cold dilute hydrochloric acid and the solid so obtained was extracted with cold aqueous sodium carbonate solution. The insoluble portion was benzoylated with benzoyl chloride in the presence of sodium hydroxide solution and benzoylresorcinol was obtained (1.1 g.).

Acidification of the carbonate solution followed by crystallization of the separated product gave colorless crystals (0.9 g.), identified as benzoic acid.

GIZA, CAIRO, EGYPT

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Researches on Pyrimidines. Certain Derivatives of 2-Propylpyrimidine[1]

BY HENRY R. HENZE AND STANLEY O. WINTHROP[2]

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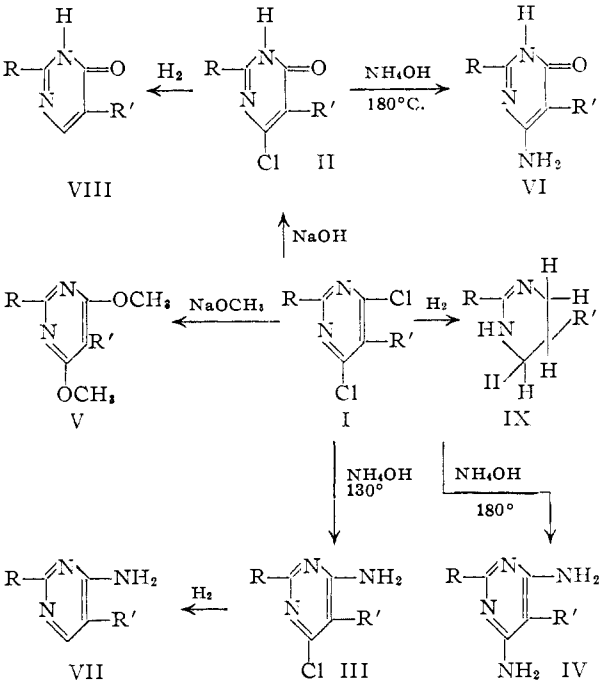
Series of 2-propyl-4,6(1,5)-tetrahydropyrimidinediones and 2-propyl-4,6-dichloropyrimidines have been synthesized. The dichloropyrimidines are useful starting materials for the synthesis of various pyrimidine derivatives, some of which are described.

In continuation of our investigation of the synthesis of pyrimidine derivatives through condensation of amidines with malonic esters,[3,4] we have now studied the interaction of butamidine with ethyl malonate and five ethyl alkylmalonates. The 2-propyl-4,6(1,5)-tetrahydropyrimidinediones thus obtained were converted into 4,6-dichloro derivatives by treatment with phosphorus oxychloride. With the appropriate reagents and reaction conditions, as shown below, the 4,6-dichloropyrimidines (I) yielded the corresponding 6-chloro-4(3)-dihydropyrimidones(II), 4-amino-6-chloropyrimidines (III), 4,6-diaminopyrimidines (IV) and 4,6-dimethoxypyrimidines (V). These derivatives in their turn gave 6-amino-4(3)-dihydropyrimidones (VI), 4-aminopyrimidines (VII) and 4(3)-dihydropyrimidones (VIII).

Catalytic hydrogenolysis of the monochloropyrimidines took place with ease. It was noted, however, that in each case there was an amino or keto substituent present which could have the effect of stabilizing the ring against reduction. Catalytic hydrogenolysis of the dichloropyrimidines did not stop at dechlorination but proceeded with the reduction of the pyrimidine ring. Instead of the anticipated 2-propylpyrimidine, the catalytic hydrogenolysis of 2-propyl-4,6-dichloropyrimidine, in the presence of barium oxide,[5] gave a product which analyzed for a 2-propyltetrahydropyrimidine[6] hydrochloride (IX). A search of the literature reveals little on the chemistry of partially reduced pyrimidines and usually the latter have been prepared directly through condensation reactions, rather than as a direct result of hydrogenation of pyrimidines. Thus, Aspinall[7] has reported the preparation of 2-methyl-1,4,5,6-tetrahydropyrimidine by the interaction of trimethylenediamine and ethylacetate. Naff and Christensen[8] have described a dihydrobenzopyrimidine and its conversion by catalytic dehydrogenation to the more stable benzopyrimidine. Attempts to convert our tetrahydropyrimidine to 2-propylpyrimidine by a similar catalytic dehydrogenation were not successful.



Experimental

Butamidine Hydrochloride.—The procedure utilized followed that of Derby's modification[9] of the method of Pinner[10] for the preparation of amidines. A solution was prepared containing 345 g. (5 moles) of butyronitrile, 230 g. (5 moles) of absolute ethanol, 600 ml. of dry ether and 182.5 g. (5 moles) of dry hydrogen chloride. It was stirred for four days at 0°. After standing for two weeks in the cold the imido ester hydrochloride separated and was removed by filtration. The filtrate, on standing in the cold an additional week, produced a second crop of crystals. The initial crop of imido ester was dissolved in 300 ml. of absolute ethanol, 1000 ml. of 10% alcoholic ammonia was

(1) From the Ph.D. dissertation of Stanley O. Winthrop, University of Texas, 1952.

(2) Humble Oil and Refining Co. Fellow in Chemistry, 1951–1952.

(3) H. R. Henze, W. J. Clegg and C. W. Smart, *J. Org. Chem.*, **17**, 1320 (1952).

(4) H. R. Henze and J. L. McPherson, *ibid.*, **18**, 653 (1953).

(5) After this work had been completed, a paper by N. Whittaker (*J. Chem. Soc.*, 1565 (1950)) came to our attention. This investigator showed that catalytic hydrogenolysis of 2,4,6-trichloropyrimidine in the presence of sodium acetate took place with the uptake of five equivalents of hydrogen indicating the formation of a tetrahydropyrimidine, while in the presence of magnesium oxide, only three equivalents of hydrogen were taken up, and pyrimidine was isolated as a mercuric chloride addition complex.

(6) The position of the remaining double bond has not been proven. The compound is most likely a 1,4,5,6-tetrahydropyrimidine.

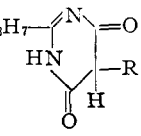
(7) (a) S. R. Aspinall, THIS JOURNAL, **62**, 2160 (1940); (b) G. S. Skinner and P. R. Wunz, *ibid.*, **73**, 3814 (1951).

(8) M. B. Naff and B. E. Christensen, *ibid.*, **73**, 1372 (1951).

(9) I. H. Derby, *Am. Chem. J.*, **39**, 437 (1908).

(10) A. Pinner and F. Klein, *Ber.*, **11**, 1484 (1878).

TABLE I

2-PROPYL-4,6(1,5)PYRIMIDINEDIONES C_3H_7—  —R

R	M. p., °C	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Hydrogen	[a]	71	$C_7H_{10}N_2O_2$	54.33	54.30	6.53	6.81
Methyl	[a]	73.5	$C_8H_{12}N_2O_2$	57.14	57.45	7.14	6.87[d]
Ethyl[b,c]	[a]	85.5	$C_9H_{14}N_2O_2$	59.32	59.15	7.74	7.61
Propyl[b]	[a]	72	$C_{10}H_{16}N_2O_2$	61.19	61.08	8.22	7.70
Butyl[b]	[a]	94	$C_{11}H_{18}N_2O_2$	62.82	62.67	8.61	8.52
Amyl[b]	[a]	69.5	$C_{12}H_{20}N_2O_2$	64.27	64.36	8.99	8.84
Hexyl	[a]	75.5	$C_{13}H_{22}N_2O_2$	65.51	65.30	9.30	9.45[e]

[a] Does not melt below 300° and decomposes slowly at that temperature. [b] Analysis by Clark Microanalytical Laboratories, Urbana, Ill. [c] This compound has been previously reported by F. G. P. Remfry (*J. Chem. Soc.*, 99, 620 (1906)), who prepared it by interaction of ethylmalonamide and ethyl ethylmalonate. [d] Calcd.: N, 16.67. Found: N, 16.89. [e] Calcd.: N, 11.75. Found: N, 11.71.

5-Alkyl-2-propyl-4,6(1,5)-pyrimidinediones (Table I).—The pyrimidinediones were prepared by interaction of butamidine hydrochloride and ethyl alkylmalonates.[3,4]

5-Alkyl-2-propyl-4,6-dichloropyrimidines (Table III).—The dichloropyrimidines were prepared from interaction of the pyrimidinediones and phosphorus oxychloride.[3]

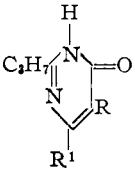
5-Alkyl-6-chloro-2-propyl-4(3)-pyrimidones (Table II).—The chloropyrimidones were prepared by the controlled hydrolysis of the corresponding dichloropyrimidines. The 5-alkyl-4,6-dichloro-2-propylpyrimidine (0.05 mole) was refluxed for approximately 48 hr. with 4 g. (0.1 mole) of sodium hydroxide in 70 ml. of water; the reaction was considered complete when all the dichloropyrimidine had gone into solution. Upon cooling, the solution was acidified by addition of glacial acetic acid and the chloropyrimidone precipitated. The product was purified by recrystallization from aqueous ethanol or benzene.

In the case of the 5-hexyl derivative, hydrolysis with sodium hydroxide gave very poor yields of product, and the major portion of the starting material was recovered. It was found that acid hydrolysis gave better yields. A mixture of 3.5 g. (0.015 mole) of 4,6-dichloro-5-hexyl-2-propylpyrimidine, 20 ml. of concentrated hydrochloric acid and 50 ml. of water was refluxed for 12 hr. During this period, the dichloropyrimidine layer disappeared and a solid settled out on the sides of the flask. Upon cooling, an additional amount of solid separated. The solid product was removed by filtration and purified by recrystallization from methanol.

5-Alkyl-6-amino-2-propyl-4(3)-pyrimidones (Table II).—The chloropyrimidone (1–2 g.) and 50 ml. of concentrated ammonium hydroxide were placed in the glass liner of a small steel pressure vessel and heated at 180–190° for 10 hr. When cool, the bomb was opened and the solid material was removed and recrystallized from aqueous ethanol.

5-Alkyl-6-propyl-4(3)-pyrimidones (Table II).—The pyrimidones were prepared by catalytic hydrogenolysis of the corresponding chloropyrimidones. Palladium supported

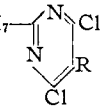
TABLE II

2-PROPYL-4(3)-PYRIMIDONES C_3H_7—  —R

R	R^1	M.p., °C.	Yield, %	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Hydrogen	Cl	168–169	72	$C_7H_9ClN_2O$	16.23	16.48				
Methyl	Cl	170–171	75	$C_8H_{11}ClN_2O$	15.02	15.11	51.45	50.90	5.89	5.98
Hexyl[a]	Cl	114–115	46	$C_{13}H_{21}ClN_2O$	10.89	10.78				
Hydrogen	NH_2	293–295 d.	32	$C_7H_{11}N_3O$	27.47	27.32	57.45	57.48	7.78	7.85
Methyl	NH_2	209–210	64	$C_8H_{13}N_3O$	25.15	25.27				
Hexyl	NH_2	199–200	81	$C_{13}H_{23}N_3O$	17.70	17.95				
Hydrogen[b]	H	106–107	25	$C_7H_{10}N_2O$	20.31	20.62				
Methyl	H	145–146	81	$C_8H_{12}N_2O$	18.41	18.12	63.12	62.70	7.94	7.86
Hexyl[b]	H	65–67	72	$C_{13}H_{22}N_2O$	12.54	12.82				

[a] This compound was prepared by acid hydrolysis of the dichloropyrimidine. [b] These compounds were purified by vacuum sublimation.

TABLE III

4,6-DICHLORO-2-PROPYLPYRIMIDINES C_3H_7—  —R

R	B.p. °C.	Mm.	Yield, %	$n^{20}D$	d^{20}_4	M. R. Calcd.	M. R. Found	Formula	Chlorine, % Calcd.	Chlorine, % Found
Hydrogen	98–99	12	65	1.5206	1.2435	46.82	46.73	$C_7H_8Cl_2N$	37.18	36.75
Methyl[a]	100–101	5	61	1.5203[b]	1.2146[b]	51.44	51.33	$C_8H_{10}Cl_2N_2$	34.63	34.90
Ethyl[c]	115–116	7	53	1.5208	1.1841	56.06	56.20	$C_9H_{12}Cl_2N_2$	32.37	32.02
Propyl[c]	119–120	5	50	1.5165	1.1552	60.68	61.15	$C_{10}H_{14}Cl_2N_2$	30.41	30.40
Butyl[c]	130–131	5	44.5	1.5123	1.1258	65.30	65.93	$C_{11}H_{16}Cl_2N_2$	28.68	28.77
Amyl[c]	153–154	9	46	1.5083	1.1102	69.92	70.17	$C_{12}H_{18}Cl_2N_2$	27.15	27.28
Hexyl	160–161	7	45	1.5060	1.0881	74.54	75.15	$C_{13}H_{20}Cl_2N_2$	25.76	25.35

[a] M.p. 24–26°. [b] Taken at 30°. [c] Analysis by Clark Microanalytical Laboratories, Urbana, Ill.

added and the mixture was stirred for 24 hr. The ammonium chloride, which had separated, was removed by filtration. Approximately 800 ml. of ethanol was removed from the filtrate by distillation to leave a heavy, viscous liquid which solidified on cooling. The second crop of imido ester was worked through in the same manner. The butamidine hydrochloride weighed 372 g. (62% yield) and melted from 95–98° in agreement with the datum recorded in the literature.[11]

(11) Richter, "Beilstein Handbuch der Organischen Chimie," Vol. II, 4th Ed., Springer Verlag, Berlin, 1920, p. 276, recorded a m.p. of 96° for butamidine hydrochloride.

TABLE IV

2-PROPYLPYRIMIDINES $C_3H_3N_2(R'')(R)(R')$

R	R'	R"	M.p., °C.	Yield, %	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Hydrogen	NH_2	Cl	127–128.5	58	$C_7H_{10}ClN_3O$	24.06	24.28				
Methyl	NH_2	Cl	171–172	67	$C_8H_{12}ClN_3O$	22.65	22.96	51.75	51.76	6.47	6.72
Hexyl	NH_2	Cl	101–102	94	$C_{13}H_{22}ClN_3O$	16.46	16.45				
Hydrogen	NH_2	NH_2	202–203	81	$C_7H_{12}N_4$	35.97	35.67				
Methyl	NH_2	NH_2	181–182	66	$C_8H_{14}N_4$	33.74	33.34	57.81	57.98	8.45	7.93
Hexyl	NH_2	NH_2	139–140	87	$C_{13}H_{24}N_4$	23.71	23.50				
Hydrogen[a,e]	NH_2	H	78–79	60	$C_7H_{11}N_3$	30.62	30.86				
Methyl	NH_2	H	129–130	62	$C_8H_{13}N_3$	27.77	27.69	63.55	63.90	8.68	9.06
Hexyl	NH_2	H	84–85	52	$C_{13}H_{23}N_3$	18.98	19.33				
Hydrogen[c]	CH_3O	CH_3O	93–94[b] (7.5)	59	$C_9H_{14}N_2O_2$	15.34	15.23				
Ethyl[d]	CH_3O	CH_3O	106–107[b] (7)	58	$C_{11}H_{18}N_2O_2$	13.33	13.10				

[a] Molecular weight; calcd. 137, found 142. [b] Boiling points (mm.). [c] $n^{20}D$ 1.4840, d^{20}_4 1.0480; *MR* calcd. 49.62, found 49.86. [d] $n^{20}D$ 1.4870, d^{20}_4 1.0212; *MR* calcd. 58.86, found 59.25; methoxyl, calcd. 2.0, found 1.8. [e] Final purification by vacuum sublimation.

on barium sulfate, prepared by the method of Schmidt,[12] was found to be a suitable catalyst. One gram of catalyst and 1 g. of chloropyrimidone dissolved in 100 ml. of ethanol were shaken with hydrogen at an initial pressure of 60 cm. at room temperature; the calculated amount of hydrogen was taken up in from 1 to 4 hr. It was found that unless the ethanol solution of the chloropyrimidone was first shaken in the cold with some Raney nickel, to remove catalyst poisons, the reduction would take place only very slowly if at all. When the hydrogen uptake had ceased, the catalyst was removed by filtration and the solution evaporated to about 10 ml. On cooling, the solid product precipitated. Ethyl acetate was found to be a suitable solvent for recrystallization. In some cases, an analytical sample was prepared by vacuum sublimation.

5-Alkyl-6-amino-4-chloro-2-propylpyrimidines (Table IV).—The dichloropyrimidine (2–5 g.) and 50 ml. of concentrated ammonium hydroxide were placed in the glass liner of a small steel pressure vessel and heated at 130–140° for 12 hr. Upon cooling to room temperature, the bomb was opened and the solid product removed by filtration and recrystallized from dilute alcohol.

5-Alkyl-4,6-diamino-2-propylpyrimidines (Table IV).—The diaminopyrimidines were prepared in the same manner as the aminochloropyrimidines. A temperature of 180–190° was required for replacement of both chloro substituents by amino. Upon cooling, the product separated and was purified by recrystallizations from water or aqueous ethanol. In the case of the 4,6-diamino-2-propylpyrimidine, it was found necessary to evaporate the solution to about 20 ml. and then to add approximately 20 ml. of 30% sodium hydroxide solution in order to cause the product to separate.

5-Alkyl-4-amino-2-propylpyrimidines (Table IV).—The monoaminopyrimidines were prepared by catalytic hydrogenolysis of the corresponding aminochloropyrimidines. The same conditions and catalyst were used as in the preparation of the pyrimidines from the chloropyrimidines. When the hydrogenation was complete, the catalyst was removed by filtration and the solution evaporated down to a volume of 15 ml. The addition of 25 ml. of concentrated ammonium hydroxide caused the product to precipitate. Recrystallization from benzene gave an analytically pure aminopyrimidine.

5-Alkyl-4,6-dimethoxy-2-propylpyrimidines (Table IV).—The dimethoxypyrimidines were prepared by the interaction of the dichloropyrimidines with sodium methoxide. The dichloropyrimidine (0.04 mole), dissolved in 10 ml. of methanol, was added dropwise to a solution of 2.3 g. (0.1 g. atom) of sodium in 50 ml. of methanol. Reaction took place immediately with the evolution of heat, and sodium chloride separated from solution. When all the dichloropyrimidine had been added, the reaction mixture was refluxed for 14 hr. Methanol was then removed *in vacuo* and the residue taken up in ether. Sodium chloride was filtered off and the ether solution dried over sodium sulfate. Ether was removed *in vacuo* and the product purified by vacuum distillation.

2-Propyltetrahydropyrimidine Hydrochloride.—4,6-Dichloro-2-propylpyrimidine 13.7 g. (0.072 mole), was dissolved in 50 ml. of butanol. The solution was shaken with Raney nickel and allowed to stand at 0° for 12 hr. This procedure was found necessary to remove catalyst poisons which made the subsequent hydrogenation difficult. The Raney nickel was removed by filtration and the filtrate, together with 10.9 g. (0.02 mole) of barium oxide and 10 g. of fresh catalyst, was subjected to hydrogenation in the same manner as described for the monochloropyrimidines. The hydrogenation was considered complete after 4 hr. with the uptake of 0.25 mole (3.6 equivalents) of hydrogen. The catalyst and other solid material was removed by centrifugation and the butanol by distillation. A heavy, viscous oil remained which solidified on cooling. It was recrystallized from acetone to give 5.0 g. (43% yield) of 2-propyltetrahydropyrimidine hydrochloride as hygroscopic white crystals, m.p. 98–100°. *Anal.* Calcd. for $C_7H_{15}ClN_2$: C, 51.65; H, 9.29; N, 17.22; Cl, 21.78. Found: C, 51.28; H, 9.44; N, 16.88; Cl, 21.50.

A picrate was prepared in the usual manner. Two recrystallizations from hot water gave long yellow needles of m.p. 107–109°. *Anal.* Calcd. for $C_{13}H_{17}N_5O_7$: C, 43.94; H, 4.82; N, 19.72. Found: C, 43.84; H, 4.65; N, 19.50.

(12) E. Schmidt, *Ber.*, **52**, 409 (1919).

AUSTIN, TEXAS