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In recent years nuclear reduction of pyrimidines by catalytic hydrogenation in acid media has been considered a possible synthetic method for the preparation of substituted tetrahydropyrimidines. This technique has the advantage of simplicity over the older condensation methods and is limited only by the preparation of the appropriately substituted pyrimidines. During an investigation of the scope of this nuclear reduction technique, Aft and Christensen found that the tetrahydropyrimidines could not be isolated in pure form as the hydrochloride salts, as shown by deviations between the corresponding actual and theoretical chloride percentages. These surprising results suggested that the nuclear reduction reaction in acid media was not straightforward, contrary to the results of earlier studies, but yield mixtures as shown by paper chromatographic analysis consisting of degradation products along with the desired tetrahydropyrimidine.

In order to get a better understanding of the nature of this nuclear reduction reaction, an investigation was undertaken to identify the corresponding degradation products of one of these nuclear reductions. 4-Amino-2,6-dichloropyrimidine was chosen for the investigation since it was found by Aft and Christensen to undergo considerable degradation during nuclear reduction. 4-Amino-2,6-dichloropyrimidine upon nuclear reduction would be expected to yield 4-amino-3,4,5,6-tetrahydropyrimidine which upon decomposition could form low molecular weight products such as methylamine, propylamine, ammonia, propanol, etc. which should be easily detected by gas-chromatography.

Upon basification of the isolated hydrochloride salts of the reduction products basic material was collected which was found to contain five components by gas chromatography, four of which were identified as ammonia, n-propylamine, propionaldehyde, and n-propanol. Gas chromatographic analysis of the reaction mixture before isolation of the hydrochloride salts showed that carbon dioxide, but not propionaldehyde and n-propanol, was among the reduction products. It was, therefore, concluded that propionaldehyde and n-propanol must have been formed by basic hydrolysis of the tetrahydropyrimidine set free during basification of the hydrochloride salts, and a mechanism was postulated for the formation of ammonia, n-propylamine, and carbon dioxide during nuclear reduction of 4-amino-2,6-dichloropyrimidine. According to this mechanism, 4-amino-3,4,5,6-tetrahydropyrimidine undergoes

hydrolysis in the aqueous acid media yielding the degradation products, accounting for both the low yields and impure nature of this tetrahydropyrimidine obtainable from the nuclear reduction reaction.

AN INVESTIGATION OF THE REDUCTION PRODUCTS OF 4-AMINO-2,6-DICHLOROPYRIMIDINE BY CATALYTIC HYDROGENATION

by

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AN INVESTIGATION OF THE REDUCTION PRODUCTS OF 4-AMINO-2,6-DICHLOROPYRIMIDINE BY CATALYTIC HYDROGENATION

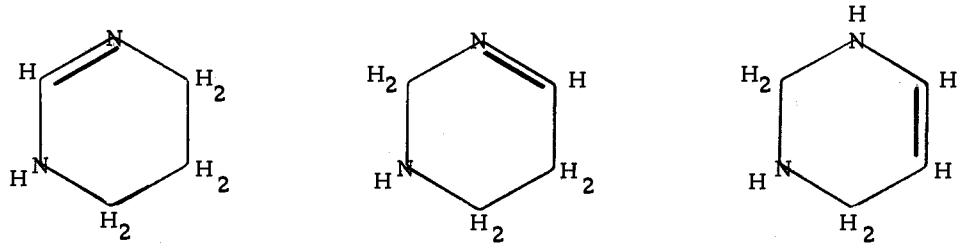
INTRODUCTION

In recent years the nuclear reduction of pyrimidines by catalytic hydrogenation in acid media has received attention as a procedure particularly for the preparation of the 4-, 5-, and 6-substituted tetrahydropyrimidines (1, p. 2170), since the synthesis of these derivatives by conventional methods is limited by the difficulty of obtaining the appropriately substituted propanediamines or propanediols; catalytic nuclear reduction offers, therefore, an advantage over the condensation methods in view of the availability of the more easily obtained substituted pyrimidines. However, more information must be uncovered regarding the effect of conditions on the nuclear reductions before this procedure can be made a useful method for the preparation of tetrahydropyrimidines.

Nuclear reduction of a pyrimidine may yield a dihydro-, a tetrahydro-, or a hexahydropyrimidine, depending upon the type and conditions of reduction (6, p. 430). When nuclear reduction occurs by catalytic hydrogenation, a tetrahydropyrimidine is more likely to be formed than either a dihydro- or a hexahydropyrimidine (6, p. 450). Furthermore, the tetrahydropyrimidine that is formed is found in most cases to be a 3,4,5,6,-(1,4,5,6-) tetrahydropyrimidine (I) rather than a 2,3,4,5-(1,2,5,6-)tetrahydropyrimidine (II) or a 1,2,3,4-(1,2,3,6-)tetrahydropyrimidine (III) which could also be formed (6, p. 430). These isomeric tetrahydropyrimidines are

shown in Figure 1.

FIGURE 1. Isomeric Tetrahydropyrimidines



The earliest nuclear reductions of pyrimidines that are reported in the literature are those of Tafel and Weinschenk (29, p. 3378). These investigators reported a smooth reduction of 4-methyluracil yielding 1, 4, 5, 6-tetrahydro-4-methyl-2-hydroxypyrimidine, and a large amount of an unknown isomer of tetramethylenediamine via electrolysis in 50 percent sulfuric acid solution. Upon completion of the electrolysis which was carried out with a lead cathode in a closed vessel, the acid solution was neutralized with barium hydroxide, filtered and distilled yielding a brown semi-solid. The tetrahydropyrimidine was isolated from the distillate by extraction with chloroform from which it was obtained by crystallization. Barbituric acid, in a like manner, was reduced to 1, 4, 5, 6-tetrahydro-2-hydroxypyrimidine and 4, 5-dihydro-2, 6-dihydroxypyrimidine (30, p. 3384).

In 1901 Tafel and Reindl (32, p. 3286) reported the isolation of 1, 4, 5, 6-tetrahydro-2-hydroxypyrimidine and 4, 5-dihydro-2, 6-dihydroxypyrimidine from the reduction products of dialuric acid. Both uramil and alloxan yielded 4, 5-dihydro-2-hydroxypyrimidine upon electrolysis in sulfuric acid solution (32, p. 3287-3288).

Six years later Tafel and Thompson (31, p. 4489) isolated 1, 4, 5, 6-tetrahydro-5-ethyl-2-hydroxypyrimidine and 4, 5-dihydro-5-ethyl-2, 6-dihydroxypyrimidine from an electrolytic reduction of 5-ethyl-barbituric acid under the same conditions as used in the earlier reductions. Very few examples of electrolytic reductions of pyrimidines appear in the literature thereafter.

Classical chemical reducint agents do not ordinarily affect the pyrimidine nucleus (13, p. 314). However, a few scattered reports of such nuclear reductions are found in the literature. In 1889 E. Von Meyer (27, p. 262) reported the reduction of 2, 4-diethyl-5-methyl-6-aminopyrimidine with sodium amalgam in acid media yielding ammonia, propionaldehyde, and an oil of unknown constitution; no reduced pyrimidine was isolated.

Other classical reducing agents were tried, but the results were essentially the same. Alfred Byk (9, p. 1917) reported the reduction of 4-methylpyrimidine with metallic sodium and alcohol. The only products which he isolated were formaldehyde and the hydrochloride salt of 1, 3-diaminobutane.

This same behavior was observed four years later when Einhorn and Diesbach (12, p. 4902) reduced 2-thio-5, 5-diethyl-barbituric acid with sodium amalgam in aqueous media under the

same conditions Von Meyer had used earlier. This reduction was reported to yield hydrogen sulfide, formic acid, 5, 5-diethyl-4, 6-dioxy-2, 5-dihydropyrimidine, small amounts of diethylmalonic acid and diethylmalonamide, and a substance that was named bisdiethylmalonyltetraminoethane. The formation of diethylmalonic acid and diethylmalonamide was rationalized as a result of hydrolysis of a reduced pyrimidine that was initially formed in the reduction.

Similarly Johnson and Joyce (20, p. 1389; 21, p. 1855) observed the formation of aliphatic diamines during the reduction of various thiopyrimidines with metallic sodium and alcohol. The reduction products were isolated as the hydrochloride salts by distilling the reaction mixture directly into hydrochloric acid solution. Formation of an aliphatic diamine in these reductions gives further evidence that hydrogenolysis of a reduced pyrimidine must have occurred.

In 1956 Marshall (26, p. 3696) reported the successful reduction of several pyrimidines with lithium aluminum hydride. 5-Ethyl-5-phenylbarbituric acid was refluxed with lithium aluminum hydride in dry ether for 44 hours. The mixture was hydrolyzed in a basic solution and then extracted with ethyl alcohol. Upon crystallation from alcohol a 44 percent yield of 5-ethyl-2-hydroxy-5-phenylpyrimidine was obtained. In a like manner, but in lower yields, both 5-ethyl-6-phenyl-2-thiouracil and 6-phenyl-2-thiouracil were reduced to the corresponding 1, 2, 3, 4-tetrahydro-2-pyrimidinethiones. This property of lithium aluminum hydride has found some use in nuclear reductions for reducing the pyrimidine nucleus in the

presence of a mercapto group (13, p. 314).

Although a few tetrahydropyrimidines have been prepared by electrolytic and chemical methods, these procedures as indicated above often give mixtures of products and consequently low yields. Furthermore, these methods are not specific anough for the tetrahydropyrimidines to be of any preparative value while procedures based on catalytic nuclear reduction have been found to be more practical. For these reasons, electrolytic and chemical methods have not been subjected to more study.

The first catalytic nuclear reduction of a pyrimidine described in the literature was that of 3-β-(D-ribofuranosido)-uracil to 3-β-(D-ribofuranosido)-2, 6-diketohexahydropyrimidine by Levene and La Forge (24, p. 619) in 1912. A 20-1 ratio of the substituted uracil and colloidal palladium was allowed to react for 30 to 35 hours. After the reaction was complete, acetic acid was added to precipitate the colloidal palladium and the solution concentrated to a syrup. Upon addition of hot alcohol a second syrup separated from which the product was obtained by crystallization.

In 1923 Brown and Johnson (7, p. 2704) extended this reduction to unsubstituted uracil and obtained quantitative yields. Uracil and gum arabic in a 2:1 ratio together with ten milliliters of a ten percent chloroplatinic acid solution was shaken under an atmosphere of hydrogen at 75°; after five or seven hours acetone was added to the reaction mixture to precipitate the colloidal platinum which was then removed. Upon evaporation of the aqueous solution approximately a 93 percent yield of

4, 5-dihydro-2, 6-dihydroxypyrimidine was obtained.

In an attempt to make the reduction even more quantitative, aqueous alkali in which uracil is more soluble was tried as solvent, thus, assuring a homogeneous reaction mixture. However, the reduction was found to be too slow to be of any practical value (7, p. 2702).

Similarly, cytosine was reduced with colloidal platinum and hydrogen under pressure to 4, 5-dihydro-2, 6-dihydroxypyrimidine (8, p. 704).

In 1945 a breakthrough was made when Davies and Piggott (11, p. 347) obtained a tetrahydropyrimidine upon reduction of 4-chloro-5-phenyl-pyrimidine with hydrogen using a palladium catalyst on a solid support. Approximately 2:1 ratios of 4-chloro-5-phenylpyrimidine and 1.2 percent palladized calcium carbonate was shaken with hydrogen in a methanolic media. After the reaction was completed the catalyst was removed and the solution evaporated to dryness, yielding 5-phenyltetrahydropyrimidine.

In 1951 Lythogoe and Rayner (25, p. 2324) reported the reduction, in a like manner, of 5-chloro-2-phenylpyrimidine with hydrogen using palladized barium sulfate to yield 1, 4, 5, 6-tetrahydro-2-phenylpyrimidine. The tetrahydropyrimidine isolated was shown to be identical to one that was prepared earlier by Aspinall (3, p. 2160) by a cyclization of monobenzoyltrimethylenediamine.

A study of these reduction reactions by Lythgoe and Rayner revealed that nuclear reduction is suppressed by the presence of base, resulting in either dehalogenation or partial solvolytic

displacement of an active chloro group (25, p. 2424). For example, dehalogenation to 2-phenylpyrimidine was observed when 5-chloro-2-phenylpyrimidine was shaken with hydrogen and palladized barium sulfate in the presence of base. Attempted reduction of 2, 5-dichloropyrimidine in a like manner yielded 5-chloro-2-hydroxypyrimidine. However, using an aqueous suspension of calcium carbonate reduction of 2, 5-dichloropyrimidine yielded pyrimidine in largest amount along with some 5-chloropyrimidine and some tetrahydropyrimidine (25, p. 2324).

In 1953 Kitani and Sodoeka (23) produced further evidence to show that the nuclear reduction was suppressed by the presence of base. Dehalogenation to 2-aminopyrimidine was observed when 2-amino-4, 6-dichloropyrimidine and palladized calcium carbonate in a ratio of 1:2 was shaken with hydrogen in the presence of base, while reduction in the absence of base yielded 2-aminohexahydropyrimidine.

A preparative procedure which was claimed to be straightforward and to give good yields of the tetrahydropyrimidine was reported by Smith and Christensen (28, p. 829-830) in 1955. According to their report, nuclear reduction of chloro substituted pyrimidines was accomplished by shaking 0.025 moles of the pyrimidine and 3000 milligrams of ten percent palladized charcoal in an ether-water solution with hydrogen under three atmospheres pressure and at room temperature. After reaction the catalyst was removed by filtration and the solution evaporated to dryness, yielding the tetrahydropyrimidine hydrochloride salt. Any excess

hydrochloric acid present was removed by addition of ethanol and evaporating again to dryness; the same procedure was repeated using dry benzene. Nuclear reduction of non-chloro substituted pyrimidines was accomplished in a like manner, with the exception that a slight excess of acid was added to the mixture of pyrimidine and catalyst before reduction. Since the reduction products were found to be extremely hydroscopic and difficult to isolate as the hydrochloride salts, benzoyl derivatives were prepared according to the Schotten-Baumann reaction and used for characterization purposes (28, p. 830).

In 1957 Henze and Winthrop (16, p. 2230-2232) reported the catalytic reduction of 2-propyl-4, 6-dichloropyrimidine to 2-propyltetrahydropyrimidine with a Raney nickel catalyst. 2-Propyl-4, 6-dichloropyrimidine in butanol was shaken with Raney nickel and allowed to stand at 0° for 12 hours. After the reaction was completed the catalyst was removed and the filtrate was hydrogenated for four more hours in the presence of freshly added Raney nickel and barium oxide. A heavy oil was obtained from the reaction mixture which solidified on standing; upon recrystallization, this material gave a 43 percent yield of 2-propyltetrahydropyrimidine hydrochloride. Only a few other reports (4, p. 526-528; 15, p. 487-488) appear in the literature whereby tetrahydropyrimidines were obtained by reduction with Raney nickel.

A later attempt to use the procedure of Smith and Christensen for the preparation of tetrahydropyrimidines was unsuccessful (1, 1. 2170). Accordingly, Aft and Christensen (1, p. 2170)

undertook a reinvestigation of the entire scope of catalytic nuclear reduction in acid media and found that a larger catalyst to compound ratio than the one used by Smith and Christensen was necessary to effect the nuclear reductions. On making this change, nuclear reduction of chloro substituted pyrimidines was accomplished by shaking 0.025 moles of the pyrimidine in 50 milliliters of water and 4500 milligrams of ten percent palladized charcoal with hydrogen in a Parr low-pressure hydrogenation apparatus at room temperature at an initial pressure of 45 psi. After reaction the catalyst was removed and the filtrate warmed to 50°-60° with norite and filtered. The catalyst was washed with water and the combined filtrates evaporated to dryness under vacuo, yielding the tetrahydropyrimidine hydrochloride. Any residual hydrochloric acid was removed by addition of 25 milliliters of absolute alcohol and the solution evaporated to dryness; the same procedure was repeated using dry benzene. Nuclear reduction of non-chloro substituted pyrimidines was accomplished in a like manner with the exception that a slight excess of acid was added to the mixture of pyrimidine and catalyst before reduction.

During the investigation Aft and Christensen found that the tetrahydropyrimidines could not be isolated in pure form as the hydrochloride salts; deviations between actual and theoretical chloride percentages were observed for all the tetrahydropyrimidine hydrochlorides. For this reason the picrate derivatives were prepared for characterization purposes. However, preparation of these picrate derivatives were tedious and the yields were low.

These results suggested to Aft and Christensen that the nuclear reduction reaction in acid media was not straightforward but yield mixtures of products together with the tetrahydropyrimidines (1, p. 2171).

Furthermore, the fact that a high catalyst to compound ratio was necessary for nuclear reduction suggested that the tetrahydropyrimidines underwent degradation in the aqueous acid media during hydrogenation yielding products toxic to the catalyst (1, p. 2170). These suspicions were confirmed by Aft and Christensen who subjected the reduction products to paper chromatographic analysis. This analysis showed that all the nuclear reductions gave mixtures of products with as many as five components among the reduction products of some of the pyrimidines. Four components were detected by ninhydrin, three components by iodine vapor, on the chromatogram of the reduction products of 4-amino-2, 6-dichloropyrimidine; one of the products was identified as 4-amino-3, 4, 5, 6-tetrahydropyrimidine. The presence of substituted tetrahydropyrimidines were also found among the reduction products of the methylpyrimidines and their dichloro derivatives, and 2-aminopyrimidine and it's dichloro derivative. Ammonium chloride was identified among the reduction products of 5-aminopyrimidine (1, p. 2173).

In view of the paper chromatographic studies, the identity of the degradation products had to be uncovered if one were to understand the nature of nuclear reduction. For this reason the development of a procedure for the determination of the degradation products of the nuclear reduction was undertaken.

EXPERIMENTAL

Since, in the studies by Aft and Christensen 4-amino-2, 6-dichloropyrimidine appeared to undergo a marked degree of degradation during nuclear reduction it was the compound chosen for the current study. 4-Amino-2, 6-dichloropyrimidine upon nuclear reduction would be expected to yield 4-amino-3-4, 5, 6-tetrahydropyrimidine along with smaller molecular weight products such as methylamine, propylamine, ammonia, propanol, methanol, resulting from possible competing reactions. These low molecular weight substances should be easily detected by gas chromatography. It was for this reason that the reaction products of nuclear reduction of 4-amino-2, 6-dichloropyrimidine were subjected to gas chromatography.

The degradation products, however, were either basic materials such as amines, or neutral materials such as alcohols or aldehydes. The basic materials form non volatile hydrochlorides during the reduction and for this reason the non-basic volatile products must be determined separately from the volatile amines. The volatile products were therefore removed and analyzed apart from the non-volatile amine hydrochlorides.

The hydrochloride salts obtained by evaporation of the reaction mixture from the nuclear reduction of the 4-amino-2, 6-dichloropyrimidine on the other hand were converted to the free bases and then likewise subjected to gas chromatographic analysis. In order to obtain volatile amines for analysis it was necessary to devise an

apparatus for liberating and collecting samples. The collector finally devised for this investigation is shown in Figure 2. The collector (Figure 2) consisted of four parts; a main reactor tube, capillary tube containing the standard alkali, a condensor and a connector.

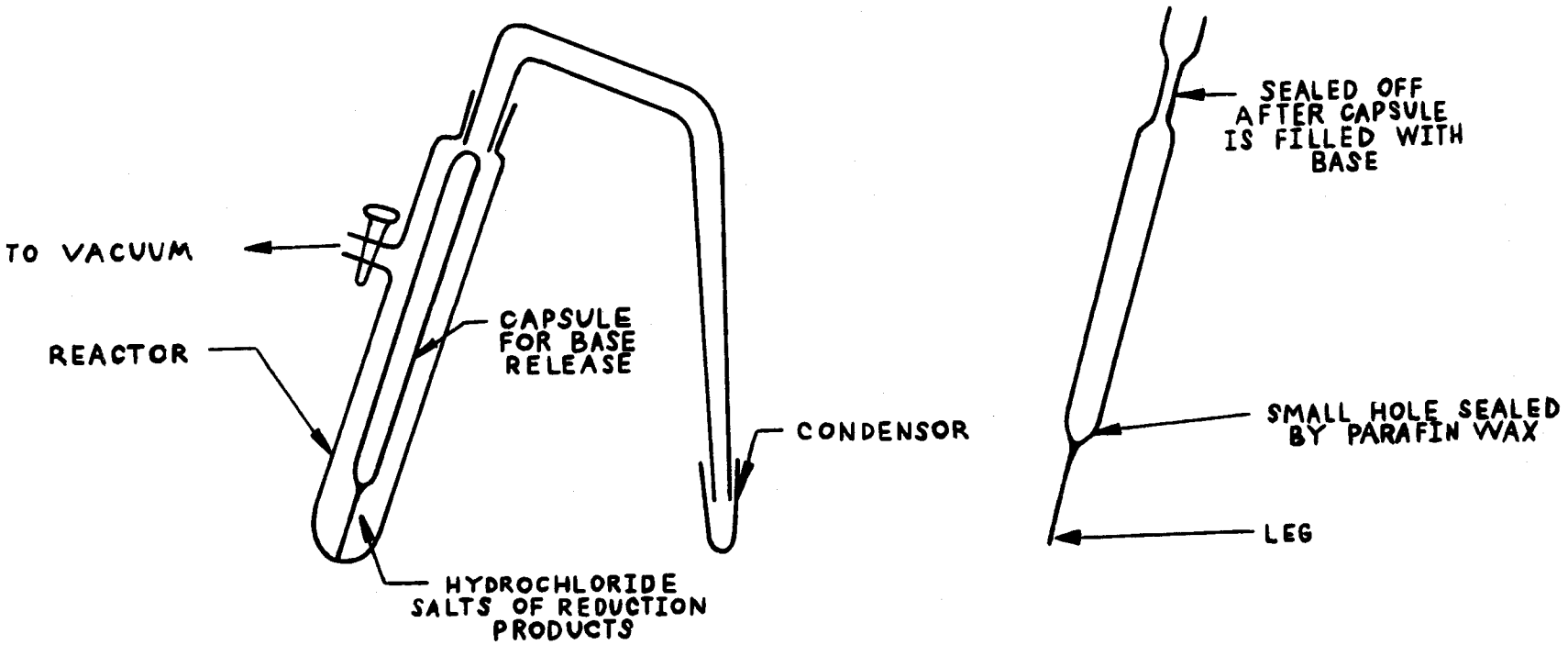
The main reactor tube was constructed of 11 mm O.D. pyrex glass tubing, was 16 mm in length. One end was fitted with a 10/18 standard tapar joint. The stopcock was placed 65 mm from the closed end.

The capillary tube which held the known amount of standard alkali was made of 6 mm soft glass tubing. One end was sealed off in such a manner as to leave a solid glass tip 12 mm in length in order to keep the outlet of this tube above the liquid level at all times. A small hole was blown in the base of this unit (as shown in the Figure 2) and then closed with paraffin wax.

The connector was constructed of 5 mm pyrex glass tubing with male 5/20 standard taper fitting at one end and 10/18 male standard tapar fitting at the other. The condensor (which was immersed in dry ice-acetone mixture) was merely a female 5/20 standard tapar joint which had been closed 5 mm below the joint; the unit was 38 mm in length overall.

The solid hydrochloride salts were placed in the reactor and the capillary tube was charged with an equivalent amount of potassium hydroxide (0.398 g/ml). The collector was then assembled with the condensor immersed in dry ice-acetone mixture. The stopcock was connected to a protected high vacuum pump and the assembly

Figure 2


TO VACUUM
REACTOR
CAPSULE FOR BASE RELEASE
CONDENSOR
HYDROCHLORIDE SALTS OF REDUCTION PRODUCTS
SEALED OFF AFTER CAPSULE IS FILLED WITH BASE
SMALL HOLE SEALED BY PARAFIN WAX
LEG

evacuated. As pressure diminished, the air in the capillary blew out the paraffin plug allowing the potassium hydroxide solution out of the capillary.

In the operation of the collector, it was important to have the capillary extend well above the hydrochloride salts in the reactor, otherwise base that was released could be drawn back into the capillary which, thus, rendered the reaction incomplete.

The collector was tested with known mixtures of amines in order to test it's applicability for collecting volatile bases quantitatively from the corresponding hydrochloride salts. The results of these tests are shown in Table 1 which give a comparison between the actual percentages and the percentage calculated from the chromatographic analysis of the components of the amine mixtures.

TABLE 1. Comparison of Actual Percentages with Percentages Calculated from Chromatographic Analysis of the Components of the Amine Mixtures.

Amine	Grams of Amine Hydrochloride	Weight % Amine	Weight % Amine Calculated from Chromatographic Analysis
Ammonia	0.0200	42.3	41.0
Methylamine	0.0132	27.9	29.5
Ethylamine	0.0075	15.8	17.5
n-Propylamine	0.0066	14.0	12.0

The next problem was to find a satisfactory column stationary liquid for gas chromatographic separation of a mixture of volatile amines. Choice of the stationary liquids studied were made on the

basis of the general rule that for an efficient separation the components of a mixture should be compatible with the stationary liquid (22, p. 20). Generally, polar components are best separated with a polar stationary liquid while non-polar components are best separated with a non-polar stationary liquid (22, p. 20). Accordingly a fairly wide variety of stationary liquids of varying degrees of polarity were studied as possibilities for the separation of mixtures of volatile amines. Table 2 contains a list of stationary liquids studied in this investigation. Of these stationary liquids, only o-toluidine and 20% 1-hexadecanol were found to give good separations of mixtures of simple aliphatic amines, and 20% 1-hexadecanol was found to be most satisfactory since it gave nearly quantitative separations with symmetrical peaks for a mixture of ammonia, methylamine, ethylamine, isopropylamine, n-propylamine, and n-butylamine ranging in boiling points from -33 to 78.8°.

TABLE 2. Stationary Liquids Studied in the Separation of Simple Aliphatic Amine Mixtures.

Paraffin Oil	Apiezon K
Ucon Non-Polar	Reoplex 400
Ucon Polar	Carbowax 40 M
10% Flurosilicone	Glycerol
15% Fluosilicone	O-Toluidine
10% Craig Polyester	20% 1-Hexadecanol
Diisodecyl Phthalate	

Using 20% 1-hexadecanol as the stationary liquid, five components, two of which were identified as ammonia and n-propylamine, were detected in the basic volatile material by gas chromatographic analysis. Identification of these components was made by comparison of their retention times with those of pure ammonia and of pure n-propylamine. Although the retention time is characteristic for a given compound when all operating conditions are the same (10, -. 242), it was found in this investigation that the retention times of some amines and aldehydes in a given mixture varied somewhat from those for the pure compounds. Therefore, to confirm the identifications, a mixture of the unknown and the known pure compound (suspected as one of the components) was injected into the gas chromatographic column. If the component peak in question was reinforced the identification was considered positive. However, if either a shoulder on the component peak or a new peak were formed in the chromatogram as a result of this injection then the prior identification could not be confirmed (22, p. 27). In this event other logical choices of pure compounds were injected with the unknown until the component peak in question was positively identified by the reinforcement procedure.

Upon identification of n-propylamine and ammonia in the basic volatile material, it became apparent that another degradation product must be a one-carbon fragment. It seemed likely that this one-carbon fragment could be an alcohol, an aldehyde, or an acid, such as methanol, formaldehyde, or formic acid, respectively, or carbon dioxide. If carbon dioxide had formed in the reduction it

would have escaped when the hydrogen gas was bled from the hydrogenation apparatus or if dissolved in the aqueous media of the reduction mixture it would be lost upon isolation of the hydrochloride salts.

To test the possibility of formation of carbon dioxide in the reduction, hydrogen gas from the hydrogenation apparatus was allowed to escape through a saturated solution of barium hydroxide after the reaction was complete; a heavy white precipitate was formed which disappeared upon acidification, with evolution of a gas, thus indicating the presence of carbon dioxide.

The formation of carbon dioxide in the reduction reaction was confirmed by gas chormatographic analysis of the reduction mixture before isolation of the hydrochloride salts. Some difficulty was encountered in this analysis since both carbon dioxide and propionaldehyde have retention times similar enough to limit the usefulness of the reinforcement procedure for confirming an identification. To overcome this problem, the vapors from the reaction mixture upon evaporation under vacuum were passed through a plug of ascarite before condensation in a receiver immersed in a dry ice-acetone mixture. If carbon dioxide were present it would be removed by the ascarite. When this experiment was performed, gas-chromatographic analysis of the condensate revealed that the component previously detected was completely removed. A control experiment performed in exactly the same manner with a small amount of propionaldehyde in water showed that propionaldehyde was not removed by ascarite, thus proving the formation of carbon

dioxide in the reduction reaction. Control experiments were also run on the carbon dioxide content of exhaust hydrogen gas and the solvent for the reaction which showed that the observed carbon dioxide resulted from the reduction reaction and not from it's presence in the starting materials.

Preparation of Crude Hydrochloride Salts

The preparation of the crude hydrochloride salts of the nuclear reduction products of 4-amino-2, 6-dichloropyrimidine was done according to the procedure of Aft and Christensen (1, p. 2170). 4-Amino-2, 6-dichloropyrimidine (0.025 moles) and ten percent palladized charcoal (4500 milligrams) in 50 milliliters of distilled water was shaken with hydrogen under an initial pressure of 45 psi in a low pressure Parr hydrogenation apparatus at room temperature. After reaction the catalyst was removed and washed with two five milliliter portions of distilled water. The washings were added to the filtrate which was then evaporated to dryness under vacuo, yielding 4-amino-3, 4, 5, 6-tetrahydropyrimidine hydrochloride. Residual hydrochloride acid was removed by addition of absolute ethanol and evaporating to dryness; the procedure was repeated using dry benzene.

Preparation of the Column

The solid support of the packing was treated according to the procedure of James et al. (19, p. 238). Size graded (42-60 mesh) Johns-Manville C-22 firebrick was ignited at 300° for three hours

after which it was washed with concentrated hydrochloric acid, to remove iron and basic compounds, washed with distilled water and dried at 145°. After drying at 145° the firebrick was treated with approximately 200 milliliters of 5% (w/v) methanolic sodium hydroxide solution. Upon evaporation of the methanol, the firebrick was dried at 100° and stored over solid sodium hydroxide until use. The base treatment coats the solid support with sodium hydroxide which diminishes the exposed area of the support that would otherwise give rise to residual adsorption and consequently tailing of the elution peaks of basic compounds (18, p. 679).

The treated firebrick (18.65 grams) in a solution consisting of n-pentance and 3.75 grams of 1-haxadecanol was evaporated on a steam bath. Last traces of solvent was removed from the packing by warming under slight vacuum.

Collection of Volatile Bases from the Corresponding Hydrochloride Salts

The crude hydrochloride salts (0.6 grams) of the reduction products of 4-amino-2,6-dichloropyrimidine was placed in the reactor tube of the collector and the assembled apparatus was evacuated. While still under vacuum and with the condensor immersed in acetone-dry ice mixture, exactly one milliliter of potassium hydroxide solution (0.398 g/ml) was released in the reactor by means of the capillary described previously. After collection the vacuum was released, and triethylamine (approximately 0.1 milliliter), as solvent, was added to the distillate keeping

the condensor immersed in acetone-dry ice mixture as much as is possible during the operation. The liquid was removed from the condensor for chromatographic study by means of a hypodermic syringe that was precooled in a test tube immersed in acetone-dry ice mixture.

Gas Chromatographic Analysis of the Reduction Products

To effect the separation of the components of the reduction products a 5.75 ft by 3/8 in I.C. column packed with 20% 1-hexadecanol on 42-60 mesh base washed Johns-Manville C-22 firebrick (2, p. 1805) was used, employing a helium flow rate of 7.5 cc/min at 100°. Detection of the components was made with a thermal conductivity cell installed in a Perkin-Elmer Model 154B Vapor Fractometer. Sample sizes ranging from 0.01 to 0.03 cc were found most satisfactory for injection into the column since larger samples impaired the separation. Use of smaller sample sizes generally allowed for better quantitative separation, but detection of trace components was then more difficult (22, p. 25-26) The chromatograms were recorded at a sensitivity setting of 1 on the Perkin-Elmer Model 154B Vapor Fractometer.

The separation of the reduction products is shown in Figure 3. The peak areas in these chromatograms do not exactly correspond to the relative concentrations of the components in the mixture since the attenuation steps have been omitted for clarity. The chromatograms were recorded on a Leeds and Northrup Speedomax recorder with a constant chart speed of 1/2 inch per minute.

Figure 3

(a) CHROMATOGRAM OF BASIC VOLATILE MATERIALS COLLECTED FROM THE CORRESPONDING HYDROCHLORIDE SALTS

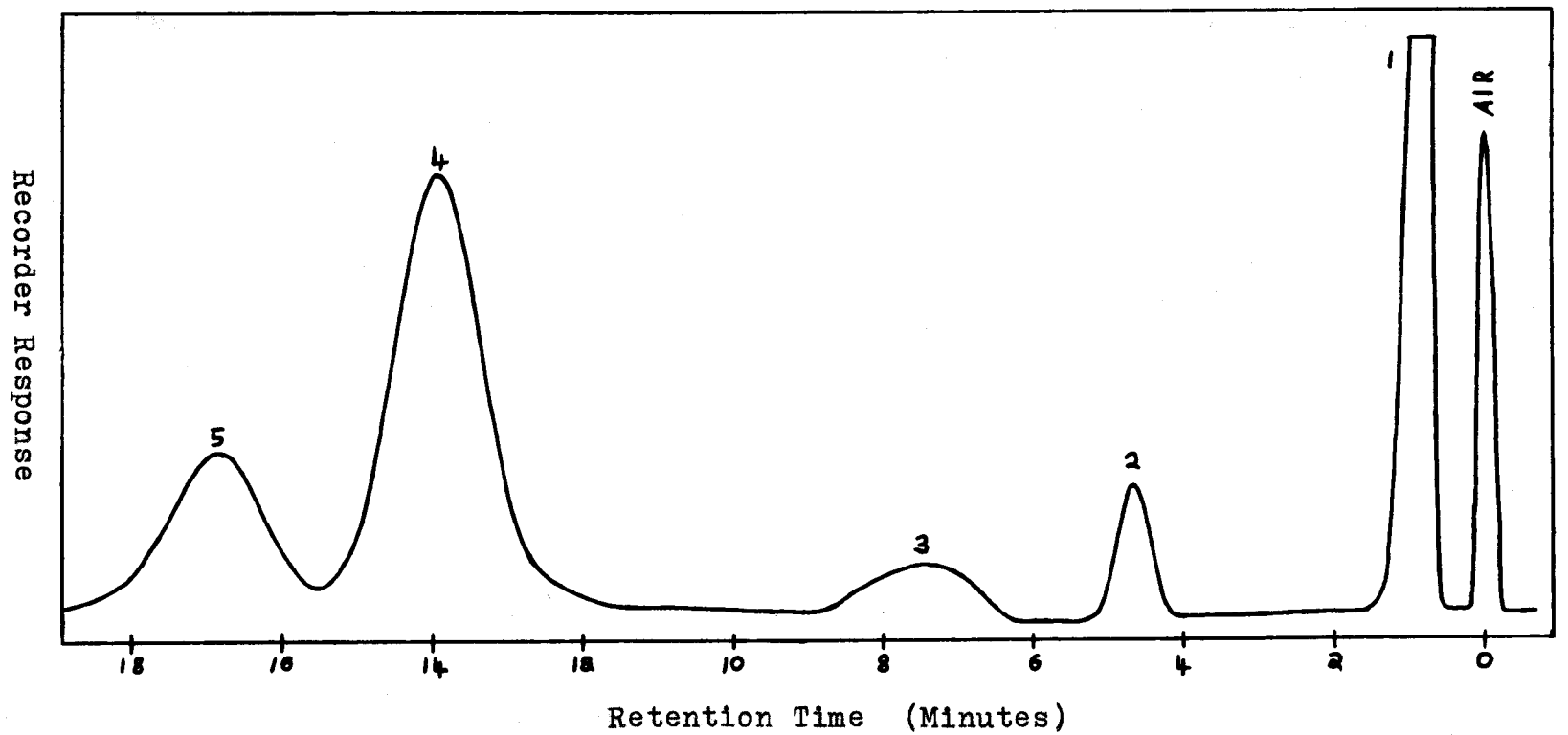
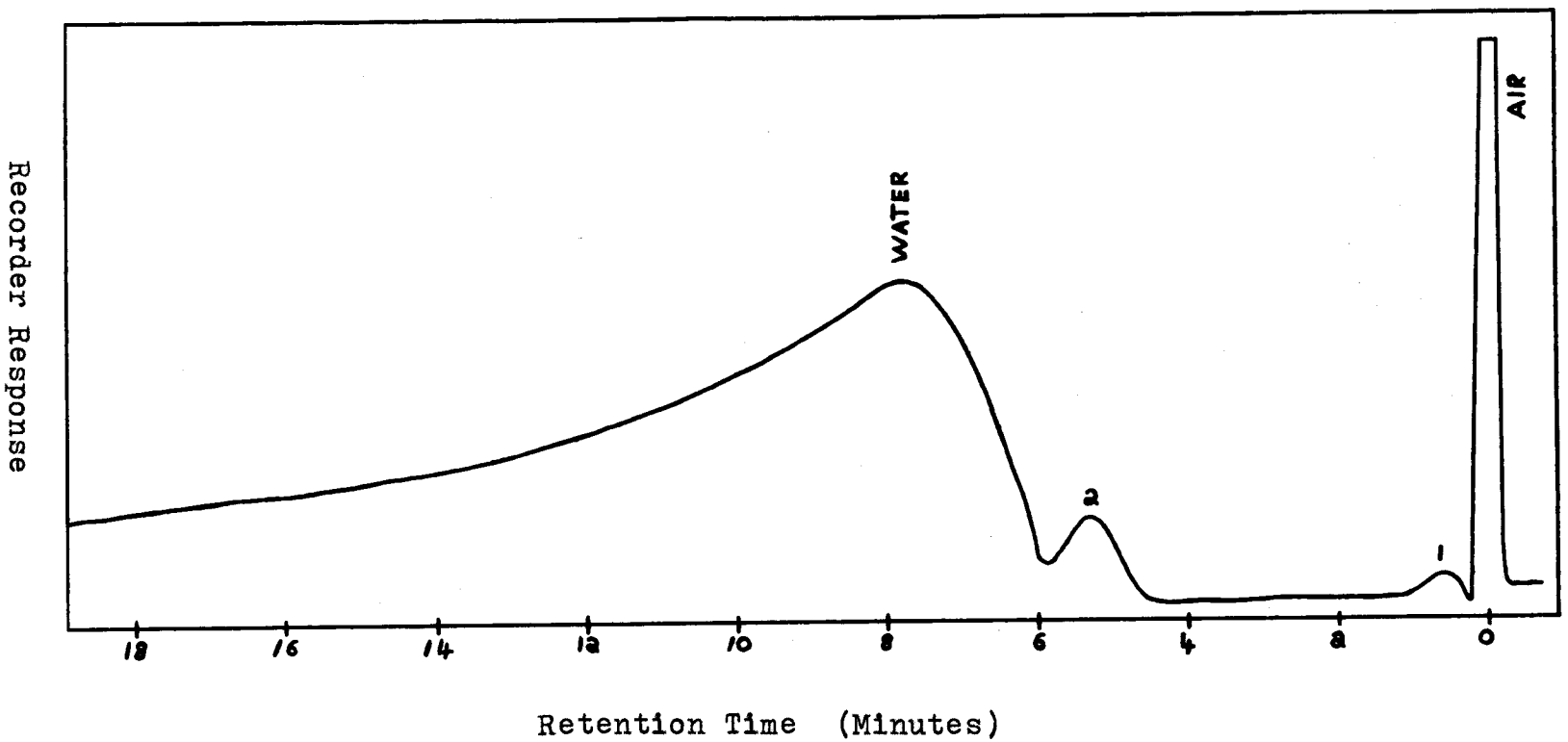


Figure 3

(b) CHROMATOGRAM OF REACTION MIXTURE BEFORE ISOLATION OF THE HYDROCHLORIDE SALTS



In the second chromatogram shown in Figure 3(b), water presented difficulty since it gave severe tailing. Thus, masking any components that might have been eluted from the column following shortly after the water peak. Probably the best practical solution to this problem would be the use of some method by which the water could be removed prior to analysis without losing any of the sought-for components.

Analytical Data

Retention times were measured from the air peaks in the chromatograms, for both the reduction products and for the known volatile amines, alcohols, and aldehydes, using a 5.75 ft by 3/8 in I.D. column packed with 20% 1-hexadecanol on 42-60 mesh base washed Johns-Manville C-22 firebrick employing a helium flow rate of 7.5 cc/min at 100^{o}.

The retention time for carbon dioxide was determined in water solution and was found to vary from 4.80 to 5.10 minutes.

TABLE 3. Products Identified.

Products Obtained by Basification of the Hydrochloride Salts			Products Obtained Before Isolation of the Hydrochloride Salts	
Component	Retention Time. Min.	%	Component	Retention Time. Min.
1. Ammonia	0.90	49.17	?	0.62 (trace)
2. Propionaldehyde	4.65	4.70	2. Carbon Dioxide	5.26
3. ?	7.50	5.23		
4. n-Propylamine	13.94	28.40		
5. n-Propanol	16.90	12.50		

TABLE 4. Retention Data For Known Amines

Component [1]	Retention Time, Min.
Ammonia	0.80
Methylamine	3.01
Dimethylamine	4.66
Ethylamine	5.98
Isopropylamine	8.82
n-Propylamine	13.94
n-Butylamine	31.45

[1] Analyses were made on mixtures of approximately equal quantities of the components.

TABLE 5. Retention Data For Known Alcohols and Aldehydes

Component [1]	Retention Time. Min.
Methanol	4.28
Ethanol	7.75
n-Propanol	17.10
Formaldehyde	5.33
Propionaldehyde[2]	4.96

[1] Analyses were made on individual components in triethylamine as solvent.
[2] Propionaldehyde was chromatographed in absence of triethylamine.

Inasmuch as carbon dioxide was the only volatile degradation product observed in either the aqueous media or the hydrogen atmosphere, it is apparent that propanal and propanol observed during the basification of the hydrochloride salt residue must stem from the reaction of the base on the reaction product.

In order to account for the 4-amino-3, 4, 5, 6-tetrahydropyrimidine, carbon dioxide, propanal, propanol and propylamine, it is apparent that there must be several reactions, some complex, involving the rupture of the ring via hydrogenolysis to yield a basic compound which is hydrolyzed by the base leading eventually to the observed volatile products.

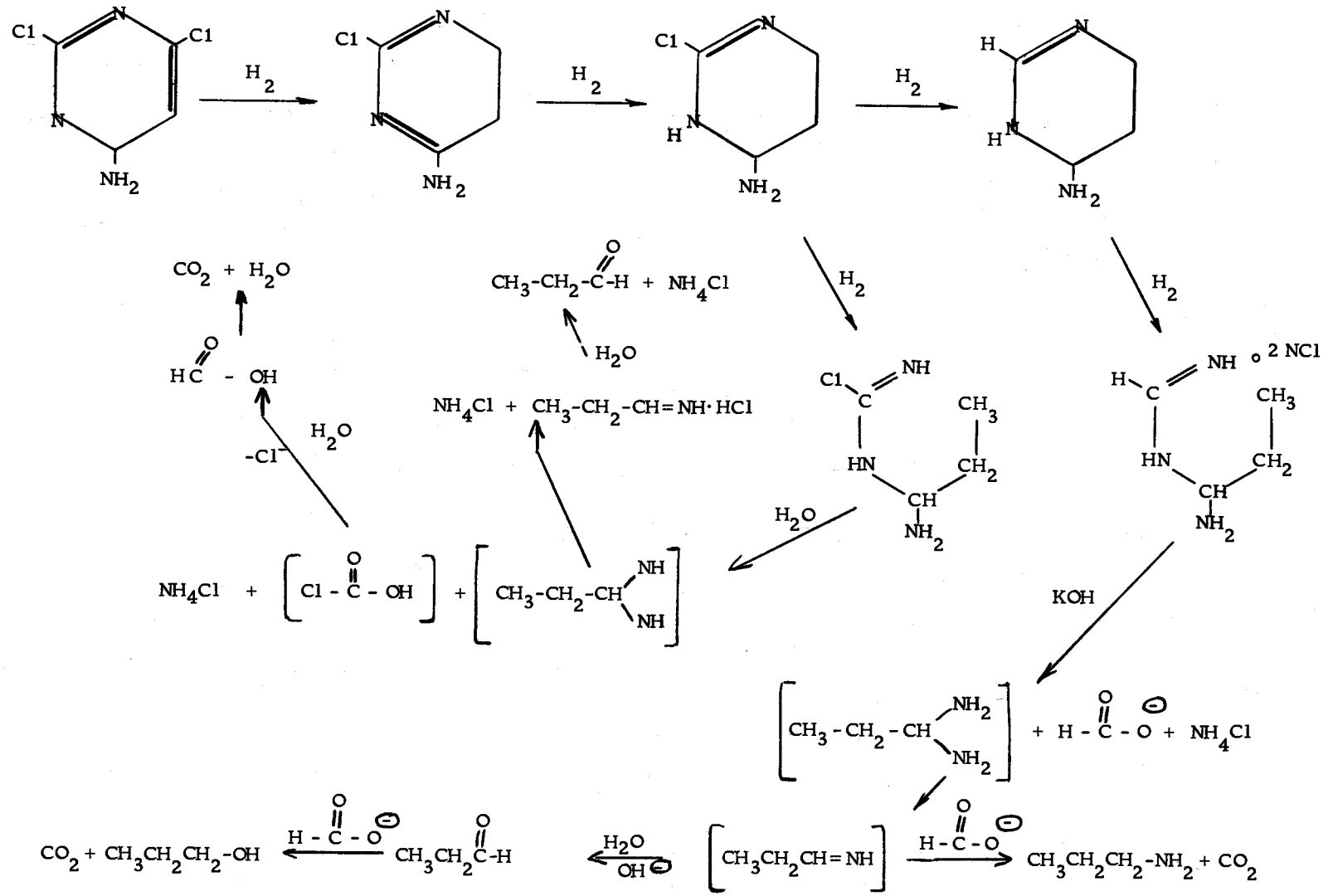
It is not difficult to account for the carbon dioxide observed in the hydrogen atmosphere. This observation suggests that hydrogenolysis under acid conditions proceeds by a different route than under alkaline conditions, and furthermore it would involve the hydrogenolysis of the ring.

Moreover it is not difficult to account for the propanal which must have resulted from reaction of the ruptured ring with potassium hydroxide. The presence of propylamine and propanol is another matter. This must have resulted from the reduction of propylamine and propanal, respectively. For such a reaction to take place one must have a reducing agent. The only plausible reducing agent in the basified media is the formate ion. Whether or not it would reduce either the propylamine or propanal under alkaline conditions is not known.

A mechanism which can account for these changes is on the following page.

A component was detected in the basic volatile material with a retention time of 4.65 minutes which was similar to that for dimethylamine. However, on examination of 4-amino-3,4,5,6-tetrahydropyrimidine, it would not be expected to be a possible degradation product. Methylamine, which could conceivably be a product had too short a retention time for serious consideration as a possible identification of this unknown component. Methanol, even though a conceivably possible degradation product, would not be an easily explained component in the basic volatile material since it would be lost during isolation of the hydrochloride salts. Furthermore, methanol was not found in the reduction mixture before isolation of the hydrochloride salts. However, in view of this possibility the basic volatile material along with some pure methanol was injected into the chromatographic column; no reinforcement of the unknown component peak was obtained. The next best choice was that of propionaldehyde, which was found to reinforce the unknown peak.

n-Propylamine was easily detected in the basic volatile material and confirmed by the reinforcement procedure. No identification could be made for a component with a retention time of 7.50 minutes, however ethanol with a retention time of 7.75 minutes comes nearest to this unknown component. Because of the small and ill-defined peak for this unknown component, the reinforcement procedure added little information of value to the



solution of this identification problem.

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