# New Compounds: Synthesis of 1-Aryl Substituted Hydantoins

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**Abstract** □ A series of 1-aryl substituted hydantoins was synthesized by condensation of monosubstituted ureas and glyoxal. The method is facile and applicable for the preparation of 1-alkyl substituted hydantoins as well as analogs of the compounds.

**Keyphrases** □ Hydantoins, 1-aryl substituted—synthesis, condensation of monosubstituted ureas and glyoxal □ 1-Aryl-substituted hydantoins—synthesis, condensation of monosubstituted ureas and glyoxal

Because hydantoins manifest a variety of biological activities and function as intermediates in the preparation of some important organic compounds, their chemistry has been investigated extensively. Few reports of the chemistry of 1-aryl substituted hydantoins[1] (1), however, are available. This fact may be ascribed to the difficulty in synthesizing these compounds by the usual procedure involving reaction of an *N*-substituted glycine and an isocyanate.

This report describes a synthetic method for the synthesis of a few representative 1-aryl substituted hydantoins. The method is facile, unequivocal, and applicable to the synthesis of alkyl or aryl analogs of the compounds listed in Table I. It consists of an acid-catalyzed condensation of a substituted urea with glyoxal in relatively polar medium. Some small quantities (less than 5%) of a 1,3-disubstituted tetrahydroimidazo[4,5-*d*]imidazole-2,5-dione (2) and a 3-substituted hydantoin which were formed along with the 1-substituted isomer, were separated simply by fractional crystallization.

The structures of the compounds were elucidated by elemental analysis and spectral data. The NMR spectra were particularly useful both for determining the relative quantity of 1- and 3-substituted isomers present in the product of the reaction and for determining their structures. The peak positions at $\delta$ 4.6 and 4.4 (using trifluoroacetic acid as a solvent and sodium 2,2-dimethyl-2-silapentane-5-sulfonate as a reference) for $CH_2$ were assigned to 1- and 3-substituted hydantoins, respectively, based on comparison with the spectra of authentic samples of 3-substituted hydantoins (3).

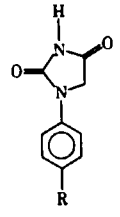
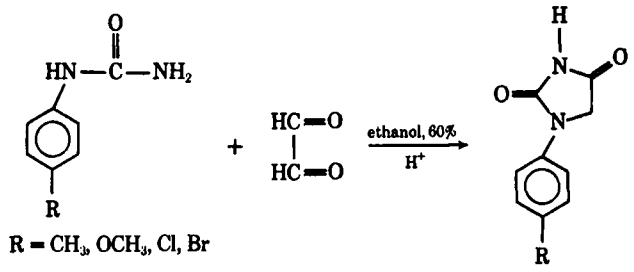


Table I—Data for 1-Substituted Hydantoins

| Number | R | Yield, % | Melting Point | Formula | Analysis, % Calc. | Found |
|---|---|---|---|---|---|---|
| I | $CH_3$ | 43 | 212–214° | $C_{10}H_{10}N_2O_2$ | C 63.15 | 63.29 |
| | | | | | H 5.30 | 5.26 |
| | | | | | N 14.47 | 14.73 |
| II | $OCH_3$ | 30 | 197–198° | $C_{10}H_{10}N_2O_3$ | C 58.25 | 58.30 |
| | | | | | H 4.85 | 5.10 |
| | | | | | N 13.59 | 13.21 |
| III | Cl | 30 | 231–233° | $C_9H_7ClN_2O_2$ | C 51.32 | 51.22 |
| | | | | | H 3.35 | 3.36 |
| | | | | | N 13.30 | 13.66 |
| IV | Br | 35 | 235–237° | $C_9H_7BrN_2O_2$ | C 42.35 | 42.27 |
| | | | | | H 2.74 | 3.01 |
| | | | | | N 10.98 | 10.76 |

Four *para*-substituted 1-phenylureas, varying in electronic and steric properties, were prepared as representatives for the synthesis of 1-substituted hydantoins. The substituents are $CH_3$, $OCH_3$, Br, and Cl (Scheme I). The Hammett $\sigma$ values for the first two groups are about the same; for Cl and Br, they are identical. The van der Waals' radii for $CH_3$ and Br are about the same. An analysis of the experimental results using reactants containing such electronic and steric factors is envisaged to contribute both to the synthetic and mechanistic aspects of the urea–glyoxal condensation reaction. So far, the data obtained from this particular series of reactions seem to indicate that

[1] The report by A. Hill *et al.*, *J. Amer. Chem. Soc.*, **44**, 2357(1922), of the synthesis of 3-substituted hydantoins, erroneously designated them as 1-substituted hydantoins.




*Scheme I*

the nature or the yield of the reaction products is not influenced significantly by either factor.

## EXPERIMENTAL[3]

The preparation of compounds listed in Table I is exemplified by the following method described for 1-*p*-methylphenylhydantoin (I).

To a hot solution of 3.0 g. (0.02 mole) of *p*-tolylurea in 50 ml. of 50% ethanol was added 1.56 g. (0.02 mole) of 80% glyoxal, followed by 10 ml. of a 10% solution of hydrochloric acid in ethanol. The solution was heated under reflux for 6–10 hr. A solid that formed was separated from the hot reaction medium to give 1.05 g. of first crop, whose NMR spectrum indicated that it was a mixture of I containing less than 5% 1,4-di-*p*-tolyltetrahydroimidazo[4,5-*d*]imidazole-2,5-dione. Crystallization of this crop from methanol gave 0.9 g. of pure I. The filtrate from the reaction mixture was allowed to remain at room temperature for about 2 hr., at which time an additional 0.4 g. of solid was separated. This crop was identified to be I. A third crop, 0.5 g., obtained after complete evaporation of filtrate, contained about 10% of the 3-substituted isomer of I. Crystallization of this crop from methanol gave 0.3 g. of pure I. The combined yield of I was 1.6 g. (43%), m.p. 212–214°. Microanalysis is recorded in Table I.

[3] Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. The NMR spectra were determined on a Perkin-Elmer R-12. Sodium 2,2-dimethyl-2-silapentane-5-sulfonate was used as a reference; trifluoroacetic acid was used as a solvent except for Compound II for which dimethyl sulfoxide was used. The IR spectra were determined in KBr disk with a Beckman IR-8 instrument.

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# *COMMUNICATIONS*

## Effect of Chain Length in Homologous Series of Anionic Surfactants on Irritant Action and Toxicity

**Keyphrases** □ Chain length effect—irritant action and toxicity of homologous series of anionic surfactants □ Surfactants, anionic—effect of chain length in homologous series on irritant action and toxicity □ Toxicity, anionic surfactants—effect of chain length in homologous series □ Irritant action, anionic surfactants—effect of chain length in homologous series □ Skin—effect of chain length of anionic surfactants on swelling and irritant action

*Sir:*

Among the investigations into the irritant action and toxicity of homologous series of anionic surfactants containing a single normal alkyl chain are the following. Choman investigated the swelling of human skin in solutions of sodium alkyl sulfates (1) and the swelling of dermal collagen of calf in sodium soaps (2). Edwards (3) studied the effect of sodium soaps on the lysis of red blood cells and on segments of earthworms, while Emery and Edwards (4) studied their irritant action on human skin. Gale and Scott (5) investigated the intraperitoneal and oral toxicity of sodium alkyl sulfates as well as their effects on various types of muscles. In these and other investigations, the greatest effects among the sodium alkyl sulfates ranging from octyl to octadecyl were shown by the dodecyl sulfate. In the series of soaps ranging from sodium octanoate to stearate, sodium laurate displayed the highest activity. Representative curves are shown in Figs. 1 and 2. Figure 1 refers to the net swelling, *i.e.*, swelling in the surfactant solutions minus swelling in pure water, measured as increase in thickness. The surfactant solutions were at or slightly above the CMC.

The purpose of this communication is to present a hypothesis to explain the maximum effectiveness observed for intermediate members of the homologous series. Maxima or minima in the relationship between two variables often arise from the effect of two opposing factors on these variables, one of which tends to enhance the relationship while the other tends to diminish it. In the present case, one of the two factors affecting the relationship between the length of the alkyl chain of