The reaction was run 2 times, and the data are recorded in Table III. Each reaction was run with the following quantities of reactants: O-dichloroacetyl-^{18}O-N-acetyl-N-phenylhydroxylamine, 3.162 g (0.012 mole), prepared from 2.000 g (0.0135 mole) of dichloroacetylchloride-^{18}O and 2.040 g (0.0135 mole) of N-acetyl-N-phenylhydroxylamine in carbon tetrachloride solution (1). After the carbon tetrachloride was removed, 8.0 ml of dichloroacetic acid was added to the syrup and stirred at room temperature for 120 hours. After 120 hours, the reaction mixture was poured onto ice while the ice was being stirred. The mixture was then neutralized to a pH of 7. The light brown solid which formed was filtered and washed with 50 ml of water. The solid was then subjected to sublimation at 80-90°C/0.005 mm. The first fraction, which was a fluffy white solid, showed an nmr spectrum similar to that of the original reaction mixture before it was poured over ice and neutralized. If the temperature of the mixture during addition of sodium carbonate was not kept at 0°C, then there was more hydrolyzed ester present. This was evidenced by the large amount of

the second fraction of the sublimation (120-130°C/0.005 mm) which was identified from its melting point (201-205°C) as o-hydroxyacetanilide. The dichloroacetates obtained from the sublimation were hydrolyzed in sodium carbonate and aqueous-acetone solution to give o-hydroxyacetanilide which is reported to have a melting point of 201°C (34). The dichloroacetate of the p-hydroxyacetanilide was isolated only once.

Rearrangement of O-Dichloroacetyl-D-N-Acetyl-N-Phenylhydroxylamine in Dichloroacetic Acid

The dichloroacetyl chloride-d_1 (99.5 atom percent-d_1) was prepared by Mr. Michael Tuxson by reduction of trichloroacetic acid with elemental zinc in the presence of deuterium oxide, and then the salt was treated with thionylchloride. N-acetyl-N-phenylhydroxylamine, 0.5010 g (0.0038 mole) was allowed to react with 0.5000 g (0.0038 mole) of dichloroacetyl chloride-d_1 in carbon tetrachloride as described earlier.

After the hydrogen chloride and carbon tetrachloride had been removed in vacuo, 0.4 g of the product was dissolved in 2.0 ml of isotopically normal dichloroacetic acid. The nmr spectrum of this solution was analyzed to determine how much of the labelled dichloroacetyl group was exchanged for the protio dichloroacetyl function during the rearrangement. The rearrangement took 5 days at room temperature for completion of reaction. At the end of this time, a spectrum was obtained of the dichloroacetyl and methyl regions at a sweepwidth of 250 Hz. Integration was carried out by Xeroxing the absorptions, smoothing the overlapping absorptions by eye, and cutting out the peaks and weighing them. The ratio of dichloro-

acetyl proton/methyl proton for each isomer could thus be determined directly. By this procedure it was estimated that the ortho isomer lost 18 percent of its label and the para isomer lost 60 percent of its label.

Rearrangement of O-Dichloroacetyl-^{18}O-N-Acetyl-N-Phenylhydroxylamine in Chloroform

O-dichloroacetyl-^{18}O-N-acetyl-N-phenylhydroxylamine was prepared by the method already discussed; the dichloroacetic acid was removed by vacuum pumping or shaking the carbon tetrachloride solution containing the ester with anhydrous sodium carbonate.

O-dichloroacetyl-^{18}O-N-acetyl-N-phenylhydroxylamine, 1.5800 g, (0.0067 mole), was dissolved in 5 ml chloroform and was placed in a round bottom flask. The flask was evacuated and placed in a constant temperature oil bath at 68.6°C±.05°C. The reaction was monitored by nmr. Time required for complete reaction was about 16 hours.

After the completion of the reaction, the nmr showed about 100 percent of one product. The chloroform was stripped off, and 0.6278 g of a light tan solid was left. When the product was recrystallized carefully from carbon tetrachloride and charcoal, a white microcrystalline solid was obtained with a melting point of 101.8-104.0°C (XIII); nmr ($CDCl_3$) (Figure 6) 2.11δ (s, 3), 6.17δ (s, 1,) 7.21δ (m, 3), 8.12δ (broad m, 2, N-H and aromatic hydrogen).

The product was very easily rearranged further to another compound by heating or treating with triethylamine; melting point 118.8-120.2°C (XIV); nmr ($CDCl_3$) (Figure 8) 2.33δ (s, 3), 6.01δ (s, 1), 7.19δ (m, 3), 8.02δ (m, 1), 8.30δ (broad s, 1). There was no para ester formed in this

Figure 6. NMR Spectrum ($CDCl_3$) of XIII, the Product of Rearrangement of XII in Chloroform.

Figure 7. NMR Spectrum ($CDCl_3$) of the Isolated Product after Neutralization of the Dichloroacetic Acid from the Reaction Mixture of N-Acetyl-N-Phenylhydroxylamine with Dichloroacetyl Chloride in Dichloroacetic Acid.

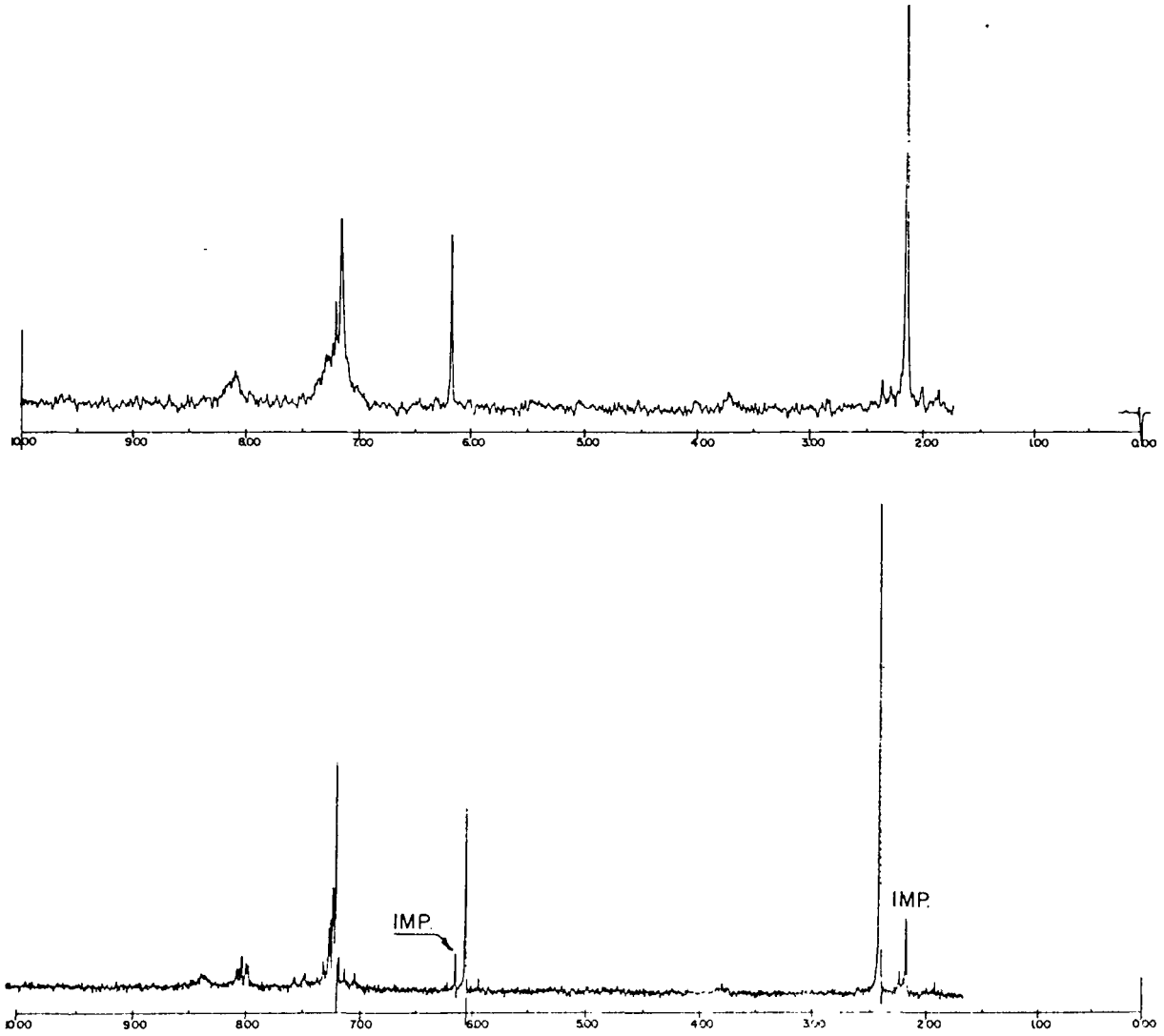
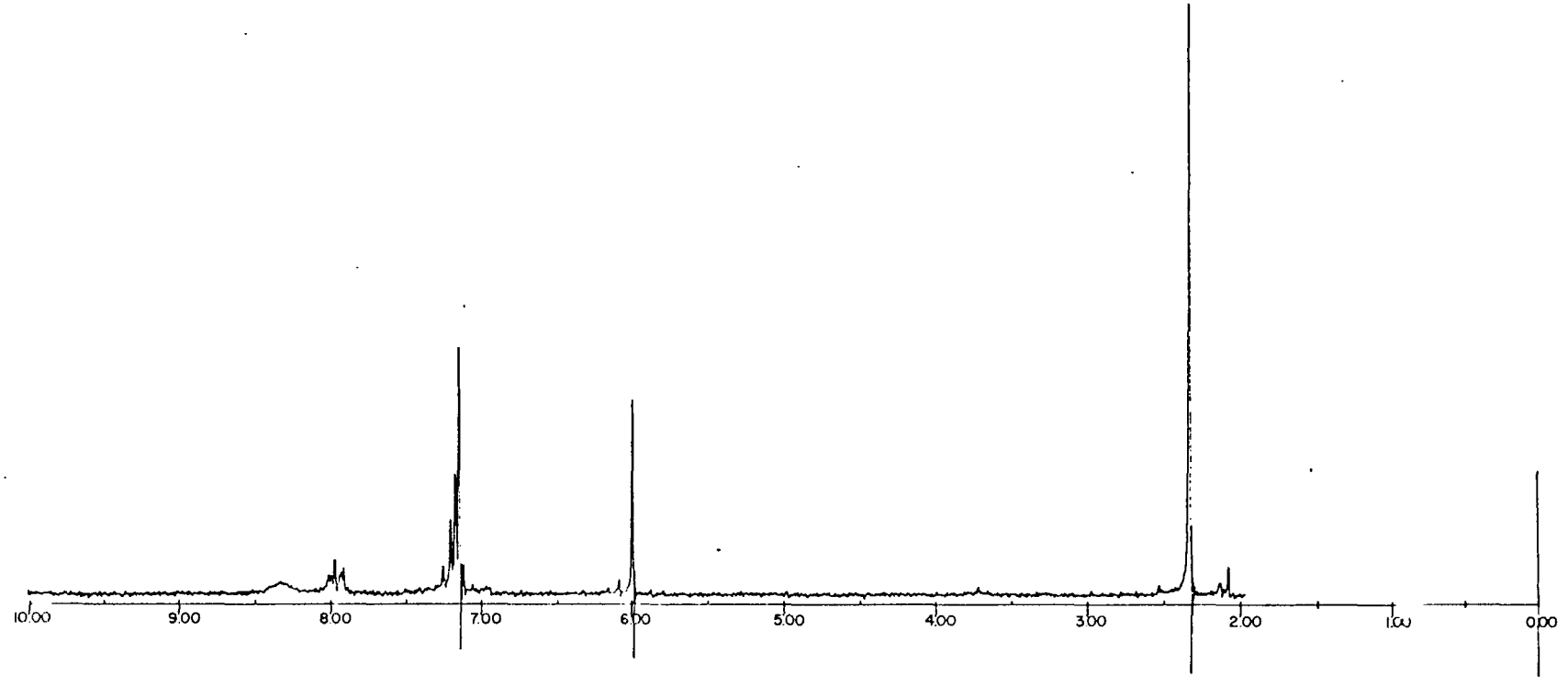

IMP.
IMP.

Figure 8. NMR Spectrum ($CDCl_3$) of XIV, the Product of Rearrangement of XII in the Presence of a Trace of Triethylamine.


10.00
9.00
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.00

rearrangement. The para isomer would have shown up easily in the nmr because of the AA'BB' pattern in the aromatic region. See Table II for results of isotope ratios.

Comparison of Products from the Rearrangement of O-Dichloroacetyl-N-Acetyl-N-Phenylhydroxylamine in Chloroform and in Dichloroacetic Acid

The product of the rearrangement of XII in chloroform had a melting point of 100.4-102.4°C. Its nmr in deuterochloroform is shown in Figure 6. After recrystallization in the presence of triethylamine, its melting point was 118.8-120.2. The nmr spectrum in deuterochloroform is shown in Figure 8. The nmr spectrum of the compound with a melting point of 101.8-104.0°C was determined in dichloroacetic acid (Figure 9). Similarly, the product with a melting point of 118.8-120.2 was examined in dichloroacetic acid (Figure 10). Figures 9 and 10 are obviously different.

The isolatable products from the rearrangements in dichloroacetic acid were examined in detail both by myself and Dunn (35). Figure 11 shows the spectrum of the original mixture before the dichloroacetic acid was neutralized with aqueous sodium carbonate. The ortho isomer that was isolated had a melting point of 118.8-120.4°C. It was redissolved in dichloroacetic acid, and its nmr spectrum is shown in Figure 12. The spectrum of Figure 12 is identical with that of Figure 10, but obviously different from that of Figure 11 even when the para isomer in Figure 11 is ignored. Figures 9 and 11 are very similar when the para isomer present in Figure 11 is disregarded. Spectra of samples of XIV isolated from rearrangement in chloroform and in dichloroacetic acid were identical (Figures 7 and 8).

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Figure 9. NMR Spectrum (HCl_2CCOOH) of XIII, the Product of the Rearrangement of XII in Chloroform.

Figure 10. NMR Spectrum (HCl_2CCOOH) of XIV, the Product of the Rearrangement of XII in the Presence of a Trace of Triethylamine.

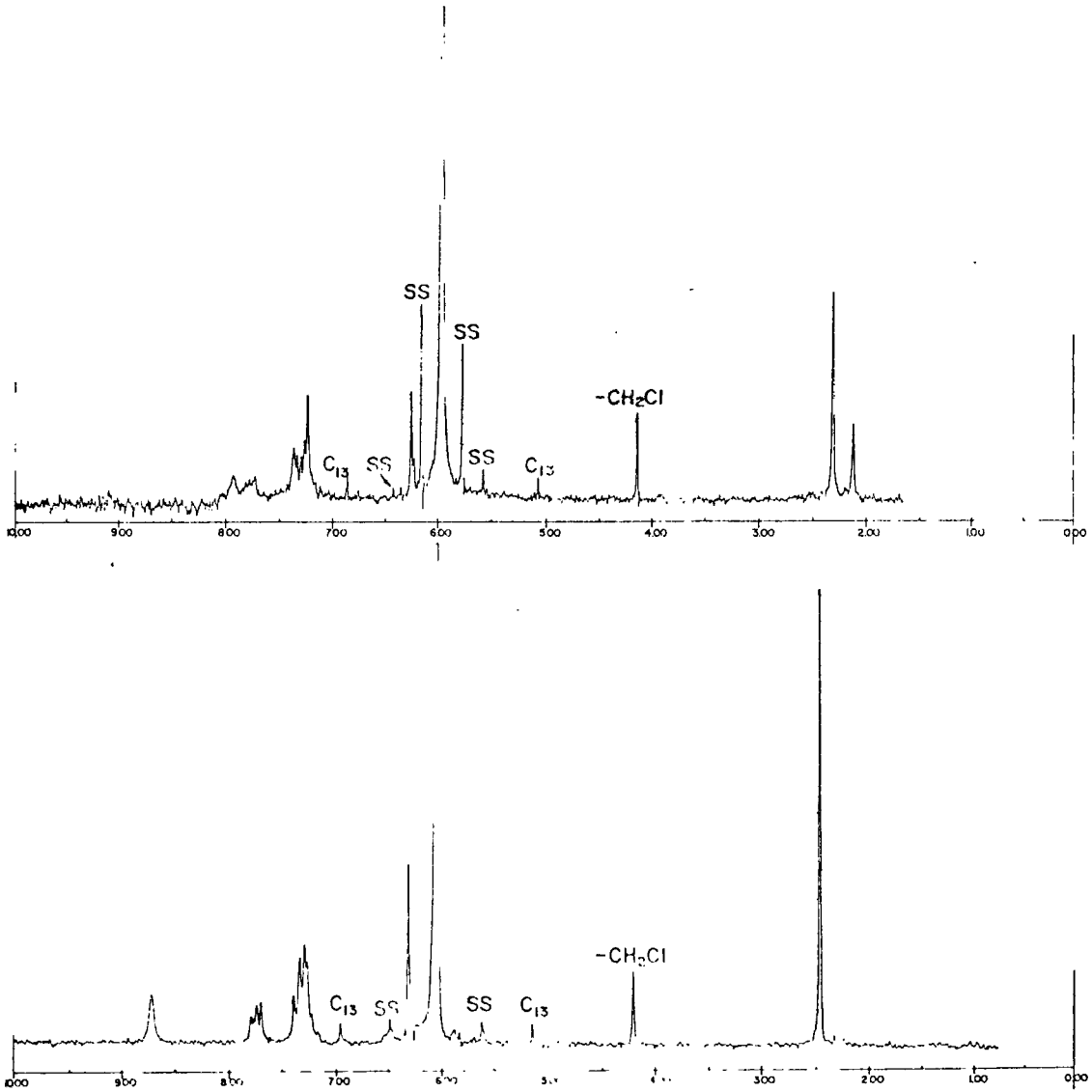
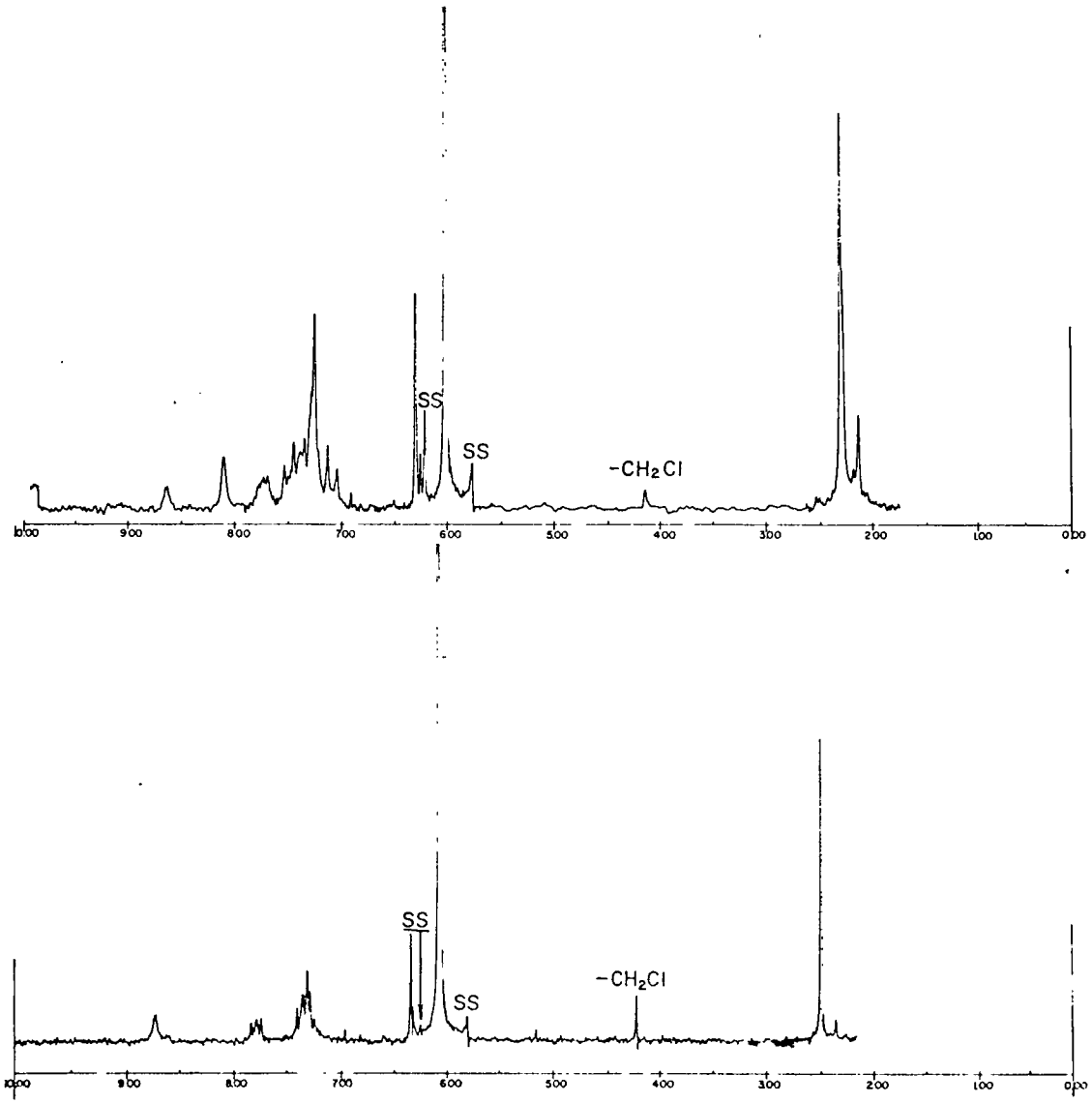

SS
SS
-CH2Cl
C13
SS
SS
C13
SS
C13
-CH2Cl
C13
SS
SS
C13

Figure 11. NMR Spectrum (HCl_2CCOOH) of the Rearrangement Reaction Mixture of XII in Dichloroacetic Acid.

Figure 12. NMR Spectrum (HCl_2CCOOH) of the ortho Isomer "Isolated" after Neutralizing the Dichloroacetic Acid of the Rearrangement Reaction Mixture of XII in Dichloroacetic Acid.


SS
SS
-CH2Cl
SS
SS
-CH2Cl

Since the difference in the nmr spectrum of XIII between samples dissolved in deuterochloroform and dichloroacetic acid was striking (Figures 6 and 9), the attempt was made to remove the dichloroacetic acid from the solution in order to test the reversibility of the phenomenon. For reasons of convenience only, X-d_3 was utilized. (X displayed the same phenomenon, see Figures 4 and 13).

The solution used to measure the spectrum of X-d_3, Figure 15, was exposed to a high vacuum for approximately 8 hours to attempt removal of the dichloroacetic acid. At the end of this time, the nmr spectrum in deuterochloroform, Figure 16, showed that the absorption at 2.35δ had increased at the expense of the absorption at 2.40δ (upfield to downfield 3:1). Similarly, one dichloroacetyl absorption had nearly disappeared, and the aromatic region was starting to approach that of the spectrum of pure X-d_3 in deuterochloroform. The absorption at 2.23δ and 6.69δ were from the N-(4-methyl-2-hydroxyphenyl)ethanamide which was present when making the sample.

In contrast, dichloroacetic acid was removed in one hour quantitatively from a sample of XIV under the same conditions as above. A white solid obtained afforded an nmr spectrum in deuterochloroform identical with that measured in deuterochloroform before dissolving in dichloroacetic acid.

Kinetics of the Thermal Rearrangement of O-Dichloroacetyl-N-Acetyl-N-Phenylhydroxylamine

The preparation of the starting material and the product from the thermal reaction have already been described.

Figure 13. NMR Spectrum (HCl_2CCOOH) of X, the Product of Rearrangement of IX in a Neat Solution.

Figure 14. NMR Spectrum (HCl_2CCOOH) of XI, the Product of Rearrangement of IX in the Presence of a Trace of Triethylamine.

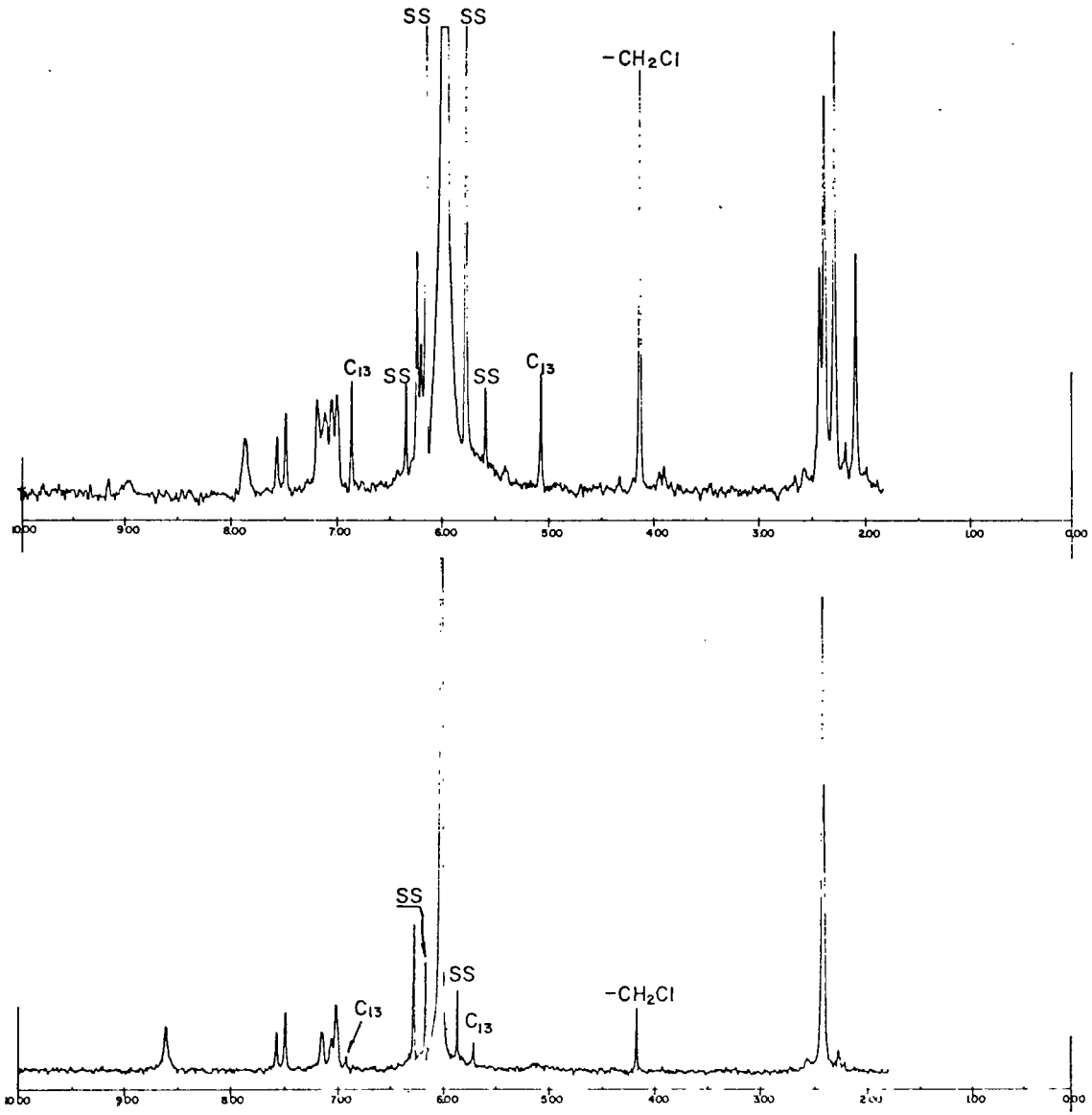
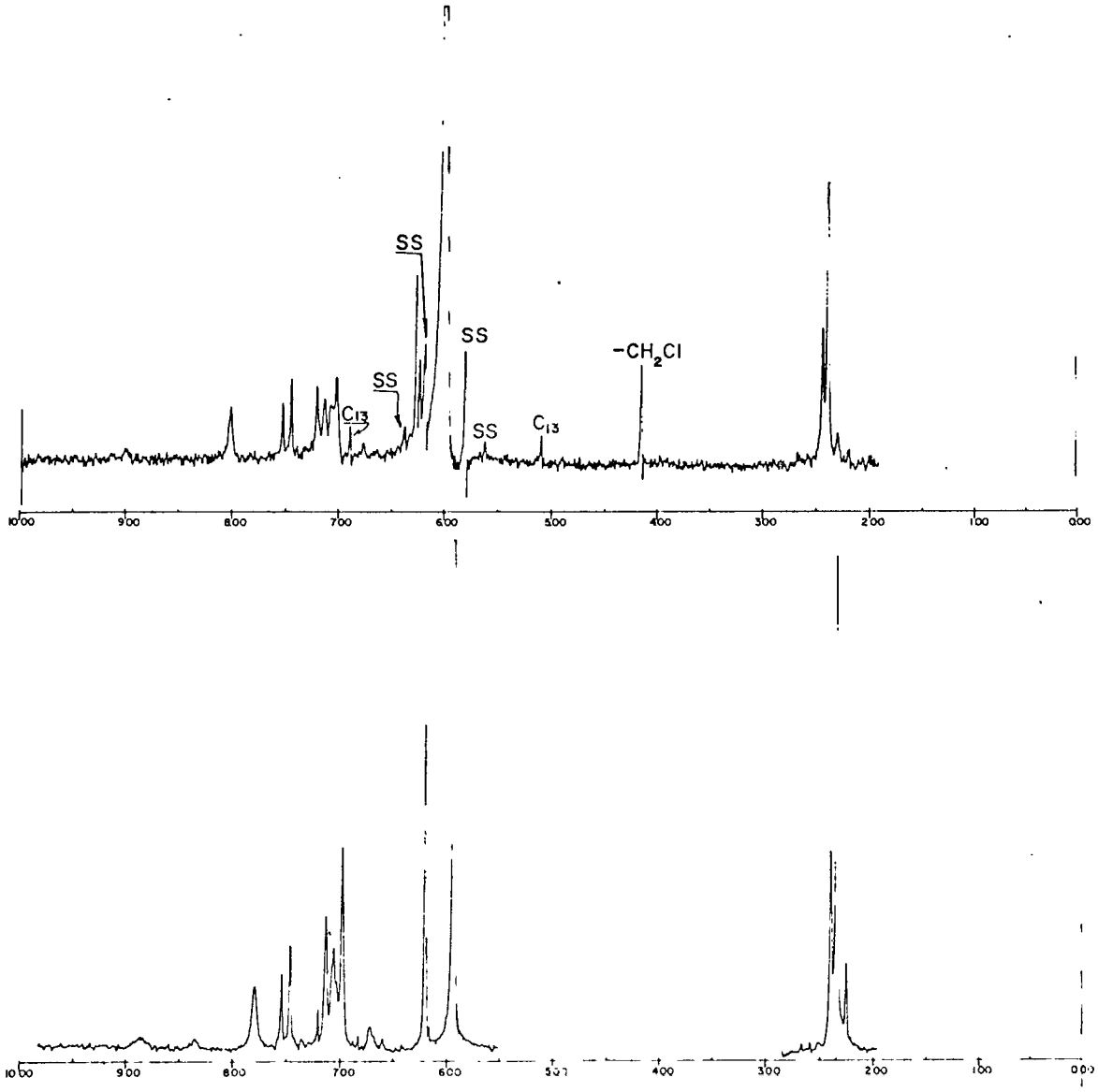

SS
SS
-CH2Cl
C13
SS
SS
C13
SS
SS
C13
-CH2Cl
10.00
9.00
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.00

Figure 15. NMR Spectrum (HCl_2CCOOH) of X-d_3.

Figure 16. NMR Spectrum ($CDCl_3$ + HCl_2CCOOH) of X-d_3 after 10 Hours of Attempted Removal of Dichloroacetic Acid by Means of a High Vacuum.


SS
SS
SS
SS
C_{13}
C_{13}
$-CH_2Cl$
1000
900
800
700
600
500
400
300
200
100
000

Kinetics were followed by nmr by monitoring the dichloroacetyl protons, as was the case in the p-methyl compound. A 20 percent solution of the starting material of deuterochloroform was prepared in an nmr tube. The initial scan was taken, and there was no rearrangement at t = 0. The tube was then immersed in a constant temperature bath at 68.6°C±.05°C. The tube was removed at intervals and the integrations made on 100 Hz sweep width and integrated at 10 Hz per second sweep time. The sample was out of the bath for no longer than 30 minutes. A rate constant, $k = 3.4 \times 10^{-5}$ sec^{-1}, and a half life, $t_{1/2}$ = 335 min were obtained.

Preparation of N-Acetyl-N-(2-Methylphenyl)hydroxylamine

Freshly distilled acetic anhydride, 3.78 g (0.038 mole), was added dropwise to a stirred solution of 50 ml of anhydrous ether containing 4.78 g (0.038 mole) N-(2-methylphenyl)hydroxylamine (melting point 40-42°C, prepared by the procedure of Bamberger and Rising; lit (36) melting point 42°C) while the ether solution was cooled in a salt-ice slurry at 0°C or below. At the end of three hours, the ether was stripped off with a flash evaporator at which time the solution turned purple. As the solution was subjected to a 0.05 mm vacuum to remove the acetic acid, the solution turned black. In carbon tetrachloride the nmr spectrum of the black syrup showed high purity of one compound with absorptions at 1.83δ (s, 3), 2.29δ (s, 3), 7.18δ (s, 5), 9.43δ (broad s, 1). As the pumping was continued, plate-like crystals formed on the wall of the vessel but stopped forming after a short time. The syrup formed was

dissolved in ether and immersed in a dry ice-acetone bath, and after 1 minute, a black solid formed on the side of the flask leaving a dark brown solution. The brown solution was filtered, and the ether solution was cooled repeatedly until no more tar was obtained (3 times). The ether was stripped, and the syrup placed in a sublimation apparatus. There was no heat applied, but a vacuum of 0.005 mm was used. After approximately 10 hours, a red to orange liquid and white crystals formed on the sublimation cold finger. The liquid crystallized after awhile but only completely after scratching the cold finger. The cold finger was removed, and a glass stopper was put in its place. The syrup was then heated with a steam bath, and the orange liquid distilled to the top of the apparatus where it crystallized on the stopper. This was done until only a hard, black residue was left in the bottom of the sublimation bulb. The sublimed material, melting point 77.0-78,6°C, was recrystallized from a mixture of low boiling petroleum ether and carbon tetrachloride. Scratching the walls of the vessel caused crystallization which gave 2.71 g (41.6 of the theoretical amount) of the acetylated hydroxylamine: melting point 78.0-79.6; nmr in CCl_4, 1.83δ (s, 3), 2.29δ (s, 3), 7.18δ (s, 4), 9.43δ (broad s, 1).

Attempted Preparation of O-Dichloroacetyl-N-Acetyl-N-(2-Methylphenyl)-hydroxylamine

N-acetyl-N-(2-methylphenyl)hydroxylamine, 2.00 g (0.012 mole), was dissolved in 60 ml of anhydrous ethyl ether. Dichloroacetyl chloride, 1.10 ml (0.012 mole), was added dropwise to the ether solution which had been cooled to 0°C in a salt-ice slurry. After the addition of the

chloride, the solution was stirred for 1.5 hours at 5°C and placed in the freezer for 24 hours. The ether and hydrogen chloride were then removed by aspirator vacuum. A vacuum of 0.025 mm was employed by means of a mechanical pump to remove the residual hydrogen chloride and any unreacted dichloroacetyl chloride. While the mixture was pumped, the flask was immersed in an ice bath. After pumping was continued for 4 days, a yellow syrup was obtained. The nmr spectrum and ir spectrum showed a complex mixture which indicated rearrangement to the ring had taken place.

The product was hydrolyzed in a 10 percent sodium bicarbonate solution. The solution was neutralized and extracted with chloroform. After the chloroform was removed, the nmr spectrum of the solid indicated a mixture of phenols. There was no absorption that could be attributed to the authentic N-o-benzylol ethanamide prepared by acetylation of o-aminobenzyl alcohol (Aldrich) in ethylacetate (37). This compound could be recognized easily because the chemical shift (4.63δ s, acetone-d_6) of the methylene group is not obscured by any other absorption. In chloroform-d_1, the methylene is a doublet and the hydroxyl hydrogen is a triplet.

Preparation of N-(4-Acetylphenyl)hydroxylamine

Under a nitrogen atmosphere, 16 g of zinc dust was added to a stirred mixture of 4 g of ammonium chloride, 16.50 g (0.5 mole), p-nitroacetophenone, 50 ml water, 60 ml of methanol (tech.), and 16 ml of chloroform fast enough to allow the temperature to rise to 42°C. The mixture was stirred and heated to 50°C for 0.5 hour, then it was stirred while under nitrogen at room temperature for 24 hours.

At the end of the 24 hours, the solvents were all removed by an aspirator vacuum at room temperature, and then the removal was completed at 0.05 mm. The solid was sitrred into a sufficient amount of acetone to dissolve all organic material, and the inorganic material was filtered.

The acetone was removed by means of a flash evaporator. The solid deposited was recrystallized from chloroform to give a melting point of 123.4-124.8°C and a yield of 6.00 g (42 percent of the theoretical amount).

The ir spectrum showed an -OH absorption at 3570 cm^{-1} and an -NH absorption at 3300 cm^{-1}. The nmr spectrum had absorptions in acetonitrile-d_3 as follows: 2.42δ (s, 3), 6.78δ (s, 1), 6.86δ (d of t, 2), 7.56δ (broad s, 1), 7.86δ (d of t, 2). A second compound was isolated with the inorganic material. The compound was a yellow solid melting at 191.2-192.2°C. Its ir spectrum gave no real information except that there was a carbonyl group present. The nmr spectrum showed 2 nonequivalent methyl groups at 2.64δ and 2.67δ and a complex multiplet at 8.28δ. Rising (38) reported that he isolated the azoxy compound when using p-nitroanisole in the reduction with ammonium chloride; the structure has been assigned the azoxy compound, Figure 17.

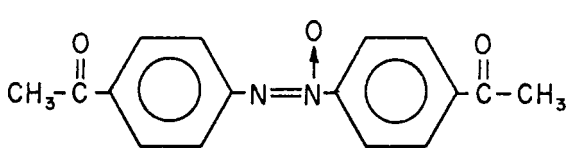


FIGURE 17

Calc'd. for $C_{16}H_{14}N_2O_3$: C, 68.08 percent; H, 4.99 percent; N, 9.92 percent. Found: C, 68.47 percent; H, 4.79 percent; N, 9.96 percent.

Preparation of N-Acetyl-N-(4-Acetylphenyl)hydroxylamine

To a stirred solution of 11.20 g (0.074 mole) of N-(4-acetylphenyl)-hydroxylamine in 265 ml of acetonitrile (Baker) which was immersed at 0°C in an ice slurry, 7.55 g (0.074 mole) of acetic anhydride (99 percent) was slowly added while the reaction mixture was under a blanket of nitrogen. The solution was stirred for 3 hours at 0°C. After 3 hours, the acetonitrile was removed by aspirator, and then the excess anhydride and by-product acetic acid were removed at 0.025 mm by mechanical vacuum pump. The solid residue was subjected to extraction with a volume of absolute ethyl alcohol. The mixture was filtered and subjected to evaporation. The solid residue was recrystallized from benzene to produce glistening white needles with a melting point of 143.2-145.0°C; yield 5.78 g (44.70 percent or the theoretical amount); nmr (acetone-d_6) 2.29δ (s, 3), 2.51δ (s, 3), 3.30δ (s, 1), 7.87δ (q, AA'BB', 4).

Attempted Rearrangement of O-Dichloroacetyl-N-Acetyl-N-(4-Acetylphenyl)-hydroxylamine

A solution of p-dioxane (Reagent), 12 ml, and 0.480 g (0.0025 mole) of N-acetyl-N-(4-acetylphenyl)hydroxylamine in a round bottom flask was stirred while .31 ml (0.0025 mole) of dichloroacetyl chloride was added dropwise over a period of 15 minutes. The nmr showed a different AA'BB' pattern than the starting material. The p-dioxane was removed by means of a vacuum pump to produce a yellowish-white solid which was washed into a filter funnel with 10 ml of dry carbon tetrachloride and allowed

to air dry. The nmr spectrum showed absorptions in acetone-d_6 at 2.19δ (s, 3), 2.58δ (s, 3), 6.19δ (s, 1), 7.64δ (d of t, 2), 8.05δ (d of t, 2); ir in chloroform-d_1 at 1820 cm^{-1} (dichloroacetyl C = O), 1690 cm^{-1} (amide C = O). These spectral results indicated the O-dichloroacetyl-N-acetyl-N-(4-acetylphenyl)hydroxylamine structure assignment.

A 20 percent W/W solution was prepared in dichloroacetic acid. The nmr spectrum showed absorptions at 2.35δ (s, 3), 2.77δ (s, 3), 6.18δ (s, dichloroacetic acid), 6.35δ (s, 1), 7.70δ (broad d, 2), 8.16δ (broad d, 2). The solution was subjected to a 70°C oil bath for 18 hours. At the end of this time, the solution had turned dark brown, but the nmr spectrum showed no observable change. The solution was diluted with 2 ml of p-dioxane and heated at 100°C for 8 hours. At this time, there was an appearance of new signals in all previous regions. The signals were broadened which made determining how much had rearranged difficult. The solution was replaced in the oil bath at 100°C for 10 hours. After this time, the nmr showed that nearly all the starting material had rearranged. The p-dioxane and what dichloroacetic acid would come off were removed under high vacuum. A black, syrupy residue was left which was diluted with 5 ml of water and neutralized with sodium carbonate. The black solid which precipitated was filtered and dried. In nitromethane the nmr spectrum showed absorptions at 2.59δ (s, 3), 2.68δ (s, 3), 7.13δ (s, 1), 7.66δ-8.31δ (m, 4). This was probably some isomer of the starting material which did have a functional group in three positions, 1,2 and 4-because the nmr spectrum showed no AA'BB' structure. The aromatic

region resembled a large number of nmr spectra of aromatic regions which were 1, 2 and 4- substituted with the same type of functional groups (39,40).

Preparation of O-Trifluoroacetyl-N-Acetyl-N-(4-Acetylphenyl)hydroxylamine

N-acetyl-N-(4-acetylphenyl)hydroxylamine, 0.772 g (0.004 mole), was dissolved in 5 ml of p-dioxane. While the solution was being stirred, an excess of trifluoroacetic anhydride (Curtin), 1.260 g (0.006 mole), was added. After half the anhydride had been added, the nmr spectrum of the aromatic region in p-dioxane showed the appearance of a new AA'BB' pattern, Figure 18. The p-dioxane and trifluoroacetic acid were removed

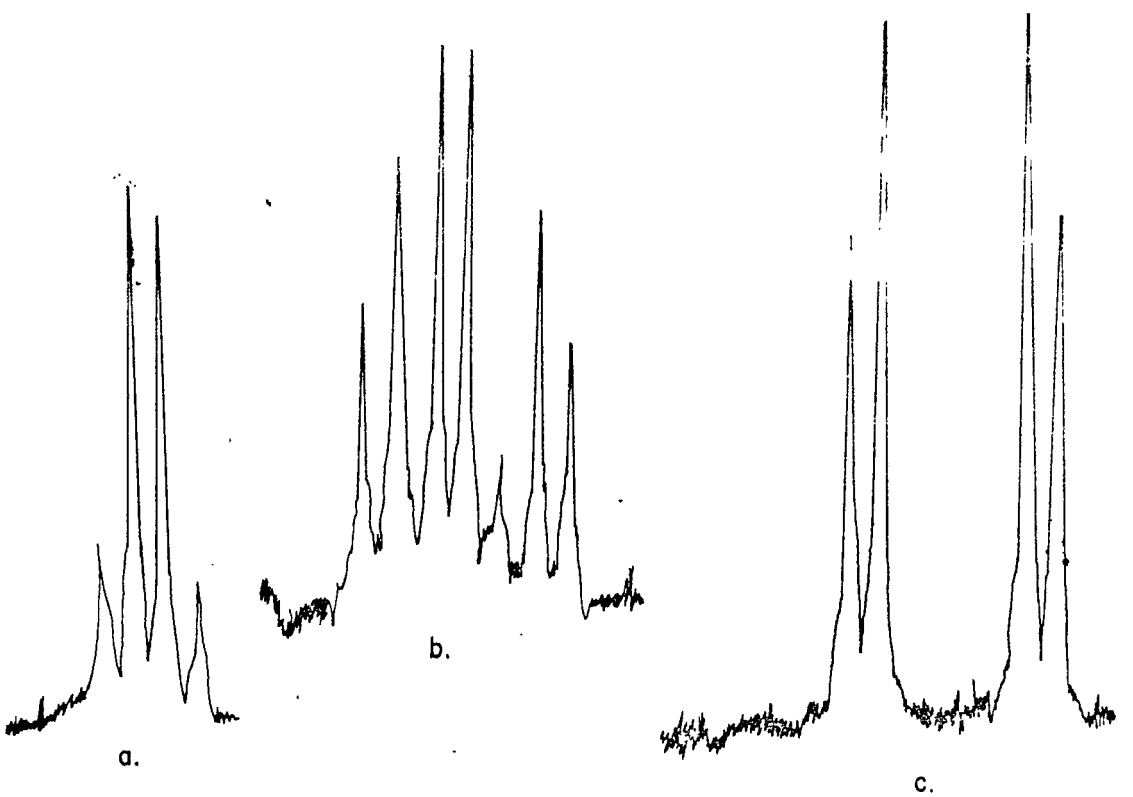


FIGURE 18

in vacuo, and an attempt was made to crystallize the syrup produced from ether and low boiling petroleum ether. This could not be done because it would hydrolyze first.

The nmr spectrum in p-dioxane showed absorptions at 2.18δ (s, 3), 2.56δ (s, 3), 3.56δ (solvent), 7.59δ (d of t, 2), 8.55δ (d of t, 2).

Rearrangement of O-Trifluoroacetyl-N-Acetyl-N-(4-Acetylphenyl)hydroxylamine in Trifluoroacetic Acid

O-trifluoroacetyl-N-acetyl-N-(4-acetylphenyl)hydroxylamine from the previous reaction was dissolved in 1 ml of p-dioxane and 0.1 ml trifluoroacetic acid. The sample was placed in a round bottom flask which was evacuated. This was then placed in an oil bath for the heating period of 12 hours at a temperature of 68.6±0.05°C. After 12 hours, the solution was allowed to cool. A light fluffy solid crystallized and was then washed with 15 ml carbon tetrachloride. A yield of .669 g (melting point 128.8-150.0°C) was obtained. The nmr spectrum showed a mixture of the starting material, rearrangement product, and some hydrolyzed product. However, the nmr spectrum was obtained before all the material hydrolyzed. In deuteroacetonitrile there were absorptions at 2.12δ (s, 3), 2.54δ (s, 3), 7.39δ-8.17δ (cm, 3), 8.29δ (broad s, 1). During the work up, the rearranged material hydrolyzed from slightly wet solvents. The product was finally hydrolyzed with water. A yellow crystalline solid, 0.1800 g (58 percent of theoretical, melting point 226.0-229.0°C) was isolated. This gave an nmr in dimethylsulfoxide-d_6 and 20 µl of deuterochloroform with absorptions at 2.17δ (s, 3), 2.48δ (s, 3), 7.40δ (m, 2), 8.05δ (d, 1), 9.25δ (broad s, 1), 10.10δ (broad s, 1).

Again, these absorptions agreed with 1, 2, and 4-position substituents as was shown in the case of the O-dichloroacetyl-N-acetyl-N-(4-acetylphenyl)hydroxylamine rearrangement product.

The solid was then subjected to hydrolysis by aqueous sodium carbonate for about 1 hour at 60°C. Another solid was obtained which displayed an nmr spectrum in dimethylsulfoxide-d_6 with absorptions at 2.17δ (s, 3), 2.48δ (s, 3), 7.40δ (m, 2), 8.05δ (d, 1), 9.25δ (broad s, 1), 10.10δ (broad s, 1).

Reduction of 3-Hydroxy-4-Nitrobenzoic Acid and Isolation of 3-Acetoxy-4-Acetamidobenzoic Acid

Into an Erlenmeyer flask, 18.3 g (0.1 mole) 3-hydroxy-4-nitrobenzoic acid (Aldrich) was introduced together with 25 g of granulated tin. Concentrated hydrochloric acid, 45 ml, was added to the mixture which was being stirred with a magnetic stirrer. The reaction became exothermic, and the 3-hydroxy-4-nitrobenzoic acid dissolved. The solution was cooled to room temperature and was made basic (pH 9). The tin salts which precipitated were removed by vacuum filtration. The filtrate was shaken with 50 ml of ether containing an excess of acetic anhydride. The two-phase mixture was then neutralized with dilute hydrochloric acid utilizing a pH meter. The two phases were separated and the aqueous layer was discarded. The ether was removed from the upper layer by flash evaporation. The acetic acid and unreacted acetic anhydride were removed by means of a vacuum pump, leaving a light yellow solid, melting point 216.6-219.0°C. The nmr spectrum in acetone-d_6 showed only one compound with absorptions at 2.13δ

(s, 3), 2.32δ (s, 3), 7.54δ (m, 2), 8.43δ (d, 1), 8.87δ (broad s, 1). The next step in the sequence was to prepare the acylchloride of the reduction product.

Synthesis of N-(4-Acetyl-2-Hydroxy)ethanamide from 3-Acetoxy-4-Acetamidobenzoic Acid

The reduction product, 1.49 g (0.0063 mole), was added to 150 ml of dry benzene. To this solution was added 0.71 ml (0.010 mole) of thionyl chloride, and the mixture was then refluxed for 10 hours or until all the reduction product dissolved. The benzene and thionyl chloride were removed on a flash evaporator to leave a white solid; yield 1.51 g (94 percent of theoretical); melting point 203-208.0°C, nmr (acetone-d_6), 2.13δ (s, 3), 2.32δ (s, 3), 7.75-7.92δ (m, 2), 8.315δ (d, J = 9Hz, 1), 8.88δ (broad s, 1).

The procedure of Biggerstaff and Wilds (41) was used to prepare dimethylcadmium. The acid chloride, 1.238 g (0.009 mole), dissolved in benzene was added to a solution of dimethylcadmium prepared from 0.0157 mole of magnesium, 1.4 g (0.0078 mole) of cadmium chloride, excess methyl bromide in dry ether. The mixture was stirred and heated under reflux for 3 hours and allowed to stir at room temperature overnight. When excess cold dilute hydrochloric acid was added, a yellow solid precipitated. This was then subjected to sodium hydroxide hydrolysis for 30 minutes. After being neutralized, a brown solid precipitated. This precipitate showed an nmr which was mainly one compound but which was contaminated. The solid, 0.21 g (12 percent of theoretical) was recrystallized from acetone to yield a yellow solid, melting point 220.0-224.0°C;

nmr dimethylsulfoxide-d_6 2.17δ (s, 3), 2.48δ (s, 3), 7.40δ (m, 2), 8.05δ (d, 1), 9.25δ (broad s, 2).

The nmr spectrum of the above was superimposable with the nmr spectrum of the hydrolyzed rearrangement product of O-trifluoroacetyl-N-acetyl-N-(4-acetylphenyl)hydroxylamine. The melting points were also the same.

Kinetics of the Rearrangement of O-Trifluoroacetyl-N-Acetyl-N-(4-Acetylphenyl)hydroxylamine

O-trifluoroacetyl-N-acetyl-N-(4-acetylphenyl)hydroxylamine was prepared with 0.193 g (0.001 mole) N-acetyl-N-(4-acetylphenyl)hydroxylamine and 0.13 ml (0.001 mole) trifluoroacetic anhydride (more anhydride had to be added because trifluoroacetic anhydride hydrolyzes readily) in p-dioxane as has already been described.

After removal, in vacuo, of the excess trifluoroacetic acid, anhydride, and p-dioxane, 0.7 ml trifluoroacetic acid (Eastman Red Label) was added to the syrup. Only enough p-dioxane was added to make the solution less viscous (0.2 ml). The sample was placed in an nmr tube, and a scan of the methyl region was taken. A very clean spectrum of the two methyl absorptions was obtained. After capping, the tube was placed in a constant temperature water bath at 49.5°±0.2°C. Over a period of a week, the sample was removed at different intervals and integrated over the methyl region. During this time period, the absorptions at 2.18δ and 2.56δ decreased and two new absorptions at 2.70δ and 2.54δ increased. The plot obtained was nearly a straight line. A rate constant at 49.5°±0.2°C was $k = 3 \times 10^{-6}$ sec^{-1} and a half life $t_{1/2} = 51.2$ hours.

Preparation of 4-Nitrophenylmethylsulfide

According to the procedure of Hanson (42), a stirred solution of 1500 ml of methanol and 15 g sodium hydroxide in 420 ml water was heated to near boiling while 78.70 g (0.50 mole) p-chloronitrobenzene was added. Once the p-chloronitrobenzene was dissolved, the solution was saturated with hydrogen sulfide. At this time the solution turned dark red. The red solution was heated on a steam bath for 0.5 hours. Sodium hydroxide, 15 g, in 420 ml water was added and then stirred and heated for another 0.5 hour.

After the solution had been cooled to room temperature, 71.0 g (0.50 mole) of methyl iodide in 50 ml ethanol was added, and the solution turned yellow. Another 15 minute heating period was employed. As the solution cooled, yellow crystals formed. The alcoholic solution was diluted to twice its volumne with water. On further cooling, more solid crystallized. This was filtered and recrystallized from an acetic acid: water mixture. The light yellow solid, 39.6 g (46.0 percent of theoretical) melted at 69.0-70°C [lit. (43) 72°C].

Synthesis of 4-Nitrophenyl Methylsulfone

This procedure of A. Palmerantz and R. Connor (44) was used. The 4-nitrophenyl methylsulfide, 7.3 g (0.043 mole), was dissolved in 100 ml of a 50:50 acetic acid and acetic anhydride mixture, placed in a round bottom flask, and stirred with a magnetic stirrer. The mixture was then cooled in a salt-ice slurry to 0°C, and 10.8 ml of 30 percent hydrogen peroxide was added dropwise by means of a pressure-compensating funnel. The charge was

stirred during the addition and for an additional 3 days at room temperature. Manganese dioxide was used to destroy the excess hydrogen peroxide (the sulfone had precipitated over the 3-day period). The solution was diluted to twice its volume with water. Filtering the mixture produced a grayish solid (contaminated with manganese dioxide) weighing 7.5 g (85 percent of theoretical); melting point 139.0-140.6 [lit. (43) 142.5°C]. The sulfone was recrystallized from ethanol to give a melting point 141.5-142.8°C.

Synthesis of N-(4-Methanesulfonylphenyl)hydroxylamine

4-Nitrophenyl methylsulfone, 12.35 g (0.0615 mole) was dissolved in 200 ml of acetone (Reagent). To this mixture was added 3.6 g ammonium chloride in 54 ml water. The mixture was stirred with a mechanical stirrer in a 3-neck flask fitted with a nitrogen inlet into the solution. Zinc dust, 9.8 g, was added slowly to the solution while the mixture was vigorously stirred. The temperature rose only 4 or 5°C; however, when all the zinc was added, the mixture was heated to 60°C and maintained for 30 minutes. After 48 hours (beneficial for higher yields) of stirring the solution under nitrogen, the solid residue was filtered by vacuum filtration. The filtrate was subjected to a flash evaporator to remove the water and acetone. Since ammonium chloride is soluble in the water, the solid residue was extracted with hot p-dioxane and filtered. The crystalline hydroxylamine was recrystallized from a hot solution in ether very well by adding carbon tetrachloride until it turned cloudy, then cooling. The hydroxylamine crystallized in small plates, melting point 154.6-157.0°C; yield 6.20 g (54.3 percent of theoretical).

The nmr spectrum did not clearly show the N-H and N-OH region in acetonitrile-d_3, but in p-dioxane the two protons appeared nicely, Figure 19. In acetonitrile-d_3, the absorptions were at 2.96δ (s, 3), 6.50δ (broad s, 1), 7.19δ (d of t, 2), 7.69δ (d of t, 3).

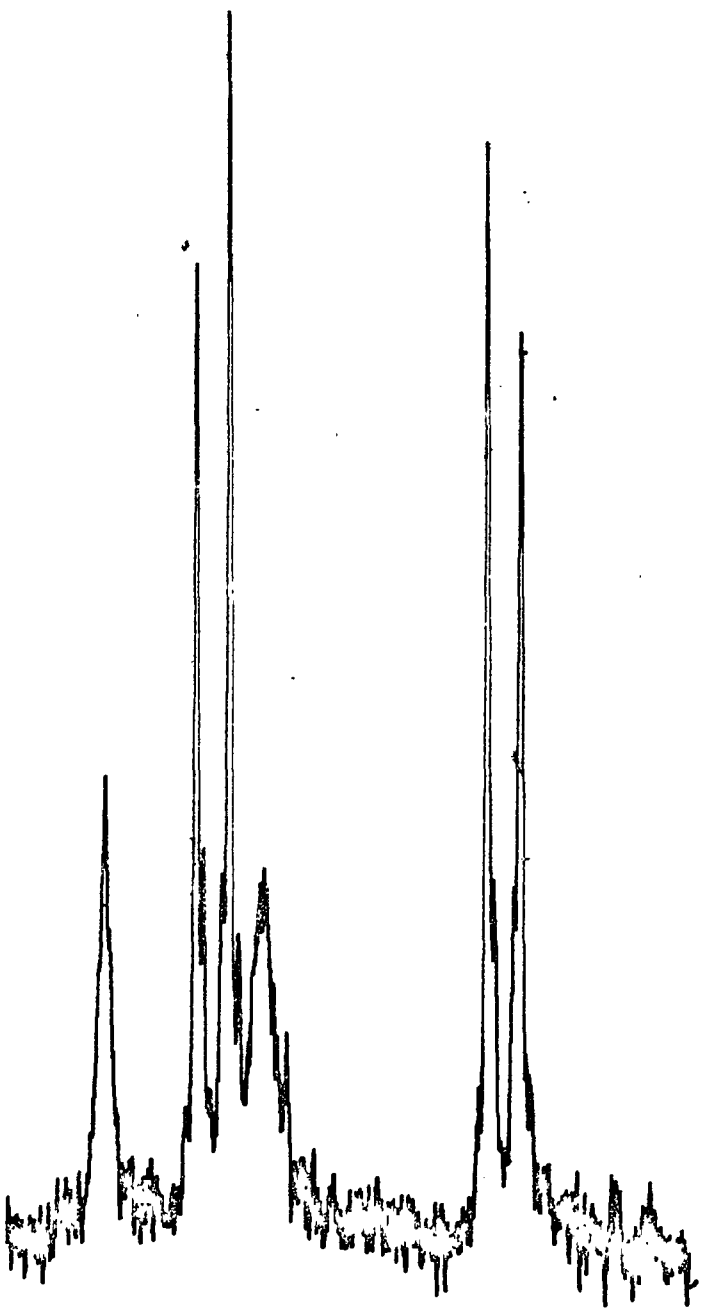
Synthesis of N-Acetyl-N-(4-Methanesulfonylphenyl)hydroxylamine

It was found that if the ammonium chloride was not removed from the hydroxylamine, acetylation would not be complete; therefore, the hydroxylamine was washed with large quantities of water before it was reacted with acetic anhydride. The hydroxylamine was vacuum dried after being washed.

To 125 ml of acetonitrile (Reagent), 3.00 g (0.015 mole), N-(4-methanesulfonylphenyl)hydroxylamine was added with stirring. Acetic anhydride (99.9 percent), 1.63 g (0.015 mole), was added, and the charge was stirred for 120 hours at room temperature. At the end of the stirring period, the acetonitrile, acetic acid, and excess acetic anhydride were removed in vacuo. The residue was recrystallized from acetonitrile to give a compound, 0.78 g (22.7 percent of theoretical), melting point 163.6-165.3°C, nmr (acetone-d_6) 2.31δ (s, 3), 3.07δ (s, 3), 7.92δ (m, AA'BB', 4), 9.84δ (s, 1); Anal. Calc'd. for $C_9H_{11}NSO_4$: C, 47.17; H, 4.83. Found: C, 47.41; H. 4.61.

There was a by-product, diacetylated hydroxylamine, that contaminated the acetylated hydroxylamine. The recrystallization from acetonitrile caused a low yield because of the high solubility of the acetylated hydroxylamine. It was found that ethanol was a better recrystallization solvent. A melting point 165.2-165.6°C was obtained upon recrystallization from ethanol.

Figure 19. NMR Spectrum (p-dioxane) of the Aromatic Region of N-(4-Methanesulfonylphenyl)hydroxylamine Depicting the N-H and O-H Absorptions which were not Present in the Spectrum Obtained in Acetonitrile-d_3.

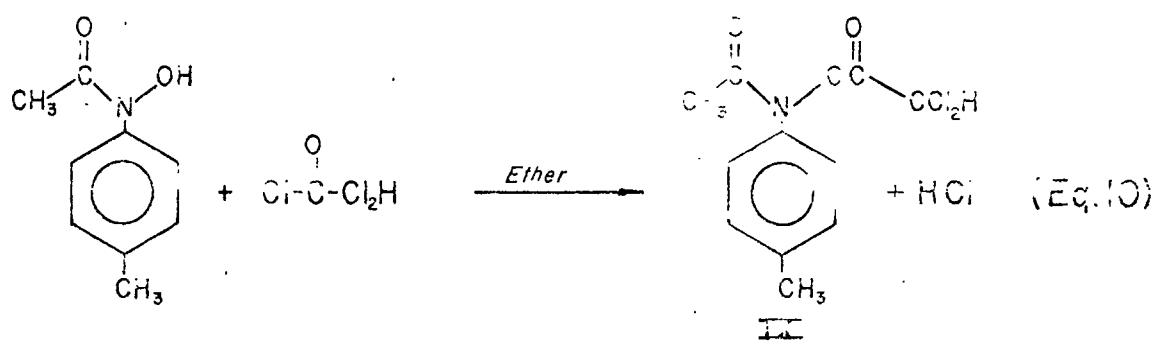


DISCUSSION OF RESULTS

DISCUSSION OF RESULTS

Reaction of Dichloroacetyl Chloride with N-Acetyl-N-(4-Methylphenyl)-hydroxylamine and Related Experiments

When the reaction between dichloroacetyl chloride and N-acetyl-N-(4-methylphenyl)hydroxylamine was carried out either with or without one equivalent of triethylamine, a yellowish solid which decomposed during the course of about an hour at room temperature was isolated. The nmr and ir spectra agreed well with the expected structure O-dichloroacetyl-N-acetyl-N-(4-methylphenyl)hydroxylamine (IX) (Eq. 10). N-H and

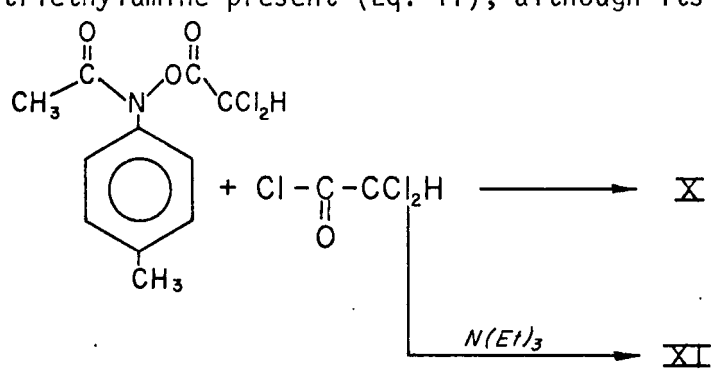


IX

O-H absorptions had disappeared, and the aromatic region of the nmr spectrum remained an AA'BB' pattern. The yellowish solid rearranged to form a single compound in a reaction which could easily be monitored by nmr. Kinetically, the reaction was fairly rapid with a half life of 31.5 min ($k = 3.6 \times 10^{-4}$ sec^{-1}) at probe temperature, 38°C. The nmr spectrum of the product, Figure 5, shows an absorption attributable to N-H as does the infrared spectrum, an indication that the rearrangement took the expected course. The two different methyl absorptions, the

single dichloroacetyl absorption and the complex absorptions in the aromatic region are all in good agreement with the nmr absorptions predicted for the dichloroacetate of N-(4-methyl-2-hydroxyphenyl)ethanamide. The rearrangement product was hydrolyzed spontaneously upon addition of water to its solution in acetone. A white precipitate formed immediately which was isolated and identified as N-(4-methyl-2-hydroxyphenyl)ethanamide by comparison with an authentic sample. However, it transpired that these data, which initially seemed to define the structure of the rearrangement product, were in fact ambiguous.

When the rearrangement of IX was carried out for the first time, the only product isolated was the product just described. When triethylamine was added, again a rearranged product was isolated, but it was not the same compound that had been isolated from rearrangement of IX without triethylamine present (Eq. 11), although its spectral features were similar



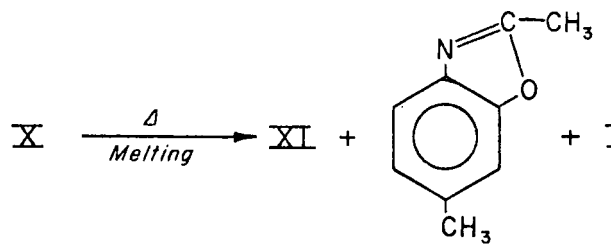
(Eq. 11)

in all respects to those of the other rearrangement product. Each of the two reactions produced only one product quantitatively (by nmr), but each product was distinctly different. That the two products are different is obvious from a detailed comparison of their nmr spectra and

and melting points. The nmr spectrum of X (Figure 5) showed two methyl groups of distinctly different chemical shifts (2.06δ and 2.30δ). The nmr spectrum of XI (Figure 6) shows two methyl groups which possess identical chemical shifts (2.32δ). The dichloroacetyl proton in each is definitely in a different chemical environment (6.17δ in X and 6.00δ in XI). The aromatic and N-H regions are very similar in each spectrum. The melting points of the two substances are separated by 8°C. Analytical analyses show they are isomers of one another. Upon hydrolysis XI gives exactly the same product as X, N-(4-methyl-2-hydroxyphenyl)ethanamide, but the hydrolysis of XI is much slower than that of X. All the data for each compound could support the structure of the dichloroacetate of N-(4-methyl-2-hydroxyphenyl)ethanamide, but both obviously cannot have this same structure.

To determine if X could be converted to XI, or vice versa, X was recrystallized from carbon tetrachloride and a few drops of triethylamine. X was converted to XI quantitatively with triethylamine, but after the addition of hydrogen chloride gas to XI no X was detectable.

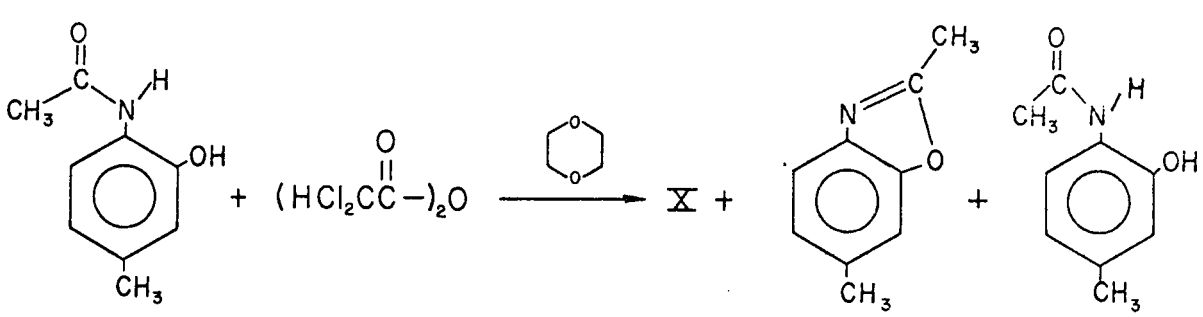
A most interesting chemical fact was learned when X and XI were heated to their melting points while under vacuum and allowed to cool. The nmr spectrum of X after this treatment showed that 67 percent had been converted to two other products: 40 percent XI and 27 percent (based on amount of dichloroacetic acid produced) 2,6-dimethylbenzoxazole (Eq. 12) (identified by comparing nmr spectra of an authentic sample). When XI was heated to melting while under vacuum, there was no change whatsoever in the nmr spectrum (Eq. 13).



(Eq. 12)

(Eq. 13)

In an attempt to determine which compound could be assigned the structure of the expected 2-position ester, dichloroacetic anhydride was allowed to react with N-(4-methyl-2-hydroxyphenyl)ethanamide in p-dioxane. The nmr spectrum of the reaction mixture showed small amounts of 2,6-dimethylbenzoxazole and of starting material. The rest of the mixture was mainly X which was definitely identified by nmr after isolation from p-dioxane (Eq. 14).



(Eq. 14)

With the knowledge of the above reaction, N-(4-methyl-2-hydroxyphenyl)-ethanamide-d_3 was prepared from deuteroacetic anhydride and the 4-methyl-2-hydroxyaniline. The product was allowed to react with dichloroacetic anhydride as was the protio compound above. The isolation of the deuterated material (X-d_3) showed, in the nmr, only one methyl absorption at 2.30δ. The absorption at 2.06δ was no longer present. This product was recrystallized from carbon tetrachloride in the presence of triethylamine to produce XI-d_3. Where the nmr spectrum showed one absorption at 2.32δ in X, displaying six protons, the nmr spectrum of XI-d_3 showed an absorption at 2.32δ worth only three hydrogens.

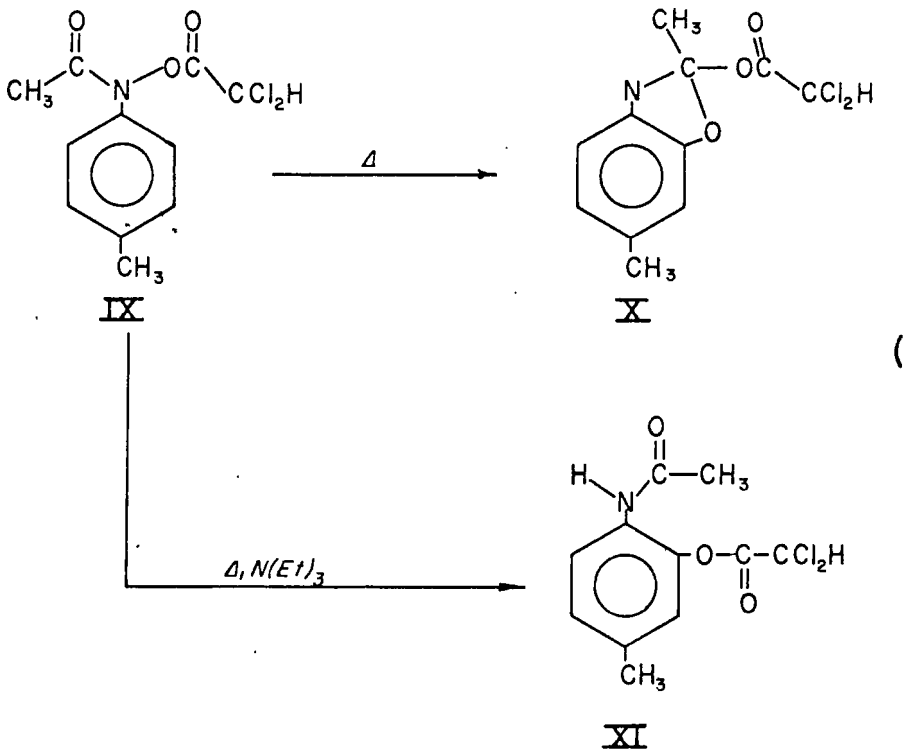
In the attempt to duplicate some conditions for kinetics used by Dunn (45), an interesting phenomenon was detected. A solution of IX in dichloroacetic acid showed many absorptions in the methyl and aromatic regions of the nmr spectrum as soon after mixing as the spectrum could be measured. These appear to arise from a complex mixture of rearranged products. However, in a solution of 25 percent IX in 80 percent dichloroacetic acid 20 percent ether, the reaction was slowed sufficiently for the nmr to be used to see IX disappear; furthermore, the product appeared to be X, exclusively. In an attempt to try to establish what absorptions are due to what compounds in the complex mixture mentioned above, the nmr spectra of X and XI were measured in dichloroacetic acid. The nmr of XI (Figure 14) is essentially the same as it is in deuterochloroform (Figure 6), whereas X shows a somewhat different spectrum (Figure 13) than it does in deuterochloroform (Figure 5). The nmr spectrum of the rearrangement product X in dichloroacetic acid is viewed in Figure 13.

It showed 4 absorptions (at a ratio of 1:2:2:1) in the methyl region where there were only two in deuterochloroform. Also, the compound X-d_3 (Figure 15) was run in dichloroacetic acid, and the only difference in its spectrum and that of X are the two absorptions missing due to the acetyl amide or some group emanating from the acetyl amide function.

In order to test the possibility that a reversible protonation of X occurs in dichloroacetic acid, but that XI is not protonated in dichloroacetic acid, the attempt was made to recover each from solution in dichloroacetic acid. The dichloroacetic acid was removed quantitatively from a solution of XI by subjecting the solution to high vacuum (~10^{-5} mm) for 1 hour. The recovered solid showed an nmr spectrum in deuterochloroform identical with that obtained before it was dissolved in dichloroacetic acid.

In contrast, the nmr spectrum measured in deuterochloroform of the residue left after vacuum evaporation of the solution of X in dichloroacetic acid for 8 hours still showed dichloroacetic acid as well as the downfield methyl absorption which is absent from a spectrum of a freshly prepared solution of X in deuterochloroform. However, the relative intensity of this peak, compared to that of the upfield methyl, was smaller than that in dichloroacetic acid solution, and it appeared to diminish with increasing length of evacuation.

On the basis of the data that have been given so far, we assign the structures for X and XI shown in Eq. 15, and present arguments in favor of these assignments. A strong indication of the structure of X was the production of 21 percent of the 2,6-dimethylbenzoxazole when X was



(Eq. 15)

heated at 120°C. The elimination of dichloroacetic acid from the ortho-amide anhydride structure assigned to X to produce the benzoxazole is analogous to the pyrolysis of aliphatic acetates to produce alkenes. It is difficult to imagine benzoxazole formation from the open ester structure assigned to XI under comparable conditions, and XI is, in fact, stable to heating at 120°C.*

The fact that the two compounds, X and XI, hydrolyze at different rates indicates that the two compounds are definitely different in structure.

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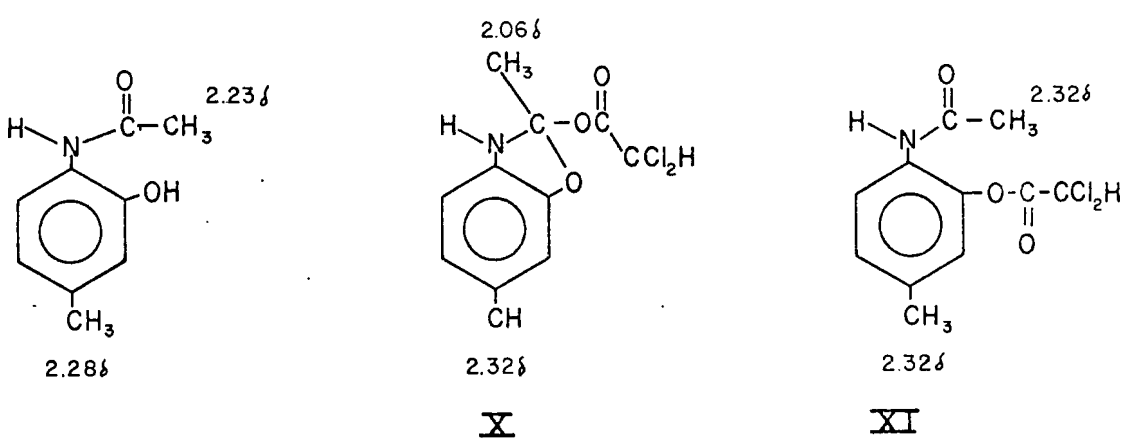
*When the 2,6-dimethylbenzoxazole was prepared by heating at least a 3 mole excess of acetic anhydride with N-(4-methyl-2-hydroxyphenyl)ethanamide, the temperature for the transformation was at least 250°C. Below this temperature, only the acetate ester was isolated.

However, there is no outstanding feature which allows one to predict which one would hydrolyze with greater ease. Intuitively, one might expect the less stable isomer to hydrolyze more rapidly, and the fact that X is hydrolyzed more easily than is XI is in agreement with the cyclic ester structure assigned to X.

The absorption of the amide methyl group in N-(4-methyl-2-hydroxyphenyl)ethanamide in deuterochloroform appears at 2.23δ, Figure 20. This



X XI

FIGURE 20

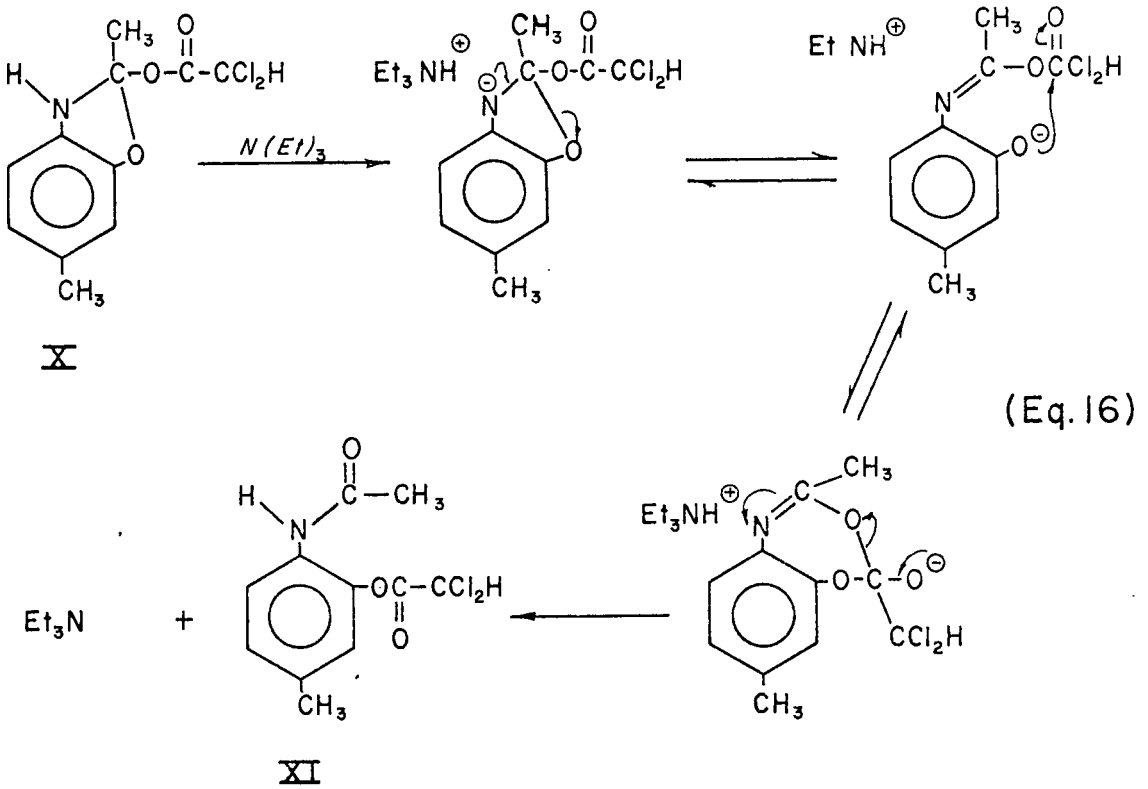
value is very close to that of the ester structure assigned to XI. After the formation of the dichloroacetyl ester, the absorption would be expected to move even further downfield, which it does (2.32δ in XI). In the ester of X, the upfield methyl group absorbs at 2.06δ which is somewhat removed from 2.32δ.

An interesting fact about the nmr spectrum of X in dichloroacetic acid is the formation of another compound that has been ascribed as the protonation of the nitrogen atom which should be more basic than the nitrogen atom of the structure assigned to X. The reasonsing for this prediction is that the lone pair electrons on nitrogen cannot be delocalized over the carboxyl function as they can in the open ester XI. This same phenomenon is associated with acetanilide and aniline. Aniline is a much stronger base than is acetanilide because acetanilide has two contribution delocalization structures, and aniline has only one. These structures for acetanilide are where the lone pair electrons on nitrogen are delocalized to the carboxylate function and the second one is where the lone pair electrons are delocalized into the ring. Aniline has only the delocalization structure where the lone pair electrons are delocalized into the ring.

The only questionable aspect of these assignments lies in the infrared spectra of each of the compounds. Both compounds show what was at first thought to be two different carbonyl absorptions in each spectra (X, 1703 cm^{-1}, 1790 cm^{-1}, and X, 1718 cm^{-1}, 1783 cm^{-1}). Two carbonyl absorptions for X would not be predicted from elementary considerations if the structure is correctly assigned. Dichloroacetyl functions do produce more than one band in the infrared due to a steric association of the halogens to the carboxyl oxygen (46), and this probably accounts for the result in this case. Fermi resonance can also produce doubling of carbonyl absorptions (47), but no obvious relationship of overtones exists in this compound which would be expected to produce Fermi resonance.

The quantitative, irreversible transformation of X to XI in the presence of a trace of triethylamine, but not in acid, and the failure of XI to be reconverted to X in acid established that XI is thermodynamically favored. However, X is the kinetic product in acid, and its isomerization to XI required a basic catalyst.

On the basis of these considerations, we propose that the conversion of X to XI can be formulated in Eq. 16. Most of the added stability

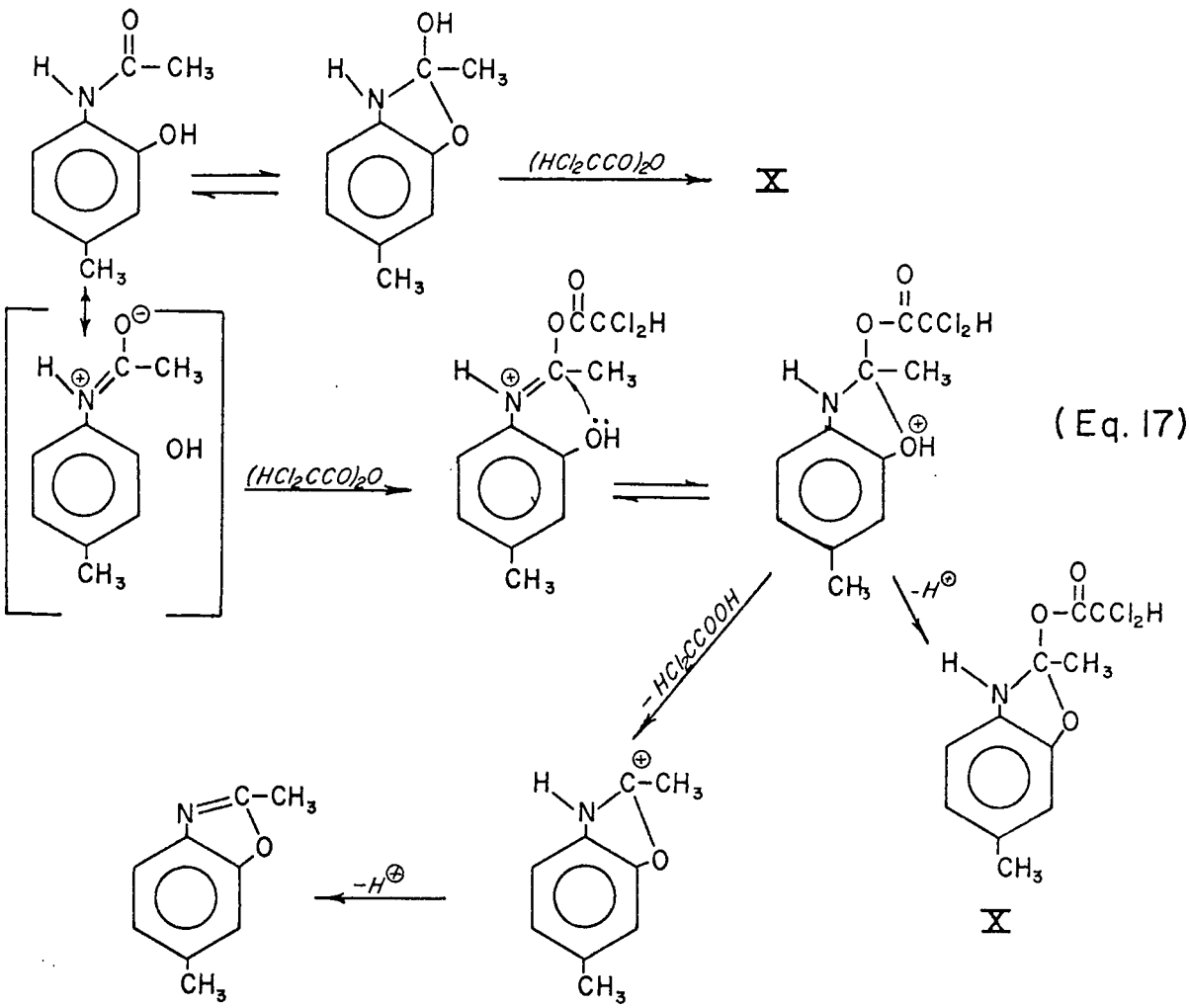


X XI (Eq. 16)

derives from resonance stabilization of the amide function by delocalization of electrons into the carbonyl function.

The reaction of dichloroacetic anhydride with N-(4-methyl-2-hydroxyphenyl)ethanamide to produce X and a small amount of 2,6-dimethylbenzoxazole

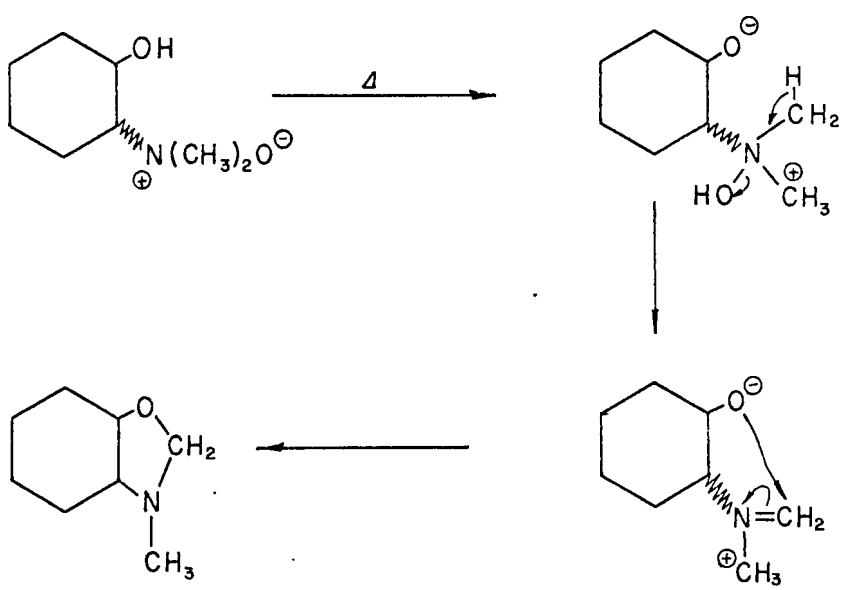
can be rationalized as seen in Eq. 17. The delocalization structure pictured is a very important one in amides. An alternate intermediate could



(Eq. 17)

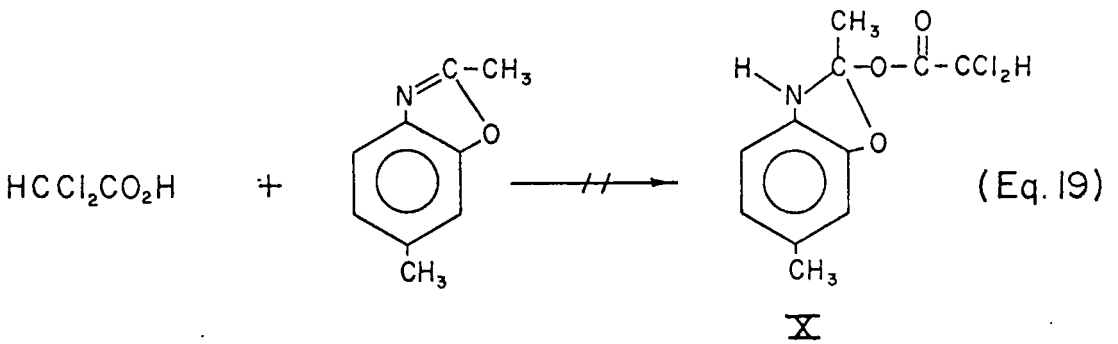
be the production of the cyclic phenolamide in equilibrium with the open structure of the 2-hydroxyamide. Also, the 2,6-dimethylbenzoxazole was always present in measureable amounts. The internal addition of oxygen

to the $\rangle C{=}N$ to produce protonated X is reminiscent of the pathway proposed for the Polonovski rearrangement by Cope, Ciganek, and Lazar (48) (Eq. 18).



(Eq. 18)

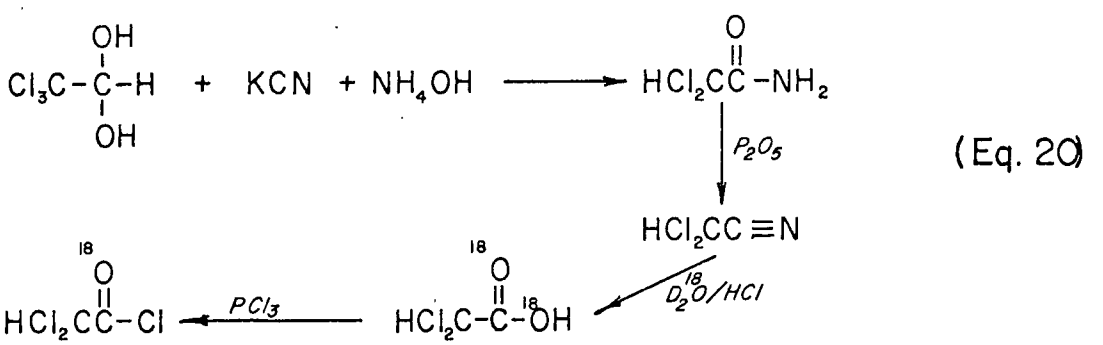
If the structure assigned to X and XI are correct, it can readily be seen that the rearrangement of IX to X without intervention of XI must proceed along a highly unusual pathway. Since X could conceivable be formed by addition of the elements of dichloroacetic acid to the heterocyclic ring of 2,6-dimethylbenzoxazole, that compound was prepared and subjected to the conditions of the rearrangement reaction. It remained unchanged over a period of several times the duration required for complete formation of X from IX (Eq. 19). None of the other routes which occurred to the present research group as possibilities could be considered to have close analogs, and an investigation of the mechanism was



(Eq. 19)

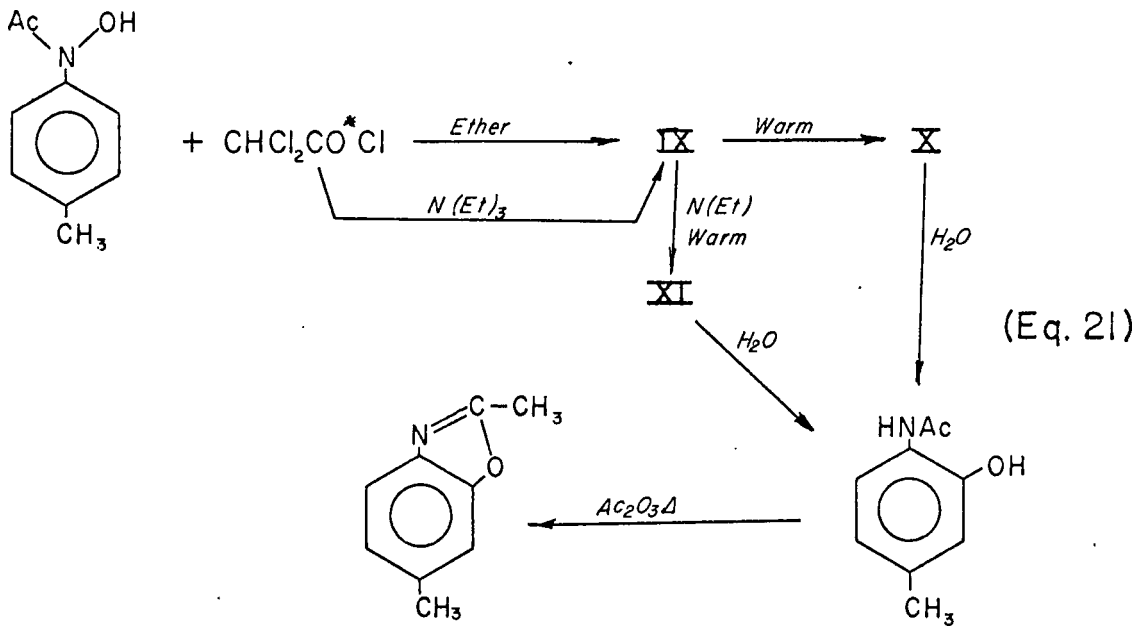
clearly of interest. It appeared that the single most powerful tool would be isotopic tracer studies of reaction products, and to this end much of the effort described herein was devoted.

The carboxyl function of dichloroacetyl chloride was labelled with oxygen-18 by synthesis from water enriched to 1.31 atom percent excess O^{18} by the route outlined in Eq. 20.



(Eq. 20)

The following reaction sequence (Eq. 21) was then employed to follow the labelled oxygen atom through the rearrangement. Samples of each appropriate compound were pyrolyzed to carbon dioxide in the presence of mercuric chloride (26) and the carbon dioxide was collected and measured



in an isotope ratio mass spectrometer. The results of the isotopic analyses are given in Table I.

Since the reaction was carried out on the neat compound, the labelling data cannot be used as evidence for the intermolecularity or the intramolecularity of the rearrangement. However, the results do indicate that exactly half of the oxygen label derived from the carbonyl group of the hydroxamic ester becomes phenolic oxygen in X. The simplest explanation for this result is that fragmentation--either the anion or the radical--which can recombine through either oxygen with the ortho ring carbon. Since no decarboxylation occurs, the free radical is improbable; hence, the dichloroacetate anion, probably as part of a tight ion pair, seems to be implicated as an intermediate.

TABLE I

ISOTOPE RATIOS OF LABELLING EXPERIMENT OF THE THERMAL REARRANGEMENT OF O-DICHLOROACETYL-^{18}O-N-ACETYL-N-(4-METHYLPHENYL)HYDROXYLAMINE

Compound	Average ^{18}O Atom Percent Excess over Natural Abundance	Average Atom Percent Excess ^{18}O Multiplied by Number of O Atoms in Molecule
Dichloroacetyl Chloride-^{18}O	1.350	1.350
X	0.450	1.326
XI	0.442	1.326
Hydrolysis Product from X	0.335	0.670
Hydrolysis Product from XI	0.432[a]	0.864[a]
2,6-Dimethylbenzoxazole from hydrolysis product from X	0.670	0.670

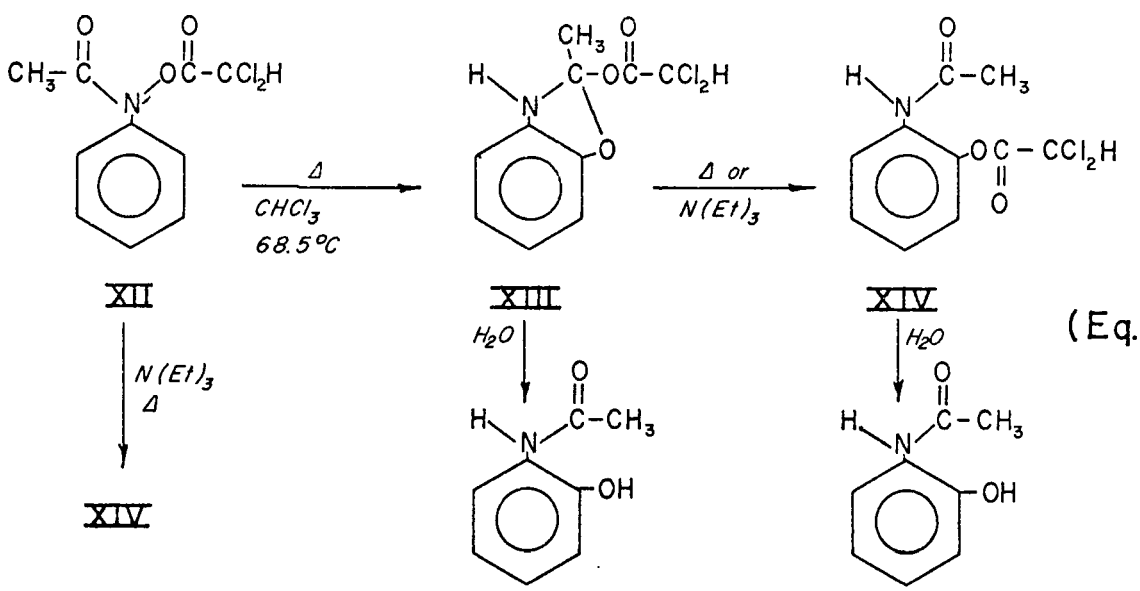
[a]The large increase in this number vis-a-vis the product from XI is probably due to contamination by XI, which was difficult to hydrolyze in the neutral solution. Reexamination of the mp supported this view.

Numerically, an identical figure could result from the mixing of two pathways which produce specific labelling, but the coincidence of equal distribution of the oxygen label is most unlikely.

The Reinvestigation of the Reaction of Dichloroacetyl Chloride and N-Acetyl-N-Phenylhydroxylamine

After the discovery of the new rearrangements of IX, it was most important to determine how many other derivatives undergo the same reaction pathway to products such as X and XI. Therefore, the thermal rearrangement of O-dichloroacetyl-N-acetyl-N-phenylhydroxylamine was investigated in closer detail than that reported by Dunn (49).

As the data were compiled, it was evident that analogous to those which accompany rearrangement of IX, phenomena occur in the rearrangement of O-dichloroacetyl-N-acetyl-N-phenylhydroxylamine. Outlined in Eq. 22



(Eq. 22)

are some of the results of the rearrangement. Again, two different rearrangement products were isolated, depending on whether triethylamine was present or not. However, at no time was there any trace of the para isomer detected during a kinetics run on the nmr spectrometer. The rate of the rearrangement of XII to XIII is much slower than is the rate of rearrangement of IX to X. A half life of 335 min ($k = 3.4 \times 10^{-5}$ sec^{-1}) was obtained at 68.5°±0.05°C. About 16 hours were necessary for complete reaction.

The two products hydrolyzed at completely different rates. Compound XIII hydrolyzed much more easily than XIV but not as readily as X.

NMR spectra of the two products in deuterochloroform are different (Figures 6 and 8). The shifts of the acetyl methyl groups and the dichloroacetyl proton in going from XIII and XIV (2.11δ, 6.17δ and 2.33δ, 6.01δ, respectively) are nearly the same as those in X and XI (2.06δ, 6.17δ and 2.32δ, 6.00δ, respectively). The aromatic regions are distinguishably different from each other. The nmr spectra of XIII and XIV in dichloroacetic acid exhibit the same phenomena (see Figures 9 and 10 for spectra) as did X and XI in dichloroacetic acid. However, there is a difference in the composition of the protonated form and the neutral form; the neutral to protonated form is 2.6:1. This decrease in the protonated form over that of the 4-methyl compound could be the lower basicity of the nitrogen in XII because of the decrease in electron donating ability on going from methyl to hydrogen in the para position.

Using the same labelling techniques, results were derived which varied considerably from those obtained from the 4-methyl compound (Table II).

TABLE II

ISOTOPE RATIOS OF LABELLING EXPERIMENT OF THE THERMAL REARRANGEMENT OF O-DICHLOROACETYL-N-ACETYL-N-PHENYLHYDROXYLAMINE IN CHLOROFORM

Compound	Results Containing 1.350 Average ^{18}O Atom % Excess over Natural Abundance in the Dichloroacetyl Chloride	Results Containing 1.194 Average ^{18}O Atom % Excess over Natural Abundance in the Dichloroacetyl Chloride	Average Atom Percent Excess ^{18}O, Multiplied by Number of O Atoms in Molecule
XIII	---	0.393	1.179
XIV	0.436	0.402	1.206
Hydrolysis product XIII	---	0.428	0.856
Hydrolysis product XIV	0.448	0.415	0.830
2-Methylbenzoxazole from the amidophenol containing 0.428 atom % excess	---	1.082	

Since the benzoxazole product has nearly all of the label originally in the hydroxamic ester carbonyl, the majority of the reaction has proceeded without production of a symmetric dichloroacetate ion.

Again, some discrepancy exists between the values obtained for the labelled phenolamides and for the benzoxazole. Probably impurities which were difficult to remove contaminated the amides.

A reinvestigation of Dunn's work on XII-^{18}O in dichloroacetic acid was carried out at this point in the research. The same procedure and concentrations as Dunn used were employed. The only difference in procedure was that in this work, the rearrangement was carried out at room temperature (~23°C), whereas Dunn carried out the reaction at 40.0°C. Dunn's preliminary results suggested that both the ortho and para isomers contained the whole label, as expected for an intromolecular ionic rearrangement. A striking difference between the rearrangement of XII-^{18}O in chloroform and the rearrangement in dichloroacetic acid is that there was no para isomer detected among the thermal products, whereas Dunn reported 25 percent of the para isomer among the rearrangement products from acid solution.

Table III depicts the results for the rearrangement of XII-^{18}O in isotopically normal dichloroacetic acid. After five days, the acid solution was poured over ice and neutralized with sodium carbonate to a pH of 7.0. The two isomers were then separated by sublimation.

The ortho isomer isolated from the dichloroacetic acid after neutralization has been shown not to be the same compound that the rearrangement produced initially, which is present in solution before neutralization (compare Figures 11 adn 12). The ortho isomer produced on rearrangement

TABLE III

REARRANGEMENT OF XV-^{18}O IN DICHLOROACETIC ACID

Compound	Average ^{18}O Atom Percent Excess over Natural Abundance	Average Atom Percent Excess ^{18}O Multiplied by Number of O Atoms in Molecule
Dichloroacetyl chloride-^{18}O	1.350	1.350
Ortho isomer ester	0.370	1.110
Para isomer ester	0.203	0.609
Hydrolysis product of ortho isomer ester	0.137[a] 0.136[a]	0.274 0.272
2-Methylbenzoxazole from hydrolysis product containing 0.137 atom % excess ^{18}O	0.280	

[a]These results are from two different reactions.

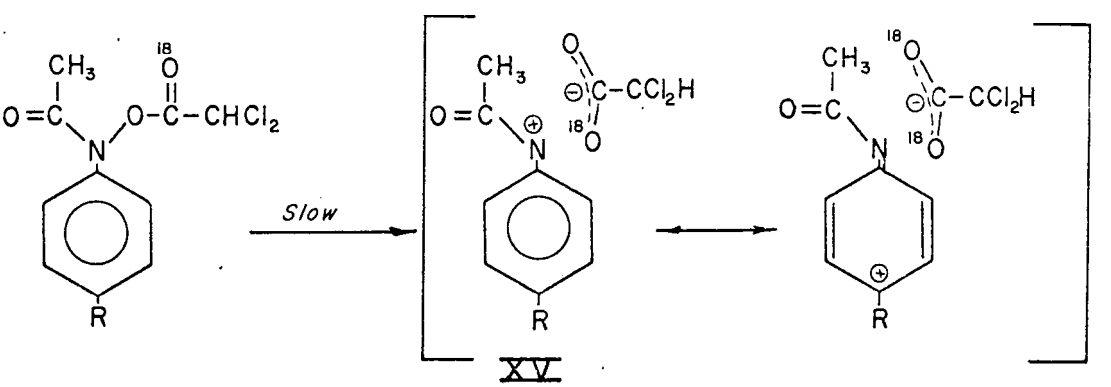
in dichloroacetic acid before neutralization has been shown to be the same product as the thermal rearrangement product, XIII, of XII (compare Figures 11 and 9). The ortho product obtained after neutralization of one dichloroacetic acid is the same as that from the thermal rearrangement of XII in Triethylamine (Compare Figures 12 and 10; and in deuterochloroform, Figure 7).

A definite loss of isotope has occurred in both the ortho and para esters (theoretically they should contain 0.450 atom percent excess). The ortho ester has lost 18 percent of the original label. On the other hand, the para isomer has lost 55 percent of the original quantity of isotope. Data from the 2-methylbenzoxazole also show that all of the label is attached to the ring; therefore, none is in the acetyl carbonyl oxygen. Only 21 percent of the original carbonyl label found its way into the ortho position; this value contrasts sharply with the value of 41 percent predicted for scrambling of the oxygens in the 82 percent of the product. Since the above data were thought to be a major clue to understanding of the reaction sequence, an experiment from a different approach was carried out in an attempt to corroborate the value measured for the degree of intermolecularity of the ortho and the para rearrangement. A means was sought whereby it was possible, independent of the fate of the ^{18}O label, to measure how much dichloroacetate from the solvent replaced the dichloroacetoxy group of XII in forming the products. O-dichloroacetyl-d_1-N-acetyl-N-phenylhydroxylamine was prepared from dichloroacetyl chloride-d_1 (>99.5 atom percent-d_1) and N-acetyl-N-phenylhydroxylamine and rearranged in isotopically normal dichloroacetic acid.

The resulting data support the data obtained from the oxygen-18 experiment in detail. In the deuterium experiment, 18 percent of the deuterium label was replaced by protio label in the ortho isomer by exchanging dichloroacetyl functions; for the para isomer, 60 percent of the label exchanged with protio material.

No single reaction pathway which the author or his colleagues have been able to devise will accommodate all of the experimental observations. A network of pathways which are rather evenly balanced in their energy requirements and which have certain features in common does serve to systematize the observations.

Since the rates of all of these reactions are strongly accelerated by electron-releasing substituents on the ring and by electron-withdrawing substituents in the leaving group, a high degree of charge separation in the transition state is indicated. This process is indicated in Eq. 23.

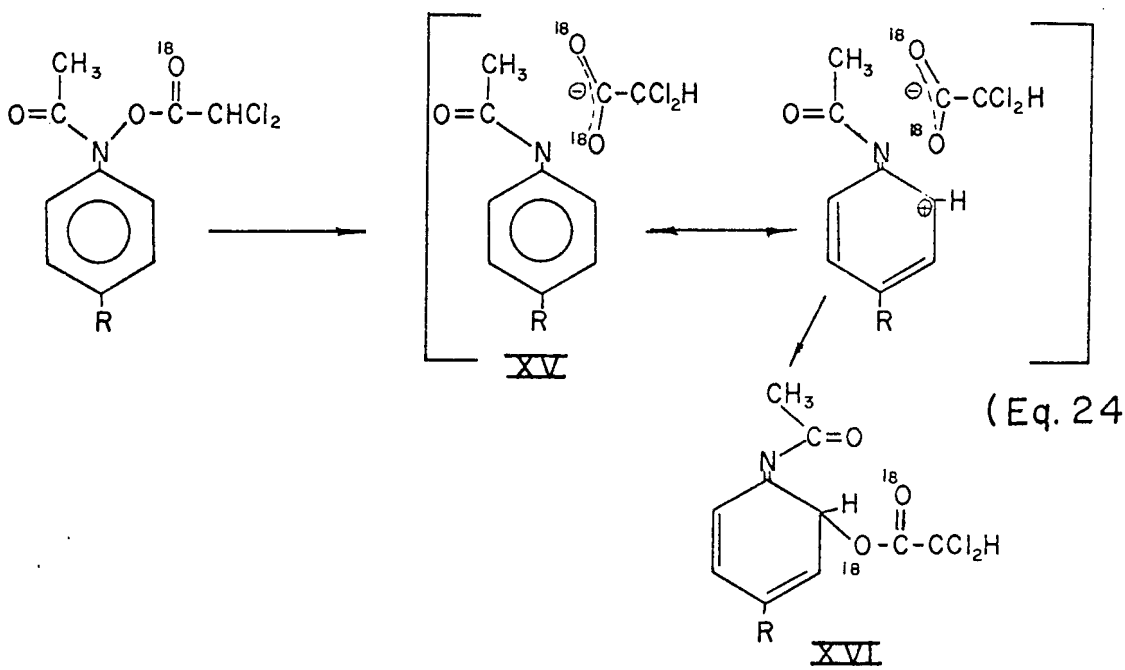


(Eq. 23)

In solvents of low ion-solvating ability, the ion pair collapses more rapidly than rotation of the dichloroacetate ion occurs, preventing exchange of the two oxygen atoms. Such a process is indistinguishable by

the isotopic tracer technique from a concerted, cyclic process, but concerted reactions are characterized by much smaller electronic effects than those found in this work (50).

Under the proper conditions, the ion pair (XV) may be separated sufficiently for the dichloroacetate ion to rotate before formation of the bond between oxygen and the ortho carbon atom. In this case, half of the label appears in the ortho position of the phenol amide (Eq. 24).



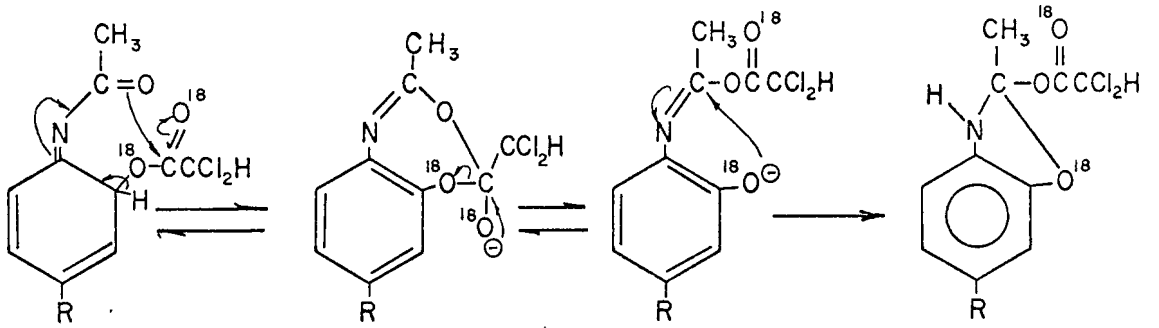
XV

(Eq. 24)

XVI

Each of these sequences leads to the same intermediate (XVI), although with different labelling consequences, as has been shown. The requirement that neither XI nor the benzoxazole be an intermediate in the formation of X necessitates postulation that XVI undergoes rearrangement to X faster than it tautomerizes to XI. A possible, although unprecendented, course for this might be the sequence shown in Eq. 25.

In solvents which solvate ions well, the ion pair may be solvated and solvent separated. This apparently happens to a considerable extent

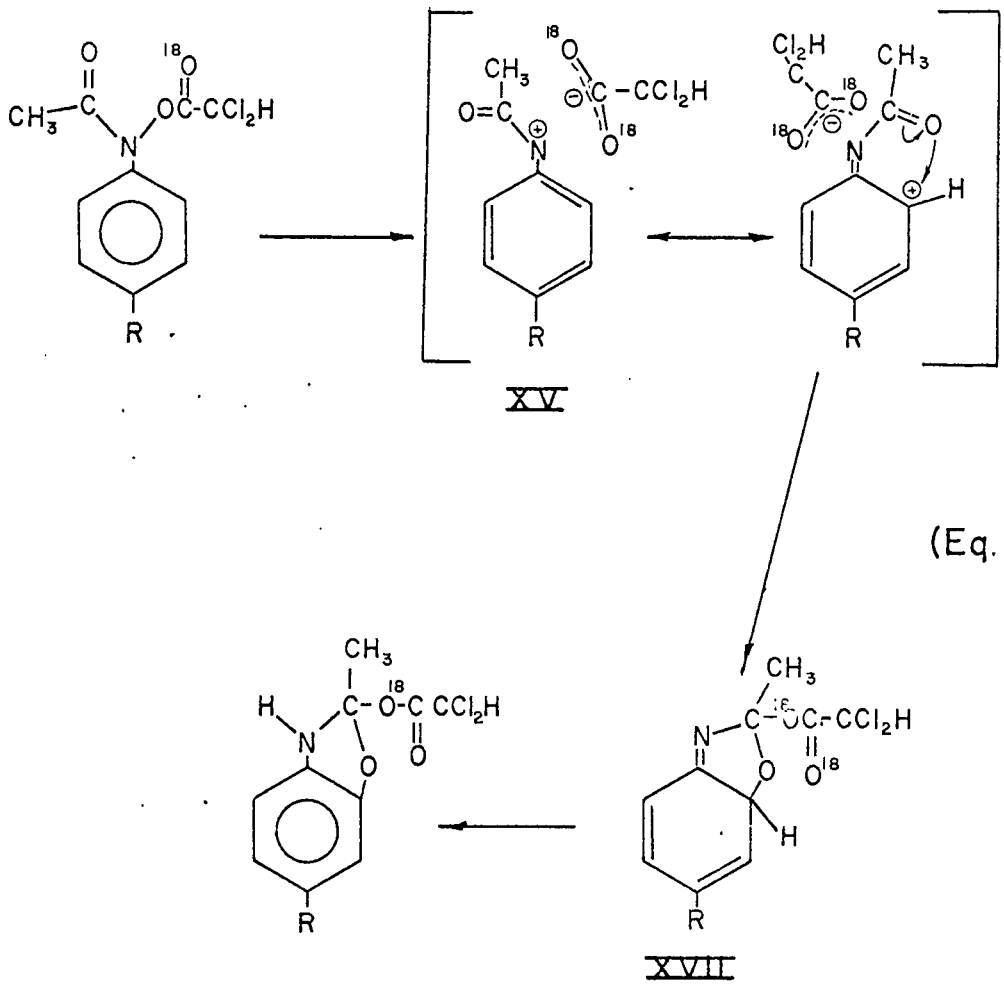


XVI

(Eq. 25)

in dichloroacetic acid. Under these conditions, though, a new process appears, since the cation has available to it the electrocyclic process of ring closure shown in Eq. 26.

In this sequence the unlabelled carbonyl oxygen of the acetamide function becomes attached to the ring in the ortho position. This intermediate can readily capture dichloroacetate ion and undergo proton transfer to complete the formation of X or XIII. As was the case in Eq. 25, timing of the proton transfers relative to nucleophile capture is critical, since loss of a proton from the ortho carbon in XVII would form the benzoxazole which has been shown to be inert under the reaction conditions.



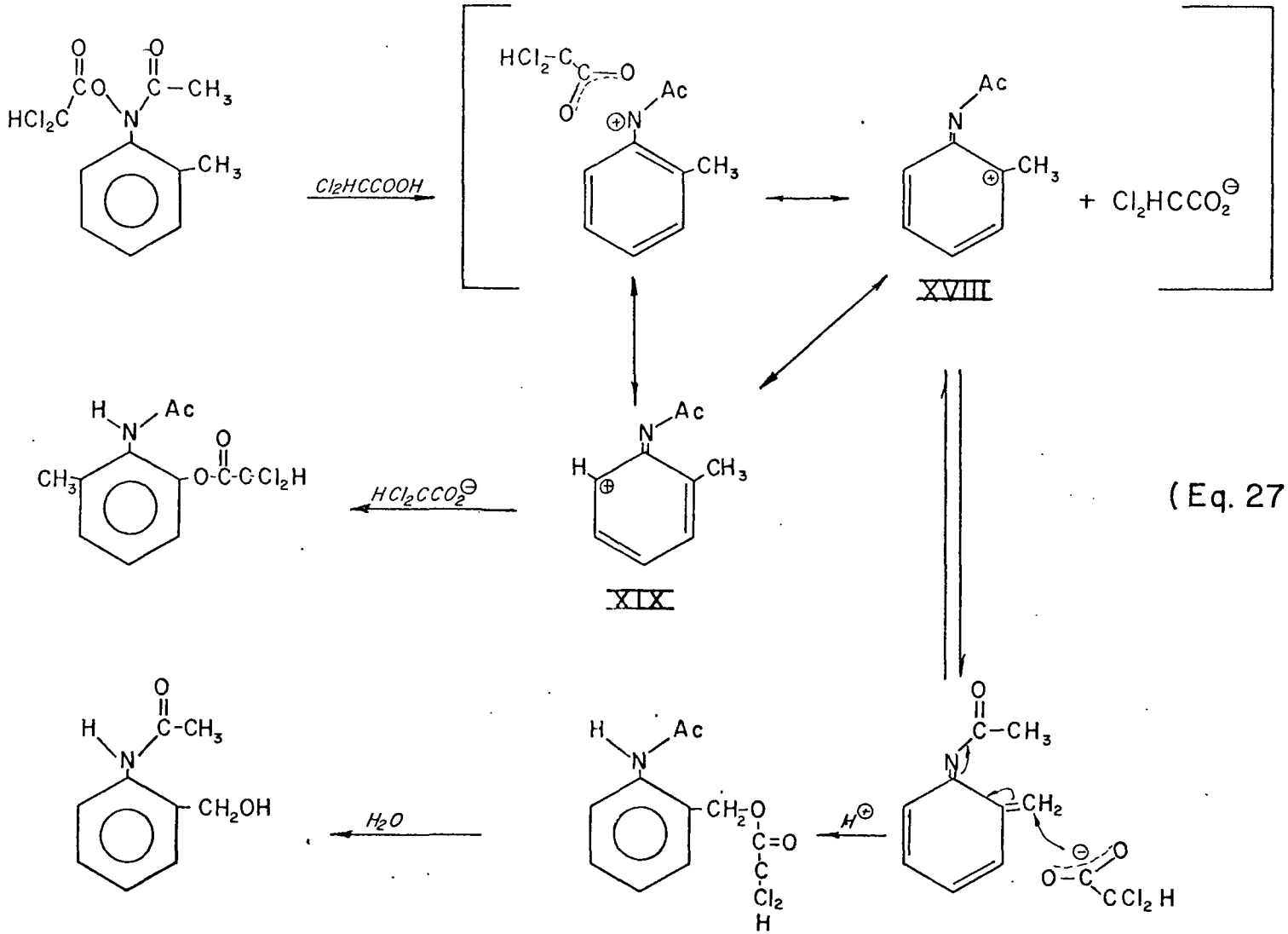
XV

(Eq. 26)

XVII

Reaction of Dichloroacetyl Chloride with N-Acetyl-N-(2-Methylphenyl)-hydroxylamine and Subsequent Rearrangement

An attempt was made to determine if any N-2-benzylol ethanamide was a product in this reaction. By analogy to the results of Oae (24) on the production of 2-pyridyl methanol from 2-picoline N-oxide (Eq. 26), a conceivable pathway in the O-dichloroacetyl-N-acetyl-N-(2-methylphenyl)-hydroxylamine rearrangement could also be imagined (Eq. 27). However, since no N-2-benzylol ethanamide was detected in the rearrangement, the



(Eq. 27)

above scheme does not appear to lend much support to the sequence in Eq. 27. The contribution of XVIII is probably very small as compared to XIX. One would think, however, structure XVIII should be a good contributing structure, energetically; especially being a tertiary allyl carbonium ion.

The rearrangement produced a number of products which were not identified. A more extensive study of this reaction sequence could possibly find evidence of contribution from structure XVIII.

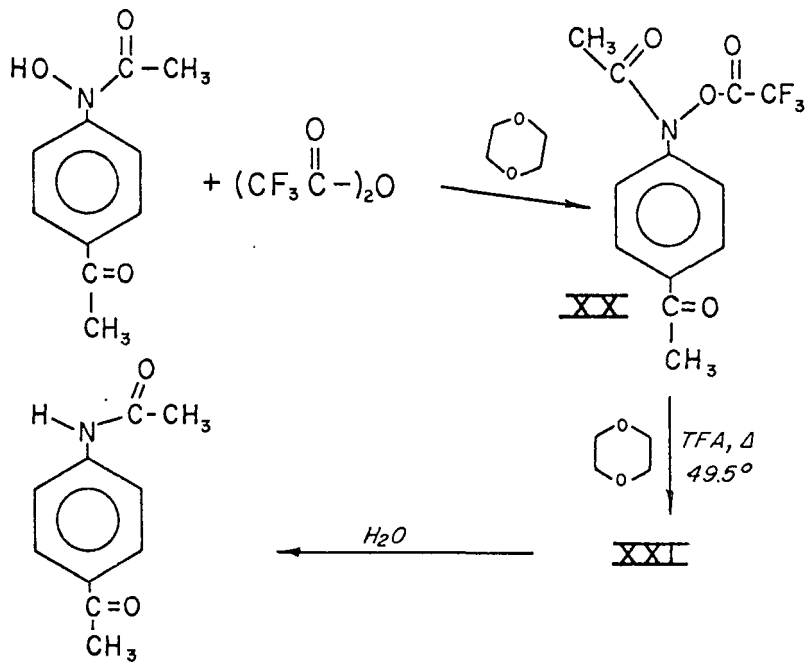
Reaction of Trifluoroacetic Anhydride with N-Acetyl-N-(4-Acetylphenyl)-hydroxylamine and Subsequent Rearrangement

Kinetically this rearrangement in trifluoroacetic acid appeared to be much faster than that of the dichloroacetyl ester. At 49.5°C, the trifluoroacetic ester, XX, rearranged in agreement with first-order kinetics ($t_{1/2}$ = 51.2 hours, k = 3 x 10^{-6} sec^{-1}).

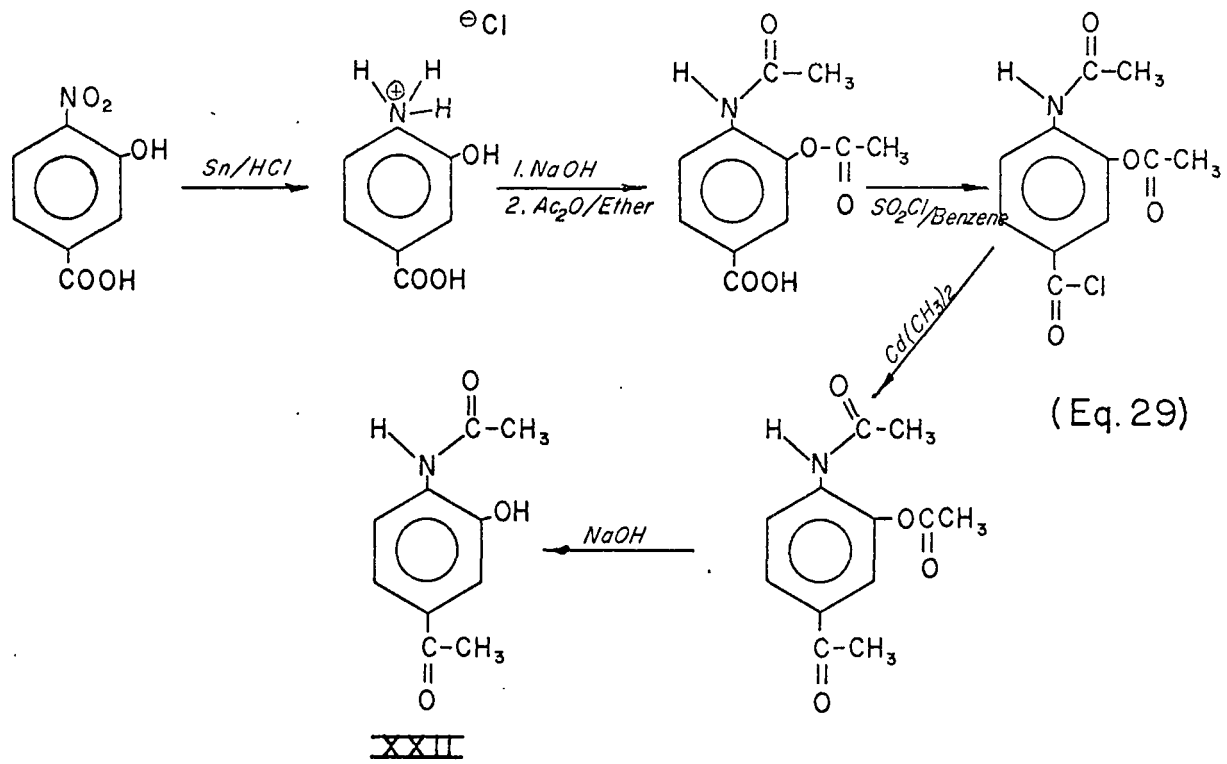
The rearrangement product after hydrolysis was shown to be XXII by comparing nmr and melting points of the product with an authentic sample (Eq. 28). A preparation of the suspected rearrangement-hydrolysis product, N-(4-acetyl-2-hydroxyphenyl)ethanamide, was carried out following the scheme in Eq. 29.

Reaction of Dichloroacetyl Chloride with N-Acetyl-N-(4-Acetylphenyl)-hydroxylamine and Subsequent Rearrangement

Rearrangement of O-dichloroacetyl-N-acetyl-N-(4-acetylphenyl)-hydroxylamine was shown to be very much slower in dichloroacetic acid than that of the parent compound. The temperature needed was 100°C for rearrangement at a convenient rate. Following the reaction by nmr was found to be difficult because hydrolysis products were formed and di-


HO
N
C-CH3
C=O
CH3
+ (CF3C-)2O
CH3
O-C-CF3
XX
TFA, Δ
49.5°
XXI
H2O

(Eq. 28)


NO2
OH
COOH
Sn/HCl
⊖Cl
1. NaOH
2. Ac2O/Ether
SO2Cl/Benzene
OC-CH3
C-Cl
Cd(CH3)2
NaOH
C-CH3
XXII

(Eq. 29)

chloroacetic acid decomposes at the temperature used. No hydrolysis of the isolated ester was attempted, but the ester produced was found to be a rearrangement product having characteristics of the same substitution as the products from the 4-methyl compound and the rearranged trifluoroacetic ester of N-acetyl-N-(4-acetylphenyl)hydroxylamine.

CONCLUSION

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The novel rearrangement of IX to X has been shown to afford the kinetic controlled product of the rearrangement. Irreversible conversion of X to XI in the presence of triethylamine establishes that XI is the thermodynamic product. Also, the same phenomenon occurs with XII. All of these transformations depict a very delicate balance in mechanistic pathways. There is a hint here that, under given conditions, all the pathways can be observed. These pathways may be altered by the addition of a different ion solvating solvent system. At the other end of the spectrum of pathways, the ring substituent has been shown to control the mechanism. The rates of rearrangement of the different compounds with para substituents other than hydrogen have been shown to be highly dependent on the electronic effects of these substituents. Electron-withdrawing substituents show the rearrangement drastically, and electron-donating substituents increase the rate.

With the ^{18}O labelling scheme, it has been determined that there is a definite changeover in pathways from having a 4-methyl substituent to having a 4-H substituent. All of these facts indicate the large sensitivity to electronic effects. With the addition of dichloroacetic acid, the balance between pathways is altered to the degree that no one distinct pathway is observed. The process in which the isotopically normal oxygen becomes attached to the ortho carbon, over and above a scrambling of the carboxyl and hydroxylamine oxygens, is not quite clear. Further studies are going to be employed which should clarify the true pathway. These

pathways, it is felt, are extensively sensitive to the solvating properties of the solvent which alters the transition state or intermediates.

Rearrangement of O-substituted and ring-substituted N-acetyl-N-phenylhydroxylamines appears to be a close analog to the benzidine rearrangement depending upon the conditions of the rearrangement and the substituents present. These systems could even be as complex or even more complex than the benzidine rearrangement. All of these studies of these systems certainly point out many variable processes by which each compound may proceed.

RECOMMENDATIONS FOR FURTHER WORK

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Rearrangement of IX in dichloroacetic acid needs to be investigated to determine the products and the mechanistic pathway by employing the same oxygen-18 labelling scheme used here. Also, the same deuterium labelling of the dichloroacetyl function needs to be employed in the rearrangement of IX in dichloroacetic acid. Since a complex mixture of products is present from this reaction, it is not unlikely that more new compounds will be found.

Reactions of the type reported in this research which have been reported elsewhere should be reinvestigated to determine if the same phenomena occur in the presence of triethylamine. There are many derivatives of phenylhydroxylamine that have been reported in which triethylamine or a tertiary base has been employed.

The rearrangement of the O-trifluoroacetyl-N-acetyl-N-(4-acetylphenyl)-hydroxylamine thermally and in acid solution needs further investigation. With electron-withdrawing substituents present in the 4-position, a decrease in the rearrangement products should be noticed.

Since the rearrangement of the product of the reaction between dichloroacetyl chloride and N-acetyl-N-(2-methylphenyl)hydroxylamine occurred without producing any N-2-benzylol ethanamide, it would be safe to reinvestigate the rearrangement. The reaction was complicated by numerous products, and the reaction was not carried out with great scrutiny.

Another reaction to be investigated is the rearrangement of derivatives of 2,4,6-trimethylphenylhydroxylamine which would be a better sequence for investigating the 2-pyridinemethanol type products.

A most important segment of the work should be to repeat the labelling scheme of the rearrangement of O-dichloroacetyl-N-acetyl-N-phenylhydroxylamine in varying concentrations of dichloroacetic acid. Varying the concentrations may show a spectrum of label distributions.

The only way to determine if Lwowski and Tisue's work does agree with the work presented here is to repeat the rearrangement reported by them.

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