

The Oxidation of Phenyl Substituted Hydantoins

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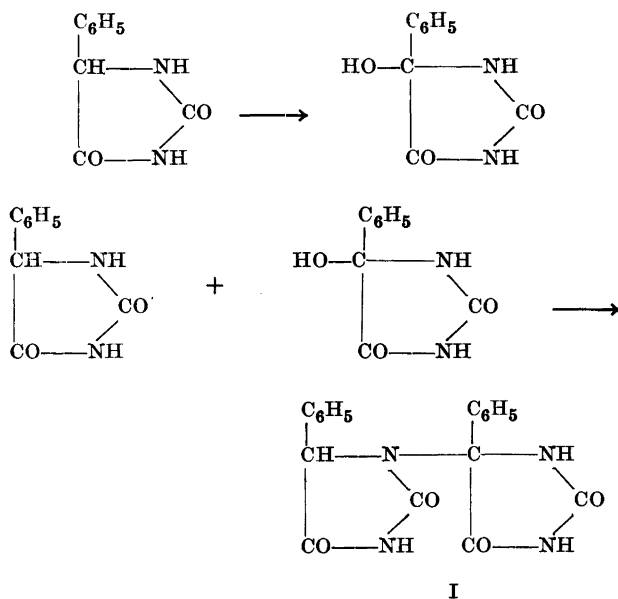
In two papers Aspelund¹ has shown that dialuric and hydurilic acids are formed when barbituric acids substituted with one alkyl, aryl, or aralkyl group in the 5-position are oxidized. The yields of these products vary with the oxidizing agent used. 5-Ethyl- and 5-benzylbarbituric acids give considerable amounts of the corresponding dialuric acids when aqueous hydrogen peroxide or potassium dichromate in acetic acid is used. Potassium permanganate in dilute sulfuric acid oxidizes these barbituric acids to both dialuric and hydurilic acids. In the oxidation of 5-phenylbarbituric acid aqueous hydrogen peroxide gives principally 5-phenyldialuric acid and a small amount of 5,5'-diphenylhydurilic acid. Potassium permanganate in dilute sulfuric acid causes the formation of 5,5'-diphenylhydurilic acid and a small amount of 5-phenyldialuric acid, whereas only the corresponding hydurilic acid is isolated when potassium dichromate in acetic acid is used.

As monosubstituted barbituric acids are very easily oxidized because the hydrogen attached to the central carbon atom between the two CO groups is mobile, it seemed to be of some interest to study the oxidation of the more stable hydantoins. Experiments with 5-methyl- and 5-phenylhydantoins have previously been carried out by Gabriel², who found that the hydantoins in question were oxidized by half an equivalent of bromine in acetic acid solution. The reaction products were pyruvureide and "diphenylhydantil" (5-[5'-phenylhydantoin-1'-yl]-5-phenylhydantoin, *cf.* Formula I). Gabriel did not study the action of other oxidizing agents.

In order to avoid by-reactions only phenyl substituted hydantoins, *viz.* 5-phenylhydantoin, 1,5-diphenylhydantoin, and 3,5-diphenylhydantoin, were studied in the present work. Because the two last-mentioned substances are only sparingly soluble in water, they could not be oxidized in aqueous solution. In these cases only potassium dichromate in acetic acid was used, but 5-phenylhydantoin could also be oxidized with hydrogen peroxide both in the

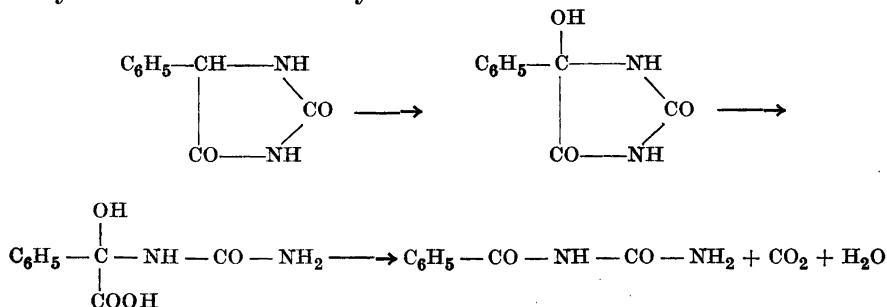
presence of a small amount of sodium bicarbonate and in alkaline solution, and with potassium permanganate in dilute sulfuric acid.

The last-mentioned oxidizing agent led to the formation of "diphenylhydantil" only. The same reaction product was also obtained when hydrogen peroxide together with a small amount of sodium bicarbonate was used. Oxidation with hydrogen peroxide in alkaline solution, however, leads to different results. With an excess of 0.15 equivalents of potassium hydroxide both "diphenylhydantil" and benzoylurea were formed. When the excess was increased to 1.12 equivalents of potassium hydroxide, benzoylurea and benzoic acid could be isolated, but no "diphenylhydantil". The formation of "diphenylhydantil" may be interpreted as an oxidation of the hydantoin to the corresponding hydroxy derivative and a reaction between this compound and unreacted 5-phenylhydantoin, *i. e.*



This sequence of reactions is supported by Gabriel's observation that "diphenylhydantil" is easily formed from a mixture of 5-hydroxy-5-phenylhydantoin and 5-phenylhydantoin. The formation of benzoylurea does not apparently derive its origin from "diphenylhydantil" because this substance cannot be converted into benzoylurea under the same experimental conditions. A plausible explanation is the following. 5-Phenylhydantoin is oxidized to 5-hydroxy-5-phenylhydantoin and the ring of the latter is opened by the alkali.

These reactions are then followed by another oxidation which converts the hydroxyureido acid into benzoylurea:



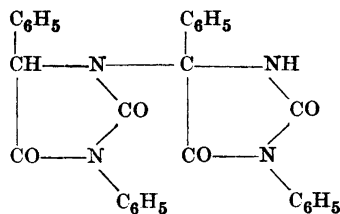
The carbon dioxide formed neutralizes the alkali and benzoylurea precipitates. This sequence of reactions is supported by the fact that 5-hydroxy-5-phenylhydantoin is converted into benzoylurea when it is oxidized in alkaline solution with hydrogen peroxide.

Potassium dichromate in acetic acid oxidizes the hydantoin mentioned in this paper to the corresponding hydroxyhydantoin. In all cases the reaction came to a standstill before all of the substance had reacted. The mixtures thus obtained were difficult to separate into their components, but by taking advantage of the fact that the hydroxyhydantoin is more readily soluble in water and alcohol than the corresponding hydantoin, fractional crystallization finally led to successful results. In the oxidation of 5-phenylhydantoin and 3,5-diphenylhydantoin the corresponding "hydantils" (*cf.* Formulae I and II) were formed as by-products. That the formation of these substances occurs in the way indicated in the first reaction sequence is evident from the fact that the "diphenylhydantil" is formed principally during the evaporation of the solvent after a half an hour's oxidation, *i. e.* when considerable amounts of 5-phenylhydantoin are still present.

Both 5-hydroxy-1,5-diphenylhydantoin and 5-hydroxy-3,5-diphenylhydantoin crystallize with one molecule of water. The hydrate of the latter is, however, much more stable than that of the former.

Although Gabriel prepared 5-hydroxy-5-phenylhydantoin by dissolving 5-bromo-5-phenylhydantoin in water, no melting point is given in his communication. In order to determine this constant for identifying purposes Gabriel's experiment was repeated.

3,5-Diphenylhydantoin was also oxidized with half an equivalent of bromine in acetic acid in order to obtain "tetraphenylhydantil" (5-[3',5'-diphenylhydantoin-1'-yl]-3,5-diphenylhydantoin, *cf.* Formula II). The formation of this substance is, however, much slower than that of "diphenylhydantil".



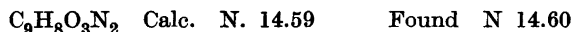
II

This is also evident from the fact that "diphenylhydantil" is formed in considerable amounts and "tetraphenylhydantil" only in comparatively small amounts in the oxidations of the corresponding hydantoins with potassium dichromate in acetic acid.

EXPERIMENTAL

Preparation of 5-hydroxy-5-phenylhydantoin

Four grams of 5-phenylhydantoin were dissolved in 13.5 ml of acetic acid and to this solution 4.45 g of bromine in 8 ml of acetic acid were added. The mixture was warmed on the water bath for 20 minutes. The resulting colourless solution was allowed to stand until the next morning. The precipitated crystals of 5-bromo-5-phenyl-hydantoin (3.34 g or 58 per cent of the theoretical amount, m. p. 210—212°) were collected and washed with a small amount of dry ether. The crystals were dissolved in 21 ml of water and the insoluble matter (0.22 g of "diphenylhydantil", m. p. > 300°) was filtered and washed with a small quantity of water. 5-Hydroxy-5-phenyl-hydantoin crystallized from the filtrate and was separated by suction. It melted at 180—181° (evolution of gas) and the yield was 1.71 g.



The filtrate was evaporated until almost dry. The substance that separated (0.49 g) could be identified as impure 5-hydroxy-5-phenylhydantoin. The total yield of the hydroxy derivative was accordingly 85 per cent calculated from the amount of the bromo derivative.

Oxidation of 5-phenylhydantoin by potassium dichromate

Two grams of 5-phenylhydantoin were dissolved in 25 ml of acetic acid, 2 g of finely powdered potassium dichromate were added and the mixture was heated on the steam bath. After five minutes' heating the colour of the mixture changed from orange to green. After two hours' heating the solution was left to cool. The solid substance that had separated was filtered together with unchanged potassium dichromate and washed with a small quantity of acetic acid. When the mixture had dried, it was treated with water to dissolve the dichromate. The insoluble "diphenylhydantil" (0.64 g, m.p. > 300°) was filtered and the filtrate was three times extracted with ether, but the residue was very slight (0.01 g) and was not examined.

The acetic acid filtrate from the separation of "diphenylhydantil" and unchanged potassium dichromate was evaporated until dry. The residue was treated with dilute hydrochloric acid and the mixture was again evaporated in order to drive away most of the acetic acid. The solid substance remaining (0.15 g of "diphenylhydantil") was filtered and the filtrate was four times extracted with ether. The residue of the combined ether solutions (0.72 g) was treated with water, whereupon 0.40 g of rather impure 5-hydroxy-5-phenylhydantoin separated. After two recrystallizations from water the substance was found to be pure (m. p. 179–180°).

The aqueous filtrate was evaporated and the residue was treated with 1 ml of water. The insoluble substance was filtered and after recrystallization from water identified as 5-hydroxy-5-phenylhydantoin, m. p. 178–179° (0.13 g).

Another sample of 5-phenylhydantoin was heated for only a half an hour. "Diphenylhydantil" was isolated as the only product and this appeared principally during the evaporation of the solvent.

Oxidation of 5-phenylhydantoin with potassium permanganate in dilute sulfuric acid

Two grams of 5-phenylhydantoin were added to a solution of 0.70 g of potassium permanganate and 0.35 ml of conc. sulfuric acid in 20 ml of water and the mixture was boiled for half an hour *i. e.* until the colour of the permanganate had disappeared. The substance that had separated was filtered while the mixture was still hot and was identified as "diphenylhydantil" (0.88 g). From the filtrate 0.51 g of unchanged 5-phenylhydantoin separated. When the aqueous solution was evaporated 0.08 g of the same substance were obtained.

Oxidation of 5-phenylhydantoin with hydrogen peroxide

Experiment 1. Two grams of 5-phenylhydantoin were dissolved in 13 ml of water and a small quantity of sodium bicarbonate and 2.5 ml of hydrogen peroxide were added. The mixture was boiled. Almost at once crystals began to separate. The quantity of the solid substance gradually increased, so that when three-quarters of an hour had passed the mixture bumped considerably. After boiling for one hour, the mixture was filtered while hot. "Diphenylhydantil" (0.26 g) was obtained. Crystals began to separate in the filtrate and after the solution had cooled they were isolated and identified as 5-phenylhydantoin (1.70 g).

Experiment 2. Two grams of 5-phenylhydantoin were dissolved in 13 ml (1.15 equivalents) of *N* potassium hydroxide and 4 ml of 30 per cent hydrogen peroxide were added to the solution. The mixture was then allowed to stand at room temperature. As a consequence of the reaction the temperature rose a little. A solid substance gradually formed and after three hours and a half the substance was filtered and boiled with water. The insoluble part 0.25 g of "diphenylhydantil" was filtered off and from the filtrate 0.40 g of benzoylurea, m. p. 212–214°, crystallized.

When the alkaline filtrate was acidified 0.30 g of "diphenylhydantil" were isolated.

Experiment 3. Four grams of 5-phenylhydantoin were dissolved in 48.3 ml (2.12 equivalents) of *N* potassium hydroxide and 7.5 ml of 30 per cent hydrogen peroxide were

added. After four hours and a half impure benzoylurea that had formed was filtered. It weighed 0.85 g and melted at 206–209°, but on recrystallization from water the melting point rose to 211–212°.

When 7.5 ml of 30 per cent hydrogen peroxide were added to the filtrate, the reaction started again and the mixture became turbid. After twenty-three hours from the beginning of the experiment 0.91 g of benzoylurea, m. p. 214°, were filtered. The filtrate was slowly acidified. When 32 ml of *N* hydrochloric acid had been added, the solution was neutral to litmus and a solid substance had separated. It was identified as 5-phenylhydantoin (0.19 g). More hydrochloric acid was now added, and at first the solution remained clear, but when it was neutral to congo red a solid substance began to separate. When the solution was acid to congo red, the substance was filtered. It weighed 0.20 g and consisted of benzoic acid (m. p. 121–122°).

Oxidation of 1,5-diphenylhydantoin with potassium dichromate

Four grams of 1,5-diphenylhydantoin were dissolved in 50 ml of acetic acid, and 4 g of finely powdered potassium dichromate were added. The mixture was heated on the steam bath and turned green rather soon. After five hours' heating the solution was decanted from unchanged potassium dichromate. The solution was evaporated and the residue was treated with water containing a few drops of hydrochloric acid. At first an oily product separated that crystallized after some time. It was filtered and dissolved in alcohol containing a few drops of hydrochloric acid. The solution, which was slightly green-coloured, was placed in a refrigerator and after some time 1.27 g of unchanged 1,5-diphenylhydantoin, m. p. 202–204°, was separated by filtration.

Water was added to the filtrate and after a while a solid substance (1.80 g, m. p. 160–165°) was filtered. It was recrystallized several times from mixtures of alcohol and water, yielding colourless leaves, m.p. 170–171°.

$C_{15}H_{12}O_3N_2 \cdot H_2O$	Calc.	C	62.91	H	4.93	N	9.79	H_2O	6.30
	Found	»	63.13	»	4.98	»	9.79	»	6.44

The monohydrate of 5-hydroxy-1,5-diphenylhydantoin is readily soluble in alcohol, soluble in ether and insoluble in water and in in polar solvents.

Oxidation of 3,5-diphenylhydantoin with potassium dichromate

Two grams of 3,5-diphenylhydantoin, 2 g of finely powdered potassium dichromate, and 25 ml of acetic acid were heated on the steam bath for three hours. The potassium dichromate that had not reacted was filtered off and water was added to the filtrate. The precipitate that formed was filtered at once and after it had dried in the air it was boiled with alcohol. The hot mixture was filtered. The substance that remained on the filter was "tetraphenylhydantil". The yield was 0.04 g.

$C_{30}H_{22}O_4N_4$	Calc.	N	11.13	Found	N	11.14
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"Tetraphenylhydantil" does not melt under 300° and is insoluble in alcohol and water, but is slightly soluble in acetic acid.

The alcohol filtrate was diluted with water and the substance formed was filtered and identified as unchanged 3,5-diphenylhydantoin. It weighed 0.10 g.

More water was added to the acetic acid filtrate and next morning 1.05 g of solid substances had separated. After repeated fractional recrystallization 0.69 g of 5-hydroxy-3,5-diphenylhydantoin monohydrate, m. p. 168–169°, were isolated. The water is very firmly bound and its removal requires about one week over phosphorous pentoxide *in vacuo*.

$C_{15}H_{12}O_3N_2 \cdot H_2O$	Calc.	N	9.79	H ₂ O	6.30
	Found	»	9.67	»	6.11

The solubility of 5-hydroxy-3,5-diphenylhydantoin is approximately the same as the solubility of the corresponding 1,5-diphenyl derivative.

Oxidation of 3,5-diphenylhydantoin with bromine

Two grams of 3,5-diphenylhydantoin were dissolved in 25 ml of acetic acid. To this solution 0.635 g (0.5 equivalents) of bromine in 5 ml of acetic acid were added and the mixture was heated on the steam bath for one hour, *i. e.* half an hour after the disappearance of the bromine colour. The mixture was then diluted with water and the substance that separated was immediately filtered. When the substance was dry it was boiled with alcohol and filtered. In this way 0.43 g of "tetraphenylhydantil" were isolated. It had the same properties as the substance isolated in the foregoing experiment.

From the filtrates 0.73 g of unchanged 3,5-diphenylhydantoin were isolated.

Action of hydrogen peroxide on 5-hydroxy-5-phenylhydantoin

Two grams of 5-hydroxy-5-phenylhydantoin were dissolved in 21 ml (2.02 equivalents) of potassium hydroxide, and 4 ml of 30 per cent hydrogen peroxide were added. After 24 hours 0.51 g of benzoylurea were isolated. When the corresponding experiment was carried out with "diphenylhydantil" no benzoylurea was isolated.

SUMMARY

The oxidation of 5-phenylhydantoin, 1,5-diphenylhydantoin, and 3,5-diphenylhydantoin has been studied.

REFERENCES

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