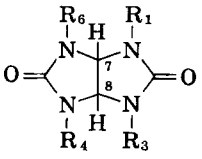
Imidazomidazoles II. Structural Features Affecting Formation of Hydantoins or Tetrahydroimidazo[4,5-*d*]imidazole-2,5-diones

By JAY NEMATOLLAHI and ROGER KETCHAM

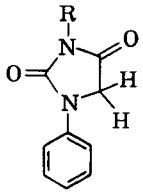
A series of *N*-aryl and *N*-alkyl substituted hydantoins were synthesized by condensation of substituted ureas with glyoxal. The molecular structure of the hydantoins was elucidated, and the influence of steric and electronic factors responsible for formation of only one of the two possible isomers was studied.

In an earlier paper (1) on the acid-catalyzed alkyl- and arylurea glyoxal condensation, the authors observed formation of 1-arylhydantoins (II) in addition to or to the exclusion of the bicyclic products (I), whereas with urea, methylurea, and 1,3-dimethylurea only the bicyclic products were obtained.

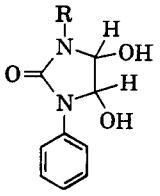
This research was undertaken to determine the structural features which give rise to the bicyclic products or hydantoins. Also of interest was the fact that only 1-arylhydantoins were obtained from either phenylurea or 1-phenyl-3-methylurea rather than the isomeric 3-arylhydantoins.



I



IIa, R = H
IIb, R = CH_3

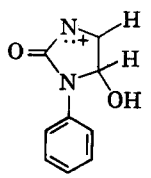


III

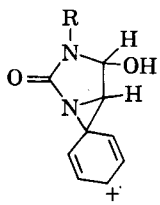
Consideration of the possible reaction path suggested that an intermediate, 4,5-dihydroxy-2-imidazolone (III), might be involved. A product of analogous structure has been reported (2) from the condensation of urea and glyoxal.

One might expect if the dehydration proceeds *via* a carbonium ion, as is common in acid-catalyzed reactions (3), that the intermediate should be IV, stabilized by the adjacent more basic unsubstituted or alkyl substituted nitrogen. This, however, should lead to 3-phenylhydantoins.

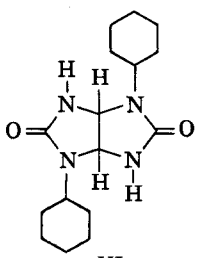
The possibility of a phenyl group participation analogous to that proposed in the solvolysis of 3-phenyl-2-butyl *p*-toluenesulfonates (4) then was considered. This system (V), however, involves phenyl on nitrogen, and there exists no previous reference to phenonium ions involving a phenyl group bound to nitrogen. To determine if the course of the reaction is determined by some such phenyl group participation, the condensations of glyoxal with cyclohexyl- and 1-methyl-3-cyclohexylurea were studied. In addition to bicyclic products VI, VII, and VIII, both condensations afforded hydantoins (IX and X) in which the larger cyclohexyl group was found on the number one nitrogen. The identity of these compounds was determined by comparing their infrared and NMR spectra with those of 1-cyclohexylhydantoin (5) and 1-cyclohexyl-3-methylhydantoin prepared from *N*-cyclohexylglycine and methyl isocyanate. Thus, neither the formation of the hydantoins nor the orientation of the substituents is specifically associated with the presence of a phenyl group.



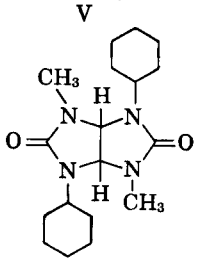
IV



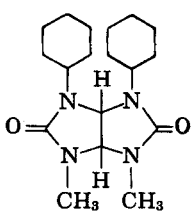
V



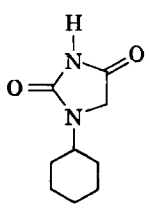
VI



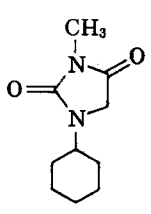
VII



VIII



IX



X

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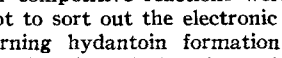
Previous paper: Nematollahi, J., and Ketcham, R., *J. Org. Chem.*, **28**, 2378(1963).

A series of competitive reactions were designed in an attempt to sort out the electronic and steric factors governing hydantoin formation. Glyoxal was condensed with 1-phenyl-3-cyclohexylurea (XI*a*), 1-phenyl-3-*p*-methoxyphenylurea (XI*b*), 1-phenyl-3-*p*-nitrophenylurea (XI*c*), dicyclohexylurea (XI*d*), and 1-*p*-methoxyphenyl-3-*p*-nitrophenylurea (XI*e*).



XI*a*, $R_1 = C_6H_5$, $R_3 = C_6H_{11}$
b, $R_1 = C_6H_5$, $R_3 = p\text{-}CH_3O\text{—}C_6H_4$
c, $R_1 = C_6H_5$, $R_3 = p\text{-}O_2N\text{—}C_6H_4$
d, $R_1 = R_3 = C_6H_{11}$
e, $R_1 = p\text{-}CH_3O\text{—}C_6H_4$, $R_3 = p\text{-}O_2N\text{—}C_6H_4$

The reaction of glyoxal with XI*e* produced only tars. Glyoxal and XI*c* afforded only a small amount of yellowish crystals; the infrared and NMR spectra of which were identical to those of 1-phenyl-3-*p*-nitrophenylhydantoin prepared from *N*-phenylglycine and *p*-nitrophenyl isocyanate. The product was thus assumed to be 1-phenyl-3-*p*-nitrophenylhydantoin. Attempts to react glyoxal with dicyclohexylurea (XI*d*) failed; only starting material was recovered, even after heating under reflux for 48 hr.

The condensation of glyoxal with XI*a* afforded 1-cyclohexyl-3-phenylhydantoin as the only characterizable product. Thus, the cyclohexyl group takes priority for the 1-position. The sequence for orientation in the 1-position is then methyl < phenyl < cyclohexyl. This is also the order of increasing size and indicates that the larger group is directed to the 1-position. That electronic effects are of minor importance in orientation can be ascertained from the condensation of glyoxal with XI*b* which afforded a mixture of 1-*p*-methoxyphenyl-3-phenylhydantoin and the isomeric 1-phenyl-3-*p*-methoxyphenylhydantoin in approximately equimolar amounts.

These facts indicate that steric rather than electronic factors are more important in determining the position of substituents in the isomeric hydantoins. The mechanistic details through which this steric effect is manifest remain obscure and, together with other aspects of the reaction mechanism, is the subject of studies now in progress.

EXPERIMENTAL

Melting points were determined in capillary tubes on a Thomas-Hoover apparatus and those below 250° were corrected. Infrared spectra were determined in KBr disks with a Beckman IR-5 spectrophotometer and NMR spectra with a Varian A60 spectrophotometer at room temperature. Chemical shifts are reported in parts per million, δ, downfield from tetramethylsilane. Analyses are by the Microanalytical Laboratory, Department of Chemistry, University of California, Berkeley.

1,4 - Dicyclohexyltetrahydroimidazo[4,5 - d]imidazole-2,5-dione (VI) and 1-Cyclohexylhydantoin (IX).—A solution of 14.2 Gm. (0.1 mole) of 1-cyclohexylurea and 3.6 Gm. (0.05 mole) of 80% crystalline glyoxal[1] in 200 ml. of 80% ethanol and 2 ml. of concentrated hydrochloric acid was heated under reflux. Crystals began to separate after 45 min. Heating was stopped after 2 hr., and the solid was collected after cooling the reaction mixture to room temperature. Crystallization of the solid from 95% ethanol gave 6.4 Gm. (39%) of 1,4-dicyclohexyltetrahydroimidazo[4,5 - *d*]imidazole - 2,5-dione, m.p. 347–351°; $\nu_{max.}$ 3180 (NH); 1690 cm.$^{-1}$ (C=O).

Anal.—Calcd. for $C_{16}H_{26}N_4O_2$: C, 62.72; H, 8.55; N, 18.29. Found: C, 62.87; H, 8.84; N, 18.31.

The ethanol filtrate was evaporated on a steam bath and the residue crystallized from methanol to give 1.3 Gm. (14.2%) of 1-cyclohexylhydantoin, m.p. 179–182°. This was identical to an authentic sample (5) prepared from *N*-cyclohexylglycolonitrile and potassium isocyanate, m.p. 179–182° [lit. (5) m.p. 182.7–184.2°]; $\nu_{max.}$ 3150 (broad NH); 1775 and 1700 cm.$^{-1}$ (C=O).

1,4 - Dicyclohexyl - 3,6 - dimethyltetrahydroimidazo[4,5-d]imidazole-2,5-dione (VII), 1,6-Dicyclohexyl - 3,4 - dimethyltetrahydroimidazo[4,5-d]imidazole-2,5-dione (VIII), and 1-Cyclohexyl-3-methylhydantoin (X).—A solution of 15.6 Gm. (0.1 mole) of 1-cyclohexyl-3-methylurea and 3.6 Gm. (0.05 mole) of 80% crystalline glyoxal in 180 ml. 80% ethanol and 1.5 ml. of concentrated hydrochloric acid was heated under reflux for 3 hr. The solvent was evaporated in a rotatory evaporator to afford 14.5 Gm. of a yellowish solid, which was a mixture of VII, VIII, and X. The solid was placed in 125 ml. of carbon tetrachloride and heated on a steam bath. The undissolved portion was filtered by suction to afford 4.2 Gm. (25.2%) of 1,4-dicyclohexyl - 3,6 - dimethyltetrahydroimidazo[4,5 - *d*] - imidazole-2,5-dione, m.p. 263–265°; $\nu_{max.}$ 1700 cm.$^{-1}$ (C=O); NMR, δ 5.02 (angular CH), 2.97 (CH_3), 1–2 (C_6H_{11}).

The carbon tetrachloride filtrate was evaporated. The residue was placed in 50 ml. of distilled water and heated to boiling, then cooled to room temperature. The water insoluble material was filtered by suction and crystallized from 50% methanol to afford 2.9 Gm. (17.0%) of 1,6-dicyclohexyl-3,4-dimethyltetrahydroimidazo[4,5 - *d*]imidazole - 2,5 - dione, m.p. 151–153°; $\nu_{max.}$ 1700 cm.$^{-1}$ (C=O); NMR, δ 5.13 (C_8H), 4.91 (C_7H); 2.97 (CH_3), 1–2 (C_6H_{11})$J_{7,8}$ = 9.0 c.p.s.

Anal.—Calcd. for $C_{18}H_{30}N_4O_2$: C, 64.64; H, 9.04; N, 16.75. Found: C, 64.79; H, 8.81; N, 16.88.

The aqueous filtrate was evaporated in a rotatory evaporator to give 1.8 Gm. (18.4%) of 1-cyclohexyl-3-methylhydantoin, m.p. 150–152°; $\nu_{max.}$ 1700 cm.$^{-1}$ (C=O); NMR, δ 3.65 (CH_2), 2.85 (CH_3), 1–2 (C_6H_{11}).

Anal.—Calcd. for $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.22; N, 14.28. Found: C, 61.13; H, 8.13; N, 14.14.

1-Cyclohexyl-3-phenylhydantoin.—A solution of 21.8 Gm. (0.1 mole) of 1-cyclohexyl-3-phenylurea and 3.6 Gm. (0.05 mole) of 80% crystalline glyoxal in 200 ml. of 90% *n*-butanol and 10 ml. of concentrated hydrochloric acid was heated under reflux for 48 hr. The solvent was removed and the residue crystallized from 60% methanol to afford 5 Gm. (38.5%) of 1-cyclohexyl-3-phenylhydantoin,[2] m.p. 119–120°, $\nu_{max.}$ 1710, 1775 cm.$^{-1}$ (C=O).

[1] Obtained from F. Jonas Co., New York, N. Y.

[2] On prolonged heating, these reactions are accompanied by a large amount of tar formation. This is presumably from decomposition and/or polymerization of glyoxal.

This material was identical to a sample prepared from phenyl isocyanate and *N*-cyclohexylglycine.

Anal.—Calcd. for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.85. Found: C, 69.46; H, 6.79; N, 10.74.

1-Phenyl-3-p-methoxyphenyl- and 1-p-Methoxyphenyl-3-phenylhydantoin.—A solution of 24.2 Gm. (0.1 mole) of 1-*p*-methoxyphenyl-3-phenylurea, 3.6 Gm. (0.05 mole) of 80% glyoxal, and 20 ml. concentrated hydrochloric acid in 300 ml. of 90% butanol was heated under reflux for 11 hr. The solvent was removed in a rotatory evaporator and the residue collected and crystallized from ethanol to give 12 Gm. (85%) of the mixture 1-*p*-methoxyphenyl-3-phenylhydantoin and 1-phenyl-3-*p*-methoxyphenylhydantoin, m.p. 132–135°; $\nu_{max.}$ 1710, 1775 cm.$^{-1}$ (C=O); NMR, δ 4.32 (CH_2), 3.79 and 3.80 (CH_3), 6.7–7.6 (C_6H_4).

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Separation and Estimation of Methyl and Propyl Esters of *p*-Hydroxybenzoic Acid by Gas Chromatography

By SAM JOSEPH DONATO

Some of the esters of *p*-hydroxybenzoic acid have been separated and identified by direct gas chromatography. The trimethylsilyl ethers of these compounds lend themselves more readily to gas chromatography since they show little or no tailing and therefore can be measured quantitatively. The method is rapid and sensitive.

RELATIVELY pure single esters of *p*-hydroxybenzoic acid (parabens) can easily be identified by a number of methods (1). However, when more than one ester of *p*-hydroxybenzoic acid is present, especially in very dilute aqueous solution, they are difficult to identify individually. In this case it is necessary to perform a separation prior to the identification (2). Because partition chromatography and adsorption chromatography are only applicable to specific problems of limited complexity and since paper chromatography is time-consuming and insensitive with respect to these esters, gas liquid chromatography was attempted and found to be applicable and furthermore simple and sensitive. This tool will give both the qualitative and quantitative analysis of these compounds (3). The tailing of the esters as shown in Fig. 1 makes the separation and measurement difficult because of the overlapping and indefinite character of the curve. For this reason the esters were converted into the trimethylsilyl ethers which are more volatile, more stable, and better suited to separation by gas chromatography. This is illustrated in Fig. 2.

EXPERIMENTAL

The F & M model 609 gas chromatograph equipped with a flame ionization detector was used. The column was 6 ft. long, $^3/_{16}$-in. O.D. stainless steel, with 10% SE-30 as substrate coated on diatoport S (80–100 mesh) the support.

The reagents were hexamethyldisilazane (JU3), Analabs; trimethylchlorosilane (JU4), Analabs; pyridine (analytical reagent), Mallinckrodt Chemical Works. All the above reagents were used as received, with the exception of pyridine, which was kept over potassium hydroxide pellets.

The procedure was as follows. An aliquot of sample containing an equivalent of 1–20 mg. of esters was transferred to a separator where the esters were extracted with two portions of 10 ml. each of diethyl ether. The ether phase was collected and washed with distilled water and transferred to a 0.5-oz. vial where the ether phase was evaporated almost to dryness. This was achieved by using both steam and a current of dry air. The last several milliliters of solution were evaporated at room temperature since these compounds are volatile on the steam bath. To this was added 1.0 ml. of anhydrous pyridine, and the dry residue in the vial was mixed with the liquid until it was completely dissolved. Subsequently, 0.2 ml. of hexamethyldisilazane and 0.1 ml. of trimethylchlorosilane were added, and the vial was stoppered with a plastic stopper. The mixture was shaken vigorously for 30 sec. and allowed to stand at room temperature for 15 min. (4, 5). The fine ammonium chloride precipitate formed was not removed since it did not interfere with the subsequent gas chromatography (6). A 1.0-μl. quantity of the trimethylsilyl ethers was introduced into the injection port with a Hamilton microsyringe.

The conditions for operating the F & M 609 were as follows. The injection port was kept at about 235°, the detector block temperature at 200°, a flow rate of nitrogen of 40 ml./min. with an attenuation of 64 and a range of 100. The column temperature was programmed from 90° to 200° at 6.4°/min. The peaks were measured with a compensating polar planimeter. At the present time the author is combining these results with those obtained for the total esters by U. V. spectrophotometry and then quantitatively estimating the per cent of each constituent in the mixture or preparation.

The E(1%, 1 cm.) in water for methyl and propyl *p*-hydroxybenzoate was found to be, respectively, 1012 and 875, with peak at 255.75 mμ for both, using a Beckman DU spectrophotometer.

Table I shows results found by this method for a

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