[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF NEBRASKA]

PREPARATION OF SEVERAL SUBSTITUTED HYDANTOINS[1]

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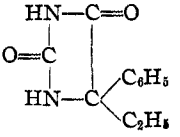
The purpose of this investigation was the preparation of several homologs of 4,4-phenyl-ethyl-hydantoin, known commercially as Nirvanol.



4,4-Phenyl-ethyl-hydantoin[2] was first used as an hypnotic in 1916. Four homologs, namely, 4,4-phenyl-propyl-, 4,4-phenyl-*iso*propyl-, 4,4-phenyl-butyl-, and 4,4-phenyl-*iso*butyl-hydantoin, have been prepared during this research. The first of these is mentioned in the patent literature.

Nirvanol and each of its homologs were prepared by two methods. By one method alkali cyanate reacted with disubstituted amino-acetonitrile.[3] According to the other method alkali hypobromites were allowed to react upon disubstituted cyano-acetamides.[4] The crucial points in the first and in the second method are the preparation of the disubstituted amino-acetonitrile and the disubstituted cyano-acetamide, respectively.

Experimental Part

First Method.—W. T. Read[5] prepared the amino-acetonitrile of Nirvanol by the action of ammonium cyanide upon the ketone in absolute alcohol. The ammonium cyanide is prepared by distilling dry hydrogen cyanide into absolute alcohol and then bubbling dry ammonia through the alcohol solution. During the course of this investigation the nitriles were prepared by this method a number of times. However, in preparing the nitriles a method was found which gives as good yields as Read's and which, it is believed, has other advantages.

Instead of going through the troublesome procedure of preparing dry liquid hydrogen cyanide the cyanohydrin was prepared, using the method of Albert.[6] In this method the cyanohydrins are prepared by the action of equimolecular parts of ammonium chloride and potassium cyanide on the ketones. The ketones were dissolved in ether above the aqueous solution. The solution was agitated vigorously for two hours. The ether layer was removed, dried and the ether distilled.

The amino-acetonitriles were prepared by dissolving the cyanohydrin in three parts of absolute alcohol, saturating the alcoholic solution with dry ammonia and allowing

[1] Presented before the Organic Division of the American Chemical Society at Ithaca, September, 1924.

[2] Wernecke, *Deutsch. med. Wochschr.*, **42**, 1193 (1916).

[3] Ger. pat. 310,427.

[4] U. S. pat. 1,285,703 (1918); Swiss pat. 72,561, 74,094 (1917).

[5] Read, THIS JOURNAL, **44**, 1746 (1922).

[6] Albert, *Ber.*, **49**, 1382 (1916).

the solution to stand for 12 hours. Better results were obtained when the mixture was placed in a bomb tube and heated at 85° for six hours.

To recover the unchanged ketone the mixture is poured into dil. hydrochloric acid and extracted with ether. The aqueous solution is then made alkaline with ammonia, whereupon the amino-acetonitrile separates as an oil. It is extracted with ether, dried, and the ether distilled. Read's method[6] was used to convert the amino-acetonitriles into the hydantoins. The yield is 60% on the basis of the recovered ketone.

Second Method.—The second method is based upon the action of alkaline hypobromites on disubstituted cyano-acetamides. The preparation of 4,4-phenyl-ethyl-hydantoin may be taken as typical of this method.

To a solution of 20 g. of phenyl-cyano-acetamide[7] (which can be prepared in a 30% yield) in 300 cc. of absolute alcohol is added 2.9 g. of sodium dissolved in 100 cc. of absolute alcohol. To the sodium salt thus formed is added 10 cc. of ethyl iodide. The whole is heated to boiling on the air-bath until the solid that was formed when the sodium was added has disappeared and the reaction is complete. About 150 cc. of the excess alcohol is distilled and the remaining solution is cooled. An excess of ice-cold distilled water is added and the phenyl-ethyl-cyano-acetamide precipitates as yellowish, flaky crystals.

The Preparation of Phenyl-Ethyl-Hydantoin.—Twelve g. of phenyl-ethyl-cyano-acetamide is added to a sodium hypobromite solution (made by dissolving 25 g. of sodium hydroxide and 11 g. of bromine in 100 g. of water) and the mixture vigorously shaken, heated just below the boiling point for about an hour and then completely cooled. Twenty cc. of freshly prepared 10% sodium sulfite solution is added and the solution is filtered. The hydantoin is precipitated by acidifying with concd. hydrochloric acid. All the hydantoins are white crystalline solids soluble in hot alcohol and boiling hot water from which they may be recrystallized.

Physiological Action.—Preliminary tests indicate that the general physiological reaction of phenyl-propyl- and phenyl-*iso*butyl-hydantoin

TABLE I

ANALYSES AND PROPERTIES OF THE HYDANTOINS

Hydantoin	Yield of alkyl-phenyl-cyano-acetamide in terms of phenyl-cyano-acetamide	M. p. of alkyl-phenyl-cyano-acetamide	Yield of phenyl-alkyl-hydantoin in terms of alkyl-phenyl-cyano-acetamide	M. p. of hydantoin	Solubility in 100 g. of water at 25° × 10^3	—Nitrogen— Calcd.	—Nitrogen— Found	Physiological action
	%	°C.	%	°C.		%	%	
Phenyl-ethyl-	60	117	75	196	13.8	13.7	13.4	+
Phenyl-propyl-	70	120	75	165–6	17.5	12.3	12.3	+
Phenyl-*iso*propyl-	60	130	70	211	2.2	12.3	11.9	−
Phenyl-butyl-	75	126	93	204–5	1.60	12	12.3	−
Phenyl-*iso*butyl-	70	100	80	177–8	3.8	..	..	+

[7] Hessler, *Am. Chem. J.*, **32**, 120 (1904).

is about the same as that of Nirvanol, whereas phenyl-*iso*propyl- and phenyl-butyl-hydantoin have no hypnotic effect. These results, together with the observations of Lumière and Perrin[8] working with dialkyl hydantoins, seem to show that the hypnotic reaction is concerned in some way with the number of carbon atoms in a compound as well as with their arrangement. A further study of the relationship of the hypnotic action to the solubilities of these hydantoins indicates that they are exceptions to the general conditions proposed by H. Meyer[9] as being necessary for a narcosis reaction.

Summary

1. Four homologs of 4,4-phenyl-ethyl-hydantoin were prepared by each of the following general methods: (1) the action of alkali cyanate with amino-aceto-nitriles; (2) the action of alkali hypobromites with disubstituted cyano-acetamides.

2. The better yields (those reported in Table I) were obtained with the disubstituted cyano-acetamide method.

3. Melting-point determinations of the mixed products obtained by the two methods showed them to be identical.

4. The solubilities, the melting points and the yields of the several hydantoins are given.

5. Preliminary tests seem to show that there is a wide variation in the narcotic action of the hydantoins.

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ANTIMONYL TARTRATES OF SOME ORGANIC BASES

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In attempting to develop trypanocidally active antimony compounds which might be useful as substitutes for tartar emetic (potassium antimonyl tartrate), some antimonyl tartrates have been studied in which organic radicals replace the potassium atom of tartar emetic. To this end, alkyl antimonyl tartrates and antimonyl tartrates of aliphatic and aromatic amines have been compared with the potassium salt. The use of a series of substitution products of aniline for this purpose makes it possible to vary the nature of the organic base over a wide range without altering the mode of combination between the tartrate and the base. On the other hand, when the alkyl and aniline antimonyl tartrates are employed, different types of compounds, esters and salts, are being compared. The

[8] Lumière and Perrin, *Bull. soc. chim.*, [4] **35-36**, 1022 (1924).

[9] Meyer, *Chem. centr.*, **1899**, II, 64; from *Arch. exptl. Path. Pharm.*, **42**, 109.