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Title THE CHEMISTRY OF CERTAIN TETRAHYDROPYRIMIDINES

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Since many 1, 4, 5, 6-tetrahydropyrimidines have become available and commercially useful in recent years, a study of the chemistry of certain of these compounds has been undertaken.

2-Hydroxy- and 2-mercapto-1, 4, 5, 6-tetrahydropyrimidine have been synthesized by the condensation of urea and thiourea, respectively, with 1, 3-propanediamine, with yields of 30 and 50 percent.

2-Phenyl-1, 4, 5, 6-tetrahydropyrimidine hydrochloride was prepared in quantitative yield by the addition of hydrogen chloride gas to the free base in either benzene or absolute ethanol.

A nuclear acylation of 2-phenyl-1, 4, 5, 6-tetrahydropyrimidine with acetic anhydride produced 1-acetyl-2-phenyl-1, 4, 5, 6-tetrahydropyrimidine in about 70 percent yield. The same reaction with 2-methyl-1, 4, 5, 6-tetrahydropyrimidine gave an unidentified amorphous material.

2-Phenyl-1, 4, 5, 6-tetrahydropyrimidine hydrolyzed in an aqueous solution to only a small extent at room temperature; however, at

100 degrees, the tetrahydropyrimidine ring was completely disrupted after one hour. Some destruction of the ring was also observed in boiling xylene and in boiling ethanol. 2-Amino-1, 4, 5, 6-tetrahydropyrimidine hydrolyzed slowly in neutral and alkaline media at room temperature; it was found to be less stable in an alkaline solution than in a neutral one.

Dehydrogenation of 1, 4, 5, 6-tetrahydropyrimidines to the corresponding pyrimidines was attempted using several different techniques. Catalytic oxidation with ten percent palladium on charcoal produced small amounts of 2-phenyl-, 2-methyl-, and 2-aminopyrimidine from the corresponding tetrahydropyrimidine. Linstead's catalyst-d was used to dehydrogenate 2-phenyl, 2-methyl-, 2-amino-, and 2-mercaptopyrimidine, in yields ranging from less than five to 51 percent.

Two quinones, chloranil and phenanthrenequinone, were studied as dehydrogenation agents. Small amounts of 2-phenyl- and 2-aminopyrimidine were prepared by treating the appropriate tetrahydropyrimidine with chloranil. Phenanthrenequinone proved completely unsuccessful.

Sulfur was used to dehydrogenate 2-phenyl-1, 4, 5, 6-tetrahydropyrimidine and 2-amino-1, 4, 5, 6-tetrahydropyrimidine hydrochloride, again in only small yields.

In reactions in which only a small amount of pyrimidine was obtained, ultraviolet spectroscopy was used for the identification of the pyrimidine. In general, none of the methods of dehydrogenation studied appeared to be useful as preparative techniques for pyrimidines.

THE CHEMISTRY OF CERTAIN TETRAHYDROPYRIMIDINES

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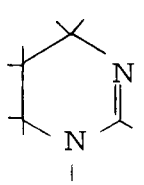
THE CHEMISTRY OF CERTAIN TETRAHYDROPYRIMIDINES

INTRODUCTION

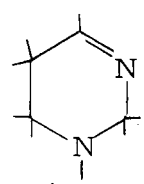
The chemistry of the tetrahydropyrimidines is receiving increasing attention through developments which have been stimulated by the numerous uses for which these compounds are being employed. For example, the tetrahydropyrimidines have been found to be useful as insecticides, fungicides, inhibitors of bacteria, detergents, preventors of corrosion, and asphalt additives. Many derivatives have physiological properties, acting as antihistamines, bronchodilators, antihypertensive agents, and antituberculous compounds. Some have sympatholytic and adrenolytic activity; others protect the skin against sunburn.

As more and more tetrahydropyrimidine compounds are becoming available, attention has naturally turned to the investigation of these materials as intermediates for the preparation of pyrimidines.

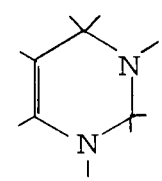
A tetrahydropyrimidine may be defined as a pyrimidine nucleus with only one double bond in or directly attached to the nucleus (15, p. 430). Three isomeric forms exist and the derivatives are named as follows (15, p. 430):



1, 4, 5, 6-Tetrahydropyrimidine



1, 2, 5, 6-Tetrahydropyrimidine



1, 2, 3, 4-Tetrahydropyrimidine

The 1, 4, 5, 6- tetrahydropyrimidine derivatives as potential intermediates for pyrimidine synthesis are the subject of investigation reported in this paper.

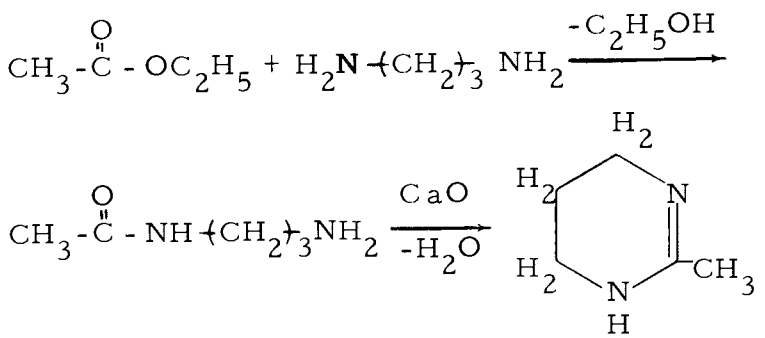
Hofmann (42), in 1888, is credited with the first preparation of a 1, 4, 5, 6-tetrahydropyrimidine, although he did not obtain it in pure form. This investigator heated 1, 3-diacetamidopropane in a stream of hydrogen chloride and obtained, among other products, a dark brown oil which was identified by the picrate as 2-methyl-1, 4, 5, 6-tetrahydropyrimidine. The 2-phenyl derivative was also reported, but the description of the procedure and compound were vague; no yields or physical constants were given for either compound.

The principal synthetic route to the 1, 4, 5, 6-tetrahydropyrimidines, of which Hofmann's work is an example, is via the condensation of a 1, 3-diamine with an oxidized carbon atom of another molecule, followed by cyclization between the two ends of the condensed intermediate.

Acids and their derivatives have been one of the main sources of the carbon atom occupying position two in a tetrahydropyrimidine molecule. In 1899 Harries and Haga (40) fused the dihydrochloride of 2, 4-pentanediamine with sodium acetate and prepared 2, 4, 6-trimethyl-1, 4, 5, 6-tetrahydropyrimidine, which was isolated as the nitrate in 63 percent yield. Four years later Haga and Majima (38) used the same technique to synthesize

2-methyl-1, 4, 5, 6-tetrahydropyrimidine from 1, 3-propanediamine and sodium acetate; this was isolated as the nitrate in 50 percent yield.

Aspinall (5), in 1940, was the first to report an efficient synthesis, using a sealed tube technique, for preparing the 1, 4, 5, 6-tetrahydropyrimidines as free bases. Monoacylated 1, 3-propanediamines, prepared from the appropriate esters, were dehydrated in the presence of lime at 250 degrees to yield a 2-substituted-1, 4, 5, 6-tetrahydropyrimidine. The 2-methyl- and 2-phenyl-derivatives were prepared in this way, as indicated below:



The intermediate monoacylamino derivative need not be isolated; the yield of the tetrahydropyrimidines were 70 percent.

Skinner and Wunz (63) modified Aspinall's procedure by replacing the lime fusion operation in the sealed tube by merely heating the monoacylated intermediate under reduced pressure at a high temperature. 1, 4, 5, 6-Tetrahydropyrimidine itself was prepared in this way, as well as several 2-; 2, 4; and 2, 5, 5-derivatives.

A number of 1, 4, 5, 6-tetrahydropyrimidines with unusual substituents in the 2-position have been prepared by Baganz, Domaschke, and their coworkers, by the aminolysis of an appropriate ester with 1, 3-propanediamine in an alcoholic solution for several hours. Among the compounds prepared in this way were 2-butoxymethyl-1, 4, 5, 6-tetrahydropyrimidine (9), trifluoromethyl-1, 4, 5, 6-tetrahydropyrimidine (8), and 2-(N-morpholinomethyl)-1, 4, 5 6-tetrahydropyrimidine (6); yields were reported to be around 60 percent.

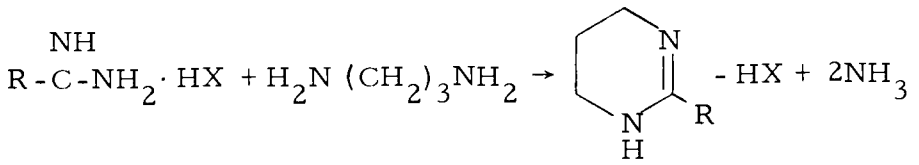
Organic acids--for example, fatty acids (23, 65), amino acids (53), and diphenylacetic acid (32, 45)--have also been cyclized with 1, 3-propanediamine at elevated temperatures to produce the corresponding tetrahydropyrimidines.

2-Hydroxy-1, 4, 5, 6-tetrahydropyrimidines have been prepared by procedures analagous to those so successfully applied to pyrimidine synthesis--the condensation of a 1, 3-diamine with diethyl carbonate (30, 32), phosgene (39), and ethylchlorocarbonate (30).

The condensation of 1, 3-propanediamine with a nitrile is another often used technique for the preparation of 1, 4, 5, 6-tetrahydropyrimidines, which again leads to substituents on the 2-position. Oxley and Short (56, 61) were among the first to have used this approach. Faust and Sahyun (28, 29) modified the procedure, making it applicable to the cyanohydrins.

In 1962 D. J. Brown and R. F. Evans (17) devised a general

synthesis for 1, 4, 5, 6-tetrahydropyrimidines, by refluxing the salt of an amidine derivative with 1, 3-propanediamine, which reacted as follows:



The process was a short, one-step synthesis; the products were obtained in high yield. The reaction has been applied by Brown and Evans to compounds were X was a chloride, bromide, or acetate ion and R was a hydrogen, methyl, butyl, benzyl, phenyl, or amino group. Tetrahydropyrimidine molecules with substituents on the four and five positions can be formed by using the appropriately substituted diamine, as in the preparation of 4-carboxy-1, 4, 5, 6-tetrahydropyrimidine from 2, 4-diaminobutanoic acid and formamidine acetate. When N-methylated diamines were used, ammonia and not methylamine or dimethylamine was evolved, showing the nitrogenous groups were expelled from the amidine. If either nitrogen atom of the diamine is disubstituted, as in $H_2N\text{-}CH_2)_3\text{-}N(CH_3)_2$, reaction occurs only at the non-substituted end and cyclization will not occur (17).

S-Methylisothiourea reacting with 1, 3-propanediamine produced 2-amino-1, 4, 5, 6-tetrahydropyrimidine by the above procedure. On the other hand Brown and Evans (17) found that O-methylisourea was a less satisfactory intermediate for this preparation.

Prior to the report of the extensive work by Brown and Evans, McKay and Wright (51) had reported the preparation of 2-nitramino-1, 4, 5, 6-tetrahydropyrimidine from nitroguanadine in 55 percent yield, by a process very similar to that later employed by Brown and Evans. L. S. Hafner and Robert Evans (36, 37) have also used nitroguanidine in a similar preparation.

In 1964 Skaric, et al. (62), reported that urea itself can be made to condense with 1, 3-propanediamine, if heated with a trace of water, to yield 2-hydroxy-1, 4, 5, 6-tetrahydropyrimidine.

Other compounds with which 1, 3-diamines have been condensed to form 1, 4, 5, 6-tetrahydropyrimidines are carbon disulfide (34, 59) potassium cyanate (33), thiocyanic acid (46) triazine (35), the trialkylester of orthocarbonic acid (7), cyanogen halides (27), and alkoxyacetylene (55).

1, 3-Dihalocompounds have served occasionally as intermediates in reactions leading to 1, 4, 5, 6-tetrahydropyrimidines. Pinner (58), as early as 1893, prepared 2-phenyl-1, 4, 5 6-tetrahydropyrimidine by reacting benzamidine with 1, 3-dibromopropane. The tetrahydropyrimidine was formed as a by-product in low yield, and could not be purified. Branch and Titherley (14) in 1912 performed the same reaction and isolated 2-phenyl-1, 4, 5, 6-tetrahydropyrimidine as the oxalate, in seven percent yield.

1, 4, 5, 6-Tetrahydropyrimidines have also been reported in

numerous references as prepared by the nuclear reduction of pyrimidines. This reduction, not directly concerned in the present work, has been reviewed by Leutzinger (47, p. 2-10).

One other synthetic route to tetrahydropyrimidines is via the condensation of ammonia or substituted amines with ketones or aldehydes. These condensations, however, lead in nearly every instance to 1, 2, 3, 4- or 2, 3, 4, 5-tetrahydropyrimidines and are beyond the scope of the present work.

In this work the general synthesis of Brown and Evans has been expanded and modified to include new preparations for 2-hydroxy- and 2-mercapto-1, 4, 5, 6-tetrahydropyrimidine. 2-Hydroxy-1, 4, 5,6-tetrahydropyrimidine was prepared by condensing urea with 1, 3-propanediamine, by refluxing the urea solution until evolution of ammonia ceased; cyclization was then effected by a more vigorous heating. Urea nitrate proved to be less satisfactory in a similar experiment, although a small amount of 2-hydroxy-1, 4, 5, 6-tetrahydropyrimidine was obtained.

2-Mercapto-1, 4, 5, 6-tetrahydropyrimidine was prepared in this laboratory in an analagous manner, by refluxing thiourea with 1, 3-propanediamine for several hours. The hydrochloride of thiourea and the same diamine, however, failed to condense after several hours of refluxing; the products recovered included the dihydrochloride of 1, 3-propanediamine and thiourea.

Until the 1960's the chemistry of the tetrahydropyrimidines had received little attention. D. J. Brown states in his book, The Pyrimidines,

> The most noticeable aspect of hydropyrimidines is the very small number of other reactions recorded. In this respect they lag behind the pyrimidines by perhaps eighty years (15, p. 454).

Since the time the above statement was written, Brown and R. F. Evans have published a series of papers dealing with this chemistry.

The 1, 4, 5, 6-tetrahydropyrimidines are extremely basic compounds, as might be expected from their amidine structure. 1, 4, 5, 6-Tetrahydropyrimidine has a pK_a of about 13 at 20 degrees centigrade. This value, determined potentiometrically on concentrated solutions with a hydrogen electrode, is approximate, since large activity corrections had to be applied in the calculations. It sufficed to show that the molecule is highly basic (16). The pK_a values of several derivatives are shown in Table 1. These values were determined spectrophotometrically or potentiometrically and, in the case of the 2-benzyl and 2-amino derivatives, the high pK_a values made it necessary to apply a graphical procedure to obtain the extinction coefficient of the free base.

Infrared data shows that 1, 4, 5, 6-tetrahydropyrimidine is hydrogen bonded in the free base (16).

TABLE 1. pK_a values of certain 1, 4, 5, 6-tetrahydropyrimidines

Derivative	pK_a	Reference
2-phenyl	12.8*	17
2-benzyl	13.0*	17
2-amino	14.1*	17
2-acetamido	8.34 ± 0.01	24
2-benzamido	7.12 ± 0.02	24
5-amino	>12	24
	4.89 ± 0.01	
5, 5-dihydroxy	10.03 ± 0.05	24
perimidine	6.39 ± 0.05	17

*Values in this region must be considered uncertain (17).

Most of the alkyl and aryl substituted 1,4, 5,6-tetrahydropyrimidines are unstable as free bases, although the degree of stability varies considerably. When the unsubstituted 1, 4, 5, 6-tetrahydropyrimidine was allowed to stand in water for 15 minutes it decomposed completely, yielding only monoformamido-1, 3-propanediamine. The easy ring opening has also been shown by the reaction with α-naphthylisocyanate, which yields 1, 3-di-1'-naphthylureidopropane (16). Bi-(1, 4, 5, 6-tetrahydropyrimidin-2-yl) on alkaline hydrolysis produces 1, 3-propanediamine and oxalic acid (16).

The 2-phenyl derivative is somewhat more stable than the unsubstituted 1, 4, 5, 6-tetrahydropyrimidine at high pH. This can be ascribed to the combined effect of resonance stabilization of the C=N structure by the phenyl group and the latter's steric hindrance

to the approach of a nucleophilic hydrolytic species towards carbon atom two (16). It does hydrolyze in base, however. For example, when heated in dilute ammonia at 80 degrees, it slowly takes up water and forms monobenzoyl-1, 3-propanediamine (14). The reaction occurs readily enough that Branch and Titherley (14) used it as a preparation for the above monobenzoyl compound.

The ring of the free base 2-amino-1, 4, 5, 6-tetrahydropyrimidine is cleaved only in boiling water and not at room temperature, as with the unsubstituted ring. It has been proposed that the attack of the hydrolytic group on carbon atom two is hindered by the combined steric and electronic effects of the amino group. In boiling water the compound breaks apart to form a mixture of 3-ureidopropylamine and 1, 3-propanediamine. It can be recovered, however, from an aqueous solution after treatment with excess potassium hydroxide for one and one-half hours at room temperature. Hydrolysis of 2-amino-1, 4, 5, 6-tetrahydro-4, 6-dimethylpyrimidine monohydrochloride in excess aqueous sodium hydroxide, at reflux temperature, gave ammonia and β-DL-2, 4-pentanediamine. 2-Acetamido-1, 4, 5,6-tetrahydropyrimidine under the above conditions gave 1, 3-propanediamine; 5-amino-1, 4, 5, 6-tetrahydropyrimidine, treated with alkali, gave 1, 2, 3-propanetriamine (24).

2-Methoxy-1, 4, 5, 6-tetrahydropyrimidine subjected to alkaline hydrolysis produced 1, 3-propandiamine; its picrate, however,

yielded ammonia, presumably by dehydrogenation of the 1, 3-propanediamine followed by hydrolysis (26). Although this assumption does not appear to have been verified. Alkaline hydrolysis of 5-methoxy-1, 4, 5, 6-tetrahydropyrimidine gave 2-methoxy-1, 3-propanediamine (26).

The salts of the 1, 4, 5, 6-tetrahydropyrimidines contain the resonating amidinium system and are more stable than the free bases. Therefore, the compounds are preferably handled as their salts, particularly as chloromercurates. These are nonhygroscopic and give infrared spectra which are those of the cations undistorted by hydrogen bonding (25).

The hydrobromide of 1, 4, 5, 6-tetrahydropyrimidine, in contrast to the free base, can be boiled four hours in water with no decomposition occurring (16). In acid solution this tetrahydropyrimidine is more stable than pyrimidine to permanganate or dichromate ions (16).

Additional studies on the stability of 2-amino- and 2-phenyl-1, 4, 5, 6-tetrahydropyrimidine are presented in this paper. In this laboratory it was observed that 2-phenyl-1, 4, 5, 6-tetrahydropyrimidine in an aqueous solution at room temperature hydrolyzes to only a small extent; 94 percent of the starting tetrahydropyrimidine was recovered (as the picrate) after 24 hours exposure at room temperature. When boiled in water for one hour, however, the

ring was completely destroyed and no starting material could be recovered. Furthermore, a good nucleophilic species was not necessary to effect cleavage. After boiling the above tetrahydropyrimidine in 100 percent ethanol for one hour, only 56 percent of the starting material was recovered; from a refluxing xylene solution, 60 percent of the starting material was obtained after one hour.

As reported by Brown and Evans, 2-amino-1, 4, 5, 6-tetrahydropyrimidine free base could be recovered after standing in excess alkali for one and one-half hours at room temperature. It was observed in this laboratory that standing over a longer period of time (24-48 hours) caused some decomposition to occur, in the presence of either equimolar or excess potassium hydroxide. For example, from a solution of 2-amino-1, 4, 5, 6-tetrahydropyrimidine in excess potassium hydroxide, after contact for 48 hours at 20 degrees, only 60 percent of the starting material could be recovered (as the picrate).

A few attempts at dehydrogenation of 1, 4, 5, 6-tetrahydropyrimidines have been reported. Brown and Evans found that heating 1, 4, 5, 6-tetrahydropyrimidine in the presence of palladized charcoal produced, instead of the expected pyrimidine, a coupling at the two position, giving bi-(1, 4, 5, 6-tetrahydropyrimidin-2-yl)(16). An attempted dehydrogenation of the same compound with sulfur yielded 2-mercapto-1, 4, 5, 6-tetrahydropyrimidine (16). Dehydrogenation with chloranil gave ill-defined, highly-colored products (25).

The only successful dehydrogenation of a tetrahydropyrimidine has been reported by Lythgoe and Rayner (49), who heated 100 milligrams of 2-phenyl-1, 4, 5, 6-tetrahydropyrimidine with Linstead's catalyst-d[1] at 260-270 degrees for three hours in a stream of carbon dioxide, and obtained 70 milligrams of 2-phenylpyrimidine.

No examples have been reported of the hydrogenation of a 1, 4, 5, 6-tetrahydropyrimidine to the fully reduced hexahydropyrimidine.

Acylations have been performed with a few 1, 4, 5, 6-tetrahydropyrimidine derivatives. When 5-amino-1, 4, 5, 6-tetrahydropyrimidine was refluxed in acetic anhydride and benzene, the amino substituent was monoacetylated, producing 5-acetamido-1, 4, 5, 6-tetrahydropyrimidine. This product could be converted to the dihydrochloride of 5-amino-1, 4, 5, 6-tetrahydropyrimidine by refluxing with 0. 5 N hydrochloric acid for two hours (24). 2-Hydroxy-4-phenyl-5-carboethoxy-6-methyl-1, 4, 5, 6-tetrahydropyrimidine, when treated with acetic anhydride, gave the nuclear diacylated product. The acetyl groups could be removed by treatment with alcoholic alkali (31).

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[1]Five grams of platinum to 11 grams of Norit charcoal (48).

Benzoylation has been performed successfully on 2-amino-1, 4, 5, 6-tetrahydropyrimidine, using benzoyl chloride in pyridine. The product was 2-benzamido-1, 4, 5, 6-tetrahydropyrimidine hydrochloride (24). When the Schotten-Baumann technique of benzoylation was applied, the product isolated was tribenzoyl-1, 3-propanediamine, probably resulting from a nucleophilic attack by the hydroxide ion at carbon atom two. Smith and Christensen (64) had reported that 1, 4, 5, 6-tetrahydropyrimidine and its homologs formed the mononuclear benzamide. Aft and Christensen (1) later contradicted this finding, reporting they were able to obtain only degradation products.

In the current work, nuclear acetylations were attempted with 2-phenyl- and 2-methyl-1, 4, 5, 6-tetrahydropyrimidine. The 2-phenyl derivative was allowed to stand in an excess of acetic anhydride at room temperature for 24 hours, after which time the excess anhydride was removed by evaporation at reduced pressure. The product, purified by distillation, was identified as 1-acetyl-2-phenyl-1, 4, 5, 6-tetrahydropyrimidine; the yield was 65 percent. The acetyl group can be removed by treatment with excess alkali as judged by spectroscopic data.

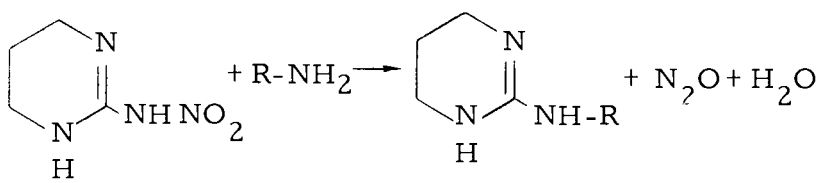
A small amount of the above acetylated product was prepared by refluxing 2-phenyl-1, 4, 5, 6-tetrahydropyrimidine with an equimolar quantity of acetic anhydride in a benzene solution; the main product to be recovered was the starting material. Refluxing the

same tetrahydropyrimidine in excess acetic anhydride yielded only starting material, after removal of the excess anhydride. When acetyl chloride was used in place of acetic anhydride, the hydrochloride of 2-phenyl-1, 4, 5, 6-tetrahydropyrimidine was precipitated from the reaction solution; the mother liquor, however, was not investigated.

Acetylation of 2-methyl-1, 4, 5, 6-tetrahydropyrimidine was attempted by allowing the tetrahydropyrimidine to stand in excess anhydride at room temperature for 20 hours. Removal of the excess anhydride, followed by distillation under reduced pressure, yielded a white amorphous material which was not the starting compound. Positive identification could not be made.

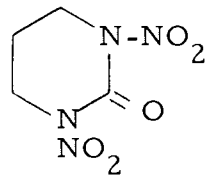
A few other miscellaneous reactions of tetrahydropyrimidines have been reported in the literature. Alkylation of 1, 4, 5, 6-tetrahydropyrimidine with methyl iodide gave a mixture of 1, 4 5, 6-tetrahydropyrimidine hydroiodide, 1-methyl-1, 4, 5, 6-tetrahydropyrimidine hydroiodide, and 1,4,5,6-tetrahydro-1,3-dimethylpyrimidinium iodide (16).

2-Nitramino-1, 4, 5 6-tetrahydropyrimidine and its 5-methyl derivative reacted with primary alkyl or aralkylamines, producing N-substituted products (52):



R is an alkyl or aralkyl group.

Treatment of 2-hydroxy-1, 4, 5, 6-tetrahydropyrimidine with nitric acid was reported to yield



1, 4, 5, 6-Tetrahydropyrimidine and most of its alkyl and aryl derivatives are extremely hygroscopic (5, 35, 40), as are many of their salts (16, 17, 38). Moreover, many of the alkyl and aryl-substituted free bases are sufficiently alkaline as to readily absorb carbon dioxide from the air (35, 63), producing, as in the case of 2-phenyl-1, 4, 5, 6-tetrahydropyrimidine, a crystalline carbonate (14).

There is little information on the stereoisomerism of tetrahydropyrimidines. Harries and Haga (40), in 1899, were able to isolate cis and trans forms of 2, 4, 6-trimethyl-1, 4, 5, 6-tetrahydropyrimidine, both as free bases and as their nitrate salts. Evans and Shannon suggested, from the observation that two symmetrically tri-substituted pyrimidines examined after reduction to the tetrahydro derivative gave the same DL diamine on hydrolysis, that the methyl groups in the four and six positions after reduction are situated trans to each other (26).

Dehydrogenation of 1, 4, 5, 6-tetrahydropyrimidines was of prime interest in the work reported in this paper. Therefore, several dehydrogenation techniques have been investigated as possible means of preparing pyrimidines from their reduced

derivatives. The methods selected were catalytic removal of hydrogen by a metal-charcoal catalyst, and chemical removal of hydrogen by sulfur and by quinones. All of these methods have been successfully applied to other nitrogen heterocyclic compounds.

Catalytic dehydrogenation of heterocyclic compounds is a widely-used technique. The only example reported in the pyrimidine series, however, was that of 2-phenyl-1, 4, 5, 6-tetrahydropyrimidine by Lythgoe and Rayner, as mentioned previously in this paper.

In other nitrogen systems, platinum and palladium on silica gel at temperatures ranging from 200 to 500 degrees have been used to convert piperidine to pyridine in 96 percent yield (66); a five percent palladium-charcoal on magnesium oxide catalyst at 350-360 degrees converts heptindole to 1-azabenz(b)azulene (2); and methyltetrahydrocarbazole-7-carboxylate, when treated with 25 percent its weight of palladium on charcoal at 280 degrees for several hours gives carbazole-2-carboxylic ester in 100 percent yield (54).

In one instance sulfur dehydrogenation has been reported as applicable in the pyrimidine series. 2-Amino-5-aryl-4-ethyl-6-hydroxy-dihydropyrimidine, when heated in sulfur at 180-190 degrees for four hours, gave the corresponding pyrimidine (41).

Sulfur dehydrogenation has been successfully used by Asinger, Thiel and Sowada (4) in the imidazoline series, the five-membered

structural homologs of the tetrahydropyrimidines. For example, 2, 2, 4-triethyl-5-methyl-Δ-3-imidazoline was dehydrogenated with sulfur at 65-80 degrees over a period of two hours; the product was the corresponding imidazole.

A final example of sulfur dehydrogenation in the heterocyclic series was that reported by Perkin and Plant (57), in which several tetrahydrocarbazole derivatives were treated with sulfur in quinoline, giving the corresponding carbazole derivative in 15-30 percent yield.

Quinones have been particularly effective for the dehydrogenation of heterocyclic compounds. The lone pair of electrons of the hetero atoms provide a driving force for the hydride ion abstraction (44, p. 339).

One of the first references to the dehydrogenation of a nitrogen heterocyclic by a quinone was that of Schmidt and Sigwart (60), in 1913, who noted that dihydrocarbazole was partly oxidized by benzoquinone to carbazole and that 9-methyl-hexahydrocarbazole reduced benzoquinone to quinol; they did not investigate the matter further.

Barclay and Campbell (10) found that benzoquinone did not oxidize tetrahydrocarbazole to any extent, but used chloranil (2,3,5,6-tetrachlorobenzoquinone) to successfully dehydrogenate 25 di-, tetra-, and hexahydrocarbazoles, with nearly all yields ranging from 75-90 percent.

Buu-Hoi, Hoan, and Khoi (21) have applied the above method

to several dihydrodibenzocarbazoles and report yields as high as 100 percent. Buu-Hoi has also used chloranil to dehydrogenate 2'-methyl-3, 4-dihydro-1, 2-benazcridine; the yield was not given (20).

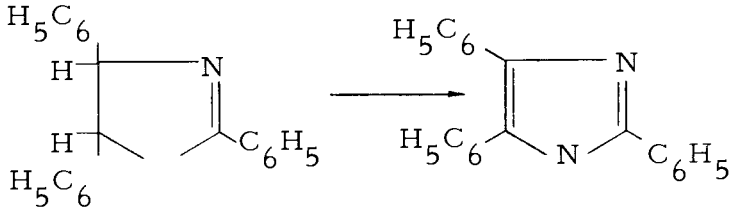
The dihydro derivatives of pyridine, quinoline, isoquinoline acridine, and phenanthridine can all be dehydrogenated by quinones, and in most cases the reactions are very rapid (44 p. 340).

Masamune, Saito, and Homma (50) have used chloranil to dehydrogenate tetrahydroquinoline to quinoline (38 percent yield), dihydroindole to indole (85 percent), tetrahydro-, cis-octahydro-, and trans octahydroacridine to acridine (17, 10, 11 percent, respectively), tetrahydro- and octahydrophenanthridine to phenanthridine (44, 34 percent), and tetrahydro-, cis-hexahydro-, octahydro-, and decahydrocarbazole to carbazole (75, 77, 15, 42 percent). α-Perhydroacridine, perhydrophenanthridine, and perhydrocarbazole gave no dehydrogenation under the same conditions.

It has been postulated (44, p. 340) that the lower yields usually obtained with the more highly reduced derivatives with halogenated quinones are the result of replacement reactions which compete more favorably than the slower dehydrogenation process. N-ethylpiperidine, for example, undergoes a substitution reaction to give a blue quinone (19).

The difficulty caused by competing replacement reactions may be overcome by the use of phenanthraquinone or its derivatives,

which cannot react with nonionic nucleophiles (44, p. 336). Phenanthraquinone has been used to successfully dehydrogenate amarine to lophine, as shown below, whereas amarine with chloranil gives only brightly colored salts (44, p. 340).



In our work, dehydrogenations have been attempted using ten percent palladium on charcoal, platinum on charcoal (Linstead's catalyst-d), sulfur, chloranil, and phenanthraquinone.

2-Phenyl-1, 4, 5, 6-tetrahydropyrimidine, when heated with ten percent palladium on charcoal in a stream of carbon dioxide, underwent less than five percent dehydrogenation. Refluxing the same tetrahydropyrimidine and catalyst in phenyl ether for several hours produced a maximum yield of seven percent of the corresponding pyrimidine.

2-Methyl-1, 4, 5, 6-tetrahydropyrimidine, refluxed with the above catalyst in phenyl ether for several hours, yielded about five percent of the corresponding pyrimidine, as judged from spectroscopic measurements. A few milligrams of the liquid 2-methylpyrimidine were obtained by extraction. A second material produced in the above reaction was identified as a mixture containing a dimer of 2-methylpyrimidine.

2-Amino-1, 4, 5, 6-tetrahydropyrimidine, with the same catalyst in phenyl ether, dehydrogenated to give 2-aminopyrimidine in 15 percent yield. When the same reaction was run on the hydrochloride, the yield was decreased to seven percent, and some starting material was recovered. 2-Amino-1, 4, 5, 6-tetrahydropyrimidine, heated with palladium on charcoal in a current of carbon dioxide, gave a 12 percent yield of the dehydrogenation product, as indicated by spectroscopic measurements. A small amount of dehydrogenation also occurred when this technique was applied to the hydrochloride of the above tetrahydropyrimidine.

The use of Linstead's catalyst-d (platinum on charcoal) as a dehydrogenation catalyst was somewhat more successful in a few cases. Thus, 2-phenyl-, 2-methyl-, and 2-mercapto-1, 4, 5, 6-tetrahydropyrimidine, when refluxed in phenyl ether for several hours, gave yields of 25, 15, and 51 percent, respectively, of the corresponding pyrimidine.

Attempts to repeat the dehydrogenation procedure of Lythgoe and Rayner, i. e., heating 2-phenyl-1, 4, 5, 6-tetrahydropyrimidine and the catalyst under a current of carbon dioxide, were unsuccessful. It may well be that any 2-phenylpyrimidine produced was lost by evaporation. Evidence that this occurred to some extent was obtained by spectroscopic measurements--a solution formed by trapping a gas evolved in the reaction in a dilute hydrochloric acid solution

gave the characteristic absorption spectrum of 2-phenylpyrimidine; the yield indicated was very low.

A final dehydrogenation attempt with the above catalyst was made by heating several tetrahydropyrimidine derivatives with Linstead's catalyst-d in a sealed bomb. This, too, was unsuccessful, with 2-phenyl- and 2-hydroxy-1, 4, 5, 6-tetrahydropyrimidine yielding no corresponding pyrimidine and 2-amino-1, 4, 5, 6-tetrahydropyrimidine yielding less than five percent of the desired 2-aminopyrimidine.

An attempted dehydrogenation of 2-phenyl-1, 4, 5, 6-tetrahydropyrimidine with sulfur at 200 degrees produced a small quantity of 2-phenylpyrimidine, which was not isolated but identified by its ultraviolet absorption spectrum. 2-Amino-1, 4, 5, 6-tetrahydropyrimidine hydrochloride under the same conditions produced a seven percent yield of 2-aminopyrimidine, which was isolated and identified by its ultraviolet spectrum and by its melting point.

2-Phenyl-1, 4, 5, 6-tetrahydropyrimidine, refluxed with a slight excess of chloranil in benzene, precipitated a black tar from which the only product isolated was impure 2-phenyl-1, 4, 5 6-tetrahydropyrimidine hydrochloride. A change in the solvent to a benzene-ether mixture again precipitated the above hydrochloride from the reaction solution, in about 93 percent yield, based on the quantity of 2-phenyl-1, 4, 5, 6-tetrahydropyrimidine used. Although the source of the

hydrochloride was unknown, it was apparent the chlorine must have come from the chloranil; the hydrogen may have been formed from trace amounts of dehydrogenation, from water in either the solvent or the tetrahydropyrimidine, or from a combination of the above. When the solvent was changed to xylene and the reaction time increased, some dehydrogenation occurred, although only in trace amounts. A hydroquinone of unknown structure was also obtained.

From a mixture of 2-phenyl-1, 4, 5, 6-tetrahydropyrimidine and phenanthrenequinone in refluxing benzene only starting material was recovered. Identical results were obtained with xylene as the solvent.

Chloranil failed to dehydrogenate 2-methyl-1, 4, 5, 6-tetrahydropyrimidine, when a mixture of the two was refluxed in benzene. Phenanthrenequinone with the same tetrahydropyrimidine in xylene produced a black tar, which could not be separated into identifiable components. An oxidation of some type evidently took place, however, as phenanthrenehydroquinone was precipitated from the cooled solvent.

2-Amino-1, 4, 5, 6-tetrahydropyrimidine and chloranil, after refluxing for several hours in absolute ethanol, produced only traces of the corresponding pyrimidine.

EXPERIMENTAL

Preparation of 1, 4, 5, 6-Tetrahydropyrimidine (63)

With the temperature maintained at 50°, ethyl formate (56.5 grams) was added dropwise to 1, 3-propanediamine (154 grams). The temperature was then raised to 100° and the solution stirred for 21 hours to effect initial condensation. The low-boiling components were removed by distillation at 30-45°/32 mm, and the remaining solution then heated at 140-150° for three hours at reduced pressure to effect the final cyclization. Vacuum distillation (59-65°/0.1-0.2 mm) gave a 32 percent yield of 1, 4, 5, 6-tetrahydropyrimidine, n_D^{23} 1.5142. Skinner and Wunz (63) report b.p. 88-89°/1 mm, $n_D^{23.5}$ 1.5143.

Preparation of 2-Phenyl-1, 4, 5, 6-tetrahydropyrimidine

The procedure was the same as that used for the preparation of the unsubstituted tetrahydropyrimidine. Ethyl benzoate (34.6 grams) was added to 1, 3-propanediamine (51 grams) with the temperature maintained in the neighborhood of 100° during the addition. The cyclization step was performed at 155°/14 mm. Distillation (122-126°/0.9-1.0 mm) gave 2-phenyl-1, 4, 5, 6-tetrahydropyrimidine; recrystallization from n-hexane gave white needles, m.p. 86-88°.

Skinner and Wunz (63) report b. p. 152-156°/6 mm and m. p. 86-87. 5°; the yield was 65 percent.

Preparation of 2-Methyl-1, 4, 5, 6-tetrahydropyrimidine

The same procedure was again used, with ethyl acetate (32 grams) added dropwise to 1, 3-propanediamine (80 grams). The cyclization step was effected at 175 ± 10°/100 mm; distillation (60 ± 5°/3 mm) gave 2-methyl-1, 4, 5, 6-tetrahydropyrimidine in 25 percent yield. Aspinall (5) reports b. p. 91°/4 mm.

Preparation of 2-Phenyl-1, 4, 5, t-tetrahydropyrimidine Hydrochloride

2-Phenyl-1, 4, 5, 6-tetrahydropyrimidine (0. 14 grams) was dissolved in dry benzene, and hydrogen chloride gas bubbled into the solution. A white precipitate formed, which was removed by filtration and dried in vacuo over calcium chloride. The product was 2-phenyl-1, 4, 5, 6-tetrahydropyrimidine hydrochloride, m. p. 242-244°. A second portion of the free base (0. 8 grams) was dissolved in ethanol, hydrogen chloride bubbled into the solution, and the ethanol removed by evaporation. The hydrochloride formed had m. p. 243-245° [Lit., m. p. 244-246° (17)]. The yields were quantitative in both reactions; the hydrochloride formed was extremely hygroscopic.

Preparation of 2-Amino-1, 4, 5, 6-tetrahydropyrimidine Hydrochloride (17)

A mixture of guanadine hydrochloride (15. 8 grams) and 1, 3-propanediamine (16. 2 grams) were heated at 140° for three hours. The reaction mixture solidified on cooling; recrystallization from isopropyl alcohol gave white crystals of 2-amino-1, 4, 5, 6-tetrahydropyrimidine hydrochloride, m. p. 155-157° [Lit., m. p. 152-157° (17)].

Preparation of 2-Hydroxy-1, 4, 5, 6-tetrahydropyrimidine

(a) Urea (11 grams) and 1, 3-propanediamine (14 grams) were heated at 115 ± 10° for 12 hours. The solidified residue, heated vigorously with a flame, cyclized to give 2-hydroxy-1, 4, 5, 6-tetrahydropyrimidine in 30 percent yield, m. p. 261° [Lit., m. p. 264° (62)] .

Anal. Calc'd for $C_4H_8N_2O$: C, 48. 0; H, 7. 94; N, 27. 7

Found: C, 47. 5; H, 8. 00; N, 28. 0

(b) Urea nitrate (3. 2 grams) and 1, 3-propanediamine (3. 0 grams) were refluxed four hours; a tan solid formed on cooling. An ultraviolet spectrum of this material had a λ_{max} of 260 mμ. The tan solid, since it absorbed in the range 220-320 mμ, could not be 2-hydroxy-1, 4, 5, 6-tetrahydropyrimidine. A thin-layer chromatogram of the material showed it to be a mixture of at least four

compounds, including urea and urea nitrate, identified by a comparison of Rf values with those of known samples. The adsorbent used was alumina; the developing solvent was butanol-acetic acid-water, 5:2:3; and the detector was iodine.

Preparation of 2-Mercapto-1, 4, 5, 6-tetrahydropyrimidine

(a) Thiourea (5 grams) and 1, 3-propanediamine (6 grams) were refluxed seven hours, during which time the solution turned from green to a bright red-brown color. On cooling, the solution solidified to a yellow mass. Ethanol (95%, 100 ml) was added, which dissolved the uncyclized material leaving 1.0 grams of white, insoluble 2-mercapto-1, 4, 5, 6-tetrahydropyrimidine; the dissolved impurities were removed by filtration. An additional 0.5 gram was obtained by concentration of the mother liquor. The product had m.p. 208-209° [Lit., m.p. 208° (11, Vol. 24, p. 5)].

Anal. Calc'd for $C_4H_8N_2S$: C, 41.3; H, 6.90; N, 24.1

Found: C, 41.6; H, 7.00; N, 23.9

(b) Thiourea (10 grams) was dissolved in concentrated hydrochloric acid and the solution evaporated to dryness. This solid (4 grams), thiourea (2 grams), 1, 3-propanediamine (5 grams) and ethanol (95%, 11 ml) were refluxed three hours. The low-boiling components were removed by evaporation, leaving a tan solid residue. Recrystallization of this solid from isopropyl alcohol yielded

the dihydrochloride of 1, 3-propanediamine, identified by its melting point [found, m.p. 244-245°; and lit., m.p. 243° (38)], a comparison of the infrared spectrum with that of a known sample, and by an elemental analysis.

Anal. Calc'd for $C_3H_{12}N_2Cl_2$: C, 24.5; H, 8.15

Found: C, 24.8; H, 8.12

A thin layer chromatogram indicated the presence of thiourea in the mother liquor.

Preparation of 1-Acetyl-2-phenyl-1, 4, 5, 6-tetrahydropyrimidine

(a) 2-Phenyl-1, 4, 5, 6-tetrahydropyrimidine (1 gram) was dissolved in acetic anhydride (30 ml) and allowed to stand at room temperature, with occasional stirring, for 24 hours. The excess acetic anhydride was then removed by distillation (30°/4-5 mm) and the product distilled in vacuo (110-125°/0.1-0.5 mm). On cooling to zero degrees, 0.81 gram of white, solid 1-acetyl-2-phenyl-1, 4, 5, 6-tetrahydropyrimidine was obtained, m.p. 55.5-57°. Ultraviolet spectral data showed a bathochromic shift from the parent tetrahydropyrimidine (λ_{max}, 228 mμ) to λ_{max}, 235 mμ, E, 14,300 (in ethanol). The acetyl group was removed easily by excess base, yielding free 2-phenyl-1, 4, 5, 6-tetrahydropyrimidine; the reaction was followed spectroscopically.

Anal. Calc'd for $C_{12}H_{14}N_2O$: C, 71.3; H, 6.97; N, 13.8

Found: C, 70.6; H, 6.96; N, 13.6

The acetylated compound forms a picrate with m.p. 133-135°.

Anal. Calc'd for $C_{18}H_{17}N_5O_8$: C, 50.2; H, 4.0; N, 16.2

Found: N, 16.2

(b) 2-Phenyl-1, 4, 5, 6-tetrahydropyrimidine (1 gram) and acetic anhydride (1.1 ml) were refluxed in benzene (5 ml) for two hours. On cooling, two layers formed; 0.4 grams of starting material were recovered from the benzene solution. From the acetic anhydride portion a little 1-acetyl-2-phenyl-1, 4, 5, 6-tetrahydropyrimidine was obtained, identified by a comparison of its picrate, m.p. 133-135°, with that of the compound prepared above. A thin layer chromatogram showed the presence of additional starting material in the acetic anhydride layer.

(c) Refluxing the same tetrahydropyrimidine in excess acetic anhydride for one hour, followed by removal of the excess anhydride, gave the starting material as the only recoverable product.

(d) The above tetrahydropyrimidine (0.74 gram) and acetyl chloride (14 ml) were refluxed for one hour. The insoluble material precipitated during the reaction was identified as 2-phenyl-1, 4, 5, 6-tetrahydropyrimidine hydrochloride by its ultraviolet and infrared spectra, which were identical with those of a known sample, and by the melting point [found, m.p. 244-245°; and lit., m.p. 244-246°

(17)] . The yield was 45 percent, based on the amount of starting material used. The reaction solution was not investigated further.

2-Methyl-1, 4, 5, 6-tetrahydropyrimidine with acetic anhydride

2-Methyl-1, 4, 5, 6-tetrahydropyrimidine (1 gram) and acetic anhydride (20 ml) were mixed and kept at room temperature for 20 hours, with occasional stirring. The excess anhydride was removed by distillation (25°/3-4 mm); the residue solidified when the vacuum was removed. Purification was effected by distillation at 125± 5° / 0. 3-0. 4 mm., yielding 0. 96 gram of a white amorphous compound, m. p. range 85-100°. On standing in a sealed container at room temperature, the product gradually turned yellow; if exposed to air, an odor resembling that of acetic acid could be detected. The product could not be identified.

Anal. Calc'd for 1-acetyl-2-methyl-1, 4, 5, 6-tetrahydropyrimidine, $C_7H_{12}N_2O$: C, 60. 0; H, 8. 57; N, 20. 0

Found: C, 56. 3; H, 8. 34; N, 14. 8

Preparation of Linstead's catalyst-d (48)

Norit charcoal (10 grams) and 10% nitric acid (200 ml) were heated on a steam bath for 24 hours. The charcoal was filtered, washed with water, and dried at 100° for three days. It was then heated at 340° and 0. 5 mm pressure for one hour, and cooled.

A 10% chloroplatinic acid solution (28.4 grams) was concentrated by evaporation to give 10.3 milliliters of solution. Concentrated hydrochloric acid (1.02 ml) was added, and the mixture cooled in an ice bath. This was mixed with 40% formaldehyde (10.3 ml) and the activated charcoal (2.3 grams). With the temperature maintained at 3-10°, a solution composed of 10.3 grams of potassium hydroxide and 10.3 milliliters of water was added with stirring; the temperature was then raised to 60° for 15 minutes. The catalyst thus prepared was washed with water, dilute acetic acid, again with water, and dried at 100°.

Catalytic Dehydrogenation--Procedure a

The tetrahydropyrimidine derivative and the catalyst, in a 2:1 ration, were refluxed several hours[2] in phenyl ether. The catalyst was removed by filtration and the phenyl ether extracted with 1 N hydrochloric acid. The products of dehydrogenation were isolated as the hydrochloride by evaporation of the aqueous solution; the free base was obtained by basification of the acid solution with aqueous alkali, extraction with ethyl ether, and evaporation of the ether. The results are shown in Table 2, part a.

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[2]Reflux time with 10% palladium-charcoal: 5 hours; with Linstead's catalyst-d: 3 hours.

Catalytic Dehydrogenation--Procedure b

The tetrahydropyrimidine and catalyst, in a 2:1 ratio, were heated at 260-270° for three hours in a current of carbon dioxide. The mixture was cooled, the catalyst washed with ethyl ether, the ether extracted with dilute acid, and an ultraviolet spectrum taken. The data is tabulated in Table 2, part b.

Catalytic Dehydrogenation--Procedure c

The tetrahydropyrimidine and catalyst, in a 2:1 ratio, were heated at 270° for three hours in a sealed bomb. The resulting mixture was dissolved in water and the catalyst removed by filtration. The products were obtained by evaporation of the water. The data is shown in Table 2, part c.

Isolation and Analysis of a Side Product

The attempted dehydrogenation of 2-methyl-1, 4, 5, 6-tetrahydropyrimidine with ten percent palladized charcoal in refluxing phenyl ether yielded, in addition to a small amount of 2-methylpyrimidine, a side product with a λ_{max} of 278 mμ. This compound was separated by neutralization of the acid extract, followed by extraction with ethyl ether and evaporation of the ether. The yellow compound so obtained was purified by sublimation (40° /0. 1 mm) to give white crystals

TABLE 2. Dehydrogenation of 1, 4, 5, 6-tetrahydropyrimidines

Part a

Tetrahydropyrimidine Derivative	(grams)	Catalyst	Phenyl ether (ml)	Ultraviolet Spectrum (λ_{max})	Pyrimidine isolated (mg)
2-phenyl	1.0	10% Pd/C	15	250 mμ (pH 7)[1] 251 mμ, 290 mμ (pH < 2)[1]	73[2, 3]
2-phenyl	1.0	10% Pd/C	15	251 mμ (pH 7)[1] 254 mμ, 287 mμ (pH < 2)[1]	20[4]
2-methyl	1.0	10% Pd/C	15	248 mμ[5] 278 mμ[6]	20
2-amino[7]	1.0	10% Pd/C	15	221 mμ, 303 mμ (pH 1.9)[8]	trace quantities[9]
2-amino[10]	1.2	10% Pd/C	8	220 mμ, 299 mμ (pH~3)[8]	200[11]
2-phenyl	0.100	Linstead's catalyst-d	1	252 mμ (pH 7)[1]	25[12]
2-methyl	0.200	Linstead's catalyst-d	2	248 mμ[5]	15[13]
2-mercapto	0.200	Linstead's catalyst-d	2	----------	102[14]

TABLE 2. Dehydrogenation of 1, 4, 5, 6-tetrahydropyrimidines

Part b

Tetrahydropyrimidine Derivative	(mg)	Catalyst	Ultraviolet Spectrum (λ_{max})	% Dehydrogenation (judged by ultraviolet data)
2-phenyl	100	10% Pd/C	251 mμ (pH 7)[1]	<5
2-amino	75	10% Pd/C	223 mμ, 291 mμ (pH 6)[8]	11
2-amino[7, 15]	100	10% Pd/C	223 mμ, 292 mμ (pH 7)[8]	<5
2-phenyl	108	Linstead's catalyst-d	252 mμ, 290 mμ (pH 2)[1]	<5

Part c

Tetrahydropyrimidine Derivative	(mg)	Catalyst	Ultraviolet Spectrum (λ_{max})	% Dehydrogenation (judged by ultraviolet data)
2-phenyl	100	Linstead's catalyst-d	228 mμ, 270 mμ (infl)[17]	0[18]
2-hydroxy	100	Linstead's catalyst-d	----------	0[19]
2-amino[7]	100	Linstead's catalyst-d	220 mμ, 300-303 mμ (pH 1)[8]	<5[20]

TABLE 2. Dehydrogenation of 1, 4, 5, 6-tetrahydropyrimidines

1 lit. for 2-phenylpyrimidine: λ_{max}, 251 mμ (pH 6.98); 256-258 and 287 mμ (pH 0.00) (13)
2 identified as the picrate: found, m.p. 108-109; and lit., m.p. 108° (11, vol. 23 II, p. 211)
3 30 mg of benzamide were obtained as a by-product
4 isolated as the hydrochloride and identified by the ultraviolet spectrum
5 lit. for 2-methylpyrimidine: λ_{max}, 248.5 mμ (43); λ_{max} is pH independent (3)
6 45 mg of this side product were obtained. See p. 32
7 as the hydrochloride
8 lit. for 2-aminopyrimidine: λ_{max}, 221 mμ and 302-303 mμ (pH 1); 224 mμ and 292 mμ (pH 7) (8)
9 identified by the ultraviolet spectrum
10 ratio of tetrahydropyrimidine to catalyst, 3:1
11 identified by the ultraviolet spectrum
12 found, m.p. 34-36°; lit. for 2-phenylpyrimidine, m.p. 36.5° (49)
13 2-methylpyrimidine distilled during the reaction, was caught in an acid trap and identified as the hydrochloride
14 found, m.p. 227-229; lit. for 2-mercaptopyrimidine, m.p. 230° (12)
15 an aqueous rinse was substituted for the ether rinse
16 the 2-phenylpyrimidine produced distilled during the reaction and was caught in an acid trap
17 λ_{max} for 2-phenyl-1, 4, 5, 6-tetrahydropyrimidine: 228 mμ and 270 mμ (infl); determined from a known sample prepared in this laboratory
18 less than 5% of the starting material was recovered
19 85% of the starting material was recovered
20 75% of the starting material was recovered

which melted at 96-97°. The ultraviolet absorption shifted in an acidic solution to λ_{max}, 286 mμ. A nuclear magnetic resonance spectrum showed the presence of a methyl group on an aromatic nucleus (δ = 2.65, s, 3H) and two adjacent aromatic hydrogens (δ = 7.81, d, 1H; δ = 8.71, d, 1H). This would indicate the compound was a dimer of 2-methylpyrimidine. Elemental analysis, however, did not confirm this assumption; it is postulated that the material is a mixture containing a large percentage of a dimerized compound.

Anal. Calc'd for $C_{10}H_{10}N_4$; C, 64.5; H, 5.39; N, 30.1

Found: C, 64.7; H, 6.14; N, 27.7

Dehydrogenation with Quinones

(a) 2-Phenyl-1, 4, 5, 6-tetrahydropyrimidine (0.5 gram) was dissolved in benzene (20 ml) and chloranil (1.8 grams) then added. The solution, which turned purple immediately, was refluxed for one hour. A black precipitate which formed was removed by filtration and treated with a boiling ether-benzene mixture; the resulting insoluble purple solid had an infrared spectrum identical with that of 2-phenyl-1, 4, 5, 6-tetrahydropyrimidine hydrochloride.

The above reaction was modified by using a benzene-ether solvent, and refluxing one and one-half hours. A pale purple solid (0.65 gram) was removed by filtration from the hot solution and identified as impure (93 percent)2-phenyl-1,4,5,6-tetrahydropyrimidine

hydrochloride by its ultraviolet spectrum (Found: λ_{max}, 228 mμ, E, 12,900; known sample: λ_{max}, 228 mμ, E, 13,900), and from its infrared spectrum. The elemental analysis agreed with the calculated values within the degree of purity indicated above. From the cooled reaction solution, a yellow quinone precipitated.

2-Phenyl-1,4,5,6-tetrahydropyrimidine (1 gram) and chloranil (3.6 grams) were dissolved in xylene and refluxed eight hours. A dark precipitate was removed by filtration and washed with ether. The brown solid remaining had an ultraviolet absorption spectrum identical with that of the starting tetrahydropyrimidine. The xylene solution was extracted with a four percent sodium hydroxide solution, and a heavy black precipitate formed. This solid, recrystallized from dilute hydrochloric acid solution, gave an orange, crystalline material which sublimed above 230°. In the ultraviolet region this compound had a λ_{max} of 302 mμ at pH< 2, and λ_{max} of 331 mμ at pH 7. It could not be identified.

Anal. Found: C, 34.6; H, 1.16; N, 0.00

The remaining xylene solution was extracted with three percent hydrochloric acid; an ultraviolet spectrum of a portion of the extract showed some 2-phenylpyrimidine to be present (λ_{max}, 253-255 mμ and 286-287 mμ, at pH 0). This solution was made alkaline, extracted with ether, and a few milligrams of 2-phenylpyrimidine obtained. The remaining xylene solution was evaporated to dryness and extracted

again with dilute acid, yielding a little more 2-phenylpyrimidine.

2-Methyl-1, 4, 5, 6-tetrahydropyrimidine (0.4 gram) and chloranil (1 gram), when refluxed in benzene for one hour, produced a black tar. Extraction of the benzene solution with base, followed by acid, yielded no 2-methylpyrimidine; no identifiable products were obtained from the tar.

2-Amino-1, 4, 5, 6-tetrahydropyrimidine hydrochloride (1 gram), 1 N-sodium hydroxide (7.4 ml) and chloranil (4 grams) were refluxed four hours in a water-ethanol solution. Unreacted chloranil was removed by filtration from the cooled solution. The aqueous-alcoholic solution contained a small amount (less than 5% yield) of 2-aminopyrimidine, identified by its ultraviolet spectrum.

2-Amino-1, 4, 5, 6-tetrahydropyrimidine hydrochloride (1 gram) in absolute ethanol (5 ml) was mixed with sodium (0.2 gram) in absolute ethanol (5 ml) and the sodium chloride which formed removed by filtration. Chloranil (3.6 grams) in ethanol (10 ml) was added and the reaction run as before. The same results were obtained.

(b) 2-Phenyl-1, 4, 5, 6-tetrahydropyrimidine (0.1 gram) and phenanthrenequinone (0.26 gram) were refluxed in benzene for 24 hours. The starting materials were recovered in nearly quantitative yield. The use of xylene as the solvent gave similar results.

2-Methyl-1, 4, 5, 6-tetrahydropyrimidine (0.2 gram) and phenanthrenequinone (0.42 gram), treated as above, reacted to

to form a black tar which could not be isolated into known products. That some type of oxidation occurred was indicated by the fact that phenanthrenehydroquinone was precipitated from the cooled solvent.

Dehydrogenation with Sulfur

2-Phenyl-1,4, 5, 6-tetrahydropyrimidine (2 grams) and sulfur (0. 9 gram) were heated at 200° under nitrogen for eight hours. The cooled residue was extracted first with carbon disulfide and then with dilute hydrochloric acid. An ultraviolet spectrum of the acid extract indicated a small amount of dehydrogenation had occurred (λ_{max}, 250-252 mμ, pH≅6).

2-Amino-1, 4, 5, 6-tetrahydropyrimidine hydrochloride (2 grams) and sulfur (1 gram) under the above conditions yielded some 2-amino-pyrimidine hydrochloride. The free base (55 mg) was obtained by evaporation of the acid solution, addition of concentrated alkali, and extraction with ether; it was identified by its ultraviolet spectrum (λ_{max}, 291 mμ and 224 mμ, pH 7).

Hydrolysis of 2-Amino-1, 4, 5, 6-tetrahydropyrimidine

2-Amino-1, 4, 5, 6-tetrahydropyrimidine (I) was allowed to stand in neutral and basic solutions for several hours at room temperature and the resulting solutions were examined by thin layer chromatography. The starting material was recovered as the

picrate. The adsorbent used was silica gel and the developing solvent, butanol-acetic acid-water, 4:1:5. Spots were detected with iodine. The results are shown in Table 3.

TABLE 3. Hydrolysis of 2-amino-1, 4, 5, 6-tetrahydropyrimidine

Solution	Ratio of I to base added	Time	Rf values	% of I recovered as picrate
I, KOH	1:1	5 min.	0.295	---
I, NaOH	1:1	24 hrs.	0.290, 0.130	78
I, NaOH	1:1	48 hrs.	0.295, 0.122	62
I, NaOH	2:3	24 hrs.	0.288, 0.118	70
I, NaOH	2:3	48 hrs.	0.307, 0.131	59

Hydrolysis of 2-Phenyl-1, 4, 5, 6-tetrahydropyrimidine

2-Phenyl-1, 4, 5, 6-tetrahydropyrimidine was allowed to stand in water at room temperature for one hour. A thin layer chromatogram run on the resulting solution showed some decomposition had occurred. After standing in water for 24 hours at room temperature, 94 percent of the original tetrahydropyrimidine was recovered as the picrate.

Boiling this tetrahydropyrimidine in a variety of solvents caused some degradation to occur, as indicated by thin layer

chromatography. The results are tabulated in Table 4. The adsorbent used was alumina; the solvent, butanol-acetic acid-water, 4:1:5; the indicator, iodine.

TABLE 4. Hydrolysis of 2-phenyl-1, 4, 5, 6-tetrahydropyrimidine

Time (hrs)	Temperature (°C)	Solvent	Rf values	% Starting material recovered as picrate
1	25	Water	0.193, 0.137	--
24	25	Water	-------	94
1	100	Water	0.232, 0.101, 0.0	0
1	80	Ethanol	0.267, 0.238, 0.192	56
1	130	Xylene	0.268, 0.228, 0.200	61

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