# INVESTIGATION OF SOME ROUTES TO AZETIDINE

by

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## HISTORICAL

The compounds with three- and four-membered rings have been among the most attractive subjects in chemistry due to their unique stereochemical problems and exceptional reactivity. Although azetidine and its derivatives have been known since the latter part of the nineteenth century, they have been little investigated. The lack of interest in these compounds was undoubtedly due to an apparently inherent difficulty of preparation. According to Ruzicka and co-workers (1) the formation of a ring system from acyclic reagents is influenced by two factors. The first of these is a strain factor which is introduced by a deviation of bond angles from the normal bond angles. It operates against the formation of the three- and, to a less extent, of the four-membered rings. The second is a probability factor; this is related to the distance between the two atoms which will close to form the ring and the probability that they will come sufficiently close to one another to be joined by a valence bond. With these two factors it is predicted that the four-membered ring is least disposed to form. This was verified experimentally in a kinetic study of the intramolecular condensations of bromoalkylamines (2) and by an aziridine formation in better yield than azetidine by treatment of 2-bromoethylamine hydrobromide or 3-bromopropylamine hydrobromide with strong aqueous potassium hydroxide (3)(4).

Acyclic compounds have been cyclized to azetidine by a number of methods, none of which, however, can be considered a general synthesis. Yields in most cases are low. The preparative methods which have been reported are:

1) dehydrohalogenation of 3-haloalkylamines,

2) reaction of dihalides with amides or amines,

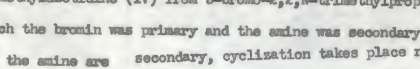
3) reaction of 3-aminoalkyl hydrogen sulfates with base, and

4) pyrolysis of diamines and related compounds.

Azetidine and its alkyl derivatives have been commonly prepared by intramolecular dehydrohalogenation of 3-haloalkylamines in which the amine is primary or secondary. The first application of this method was described in 1888 by Gabriel and Weiner (4), who obtained a small amount of impure azetidine (II) by the action of alkali on 3-bromopropylamine hydrobromide (I). Azetidine was prepared by this method on 1957 by Ruzicka and collaborators (5); after careful purification, the imine was obtained in very pure form but in unspecified yield. In a recent work Schaefer (6) determined that the yields of steamvolatile amine produced by this reaction varied between 6 and 26 percent.

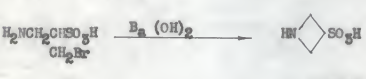
I II

Application of this reaction to substituted 3-haloalkylamines has given some insight to its generality. Mannich and Baumgarten (7) have reported that cyclization did not take place readily with 3-bromoalkylamines in which the halogen is secondary and that the cyclization ability increases with the following series of halogen; Cl<Br<I. They obtained an 80% yield of 1,3,3-trimethylazetidine (IV) from 3-bromo-2,2,N-trimethylpropylamine (III) in which the bromin was primary and the amine was secondary. If both the halogen and the amine are secondary, cyclization takes place readily (8).

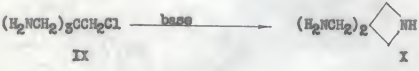


III IV

Although the original preparation of azetidine indicates that only a small amount of cyclization takes place when both the halogen and amine are primary, 3-haloalkylamines of this type have been used to prepare substituted azetidines. Thus, 2-methylazetidine and 2,3-dimethylazetidine have been prepared from 3-aminobutyl chloride and 2-methyl-3-aminobutyl chloride, respectively (9), and azetidine-3-sulfonic acid (VIII) from -bromomethyltaurin (VII) (10). Also, steam distillation of a mixture of 2,2,2-tris-aminomethylethyl chloride (IX) and base gives a small amount of 3,3-diaminomethylazetidine (X) (11).

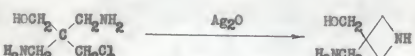


VII VIII



IX X

In all of the preceding reactions strong base and refluxing temperature had been used to get the cyclization. It has been reported, however, that silver oxide can be used to effect ring closure of 2,2-diaminomethyl-3-chloro-1-propanol (XI) to 3-hydroxymethyl-3-aminomethylazetidine (XII) (12). Also using



XI XII

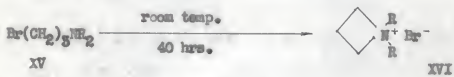
relatively mild conditions, azetidine-2-carboxylic acid (XIV) has been synthesized from 2-bromo-4-amino-1-butyric acid (XIII) by refluxing with 0.5N

barium hydroxide for ten minutes (15).

XIII XIV

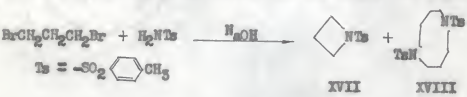
3-Bromo-N, N-dialkylpropylamine (XV) is converted to 1,1-dialkylazetidinium bromide (XVI) by standing in ethyl alcohol at room temperature (14) (15).

The reaction of a 1,3-dihalopropane with p-toluenesulfonamide in the



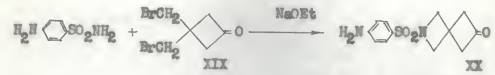
XV XVI

presence of base yields p-toluenesulfonazetidide. Marckwald and Van Droste-Huelshoff (16) obtained p-toluenesulfonazetidide (XVII) and N,N' -bis-p-toluenesulfonyl-1,5-diazacyclooctane (XVIII) starting with 1,3-dibromopropane. Using 1-bromo-3-chloropropane, Searles and co-workers (17) obtained a 55%

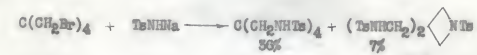


XVII XVIII

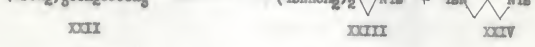
yield of p-toluenesulfonazetidide. This method has also been used to produce the azetidine ring as part of a spirocompound. 6-Sulfanilyl-2-oxo-6-azaspiro (3,3)heptane (XX) was obtained when sulfanilamide and 3,3-dibromomethyl-cyclobutanone (XIX) were refluxed with sodium ethoxide (18). Litherland and Mann (11) have extended the method by employing the sodium slat of p-



toluenesulfonamide to produce a small amount of 1-p-toluenesulfonyl-3,3-di-(p-toluenesulfonamidmethyl) azetidide (XXI).

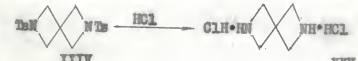


With pentaerythrityl tribromide monoacetate (XXII) ring closure occured to give 2,6-di-(p-toluenesulfonyl)-2,6-diazaspiro(3,3)-heptane (XXIV). In addition to this spirocompound, some 1,1-di-(p-toluenesulfonamidomethyl)-2-p-toluenesulfonamidocyclopropane (XXIII) was produced. 1-Phenylazetidine was

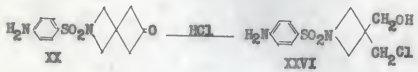


obtained by a reaction of 1,3-dibromopropane with aniline (19).

To liberate azetidines from the corresponding p-toluenesulfonazetidides many procedures have been studied. p-Toluenesulfonazetidide undergoes acid hydrolysis but the azetidine ring is cleaved concurrently in the acid solution to give 3-chloropropylamine and 3-hydroxypropylamine. Litherland and Mann (11), however, were able to isolate 2,6-diazaspiro(3,3)-heptane (XXV) from a mixture of 2,6-di-p-toluenesulfonyl-2,6-diazaspiro(3,3)heptane (XXIV) and concentrated hydrochloric acid which was heated to 140° for six hours in a sealed



tube. Refluxing of a hydrochloric acid solution of 6-sulfanilyl-2-oxo-6-aza-spiro(3,3)heptane (XX) did not affect the azetidine ring but opened the cyclobutanone ring to form 1-sulfanilyl-3-chloro-methyl-3-hydroxymethyl-azetidine (XXVI) (18).

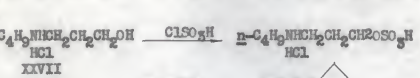


XX XXVI

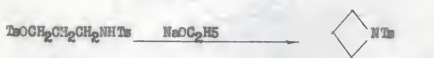
Reductive cleavage of p-toluenesulfonazetidide with sodium in amyl alcohol has been reported by Howard and Marckwald (20) to give azetidine almost quantitatively. However, most subsequent reports of the method have been discouraging. Thus Jones (21) obtained only a 14% yield, Yanbikov and Dem'yanov (22) obtained a 36% yield of azetidine and isolated 3-hydroxypropylamine and di(3-hydroxypropyl)amine as by-products, and Schaefer (6) obtained a 42% yield of volatile amine. The reduction of p-toluenesulfonazetidide has been effected with sodium in liquid ammonia to give a 30% yield of azetidine (23). Recently Kolonowski obtained a 78% of 2-methylazetidine from 2-methyl-p-toluenesulfonazetidide using sodium and n-amyl alcohol as a reducing agent (24). Treatment of p-toluenesulfonazetidide with methyl iodide gave a 17% yield of 1,1-dimethylazetidinium iodide. The major product of the reaction was trimethylene diiodide produced by ring fission (25). Catalytic reduction of p-toluenesulfonazetidide using a copper chromite catalyst has been attempted but practically no volatile base was produced (6).

Elderfield and Hageman (26) reported the preparation of 1-n-butylazetidine (XXVIII) from 3-butylaminopropanol hydrochloride (XXVII) in a 30% yield by treatment with chlorosulfonic acid followed by an alkali treatment. By

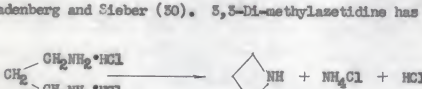
this method 1-methyl- (17), 1-ethyl- and 1-t-butylazetidine (27) were pre-



pared in yields of 8, 15 and 47% respectively. Under the same conditions which produced aziridine in an 83% yield from ethanolamine (28), 3-amino-propanol gave only a 1.7% yield of azetidine (29). Esterification of 3-benzylamino-1-propanol with sulfuric acid and subsequent treatment with alkali gave 1-benzylazetidine in a 9% yield (24). An 80% yield of p-toluenesulfonazetidide (XVII) was obtained by a treatment of 3-(p-toluenesulfonamido)-propyl p-toluenesulfonate (XXIX) with sodium ethoxide (24).

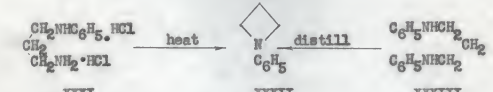


The preparation of azetidine (II) in low yield and impure form by dry distillation of trimethylenediamine dihydrochloride (XXX) has been described by Ladenberg and Sieber (30). 3,3-Di-methylazetidine has been similarly pre-



pared by pyrolysis of 2,2-dimethyl-1,3-diaminopropane dihydrochloride, but azetidine was isolated as the picrate in only a 6% yield (31). Balbiano (32)

reported the preparation of 1-phenylazetidine (XXXII) by heating N-phenyltrimethylenediamine dihydrochloride (XXXI).




XXXI XXXII XXXIII

Again the yield was low and the free base was isolated as the chloroplatinate. 1-Phenylazetidine has also been prepared by distilling N,N'-diphenyltrimethylenediamine (XXXIII) (19).

2,6-Diazaspiro(3,3)heptane (XXV) was isolated by Govert (33) from the pyrolysis product of pentaerythrityl tetramine (XXXIV).


XXXIV XXXV

Pyrolysis of ethyl N-(1-methyl-3-hydroxypropyl)-carbamate (XXXVI) was reported in a patent literature (34) to give ethyl 2-methylazetidine-1-carboxylate (XXXVII).


XXXVI XXXVII

It is seen, therefore, that no general method for the preparation of the azetidine ring is known. The yield and purity for all preparation are usually low and dependent on the nature of the functional groups undergoing ring closure and on the substituents attached to the alkyl chain.

## STATEMENT OF THE PROBLEM

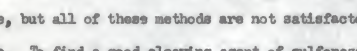
Pyrolysis of the cyclic carbonates of 1,3-diols with potassium carbonate or potassium thiocyanate gives oxetanes or thietanes respectively. So a new approach to azetidines could be expected by pyrolysis of the cyclic carbonates of 1,3-diols with potassium cyanamides. Pyrolysis of the corresponding cyclic ureas or urethanes with an alkali catalyst could be also expected as a preparative method of azetidines.

Cleavage of sulfonazetidides has been a usual preparative method of azetidine, but all of these methods are not satisfactory to get a pure azetidine. To find a good cleaving agent of sulfonazetidides is important in preparation of azetidines.

## DISCUSSION

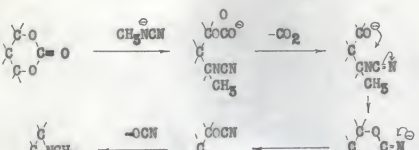
### Pyrolysis of 1,3-Dioxane-2-one with Potassium Methylcyanamide

The facile preparation of thiiranes (ethylene sulfides) and thietanes (XXXVIII) by a heating of the cyclic carbonates of 1,2-diols and of 1,3-diols respectively, with a mole equivalent of potassium thiocyanate has been reported (35). It thus appeared possible that compounds of the azetidine series

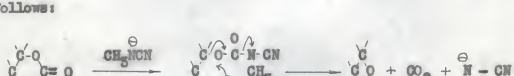



XXXVIII

could be obtained by the pyrolysis of the cyclic carbonates of 1,3-diols with potassium methylcyanamide. Methylcyanamide anion may react like thiocyanate ion and produce azetidine derivatives.



5,5-Dimethyl-1,3-dioxane-2-one (XL) was selected for this investigation because a gem-dimethyl substitution would be expected to stabilize the four membered ring and lack of β-hydrogen would prevent the formation of olefinic compounds. This was prepared in a yield of 60% from 2,2-dimethyl-1,3-propanediol (XXXIX) and diethyl carbonate with an alkali catalyst. Potassium methylcyanamide was prepared from cyanogen bromide, methylamine and potassium hydroxide by the methods reported by Baum (56) and Kaess and Gruszkiewies (57) with a little modification. The pyrolysis was carried out at 200-250° and gave a 51.8% yield of 5,5-dimethyloxetane but no 1,3,3,-trimethylazetidine. The formation of 5,5-dimethyloxetane is explained by an attack at the carbonyl carbon by a methylcyanamide anion followed by an elimination of carbon dioxide as follows:



Synthesis and Pyrolysis of Hexahydro-2-pyrimidones and Tetrahydro-1,3-oxazin-2-ones

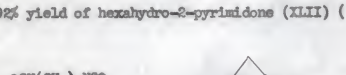
The pyrolysis of cyclic carbonates of 1,3-diols with an alkali catalyst gives the corresponding oxetanes and the pyrolysis of 1,3-oxathiolan-2-one

Chart I

Pyrolysis of 5,5-Dimethyl-1,3-dioxane-2-one with Potassium Methylcyanamide

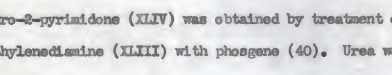
over potassium carbonate yields ethylene sulfide (38). Therefore, azetidines may be expected as a pyrolysis product of hexahydro-2-pyrimidones or tetrahydro-1,3-oxazin-2-ones over an alkali catalyst.

Several syntheses of hexahydro-2-pyrimidones have been reported. Standing of trimethylene diisocyanate (XLI) at room temperature in moist acetone gives a 92% yield of hexahydro-2-pyrimidone (XLII) (39). 1,3-Dimethylhexa-



XLI XLII

hydro-2-pyrimidone (XLIV) was obtained by treatment of N,N'-dimethyltrimethylenediamine (XLIII) with phosgene (40). Urea was condensed with acrolein



XLIII XLIV

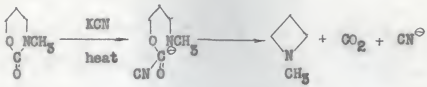
(41), malonitriles (42) and phenylacetaldehyde (43) to form the corresponding cyclic ureas. The reaction of alcohols with urea has been studied by Paquin (44). According to his work 1,3-butanediol (XLV) was converted to the diurethane (XLVI) by heating with 2 moles of urea and zinc acetate in a 78% yield, and heating of the produced diurethane at 240° gave cyclization to 4-methylhexahydro-2-pyrimidone (XLVII). Pyrolysis of the resin which was produced by a heating of ethlene glycol and urea in reduced pressure at 240-270° has been reported to form ethylene urea (45).


XLV XLVI XLVII

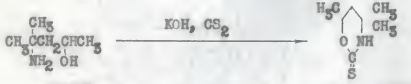
Syntheses of the cyclic ureas from 1,3-diols and urea were tried because of the great availability of starting materials and simple procedures. 1,3-Butanediol and urea formed the diurethane (XLVI) by a heating in the presence of zinc acetate. But the pyrolysis of the diurethane at 250-500° gave no 4-methylhexahydro-2-pyrimidone (XLVII) but gave trace amount of a viscous brown liquid, easily sublimed white flakes and a black resinous residue. Heating of 1,3-butanediol with a large excess of urea produced a resinous material. A small amount of urea was sublimed out by heating the polymer resin under reduced pressure, but no cyclic urea was obtained. Pyrolysis of the polymer resin with potassium carbonate gave a trace amount of basic liquid with ammonia-like odour which boiled at 75-76°, but the amount was so small that the compound could not be identified. Although the same pyrolysis was tried with the reaction product of 2,2-dimethyl-1,3-propanediol and urea, no cyclic urea and no 5,5-dimethylazetidine could be obtained.

Another approach to the cyclic urea, a reduction of 5,5-diethylbarbituric acid with lithium aluminum hydride was attempted. This approach was unsuccessful, as the starting material was recovered in a good yield.

There are, of course, other preparations for cyclic ureas which undoubtedly will work, but before pursuing this approach further, it seemed wise to work with cyclic urethanes, as one might expect these to be easier to pyrolyse. It was supposed that pyrolysis should break the C-N bond before the C-O bond, on the basis of bond energy, so that a new trimethylene imine synthesis might be anticipated as following:



Some syntheses of tetrahydro-1,3-oxazine-2-ones have been reported: Monourethanes of 1,3-glycols obtained by reaction of 1,3-glycols and urea were converted to the corresponding cyclic urethanes (44). 3-Aminoalcohols reacted with diethylcarbonate to form cyclic urethanes (46), and 3-chloropropyl carbamates are condensed to cyclic urethanes by an equivalent amount of alkali (47). 4,4,6-Trimethyl-2-thio-tetrahydro-1,3-oxazine (XLIX) was prepared by a treatment of 4-methyl-4-amino-2-pentanol (XLVIII) with potassium



XLVIII XLIX

hydroxide and carbondisulfide (48). 2-Imino-5-methoxy-tetrahydro-1,3-oxazine (LI) was formed by boiling of 3-bromo-2-methoxypropylurea (L) with water (49).

L LI

Heating of 1,3-butanediol monourethane with zinc chloride was tried to obtain the cyclic urethane, but no cyclic urethane could be obtained, and a 77% yield of 1,3-butanediol and a viscous resinous material were obtained.

3-Methyltetrahydro-1,3-oxazin-2-one was prepared by the method of Pierce and Adams (47): 3-Chloropropyl chloroformate was treated with aqueous monomethylamine and the produced 3-chloropropyl methylcarbamate (LII) was treated with equimolar alcoholic potash. A 36% yield of 3-methyltetrahydro-1.3-oxazin-2-one (LIII) was obtained based on 3-chloropropyl chloroformate. Pyrolysis of the cyclic urethane with potassium carbonate gave a 68% yield of methylallyl amine (LIV), but no N-methylazetidine was detected. It was concluded, therefore, that this method would apply only to compounds which have no β-hydrogen atoms. Then, 5,5,5-trimethyltetrahydro-1,3-oxazin-2-one was prepared by two methods; the one was the Pierce and Adams' method starting with 2,2-dimethyl-1,3-propanediol, the other was a reaction of 2,2-dimethyl-3-methylamino-1-propanol with diethyl carbonate. These two methods gave the same product which had the same boiling point, refractive index and infrared spectrum. Pyrolysis of the cyclic urethane with potassium cyanide, sodium methoide and potassium carbonate were tried, and 1.0%, 15.7% and 7.2% of a volatile amine which was supposed to contain 1,3,3-trimethylazetidine, respectively. The 5,5-dimethyl-substituted cyclic urethane was more stable than the unsubstituted one and its pyrolysis required stronger alkaline catalyst, higher temperature and longer heating, and an appreciable amount of the unpyrolyzed starting material was recovered. The volatile amine obtained in this pyrolysis was not a pure substance but a mixture of some undetermined amines, and it was difficult to separate each other. The total yield of the volatile amine was only 15% and a high yield of 1,3,3-trimethylazetidine could not be expected. The more extensive study was not tried.

Chart II

Synthesis and Pyrolysis of
3-Methyltetrahydro-1,3-oxazin-2-one

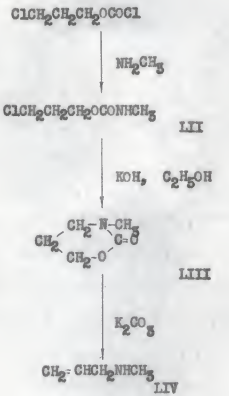
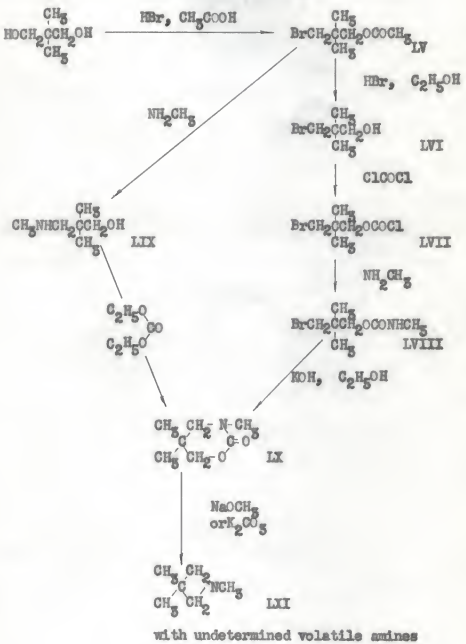


Chart III

Synthesis and Pyrolysis of
5,5,5-Trimethyltetrahydro-1,3-oxazin-2-one



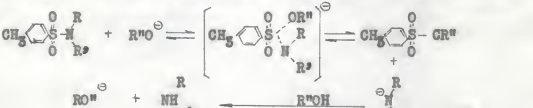

with undetermined volatile amines

## Cleavage of Sulfonazetidides

Since it appeared that the pyrolysis of the cyclic ureas, urethanes and carbonates could not give a good way to azetidines, cleavage of sulfonazetidides seemed to be the most promising approach to azetidines. Aromatic sulfonazetidides may be prepared in fairly good yield by reaction of sulfonamides with 1,3-dihalopropane, and cleavage of sulfonamide has been used to prepare primary and secondary amines.

Acid catalyzed hydrolysis is the most usual process to cleave sulfonamides to sulfonic acids and amines, but high concentration of hydrochloric acid and high temperature used in this procedure easily convert the produced azetidine to 3-chloropropylamine and 3-hydroxypropylamine (16). Aminolysis of sulfonamide also needs acid catalysts (50,51) and can not be used for preparation of azetidines. Other practical methods of cleavage of sulfonamides are base catalyzed alcoholysis and reduction, and these may be available for the preparation of azetidines because azetidines are stable to alkali.

Sulfonamides are very stable to alkali because the positively charged sulfur atom is shielded by negatively charged oxygens from attack by anions.



LXII

Recently Klamann and Bertsch (52) studied the cleavage of sulfonamides by concentrated sodium amyloxide at high temperature. They found sulfonamides of arylamines were cleaved easily but sulfonamides of higher aliphatic amines were

not cleaved, and they explained by electronegativity of aryl groups and steric hindrance of higher alkyl groups. They got a 70.2% yield of hexamethyleneimine, a 80.7% yield of piperidine and a 92.5% yield of pyrrolidine from the corresponding p-toluenesulfonamides by treatment with sodium iso-amyloxide. From the point of view of steric hindrance p-toluenesulfonazetidide should be cleaved more easily than p-toluenesulfonpyrrolidide inspite of a report (55) of no cleavage of p-toluenesulfonazetidide by sodium iso-amyloxide. So alcoholysis of N,N-diethyl-p-toluenesulfonamide and p-toluenesulfonazetidide were tried with 5% iso-amyl alcoholic solution of sodium iso-amyloxide at 170-175°; the former gave a 26.0% of diethylamine but the latter gave no azetidine. This might be due to the difficulty of azetidine anion (correspond to LXII) formation.

Reduction of sulfonamides is little effected by steric hindrance or electronic factors except in the case of an anion reducing agent such as lithium aluminum hydride, and this is the most promising method to obtain azetidines.

Lithium aluminum hydride is not a good reducing agent for sulfonamides (54, 55) and Kolonowski (24) obtained a 10% yield of azetidine as the picrate when the ether solution of p-toluenesulfonazetidide had refluxed with lithium aluminum hydride for 18 hours. Hydrogenolysis of p-toluenesulfonazetidide with Raney nickel and 500 psi hydrogen did not proceed and the starting material was recovered (24). Sodium-amylalcohol has been used as a reducing agent of p-toluenesulfonazetidide and 8-30% yields of azetidine have been reported. Kolonowski reported a 78% yield of 2-methylazetidine from 2-methyl-p-toluenesulfonazetidide by the same procedure. This procedure required large excess (19.5 g.-atom of solium for 1 mole of the sulfonazetidide) and large

amount of amyl alcohol, so it could be applied only in small scale. It is difficult to isolate azetidine in pure form because azetidine forms a azeotropic mixture with amyl alcohol. The use of other reducing systems was tried to find a better method.

Alkali metal and amines, for example lithium and ammonia (56), lithium and ethylenediamine (57), have been reported as good reducing agents. Sodium-ammonia, sodium-ethylenediamine and lithium-ethylenediamine was tried to reduce N,N-diethyl-p-toluenesulfonamide; they gave 51.5%, 52.0% and 42.4% of diethylamine. Sodium or lithium-ethylenediamine was useful as a reducing agent because the reaction proceeded at moderate temperature (70-100°) and the produced diethylamine was easily purified by mere distillations.

Sodium-ethylenediamine was adopted for the reductive cleavage of sulfonazetidides after preliminary experiments. p-Toluenesulfonazetidide (95 g.) gave 1 g. (5.9%) of azetidine and 54.7 g. of a mixture of azetidine and toluene. The isolation of azetidine from the mixture by the method of Howard and Marckwald (20) gave 5.7 g. of pure azetidine. The total yield of azetidine was 18.5%. The isolation of azetidine as the p-toluenesulfonazetidide gave a slightly higher yield and the total yields of azetidine reached to 20.1% Benzenesulfonazetidide gave a mixture of azetidine and benzene, and a separation of azetidine by Howard and Marckwald method gave 22.2% of azetidine and 42.9% of benzene. 2-Naphthalenesulfonazetidide gave 9.4% of fairly pure azetidine by a mere distillation, and 15.7% of naphthalene was also obtained.

The sodium-ethylenediamine system also cleaved the C-S bond of the sulfonamide and produced the corresponding aromatic hydrocarbons. The formation of hydrocarbon prevented a simple purification of azetidine especially

in the case of benzenesulfonazetidide. The molar ratios of the obtained hydrocarbons to azetidine are as follows:

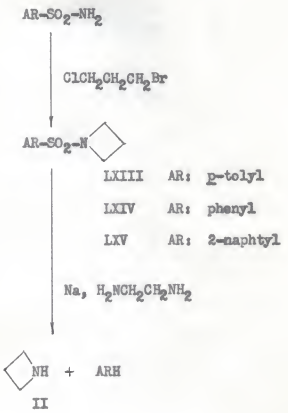
| | |
|---|---|
| toluene | 2.70 |
| benzene | 1.93 |
| naphthalene | 1.45 |

The relative ease of cleavage of the C-S bond to the S-N bond decreases with the series of toluene, benzene and naphthalene; electron withdrawing groups on the benzene ring of sulfonic acid weaken the S-N bond. The same result has been reported (52) in the case of alcoholysis of N-ethyl-sulfonanilides; practically quantitative cleavage of N-ethyl-2-naphthalenesulfonanilide, 84% cleavage of N-ethylbenzenesulfonanilide and 64% cleavage of N-ethyl-p-toluenesulfonanilide in the same condition were reported. The better yield of azetidine would be expected from the sulfonazetidides which has the stronger electron withdrawing substituent, but it is difficult to introduce an electron withdrawing group which is stable to the reduction. The low yield of azetidine in the case of 2-naphthalenesulfonazetidide might be due to little solubility of the sulfonazetidide in ethylenediamine which prevented the uniform reaction.

The reduction with sodium-ethylenediamine has some advantages compared to the sodium-iso-amyl alcohol method; the former required only a small excess of sodium (4 g.-atom of sodium for 1 mole of sulfonazetidide) and very short reaction time and the produced azetidine could be purified by distillation and easily obtained in water free state in the case of p-toluenesulfonazetidide and 2-naphthalenesulfonazetidide.

Chart IV

Preparation and Reductive Cleavage of Sulfonazetidides



## SUMMARY OF RESULTS

(1) The pyrolysis of 5,5-dimethyl-1,3-dioxane-2-one with potassium methylcyanamide gave a 32% yield of 3,3-dimethyloxetane instead of 1,3,3-trimethyl azetidine.

(2) The pyrolysis of the polymer produced by a reaction of 1,3-butanediol and urea with potassium carbonate gave a small amount of volatile basic compound, but the yield was so small that the identification of the compound could not be done and it is not a good synthetic method of azetidines.

(3) The pyrolysis of 3-methyltetrahydro-1,3-oxazin-2-one gave a 68% yield of methylallylamine but no 1-methylazetidine.

(4) The pyrolysis of 3,5,5-trimethyltetrahydro-1,3-oxazine-2-one gave a 15.7% yield of a volatile amine which was supposed to be 1,3,3-trimethylazetidine with other basic compounds.

(5) The reductive cleavage of p-toluenesulfonazetidide with sodium-ethylenediamine gave a 18.3% of azetidine, but a part of it boiled with toluene. Benzenesulfonazetidide and 2-naphthalenesulfonazetidide gave 22.2% and 9.4% yields of azetidine respectively.

## EXPERIMENTAL

### Pyrolysis of 1,3-Dioxane-2-one with Potassium Methylcyanamide

Cyanogen Bromide. Sodium cyanide (54 g.) in 240 ml. of water was added dropwise to 100 g. of bromine covered with 10 ml. of water with external cooling and stirring. It took about one and half hours. Stirring was continued for 2 hours after the addition of sodium cyanide. Distillation of the reaction mixture gave 52 g. (yield: 78.5%) of cyanogen bromide, b.p. 60-65°.

Potassium Methylcyanamide. Cyanogen bromide (30 g.) in 20 g. ether was added to 54 g. of 50% aqueous methylamine in a 250 ml. three-neck flask fitted with a stirrer, a dropping funnel and a reflux condenser dropwise with external cooling by an ice bath. The addition was done in one hour, then 32 g. of 50% aqueous potassium hydroxide was added. Stirring was continued for 2 hours with external cooling after the addition. The reaction mixture was extracted with ether. Ether was evaporated off from the extract, and the residue was adjusted to pH 13.0 by an addition of alcoholic potash. Viscous matter was obtained on drying of the product. White precipitate (8 g.) was obtained by an addition of 100 g. of chloroform.

Pyrolysis of 5,5-dimethyl-1,3-dioxane-2-one with Potassium Methylcyanamide. Ten gram of 5,5-dimethyl-1,3-dioxane-2-one and 7.2 g. of potassium methylcyanamide were placed in a 25 ml. three-neck flask fitted with a gas delivery tube, a thermometer and an outlet tube. The outlet tube led to a trap cooled in a dry ice bath and then to the atmosphere through a calcium chloride tube. Heating was accomplished with a sand bath. When the temperature in the

acetate at 175-195° for 5 hours. A distillation of the reaction mixture gave 46 g. (yield: 34.4%) of crude 1,3-butanediolmonourethane, b.p. 130-150° at 15 mm Hg. (reported (44), b.p. 174-178° at 15 mm Hg.). The fraction (48 g.) was heated with 3 g. of zinc chloride at 185-200° for 8 hours. A distillation of the reaction mixture gave 25 g. of a fraction which boiled at 120-160° at 25 mm Hg., $n_D^{25}$: 1.4420, and was supposed to be a mixture of 1,3-butanediol and the monourethane. The residue was a viscous resinous matter.

3-Chloropropyl Methylcarbamate (LII). Chloropropyl chloroformate (185 g.) was added dropwise into a cooled aqueous solution of methylamine at 17-20° with stirring and external cooling. It took one hour to complete the addition of the chloroformate. Stirring was kept at 20-30° for 5 hours. The two layers were separated and the aqueous layer was extracted with ether. The ether extract was combined with the ester layer. Ether was evaporated off in vacuum, and a distillation of the residue gave 126 g. (yield: 71%) of 3-chloropropyl methylcarbamate, b. p. 92-97° at 1.5 mm Hg., $n_D^{25}$: 1.4565 (reported (47), b. p. 104.5-106° at 1 mm Hg., $n_D^{27}$: 1.4548).

3-Methyltetrahydro-1,3-oxazin-2-one(LIII). 3-Chloropropyl methylcarbamate (125 g.) was dissolved into 450 g. of 10% alcoholic solution of potassium hydroxide and refluxed for 2 hours. The precipitated inorganic salts were filtered and washed with 500 ml. of alcohol. A distillation of the combined filtrate and washing gave 33.8 g. (yield: 28.7%) of 3-methyltetrahydro-1,3-oxazin-2-one, b. p. 108-113° at 0.8 mm Hg., $n_D^{20}$: 1.4691.

Pyrolysis of 3-Methyltetrahydro-1,3-oxazin-2-one. Ten grams of 3-methyltetrahydro-1,3-oxazin-2-one and 2 g. of potassium carbonate were heated in a 25 ml. flask fitted with a thermometer and an outlet tube at 210-230° for one hour. The outlet tube was led to a trap cooled in a dry ice bath and then to

the atmosphere through a calcium chloride tube. A liquid (6.1 g.) was collected in the trap, and the amount of the residue in the reaction flask was 4.2 g. The liquid was distilled over barium oxide and 4.2 g. (yield: 68%) of N-methylallylamine (LIV), b.p. 69-71°, picrate m.p. 115-115.5° (reported (59), b.p. 64-66°, picrate m.p. 113-115.5°), was obtained.

3-Bromo-2,2-dimethyl-1-propyl acetate (LV). 2,2-Dimethyl-1,3-propanediol (100 g.) in 200 ml. of glacial acetic acid was added into a solution of 86 g. of hydrogen bromide in 400 ml. of glacial acetic acid dropeise with stirring and external cooling during a course of 40 minutes. The mixture was heated under reflux with stirring for 18 hours. Acetic acid was removed by a distillation under vacuum and the residue was distilled and 167 g. (yield: 88.5%) of 3-bromo-2,2-dimethyl-1-propyl acetate, b. p. 93-98° at 20 mm Hg., $n_D^{20}$: 1.4530, was obtained.

3-Bromo-2,2-dimethyl-1-propanol (LVI). 3-Bromo-2,2-dimethyl-1-propyl acetate (167 g.) was dissolved in 600 ml. of ethyl alcohol, 8 ml. of 48% hydrobromic acid was added and the mixture was heated under a partial reflux. After the collection of 500 ml. distillate, 500 ml. of ethyl alcohol and 11 ml. of 48% hydrobromic acid was added and the reflux was continued for 12 hours. After the evaporation of ethyl alcohol a distillation of the residue gave 128 g. (yield: 90.1%) of 3-bromo-2,2-dimethyl-1-propanol, b. p. 86-88° at 24 mm Hg., $n_D^{20}$: 1.4780.

3-Bromo-2,2-dimethyl-1-propyl Chloroformate (LVII). Phosgene (75 g.) was passed through 125 g. of 3-bromo-2,2-dimethyl-1-propanol with external cooling during a course of three hours. The quantity of phosgene was measured by the weight increase of the reaction mixture. The reaction mixture was kept in room temperature for 16 hours, washed with water, dilute sodium

carbonate solution and then water, dried over magnesium sulfate and distilled. 3-Bromo-2,2-dimethyl-1-propyl chloroformate (146 g., yield: 85%), b. p. 96-104° at 22 mm Hg., $n_D^{20}$: 1.4690, was obtained.

3-Bromo-2,2-dimethyl-1-propyl Methylcarbamate (LVIII). 3-Bromo-2,2-dimethyl chloroformate (145 g.) was added dropwise to 150 g. of 50% aqueous solution of methylamine with stirring and external cooling at 15-20° and the mixture was kept stirring for 5 hours. The two layers were separated and the water layer was extracted with ether. The combined ether extract and ester layer was dried over magnesium sulfate. Distillation of the residue after evaporation of ether gave 125 g. (yield: 88.5%) of 3-bromo-2,2-dimethyl-1-propyl methylcarbamate, b. p. 108-110° at 1.0 mm Hg., $n_D^{20}$: 1.4790.

2,2-Dimethyl-3-methylamino-1-propanol (LIX). 2,2-Dimethyl-3-bromo-1-propanol (120 g.) and 518 g. of 30% aqueous methylamine were placed in a 600 ml. pressure bottle and shaked at 70° for 30 hours. The reaction mixture was acidified with hydrochloric acid, and extracted with ether. Ether was evaporated off from the ether extract, and a distillation of the residue in vacuum gave 27 g. (yield: 29%) of 2,2-dimethyl-3-methylamino-1-propanol, b. p. 65-80° at 28 mm Hg., m. p. 39°.

5,5,5-Trimethyltetrahydro-1,3-oxazin-2-one (LX). a) Cyclization of 3-Bromo-2,2-dimethyl-1-propyl Methylcarbamate. 3-Bromo-2,2-dimethyl-1-propyl methylcarbamate (120 g.) was dissolved in 250 g. of ethyl alcohol which contained 51.5 g. of potassium hydroxide and the mixture was refluxed for 2 hours on a steam bath. The precipitated potassium bromide was filtered off and washed with 100 ml. of ethyl alcohol. Alcohol was evaporated from the combined filtrate and washing, and a distillation of the residue gave 69 g. (yield: 90.2%) of 5,5,5-trimethyltetrahydro-1,3-oxazin-2-one, B. p. 115-117°

at 1.0 mm Hg., $n_D^{20}$: 1.4680.

b) Reaction of 2,2-Dimethyl-3-methylamino-1-propanol with Diethyl Carbonate. A mixture of 26 g. of 2,2-dimethyl-3-methylamino-1-propanol and 29 g. of diethyl carbonate was heated to reflux. Two grams of sodium was added in small pieces and the heating was continued for 45 hours. The temperature of the boiling mixture decreased from 120° to 100°. The produced ethyl alcohol was distilled off and a distillation of the residue in vacuum gave 11.1 g. (yield: 34.6%) of 3,5,5-trimethyltetrahydro-1,3-oxazin-2-one, b. p. 158-160° at 24 mm Hg., $n_D^{20}$: 1.4649. Its infrared spectrum showed the same absorptions with that of the sample which was obtained in a).

Pyrolysis of 3,5,5-Trimethyltetrahydro-1,3-oxazin-2-one. a) With Potassium Carbonate. Ten grams of 3,5,5-trimethyltetrahydro-1,3-oxazin-2-one and 2 g. of potassium carbonate were placed in a 25 ml. three-neck flask fitted with a gas delivery tube, a thermometer and an outlet tube. The outlet tube led to a trap cooled in a dry ice bath, and then to the atmosphere through a calcium chloride tube. Heating was accomplished with a sand bath. A slow stream of nitrogen was introduced through the gas delivery tube. When the temperature in the reaction flask reached 250°, the flask contents began bubbling. As the temperature in the flask was gradually raised to 280°, the temperature of the vapor rose to 125°. At the end of 5 hours the distillate collected in the trap reached 1.28 g. and amount of the residue was 10.2 g. The distillate was dried over potassium carbonate and distilled. Half gram of a fraction which boiled at 65-90° and 0.4 g. of a fraction which boiled at 100-118° were obtained. Both fractions were soluble in water and alkaline to lithmus and had ammonia-like odour. The residue gave 6.5 g. of unreacted 3,5,5-trimethyltetrahydro-1,3-oxazin-2-one, b. p. 85-85° at 0.1 mm Hg., by

a distillation.

b) With Sodium Methoxide. By the same procedure as above using 10 g. of 3,3,5-trimethyltetrahydro-1,3-oxazin-2-one and 2 g. of sodium methoxide, 2.92 g. of the distillate and 8.00 g. of the residue were obtained. The distillate was dried over potassium hydroxide and distilled. Two fractions which boiled at 55-75° (1.10 g.) and 115-136° (1.08 g.) were obtained. The lower temperature boiling fraction was dissolved in 6 g. of acetone and dry hydrogen chloride was passed through until it became acidic, then viscous oily matter and colorless precipitate were separated. The crystal was washed with ether. It melted at 150-152° and it was hygroscopic. This fraction was supposed to be 1,3,3-trimethylazetidine (reported (7) b. p. 75-74°, HCl salt m. p. 150°). The residue of the pyrolysis gave 5 g. of the unreacted 3,3,5-trimethyltetrahydro-1,3-oxazin-2-one, b. p. 90-95° at 0.4 mm Hg.

c) With Potassium Cyanide. The same pyrolysis as above using 10 g. of 3,3,5-trimethyltetrahydro-1,3-oxazin-2-one and 2 g. of potassium cyanide gave 2.5 g. of distillate and 7.6 g. of the residue. Redistillation of the distillate over sodium gave 0.07 g. of volatile amine, b. p. 45-55°.

## Cleavage of Sulfonamides

Cleavage of N,N-Diethyl-p-toluenesulfonamide. N,N-Diethyl-p-toluenesulfonamide was prepared by a reaction of p-toluenesulfonyl chloride with diethylamine in the presence of aqueous sodium hydroxide and recrystallization from petroleum ether.

a) Reductive Cleavage with Sodium-Ammonia. N,N-Diethyl-p-toluenesulfonamide (22.7 g.) and 50 ml. of ether were placed in a 200 ml. flask cooled with a dry ice bath, and 17 g. of liquid ammonia was added. Sodium (23 g.) was added in

small pieces with stirring. After the addition of sodium the mixture was gradually warmed to room temperature with stirring during a course of 40 minutes. Absolute alcohol (100 ml.) was added dropwise to the mixture, and finally 80 ml. of water was added dropwise. The mixture was distilled and the fraction boiling below 95° was collected. The distillate was acidified with sulfuric acid and evaporated from an evaporating dish on a steam bath. The residue was dissolved in small amount of water and poured into 80 g. of 25% potassium hydroxide, and the mixture was distilled and 5.5 g. of a fraction boiling below 85° was collected. The distillate was dried over potassium hydroxide, and distilled. Diethylamine (2.51 g., yield: 51.5%), b. p. 56-57°, was obtained.

b) Reductive Cleavage with Sodium-Ethylenediamine. N, N-Diethyl-p-toluenesulfonamide (22.7 g.) and 70 g. of ethylenediamine were placed in a flask fitted with a reflux condenser and a stirrer. The mixture was heated at 90° and 9.2 g. of sodium was added in small pieces with stirring. After the addition of sodium the mixture was refluxed for 2 hours, then a low temperature boiling fraction which boiled below 80° was distilled into an ice cooled trap. The distillate was dried over potassium hydroxide and distilled. Diethylamine (3.80 g., yield: 52.0%), b. p. 56-58°, $n_D^{20}$: 1.3870, was obtained.

c) Reductive Cleavage with Lithium-Ethlenediamine. Using lithium instead of sodium the same treatment as above gave 3.10 g. (yield: 42.4%) of diethylamine. Low reaction temperature of 30-40° gave a less yield of diethylamine, 2.25 g. (yield: 30.8%).

d) Alcoholysis by Sodium iso-Amyloxide. Sodium (14.3 g.) was dissolved in 150 ml. of iso-amyl alcohol with stirring and heating at 170-175°. N,N-Diethyl-p-toluenesulfonamide (11.55 g.) was added and heated under reflux at

170-175° for 7 hours, then a low temperature boiling fraction was distilled into an ice-cooled trap. A redistillation of the distillate over barium oxide gave 0.95 g. (yield: 26%) of diethylamine, b. p. 45-55°.

The results of cleavage of N,N-diethyl-p-toluenesulfonamide are summarized in Table.

Table. Cleavage of N,N-Diethyl-p-toluenesulfonamide

| Sulfonamide: (g.) | Reducing Agent | Time (hr.) | Temp. (°) | Diethylamine (% Yield) |
|---|---|---|---|---|
| 22.7 | $NH_3$:17 g., Na:23 g. | 0.7 | -35 | 51.5 |
| 11.4 | i-AmOH:150ml., Na:14.5 g. | 6 | 170 | 26.0 |
| 22.7 | EDA*:70 g., Na:9.2 g. | 2 | 90 | 52.0 |
| 22.7 | EDA :60 g., Li:2.8 g. | 1.5 | 90 | 42.4 |
| 22.7 | EDA :60 g., Li:2.8 g. | 7 | 55 | 50.8 |

*EDA: ethylenediamine

p-Toluenesulfonazetidide (LXIII). 1-Bromo-3-chloropropane (236 g.) and 257 g. of p-toluenesulfonamide were dissolved in 600 ml. of 95% ethyl alcohol in a 2 l. three neck flask fitted with a stirrer, a reflux condenser and a dropping funnel. The mixture was heated to reflux, and 120 g. of sodium hydroxide in 680 g. of water was added dropwise over a period of 6 hours with stirring. Alcohol was distilled off and the separated wax was recrystallized from alcohol. p-Toluenesulfonazetidide (125 g., yield: 39.5%), m.p. 115-120° (reported (18) m. p. 120°) was obtained.

Benzenesulfonazetidide (LXIV). Benzenesulfonazetidide (67 g., yield: 22.7%), m. p. 67-68° (reported (18) m. p. 68°) was obtained by the same procedure in the preparation of p-toluenesulfonazetidide using 235 g. of benzenesulfonamide, 256 g. of 1-bromo-3-chloropropane and 120 g. of sodium hydroxide.

2-Naphthlenesulfonazetidide (LXV). 2-Naphthalenesulfonazetidide (15 g., yield: 22.5%), m. p. 78-79° was obtained by the same procedure in the previous experiments using 56 g. of 2-naphthlenesulfonamide, 47.5 g. of 1-bromo-3-chloropropane and 21.6 g. of sodium hydroxide.

Reductive Cleavage of Sulfonazetidides. a) p-Toluenesulfonazetidide. p-Toluenesulfonazetidide (95 g.) and 335 g. of ethylenediamine were placed in a 1 l. three neck flask fitted with a stirrer, a thermometer and a reflux condenser. The mixture was heated at 90° and 45 g. of sodium was added in small pieces with stirring, keeping the temperature below 100°. After the addition of sodium the mixture was kept refluxing for 2 hours at 100°, then 49 g. of a low temperature boiling fraction was distilled into an ice cooled trap. The distillate was redistilled through a Fenske column and the following fractions were obtained:

| | | | |
|---|---|---|---|
| (i) | b. p. 60-70°, | $n_D^{20}$: 1.4515 | 1.0 g. |
| (ii) | b. p. 85-105°, | $n_D^{20}$: 1.4781 | 34.7 g. |
| (iii) | b. p. 115-117°, | $n_D^{20}$: 1.4565 | 7.2 g. |

The fraction (i) formed a picrate which melted at 166-167° (azetidine picrate reported (4) m. p. 166-167°). The fraction (ii) (15 g.) was treated with 12 g. of sulfuric acid in 45 g. of water. Acid-insoluble oil (8.85 g.) was separated. The separated oil boiled at 108-109°, and its refractive index was $n_D^{20}$:1.4950, and it was converted to benzoic acid, m. p. 119-120°, by

a dichromate oxidation. The separated oil was concluded as toluene (yield: 49.5%). The acid layer was added to 45 g. of 50% potassium hydroxide aqueous solution and 11 g. of a fraction which boiled below 100° was distilled. Sodium hydroxide was added to the distillate and the separated layer was dried over barium oxide and distilled, and 1.6 g. of azetidine, b. p. 63-65°, $n_D^{20}$: 1.4300 (reported (18) b. p. 65°) was obtained. The fraction (ii)(1.2653 g.) gave 0.5906 g. of p-toluenesulfonazetidide, m. p. 120-121°, by a treatment with p-toluenesulfonylchloride and aqueous alkali. The fraction (iii) was ethylenediamine. The total yield of azetidine is 18.8% and if isolated as p-toluenesulfonazetidide it would reach to 20.1%.

b) Benzenesulfonazetidide. The same procedure as above using 55 g. of benzenesulfonazetidide, 194 g. of ethylenediamine and 25.5 g. of sodium gave the following fractions:

(i) b. p. 63-70°, $n_D^{20}$: 1.4510 0.95 g.

(ii) b. p. 70-78°, $n_D^{20}$: 1.4900 15.5 g.

(iii) b. p. 78-115°, $n_D^{20}$: 1.4619 13.8 g.

The combined fraction (i) and (ii) (14 g.) gave 9.0 g. (yield: 42.9%) of benzene and 3.4 g. (yield: 22.2%) of azetidine, b. p. 65-66°, $n_D^{20}$: 1.4298, picratem. p. 166-167°.

c) 2-Naphthalenesulfonazetidide. The same procedure as above using 14 g. of 2-naphthalenesulfonazetidide, 50 g. of ethylenediamine and 6.5 g. of sodium gave 0.30 g. (yield: 9.4%) of crude azetidine, b. p. 60-70°, $n_D^{20}$: 1.4460, which supposed to contain some ethylenediamine and naphthalene. An extraction of the reaction mixture with benzene, and a distillation of the benzene extract gave 1.0 g. (yield: 15.7%) of crude naphthalene, b. p. 105-115° at 25 mm Hg., m. p. 55-70°); it was contaminated with tarry material.

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# INVESTIGATION OF SOME ROUTES TO AZETIDINE

by

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AN ABSTRACT OF THESIS

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The purpose of this investigation was to study new methods by which azetidine and its derivatives could be prepared. The reactions studied were: 1) pyrolysis of 5,5-dimethyl-1,3-dioxane-2-one with potassium methylcyanamide, 2) synthesis and pyrolysis of hexahydro-2-pyrimidones and tetrahydro-1,3-oxazin-2-one and 3) cleavage of sulfonamides.

The pyrolysis of 5,5-dimethyl-1,3-dioxane-2-one with potassium methylcyanamide gave only 3,3-dimethyloxetane but no 3,3,5-trimethylazetidine.

A simple synthetic method of hexahydro-2-pyrimidones by a reaction of 1,3-diols and urea reported by Paquin was tried, but the reaction could not be repeated, due mainly to polymer formation. Pyrolysis of the polymer which was obtained by a reaction of 1,3-butanediol with excess of urea, over potassium carbonate gave a small amount of liquid which appeared to be impure cyclic imine from its boiling point and basic property, but the yield was so low that identification could not be done and the more extensive studies were not tried. Reduction of 5,5-diethyl-barbituric acid with lithium aluminum hydride to 5,5-diethylhexahydro-2-pyrimidone was unsuccessful. There are, of course, other preparations for cyclic ureas which undoubtedly will work, but before pursuing this approach further, it seemed wise to work with cyclic urethanes, as one might expect these to be easier to pyrolyse. It was felt that pyrolysis should break the C-N bond before the C-O bond, on the basis of bond energy.

3-Methyltetrahydro-1,3-oxazin-2-one was prepared by a treatment of 3-chloropropyl methylcarbamate with alkali, and its pyrolysis over potassium carbonate gave a 68% yield of methylallylamine, but no 1-methylazetidine. So, this method should be applied only to compounds which have no $\beta$-hydrogen atom. 3,5,5-Trimethyltetrahydro-1,3-oxazin-2-one which has no $\beta$-hydrogen atom was prepared by two methods; the one was a cyclization of 3-bromo-2,2-

dimethyl-1-propyl methylcarbamate by an alkli treatment, and the other was a cyclic urethane formation of 2,2-dimethyl-3-methylamino-1-propanol with diethyl carbonate. The pyrolysis of 3,5,5-trimethyltetrahydro-1,3-oxazin-2-one gave a mixture of volatile amines which was supposed to contain 1-methylazetidine.

Cleavage of N,N-diethyl-p-toluenesulfonamides by lithiumethylenediamine, sodium-ethylenediamine, sodium-ammonia and sodium iso-amyloxide was studied, and sodium-ethylenediamine was found to give the best yield (52.0%) of diethylamine. Cleavage of p-toluenesulfonazetidide, benzenesulfonazetidide and 2-naphthalenesulfonazetidide by sodium-ethylenediamine gave 18.3%, 22.2% and 9.4% of azetidine respectively. The sodium-ethylenediamine reductive cleavage of sulfonazetidides has advantages in the amount of sodium and reaction time compared to the usual sodium-iso-amyl alcohol method.