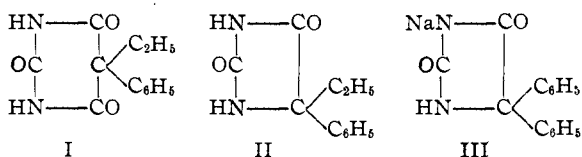


[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Researches on Phenylhydantoin¹BY HENRY R. HENZE AND LOREN M. LONG²

Probably in no branch of chemical investigation have attempts to relate chemical constitution to physiological activity met with more success than in the search among the barbiturates for satisfactory soporifics. Because of the structural similarity of barbituric acid and hydantoin, production of a useful derivative of the former has been reflected at times in an effort to prepare an analogous derivative of the latter. Thus the synthesis³ and subsequent recognition of the activity of ethylphenylbarbituric acid (I), Phenobarbital, preceded the preparation⁴ and testing of ethylphenylhydantoin (II), Nirvanol. The barbiturate

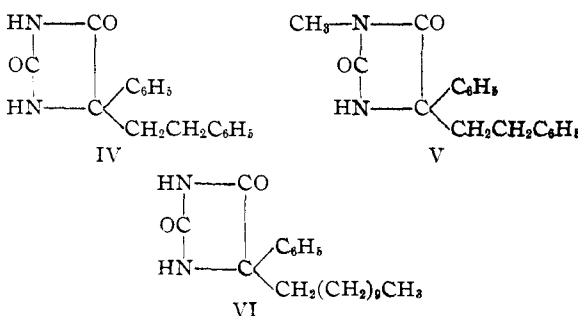


(I) is a powerful hypnotic whose sedative action is manifested rather quickly and without an initial period of excitement, hence is useful in treatment of epilepsy. At first the hydantoinate (II) was considered to be a useful hypnotic, but unfavorable aftereffects frequently followed its use and the drug fell into disrepute. More recently, however, this compound again came into use as an anticonvulsant in the treatment of chorea (St. Vitus's dance).

In later years research among the hydantoins has continued but seemingly as yet no member useful as an hypnotic has been obtained. However, diphenylhydantoin,⁵ first prepared in 1908 and later rejected as having relatively little hypnotic effect, now in the form of its sodium salt (III), Dilantin, has found use as an anticonvulsant in the treatment of epilepsy.⁶ The activity of this salt (III) is of interest because: first, it em-

phasizes the fact that a compound whose synthesis had been reported years ago nevertheless may have been tested pharmacologically but incompletely or not at all; and, second, research on hydantoins thus is shown not to be dependent upon, or completely covered by, investigation of analogous barbiturates.

We have prepared examples of five types of hydantoin derivatives in this investigation and all compounds contain one or more phenyl groups and are thus to that extent related to 5,5-diphenylhydantoin. Thus, 5-phenethyl-5-phenylhydantoin (IV) has been prepared from benzylacetophenone utilizing the procedure of Bucherer⁷; its structural relationship to Nirvanol (II) also is evident. From (IV) a soluble sodium salt has been ob-



tained and subsequently converted into the 3-methyl derivative (V). The production of 5-phenyl-5-(*n*-undecyl)-hydantoin (VI) involves much the largest alkyl group utilized as yet in hydantoin formation. Likewise, preparation of 5-methyl-5-styrylhydantoin⁸ (VII) and three *n*-alkyl homologs is of special interest because certain other unsaturated ketones, in which the ethylenic linkage is conjugated with the carbonyl group, in forming hydantoins add hydrogen cyanide also to the double bond.

(1) Presented in part before the Division of Medicinal Chemistry at the 97th meeting of the American Chemical Society at Baltimore, Maryland, April 4-6, 1939. The statements made at that meeting concerning the synthesis of bis-5-(5-phenylhydantoin) and methylene-bis-5-(5-phenylhydantoin) are withdrawn because of our inability consistently to reproduce results. However, synthesis of methylene-bis-5-(5-phenylhydantoin) by a wholly different and unique method is included herein.

(2) Parke, Davis and Company Research Fellow.

(3) Baeyer and Co., German Patent 247,952 (1912).

(4) Chem. Fabrik. v. Heyden, A.-G., German Patent 309,508 (1919).

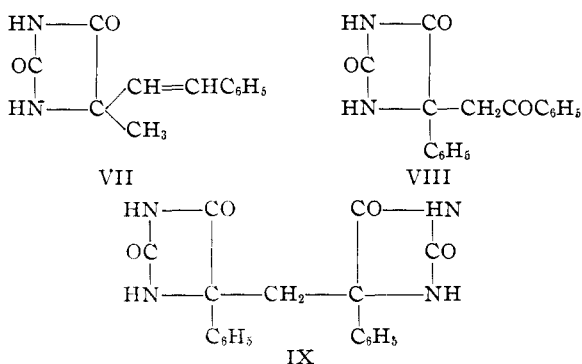
(5) Biltz, *Ber.*, **41**, 1379 (1908).

(6) Putnam and Merritt, *Science*, **85**, 525 (1937).

(7) Bucherer and Lieb, *J. prakt. Chem.*, [2] **141**, 5 (1934).

(8) Although the statement "the syntheses of 5-ethyl-5-styrylhydantoin (from benzal-methyl ethyl ketone) and of its 5-methyl analog represent the initial preparation of a new type of unsaturated hydantoin derivative" appeared in the official abstracts of the Baltimore meeting, Marsh and Lazzell [*THIS JOURNAL*, **62**, 1306 (1940)] include the methyl derivative in their note on "Some New 5,5-Disubstituted Hydantoins." It should be noted that these investigators list m. p. 217° (cor.) (dec.) for the methyl styrylhydantoin, obtained in 12% yield. In our experience, the crude product is obtained in 74% yield and melts 214-220°; after recrystallization from alcohol, m. p. 222-223° (cor.). More serious discrepancies between other data reported in this note and our own findings will be reported in a subsequent publication.

Synthesis of a bis-hydantoin (IX), related structurally to dibenzoylmethane but which we have been unable to obtain, except in minute amount, directly from the latter by utilization of the Bucherer⁷ process, has been accomplished in a unique fashion. Benzaldehyde was converted into 5-phenylhydantoin and the latter brominated to form 5-bromo-5-phenylhydantoin. This bromo compound is extremely reactive (and unstable) but could be condensed with acetophenone to form the 5-phenyl-5-phenacylmethyl-hydantoin (VIII). Finally, the latter was converted into methylene-bis-5-(5-phenylhydantoin) (IX) using a new modification⁹ of the Bucherer procedure.



Through the courtesy of Parke, Davis and Company, Detroit, Michigan, certain of these new di-substituted hydantoins have been tested for possible hypnotic and/or anticonvulsant activity. Whereas the sodium salt of 5-phenethyl-5-phenyl-hydantoin exhibits a strong anticonvulsant action, its N-methyl derivative is inactive. We wish to thank Parke, Davis and Company for their financial aid and generous assistance in this work.

Experimental

Preparation of 5-Phenethyl-5-phenylhydantoin.—Following the procedure of Bucherer,⁷ 21 g. of phenethyl phenyl ketone, 28.8 g. of ammonium carbonate, 9 g. of potassium cyanide and 275 cc. of 50% ethyl alcohol were placed in a flask, provided with a reflux condenser, and warmed at 60° for fifteen hours; a clear solution of light yellow color resulted. On cooling, shining crystals began to separate and soon the entire mixture set to a jelly of lard-like consistency. The mass was filtered on a Büchner funnel, then dried at 110° for thirty minutes; weight 37 g.; m. p. 134°. The product was dissolved in 5% sodium hydroxide solution, filtered from unreacted ketone (2 g.), treated with charcoal, and was reprecipitated by acidification with hydrochloric acid. Recrystallization of the white

solid from 60% ethyl alcohol yielded 17 g. (67% of the theoretical) of light, fluffy crystals; m. p. 201° (cor.).

Anal. Calcd. for C₁₇H₁₈N₂O₂: C, 72.86; H, 5.71; N, 10.00. Found: C, 73.20; H, 5.67; N, 10.01.

To prepare the sodium salt of this hydantoin, 12 g. of the latter was dissolved in the equivalent amount of sodium hydroxide solution and evaporated to dryness, in a vacuum during fourteen hours at 60°, forming a cream-colored solid which, after being washed with absolute ethanol and drying, weighed 12 g. This salt is readily soluble in water, from which a slight precipitate separates on standing but redissolves on warming. The sodium salt is not hygroscopic to any appreciable extent.

Preparation of 3-Methyl-5-phenethyl-5-phenylhydantoin.—Ten grams of 5-phenethyl-5-phenylhydantoin was dissolved in 50 cc. of absolute ethanol and treated with 0.8 g. of sodium. To the solution was added dimethyl sulfate (10% excess over two equivalents) and the mixture was refluxed for two and one-half hours. The excess of methylating agent was destroyed by addition of alkali and the solution then acidified with hydrochloric acid, causing the precipitation of a solid. The latter was filtered, warmed with 5% sodium hydroxide solution, again filtered and recrystallized from 80% ethyl alcohol. A yield of 8 g. (76%) was obtained of the methyl derivative; m. p. 144° (cor.).

Anal. Calcd. for C₁₈H₁₈N₂O₂: C, 73.47; H, 6.12; N, 9.52. Found: C, 73.60; H, 6.22; N, 9.62.

Preparation of 5-Phenyl-5-(*n*-undecyl)-hydantoin.—Thirteen grams of phenyl *n*-undecyl ketone¹⁰ was added to 150 g. of fused acetamide⁹ and, in turn, 4.5 g. of potassium cyanide and 14.4 g. of ammonium carbonate. The non-homogeneous mixture was placed in a monel metal autoclave and heated at 110° for fifteen hours. After cooling, the reaction mixture was stirred with 800 cc. of water and acidified with hydrochloric acid. The suspended solid was removed by filtration and was redissolved in 400 cc. of warm 5% sodium hydroxide solution; filtration of this alkaline solution did not yield any unreacted ketone. Acidification of the filtrate with hydrochloric acid caused the hydantoin to separate as an oil which solidified quickly. After two recrystallizations from petroleum ether and two from acetone, the hydantoin melted at 125° (cor.); the yield of purified material was 9 g. (54% of the theoretical).

Anal. Calcd. for C₂₀H₃₀N₂O₂: C, 72.69; H, 9.15; N, 8.47. Found: C, 72.80; H, 9.09; N, 8.61.

Preparation of 5-Methyl-5-styrylhydantoin.—To produce this unsaturated hydantoin derivative, 20 g. of benzalacetone was dissolved in 140 cc. of 95% alcohol and mixed with a solution in 100 cc. of water of 39 g. of ammonium carbonate and 12.5 g. of potassium cyanide. The mixture was warmed for fifteen hours at 59° before being evaporated to about one-third volume and acidified with hydrochloric acid. A brownish-yellow solid was removed by filtration, washed, and dried; yield, 22 g. (74%); m. p. 214–220°. After recrystallization from ethyl alcohol, 18 g. of white crystalline product remained; m. p. 222–223° (cor.).¹¹ An alcoholic solution of methylstyrylhydantoin readily decolorizes bromine solution.

(10) Purchased from Eastman Kodak Co.

(11) Marsh and Lazzell [THIS JOURNAL, **62**, 1306 (1940)] report m. p. 217° d.

(9) Reported before the Division of Organic Chemistry at the 101st meeting of the American Chemical Society at St. Louis, Missouri, April 11, 1941, "A Modification of the Bucherer Process for Synthesizing 5,5-Disubstituted Hydantoins from Ketones," by Heze and Long.

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.75; H, 5.70; N, 13.07.

Preparation of 5-Ethyl-5-styrylhydantoin.—In forming this compound, 20 g. of ethyl styryl ketone was dissolved in 100 cc. of 95% alcohol and the solution mixed with one prepared by dissolving 36 g. of ammonium carbonate and 11 g. of potassium cyanide in 70 cc. of water. The solution was warmed for fifteen hours at 60°, concentrated to one-third volume and acidified. A light-brown colored gum separated and was heated with 100 cc. of 25% ethyl alcohol. From this solution was obtained 18 g. (62.5% yield) of white, needle-shaped crystals melting at 195–196°. This hydantoin could not be secured in a state of analytical purity by recrystallization merely from organic solvents. However, by solution in 3% sodium hydroxide, treatment with Norit and reprecipitation with acid, material was obtained which could be recrystallized satisfactorily from ethyl alcohol; yield, 14 g. of hydantoin, melting at 211°, but upon cooling, resolidification and subsequent fusion, melting at 214° (cor.); this m. p. was not altered by further treatment. This unsaturated hydantoin adds bromine, although apparently not so readily as does the methyl analog.

Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.82; H, 6.12; N, 12.16. Found: C, 68.11; H, 6.22; N, 12.24.

Preparation of 5-*n*-Propyl-5-styrylhydantoin.—Thirteen grams of *n*-propyl styryl ketone,¹² 22 g. of ammonium carbonate, 6.8 g. of potassium cyanide and 150 cc. of 50% alcohol were heated for twelve hours at 60°. After concentration and acidification, a gummy mass separated and was dissolved in 200 cc. of 5% sodium hydroxide solution, treated with charcoal and reprecipitated by acidification. The hydantoin was twice recrystallized from acetone-water and once from methanol. Thus was obtained 9.8 g. (54% yield) of hydantoin; m. p. 171–174° (cor.).

Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.84; H, 6.60; N, 11.46. Found: C, 68.69; H, 6.67; N, 11.29.

Preparation of 5-*n*-Butyl-5-styrylhydantoin.—A solution was prepared from 9.4 g. of *n*-butyl styryl ketone,¹³ 14.4 g. of ammonium carbonate, 4.5 g. of potassium cyanide and 100 cc. of 50% ethyl alcohol, and warmed for twelve hours at 60°. After the typical treatment of the reaction mixture, 10 g. of hydantoin, melting at 125–130° (cor.), was obtained.

Anal. Calcd. for $C_{15}H_{18}N_2O_2$: C, 69.75; H, 7.02; N, 10.84. Found: C, 69.63; H, 7.08; N, 10.79.

Preparation of Methylene-*bis*-5-(5-phenylhydantoin)

A. Synthesis of 5-Bromo-5-phenylhydantoin.¹⁴—From 35.2 g. of 5-phenylhydantoin, and 40 g. of bromine in 200

cc. glacial acetic acid was obtained 25–35 g. of 5-bromo-5-phenylhydantoin, melting at 210–215°.

B. Synthesis of 5-Phenacyl-5-phenylhydantoin.—Twenty-five and one-half grams (0.1 mole) of 5-bromo-5-phenylhydantoin was mixed with 24 g. (0.2 mole) of acetophenone and heated to about 70°; the reaction mixture became yellow in color and much hydrogen bromide was evolved. After a few minutes the heat of reaction caused the mixture to become very hot and the mass became dark red in color. After thirty minutes the mass was stirred with 40 cc. of ether and filtered. The solid was recrystallized twice from acetic acid yielding 23 g. (78%) of white crystalline material melting at 221° (cor.).

Anal. Calcd. for $C_{17}H_{14}N_2O_3$: C, 69.37; H, 4.80; N, 9.52. Found: C, 69.20; H, 4.85; N, 9.69.

C. Synthesis of Methylene-*bis*-5-(5-phenylhydantoin).—To obtain this compound, 14.7 g. (0.05 mole) of 5-phenacyl-5-phenylhydantoin dissolved in 150 cc. of propylene glycol⁹ at 80°, was placed in a monel metal bomb and after a solution of 4.5 g. of potassium cyanide in 5 cc. of warm water and 14.4 g. of ammonium carbonate had been added, the container was closed and heated at 110° for ten hours. When the bomb had been cooled and opened, fine needle-like crystals were present. These were obtained by filtration, washed thoroughly, twice with boiling acetone and once with boiling ethyl alcohol. The residue, after drying at 110°, weighed 6 g. and melted with decomposition at 358°. This hydantoin is soluble in alkaline solution and insoluble in most organic solvents, but may be recrystallized from propylene glycol.

The filtrate from this main portion of the hydantoin was diluted with 200 cc. of water and acidified with hydrochloric acid forming a thick precipitate which was filtered and dried; weight 7.5 g.; m. p. 290°. This material was boiled with 400 cc. of water for one hour and filtered. Thus was obtained an additional 1.3 g. of the *bis*-hydantoin; the total yield of 7.3 g. represents 40% of the theoretical amount.

Anal. Calcd. for $C_{19}H_{16}N_4O_4$: C, 62.64; H, 4.43; N, 15.37. Found: C, 62.70; H, 4.27; N, 15.45.

Summary

1. Nine new hydantoins, illustrating five different types of 5,5-disubstituted hydantoins, have been prepared.
2. Strong anticonvulsant activity is exhibited by 5-phenethyl-5-phenylhydantoin, whereas no activity is evidenced by its *N*-methyl derivative.

AUSTIN, TEXAS

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(12) Harries and Bromberger, *Ber.*, **35**, 3089 (1902).

(13) Auwers and Voss, *ibid.*, **42**, 4421 (1909).

(14) Gabriel, *Ann.*, **350**, 118 (1906).