A 1-l. three-necked round bottom flask was equipped with a reflux condenser, stirrer, and dropping funnel. The flask was charged with 200 ml. of methanol, 116 g. (1 mole) of 2-thiophenethiol prepared by the method of Houff and Schuetz,[5] and 138.5 g. (1.01 moles) of *n*-butyl bromide. This reaction mixture was brought to reflux and then 56 g. (1.0 mole) of potassium hydroxide in 200 ml. of methanol was added dropwise. Refluxing and constant stirring was continued for a total of 8 hr.

After cooling, the precipitated potassium bromide was removed. Concentration of the alcoholic filtrate led to two layers and the separation of an additional quantity of potassium bromide. The organic layer was extracted with benzene and distilled. Procedure repeated two or three times until all the salt was separated. Removal of solvent and vacuum distillation gave rise to the desired products.

Acknowledgment.—The authors particularly wish to thank the Robert A. Welch Foundation of Houston, Tex., for its generous support of this work. Furthermore, thanks are also due Harry Rall, Charles Thompson, Harold Coleman, and Norman Foster, U. S. Bureau of Mines, Bartlesville, Okla., for the gas chromatography and elemental analysis.

Pyrimidines. VI. A Study of the Nuclear Reduction of Certain Pyrimidines[1]

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Received August 21, 1961

The nuclear reduction of chloro-, amino-, and methylpyrimidines (and their chloro derivatives) using platinum and supported palladium catalysts under acid conditions was investigated. The theoretical hydrogen consumption for the formation of the corresponding 3,4,5,6-tetrahydropyrimidine was observed whereupon hydrogenation ceased. The tetrahydropyrimidines could not be isolated as the pure hydrochlorides but only as the picrate derivatives in low yields. The preparation of the benzoyl derivatives leads only to degradation products.

Paper chromatography was used to show that the nuclear reduction products are unstable in aqueous media yielding a mixture of degradation products together with the desired tetrahydropyrimidine.

Nuclear reduction of substituted pyrimidines as a practical procedure for the preparation of positional isomers of the tetrahydropyrimidines has received little attention. Isolated reports of catalytic nuclear reduction of certain pyrimidines is to be found in the literature.[2-4] Smith and Christensen[5] initiated a systematic investigation of the nuclear reduction reaction as a practical preparative procedure. According to the report of their results, the acid reduction of substituted pyrimidines is straightforward yielding the expected products in good yield. Recent attempts to use their procedure for the preparation of the tetrahydropyrimidines were unsuccessful. This together with certain discrepancies in their analytical data necessitated reinvestigation of the entire scope of nuclear reduction of substituted pyrimidines in acid media by catalytic hydrogenation.

The catalyst-compound ratio necessary to effect nuclear reduction of all substituted pyrimidines at room temperature, low pressure, and aqueous acid solutions was determined by a series of experiments, the results of which are presented in Table I. 4-Amino-2,6-dichloropyrimidine absorbed only one half the amount of hydrogen required to reduce the compound to 4-amino-3,4,5,6-tetrahydropyrimidine even when more than the suggested catalyst-to-compound ratio was employed.[5] Since one half of the starting material was recovered, it is evident that the reduction does not yield a dihydropyrimidine as reported by Smith and Christensen.[5]

The fact that hydrogenation stops after absorption of the amount of hydrogen required for conversion to the tetrahydropyrimidine, yet requires a high catalyst-to-compound ratio, suggests that products are formed which are toxic to the catalyst. The relative ease of reducing dichloronitropyrimidines to the corresponding aminodichloropyrimidines is demonstrated by the data in Table I. Nitrodichloropyrimidines can be reduced stepwise to aminodichloropyrimidines and these in turn to aminopyrimidines,[5] both products being isolable. Aminodichloropyrimidines and aminopyrimidines will absorb the theoretical amount of hydrogen necessary to form the amino-3,4,5,6-tetrahydropyrimidine derivative. Reduction beyond this state cannot be effected under these conditions.

Both palladized charcoal and palladized barium sulfate[6] were equally effective as catalysts for the nuclear reduction of the substituted pyrimidines. Adams' catalyst, on the other hand, was effective only in the nuclear reduction of the amino- and methyl- substituted pyrimidines; it was inactive in experiments with chloro-substituted derivatives.

(1) Abstracted from a dissertation submitted by Harvey Aft to the faculty of Oregon State University in partial fulfillment of the requirements for the degree of Doctor of Philosophy. Published with the approval of Monographs Publication Committee, Oregon State University, as Research Paper No. 420, Department of Chemistry, School of Science.

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From the data in Table I it is evident that with the exception of the reduction products of the 4-amino-, 5-aminopyrimidines and their chloro derivatives the product of the reduction is the monohydrochloride.

Since it was not possible to isolate analytically pure tetrahydropyrimidine hydrochlorides, both benzoyl and picrate derivatives (employing the usual procedures[7]) of the reduction products were prepared for characterization purposes. Isolation and purification of these derivatives were tedious and lengthy; the yields were low.

It is evident from the analytical data in Table I that the monopicrate derivatives of the 2-amino-, 2-methyl-, and 4-methyl- 3,4,5,6-tetrahydropyrimidines were isolated. The melting points of the 2-amino and 2-methyl-3,4,5,6-tetrahydropyrimidines were in agreement with published data. Furthermore, a mixed melting point determination and infrared spectral comparison with an authentic sample of the picrate of 2-amino-3,4,5,6-tetrahydropyrimidine showed the two materials to be identical. The picrate of the 4-methyl-derivative has not been previously reported.

Judging by the analytical data, it is the dipicrate salt that is isolated from the reduction products of the 4-aminopyrimidines. This, together with the chloride data, strongly suggests that the 4-amino-3,4,5,6-tetrahydropyrimidine is present in the original reduction product as the dihydrochloride salt.

On the other hand, the analytical data of Table I shows the salt of the 2-amino-3,4,5,6-tetrahydropyrimidine to be a monohydrochloride and a monopicrate. The difference in behavior between the 2-amino and 4-amino derivatives stems from the fact that the 2-amino-3,4,5,6-tetrahydropyrimidine is actually a cyclic guanidine, and thus would be expected to form only the monohydrochloride and picrate.

Infrared spectral and elemental analyses of the benzoylated reduction products isolated in this investigation showed these materials to be benzoylated degradation products. No benzoyl derivative corresponding to that of a tetrahydropyrimidine could be isolated in an analytically pure form. This observation is in accord with the report of Branch and Titherley,[8] who found that 2-phenyl-3,4,5,6-tetrahydropyrimidine undergoes degradation in a Schotten-Baumann reaction. It is contrary to the report of Smith and Christensen,[5] who used the benzoyl derivatives for characterization of the 3,4.5,6-tetrahydropyrimidines.

To confirm the suspicion that the tetrahydropyrimidines were undergoing degradation in aqueous acid solution, as indicated by the analyses of the hydrochloride and picrate salts, the reduction products were subjected to paper chromatographic analysis. The results of these analyses are shown in Table II.

The analyses indicated that the nuclear reductions of all the pyrimidines gave mixtures of products. In an attempt to identify some of the spots on the chromatograms, a sample of the picrate of 2-amino-3,4,5,6-tetrahydropyrimidine was obtained from Boots Pure Drug Co., converted to the hydrochloride, and then chromatographed. This compound gave an R_f value of 0.49 (plus a faint spot at $R_f = 0.20$) using iodine for detection. Samples of analytically pure picrates of the 2-amino, 2-methyl, and 4-methyl-3,4,5,6-tetrahydropyrimidines obtained in these studies were treated in the same manner. These compounds also gave R_f values of 0.50 using iodine vapor for detection. It seems reasonable to conclude, therefore, that the presence of a spot in the region of 0.49 to 0.51 as detected by iodine vapor must be due to the presence of a substituted 3,4,5,6-tetrahydropyrimidine monohydrochloride.

Spots corresponding to this are found in the chromatograms of the final reduction products of all the methylpyrimidines and their dichloro derivatives, and the 2-aminopyrimidine and its dichloro derivative. This would indicate that although no analytically pure picrate derivative of the 5-methyl-3,4,5,6-tetrahydropyrimidine was isolated, this compound is present in its reduction product. No such spot (R_f 0.50) is found in the chromatograms of the final reduction products of the 4-amino and 5-aminopyrimidines, their dichloro derivatives, or the trichloropyrimidine.

The dipicrate of the 4-amino-3,4,5,6-tetrahydropyrimidine converted to the hydrochloride and chromatographed gave a spot at 0.06 (yellow with ninhydrin and light brown with iodine). A corresponding spot is found in the chromatogram of the final reduction products of the 4-aminopyrimidine and its dichloro derivative. Large variations in R_f values of aliphatic mono aminohydrochlorides and diamino hydrochlorides having the same number of chain atoms has been observed[9] by other workers. The only other spot to be identified was that of ammonium chloride at 0.32 found among the products of the 5-aminopyrimidine reduction.

From Table II it would appear that the reduction of II, III, IV, V, X, XI, and XII, yield the corresponding 3,4,5,6-tetrahydropyrimidines along with other products. Furthermore, I, VI, VII, VIII and IX, yield a mixture of reduction products which may possibly contain a tetrahydroderivative with a different R_f value.

In those experiments in which known tetrahydropyrimidines were observed in the reduction with palladized charcoal catalysts, these same compounds were also present in the reduction products from

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TABLE I

RESULTS OF CATALYTIC NUCLEAR REDUCTION OF CERTAIN PYRIMIDINES

Pyrimidine Reduced	% Chloride in Tetrahydropyrimidine Monohydrochloride: Calcd. for	Theory	Found	Picrate Derivative: Calcd. for	Theory % C	Theory % H	Found % C	Found % H	M.P.	Footnote
4-Amino-2,6-dichloro[11]	$C_4H_{10}N_3Cl$	26.2	38.8	$C_{16}H_{15}N_9O_7$	34.5	2.7	34.2	2.8	201–202	*a*
4-Amino[5]	$C_4H_{10}N_3Cl$	26.2	39.2							
2,4-Dichloro-5-methyl[12]	$C_5H_{11}N_2Cl$	26.4	28.5	$C_{11}H_{13}N_5O_7$	40.4	4.0	41.3	5.1		*b*
2,6-Dichloro-4-methyl[13]	$C_5H_{11}N_2Cl$	26.4	29.4	$C_{11}H_{13}N_5O_7$	40.4	4.0	40.2	4.2	106–107	*c*
4,6-Dichloro-2-methyl[14]	$C_5H_{11}N_2Cl$	26.4	28.8	$C_{11}H_{13}N_5O_7$	40.4	4.0	40.4	4.2	153–154	*d*
2-Amino-4,6-dichloro[11]	$C_4H_{10}N_3Cl$	26.2	28.5	$C_{10}H_{12}N_6O_7$	36.6	3.7	36.8	3.8	183–184	*e*
2-Amino-[5]	$C_4H_{10}N_3Cl$	26.2	29.4						183–184	
5-Amino-2,4-dichloro[5]	$C_4H_{10}N_3Cl$	26.2	39.6							*f*
5-Amino[5]	$C_4H_{10}N_3Cl$	26.2	36.9							*f*
4,6-Dichloro-5-nitro[15]	Reduction of nitro substituent only with 300 mg. Pd-C catalyst									*g*
2,4-Dichloro-5-nitro[16]	Reduction of nitro substituent only with 300 mg. Pd-C catalyst									*g*
2,6-Dichloro-4-methyl-5-nitro[17]	Reduction of nitro substituent only with 400 mg. Pd-C catalyst									*g,h*
4,6-Diamino-5-nitro[15]	No hydrogen uptake with 3600 mg. Pd-C catalyst									*i*

a 300 mg. 10% Pd-C catalyst, no hydrogen uptake; 900 mg. 10% Pd-C catalyst, absorbed 1/2 theoretical amount of H_2, 1/2 starting material recovered; 1500 mg. 10% Pd-C catalyst, required 72 hr. to effect reduction; 4500 mg. 10% Pd-C catalyst, required 2 hr. to effect reduction. No further hydrogen uptake after 4 additional hours. Spent catalyst removed—4500 mg. fresh catalyst added—no further hydrogen absorption observed during next 24 hr. Picrate derivative calculated as dipicrate. *b* a. 300 mg. 10% Pd-C catalyst, no hydrogen uptake in 24 hr. b. 4500 mg. 10% Pd-C catalyst, required 75 min. No further hydrogen uptake after 4 additional hr. Analysis of picrate did not agree with theory for mono-, di-, or tripicrate. *c* Samples of propionaldehyde added after cessation of hydrogen uptake were not reduced. *d* Reported m.p. of picrate 153–153.5.[20] *e* Reported m.p. of picrate 183–184,[13] 179–180.[21] *f* Theoretical value for dihydrochloride, 41.3% Cl. *g* Product isolated and identified, yield 5-amino-4,6-dichloropyrimidine 49%, 5-amino-2,4-dichloropyrimidine 18%, 5-amino-2,6-dichloro-4-methylpyrimidine 36%—hydrogen uptake theoretical for conversion to tetrahydro derivative, using 4500 mg. 10% Pd-C catalyst. *h* Reduction to 5-amino-2,6-dichloro-4-methylpyrimidine required 72 hr. *i* Nitrosubstituent of 4,6-diamino-5-nitropyrimidine has been reduced with Raney nickel catalyst.[18]

experiments using both Adams' and palladium–barium sulfate catalysts.

Since the hydrogen consumption is theoretical for formation of the tetrahydropyrimidine, it was an unexpected discovery to find that mixtures of products should result from the nuclear reduction of the pyrimidines. The isomeric 2,3,4,5-tetrahydropyrimidines have been reported to be unstable in neutral and acidic aqueous media.[10] Some of the products observed in these studies may stem from the degradation of the isomeric 2,3,4,5-tetrahydropyrimidines that could have been formed in the nuclear reduction.

Experimental

The general procedure for the dehalogenation and nuclear reduction of the chloropyrimidines was as follows: A mixture of 0.025 mole of the chloropyrimidine in 50 ml. of water and 4500 mg. of 10% palladized charcoal was shaken with hydrogen in a Parr low-pressure hydrogenation apparatus at room temperature (20–26°) at an initial pressure of 45 p.s.i. After cessation of hydrogen uptake, the catalyst was removed by filtration, washed with two 5-ml. portions of water. The washings and filtrate were combined and warmed 50–60° with Norit. The Norit was removed and the aqueous solution evaporated *in vacuo* using a bath temperature of 50–60°.

To aid in the removal of residual hydrochloric acid, 25 ml. of alcohol was added and removed *in vacuo*. The procedure was repeated with 25 ml. of dry benzene. The residue was dried *in vacuo*, over potassium hydroxide using a vacuum desiccator. The products could not be recrystallized from absolute methanol–petroleum ether,[5] absolute methanol–benzene, acetone, acetone–petroleum ether, acetone–benzene, butyl alcohol, or butyl alcohol–benzene. The reduction products, isolated as the hydrochloride salts, were generally colored and very hygroscopic.

To accomplish the nuclear reduction of nonchloro-substituted pyrimidines, the same procedure was used with the addition of a slight excess of concd. hydrochloric acid (sufficient to neutralize all primary and secondary amino groups present at the end of the reaction).

The dichloronitropyrimidines were reduced to the aminodichloropyrimidines by the following modified procedure. A mixture of 0.025 mole of the dichloronitropyrimidine in 100 ml. of diethyl ether, 10–15 ml. of water, 0.05 mole of concd. hydrochloric acid, and 300 mg. of 10% palladized charcoal was shaken with hydrogen in the Parr apparatus at room temperature and initial pressure of 45 p.s.i. After cessation of hydrogen uptake, the catalyst was removed by filtration. The ether layer was separated and the aqueous layer made strongly alkaline with potassium hydroxide pellets using an ice bath to control the temperature.

This alkaline solution was extracted with three 50-ml. portions of ether. The combined ether extracts and the original ether layer were washed once with 50 ml. of water and then dried over anhydrous magnesium sulfate. The ether was removed by distillation and the residue recrystallized from benzene–petroleum ether.

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TABLE II

CHROMATOGRAPHIC ANALYSIS OF REDUCTION PRODUCTS

Pyrimidine	M.P., Crude HCl Salts	No.	R_f Values (23–26°) Ninhydrin				Iodine vapor				
2,4,6-Trichloro-		I	0.43[a]	0.18[a]			0.43[b]	0.29[c]			
2-Amino-	116–118	II					.49 (b)[b]	.27[d]	0.21(l)[c]		
2-Amino-4,6-dichloro-		III	.21 (f)[e]				.51 (h)[b]	.26[d]	.22(f)[d]		
4-Amino-		IV	.22[e]	.18[e]	0.14[e]	0.06[e]	.33(f)[d]	.20(l)[c]	.18[b]	0.13[b]	0.06[c]
4-Amino-2,6-dichloro-	146–147	V	.22[e]	.17[e]	.11[e]	.04[e]	.19(l)[c]	.14[b]	.04[c]		
5-Amino-		VI	.30[e]	.15[a]	.06(f)[e]		.20[c]	.16[c]	.11[c]	.06[c]	
5-Amino-4,6-dichloro-		VII	.35[d]	.19[f]			.33[d]	.25[c]	.19[b]		
5-Amino-2,4-dichloro-	187	VIII	.29(f)[e]	.18[e]	.12(f)[a]	.07[h]	.29[c]	.26[b]	.16[b]	.07[b]	
2,4-Dichloro-5-nitro-	178–180	IX	.35[f]	.19[g]	.14[e]	.11[e] 0.07[e]	.33[b]	.20[c]	.15[c]	.12[b]	.05[c]
4,6-Dichloro-5-nitro-			.17[a]	.12[a]	.05[a]		.30[b]	.21[d]	.13[b]		
4,6-Dichloro-2-methyl-	121–125	X	.49(f)[e]	.30[d]			.49(h)[b]	.29[d]			
2,6-Dichloro-4-methyl-	88–91	XI	.12[h]	.05[h]			.50(h)[b]	.31[d]	.14[c]	.06[c]	
2,4-Dichloro-5-methyl-	122–129	XII	.21[g]	.10(f)[a]	.07(f)[a]		.49(h)[b]	.27[d]	.14[c]		

Color of spots: [a] Light blue. [b] Dark brown. [c] Light brown. [d] Clear. [e] Yellow. [f] Dark purple. [g] Light purple. [h] Reddish purple. h = heavy, l = light, f = faint.

For chromatographic analysis[9,22] Whatman No. 4 paper was spotted with 0.1 *M* aqueous solutions. The spotted chromatograms were allowed to equilibrate for at least 16 hr. in the developing solvent vapor prior to development. The developing solvent was butanol–acetic acid–water (4:1:5 v./v. organic phase); the descending method being used. The chromatograms were dried, sprayed with ninhydrin solution, and placed in iodine vapor for spot detection.

Synthesis of Some 8-Substituted Bis(β-chloroethyl)amino Derivatives of Naturally Occurring *N*-Methylated Purines[1]

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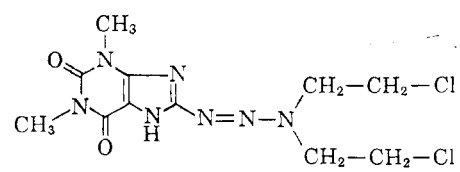
Received December 18, 1961

The derivatives of caffeine, theobromine, and theophylline containing a bis(β-chloroethyl)amino moiety attached either directly or through a methylene or an iminomethylidene group at the 8-position have been synthesized.

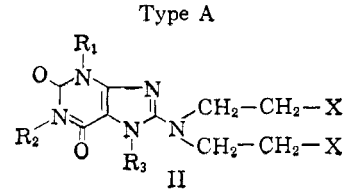
Recent indication of the activity of 8-[bis(β-chloroethyl)-triazeno]theophylline[2] (I) against a spontaneous tumor in experimental mice[3] encouraged a systematic synthetic study of certain derivatives of naturally occurring purine alkaloids related to I for further biological evaluations.



I

Three types of derivatives in this general area have been prepared in our laboratories: Type A compounds are those of which the nitrogen mustard moiety is attached directly to the 8-position of the purine ring (II. X = Cl). In Type B compounds the nitrogen mustard moiety is separated from the 8-position of the ring by a methylene bridge (III,

Type A



II

(1) This investigation was supported by research contract SA-43-ph-3025 from the Cancer Chemotherapy National Service Center, National Cancer Institute of the National Institutes of Health, Public Health Service.

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