When acetylation of authentic samples of dihydrocodeine and dihydroisocodeine is carried out as described above but the sodium bicarbonate treatment is omitted, the N,O-diacetates are obtained.

Dihydrocodeine N,O-diacetate, m.p. 106–108° (from ether). *Anal.* Calcd. for $C_{22}H_{29}NO_6$: C, 65.49; H, 7.25; N, 3.47. Found: C, 65.43; H, 7.21; N, 3.59.

Dihydroisocodeine N,O-diacetate, m.p. 162–163° (from ether). *Anal.* Found: C, 65.61; H, 7.39; N, 3.49.

Both give m.p. depressions when admixed with the O-acetates, m.p. 116–117° and 163–164°, respectively. Titration of each with sodium methoxide,[14] showed the presence of exactly one mole of acetic acid bound to nitrogen.

Saponification of Acetates—General Procedure.—The ester (30 mg.) was dissolved in ethanol (1–3 ml.) and the solution was made up to a volume of 10 ml. with 0.01 *N* sodium hydroxide solution. Aliquots of 1 ml. each were titrated from time to time with 0.01 *N* hydrochloric acid (phenolphthalein indicator).

Acknowledgment.—We thank Dr. L. F. Small for samples of all the codeine derivatives which made it possible for us to carry out this work.

REHOVOT, ISRAEL

(14) J. S. Fritz and N. M. Lisicki, *Anal. Chem.*, **23**, 589 (1951).

[CONTRIBUTION FROM THE NUTRITION AND PHYSIOLOGY SECTION, RESEARCH DIVISION, AMERICAN CYANAMID CO., LEDERLE LABORATORIES]

Syntheses of 6-Substituted Purines

BY MILON W. BULLOCK, JOHN J. HAND AND E. L. R. STOKSTAD

RECEIVED FEBRUARY 1, 1956

Several purine derivatives which are related to kinetin (6-furfurylaminopurine) have been prepared by condensing 6-chloropurine with amines. Analogs in which the 6-amino group was replaced by a sulfur atom have been prepared by treating 6-chloropurine with sodium mercaptides. The ultraviolet absorption spectra of the purine derivatives have been determined in 0.1 *N* hydrochloric acid, 0.1 *N* sodium hydroxide and in a neutral solution. Methods for the convenient preparation of some of the intermediates are presented. A modification of the conventional method of lithium aluminum hydride reductions in which only enough water is added to cause the separation of the salts as a solid phase has simplified this method of reducing nitriles. A method for preparing 2-mercaptomethyltetrahydrothiophene directly from tetrahydrofurfuryl alcohol was investigated.

The recent isolation,[1] structure determination and synthesis[2] of kinetin, 6-furfurylaminopurine, the cell division factor from deoxynucleic acid, has prompted us to prepare several analogs with the hope of obtaining an antimetabolite or competitive antagonist to kinetin which would inhibit cell mitosis and possibly be useful for cancer therapy.

Miller, *et al.*,[2] synthesized kinetin by the general method of Elion, *et al.*,[3] by treating 6-methylmercaptopurine with furfurylamine. In these Laboratories we have synthesized kinetin and several analogs by a modification of the basic method of Albert and Brown.[4] We have found that condensing 6-chloropurine with at least two equivalents of the amine in the presence of a high boiling solvent such as methyl Cellosolve gives excellent yields of pure products.

Analogs in which the 6-amino group on the purine nucleus was replaced by a sulfur atom were also conveniently prepared by allowing 6-chloropurine to react with a sodium mercaptide under similar conditions. This method appears to give about the same yields as the method of Elion, Burgi and Hitchings,[3] in which the alkyl halide is condensed with the sodium salt of 6-mercaptopurine.

The melting points and analyses of the 6-substituted purine derivatives which were prepared are given in Table I. The letters in the method column refer to the general procedures illustrated in the Experimental section. The biological activities of the compounds will be published elsewhere.

The ultraviolet absorption spectra of these compounds have been determined with a Cary recording spectrophotometer in 0.1 *N* sodium hydroxide, 0.1 *N* hydrochloric acid and in water or ethanol. Many of the compounds are so insoluble in water that the determination of the absorption spectrum in this medium was impractical. The molecular extinctions are summarized in Table II.

Most of the amines which were required as intermediates in this work and which were unavailable commercially were prepared by reducing the corresponding nitrile with lithium aluminum hydride in ether. 3-Aminomethylpyridine was prepared by reducing 3-cyanopyridine catalytically since the lithium aluminum hydride reduction was unsatisfactory. N-Methylfurfurylamine was prepared by a slight modification of the method of Schwabbauer.[5] The methods of preparation, yields and physical constants of the amines are summarized in Table III.

Acknowledgments.—The authors are indebted to Mr. L. Brancone and staff for the microanalyses and to Mr. H. Lewry for the ultraviolet absorption spectra.

Experimental[6]

Since the procedures used to prepare compounds in any one series are nearly identical, only one example will be given to illustrate each procedure.

***m*-Methylbenzylamine (A).**—A solution of 100 g. (0.854 mole) of *m*-tolylnitrile in 150 ml. of anhydrous ether was added to a stirred suspension of 38 g. (1 mole) of lithium aluminum hydride in 1 liter of ether at such a rate as to maintain a vigorous reflux. The addition required 30 minutes. The suspension was refluxed an additional 30 minutes. The heating mantle was replaced by an ice-bath, and 20 ml. of water was added dropwise from a dropping funnel. Sodium hydroxide solution (20%) was then added until a granular solid second phase was present and the ether solution was

(1) C. O. Miller, F. Skoog, M. H. von Saltza and F. M. Strong, THIS JOURNAL, **77**, 1392 (1955).

(2) C. O. Miller, F. Skoog, F. S. Okumura, M. H. von Saltza and F. M. Strong, *ibid.*, **77**, 2263 (1955).

(3) G. B. Elion, E. Burgi and G. H. Hitchings, *ibid.*, **74**, 411 (1952).

(4) A. Albert and D. J. Brown, *J. Chem. Soc.*, 2060 (1954).

(5) G. Schwabbauer, *Ber.*, **35**, 410 (1902).

(6) Melting points are uncorrected.

TABLE I

SUBSTITUTED PURINES

Purine	Empirical formula	Procedure	Yield, %	M.p., °C.	Analyses, % Calculated C	H	N	S	Found C	H	N	S
6-Furfurylamino-[a]	$C_{10}H_9N_5O$	D	95.5	267–268[b]								
6-(N-Methylfurfurylamino)-	$C_{11}H_{11}N_5O$	E	80.2	210–211[b]	63.98	4.92	31.09		64.32	5.18	30.93	
6-Thenylamino-[c]	$C_{10}H_9N_5S$	E	87.5	241.5–242	51.93	3.92	30.29		51.73	4.28	30.44	
6-Benzylamino-[c]	$C_{12}H_{11}N_5$	E	92.5	231	57.63	4.84	30.55		57.55	5.10	30.51	
6-(o-Methylbenzylamino)-	$C_{13}H_{13}N_5$	D	79.5	243–244[b]	65.25	5.48	29.27		65.11	5.89	30.01	
6-(m-Methylbenzylamino)-	$C_{13}H_{13}N_5$	E	91	233–234	65.25	5.48	29.27		65.41	5.67	29.46	
6-(p-Methylbenzylamino)-	$C_{13}H_{13}N_5$	D	88.5	263	65.25	5.48	29.27		65.26	5.19	29.50	
6-(N-Benzylmethylamino)-	$C_{13}H_{13}N_5$	D	63.5	114.5–115	65.25	5.48	29.27		65.14	5.83	29.56	
6-(α-Phenylethylamino)-	$C_{13}H_{13}N_5$	D	70	199–202	65.25	5.48	29.27		65.17	5.68	29.29	
6-(2-Pyridylmethylamino)-[c]	$C_{11}H_{10}N_6$	D	55	245–246	58.39	4.46	37.15		58.57	4.57	37.38	
6-(3-Pyridylmethylamino)-[c]	$C_{11}H_{10}N_6$	D	70.5	257	58.39	4.46	37.15		58.53	4.55	37.47	
6-(4-Pyridylmethylamino)-[c]	$C_{11}H_{10}N_6$	D	59	250–251	58.39	4.46	37.15		58.53	4.56	37.30	
6-(Carbomethoxymethylamino)-	$C_8H_9N_5O_2$	E	41	238	46.37	4.38	33.80		46.78	4.00	33.63	
6-Furfurylthio-	$C_{10}H_8N_4SO$	F	80	178–178.5	51.71	3.47	24.12	13.81	51.64	3.77	24.38	13.89
6-Tetrahydrothenylthio-	$C_{10}H_{12}N_4S_2$	F	79	192.5–194	47.54	4.79	22.29	25.38	47.59	5.11	22.16	25.82
6-Benzylthio-	$C_{12}H_{10}N_4S$	F	95.5	193–194	59.48	4.16	23.13	13.23	59.62	4.29	23.00	13.16

[a] Previously described by C. O. Miller, *et al.*; see reference 2. [b] Sealed capillary. [c] Recently reported by C. G. Skinner and W. Shive, THIS JOURNAL, **77**, 6692 (1955).

TABLE II

MOLECULAR EXTINCTIONS OF PURINES

Purine	0.1 *N* HCl λmax	ε	λmin	ε	Ethanol λmax	ε	λmin	ε	0.1 *N* NaOH λmax	ε	λmin	ε
6-Furfurylamino-	274	16,900	233	2920	212	26,100	234	3260	273	17,400	240	3490
					268	18,700						
6-(N-Methylfurfurylamino)-	280	17,900	236	3500	212[b]	24,800	238	3740	280	19,500	243	3630
					276	19,600						
6-Thenylamino-	240[a]	8,860	250	7980	208[b]	21,700	229	9600	274	19,900	251	3690
	276	17,600			236	12,100	247	9400				
					269	18,800						
6-Benzylamino-	274	16,500	233	2250	207[b]	25,400	232	3040	275	17,000	241	3890
					270	18,000						
6-(o-Methylbenzylamino)-	275	17,800	235	1170	268	19,600	236	5100	274	16,200	240	2890
6-(m-Methylbenzylamino)-	276	18,200	235	2480	269	19,500	236	2750	274	18,600	240	3100
6-(p-Methylbenzylamino)-	275	18,800	234	3080	269[b]	19,400	234	6100	275	18,900	242	5120
6-(N-Benzylmethylamino)-	280	17,400	237	2400	276	19,400	240	3540	282	11,500	245	3100
6-(α-Phenylethylamine)-	277	18,000	235	2190	270	16,500	237	2620	274	18,400	240	3520
6-(2-Pyridylmethylamino)-	277	22,600	233	1930	270	22,000	230	3160	273	17,800	236	1440
6-(3-Pyridylmethylamino)-	276	21,200	233	2100	269	21,000	229	3240	274	17,000	239	1960
6-(4-Pyridylmethylamino)-	278	18,800	233	2740	264	17,400	228	3400	275	14,900	238	4510
6-(Carbomethoxymethylamino)-	274	8,400	233	875	266	8,850	219	1370	274	15,400	239	210
6-Furfurylthio-	324	17,000	258	1900	217	21,100	258	5350	291	18,700	253	2510
					290	16,700						
6-Tetrahydrothenylthio-	324	18,700	258	1470	214[b]	13,700	241	3940	292	16,900	250	3040
					291	17,900						
6-Benzylthio-	246	9,250	228	5960	292[b]	17,400	252	1690	293	15,300	252	2500
	298	4,270	276	2530								

[a] Inflection. [b] Water solution.

TABLE III

AMINOMETHYL COMPOUNDS USED AS INTERMEDIATES

Starting material	Method	Product	Yield	B.p., °C.	Mm.	n_D
o-Tolylnitrile	A	o-Methylbenzylamine[a]	83.6	204–206		1.5420^{21}
m-Tolylnitrile	A	m-Methylbenzylamine[b]	67.6	202–206		1.5348^{21}
p-Tolylnitrile	A	p-Methylbenzylamine[c]	50.5	92	13	1.5340^{20}
2-Cyanopyridine	A	2-Aminomethylpyridine[d]	42.5	85	10	1.5378^{20}
3-Cyanopyridine	A		Less than 5%			
	B	3-Aminomethylpyridine[d]	37.4	114	18	1.5505^{20}
4-Cyanopyridine	A	4-Aminomethylpyridine[e]	34.7	94	5.2	1.5500^{20}
Furfural + CH_3NH_2	C	N-Methylfurfurylamine[f]	52	58	24	1.4725^{20}

[a] R. F. Nystrom and W. G. Brown, THIS JOURNAL, **70**, 3738 (1948), gave $n^{20}D$ 1.5412. [b] H. Rupe and F. Bernstein, *Helv. Chim. Acta*, **13**, 462 (1930), gave b.p. 201–202° at 753 mm. [c] K. G. Lewis, *J. Chem. Soc.*, 2249 (1950), gave b.p. 198–200° at 680 mm. [d] H. G. Koiloff and J. H. Hunter, THIS JOURNAL, **63**, 490 (1941), prepared the three isomeric aminomethylpyridines by hydrogenation of the nitriles over Raney nickel. [e] H. A. Adkins, I. A. Wolff, A. Paulic and E. Hutchinson, *ibid.*, **66**, 1293 (1944), gave b.p. 112–113° at 18 mm., $n^{20}D$ 1.5485. [f] J. E. Zanetti and J. J. Bashour, *ibid.*, **61**, 3133 (1939), gave b.p. 149–149.5° at 761 mm., $n^{20}D$ 1.4729.

clear. The amount of sodium hydroxide solution required was approximately 150 ml. The granular solid was filtered off and washed with ether. The ether solution was dried over sodium sulfate and the solvent distilled. The amine distilled at 202–206°, $n^{21}D$ 1.5348, yield 70.0 g. (0.577 mole), 67.6%.

2-Aminomethylpyridine (A).—A solution of 100 g. (0.96 mole) of 2-cyanopyridine in 200 ml. of anhydrous ether was added over a period of 45 minutes to a stirred suspension of 47.5 g. (1.25 moles) of lithium aluminum hydride in 1 liter of ether. The solution was refluxed 15 minutes and the heating mantle replaced by an ice-bath. Twenty ml. of water was added dropwise followed by 150 ml. of 20% sodium hydroxide solution. The clear ether solution was decanted and filtered from the granular solid. The filter cake was washed with ether. The ether solution was dried over sodium sulfate and the ether distilled off. The amine was purified by distillation *in vacuo*. The fraction distilling 66–68° at 4.5 mm. was collected as product. The yield was 40.8 g. (0.377 mole), 42.5%. A twice redistilled sample had $n^{20}D$ 1.5378 and d^{20} 1.105. This amine distills at 202° with some decomposition at atmospheric pressure. The dihydrochloride was prepared with methanolic hydrogen chloride, after recrystallization from an ethanol–water mixture the salt, m.p. 225–231°.

Anal. Calcd. for $C_6H_{10}N_2Cl_2$: C, 39.80; H, 5.57; N, 15.47; Cl, 39.17. Found: C, 40.25; H, 5.59; N, 15.61; Cl, 39.68.

3-Aminomethylpyridine (B).—A mixture of 100 g. (0.96 mole) of 3-cyanopyridine, 10 g. of Raney nickel catalyst and 250 ml. of methanol saturated with ammonia was placed in a hydrogenation bomb and shaken at room temperature and 1000 lb. pressure for 8 hr. The catalyst was filtered off and the solvent distilled. The residue was distilled under reduced pressure. The fraction distilling 110–114° at 18 mm. was collected as product. The yield was 39 g. (0.36 mole), 37.4%. The pure amine had $n^{20}D$ 1.5505.

N-Methylfurfurylamine (C).—A mixture of 48 g. (0.5 mole) of furfural and 186 g. (1.5 moles) of 25% aqueous trimethylamine was heated to boiling and transferred to a low-pressure hydrogenation apparatus. Five grams of 5% palladium–charcoal catalyst was added and the reaction mixture shaken overnight at a pressure of 60–25 lb. The catalyst was filtered off and the filtrate acidified with hydrochloric acid. The acidic solution was extracted with ether and then 20% sodium hydroxide was added until the solution was alkaline. The amine was recovered by extraction with three 300-ml. portions of ether. The combined ether extracts were dried over sodium sulfate and distilled. The amine was distilled *in vacuo*. The fraction distilling at 57–58° at 24 mm. was collected as product. The product was redistilled from barium oxide to yield 26.0 g. (0.234 mole, 52%) of a colorless product, b.p. 58° at 24 mm., $n^{20}D$ 1.4725.

2-Mercaptomethyltetrahydrothiophene.—A mixture of 102 g. (1 mole) of tetrahydrofurfuryl alcohol, 228.3 g. (3 moles) of thiourea and 422 g. (2.5 moles) of 48% hydrobromic acid was heated at gentle reflux for 18 hr. The reaction mixture was cooled and made alkaline by the addition of a solution of 100 g. (2.5 moles) of sodium hydroxide in 200 ml. of water. The alkaline solution was refluxed 1 hr., cooled and acidified with hydrochloric acid. A small amount of water was added to obtain a homogeneous solution and the product extracted with three 500-ml. portions of ethyl acetate. The combined ethyl acetate extracts were washed with 100 ml. of saturated salt solution and with 100 ml. of saturated sodium bicarbonate solution. The organic solution was dried over sodium sulfate and distilled, leaving a residue which partially crystallized on cooling. Treatment of the crude product with 150 ml. of absolute ethanol gave 8 g. of recovered thiourea. The mother liquor was evaporated and the residue distilled. The fraction distilling 90–92° at 9 mm. was collected as the desired product. The yield was 6.7 g. (0.05 mole), 5%. On redistillation, pure product was obtained, b.p. 95–96° at 12 mm., $n^{20}D$ 1.5669.

Anal. Calcd. for $C_5H_{10}S_2$: C, 44.73; H, 7.51; S, 47.76. Found: C, 44.74; H, 7.41; S, 47.43.

In addition to the 2-mercaptomethyltetrahydrothiophene, there was obtained 32.7 g. of a second product, b.p. 110–120° at 0.2 mm. Two distillations gave an apparently pure product, b.p. 99–101° at 0.02 mm., $n^{20}D$ 1.5162. The infrared spectrum showed a strong hydroxyl absorption at 3.0 mμ and a mercaptan absorption at 3.95 mμ. The compound is believed to be impure 2-mercaptopentanediol-1,5.

Anal. Calcd. for $C_5H_{12}O_2S$: C, 44.08; H, 8.88; S, 23.54. Found: C, 42.75; H, 9.40; S, 24.59.

6-Furfurylaminopurine (Kinetin) (AD).—A solution of 3 g. (0.0194 mole) of 6-chloropurine,[7] 30 ml. of methyl Cellosolve and 6 ml. (0.065 mole) of furfurylamine was heated at reflux in an oil-bath for 2 hr. A drop of the solution was removed and rubbed on a watch glass to obtain seeds. The hot solution was then seeded and allowed to cool slowly to 0°. The crystals were filtered off, washed with methyl Cellosolve, water and absolute ethanol. The yield of white plates was 3.80 g. (0.017 mole), 91% of pure product, m.p. 268° (sealed capillary).[2] A second fraction was obtained by distilling the solvents and triturating the residue with water. This fraction, wt. 0.19 g. and m.p. 262–265° (sealed capillary), brought the total yield to 95.5%.

6-(N-Methylfurfurylamino)-purine (E).—A mixture of 2.00 g. (0.0129 mole) of 6-chloropurine, 3 g. (0.027 mole) of N-methylfurfurylamine and 10 ml. of methyl Cellosolve was refluxed 90 minutes. The solvent and excess amine were distilled off under the reduced pressure (oil vacuum pump). The crystalline residue was triturated with 25 ml. of water and filtered. The filter cake was washed with water and then with methanol. The yield was 2.38 g. (0.104 mole), 80.2% of almost white crystals, m.p. 210–211° (sealed tube).

6-(2-Pyridylmethylamino)-purine (AD).—A mixture of 3 g. (0.0194 mole) of 6-chloropurine, 10 ml. of methyl Cellosolve and 6 g. (0.055 mole) of 2-aminomethylpyridine was refluxed 2 hr. The product which crystallized from the solution on cooling was filtered off, washed with methyl Cellosolve, water and 95% ethanol. The yield was 2.41 g. (0.0106 mole), 55% of crystals, m.p. 233–234°. Recrystallization from methyl Cellosolve gave pure material, m.p. 245–246°.

6-(Carbomethoxymethylamino)-purine (E).—A mixture of 6.5 g. (0.052 mole) of glycine methyl ester hydrochloride in 50 ml. of methanol was cautiously neutralized with 2.8 g. (0.052 mole) of sodium methoxide and the precipitated sodium chloride filtered off. The filtrate was added to a mixture of 2 g. (0.0129 mole) of 6-chloropurine in 20 ml. of methyl Cellosolve. The methanol was distilled off and the reaction mixture heated 125° for 90 minutes. About one-third of the reaction mixture was accidentally lost due to bumping during the distillation of the methanol. The reaction mixture was allowed to cool and a small amount of light yellow crystals filtered off. This unidentified by-product, wt. 0.1 g., m.p. 310–312°, had the following analysis: C, 41.97; H, 4.97; N, 24.56. The filtrate was evaporated to dryness under the reduced pressure of a water aspirator. The solid residue was triturated with water and filtered. The filter cake was washed with water and methanol leaving 1.1 g. (0.053 mole, 41%) of white crystals, m.p. 230°. After recrystallization from 95% ethanol, the m.p. was 238°.

6-Furfurylthiopurine (F).—A solution of the sodium salt of methyl Cellosolve was made by dissolving 0.625 g. (0.0272 mole) of sodium in 20 ml. of dry methyl Cellosolve. Then 2.96 g. (0.026 mole) of furfurylmercaptan was added and the flask swirled to mix the contents. To this solution 2.00 g. (0.0129 mole) of 6-chloropurine was added. The reaction mixture was refluxed 90 minutes and left standing overnight. The solvent was distilled off under the reduced pressure of a water aspirator. The oily layer was slurried with water and the *p*H adjusted to 6. The crystalline product was filtered off and washed with water. The yield was 2.41 g. (0.0104 mole), 80%, m.p. 176–177°. After recrystallization from 95% ethanol, the product had m.p. 178–178.5°.

6-(3-Pyridylmethylamino)-purine Dihydrochloride.—Eighteen grams (0.0795 mole) of 6-(3-pyridylmethylamino)-purine was dissolved in 900 ml. of refluxing absolute ethanol and acidified by the addition of 130 ml. of 25% methanolic hydrogen chloride. On cooling, the crystalline dihydrochloride separated. It was filtered off and washed with methanol and with ether. This gave 21.6 g. of product, m.p. 276–279°. Concentration of the mother liquors gave

(7) The 6-chloropurine used for most of this work was purchased from the Francis Earle Laboratories, Peekskill, N. Y.

an additional 1.0 g. of crystals, bringing the total yield to 22.6 g. (0.0756 mole), 95%. One gram was recrystallized from 30 ml. of acetic acid. The recrystallized product had m.p. 278–279°

Anal. Calcd. for $C_{11}H_{12}Cl_2N_6$: C, 44.16; H, 4.04; N, 28.09; Cl, 23.70. Found: C, 44.52; H, 4.38; N, 28.12; Cl, 23.37.

PEARL RIVER, NEW YORK

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Lithium Aluminum Hydride Reduction of Some Hydantoins, Barbiturates and Thiouracils

BY FREDERICK J. MARSHALL

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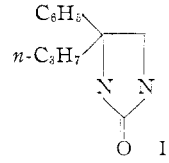
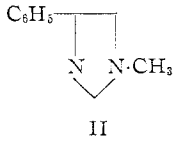
Lithium aluminum hydride, even if present in excess, has been found to reduce only partially some 5,5-disubstituted hydantoins to the corresponding 2-imidazolidinones, barbituric acids to hexahydro-2-pyrimidinones, and 2-thiouracils to 1,2,3,4-tetrahydro-2-pyrimidinethiones. The reduction appears to be general for these types of compounds and proceeds similarly with a 2-thiohydantoin and a 2-thiobarbituric acid.

In the course of studies on potential new hypnotics, some 4,4-disubstituted-2-imidazolidinones were prepared by reaction between urea and the appropriate diamine. The reduction of a hydantoin by means of lithium aluminum hydride seemed to be a means of obtaining an imidazolidine which could conceivably lead to a diamine by treatment with acid. When the first reduction was tried, however, it was found that 5-phenyl-5-*n*-propylhydantoin was only partially reduced by excess lithium aluminum hydride to yield 4-phenyl-4-*n*-propyl-2-imidazolidinone (I). The structure was established by a mixed melting point with an authentic sample prepared from 1,2-diamino-2-phenylpentane and urea.[1] Furthermore, electrometric titration revealed no basic group in the molecule, indicating the presence of the –NH–CO–NH– linkage. The general nature of the reaction was demonstrated by its application to several other hydantoins (Table I) and by the fact that 5,5-diphenyl-2-thiohydantoin was reduced in a similar manner.

These were quite unexpected results in view of the work of Wilk and Close.[2] They reported that when 3-methyl-5-phenylhydantoin was reduced using an excess of lithium aluminum hydride, under the same general conditions as employed in the present work, complete reduction took place and the imidazolidine II was obtained.



I



II

The reaction was extended to some barbituric acid derivatives to give hexahydro-2-pyrimidinones (Table II), to some 2-thiouracils to produce 1,2,3,4-tetrahydro-2-pyrimidinethiones and to 6-methyl-4,5-dihydro-3(2H)pyridazinone to obtain the tetrahydropyridazine. The only unsuccessful reactions were those involving 5-ethyl-6-phenyl- and 6-phenyluracil. This may well have been due to the greater insolubility of the uracils in ether. No further investigation was made of this point.

(1) Unpublished studies, these laboratories.

(2) I. J. Wilk and W. J. Close, *J. Org. Chem.*, **15**, 1020 (1950).

In cases where there appeared to be any possibility of ambiguity, the structures of representative compounds were verified. 5-Ethyl-5-phenylhexahydro-2-pyrimidinone was studied by electrometric titration as described above, and there was no basic nitrogen present. A sulfur analysis established the structure of its 2-thio analog.

None of the compounds showed satisfactory hypnotic activity when tested orally in rats.

Acknowledgment.—The author is grateful to Dr. E. R. Shepard for his valuable suggestions, to W. L. Brown, H. L. Hunter, G. M. Maciak and Miss Gloria Beckmann for the microanalyses and to Dr. Harold Boaz and Paul Landis for physical chemical data.

Experimental

The experimental procedures for the reductions are illustrated by typical examples. The Skelly B employed in many of the recrystallizations is petroleum ether, b.p. 60–71°.

4-Phenyl-4-*n*-propyl-2-imidazolidinone.—To 11.4 g. (0.3 mole) of lithium aluminum hydride in 600 ml. of dry ether was added, portionwise, 21.8 g. (0.1 mole) of 5-*n*-propyl-5-phenylhydantoin.[3] The mixture was refluxed for 30 hr. and was then hydrolyzed by the addition, with cooling in ice-water, of 11 ml. of water, 11 ml. of 15% NaOH solution and 33 ml. of water. After filtration, removal of the ether showed that it contained no product so the solids from the hydrolysis were extracted by boiling with alcohol.[4] Concentration and cooling gave 11 g. of product melting at 206–208°. Crystallizations from dilute ethanol and from ethanol–Skelly B gave 8.9 g. (48%) melting at 207–209°. A mixed melting point with material prepared from 1,2-diamino-2-phenylpentane and urea[1] was not depressed.

5-Ethyl-5-phenylhexahydro-2-pyrimidinone.—To 15.2 g. (0.4 mole) of lithium aluminum hydride in 600 ml. of dry ether was added, portionwise, 23.2 g. (0.1 mole) of 5-ethyl-5-phenylbarbituric acid.[5] The mixture was stirred and refluxed for 44 hr. Hydrolysis was effected as previously outlined and the solids were extracted by boiling with four 250-ml. portions of ethanol.[4] There was obtained 12 g. of material melting at 195–198°. Two crystallizations from chloroform–Skelly B and one from ethanol–Skelly B gave 9 g. (44%) melting at 195–196.5°.

(3) Prepared according to the method of H. R. Henze and R. J. Speer, THIS JOURNAL, **64**, 522 (1942), as were all the hydantoins with the exception of the 5,5-diphenyl derivative which was prepared by the procedure of H. Biltz, *Ber.*, **41**, 1391 (1908).

(4) With the dialkyl derivatives the ether contained some product and the extractions were preferably carried out with benzene.

(5) Most of the barbituric acids were kindly supplied by Mr. W. J. Doran of these laboratories. 5-Ethyl-5-phenyl-2-thiobarbituric acid was prepared by the procedure of D. Waldi, *Angew. Chem.*, **62**, 430 (1950).