3. None of the barbituric acids prepared possesses desirable physiological properties comparable in effect to barbital or amytal.

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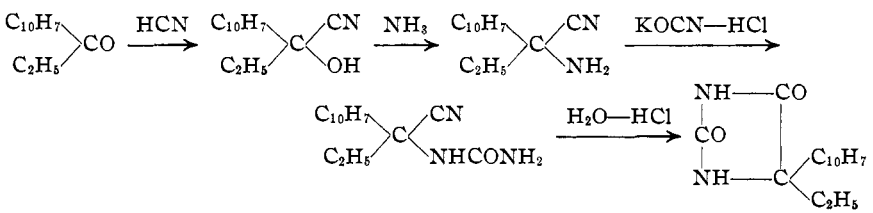
[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF YALE UNIVERSITY]

Synthesis of 5,5-α-Naphthylethylhydantoin

BY DEWITT T. KEACH

Phenylethylhydantoin (nirvanol) has been used considerably as an hypnotic, and it is probable that other hydantoins having an aryl group in the 5 position would possess similar properties. Because of this fact and the relationship of the hydantoins to the barbituric acids, the writer, in the course of work on the determination of the physiological effect of the naphthyl group introduced into the barbituric acid molecule, decided to attempt the synthesis of 5,5-α-naphthylethylhydantoin.

The method followed was essentially that used by Read[1] in his work on 5,5-phenylethylhydantoin, *i. e.*, α-naphthyl ethyl ketone reacting with anhydrous hydrocyanic acid produced the corresponding cyanohydrin and this with ammonia gave a disubstituted aminoacetonitrile. This aminoacetonitrile was dissolved in hydrochloric acid, treated with alkali cyanate, and upon boiling the solution the hydantoin precipitated. This is shown by



α-Naphthyl ethyl ketone was made by the method of E. Caille,[2] a method which avoids the difficulties connected with a separation of α- and β-naphthyl ethyl ketone.

Experimental Part

α-Naphthylethylaminoacetonitrile.—Eighty grams of α-naphthyl ethyl ketone was added to 16 g. of anhydrous hydrocyanic acid in a small amount of absolute alcohol and excess dry ammonia run in during constant stirring. The mixture was then stirred at room temperature for forty-eight hours. The very dark red reaction mixture was then poured into dilute hydrochloric acid and extracted twice with ether, made strongly alkaline with concentrated ammonia solution and again extracted twice with ether. Upon evaporation of this ether extract 23 g. of the aminoacetonitrile and 40 g. of unchanged

(1) Read, THIS JOURNAL, **44**, 1748 (1922).
(2) Caille, *Compt. rend.*, **153**, 393 (1911).

ketone were recovered. The yield of aminoacetonitrile calculated on the basis of the ketone consumed was 50%.

When dry hydrogen chloride was added to a solution of the aminoacetonitrile in ether a light brown precipitate of the hydrochloride was formed. An analysis of this material after it had stood for several weeks, apparently undamaged, gave the following result.

Anal. Calcd. for $C_{14}H_{15}N_2Cl$: N, 11.36. Found: N, 10.03.

Nitrile of α-Naphthylethylhydantoic Acid.—Ten grams of potassium cyanate was added slowly to a solution of 23 g. of α-naphthylethylaminoacetonitrile in 110 cc. of glacial acetic acid. The mixture heated considerably; after standing for three-quarters of an hour it was poured into about five volumes of cold water. A yellowish-white, sticky solid separated, which recrystallized from 80% alcohol yielded 8 g. (28.5%) of long needles, m. p. 201–202°.

Anal. Calcd. for $C_{15}H_{15}ON_3$: N, 16.60. Found: N, 16.43, 16.42.

5,5-α-Naphthylethylhydantoin.—Five grams of the nitrile of α-naphthylethylhydantoic acid was heated nearly to boiling with 1:1 hydrochloric acid. The nitrile dissolved and in a few minutes a colorless crystalline solid separated, which recrystallized once from 50% alcohol yielded four grams of needles (80%), m. p. 222–223°.

Anal. Calcd. for $C_{15}H_{14}O_2N_2$: N, 11.02. Found: N, 10.85, 10.82.

Comparative studies[3] of the hydantoin with two well-known barbituric acid derivatives, barbital and amytal, were made on white rats. For this purpose 2% solutions of the sodium salts of the several compounds were injected intraperitoneally into the test animals, which were starved for twenty-four hours previous to the injections. For each dose three to five animals were used.

The amount of each compound which caused the following symptoms was noted (a) ataxia, (b) hypnosis or light sleep, M. H. D., (c) anesthesia, *i. e.*, failure to respond to any external stimuli, M. A. D. and (d) death, M. L. D.

The hydantoin produced a condition of ataxia which was similar to that noted with barbital and amytal. It did not, however, produce a state of hypnosis or of anesthesia. The results of the tests are given in Table I.

TABLE I

Compound	No. of animals	Symptoms of ataxia, mg./kg.	M. H. D., mg./kg.	M. A. D., mg./kg.	M. L. D., mg./kg.	Therapeutic index, M. L. D. / M. A. D.
Barbital	50	150	250	375	600	1.60
Amytal	40	60	90	120	300	2.20
5,5-α-Naphthylethylhydantoin	33	200	None	None	500	None

Summary

1. α-Naphthyl ethyl ketone reacts with anhydrous hydrocyanic acid and ammonia in absolute alcohol solution to form α-naphthylethylaminoacetonitrile.

(3) I am indebted to Edward E. Swanson and H. A. Shonle of the Lilly Research Laboratories, Eli Lilly & Co., for the pharmacological work published in this paper.

2. α-Naphthylethylaminoacetonitrile reacts with potassium cyanate in glacial acetic acid to form the nitrile of α-naphthylethylhydantoic acid. When this compound is heated with 1:1 hydrochloric acid it is converted into 5,5-α-naphthylethylhydantoin.

3. 5,5-α-Naphthylethylhydantoin does not possess the properties of an hypnotic.

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Studies in the Phenanthrene Series. III. Hydroxy Aldehydes and Hydroxy Ketones[1]

BY ERICH MOSETTIG AND ALFRED BURGER

The preparation of the series of hydroxyphenanthrene ketones and aldehydes described in this communication was undertaken in order to obtain the starting materials for the synthesis of phenolic β-ethylamines, amino ketones and amino alcohols of the phenanthrene series. These amino derivatives will be the subject of pharmacological investigation, as part of the program of study of the physiological action of phenanthrene derivatives which is being carried on at the University of Michigan[2] in collaboration with this Laboratory.

3-Hydroxyphenanthrene-4-aldehyde has been previously prepared by Smith[3] by the Gattermann aldehyde synthesis.

Smith used aluminum chloride as catalyst, and stated that the yield drops to 10% when zinc chloride is used. In agreement with this, our attempts to apply Adams'[4] modified Gattermann synthesis with zinc chloride to the hydroxyphenanthrenes gave very unsatisfactory results.

We made use of the Smith procedure for the preparation of the aldehydes of 2- and 9-hydroxyphenanthrenes, in the expectation that the aldehyde group would enter the 1- and 10-positions, respectively. That this actually took place was proved by converting the 2-hydroxyaldehyde to 1,2-dihydroxyphenanthrene, and the 9-hydroxyaldehyde to 9,10-phenanthrenequinone.

It was possible in most cases to carry out the preparation of the hydroxyphenanthrene ketones in two ways, by Fries rearrangement and by Friedel–Crafts reaction.

3-Acetoxyphenanthrene, treated with aluminum chloride or bromide

(1) This investigation was supported by a grant from the Committee on Drug Addiction of the National Research Council from funds provided by the Bureau of Social Hygiene, Inc.

(2) N. B. Eddy, *J. Pharmacol.*, **45**, 3 (July, 1932); and others in press.

(3) Smith, *J. Chem. Soc.*, **109**, 568 (1916).

(4) Adams and co-workers, THIS JOURNAL, **45**, 2373 (1923); **46**, 1518 (1924).