

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

RECEIVED FEBRUARY 17, 1956

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, electro-metric 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.



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 tetrahydro-pyridazine. 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-phenyl-hexahydro-2-pyrimidinone was studied by electro-metric 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 urea¹ was not depressed.

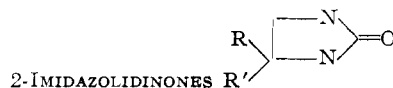
5-Ethyl-5-phenylhexahydro-2-pyrimidinone.—To 15.2 g. (0.4 mole) of lithium aluminum hydride in 600 ml. of dry ether was added, portionwise, 23.2 g. (0.1 mole) of 5-ethyl-5-phenylbarbituric acid.⁵ The mixture was stirred and refluxed for 44 hr. Hydrolysis was effected as previously outlined and the solids 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**, 434 (1950).

TABLE I



R	R'	Crystn. solvent	Yield, %	M.p., °C.	Formula	Analyses, %			
						C	Calcd.	H	Found
C ₆ H ₅	<i>n</i> -C ₃ H ₇	EtOH-Skelly B	48	207-209	C ₁₂ H ₁₆ N ₂ O	70.55	7.89	70.34	7.89
<i>p</i> -ClC ₆ H ₄	CH ₃	Ethanol	57	217-219	C ₁₀ H ₁₁ ClN ₂ O	56.93	5.26	57.20	5.23
C ₆ H ₅	C ₆ H ₅	Ethanol	38	250-252	C ₁₅ H ₁₄ N ₂ O	75.61	5.92	75.60	5.81
C ₆ H ₅ (2-thione)	C ₆ H ₅ ^a	95% EtOH	53	257-258	C ₁₅ H ₁₄ N ₂ S	70.89	5.55	70.61	5.71
CH ₃	<i>i</i> -C ₄ H ₉	C ₆ H ₆ -Skelly B	91	99-101	C ₈ H ₁₆ N ₂ O	61.45	10.32	61.68	10.29
CH ₃	3-Butenyl	^b	69	74-77 ^b	C ₈ H ₁₄ N ₂ O	62.25	9.15	62.47	9.04
CH ₃	<i>n</i> -C ₅ H ₁₁	^c	73	51-53	C ₉ H ₁₈ N ₂ O	63.49	10.66	63.32	10.61
CH ₃	<i>n</i> -C ₉ H ₁₉	Skelly B- a little C ₆ H ₆	92	91-92	C ₁₃ H ₂₆ N ₂ O	68.98	11.58	68.78	11.33
C ₂ H ₅	C ₂ H ₅	C ₆ H ₆ -Skelly B	59	159-160	C ₇ H ₁₄ N ₂ O	59.13	9.92	59.20	9.75
C ₂ H ₅	<i>n</i> -C ₄ H ₉	C ₆ H ₆ -Skelly B ^d	85	73-75	C ₉ H ₁₈ N ₂ O	63.49	10.66	63.75	10.77
C ₂ H ₅	<i>i</i> -C ₅ H ₁₁	^e	71	88-90	C ₁₀ H ₂₀ N ₂ O	65.28	10.93	65.44	10.97
<i>n</i> -C ₃ H ₇	<i>n</i> -C ₃ H ₇	C ₆ H ₆ -Skelly B	82	131-132	C ₉ H ₁₈ N ₂ O	63.49	10.66	62.58	10.33
<i>i</i> -C ₄ H ₉	<i>i</i> -C ₄ H ₉	CHCl ₃ -Skelly B							
<i>i</i> -C ₄ H ₉	<i>i</i> -C ₄ H ₉	C ₆ H ₆ -Skelly B	63	176-178	C ₁₁ H ₂₂ N ₂ O	66.65	11.17	66.45	11.01

^a The 5,5-diphenyl-2-thiohydantoin was prepared according to the method of H. Biltz, *Ber.*, **42**, 1792 (1909). ^b Distilled at 165-173° (0.4 mm.). The hydantoin was prepared in 67% yield and melted at 119.5-120.5° from benzene-Skelly B. *Anal.* Calcd. for C₈H₁₂N₂O₂: C, 57.10; H, 7.19. Found: C, 57.50; H, 7.57. ^c Distilled at 164-165° (0.45 mm.). ^d The Skelly B must be added to the cool benzene solution until just turbid and the crystallization allowed to take place slowly. The starting hydantoin was prepared in 68% yield and melted at 122-124° after crystallization from ethanol-Skelly B. *Anal.* Calcd. for C₉H₁₆N₂O₂: N, 15.19. Found: N, 15.03. ^e Distilled at 162-164° (0.25 mm.).

TABLE II



R	R'	Crystallization solvent	Yield, %	M.p., °C.	Formula	Analyses, %			
						C	Calcd.	H	Found
C ₂ H ₅	C ₆ H ₅	CHCl ₃ -Skelly B	44	195-197	C ₁₂ H ₁₆ N ₂ O	70.56	7.90	70.78	7.89
C ₂ H ₅ (2-thione)	C ₆ H ₅	Ethanol-Skelly B							
C ₂ H ₅ (2-thione)	C ₆ H ₅	Benzene	47	135-137	C ₁₂ H ₁₆ N ₂ S	65.38	7.30	65.32	7.49
C ₂ H ₅	<i>i</i> -C ₅ H ₁₁	Ethanol-Skelly B				S, 14.53		S, 14.80	
C ₂ H ₅	<i>i</i> -C ₅ H ₁₁	Benzene-Skelly B	63	144-146	C ₁₁ H ₂₂ N ₂ O	66.65	11.18	66.87	11.09
C ₂ H ₅	2-C ₅ H ₁₁	Benzene-Skelly B	8 ^a	124-126	C ₁₁ H ₂₂ N ₂ O	66.65	11.18	66.92	10.75
CH ₂ =CH-CH ₂ -	2-C ₅ H ₁₁	^b	53	114-116	C ₁₂ H ₂₂ N ₂ O	68.51	10.52	68.39	10.56

^a Great difficulty in purification. The product retained solvent and came out gelatinous. Distilled at 195-200° (0.35 mm).

5-Ethyl-6-phenyl-2-thiouracil was prepared in essential accordance with the method of Johnson and Hemingway⁶ using the sodium ethoxide prepared from 35.3 g. (1.54 g. atoms) of sodium in 600 ml. of absolute ethanol, 65.5 g. (0.85 mole) of thiourea and 148 g. (0.67 mole) of ethyl α -ethylbenzoylacetate. After crystallization from acetic acid, there was obtained 76.5 g. (49% of product which melted at 232-234°. An analytical sample melted at 233-235°.

Anal. Calcd. for C₁₂H₁₂N₂OS: C, 62.02; H, 5.21. Found: C, 62.26; H, 5.04.

5-Ethyl-6-phenyl-1,2,3,4-tetrahydro-2-pyrimidinethione.—The reduction of 30 g. (0.13 mole) of the above thiouracil, using 14.8 g. (0.39 mole) of lithium aluminum hydride, was carried out in the same manner as with the hydantoins. Stepwise concentration of the ethanol extracts gave two fractions of crude product and a third higher melting fraction. Three crystallizations from absolute ethanol gave 6.4 g. (23%) of product which melted at 209-211°.

Anal. Calcd. for C₁₂H₁₄N₂S: C, 66.02; H, 6.47; N, 12.84. Found: C, 66.84; H, 6.42; N, 12.68.

(6) T. B. Johnson and E. H. Hemingway, *THIS JOURNAL*, **37**, 378 (1915).

6-Phenyl-1,2,3,4-tetrahydro-2-pyrimidinethione.—Reduction of 30 g. (0.158 mole) of 6-phenyl-2-thiouracil⁶ in the above manner gave 5 g. (11%) of the alcoholate of the product which melted at 200.5-201° from ethanol or chloroform-Skelly B. The solvent of crystallization was not removed by drying at 110° under vacuum.

Anal. Calcd. for C₁₀H₁₀N₂S·C₂H₅OH: C, 60.92; H, 6.76; N, 11.85. Found: C, 60.44; H, 6.60; N, 11.80.

The ethanol was removed by drying at 150° under vacuum. The compound then melted at 204-204.5°.

Anal. Calcd. for C₁₀H₁₀N₂S: C, 63.16; H, 5.30; N, 14.72. Found: C, 63.82; H, 5.60; N, 14.47.

3-Methyl-1,4,5,6-tetrahydropyridazine.—To 11.4 g. (0.3 mole) of lithium aluminum hydride in 600 ml. of dry ether was added, portionwise, 22.4 g. (0.2 mole) of 6-methyl-4,5-dihydro-3(2H)-pyridazinone. After 30 hr. refluxing the reaction was worked up in the usual manner. Following drying of the combined ether and benzene solutions over anhydrous magnesium sulfate, the solvents were removed and the product was distilled twice to give 3.4 g. (17%) boiling at 100-101° (76 mm.), *n*_D²⁰ 1.4862.

Anal. Calcd. for C₆H₁₀N₂: C, 61.18; H, 10.27; N, 28.55. Found: C, 60.93; H, 10.17; N, 28.41.

INDIANAPOLIS 6, INDIANA