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PYRIMIDINES. V. DEHALOGENATION AND NUCLEAR REDUCTION OF CERTAIN PYRIMIDINES[1]

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In their studies of the catalytic dehalogenation of 2,5-dichloropyrimidine Lythgoe and Rayner (1) focused attention to the fact that the presence of acids catalyzed hydrogenation of the pyrimidine ring (2). Subsequent investigators have avoided nuclear reductions of chloropyrimidines by carrying out dehalogenation operations in the presence of a hydrogen ion acceptor, e.g. magnesium oxide, barium oxide, alkali carbonates, and hydroxides or ammonium hydroxide (3).

Dehalogenation under conditions which led to nuclear reductions of the pyrimidine have received scant attention. Relatively few of tetrahydropyrimidines reported in the literature (4) have been prepared by catalytic reduction. Most of the tetrahydropyrimidines which are described have been synthesized by the direct condensation of 1,3-diamines (5), (their salts or amides) (5) with organic acids, salts, nitriles, anhydrides or esters, yielding products which are usually incapable of enolization.

The Bignelli reaction (6) which employs various aldehydes, ureas and β-ketoesters has been used rather extensively for the synthesis of "desoxyuracils" (7) a tetrahydropyrimidine containing one substituent capable of enolization. These same preparations have been made *via* the Beckmann rearrangement (8), or by dehydration of N-arylated amino acid amides (9).

Procedures based on these condensation reactions are limited by the difficulty and labor involved in the preparation of the properly substituted diamines or acid derivatives which will yield the desired substituents at positions 4, 5, or 6, though variations at position 2 are practically unlimited.

In the course of our screening program it became necessary to synthesize a number of tetrahydropyrimidines. A consideration of (a) the availability of the intermediates, together with (b) the fact that catalytic reduction provides a practical procedure for the preparation of substituted tetrahydropyrimidines, makes this approach worth investigating. For this reason a number of typically substituted pyrimidines were hydrogenated under acidic conditions in an effort to determine the feasibility of a nuclear reduction procedure.

The pyrimidones and pyrimidinediones used in this study were converted to the chloroderivatives in straight forward reactions with phosphorus oxychloride in the presence of a tertiary amine.

The preparation of 4-amino-2,6-dichloropyrimidine from 4-aminouracil was accomplished by altering the isolation procedure and the reaction conditions

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described by Langerman and Banks (10); the yield, however, was only 27%. In all these reactions one mole of tertiary amine was required per mole of reacting phosphorus oxychloride. In the case of 5-aminouracil the chlorination was unsuccessful. The chlorination of uracil-5-carboxylic acid was only found to be possible 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. The better yields obtained with N,N-diethylaniline may stem from steric considerations which may lessen its tendency to undergo side reactions. Wheeler and Johnson (11) were unable to effect the halogenation of these compounds although Johnson prepared 2,6-dichloropyrimidine-5-carboxylate by the action of chlorine water on ethyl 6-chloro-2-ethylmercaptopyrimidine-5-carboxylate.

The tetrahydropyrimidines prepared in this study were found to be stable in dilute acids and to be unstable in strongly 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 approximately *p*H 5. Lythgoe and Rayner observed that the mercury salt of 1,4,5,6-tetrahydropyrimidine was precipitated above this *p*H (2), however, this laboratory found no immediate precipitation up to about *p*H 7. This behavior gives a method for separating the reduction product 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-1,4,5,6-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-amino-pyrimidines were found to behave in a similar fashion.

Since the isolations of the free bases were difficult (4) the compounds were isolated as their hydrochlorides, which aside from 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 *p*-toluenesulfonates.

1,4,5,6-Tetrahydropyrimidine and its homologs gave a monobenzoylated derivative. Branch and Titherly (12) obtained a tribenzoyl derivative of 1,3-diaminopropane upon the benzoylation of 2-phenyl-1,4,5,6-tetrahydropyrimidine. In the case of this study such behavior was not observed. Inasmuch as the principle product invariably was a monobenzolated compound, these derivatives most likely contain C=N unsaturation.

In the benzoylation of *dl*-4(6)-methyl-1,4,5,6-tetrahydropyrimidine (I) (see

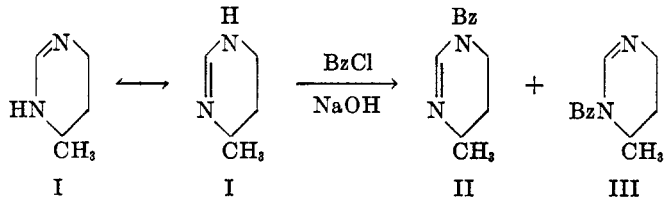

FIGURE 1

Figure 1) it might be possible to obtain the isomeric compounds *dl*-1-benzoyl-4-methyl- (II) and *dl*-1-benzoyl-6-methyl-1,4,5,6-tetrahydropyrimidine (III). Careful purification gave a product melting within a one degree range. However confirmation of only one benzolated derivative by paper chromatography, under the conditions employed, was unsuccessful. Whether both isomers were formed was not definitely demonstrated.

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 amount of hydrogen to yield 5-amino-1,4,5,6-tetrahydropyrimidine contaminated with small amounts of colored reduction products. The same product is formed from the 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 (13) has successfully catalytically dehalogenated 4,5-diamino-2-chloropyrimidine, however, under different conditions.

Lythgoe and Rayner (2) have found that solvolysis of the nuclear chlorines occurs in dehalogenations of chloropyrimidines carried out in dilute sodium hydroxide solutions, especially with di- and tri-chloropyrimidines or any pyrimidine where the halogens were more reactive than those in 5-chloro-2-phenyl- or 2-chloro-5-phenyl-pyrimidine. For this reason a series of dehalogenations were carried out in this laboratory in an ether-sodium hydroxide medium. Using such a heterogeneous system only slight hydrolysis has been noted and that in the case of the extremely reactive halogens of 4,6-dichloro-5-nitropyrimidine. See Table IV.

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 was normal 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-nitro-pyrimidine failed to yield either 5-amino- or 5-nitropyrimidine. The hydrogen uptake was quite slow and approximately 70% 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 (14) 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 (15) isolated 5-amino-2, 4-dimethoxy-6-methylpyrimidine from 2,6-dichloro-5-nitro-6-methyl-pyrimidine 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-diamino-chloropyrimidines 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 12 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 (2).

EXPERIMENTAL

The preparation of hydropyrimidines by nuclear reduction of pyrimidines. A mixture of 0.025 mole of the pyrimidine with 200 mg. of 10% palladium-on-charcoal in 100 ml. of water and a slight excess of concentrated hydrochloric acid (sufficient to neutralize all secondary or primary groups present at the end of the reaction) was shaken with hydrogen at an initial pressure of 3 atmospheres until hydrogen uptake ceased. 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.

The preparation of tetrahydropyrimidines by dehalogenation and nuclear reduction of chloropyrimidines. A mixture of 0.025 mole of a chloropyrimidine in 100 ml. of diethyl ether, 10–20 ml. of water, and 300 mg. of 10% palladium-on-charcoal was shaken with hydrogen at room temperature at an initial pressure of 3 atmospheres. After cessation of hydrogen uptake the isolation was carried out as in the case of the reduction of the pyrimidines.

The results of this series of experiments are given in Table II.

The preparation of the benzoylated hydropyrimidines. The usual Schotten-Bauman technique was used on the solid tetrahydropyrimidine hydrochloride 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.

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 0.2–1.0 g. of 10% palladium-on-carbon and 0.1 mole of the chloropyrimidine dissolved in 100–200 ml. of diethyl ether. The mixture was shaken with hydrogen at an initial pressure of three atmospheres and at room temperature until the hydrogen uptake ceased. 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 was dried over sodium or magnesium sulfate. The mixture was filtered, the residue washed once 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 was extracted with five portions each of 80 ml. of 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 was recrystallized or carefully dried and sublimed. See Table IV.

The preparation of 4-amino-2,6-dichloropyrimidine. A mixture of 10 g. of 4-aminouracil,

TABLE I

THE NUCLEAR REDUCTION OF PYRIMIDINES WITH PALLADIZED CHARCOAL

Pyrimidine	Hydropyrimidine	Yield, %	M.P., °C[a]	Benzoyl Derivative,[a] M. P., °C	Analysis				Remarks
					Calc'd		Found		
					C	H	C	H	
Pyrimidine	1,4,5,6-Tetrahydropyrimidine hydrochloride	98	122	145–146					[b]
2-Methyl	2-Methyl-1,4,5,6-tetrahydropyrimidine hydrochloride	97	139	135–136					[b]
4-Methyl	4(6)-Methyl-1,4,5,6-tetrahydropyrimidine hydrochloride	98	148	164–166					[b]
5-Methyl	5-Methyl-1,4,5,6-tetrahydropyrimidine hydrochloride	98	132	140–142					[b]
2-Amino	2-Amino-?-dihydropyrimidine dihydrochloride	91	231		28.26	5.34	28.2	5.45	
2-Amino-4-methyl	2-Amino-4-methyl-?-dihydropyrimidine dihydrochloride	93	243		33.39	6.02	33.4	6.04	
4-Amino	4-Amino-?-dihydropyrimidine dihydrochloride	77	263		28.26	5.34	28.4	5.44	
5-Amino	5-Amino-?-dihydropyrimidine dihydrochloride	98	157		28.26	5.34	28.3	5.21	

[a] All melting points were taken with Fisher-Johns melting point block. They are difficult to reproduce.

[b] No depression when mixed with corresponding derivative from reduction of the chloropyrimidine.

TABLE II

DEHALOGENATION AND NUCLEAR REDUCTION OF CHLOROPYRIMIDINE WITH PALLADIZED CHARCOAL

Substituted Pyrimidine	Substituted 1,4,5,6-Tetrahydropyrimidine	Yield, %	M.P.,[a] °C.	Empirical Formula	Analysis				Notes
					Calc'd		Found		
					C	H	C	H	
2-Chloro	Unsubstituted hydrochloride	97	121	$C_4H_8N_2 \cdot HCl$					*d*
2,6-Dichloro	Same	98	120	$C_4H_8N_2 \cdot HCl$					*d*
4,6-Dichloro	Same	97	120	$C_4H_8N_2 \cdot HCl$					*e*
2,4,6-Trichloro	Same	95	121	$C_4H_8N_2 \cdot HCl$					*f*
2,4,5,6-Tetrachloro	Same	91	119	$C_4H_8N_2 \cdot HCl$					*g*
2,6-Dichloro-4-methyl	4(6)-Methyl hydrochloride	98	149	$C_5H_{10}N_2 \cdot HCl$	44.61	8.24	44.41	8.39	
2,6-Dichloro-5-methyl	5-Methyl hydrochloride	97	131	$C_5H_{10}N_2 \cdot HCl$	44.61	8.24	44.57	8.41	
4,6-Dichloro-2-methyl	2-Methyl hydrochloride	96	139	$C_5H_{10}N_2 \cdot HCl$	44.61	8.24	44.50	8.31	*h*
2,6-Dichloro-5-nitro	5-Amino dihydrochloride	41	198	$C_4H_9N_3 \cdot 2HCl$	28.58	6.60	28.48	6.73	
4,6-Dichloro-5-nitro	5-Amino dihydrochloride	37	195	$C_4H_9N_3 \cdot 2HCl$	28.58	6.60			
5-Amino-4,6-dichloro	5-Amino dihydrochloride	98	197	$C_4H_9N_3 \cdot 2HCl$	28.58	6.60			
4-Amino-2,6-dichloro	4-Amino dihydrochloride	89	204	$C_4H_9N_3 \cdot 2HCl$	28.58	6.60	28.69	6.49	
2-Amino-4,6-dichloro	2-Amino dihydrochloride	93	208	$C_4H_9N_3 \cdot 2HCl$	28.58	6.60	28.54	6.70	*i*
2,6-Dichloro-4-methoxy	*b*								
2,6-Dimethoxy-4-chloro	*b*								
2-Mercapto-6-chloro	*c*								

[a] All melting points were taken with a Fisher-Johns melting point block. [b] No identified products were isolated. [c] No reduction. [d] The oxalate (2) melts at 150–151° (d.). [e] The *oxalate* (2) melts at 149–150°. [f] The *oxalate* (2) melts at 151–152°. [g] The *oxalate* melts at 149–151.5°. [h] The *picrate* (5a) melts at 153–154° (d.). [i] The *p-toluenesulfonate* (5b) melts at 172–174° (d.); the literature gives m.p. 174°.

TABLE III

BENZOYL DERIVATIVE OF THE REDUCED PYRIMIDINES

Hydropyrimidine	Benzoyl Hydropyrimidine	Yield, %	M.P., °C[a]	Empirical Formula	Analysis			
					Calc'd		Found	
					C	H	C	H
1,4,5,6-Tetrahydropyrimidine hydrochloride	1-Benzoyl-1,4,5,6-tetrahydropyrimidine	31	145–146	$C_{11}H_{12}N_2O$	88.36	6.43	88.2	6.45
2-Methyl-1,4,5,6-tetrahydropyrimidine hydrochloride	1-Benzoyl-2-methyl-1,4,5,6-tetrahydropyrimidine	40	136–137	$C_{12}H_{14}N_2O$	71.26	6.98	71.1	7.13
4-Methyl-1,4,5,6-tetrahydropyrimidine hydrochloride	1-Benzoyl-4(6)-methyl-1,4,5,6-tetrahydropyrimidine	23	165–166	$C_{12}H_{14}N_2O$	71.26	6.98	71.3	7.04
5-Methyl-1,4,5,6-tetrahydropyrimidine hydrochloride	1-Benzoyl-5-methyl-1,4,5,6-tetrahydropyrimidine	38	142–143	$C_{12}H_{14}N_2O$	71.26	6.98	71.1	7.05
2-Amino-1,4,5,6-tetrahydropyrimidine dihydrochloride	2-Benzamido-1,4,5,6-tetrahydropyrimidine	49	188–189	$C_{18}H_{21}N_3O_2$	70.34	5.58	70.1	5.7
4-Amino-1,4,5,6-tetrahydropyrimidine dihydrochloride	4(6)-Benzamido-1-benzoyl-1,4,5,6-tetrahydropyrimidine	61	212–214	$C_{18}H_{21}N_3O_2$	70.34	5.58	70.2	5.56
5-Amino-1,4,5,6-tetrahydropyrimidine dihydrochloride	5-Benzamino-1-benzoyl-1,4,5,6-tetrahydropyrimidine	55	178–179	$C_{18}H_{21}N_3O_2$	70.34	5.58	70.2	5.69
2-Amino-?-dihydropyrimidine-dihydrochloride	2-Benzamido-?-dihydropyrimidine	69	168–169	$C_{11}H_{12}N_3O$	65.31	5.98	65.3	6.12
2-Amino-4-methyl-?-dihydropyrimidine dihydrochloride	2-Benzamido-4-methyl-?-dihydropyrimidine	73	142–143	$C_{12}H_{13}N_3O$	66.96	6.09	67.1	6.13
4-Amino-?-dihydropyrimidine dihydrochloride	4-Benzamido-?-dihydropyrimidine	51	193–195	$C_{11}H_{12}N_3O$	65.31	5.98	65.5	5.95
5-Amino-?-dihydropyrimidine dihydrochloride	5-Benzamido-?-dihydropyrimidine	44	129–130	$C_{11}H_{12}N_3O$	65.31	5.98	65.5	5.84

[a] All melting points were taken with a Fisher-Johns melting point block.

TABLE IV

THE DEHALOGENATION OF CHLOROPYRIMIDINES

Moles of chloropyrimidine	Chloropyrimidine	Mg. of 10% Palladium-on-carbon	Product	Yield, %	B.P., °C.[a] (M.P., °C.)	mm.	Method of Isolation	References
0.10	2,6-Dichloropyrimidine	200	Pyrimidine	91	122–124 (21–22)[k]	760	A	16
.025	4,6-Dichloropyrimidine	200	Pyrimidine	89	(21–22)[k]		A	16
.025	4,6-Dichloropyrimidine[b]	200	Pyrimidine	77	(21.5–22)[k]			16
.05	2,4,6-Trichloropyrimidine	200	Pyrimidine	87	121–123	755	A	16
.05	2,4,5,6-Tetrachloropyrimidine	300	Pyrimidine	86	119–121	757	A	16
.10	4,6-Dichloro-2-methylpyrimidine	200	2-Methylpyrimidine	86–92	136–138	757	A	17
.10	4,6-Dichloro-2-methylpyrimidine[b]	200	2-Methylpyrimidine	75	136–137	759		17
.20	2,6-Dichloro-4-methylpyrimidine	200	4-Methylpyrimidine	81–93	140–142	757	A	18
.10	2,6-Dichloro-4-methylpyrimidine[b]	200	4-Methylpyrimidine	73–80	140–141	755		3
.025	2,4-Dichloro-5-methylpyrimidine	200	5-Methylpyrimidine	83–87	151–153 (30–31)[k]	755	A&B[d]	19
.025	2,4-Dichloro-5-methylpyrimidine[b]	200	5-Methylpyrimidine	72	151–152 (30–31)[k]	760		19
.01	4-Chloro-2,6-dimethoxypyrimidine	200	2,6-Dimethoxypyrimidine	62	202–204	757	B	18
.01	2,6-Dichloro-4-methoxypyrimidine	300	4-Methoxypyrimidine	57	70–71	35	B	20
.012	Ethyl 2,6-dichloropyrimidine-5-carboxylate	500	Pyrimidine-5-carboxylic acid	29	(268–270)[k]		[c]	21
.025	2-Amino-4,6-dichloropyrimidine	300	2-Aminopyrimidine	88	125–126		B[e]	22
.025	4-Amino-2,6-dichloropyrimidine	500	4-Aminopyrimidine	73	149–151		B[f]	23
.025	5-Amino-2,6-dichloropyrimidine	200	5-Aminopyrimidine	91			[g]	
.025	4,5-Diamino-2-chloropyrimidine	1000	No hydrogen uptake noted					
.025	4-Amino-2-chloro-5-nitropyrimidine	1000	4,5-Diamino-2-chloropyrimidine	68	230–232		B[h]	13
.025	4-Amino-2,6-dichloro-5-nitropyrimidine	880	4,5-Diamino-2,6-dichloropyrimidine	77	259–261		B[h]	
.025	2,6-Dichloro-5-nitropyrimidine	500	Products not identified				[i]	

[a] All melting points were taken with Fisher-Johns Melting Point Block.
[b] Prepared by the method of Whittaker (16).
[c] 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. [d] Isolation procedure B works nicely as solid can be filtered off. [e] Recrystallized from chloroform. [f] Recrystallized from ethyl acetate. [g] Recrystallized from a ligroin-benzene mixture. [h] Same product in neutral media; Reduction rate was increased seven fold in N,N-Dimethylformamide. But the solvent and product react in the cold very rapidly. [i] Hydrogen uptake, 48–79% of theory. [k] M.P.

150 ml. of phosphorus oxychloride, and 15 ml. of mono-free N,N-diethylaniline was 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 was decomposed with chipped ice. The black solution was treated with solid potassium carbonate to approximately *p*H 6–6.5 and the mixture was 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 4 hours. The dried material was extracted with four portions, each of 100 ml., of boiling ethyl acetate. The ethyl acetate extracts were evaporated and the residue was sublimed at 180–190° at 50 mm. The yield was 27%. The melting point was 270–272° (10).

The preparation of methyl or ethyl 2,6-dichloropyrimidine-5-carboxylate. A mixture of 10 g. of methyl or ethyl uracil-5-carboxylate, 90 ml. of phosphorous oxychloride, and 15 ml. of mono-free N,N-diethylaniline was 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 pressures and the residue was decomposed by slowly pouring, with vigorous stirring, into a mixture of 20 ml. of water and 20 g. of 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, were dried over 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 was cooled by ice-water. The ethyl 2,6-dichloropyrimidine-5-carboxylate boiled at 148–150°/19–20 mm. and melted at 36–37°. The methyl 2,6-dichloropyrimidine-5-carboxylate boiled at 141–143°/23–25 mm. (24) and melted at 34–34.5°. The yield of both compounds was 86%.

The methyl ester when hydrolyzed following the procedure of Sprague and Johnson (25) gave uracil-5-carboxylic acid.

Anal. Calc'd 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-thiouracil-5-carbethoxylate) (24) were added 30 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 was refluxed for one hour after solution occurred. About one-half of the phosphorus oxychloride was removed *in vacuo* at 40–45° and the residue was poured slowly onto chipped ice with vigorous stirring. The cold mixture was quickly extracted with four portions of 50 ml. of diethyl ether each; the combined ether extracts were washed with 25 ml. of water and dried over magnesium sulfate. The ether was filtered from the magnesium sulfate under slightly reduced pressure and the residue was 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 were added and removed under reduced pressure. The 2,6-dichloropyrimidine-5-carboxylic acid melted at 96–97°. 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.

Anal. Calc'd 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 monohydrate, melting at 267–269°. Wheeler gives m.p. 268–270° (11).

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. The influence of alkali on the course of nuclear reductions of pyrimidines has been demonstrated.

The effect of N,N-diethylaniline upon the course of phosphorus oxychloride halogenation of pyrimidinediones was found to be more efficacious than N,N-dimethylaniline. Two new chloropyrimidines have been characterized.

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