THE PREPARATION OF SOME TETRAHYDROPYRIMIDINES AND RELATED COMPOUNDS OF POSSIBLE BIOLOGICAL INTEREST

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INTRODUCTION PART I

The Nuclear Reduction of Pyrimidines

For the purposes of this study tetrahydropyrimidines will be classified into three groups: (1) those which are incapable of enolization, (2) those which contain one substituent capable of enolization and (3) those which contain more than one enolizable substituent. In this latter category are found most of the known tetrahydropyrimidines, e.g. uracil, barbituric acid, alloxan, their derivatives and analogues (15, pp.115-133; 47, pp.194-207; 44, pp.948-1017; 99, pp.964-877).

Tetrahydropyrimidines of the second category are not so numerous but do include a number of important derivatives. Most of these have been made by the Bignelli reaction using various aldehydes, ureas and β-ketoesters (8, pp.361-365). Johnson has made a rather extensive study of this reaction, the products of which he has designated by the generic term "desoxyuracil" (23, pp.3751-3758; 24, pp.1140-1147; 25, pp.3784-3791; 26, pp.1374-1377). Some preparations have involved the Beckmann rearrangement (64) while others have been synthesized by dehydration of N-acylated

amino acid amides (78; 79). Some of these compounds have interesting biological properties, e.g. 2-oxo-4-hexyl-6-methyl-1,2,3,4-tetrahydro-5-pyrimidinecarboxylic acid was found active against murine poliomyelitis (56, pp.203-205; 57, pp.422-431), as well as possible industrial applications, e.g. tetrahydro-1,3-bis(hydroxymethyl)-6-methyl-4-ureido-2(1H)-pyrimidone and similar compounds (71).

Almost all the work up to the present for the preparation of tetrahydropyrimidines falling into the first classification was the result of direct condensation. These condensations have been attained under a variety of conditions but may be placed conveniently into three classes:

1. The condensation of 1,3-diamines (4; 19; 45, p.746; 62; 70, pp.862-863; 74, p.124; 85, p.515; 94), their salts (18, p.491; 35, pp.334-335; 36, p.1192; 69, p.501; 81) or their amides (1, pp.2160-2161; 40, p.2336) with hydrogen chloride (40, p.2336), calcium oxide (1, pp. 2160-2161), organic acids (4; 18; 62; 74, p.124; 94), acid salts (35, pp.334-335; 36, p.1192; 45, p.746; 70, p.863), nitriles (18, p.491; 69, p.501; 70, p.862; 81), acid anhydrides (94) or esters (74, p.124; 85, p.3815).

2. The condensation of amidines with 1,3-dihalopropanes (13, pp.2347-2348; 73, p.2122), 1,3-diamines

(49, pp.431; 50, p.3993; 51, p.768; 52, p.3205-3206; 54; 83; 86) or mesityl oxide (32).

3. Miscellaneous condensation reactions which do not involve the use of amidines or 1,3-diamines (7, pp.30-35; 12, pp.1396-1397; 21, p.1385; 39; 61, p.1115; 72, p.339).

The literature indicates that some work has been done on the other approach to tetrahydropyrimidine synthesis namely, the reduction of pyrimidines which had been prepared by conventional methods. Davies and Piggott in 1945 reported the catalytic reduction of 2-chloro-5-phenylpyrimidine to 5-phenyl-1,4,5,6-tetrahydropyrimidine which was isolated and analysed as the picrate (20, p.347). Six years later Lythgoe and Rayner reduced 2,5-dichloropyrimidine and 5-chloro-2-phenylpyrimidine to 1,4,5,6-tetrahydropyrimidine and 2-phenyl-1,4,5,6-tetrahydropyrimidine, respectively (48, pp.2327-2328). Although the latter authors implied that pyrimidine was reduced to 1,4,5,6-tetrahydropyrimidine in the presence of acid and state that nuclear hydrogenation of pyrimidine was catalysed by acids (48, pp.2324,2327) no experimental evidence was given to support these opinions.

The tetrahydropyrimidines of the first category are coming increasingly to the attention of various investigators for biological screening and several appear promising. For example several have been described as germicides and mothproofing agents (19), sulfa drugs

(32; 82), anti-histamines (45, pp.745-746), antitubercular compounds (18, p.491), fungistatics (74, pp.124-125), therapeutically active or drug intermediates (54; 55) while others were reported inactive as hypnotics (85, p.3814).

Other applications cited in the literature are as intermediates in the preparation of diamines (37), and amino alcohols (38), surface-active agents (88), anti-foamants and capillary-active agents (94), dye bases (94; 54), corrosion inhibitors (10), detergents (4; 94) and asphalt additives (4).

As evidenced above, the mounting interest in the biological applications of these compounds has been limited by the difficulty and labor involved in the preparation of the properly substituted diamines or acid derivatives to yield positional isomers at positions 4,5, or 6 even though variation in substituents at carbon-2 were practically unlimited. Some of the condensation methods (21, p.1382; 39; 12, p.1396) pose another problem as well since they lead to complex tetrahydropyrimidines making positional evaluation difficult. The procedure which lends itself best to the preparation of desired isomers is the catalytic reduction method since the compounds are limited only by the preparation of the pyrimidine, and further it affords

the only satisfactory preparation of tetrahydropyrimidines unsubstituted at carbon-2.

Since only three tetrahydropyrimidines have been prepared by catalytic reduction (20, p.347; 48, pp.2327-2328) the limitations of the reaction have not been investigated. For this reason a study was initiated (1) to determine whether the reduction of chloropyrimidines to tetrahydropyrimidines was general in nature and (2) to provide a practical procedure for the preparation of positional isomers of tetrahydropyrimidines. This would be an aid in extending the correlation between structure and the possible biological properties of these compounds. In the course of the preparation of some of the pyrimidines an improved dechlorination method was evolved together with a modification of the usual chlorination procedure.

The pyrimidines used in this study were made by conventional methods. Usually the pyrimidinediones were reacted with phosphorus oxychloride in the presence of a tertiary amine to give the corresponding chloropyrimidines. The chlorination of uracil-5-carboxylic acid was found to be possible only in the presence of N,N-diethylaniline in contrast to the usual additive, N,N-dimethylaniline. Chlorination of the ester was also improved both in yield and smoothness by the former additive. Wheeler (95, p.396) and Johnson (3, pp.795-796) both were unable to effect the

halogenation of these compounds although Johnson (loc. cit.) prepared ethyl 2,6-dichloropyrimidine-5-carboxylate by the action of chlorine-water on ethyl 6-chloro-2-ethylmercapto-pyrimidine-5-carboxylate. The preparation of 4-amino-2,6-dichloropyrimidine from 4-aminouracil, although in a twenty-seven percent yield, was accomplished by altering the isolation and reaction conditions described by Langerman and Banks (46, p.3011). In all these cases the tertiary amine had to be present in an amount equivalent to the number of oxygens replaced by halogen.

The tetrahydropyrimidines prepared for this study were found to be stable in dilute acids and to be unstable in strong alkaline solutions. With strong base and chloroform the odor of isonitrile was readily apparent. The hydrochlorides were extremely hygroscopic, appreciably soluble in alcohols and were readily titratable with silver nitrate using dichlorofluoroscein as the indicator. The aqueous solutions of the free bases were moderately alkaline. In contrast to the pyrimidines these compounds were not precipitated by mercuric chloride at a pH of approximately five. Lythgoe and Rayner observed that the mercury salt 1,4,5,6-tetrahydropyrimidine was precipitated above this pH (47, p.2327), however this laboratory found no immediate precipitation up to a pH of about seven. This reaction gives a method for separating the reduced ring compounds from the pyrimidine bases.

Pyrimidine and its homologs could be readily reduced in the presence of acid to the corresponding tetrahydropyrimidines. Although 2-amino-4,6-dichloropyrimidine yielded 2-amino-3,4,5,6-tetrahydropyrimidine upon neutral reduction, 2-aminopyrimidine reduced under acidic conditions gave the dihydro derivative exclusively. No reduction occurred under neutral or basic conditions. The 4-amino- and 5-aminopyrimidines were found to behave similarly.

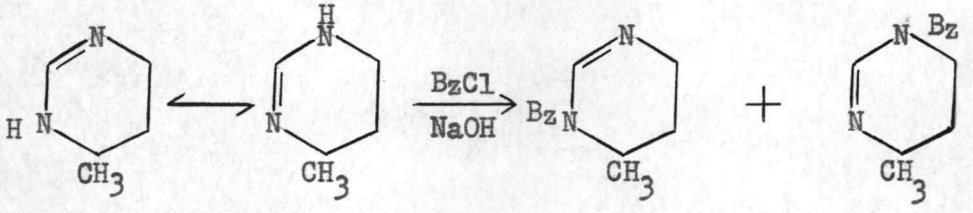
Since the isolations of the free bases were difficult (20, p.347) and they absorb carbon dioxide from the air (85, p.3815) the compounds were isolated as their hydrochlorides, which outside of their extreme hygroscopicity, were quite stable at room temperature.

The benzoyl derivatives were prepared from the hydrochlorides by the Schotten-Baumen reaction with special precautions to keep the solutions cold. On the basis of this work the use of the benzoyl derivatives for the identification of tetrahydropyrimidines is not recommended since lengthy purification procedures were involved. It is suggested that derivatives formed under acid conditions be used for characterization such as the picrates or para-toluenesulfonates.

3,4,5,6-tetrahydropyrimidine and its homologs gave a monobenzoylated derivative. Branch and Titherly (13, p.2343) reported a tribenzoyl derivative of 1,3-diaminopropane from the benzoylation of 2-phenyl-

1,4,5,6-tetrahydropyrimidine. In the case of this study such behavior was not observed. In as much as the principle product was a monobenzolated compound, these derivatives most likely contain C=N unsaturation.

In the benzoylation of 4-methyl-3,4,5,6-tetrahydropyrimidine (i) (see figure 1) it is possible to obtain the isomeric compounds 1-benzoyl-4-methyl-(ii) and 3-benzoyl-4-methyl-3,4,5,6-tetrahydropyrimidine (iii). Careful purification gave a compound melting within a one degree range however paper chromotography, under the conditions employed, was unsuccessful and whether both isomers were formed was not definitely demonstrated.



(i) (i) (ii) (iii)

Figure 1

The reductions of 2,6-dichloro-4-methoxypyrimidine and 4-chloro-2,6-dimethoxypyrimidine were unsuccessful. The hydrogen absorption was not theoretical and no products were separated from the reaction mixture in sufficient purity for characterization.

2,6-dichloro-5-nitropyrimidine absorbed very nearly the theoretical hydrogen to yield 5-amino-3,4,5,6-

tetrahydropyrimidine contaminated with small amounts of colored reduction products. The same product evolved from reduction of 5-amino-2,6-dichloropyrimidine and is more easily purified.

4-amino-2-chloro(and 2,6-dichloro)-5-nitropyrimidine failed to give dehalogenation or nuclear reduction although the nitro group was reduced to yield the corresponding chloro-4,5-diamino derivatives. These, in turn, were isolated, purified and resubjected to hydrogenation under both neutral and basic conditions and still no further absorption of hydrogen was observed. Jones (43, p.524) had successfully catalytically dehalogenated 4,5-diamino-2-chloropyrimidine, however under different conditions.

INTRODUCTION PART II

The Dehalogenation of Chloropyrimidines

The dehalogenation of the chloropyrimidines has been the subject of rather intensive study. As a result procedures are described which are based on chemical, electrolytic and catalytic operations. The most common type of chemical reagents used have been zinc with water or ammonium hydroxide, hydriodic acid and red phosphorus or phosphonium iodide, hydrazine hydrate and benzenesulphonhydrazide (11, pp.4691-4695; 15, pp. 121-122). With these reductants no nuclear reduction was noted. However, if sodium and alcohol (99, p.869), sodium and wet ether, or lithium aluminum hydride were used the reduction progressed to the hexahydropyrimidine. Sodium hydride on the other hand, failed to give appreciable reduction or dehalogenation.

Electrolytic methods of dehalogenation have been rather limited but so far no nuclear reduction has been reported (64; 91; 92).

During the past several years catalytic dehalogenation employing Raney nickel, Adams' catalyst or palladium (suspended on various carriers) in alcoholic or aqueous

media has become the standard laboratory method for removing nuclear halogens from pyrimidines (15, p.119).

The least effective of these is Raney nickel which is generally used when it is desired to reduce other groups on the ring and leave the halogens intact (15, p.121) even though there are instances recorded where halogen was removed (58, p.3130; 65; 66; 90). At low temperatures and pressures nuclear reduction is not effected but at moderate temperatures and high pressures the ring is cleaved (37; 38).

In the case of platinum catalysts so few dehalogenations of pyrimidines have been reported as to make it impossible to draw any conclusions regarding ring reduction (34, p.1295; 41, p.51; 65; 75, p.2342).

Palladium, on the other hand, has been much more widely applied. In this instance the pH of the reaction mixture in most cases determines the extent of the reduction. In acidic solutions, as mentioned, the reaction results in a nuclear-reduced product. Investigators have avoided nuclear reduction by dehalogenating in the presence of a hydrogen ion acceptor, e.g. magnesium oxide (11, pp.4693-4695; 15, p.119; 48, p.2327; 60, p.1015; 68, p.1882; 96, p.1568; 97, p.1646), barium oxide (43, p.524; 76, p.2005), alkali carbonates (5; 77, p.570), sodium, potassium or ammonium hydroxides (42, pp.3541-3542; 48, pp.2327-2329; 63; 66; 67; 77, p.369; 93; 100) or compounds

capable of accepting hydrogen chloride by an addition reaction like tetrahydronaphthalene (80). At least two exceptions to this are recorded in the literature where acid was deliberately added in excess to solubilize the compound which was then dechlorinated in good yield to the pyrimidine. In both instances the reaction involved a 4-aminopyrimidine, the compounds being 4-amino-6-chloro-2-methyl- and 4-amino-5-chloro-2-methylpyrimidine (17, pp.227, 234; 22, p.759).

The problem of making pyrimidines by either chemical or catalytic dehalogenations is further complicated by isolation difficulties and sometimes by side reactions (11, pp.4692-4694). In the recent procedure developed by Whittaker for the preparation of pyrimidine (97, p.1646) the dichloropyrimidine was reduced in the presence of magnesium oxide using palladized charcoal in an alcohol-water solution. After removal of the catalyst and excess magnesia by filtration the solution must be steam distilled (11, pp.4692). This gave a large volume of water from which the pyrimidine was recovered as the mercuric chloride complex. This complex was distilled from sodium sulfide nonohydrate giving a fairly concentrated solution of the pyrimidine which may be extracted with ether following saturation with potassium hydroxide. The ethereal extract was then dried and distilled to yield pyrimidine.

Since this procedure is long and tedious this laboratory attempted reductions in a heterogeneous system of ether and aqueous sodium hydroxide. Although the dehalogenations were somewhat slower, the isolation was simplified. It was only necessary to remove the catalyst by filtration, make the aqueous layer strongly alkaline and extract it with ether, which was then dried and distilled.

Using the aqueous sodium hydroxide-ether system 2-chloro, 2,4-dichloro-, 4,6-dichloro-, 2,4,6-trichloro- and 2,4,5,6-tetrachloropyrimidines were dehalogenated in good yields. Furthermore, the methyl derivatives of the above mentioned dichloropyrimidines gave similar results. The reduction times varied considerably with the location of the substituent in the aminodichloropyrimidine series; the 5-amino reducing most rapidly with the 2-amino and 4-amino following in that order.

Lythgoe and Rayner (48, p.2324) report that in the presence of even quite dilute sodium hydroxide solutions solvolytic replacement of the nuclear chlorines occurred and especially with di- and trichloropyrimidines or any pyrimidine where the halogens were more reactive than those in 5-chloro-2-phenyl- or 4-chloro-5-phenylpyrimidine. However using the heterogeneous system of aqueous base and ether only slight hydrolysis has been noted and that in the case of the extremely reactive halogens of

4,6-dichloro-5-nitropyrimidine. Other exceptions are also recorded in the literature (63; 67; 100).

Using the method evolved in this study the dehalogenation of ethyl 2,6-dichloropyrimidine-5-carboxylate was straight forward. Some hydrolysis of the ester group occurred during the reduction and for this reason the hydrolysis was completed and the product isolated as pyrimidine-5-carboxylic acid. The dehalogenation of the methoxychloropyrimidines went normally but some loss was encountered in the isolation of the products.

This procedure based on the ether-aqueous sodium hydroxide mixture was not applicable to all chloropyrimidines investigated. 2,6-Dichloro-5-nitro- and 4,6-dichloro-5-nitropyrimidine failed to yield either 5-amino- or 5-nitropyrimidine. The hydrogen uptake was quite slow and approximately seventy percent of theory with variations among experiments. The highly colored reaction mixture yielded only a very small amount of 5-aminouracil; no other product was identified. Whittaker (96, p.1565) reports the reduction of 2,6-dichloro-5-nitropyrimidine with palladized charcoal in an alcoholic solvent to give a water-soluble azo compound. Using the same catalyst in methanolic potassium hydroxide Yanai isolated 5-amino-2,4-dimethoxy-6-methylpyrimidine from 2,6-dichloro-5-nitro-6-methylpyrimidine and observed that the addition of hydrazine hydrate gave 5-amino-6-methylpyrimidine; no

yield was given. As already mentioned the 4-amino-5-nitro- or 4,5-diaminochloropyrimidines were not dehalogenated. 2-Mercapto-4-chloropyrimidine, as expected, also failed to dehalogenate and only the starting material was recovered.

Yields, using the aqueous alkali-ether solvent mixture, in most instances were significantly greater than those reported earlier. The pyrimidine ring was very stable towards catalytic reduction under basic conditions and no nuclear reduction was detected even after twelve hours shaking with hydrogen at three atmospheres pressure. Furthermore, the hydrolysis was extremely limited (as noted above) and no other side-products were noted. When alcohol-base systems are used alkoxylation is a frequent side-reaction and often, the main product (48, p.2824; 60, p.1015; 63; 100).

INTRODUCTION PART III

The Relative Reactivities of the Methyl Groups in the Monomethylated Pyrimidines

The reactivity of the methyl groups on the pyrimidine homologs is of interest for preparative reasons. The 2- and the 4-methyl groups are both known to react with benzaldehyde to give the corresponding styryl derivatives shwoing these are active methyl groups (27, p.3642; 30, p.3381). In addition the 4-methylpyrimidine has been oxidized to pyrimidine-4-carboxylic (28, pp.1536-1537). The preparation of pyrimidine-5-carboxylic acid has been by oxidation of quinazoline to pyrimidine-4,5-dicarboxylic acid followed by thermal decarboxylation (31, pp.3648-3651). A few experiments were run to check the ease of oxidation of the 2- and 5-methylpyrimidines under the same conditions used by Gabriel for the 4-methyl isomer (28, pp.1536-1537). In addition to see what the extent of this activation of methyl groups might be, in a qualitative manner, the action of two reagents prone to attack active methyl groups was tested.

The oxidation of 2-methylpyrimidine with neutral permanganate failed to yield the 2-carboxylic acid and twenty-eight percent of the starting material was recovered. Possibly any acid formed in the oxidation may have been decarboxylated.

Similar experiments with the 5-methylpyrimidine gave the acid in only ten percent yield. Thirty-three percent of the starting material was recovered. This may have been due to two factors: (1) a poor isolation technique and (2) increased ring oxidation due to the relative inertness of the methyl group.

Tests using selenium dioxide in acetic anhydride, dioxane and ethanol showed the 4-methyl isomer to be attacked under these conditions while the 2-isomer was only slightly attacked in acetic anhydride and 5-methylpyrimidine failed to react in any of the three solvents. A reaction with N-bromosuccinimide was limited to 4-methylpyrimidine only. These reactions tend to indicate that the 4-methyl group is quite reactive while the 5-methyl is relatively inert and the 2-methyl substituent has an activity intermediate in respect to the other two positions.

EXPERIMENTAL

The preparation of tetrahydropyrimidines from chloropyrimidines

A mixture of 0.025 moles of a chloropyrimidine in 100 ml. of diethyl ether, 10-20 ml. water and 300 mg. of 10% palladium-on-charcoal were shaken with hydrogen at room temperature at an initial pressure of 3 atmospheres until the hydrogen uptake ceases. The catalyst was removed by filtration and washed with two 5 ml. portions of hot water. The washings and filtrate were combined and evaporated to dryness at reduced pressures and a bath temperature of about 50-60°. To aid in removing any remaining water and hydrochloric acid 25 ml. each of absolute ethanol and benzene were added and evaporated as before. The resulting tetrahydropyrimidine hydrochlorides were quite pure. Any color usually resulted from impurities in the starting materials and could be removed by treatment with Norit either before evaporation or during recrystallization. Recrystallization for analysis was from absolute methanol-petroleum ether solvents on the dry crude materials. The results of these experiments are given in Table I.

TABLE I

DEHALOGENATION AND NUCLEAR REDUCTION OF CHLOROPYRIMIDINE

Pyrimidine	Tetrahydro-pyrimidine	Yield in percent	Melting point[1] °C	Empirical formula	Percentage composition Calculated % C	% H	Found % C	% H	Remarks
2-Chloro-	3,4,5,6-Tetrahydro-pyrimidine hydro-chloride	97	121	$C_4H_8N_2 \cdot HCl$					Oxalate melts at 150-1°(d.) (48,p.2327)
2,6-Dichloro-	3,4,5,6-Tetrahydro-pyrimidine hydro-chloride	98	120	$C_4H_8N_2 \cdot HCl$	39.84	7.52	39.70 39.69	7.69 7.58	Oxalate melts at 150-1° (48,p.2327)
4,6-Dichloro-	3,4,5,6-Tetrahydro-pyrimidine hydro-chloride	97	120	$C_4H_8N_2 \cdot HCl$					Oxalate melts at 149-50° (48,p.2327)
2,4,6-Trichloro-	3,4,5,6-Tetrahydro-pyrimidine hydro-chloride	95	121	$C_4H_8N_2 \cdot HCl$					Oxalate melts at 151-2° (48,p.2327)
2,4,5,6-Tetra-chloro-	3,4,5,6-Tetrahydro-pyrimidine hydro-chloride	91	119	$C_4H_8N_2 \cdot HCl$					Oxalate melts at 149-51.5° (48,p.2327)
2,6-Dichloro-4-methyl-	*4-Methyl-3,4,5,6-hydrochloride	98	149	$C_5H_{10}N_2 \cdot HCl$	44.61	8.24	44.41 44.49	8.39 8.43	
2,6-Dichloro-5-methyl-	*5-Methyl-3,4,5,6-hydrochloride	97	131	$C_5H_{10}N_2 \cdot HCl$	44.61	8.24	44.57 44.48	8.41 8.30	

TABLE I (continued)

Pyrimidine	Tetrahydro-pyrimidine	Yield in percent	Melting point[1] °C	Empirical formula	Percentage composition Calculated %C	%H	Found %C	%H	Remarks
4,6-Dichloro-2-methyl-	2-Methyl-3,4,5,6-Hydrochloride	96	139	$C_5H_{10}N_2 \cdot HCl$	44.61	8.24	44.50 44.54	8.31 8.29	Picrate melts 153-154°(d.) (35,p.336)
2,6-Dichloro-5-nitro-	*5-Amino-3,4,5,6-dihydrochloride	41	198	$C_4H_9N_3 \cdot 2HCl$	28.58	6.60	28.48 28.51	6.73 6.70	
4,6-Dichloro-5-nitro-	*5-Amino-3,4,5,6-dihydrochloride	37	195	$C_4H_9N_3 \cdot 2HCl$					
5-Amino-4,6-dichloro-	*5-Amino-3,4,5,6-dihydrochloride	98	197	$C_4H_9N_3 \cdot 2HCl$					
4-Amino-2,6-dichloro-	*4-Amino-3,4,5,6-dihydrochloride	89	204	$C_4H_9N_3 \cdot 2HCl$	28.58	6.60	28.69 28.53	6.49 6.65	
2-Amino-2,6-dichloro-	*2-Amino-3,4,5,6-dihydrochloride	93	208	$C_4H_9N_3 \cdot 2HCl$	28.58	6.60	28.54 28.54	6.70 6.58	p-toluene sulfonate melts at 172-4°(d.) Lit. given 174° (81)
2,6-Dichloro-4-methoxy-	No identified products were isolated								
2,6-Dimethoxy-4-chloro-	No identified products were isolated								
2-Mercapto-6-chloro-	No reduction								

(1) All melting points are uncorrected. They are difficult to reproduce.
* New compound.

The preparation of hydropyrimidines from non-chloro pyrimidines

A mixture of 0.025 moles of the pyrimidine with 200 mg. 10% palladium-on-charcoal in 100 ml. of water and a slight excess of concentrated hydrochloric acid (sufficient to neutralize all secondary or primary amine groups present at the end of the reaction) was shaken with hydrogen at an initial pressure of 3 atmospheres. After cessation of hydrogen uptake the isolation is carried out as in the case of the reduction of the chloropyrimidines. These results are given in Table II.

The preparation of the benzoylated hydropyrimidines

The usual Schotten-Bauman technique as described by Wild, (98) was used on the solid tetrahydropyrimidine hydrochloried or its aqueous solution. Caution was exercised to keep the reaction mixture cold by cooling under the tap and to filter the resulting precipitate immediately. Often a few drops of alcohol seemed to hasten the formation of the solid derivative. See Table III.

TABLE II

THE NUCLEAR REDUCTION OF PYRIMIDINES

Pyrimidine	Hydropyrimidine	Yield in percent	Melting point[1] °C	Melting point of the Benzoyl derivative[1] °C	Remarks
Pyrimidine	3,4,5,6-Tetrahydro-pyrimidine hydrochloride	98	122	145-6	See note (2)
2-Methyl-	2-Methyl-3,4,5,6-Tetra-hydro pyrimidine hydrochloride	97	139	135-6	See note (2)
4-Methyl-	4-Methyl-3,4,5,6-Tetra-hydro pyrimidine hydrochloride	98	148	164-6	See note (2)
5-Methyl-	5-Methyl-3,4,5,6-Tetra-hydro pyrimidine hydrochloride	98	132	140-2	See note (2)
2-Amino	*2-Amino-?-dihydro-pyrimidine dihydrochloride	91	231		Calculated for $C_4H_7N_3 \cdot 2HCl$; %C=28.26; %H=5.34 Found: %C=28.26, 28.15; %H=5.46, 5.44
2-Amino-4-methyl-	*2-Amino-4-methyl-?-dihydropyrimidine dihydrochloride	93	243		Calculated for $C_5H_9N_3 \cdot 2HCl$ %C=33.39; %H=6.02 Found %C=33.47, 33.30; %H=6.15, 5.98

TABLE II (continued)

Pyrimidine	Hydropyrimidine	Yield in percent	Melting point[1] °C	Melting point of the Benzoyl derivative[1] °C	Remarks
4-Amino-	*4-Amino-?-dihydropyrimidine dihydrochloride	77	263		Calculated for $C_4H_7N_3 \cdot 2HCl$: %C=28.26; %H=5.34 Found %C=28.36, 28.39 %H=5.45, 5.42
5-Amino-	*5-Amino-?-dihydropyrimidine dihydrochloride	98	157		Calculated for $C_4H_7N_3 \cdot 2HCl$ %C=28.26; %H=5.34 Found %C=28.37, 28.30 %H= 5.20, 5.22

(1) All melting points are uncorrected. They are difficult to reproduce.
(2) No depression when mixed with corresponding derivative from reduction of the chloropyrimidine.
* New compound.

TABLE III

BENZOYL DERIVATIVES OF THE REDUCED PYRIMIDINES

Hydropyrimidine	Benzoyl hydropyrimidine	Yield in percent	Melting point(1) °C	Empirical formula	Percentage composition Calculated %C	%H	Found %C	%H
3,4,5,6-Tetrahydropyrimidine hydrochloride	*1-Benzoyl-1,4,5,6-tetrahydropyrimidine	31	145-6	$C_{11}H_{12}N_2O$	88.36	6.43	88.20 88.18	6.40 6.50
2-Methyl-3,4,5,6-tetrahydropyrimidine hydrochloride	*1-Benzoyl-2-methyl-1,4,5,6-tetrahydropyrimidine	40	136-7	$C_{12}H_{14}N_2O$	71.26	6.98	71.20 71.04	7.11 7.14
4-Methyl-3,4,5,6-tetrahydropyrimidine hydrochloride	*1-Benzoyl-4-methyl-1,4,5,6-tetrahydropyrimidine	23	165-6	$C_{12}H_{14}N_2O$	71.26	6.98	71.31 71.28	6.93 7.14
5-Methyl-3,4,5,6-tetrahydropyrimidine hydrochloride	*1-Benzoyl-5-methyl-1,4,5,6-tetrahydropyrimidine	38	142-3	$C_{12}H_{14}N_2O$	71.26	6.98	71.17 71.11	7.08 7.03
2-Amino-3,4,5,6-tetrahydropyrimidine dihydrochloride	*2-Benzamido-1,4,5,6-tetrahydropyrimidine	49	188-9	$C_{18}H_{21}N_3O_2$	70.34	5.58	70.12 70.18	5.70 5.64
4-Amino-3,4,5,6-tetrahydropyrimidine dihydrochloride	*4-Benzamido-1(3)-benzoyl-1(3),4,5,6-tetrahydropyrimidine	61	212-4	$C_{18}N_{21}N_3O_2$	70.34	5.58	70.34 70.09	5.69 5.46
5-Amino-3,4,5,6-tetrahydropyrimidine dihydrochloride	*5-Benzamido-1-benzoyl-1,4,5,6-tetrahydropyrimidine	55	178-9	$C_{18}N_{21}N_3O_2$	70.34	5.58	70.17 70.15	5.69 5.69

TABLE III (continued)

Hydropyrimidine	Benzoyl hydropyrimidine	Yield in percent	Melting point(1) °C	Empirical formula	Percentage composition Calculated %C	%H	Found %C	%H
2-Amino- ? - dihydropyrimidine dihydrochloride	*2-Benzamido - ? - dihydropyrimidine	69	168-9	$C_{11}H_{12}N_3O$	65.31	5.98	65.48 65.20	6.10 6.14
2-Amino-4-methyl- ? - dihydropyrimidine dihydrochloride	*2-Benzamido-4-methyl - ? - dihydropyrimidine	73	142-3	$C_{12}H_{13}N_3O$	66.96	6.09	67.11 67.15	6.21 6.05
4-Amino- ? - dihydropyrimidine dihydrochloride	*4-Benzamido- ? - dihydropyrimidine	51	193-5	$C_{12}H_{13}N_3O$	65.31	5.98	65.51 65.40	5.87 6.01
5-Amino- ? - dihydropyrimidine dihydrochloride	*5-Benzamido- ? - dihydropyrimidine	44	129-30	$C_{12}H_{13}N_3O$	65.31	5.98	65.59 65.50	5.83 5.85

(1) All melting points are uncorrected

* New compounds

The preparation of pyrimidines

A slight excess of 20% carbonate-free sodium hydroxide (sufficient to neutralize the hydrogen chloride produced in the reaction) was placed in a low-pressure hydrogenation bottle followed by 0.2-1 g. of 10% palladium-on-carbon and 0.1 mole of the chloropyrimidine dissolved in 100-200 ml. diethyl ether. The mixture was shaken with hydrogen at an initial pressure of three atmospheres and at room temperature until the hydrogen-uptake ceases. The mixture was filtered, the residue washed with two 5 ml. portions of hot water and the pyrimidine isolated by one of following procedures: (The hydrogen uptake should correspond to one mole of hydrogen per halogen removed and the aqueous filtrate should test slightly alkaline.)

Isolation Procedure A. The combined filtrates were made strongly alkaline by the addition of 5-10 g. of sodium hydroxide with strong external cooling and at such a rate that the temperature remained below 5°. The solution was continuously extracted with diethyl ether for 8-12 hours and the ether extract dried over sodium or magnesium sulfate. The mixture was filtered, the residue washed with anhydrous ether and the combined ether filtrates distilled through a 1.2 by 20 cm. Vigreux column.

Isolation procedure B. The combined filtrates were saturated with potassium hydroxide under the same conditions as in A and then kept below 0° for 3-12 hours. The pyrimidine layer was separated (or if a solid filtered through a sintered-glass filter) and the aqueous layer extracted with five portions each of 80 ml. diethyl ether. The pyrimidine layer and the ether extracts were combined, dried and evaporated in vacuo (or in case of a liquid pyrimidine distilled as in A) and the solid recrystallized or carefully dried and sublimed. See Table IV.

The preparation of 4-amino-2,6-dichloropyrimidine

A mixture of 10 g. 4-aminouracil, 150 ml. phosphorus oxychloride and 15 ml. mono-free N,N-diethylaniline were refluxed until no more hydrogen chloride was evolved (about 10 hours). The excess phosphorus oxychloride was removed at water aspirator pressures and the dark residue decomposed with chipped ice. The black solution was treated with solid potassium carbonate until the pH was approximately 6-6.5 and the mixture placed in the refrigerator overnight. The mixture was filtered, the residue washed with water and with methanol-ether (to remove the water) and then dried at 100° for four hours. The dried material was extracted with four portions, each of 100 ml., of boiling ethyl acetate. The ethyl acetate

TABLE IV

THE DEHALOGENATION OF CHLOROPYRIMIDINES

Moles of chloro-pyrimidine	Chloropyrimidine	Mg. of 10% palladium on carbon	Product	Yield in percent	Boiling or Melting point[1]	Method of Isolation	References and Remarks
0.10	2,6-Dichloropyrimidine	200	Pyrimidine	91	122-4°/760mm. melts 21-2°	A	(97, p.1646)
0.025	4,6-Dichloropyrimidine	200	Pyrimidine	89	melts 21-2°	A	(97, p.1646)
0.025	4,6-Dichloropyrimidine[2]	200	Pyrimidine	77	melts 21.5-22°		(97, p.1646)
0.05	2,4,6-Trichloro-pyrimidine	200	Pyrimidine	87	121-3°/755mm.	A	(97, p.1646)
0.05	2,4,5,6-Tetrachloro-pyrimidine	300	Pyrimidine	86	119-21°/757mm.	A	(97, p.1646)
0.10	4,6-Dichloro-2-methylpyrimidine	200	2-Methylpyri-midine	86-92	136-8°/757mm.	A	(37, p.3641)
0.10	4,6-Dichloro-2-methylpryimidine[2]	200	2-Methylpyri-midine	75	136-7°/759mm.		(37, p.3641)
0.20	2,6-Dichloro-4-methylpryimidine	200	4-Methyl-pyrimidine	81-93	140-2°/757mm.	A	(29, p.2928)

TABLE IV (continued)

Moles of chloro-pyrimidine	Chloropyrimidine	Mg. of 10% palladium on carbon	Product	Yield in Percent	Boiling or melting[1] point	Method of Isolation	References and Remarks
0.10	2,6-Dichloro-4-methylpyrimidine[2]	200	4-Methy-pyrimidine	73-80	140-1°/755mm.		(68, p.1883)
0.025	2,4-Dichloro-5-methylpyrimidine	200	5-Methyl-pyrimidine	83-87	151-3°/755mm. melts 30-1°	A & B	(Isolation procedure B works nicely as solid can be filtered off (33,p.3400)
0.025	2,4-Dichloro-5 methylpyrimidine[2]	200	5-Methyl-pyrimidine	72	151-2°/760mm. melts 30-1°		(33, p.3400)
0.01	4-Chloro-2,6-dimethoxy-pyrimidine	200	2,6-Dimethoxy-pyrimidine	62	202-4°/757mm.	B	(29, p.2933)
0.01	2,6-Dichloro-4-methoxypyrimidine	300	4-Methoxy-pyrimidine	57	70-1°/35 mm.	B	(16, p.336)
0.012	Ethyl 2,6-Dichloro-pyrimidine-5-carboxylate	500	Pyrimidine-5-carboxylic acid	29	268-70°	(3)	(92, p. 3651)
0.025	2-Amino-4,6-dichloro-pyrimidine	300	2-Amino-pyrimidine	88	125-6	B	(76,p.2003) recrystallized from chloroform.
0.025	4-Amino-2,6-dichloro-pyrimidine	500	4-Amino-pyrimidine	73	149-51	B	Recrystallized from ethyl acetate (14, p.355)

TABLE IV (continued)

Moles of chloro-pyrimidine	Chloropyrimidine	Mg. of 10 % palladium on carbon	Product	Yield in Percent	Boiling or melting point(1)	Method of Isolation	References and Remarks
0.025	5-Amino-2,6-dichloro-pyrimidine	200	5-Amino-pyrimidine	91			Recrystallized from Benzene-ligroine mixture (96,p.1568)
0.025	4,5-Diamino-2-chloro-pyrimidine	1000	No hydrogen uptake noted				
0.025	4,5-Diamino-2,6-dichloropyrimidine	1000	No hydrogen uptake noted				
0.025	4-Amino-2-chloro-5-nitropyrimidine	1000	4,5-Diamino-2-chloro-pyrimidine	68	230-32	B	Same product in neutral media(4) (43, p.524)
0.025	4-Amino-2,6-dichloro-5-nitropyrimidine	880	4,5-Diamino-2, 6-dichloro-pyrimidine	77	259-61	B	Same product in neutral media(4)
0.025	2,6-Dichloro-5-nitropyrimidine	500	Products not identified				48-79% of theoretical hydrogen uptake occurred.

(1) All melting points are uncorrected.
(2) Prepared by the method of Whittaker (97, p.1646).
(3) To the aqueous reduction mixture was added one sodium hydroxide pellet and the solution was boiled for 10 minutes, cooled, volume reduced to 5 ml. and the cooled solution neutralized with HNO_3. The precipitate was slow to form.
(4) Reduction rate was increased seven fold in N,N-Dimethylformamide. But the solvent and product react in the cold very rapidly.

extracts were evaporated and the residue sublimed at 180-90° at 50 mm. $_{Hg}$. The yield was 27%. The melting point was 270-2° (46, p.3011).

The preparation of methyl or ethyl 2,6-dichloropyrimidine-5-carboxylate

A mixture of 10 g. methyl or ethyl uracil-5-carboxylate, 90 ml. phosphorus oxylchloride and 15 ml. mono-free N,N-diethylaniline were refluxed for 30-45 minutes after solution of the reactants occurred. About one-half of the phosphorus oxychloride was removed by distillation at water aspirator pressure and the residue decomposed by slowly pouring, with vigorous stirring, into a mixture of 20 ml. water and 20 g. chipped ice. Additional ice was added to always insure its presence in the mixture. After the phosphorus oxychloride was completely hydrolyzed, the mixture was rapidly extracted with five portions, each of 100 ml., of diethyl ether. The combined ether extracts were washed with 50 ml. of saturated sodium bicarbonate solution, then with 50 ml. of water and finally, dried over anhydrous magnesium sulfate. The ether was removed by distillation through a 1.2 by 20 cm. Vigreux column. The residue in turn was distilled using a Claisen head connected directly to the vacuum takeoff and the receiver cooled by ice-water. The ethyl 2,6-dichloropyrimidine-5-carboxylate boiled at

148-150°/19-20 mm. $_{Hg}$ and melted at 36-7° (3, p.797). The methyl 2,6-dichloropyrimidine-5-carboxylate boils at 141-3°/23-25 mm.$_{Hg}$ and melts at 34-34.5°. The yield of both compounds was 86%.

The methyl ester when hydrolyzed following the procedure of Sprague and Johnson (87, p.2254) gave uracil-5-carboxylic acid.

Calculated for $C_6H_4Cl_2N_2O_2$: C, 34.81%; H, 1.95%

Found: C, 34.75%, 34.72%; H, 1.98%, 1.99%

The preparation of 2,6-dichloropyrimidine--5-carboxylic acid

To 5 g. of dried, powdered, sulfur-free uracil-5-carboxylic acid (prepared by nitric acid oxidation of 2-thio-uracil-5-carbethoxylate (3) were added 20 ml. of phosphorus oxychloride and 5.2 ml. of mono-free N,N-diethylaniline. The mixture was protected from atmospheric moisture with a calcium chloride-filled drying tube and refluxed for one hour after solution occurred. About one-half of the phosphorus oxychloride was removed in vacuo at 40-45° and the residue poured slowly onto chipped ice with vigorous stirring. The cold mixture was quickly extracted with four portions of 50 ml. diethyl ether each; the combined ether extracts were washed with 25 ml. of water and dried over anhydrous magnesium sulfate. The ether was filtered

from the magnesium sulfate under slightly reduced pressure and the residue washed with a little anhydrous ether. The combined ether filtrates were evaporated in vacuo leaving a faintly yellow solid. To insure complete removal of hydrochloric acid 25 ml. of dry benzene was added and removed under reduced pressure. The 2,6-dichloropyrimidine-5-carboxylic acid melts at 96-7°. The yields on two runs were 69% and 73%. A small amount was recrystallized from petroleum ether for analysis. There was no change in melting point.

Calculated for $C_5H_2Cl_2N_2O_2$: C, 31.11%; H, 1.04%; Cl, 36.73%

Found: C, 31.08%, 31.07%; H, 1.10, 1.08%; Cl, 36.69%, 36.68%

A small amount was hydrolyzed to yield uracil-5-carboxylic acid menohydrate melting at 267-9°. Wheeler gives 268-7° (59, p.4175).

SUMMARY

A number of new tetrahydropyrimidines containing alkyl and amino substituents together with several amino dihydropyrimidines have been synthesized.

The benzoylated derivatives of these compounds have been prepared.

A new procedure for the dehalogenation of chloropyrimidines has been devised and tested with some eighteen different compounds.

The effect of N,N-diethylaniline upon the course of phosphorus oxychloride halogenation of pyrimidiones was reported to be more efficacious than N,N-dimethylaniline and two new chloropyrimidines have been characterized.

Initial studies of the qualitative activities of methyl-substituted pyrimidines indicates that only the 4-methyl group possesses appreciable activity.

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