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

# SYNTHESIS OF CERTAIN 5-(2-ALKOXYETHYL)-5-PHENYLHYDANTOINS[1]

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For a long time the only hydantoins reported as possessing an oxy-substituent attached to the 5-position of the heterocyclic nucleus were of either the 5-alkoxy-5-phenylhydantoin or the 5-phenoxy-5-phenylhydantoin types. In 1936 there was reported (1) the synthesis of a few members of the 5-alkoxymethyl-5-alkylhydantoin series and of 5-ethoxymethyl-5-phenylhydantoin. Examples of 5-phenoxymethyl-5-alkyl (or 5-phenyl) hydantoins were next announced (2). The latter resembled the alkoxymethyl derivatives in evidencing activity as anticonvulsants, rather than, as had been anticipated, as hypnotics. In an attempt to increase hypnotic effect in hydantoin derivatives, several 5-[1-(2-chloro-1-chloromethylethyl)-oxy]ethyl-5-alkyl (or 5-phenyl) hydantoins were synthesized (3). This series thus introduced $\alpha$-substitution into the well-known drug, Nirvanol (5-ethyl-5-phenylhydantoin) (4); however, the 5-phenyl analog proved to be highly toxic[3] due, perhaps, to the halogen content. In a partial attempt to test this conclusion, representatives of the 5-(1-methylpropoxy)ethyl-5-alkylhydantoin series were produced (7). Upon testing one example, it was found to be inactive.

More recently, we have returned to the synthesis of hydantoins containing alkoxyalkyl and alkyl or phenyl substituents (8). Three of these compounds, namely, 5-isopropoxymethyl-5-phenylhydantoin, 5-propoxymethyl-5-phenylhydantoin and 5-ethoxymethyl-5-phenylhydantoin, proved to be the most promising, with respect to efficiency as anticonvulsants, of all hydantoins containing an ether-grouping substituent as yet produced.

Obviously, it was of interest to attempt the synthesis of certain hydantoins isomeric with those enumerated above. It was, therefore, the purpose of the present investigation to prepare 5-(2-methoxyethyl)-5-phenylhydantoin and a few of its homologs.

The first five members of the series of 5-(2-alkoxyethyl)-5-phenylhydantoins have been synthesized by interaction of the corresponding $\beta$-alkoxypropiophenones (9) with potassium cyanide and ammonium carbonate. Each of these hydantoins exhibited some degree of activity as anticonvulsants, the 2-methoxyethyl-5-phenylhydantoin being most active. However, all are less active than are the isomeric members of the alkoxymethyl series.

Since acrylophenone was available,[4] an effort was made to convert it into

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[1] From the M. A. thesis of R. E. Leslie, June, 1948.

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[3] In almost every case, testing for anticonvulsant activity in these hydantoin derivatives (5, 6) was obtained through the courtesy of Parke, Davis & Co., Detroit, Michigan, to whom our sincere appreciation is expressed.

[4] As a by-product of the preparation of the alkoxypropiophenones, especially from attempted distillation of $\beta$-ethoxypropiophenone.

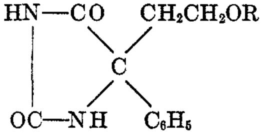
5-phenyl-5-vinylhydantoin. However, the actual product of this attempt proved to be 5-(2-cyanoethyl)-5-phenylhydantoin. This behavior of this vinyl ketone appears to be analogous to that of carvone (10) and of four substituted $\Delta^2$-cyclohexenones (11) in that, under the same conditions of reaction, these unsaturated ketones also were converted into cyano-substituted hydantoins.

## EXPERIMENTAL

The *5-(2-alkoxyethyl)-5-phenylhydantoins* were prepared according to the Bucherer method (12) by mixing 1 equivalent of a crude β-alkoxypropiophenone with 1.25 equivalents of potassium cyanide and 4–5 equivalents of ammonium carbonate (U.S.P. cubes) in 6–9 volumes of 70% ethyl alcohol. The mixture was heated in a water-bath at about 60–62° for periods of nine to twelve hours. Filtration from insoluble, inorganic material gave a filtrate which was acidified with concentrated hydrochloric acid. Usually, some solid, organic material precipitated; additional product was obtained by concentration of the filtrate by means of an air jet directed upon its surface.

TABLE I

5-(2-ALKOXYETHYL)-5-PHENYLHYDANTOINS



| R | M.P., °C. | YIELD, % | NITROGEN, % Calc'd | NITROGEN, % Found | CARBON, % Calc'd | CARBON, % Found | HYDROGEN, % Calc'd | HYDROGEN, % Found |
|---|---|---|---|---|---|---|---|---|
| $CH_3$ | 149–150 (dec.) | 70 | 11.96 | 11.92 | 61.52 | 61.11 | 6.03 | 6.28 |
| $C_2H_5$ | 123–124 (dec.) | 29 | 11.29 | 11.37 | 62.88 | 62.76 | 6.50 | 6.70 |
| $C_3H_7$ | 140–141 (dec.) | 74 | 10.68 | 10.72 | 64.10 | 64.14 | 6.92 | 7.08 |
| $CH(CH_3)_2$ | 136–137 (dec.) | 69 | 10.68 | 10.88 | | | | |
| $C_4H_9$ | 147.0–147.5 (dec.) | 49 | 10.14 | 10.22 | | | | |

The hydantoins were partially purified by solution in 10% sodium hydroxide solution and reprecipitation by addition of solid carbon dioxide. Further purification was achieved by recrystallizations from 50% ethyl alcohol or benzene-Skellysolve mixtures. Data obtained for melting points and from analyses of the hydantoins appear in Table I.

In the case of the *ethoxyethyl member*, the product after recrystallization from diluted alcohol melted at 104–105°. A sample of this material was dried to constant weight in an oven at 75° under 30-inch vacuum and then was found to melt at 123–124° (dec.). Another portion of the material of m.p. 104–105° was dissolved in a large volume of benzene, and the solution was subjected to distillation until the distillate became clear. The residual solution was diluted with anhydrous Skellysolve; material crystallized from solution and had the m.p. 123–124° (dec.). Such material was then recrystallized from 50% ethyl alcohol and, after drying in the air, melted at 104–105°. A weighed sample of the latter was dried in the vacuum oven and suffered a loss in weight of 7.03%; the calculated loss of water for a monohydrated 5-(2-ethoxyethyl)-5-phenylhydantoin is 6.77%.

*Anal.* Calc'd for $C_{13}H_{16}N_2O_3$: C, 62.88; H, 6.50; N, 11.29.
Found: C, 62.76; H, 6.70; N, 11.37.

Similarly, the recrystallized *isopropoxyethyl analog* melted at 112–114° (out of 50% alcohol), but melted at 136–137° (dec.) after drying to constant weight at 75° in an efficient vacuum oven. Duplicate determinations of the loss of weight of the product melting at

112–114° gave 6.32% and 6.54% (average 6.43%); the calculated loss of water for a monohydrated 5-[2-(1-methylethyl)oxyethyl]-5-phenylhydantoin is 6.43%. In this case also, water of hydration could be removed by partial distillation of a solution of the hydrate in anhydrous benzene; the crystalline product recovered from such treatment with benzene melted at 136–137° (dec.).

*Preparation of 5-(2-cyanoethyl)-5-phenylhydantoin.* Seven grams of impure acrylophenone,[5] 4.3 g. of potassium cyanide and 16 g. of ammonium carbonate in 70% ethyl alcohol solution was heated at 62° for twelve hours. The reaction mixture was acidified, causing precipitation of the product. The latter was dissolved in dilute sodium hydroxide solution, from which it was reprecipitated upon the addition of solid carbon dioxide. Further purification was difficult and required repeated recrystallizations from diluted alcohol and, finally, fractional recrystallization from water in order to obtain the constant m.p. 186–189°.

*Anal.* Calc'd for $C_{12}H_{11}N_3O_2$: N, 18.32. Found: N, 18.35.

*Preparation of 5-(2-carboxyethyl)-5-phenylhydantoin.* Approximately 2 g. of 5-(2-cyanoethyl)-5-phenylhydantoin was refluxed in 30 ml. of 25% hydrochloric acid for two hours. Upon cooling, a precipitate formed and was removed by filtration. It was dissolved in an aqueous solution of sodium bicarbonate and reprecipitated by addition of hydrochloric acid. After drying, the hydantoin derivative melted at 215°.

*Anal.* Calc'd for $C_{12}H_{12}N_2O_4$: Equiv. wt., 248.2; N, 11.28.
Found: Equiv. wt., 252.5; N, 11.15.

## SUMMARY

1. Five examples of 5-(2-alkoxyalkyl)-5-phenylhydantoin, a new type of hydantoin derivative, have been synthesized.

2. Acrylophenone has been converted into 5-(2-cyanoethyl)-5-phenylhydantoin, and the latter subsequently hydrolyzed to 5-(2-carboxyethyl)-5-phenylhydantoin.

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[5] Obtained as the distillate in an attempted distillation of β-ethoxypropiophenone and identified as such by the m.p. of its phenylhydrazone.