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Title: THE INVESTIGATIONS OF THE METHODS FOR THE REDUCTION OF CHLOROPYRIMIDINES

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This thesis investigated on the dehalogenation of 2, 4-dichloropyrimidine in various different conditions. These conditions were changed by varying the solvents, the amount of catalysts and the hydrogen chloride acceptors in order to study the effects on the yields.

It was found that the ether-aqueous sodium hydroxide medium with palladium on charcoal as the catalysts gave the best yield at the proper time of the reaction only when the ether: water ratio of 5: 1. The ethanol was found as the side product during the reduction.

The isolation problem of pyrimidine from the reaction mixture was studied and some organic compounds have been used as the "chaser" in the fractional distillation using Podbielniak column. Quinoline, naphthalene, and N, N-dimethylaniline were found to be the effective ones, but o-xylene and mesitylene formed the azeotropic

mixture with pyrimidine. The compositions of pyrimidine fractions were identified by the method of gas chromatography analysis.

The Investigations of the Methods For the Reduction of Chloropyrimidines

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INTRODUCTION

Since the beginning of the last century, many investigations have been carried out in an attempt to prepare pyrimidine. The first pyrimidine derivative to be isolated was alloxan, prepared in 1818 by Brugnatelli through the oxidation of uric acid using nitric acid as the oxidant.

Thirty years later, Frankland and Kolbe reported the first synthetic preparation of simple pyrimidine derivative. These investigators treated propionitrile with metallic potassium and isolated 4-amino-2, 6-diethyl-5-methylpyrimidine from the reaction product.

Most of the efforts to prepare unsubstituted pyrimidine or its hydroxylated derivatives have involved dehydroxylation procedure. This consists of first converting the hydroxylated pyrimidines to the chloro derivatives which are then reductively dehalogenated using a variety of reductants.

However, some pyrimidines have been obtained through the thionation of hydroxylated derivatives followed by desulfurization of the resultant thiopyrimidines. For example, Cavalieri and Bendich (6) have reported the preparation of pyrimidine by the reduction of 2, 6-dimercaptopyrimidine with Raney nickel; however, no details were given in regard to yields.

2, 4, 6-Trichloropyrimidine, which is readily obtained from barbituric acid, was reduced to corresponding pyrimidine by Gabriel as early as Whittaker (20) using zinc dust and water as the reductant.

In 1907, Wheeler (19) tried to reduce 2, 4-dichloropyrimidine with hydriodic acid and red phosphorus but instead of obtaining the expected product, he found that the 2-chloro substituent had been reduced while the 4-chloro substituent had been hydrolyzed yielding the product 4-hydroxypyrimidine. Ballard and Johnson (3) applied hydriodic acid and red phosphorus reductant to 2, 4-dichloropyrimidine-5-carboxylic using a glacial acetic acid medium. As in the case reported by Wheeler, only the 2-chloro substituent was reduced while the 4-chloro substituent underwent hydrolysis yielding 4-hydroxypyrimidine-5-carboxylic acid.

In the case of ethyl 2-ethylmercapto-6-chloropyrimidine-5-carboxylate, zinc dust was used in an ethyl alcohol-water medium. Removal of the solvent and excess metal left a tarry product which, when suspended in water, was extracted with ether, yielding the desired product. The yields from a series of different experiments varied between 40-50%. The product was a low melting solid (49-50^{o}C) which readily recrystallized from methanol. Attempt to apply this procedure to the reduction of ethyl 2, 4-dichloropyrimidine-5-carboxylate, however, was unsuccessful.

Johnson and Joyce (11) found that 2-mercapto-4-

chloropyrimidine was readily reduced by zinc dust to the corresponding 2-mercaptopyrimidines. Later, they discovered that the behavior of the zinc dust reductant was just the opposite of hydriodic acid and red phosphorus reductant as applied to 2, 4-dichloropyrimidines. For example, the 4-chloro substituent of 2, 4-dichloro-5-ethoxypyrimidine was readily reduced by zinc dust to 2-chloro-5-ethoxypyrimidine. However, these investigators noted that the replacement of 2-chloro substituent with benzylmercapto group prevented the reduction of 4-chloro substituent in 2-benzylmercapto-4-chloropyrimidine. This was attributed to a steric affect but may have been the consequence of other factors.

2-Amino-4-chloropyrimidine was reduced by treatment with finely divided metallic zinc in an aqueous dispersion under alkaline conditions, as reported by Northey (15). Kuh, using a mixture of activated charcoal and zinc dust, successfully dechlorinated 2-amino-4-chloropyrimidine but unfortunately failed to report any yield data.

McOmie and White (14) found that dehalogenation and desulfurization occurred simultaneously when 5-bromo-2-methylthiopyrimidine was treated with Raney nickel to yield the corresponding 2-methylpyrimidine. This reaction was carried out in an ammoniacal alcoholic medium; the pyrimidine was isolated in 38% yield as the mercuric chloride complex. However, when 5-bromopyrimidine-2-carboxylic acid was subjected to the same treatment, only degradation

products and starting materials were recovered.

Gabriel and Colman (9) were the first investigators to employ catalytic reduction methods to the dehalogenation of chloropyrimidines. These workers employed calcium carbonate, impregnated with palladium hydroxide, as a catalyst and obtained 2-amino-2-methylpyrimidine from 2-amino-6-chloro-4-methylpyrimidine.

Boarland, McOmie and Timms (4) have investigated several methods for the preparation of pyrimidines based on the reduction of the chloro derivatives. This work centered on catalytic reductions using a variety of catalysts, solvents, and hydrogen chloride acceptors in studies involving the reduction of 2-chloropyrimidine. These workers reported that the best yields were obtained with magnesium oxide, as the hydrogen chloride acceptor, using palladium-strontium carbonate, palladium-barium sulfate catalysts; Raney nickel could not be used in place of palladium catalysts in these reactions.

In all these experiments the reduction had to be stopped when the theoretical amount of hydrogen had been absorbed since the nuclear reduction continued with little decrease in the rate of hydrogen uptake. Due to the solubility of the pyrimidine mercury complex in aqueous salt solution and dilute hydrochloric acid, it was necessary to remove the pyrimidine by steam distillation from an alkaline solution prior to precipitation with mercuric chloride.

These investigators also reported the isolation of pyrimidine

from aqueous solution by the formation of flavan complexes. For example, pyrimidine and 4, 6-dimethylpyrimidine readily formed complexes with ratios of flavan to water to pyrimidine = 2: 2: 1 and 2: 1: 1, respectively. These complexes could be extracted from dilute aqueous solution in high yield, thus permitting the recovery of pyrimidine in a very pure state by distillation of the complex. Since these flavan complexes were reported to possess many advantages over the mercuric chloride complex, they appear to offer a practical approach to the bulk preparation of pure pyrimidines.

In their studies of the catalytic dehalogenation of pyrimidine derivatives, Lythgoe and Rayner (13) reported that solvolysis of the nuclear chlorines occurred when the reaction was carried out in dilute sodium hydroxide solutions. This was especially common with di- and tri-chloropyrimidines, or any pyrimidine where the halogen substituent was more reactive than those found in 5-chloro-2-phenyl or 2-chlorophenyl pyrimidines. These investigators concluded that the presence of a base desirable, in order to neutralize the hydrogen chloride liberated in the reaction, for the successful dehalogenation of the chloro-substituted pyrimidines to pyrimidines.

Lythgoe and Rayner also reported the preference of 2, 5-dichloropyrimidine, rather than the 2, 4-dichloro isomer, as the starting material for the preparation of pyrimidine, because the 5-chloro substituent was relatively unreactive as contrasted to 6-chloro

substituent while the 2-chloro substituent was not unduly reactive towards water and alcohol.

In their initial experiments, these investigators found that the reduction of 2, 5-dichloropyrimidine with hydrogen using palladized barium sulfate catalyst in the presence of dilute sodium hydroxide solution was unsatisfactory because some of the reagent was converted to 5-chloro-2-hydroxypyrimidine. Furthermore, the use of methanol containing suspended barium oxide gave 5-chloro-2-methoxypyrimidine. When water or water containing suspended calcium carbonate was employed as the solvent, nuclear reduction ensued yielding a tetrahydropyrimidine derivative. Satisfactory results were obtained when 2, 5-dichloropyrimidine was reduced in the presence of suspended magnesium oxide. However, it was necessary to control the hydrogen uptake to avoid muclear reduction. By stopping the reaction after theoretical amount of hydrogen had been absorbed, the pyrimidine was obtained as the main product, contaminated by small amounts of 5-chloropyrimidine and tetra-hydropyrimidine. The latter impurity was eliminated by precipitating the product as the mercuric chloride complex in a weekly acidic solution; the tetra-hydro compound formed a complex which is soluble in acid solution up to pH 5. The pyrimidine was then regenerated and obtained in a pure state in 45% yield by fractional distillation.

In 1951, Whittaker (20) reported the catalytic dehalogenation of

both 2, 4-dichloropyrimidine and 2, 4, 6-trichloropyrimidine using aqueous alcoholic solutions with a palladized charcoal catalyst in the presence of an appropriate hydrogen chloride acceptor. With sodium chloride present, there was some hydrolysis of the reactive halogen resulting in a lower uptake of hydrogen. In the presence of sodium acetate, the resultant solution was buffered at a slightly acidic level; nuclear reduction of the ring occurred along with the removal of the chloro substituent. With magnesium oxide, however, he found that nuclear reduction did not occur and as a consequence he obtained a good yield of pyrimidine which he isolated as the mercuric chloride complex.

The dehalogenation of 2-chloropyrimidine using polyvinyl alcohol impregnated with palladium proceeds smoothly according to Rampino and Nord (16). However, in this case, the reduction of the pyrimidine ring became a problem. Even when the hydrogen uptake was controlled by limiting the amount of hydrogen absorbed, only a 58% yield of pyrimidine was obtained.

In an effort to avoid both nuclear reduction and solvolysis of nuclear substituents, Smith and Christensen (17) employed an immiscible mixture of ether-aqueous sodium hydroxide medium. This heterogeneous system minimized losses through hydrolysis of reactive chloro substituents. Only in the case of the extremely reactive halogens of 4, 6-dichloro-5-nitropyrimidine was such side

reaction noted.

Smith and Christensen (17) reported that the procedure based on such a heterogeneous solvent system (ether-aqueous sodium hydroxide) was not applicable to all chloropyrimidines investigated; in some cases dehalogenation was unsuccessful and only starting materials were recovered.

However, the yields using the heterogeneous solvent system were significantly greater than those employing a homogeneous system. The pyrimidine ring was very stable towards catalytic reduction under basic conditions and no nuclear reduction was detected even after 12 hours agitation and exposure to hydrogen at three atmosphere pressures. Moreover, there was no evidence to hydrolysis or the formation of other side products. When alcohol-base system were used, alkoxylation was frequently observed.

Tsuda and Ogawa (18) have described a procedure for the reduction of 2-amino-4-methyl-6-chloropyrimidine and 2-amino-4, 6-dichloropyrimidine by zinc and water to the corresponding dehalogenated pyrimidines; the yields, however, were very poor. Moreover, attempts to substitute aluminum and magnesium for zinc led to no better results. However, reductions using Zn-Hg and sodium hydroxide, zinc powder, stannous hydroxide, aluminum hydroxide, and sodium hydroxide gave good results with the amino-chloropyrimidines. When pure methanol or 60% aqueous-methanol

was used as the medium in place of water, these reactions were accompanied by methoxylation.

Adrien Albert and Richard Royer (2) discovered a unique method for replacing an active chlorine atom in heterocyclic compounds by hydrogen without the use of catalytic hydrogenation or reducing agents. In this way, the hydrogenation of the nucleus could be avoided and one could preserve the easily reducible groups such as $-NO_2$ and -CN. These investigations condensed the chloro compounds with toluene-p-sulphonyl hydrazide and heated the resulting adducts with dilute alkali. The yield of the dehalogenated compounds ranged from 40 to 73%.

Since this laboratory was interested in the small scale preparation of pyrimidines and their alkyl derivatives, the resume of the earlier work in this area was most interesting.

It was apparent from the study of the literature that the best approach to the preparation of pyrimidine and alkyl pyrimidines was through the conversion of the hydroxylated pyrimidines to their chloro derivatives followed by dehalogenation to the desired product. It was also evident that the dehalogenation procedures present three major problems:

(1) Prevention of nuclear reduction during or immediately following the dehalogenation of the pyrimidine.

(2) Prevention of the hydrolysis of the reactive chloro

substituent during the reduction.

(3) Isolation of the pyrimidine which is usually prepared in small scale operations (less than 10 grams).

One of the more promising intermediates for this preparation is 2, 4-dichloropyrimidine which is readily obtained from uracil by chlorination procedures.

In an attempt to dehalogenate 2, 4-dichloropyrimidine using a palladium catalyst in an alcoholic solvent, magnesium oxide was used to control the acidity resulting from the released hydrogen chloride. Under these conditions the hydrogen uptake amounted to 200% of that required to dehalogenate the pyrimidine before absorption ceased. Nevertheless, small amounts of mercuric chloride-pyrimidine complex was isolated indicating that some of the pyrimidine had escaped nuclear reduction.

The substitution of calcium oxide in place of magnesium oxide did not prevent nuclear reduction. When sodium hydroxide was used in place of magnesium oxide to remove the released hydrogen chloride, the hydrogen uptake was less than theoretical. In this series of experiments, the pyrimidine was removed by distillation using a Podbielniak column; o-xylene was employed as a chaser. Under these conditions it was necessary to remove the water (drying agent) prior to distillation; otherwise, xylene was removed at 91.5^{o}C in form of an azeotrope which destroyed its effectiveness as a chaser.

The best procedure for the reduction of chloropyrimidines appears to be those based on an immiscible system of ether-water, using sodium hydroxide to remove the hydrochloric acid. This procedure gave yields which varied between 70 and 90%. One other product, namely ethanol, was noted in certain runs. Apparently there is some hydrogenolysis occurring during the reduction.

Because of the effectiveness of sodium hydroxide in preventing nuclear reduction during dehalogenation in an ether-water system, the behavior of this reagent was tested in a methanolic solvent. Although the hydrogen uptake indicated no nuclear reduction, the isolation of the product proved unsatisfactory, only the azeotropic mixtures being recovered.

In order to determine the optimal conditions for the dehalogenation using the immiscible solvents, ether-water, various ratios of the two solvents were investigated. When the ether to water ratio fell below 100:15, the yields dropped markedly. Using pure ether gave very poor yields although dehalogenation did occur.

Although the boiling point range of the pyrimidines appeared to be consistent with the values reported in the literature for this compound, the melting points were usually 8-10 degrees lower than literature values. Since the hydrogen uptake was usually a little less than that needed for complete dehalogenation, it appears that o-xylene may form an azeotropic mixture with pyrimidine.

In another series of experiments using the ether-water mixture, the product was isolated using different chasers: o-xylene, mesitylene, quinoline, naphthalene, and N, N-dimethylaniline. Each of the samples of pyrimidine isolated by use of "chasers" were subjected to gas chromatographic analysis. Naphthalene, quinoline, and N, N-dimethyaniline gave pyrimidine fractions which were at least 99+% pure. O-xylene gave an azeotropic product as judged by gas chromatographic data. Mesitylene also gave an azeotropic product but it was unable to demonstrate this chromatographically due to inability to find a stationary phase which was capable of separating mesitylene from pyrimidine. From these works, it was evident that naphthalene, quinoline, and N, N-dimethylaniline were superior compounds for this purpose than the aromatic hydrocarbons. Moreover, it is possible that the aromatic hydrocarbons o-xylene and mesitylene form azeotropic mixtures with pyrimidine.

To account for the ethanol, ether was subjected to aqueous sodium hydroxide under hydrogenation conditions (presence of palladized charcoal and hydrogen pressure) and in the presence of hydrogen. From this work, it was apparent that some hydrogenolysis of ether occurs during the dehalogenation of the pyrimidine. Moreover, there is some hydrolysis of ether during extraction of highly basic solutions but this is so slight that it cannot account for the amounts of ethanol which is isolated.

EXPERIMENTAL

A series of experiments were conducted using various solvent systems, various inorganic bases, and different methods of isolation of the pyrimidine product. All reductions were carried on in a Parr low pressure hydrogenation apparatus using an initial pressure of approximately 40 lbs. The reactions were continued until hydrogen uptake ceased. Pressure changes were plotted against time. In some instances the pyrimidine was isolated as the insoluble mercuric chloride complex and in others, it was recovered by distillation using an efficient Podbielniak column. After the insoluble catalyst, etc., had been removed from the reaction mixture by filtration, 20 ml of o-xylene (or some other chasers) was added prior to distillation.

The initial experiments were conducted with aqueous ethanol using magnesium oxide to control the acidity. Details of these experiments are given in Table 1, and rate of hydrogen uptake in Figure 1.

Judging by the amount of hydrogen uptake, the hydrogenation proceeded beyond the dehalogenation to some nuclear reduction of the ring.

This series of experiments were then repeated using a different solvent system (ether-water) in the presence of sodium hydroxide. In this series of experiments the insoluble material was removed by

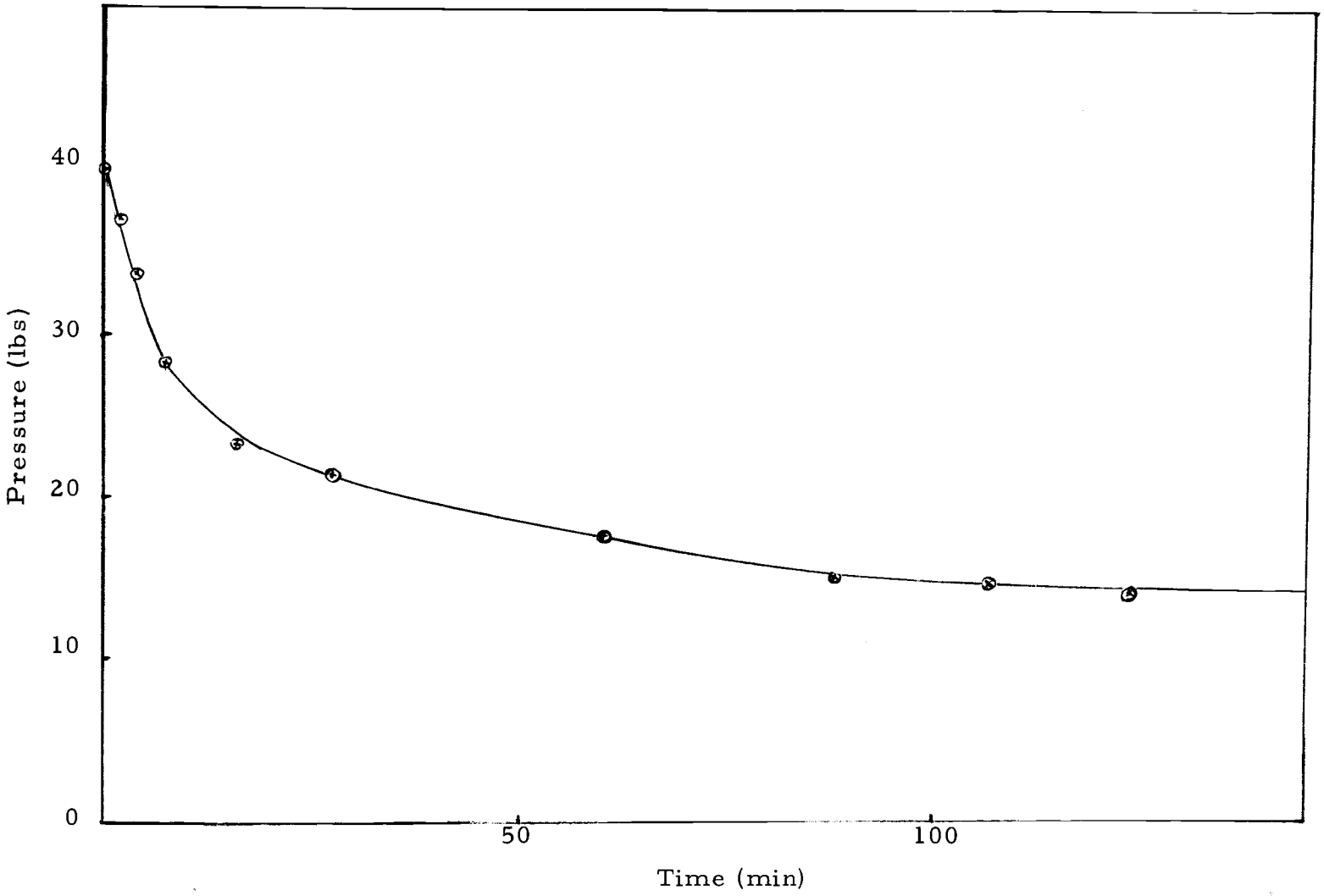

Figure 1. Rate of hydrogen uptake in aqueous ethanol in presence of magnesium oxide.

Table 1. Reduction of 2, 4-dichloropyrimidine in presence of magnesium oxide and aqueous ethanol.

2, 4-Dichloropyrimidine	8.42 g (0.056 moles)
Magnesium oxide	5.0 g
Palladized charcoal 5%	2.1 g
Ethanol	42 ml
Water	84 ml

Exp.	2, 4-Dichloropyrimidine (Moles)	Hydrogen uptake (Moles)	Mercuric chloride pyrimidine complex (g)
1	0.056	0.22	10.202*
2	0.056	0.22	1.53
3	0.056	0.21	3.07
4	0.056	0.23	3.50
5	0.056	0.22	2.51

*Probably due to the precipitation of tetrahydropyrimidine mercuric chloride complex.

filtration after the reduction. The water layer was saturated with potassium hydroxide and then extracted several times with ether. The ether fractions were combined and then diluted with 20 ml of o-xylene prior to distillation in a Podbielniak column. The results of these experiments are given in Table 2 and the rate of hydrogen uptake, in Figure 2.

These experiments were repeated using methanol as the solvent. The results are given in Table 3 and the rate of hydrogen uptake is in Figure 3.

The fraction obtained in the reduction using ether-water solvent system was ethanol. This work was repeated on a large scale to test the consistency of this unsuspected side product. The results of

Table 2. Reduction of 2, 4-dichloropyrimidine in presence of aqueous sodium hydroxide solution and ether.

2, 4-Dichloropyrimidine	7.5 g (0.05 moles)
Palladized charcoal 10%	0.5 g
NaOH pellets	5.0 g
Ether	100 ml
Water	20 ml

Exp.	2, 4-Dichloropyrimidine (Moles)	Hydrogen uptake (Moles)	Pyrimidine (g)
1	0.05	0.088	2.8
2	0.05	0.088	3.8
3	0.05	0.081	3.8
4	0.05	0.088	4.14

Table 3. Reduction of 2, 4-dichloropyrimidine in presence of methanolic sodium hydroxide.

2, 4-Dichloropyrimidine	7.5 g (0.05 moles)
Palladized charcoal 10%	0.5 g
NaOH pellets	5.0 g
Methanol	120 ml

Exp.	2, 4-Dichloropyrimidine (Moles)	Hydrogen uptake (Moles)	Pyrimidine (g)	Azeotrope B. P. 91.5°C
1	0.05	0.065	- -	3.89
2	0.05	0.062	- -	4.0
3	0.05	0.069	1.25	2.9
4	0.05	0.069	1.50	2.0
5	0.05	0.072	1.30	1.5

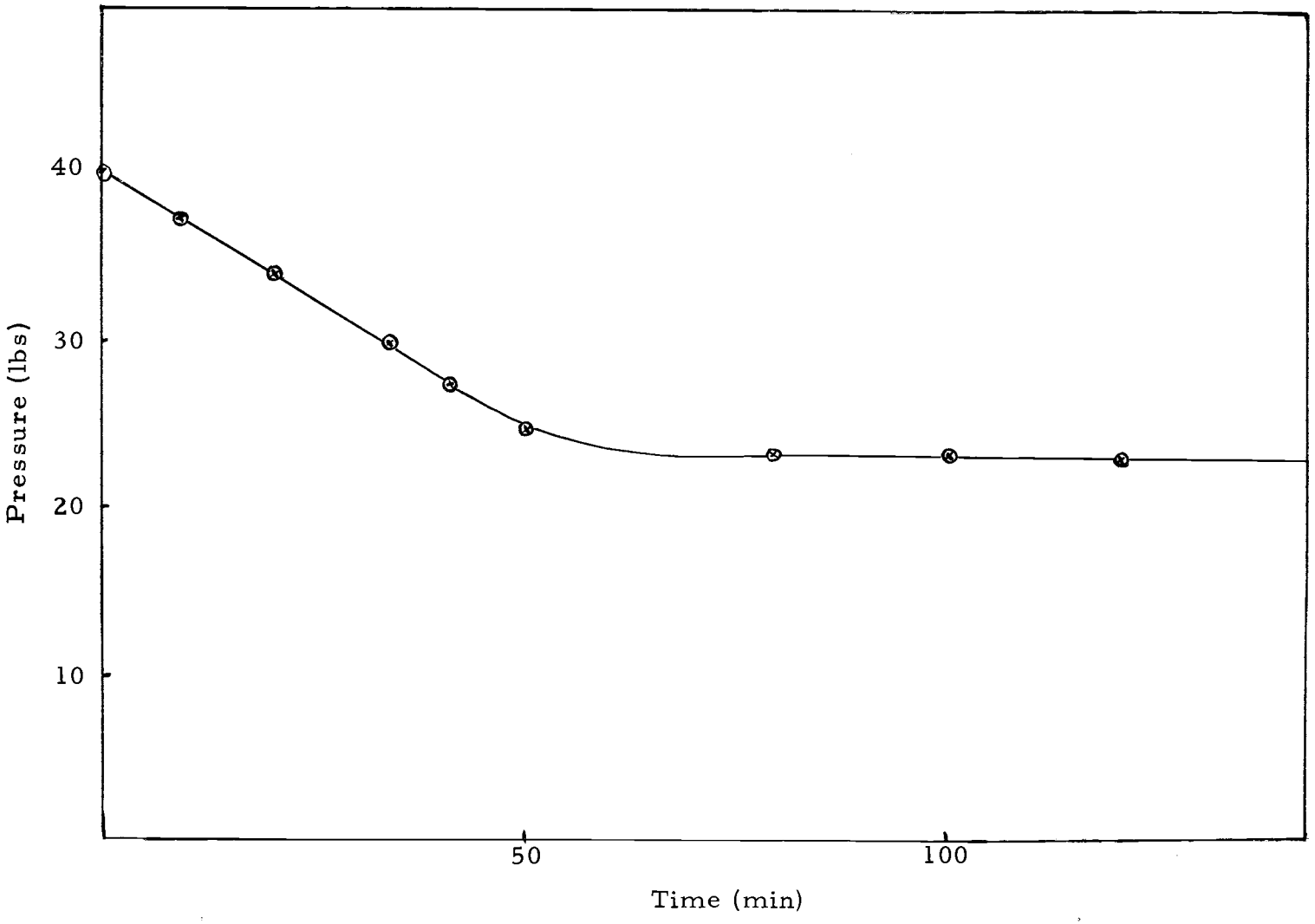

Figure 2. Rate of hydrogen uptake in ether-aqueous sodium hydroxide.

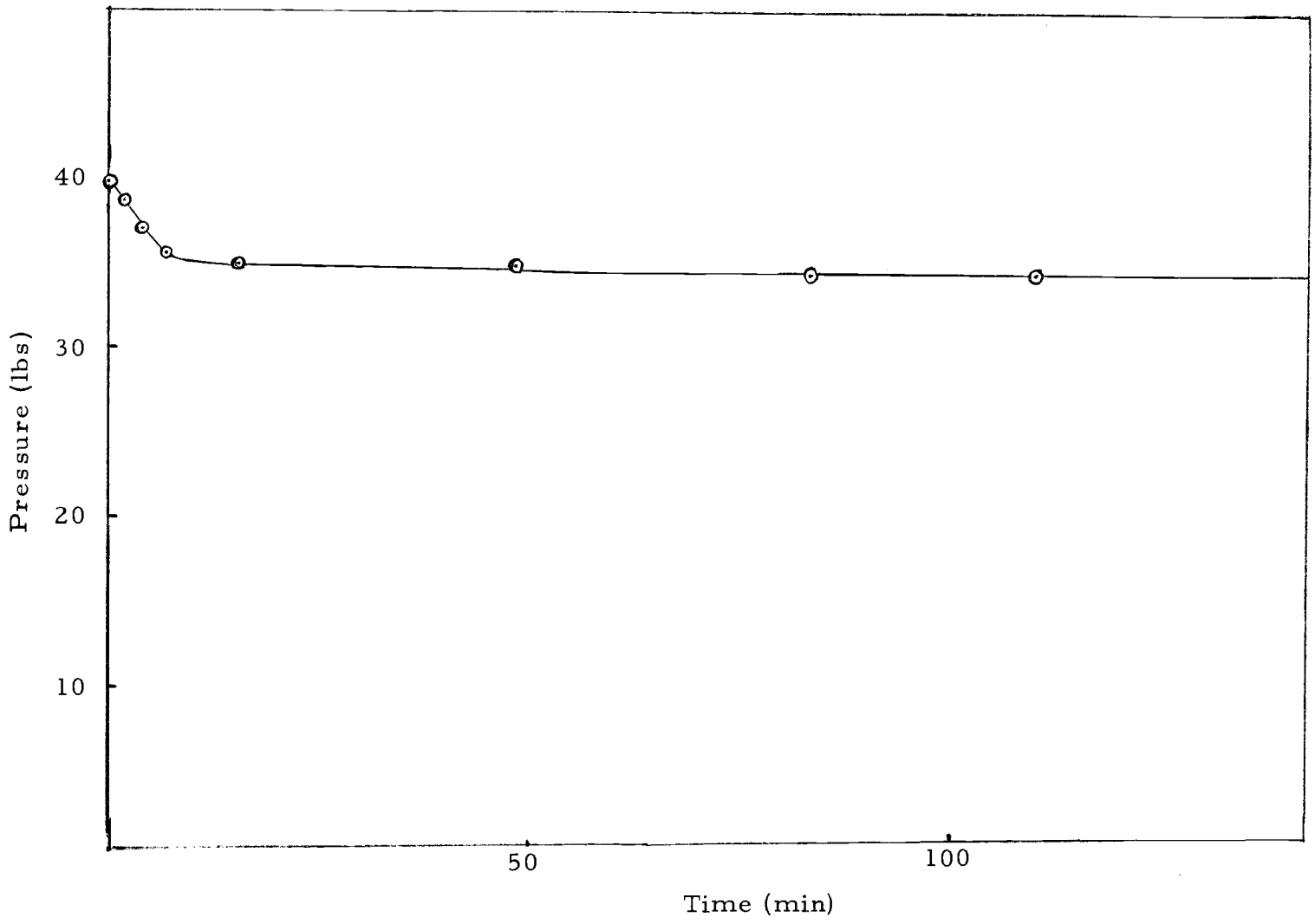

Figure 3. Rate of hydrogen uptake in methanolic sodium hydroxide.

these studies are tabulated in Table 4 and the rate of hydrogen uptake is in Figure 4.

Table 4. Reduction of 2, 4-dichloropyrimidine in presence of aqueous sodium hydroxide solution and ether.

2, 4-Dichloropyrimidine	15.0 g (0.10 moles)
Palladized charcoal 10%	1.0 g
NaOH pellets	10.0 g
Ether	100 ml
Water	40 ml

Exp.	2, 4-Dichloropyrimidine (Moles)	Hydrogen uptake (Moles)	Pyrimidine (g)	Ethanol (g)
1	0.10	0.175	8.51	4.8
2	0.10	0.175	5.70	3.8
3	0.10	0.175	6.0	3.9
4	0.10	0.175	5.3	1.5
5	0.10	0.175	5.8	1.4

A series of experiments using an ethanol-water solvent system with various inorganic bases were completed. These results are given in Table 5 and the rates of hydrogen uptake are in Figure 5.

Since magnesium oxide had not prevented nuclear reduction in solvent system such as ethanol and methanol, its effectiveness in an immiscible ether-water system was tested. These results are given in Table 6 and the rate of hydrogen uptake is in Figure 6.

Since the ether-water system gives the most consistent and best results, the effect of varying the ratio of water to ether was investigated. These results are tabulated in Table 7 and the rates of hydrogen uptake are in Figure 7.

Table 5. Reduction of 2, 4-dichloropyrimidine in aqueous ethanol in presence of different bases.

2, 4-Dichloropyrimidine	8.4 g (0.056 moles)
Palladized charcoal 5%	2.1 g
Metal oxide	5.0 g
Ethanol	42 ml
Water	84 ml

Exp.	2, 4-Dichloropyrimidine (Moles)	Metal oxide	Hydrogen uptake (Moles)	Azeotrope* B.P. 92.5
1	0.056	Magnesium oxide	0.210	6.5 g
2	0.056	Sodium Hydroxide	0.071	8.3 g
3	0.056	Calcium oxide	0.175	10.2 g

*An azeotrope was isolated in each case instead of pyrimidine.

Table 6. Reduction of 2, 4-dichloropyrimidine in varying ratios of ether and aqueous sodium hydroxide.

2, 4-Dichloropyrimidine	7.5 g (0.05 moles)
Palladized charcoal 10%	0.5 g
Magnesium oxide	3.0 g
Ether	100 ml
Water	20 ml

Exp.	2, 4-Dichloropyrimidine (Moles)	Hydrogen uptake (Moles)	Pyrimidine (g)	Ethanol (g)
1	0.05	0.11	3.3	1.1
2	0.05	0.12	2.8	1.3
3	0.05	0.11	3.0	1.2

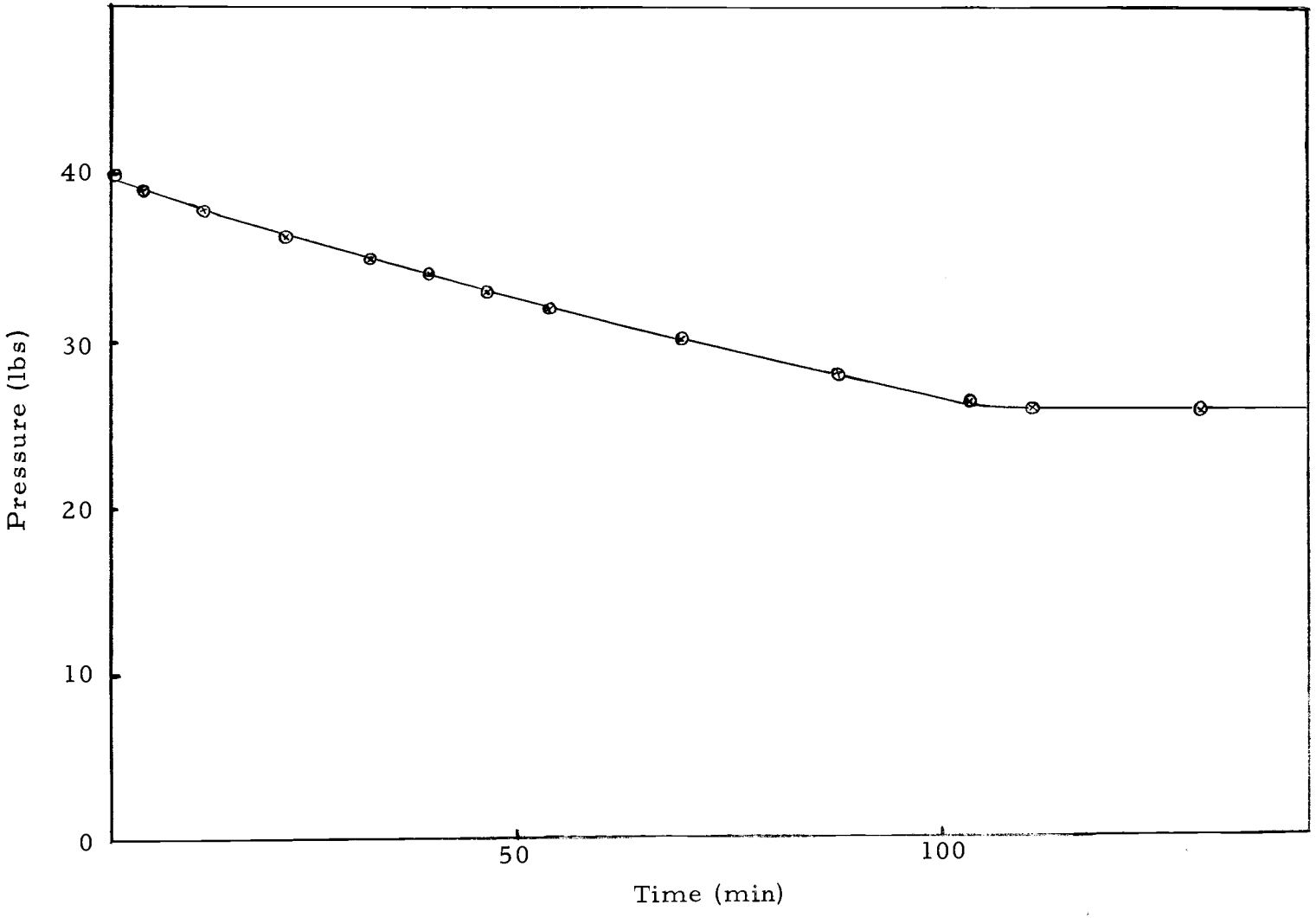

Figure 4. Rate of hydrogen uptake in ether-aqueous sodium hydroxide.

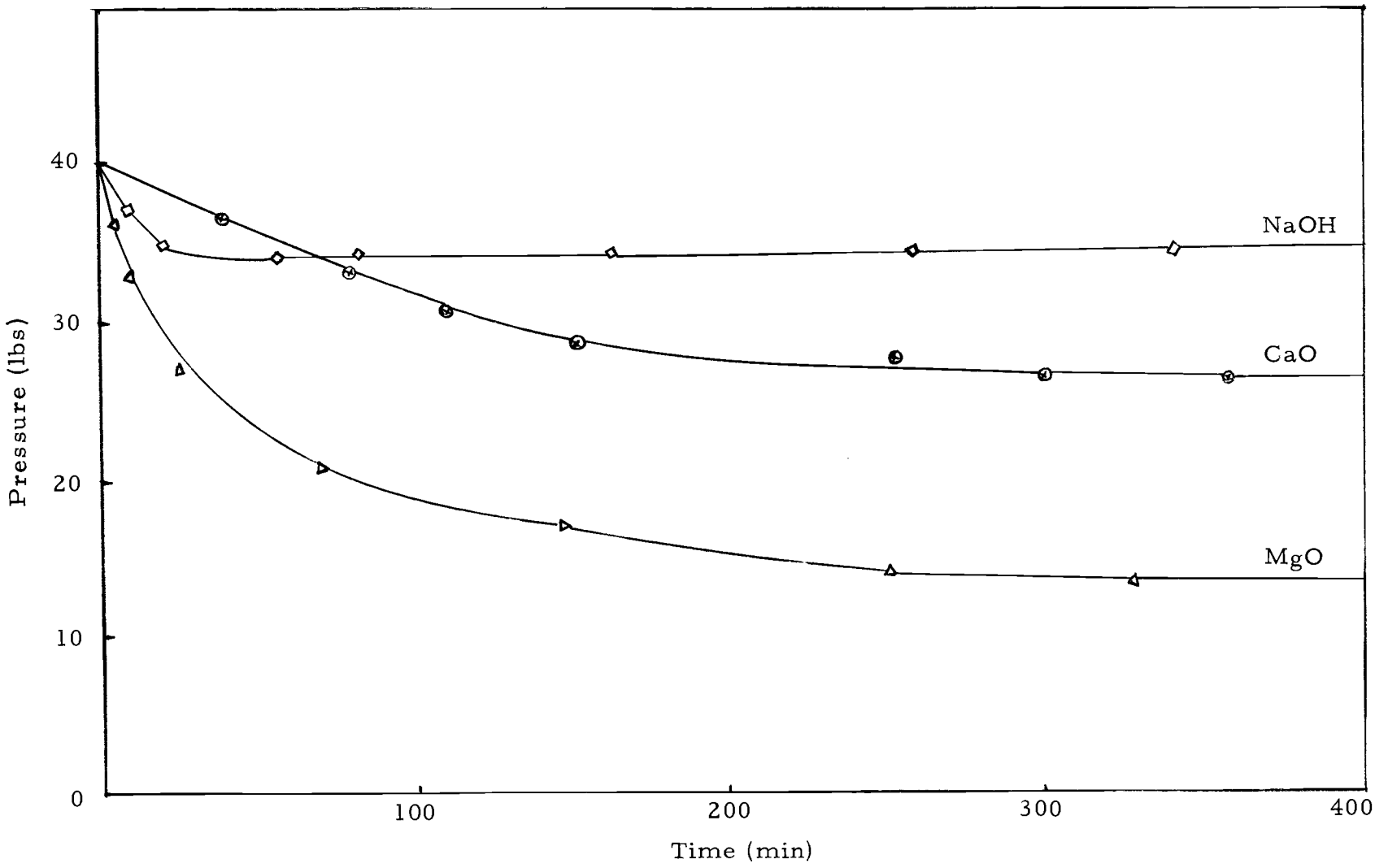

Figure 5. Rates of hydrogen uptake in aqueous ethanol in presence of different bases.

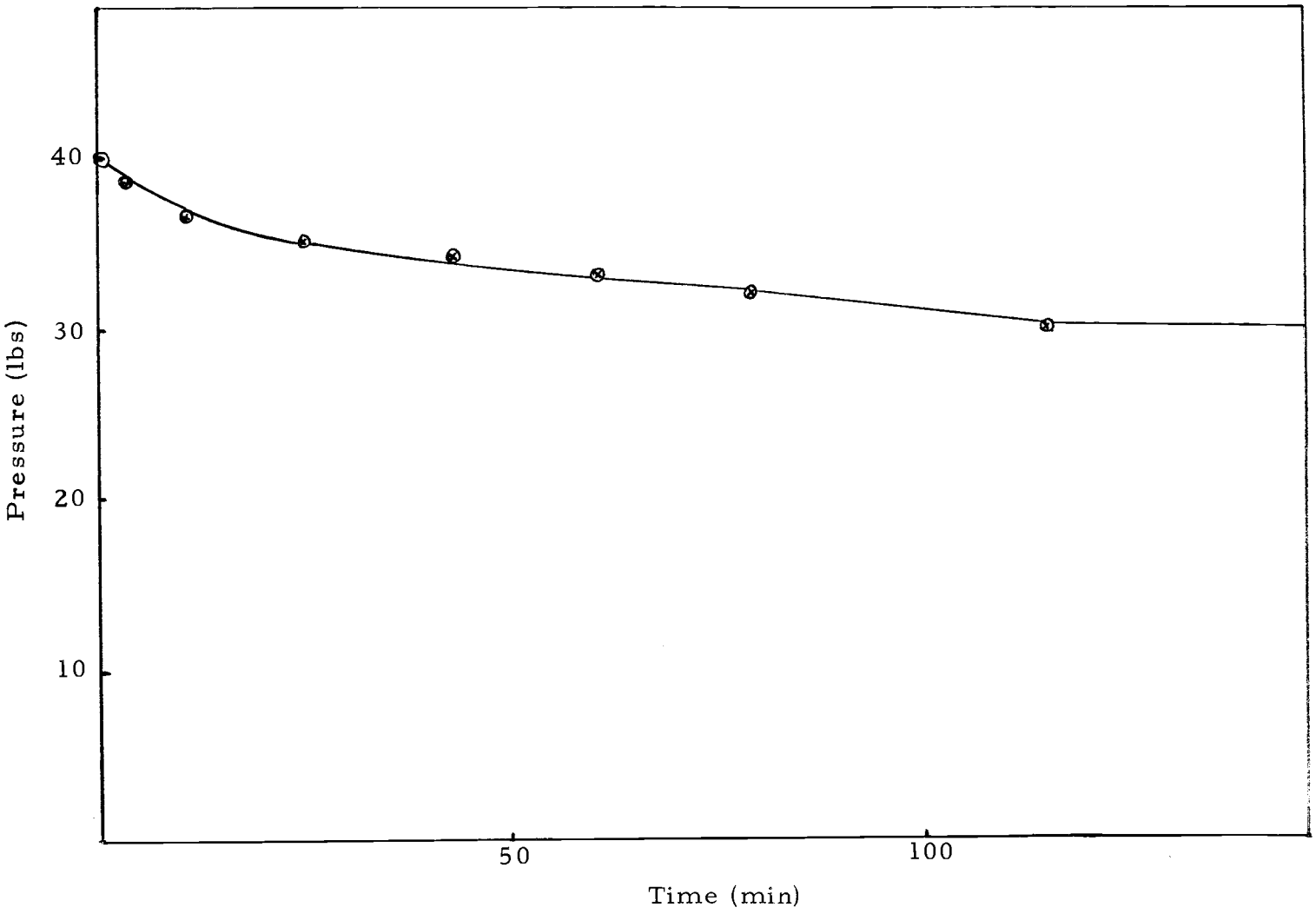

Figure 6. Rate of hydrogen uptake in ether-water in presence of magnesium oxide.

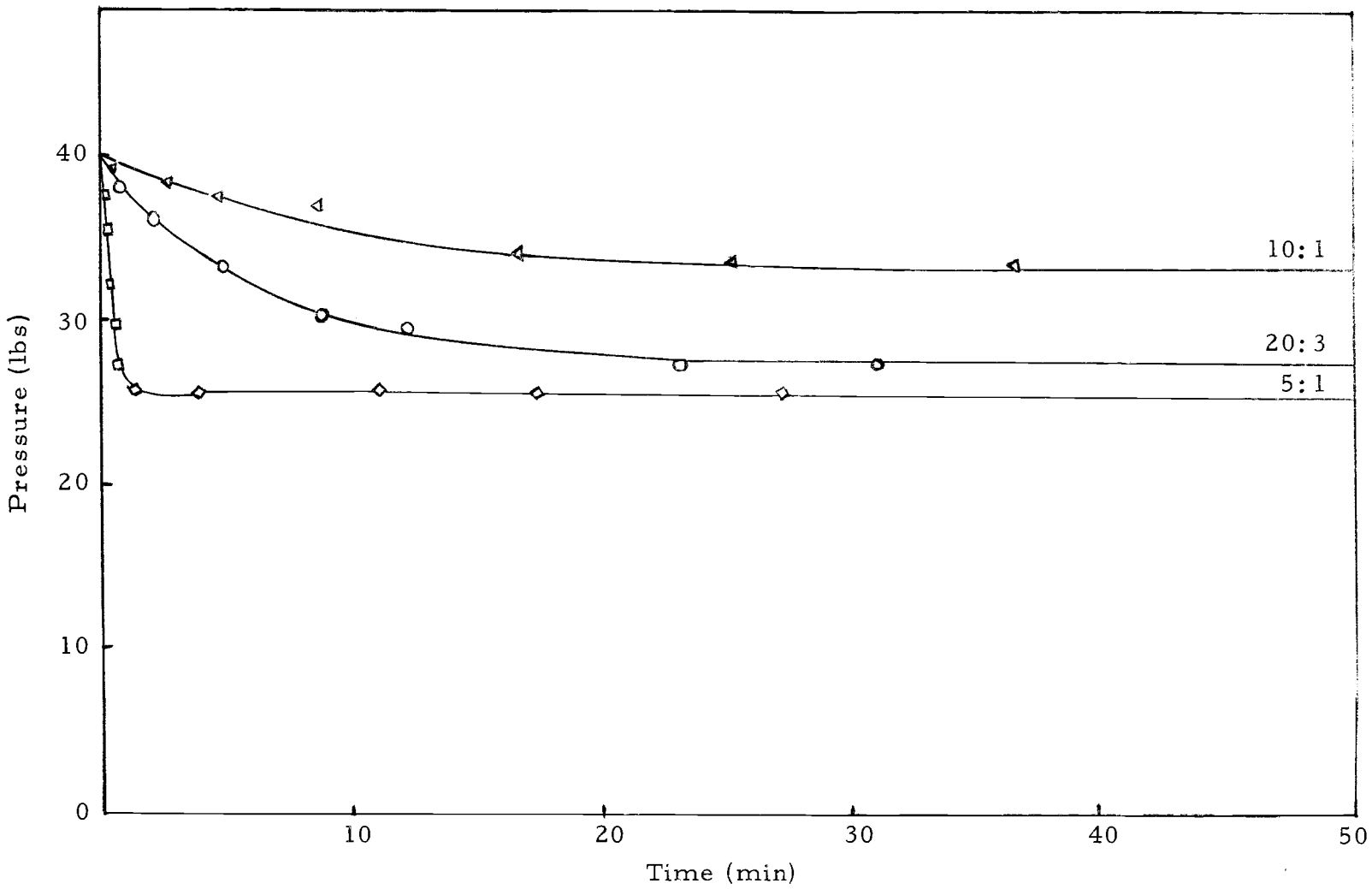

Figure 7. Rates of hydrogen uptake in various ratios ether:aqueous sodium hydroxide.

Table 7. Reduction of 2, 4-dichloropyrimidine in varying ratios of ether and aqueous sodium hydroxide.

2, 4-Dichloropyrimidine	15.0 g (0.10 moles)
Palladized charcoal 10%	1.0 g
NaOH pellets	10.0 g

Experiment	2, 4-Dichloropyrimidine (Moles)	Water (ml)	Ether (ml)	Hydrogen uptake (Moles)	Pyrimidine (g.)	Ethanol (g.)
1	0.10	20	100	0.175	7.9	1.6
2	0.10	20	100	0.175	7.5	0.8
3	0.10	20	100	0.175	7.0	1.5
4	0.10	15	100	0.162	6.8	1.5
5	0.10	10	100	0.112	2.5	0.3
6	0.10	--	120	0.020	--	1.7

Although the pyrimidine fraction isolated through distillation with Podbielniak column had narrow boiling point range at the reported boiling point of pyrimidine, the melting points were much lower than those reported in the literature. These samples, when dissolved in water, left a slight oily layer of presumably o-xylene. It would be possible for o-xylene to form an azeotrope with pyrimidine which could have a B. P. very close to that of pyrimidine itself, or this affect might be due to traces of tetrahydropyrimidine resulting from nuclear reduction and which has a boiling point quite close to that of pyrimidine.

In order to test the effectiveness of sodium hydroxide-ether-water system, a series of runs were made so as to accumulate enough pyrimidine so that distillations could be made in the absence of o-xylene. Nine runs were made with following results.

2, 4-Dichloropyrimidine used	63.3 g
Pyrimidine recovered	17.2 g
Melting point	20-21°C (22°C in literature)
% Yield	50.1*

The pyrimidine was also recovered from pyrimidine-mercuric chloride complex. The pyrimidine-mercuric chloride complex 41.5 g was mixed with 43.6 g of $Na_2S \cdot 9H_2O$ and solid mixture was then distilled until all liquid had been removed. The distillate was saturated with potassium carbonate which forced the pyrimidine out of solution. This mixture was extracted five times with 15 ml of portions of ether. The ether was dried over anhydrous $CaSO_4$ and then distilled. This yielded 9.0 g of pyrimidine m.p. 14-15°C (distilled with o-xylene) which represents 73% yield on basis of amount of complex used.

Since the pyrimidine obtained from reductions in which o-xylene was used as a chaser in the distillation procedure gave product with a depressed m.p., a series of experiments were carried out using other materials for this purpose. The results of these tests are given in Table 8.

*This does not take into account 5.8 g of hold up (which is largely pyrimidine).

Table 8. Distillation of pyrimidine using various chasers.*

2, 4-Dichloropyrimidine	7.5 g
Palladized charcoal 10%	0.5 g
NaOH pellets	5.0 g
Ether	100 ml
Water	20 ml

2, 4-Dichloropyrimidine (g)	Chaser 20 ml B. P.	Pyrimidine (g)	M. P.	Ethanol (g)
15.0	O-xylene, 144.4°C	6.5	14-15°C	3.8
7.5	Mesitylene, 164.7°C	2.9	13-15°C	1.7
22.5	Quinoline, 237.7°C	8.5	21-22°C	4.5
22.5	N, N-Dimethylaniline, 192.5°C	7.9	20-21°C	3.8
22.5	Naphthalene, 218.0°C	9.4	21-22°C	2.5

*All these amounts of materials were changed corresponding to the amount of dichloropyrimidine in all the following experiments.

In all these reduction ethanol was recovered as a by-product. In an effort to account for the presence of the ethanol, several additional experiments were conducted.

A solution of five g of NaOH in 20 ml of water was added to 100 ml of ether and the mixture was shaken for three hours. The layers were then separated and 15.0 g of potassium hydroxide was added to the aqueous fraction. After standing for one to two hours, this layer was then extracted with ether which was subsequently dried over calcium sulfate. To both ether fractions was added o-xylene. Distillation using a Podbielniak column did not reveal any ethanol in either fraction.

This same experiment was repeated under hydrogenation conditions (40 lbs. H_2 pressure, 0.5 g palladized charcoal 10%)

after 48 hours of shaking, the pressure dropped 0.5-1.0 lb. The two layers were worked up as described in the preceding experiment. No alcohol was found in the ether layer. The ether extracts of the aqueous layer, however, yielded 0.9-1.5 g of ethanol.

Finally, 100 ml of ether was added to 50 ml of 40% potassium hydroxide and allowed to stand. After two weeks, the ether layer was removed, dried over calcium sulfate, diluted with 20 ml of o-xylene, and distilled. A small fraction of ethanol (0.5 g) was isolated.

In an effort to determine whether the depression of melting points of the pyrimidine isolated by o-xylene and mesitylene was due to azeotropism, a series of experiments were designed to determine this point. These are described in Table 9.

The compositions of these pyrimidine fractions were identified by the method of gas chromatography analysis, using Carbowex 20M column. The results are given in Table 10.

Table 9. Melting points of pyrimidine fractions obtained from distillations using different chasers.*

2, 4-Dichloropyrimidine	22.5 g
Palladized charcoal 10%	1.5 g
NaOH pellets	15.0 g
Ether	300 ml
Water	60 ml

2, 4-Dichloropyrimidine (Moles)	Chaser 20 ml	Hydrogen uptake (Moles)	Pyrimidine (g)	M. P. °C	Ethanol (g)
0.150	0-xylene	0.264	1.9	13-14	5.2
			2.3	15-16	
			5.5	17-18	
0.150	mesitylene	0.265	2.1	14-15	2.9
			2.4	21-22	
			3.4	22-23	
0.150	quinoline	0.264	2.3	13-14	4.5
			2.6	21-22	
			3.5	22-23	
0.150	naphthalene	0.264	1.7	12-14	4.8
			2.4	21-22	
			5.3	22-23	
0.150	N, N-dimethyl-aniline	0.264	2.3	15-16	4.8
			2.8	22-23	
			3.5	23-24	

*Product was dried over anhydrous $CaSO_4$ prior to dilution with hydrocarbon chaser and distillation.

Table 10. Gas chromatographical data on distillation fractions of pyrimidine obtained by distillation with various chasers.

Chaser	Fraction	% Pyrimidine	% Chaser	% Ethanol
O-xylene	1. 1.9 g	70.2	8.3	21.5
	2. 2.3 g	84.2	9.8	6.0
	3. 5.5 g	82.5	15.3	2.2
Mesitylene *	- -	- -	- -	- -
Quinoline	1. 2.3 g	73.0	- -	27.0
	2. 2.6 g	96.2	- -	3.8
	3. 3.5 g	99.5	- -	0.5
Naphthalene	1. 1.7 g	77.2	- -	12.8
	2. 2.4 g	95.0	- -	5.0
	3. 5.3 g	99.0	- -	1.0
N, N-dimethylaniline	1. 2.3 g	79.0	- -	21.0
	2. 2.8 g	93.9	- -	6.1
	3. 3.5 g	99.0	- -	1.0

*The compositions could not be found due to inability to find the stationary phase which was capable of separating mesitylene from pyrimidine.

DISCUSSION

From all experiments which have been presented in this thesis, the best procedure for the dehalogenation of 2, 4-dichloropyrimidine appears to be those based on an immiscible solvent system of ether-water. Sodium hydroxide was used as the hydrogen chloride acceptor and palladized charcoal as the catalyst. The strong basic property of sodium hydroxide can prevent the hydrogenation of the ring. But some hydrogen chloride acceptors, for instance, magnesium oxide and calcium oxide, are not as effective causing the nuclear reduction. Ethanol was obtained from the reaction mixture under the above condition; this has been confirmed by the hydrogenolysis of ether under identical conditions but in the absence of 2, 4-dichloropyrimidine.

In the immiscible solvent, ether-water, the ratio of ether: water was changed in order to investigate the effect of solvents. It has been concluded that if the amount of water was very small, the yield was low and the dehalogenation reaction proceeded very slowly. Probably, this is caused by the decreasing of effectiveness of the catalyst by the precipitation of sodium chloride.

The isolation of pyrimidine from the small scale reaction mixtures was considered to be difficult because of the large amount of hold up in the column after the fractional distillation. Some organic compounds have been used as the chaser in the distillation,

three fractions of distillate at constant boiling point of pyrimidine were collected from the Podbielniak column. The compositions of every fraction were identified by gas chromatography analysis. From the amount of o-xylene in these three fractions, it is suggested that o-xylene forms azeotropic mixture with pyrimidine. Mesitylene also gave azeotropic mixture with pyrimidine but it was unable to demonstrate the composition by gas chromatography due to inability to find a suitable column to separate mesitylene from pyrimidine. However, the existence of mesitylene in each fraction was shown by the oily solution when dropping into water and the depression of the melting points in those three fractions. Naphthalene, quinoline, and N, N-dimethylaniline were found to be the very effective chasers.

SUMMARY

A series of experiments on dehalogenation of 2,4-dichloropyrimidine in various conditions were carried out in a Parr low pressure hydrogenation apparatus. The effects of solvents, hydrogen chloride acceptors, and other factors have been studied.

The ether-aqueous sodium hydroxide system has been found to be the most effective system. The ratio of ether-water was changed in order to investigate the effect of the amount of water. The most suitable in this system was 5:1. The side product, ethanol, was also found.

The isolation problem of pyrimidine from the reaction mixture was studied and some organic compounds have been used as the "chaser" in the fractional distillation using Podbielniak column. Quinoline, naphthalene, and N, N-dimethylaniline were found to be the effective ones, but o-xylene and mesitylene formed the azeotropic mixture with pyrimidine.

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