wool and silk in all tests for fastness with the exception of those containing the sulfo group which are not fast in the water, alkali and washing tests.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

RESEARCHES ON HYDANTOINS. XLI. THE SYNTHESIS OF HYDANTOINS CONTAINING PHENOLIC GROUPS IN THE GLYOXALINE NUCLEUS[1]

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Introduction

There is no doubt that a really efficient, non-toxic, internal antiseptic is one of the great needs of the medical profession today. Discussion of this topic with a prominent medical man recently brought forth from him the following statement: "There is nothing in the medical line so desperately needed today as a non-toxic, effective germicide or antiseptic for internal use. There is not a field of disease more interesting than that involving infections located in the intestinal and urinary tracts and there is certainly none over which medical practitioners have so little control." This is apparently a quite general and accepted opinion among leading medical men today. It is, therefore, quite apparent to anyone conscious of the ravages of specific diseases that this field of internal antisepsis[4] offers many problems of immediate interest to the organic chemist.

In considering the problem of developing new possible antiseptic principles applicable for internal sterilization, we have been influenced and guided by the requirements of a practical antiseptic agent so lucidly set forth by Assmann[5] and have, therefore, undertaken as a preliminary phase of this field of research, an investigation of some phenolic derivatives of hydantoin. As no phenolic derivatives of this cycle have hitherto been

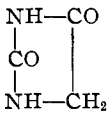
[1] A contribution to the research on antiseptics now being carried on in the Sterling Chemistry Laboratory in coöperation with the National Research Council Sub-Committee on "Internal Antisepsis."—T. B. Johnson, Chairman.

[2] Holder of the du Pont Fellowship in Chemistry, **1923–24.** Papers XLI and XLII are constructed from a dissertation presented by Robert D. Coghill in June, **1924,** to the Faculty of the Graduate School of Yale University in candidacy for the degree of Doctor of Philosophy.

[3] An abstract of this paper was presented before the Division of Medicinal Products at the Spring Meeting of the American Chemical Society, held in Washington, D. C., April, **1924.**

[4] Harris, *J. Am. Med. Assoc.*, **59,** 1344 (1912).

[5] Assmann, *Z. Tiermed.*, **15,** 122, 264, 352 (1911). Ref. 4.



described in the chemical literature, and since it has been shown that the hydantoin cycle is non-toxic and very resistant to the action of ferments[6] and bacterial enzymes, it seemed to be of especial interest to determine whether we have here a suitable vehicle for transporting antiseptic and even toxic groupings through the intestinal tract.

A further reason why these derivatives of hydantoin promise to be of practical interest as internal antiseptics is that we are dealing here with an organic carbon-nitrogen nucleus constructed of simple molecular groupings which are not unnatural to the body, but actually function in many of the chemical changes normally taking place in living organisms. Hydantoin is the mother substance of an interesting type of cyclic compounds known as polypeptide-hydantoins[7] and contains the same molecular grouping in cyclic combination —NH.CH_2.CO.NH— which functions in the natural acyclic polypeptide compounds. It has already been shown that molecular groupings of this type are effective in producing hypnotics and other drugs, which have proved to be of practical therapeutic value. To summarize, we have available here for future research an unexplored group of cyclic compounds presenting many interesting synthetic problems, which gives promise of revealing several new compounds of practical interest and importance in the study of the new field of "Chemotherapeutic Antisepsis."[8] Furthermore, it is not improbable that both hydantoin and glycine anhydride (diacipiperazine) combinations play a far more important role in life processes than has hitherto been assumed.[9] Consequently, it will be of special interest to incorporate in both of these nitrogen-carbon cycles active germicidal groups and study the physiological action of the resulting products. Several phenolic derivatives of hydantoin have already been synthesized and will be described in future publications. As this work is developed we shall also extend the research into the pyrimidine series.

In this paper we will give a description of the methods of preparation and the properties of the six *p*-phenolic derivatives of hydantoin represented below by Formulas I, II, III, IV, V and VII, respectively:[10]

[6] Lewis, *J. Biol. Chem.*, **13**, 347 (1912); **14**, 245 (1913).

[7] Johnson, *Proc. Nat. Acad. Sci.*, **2**, 69 (1916).

[8] *C. A.*, **17**, 1528 (1923).

[9] Johnson, THIS JOURNAL, **36**, 337 (1914); *Proc. Nat. Acad. Sci.*, **2**, 69 (1916). Abderhalden and co-workers, *Z. physiol. Chem.*, **131**, 281, 284 (1923). Abderhalden and Klarmann, *ibid.*, **129**, 320 (1922).

[10] In the numbering of positions in the hydantoin ring we have followed the system approved by *Chemical Abstracts* as published in the *Subject Index* for Vols. 1–10, p. 3270 (1907–1916).

p-Hydroxyphenyl-hydantoins

MONOPHENOLS

I $HOC_6H_4N.CO.NH.CH_2.CO$ (3-Phenol)

II $NH\text{-}CO.N.(C_6H_4OH).CH_2.CO$ (1-Phenol)

III $NH\text{-}CO.NH.CH(C_6H_4OH).CO$ (5-Phenol)

Di(*p*-hydroxyphenyl)hydantoins

DIPHENOLS

IV $HOC_6H_4.N.CO.N(C_6H_4OH).CH_2.CO$ (1,3-Diphenol)

V $HOC_6H_4.N.CO.NH.CH(C_6H_4OH).CO$ (3,5-Diphenol)

VI $NH.CO.N(C_6H_4OH).CH(C_6H_4OH).CO$ (1,5-Diphenol)

VII $NH.CO.NH.C(C_6H_4OH)_2.CO$ (5,5-Diphenol)

With the inclusion of the 1,5-diphenol VI, which will be described in our next paper in this series, these compounds represent all the mono- and di-*p*-phenol derivatives of hydantoin, $NH.CO.NH.CH_2.CO$, theoretically possible.

In the development of methods of synthesizing these phenolic compounds the mother substance of the series, hydantoin, was of no value to us as the starting point of our work. While aliphatic groups may be introduced into the glyoxaline ring by direct alkylation, in the case of the aromatic compounds this procedure is not applicable, and consequently we were forced to utilize indirect methods of synthesis in the preparation of all the new hydantoins. Methods of approach in great variety are revealed when one reviews carefully the literature of hydantoin chemistry, and also many new synthetical procedures are still open for research. Several of these will be studied and applied as our hydantoin researches are developed in the future. To discuss or refer to them all in this paper is not feasible or practicable, and consequently consideration will be given only to those methods of synthesis which were actually utilized in the progress of our research.

Three isothiocyanates were utilized in our synthetic work, namely, *p*-methoxy-, *p*-ethoxy and *p*-nitrophenyl-isothiocyanates. Of these only the methoxy compound was of practical value to us and, therefore, is the one compound of basic value in our present research. The replacement of the nitro group in the nitrophenyl combinations involving reduction and finally replacement of the amino group with hydroxyl by diazotization did

not prove to be a series of operations productive of results of value in the syntheses of this series.

The *p*-methoxyphenyl-isothiocyanate proved to be the most serviceable of the two ether isothiocyanates employed on account of the ease of dealkylation of the methoxyl grouping. This was readily accomplished in every case examined by heating with hydrobromic acid in glacial acetic acid solution. These transformations were easily brought about in good yields and, furthermore, the hydantoin ring is not destroyed by hydrolysis when operating under such conditions. It was found that hydrobromic acid is of far more practical use for dealkylation work than hydriodic acid. Where it has been necessary to prepare a normal hydantoin combination indirectly through its sulfur analog, we have found in every case that this change can be brought about by digestion in aqueous solution with chloro-acetic acid.[11] This method enables one to operate without rupture of the hydantoin ring by hydrolysis or oxidation. The various methods employed and the properties of the compounds synthesized are fully described in the experimental part of this paper. This research is being continued in this Laboratory.

Experimental Part

p-**Methoxyphenyl-isothiocyanate,** $CH_3OC_6H_4.NCS$.—Fifty g. of concd. aqueous ammonia was placed in a bottle, and during vigorous stirring in an ice-bath, 37 g. of carbon disulfide and 37 g. of *p*-anisidine dissolved in alcohol were added slowly. An excess of carbon disulfide was used because the heat evolved and vigorous stirring causes loss through vaporization. The stirring was continued for one-half hour and the reaction mixture allowed to stand for two hours when the insoluble ammonium salt of *p*-anisyl-dithiocarbamic acid was separated by filtration and dissolved in water. To this aqueous solution was added a cold saturated solution of lead nitrate to precipitate the lead salt of the dithiocarbamic acid. On distillation with steam the mustard oil was obtained as a colorless oil which solidified on cooling; yield, 30 g., or 60%. After crystallization from ether the mustard oil melted at 18°. This compound has been described in the literature as an oil boiling[12] at 270°. The decomposition of the lead salt is expressed by the equation, $(CH_3OC_6H_4NHCSS)_2Pb = H_2S + PbS + 2\ CH_3OC_6H_4NCS$.

p-**Ethoxyphenyl-isothiocyanate,** $C_2H_5O.C_6H_4.NCS$.—This was obtained from *p*-phenetidine, carbon disulfide and ammonia in a manner similar to that described in the previous experiment. It was a colorless solid melting at the same temperature as that given in the literature,[13] namely, 62.5°.

p-**Nitrophenyl-isothiocyanate,** $NO_2.C_6H_4.NCS$.—An attempt to prepare this compound from *p*-nitro-aniline by application of the method described above was unsuccessful and the original amine was recovered quantitatively.

Formation from *p*-Nitro-aniline and Thiophosgene.—Twenty g. of *p*-nitro-aniline was dissolved in toluene and 20 g. of thiophosgene added to the solution. There was an

[11] Method of Wheeler and Liddle, *Am. Chem. J.*, **40**, 547 (1908), and used with success by workers at this Laboratory in hydantoin and pyrimidine research.

[12] Salkowski, *Ber.*, **7**, 1012 (1874); Dains, Brewster and Olander, *Kansas Univ. Sci. Bull.*, XIII, No. 10, July, **1922**.

[13] Gattermann, *J. prakt. Chem.*, [2] **50**, 588 (1899).

immediate exothermic reaction and a heavy precipitate of *p*-nitro-aniline hydrochloride deposited. After the mixture had been heated at 100° to complete the reaction and the amine salt removed by filtration, the toluene solution was concentrated and cooled when we obtained 11 g. of the isothiocyanate; m. p.,[14] 112°. Allowing for recovered amine, this is a yield of 70%.

3-*p*-Methoxyphenyl-2-thiohydantoin, $CH_3OC_6H_4\overline{N.CS.NH.CH_2}.CO$.—This hydantoin was prepared by interaction of *p*-methoxyphenyl-isothiocyanate with ethylamino-acetate. The reaction was conducted in alcohol solution in the presence of potassium hydroxide. After heating the reaction mixture for one-half hour the excess of alcohol was evaporated and the residue warmed with hydrochloric acid. The hydantoin was then obtained in a crystalline condition, separating in the form of needles. It was purified by crystallization from 95% alcohol; m. p., 214°; yield, 80%. Hill and Kelsey[15] have previously described this compound as melting at 207°.

In the preparation of this hydantoin it is important not to use any excess over a molecular proportion of alkali, as it causes a decomposition leading to the formation of ammonium sulfide. The yield of hydantoin is lowered to about 20%.

3-*p*-Methoxyphenyl-hydantoin, $CH_3OC_6H_4\overline{N.CO.NH.CH_2}.CO$.—This compound was prepared by desulfurizing the above-mentioned thiohydantoin by digestion in water with chloro-acetic acid. It crystallized from hot water in needles; m. p.,[15] 208°; yield, 67%.

3-*p*-Hydroxyphenyl-hydantoin, I.—This hydantoin was easily prepared by heating its corresponding methyl ether under pressure with hydrobromic acid in glacial acetic acid at 100° for one hour; the acetic acid was then evaporated, the residue dissolved in boiling water and the solution decolorized by digesting with Norite. On cooling, the hydroxyphenyl-hydantoin separated in the form of needles; m. p., 267°; yield, 90%. The compound is soluble in hot water, alcohol, glacial acetic acid, and insoluble in benzene, toluene, ether and chloroform. The hydantoin gave a strong color reaction with Millon's reagent.

Anal. Calcd. for $C_9H_8O_3N_2$: N, 14.58. Found: 14.65, 14.55.

3-*p*-Ethoxyphenyl-2-thiohydantoin, THE STABLE MODIFICATION, $C_2H_5O.C_6H_4\overline{N.CS.NH.CH_2}.CO$.—This hydantoin was prepared from *p*-ethoxyphenyl-isothiocyanate and ethyl amino-acetate in a manner similar to that used for synthesizing its corresponding methyl analog described above. The hydantoin was formed by boiling the reaction product with hydrochloric acid after removal of alcohol. It separated from hot alcohol in the form of colorless plates; m. p., 197°. The hydantoin is soluble in cold acetone, boiling alcohol and hot water and insoluble in benzene, ether and toluene; yield, 75%.

Anal. Calcd. for $C_{11}H_{12}O_2N_2S$: N, 11.85. Found: 11.92, 12.02.

THE UNSTABLE MODIFICATION.—Nine g. of *p*-ethoxyphenyl-isothiocyanate and 7.5 g. of the hydrochloride of ethyl amino-acetate were dissolved in 95% alcohol and then combined with a strong aqueous solution of potassium hydroxide (6 g.). After boiling for two hours the solution was concentrated by evaporation and cooled, when the potassium salt of *p*-ethoxyphenyl-thiohydantoic acid, $C_2H_5O.C_6H_4.NH.CSNH.CH_2$-COOH separated in the form of plates. The filtrate is described below. When this salt was dissolved in water and the solution acidified with hydrochloric acid, boiled and then cooled, 6 g. of golden-yellow, boat-shaped crystals separated from the solution.

[14] Jacobson and Kwaysser, *Ber.*, **26**, 2369 (1893).

[15] Hill and Kelsey, THIS JOURNAL, **44**, 2357 (1922).

These crystals melted at 197°, or the same temperature as the colorless plates of the *stable* modification. Also, both modifications showed the same behavior when heated, giving off red fumes just below the temperature of melting. A mixture of the two forms melted at 197°.

Anal. Calcd. for $C_{11}H_{12}O_2N_2S$: N, 11.85. Found: 12.03, 11.93.

CONVERSION OF THE UNSTABLE FORM INTO ITS STABLE MODIFICATION.—A small amount of the golden-yellow, boat-shaped crystals was digested at the boiling temperature for one hour in alcohol acidified with a small amount of hydrochloric acid. On cooling, the stable modification separated in the form of colorless plates melting at 197°. The reverse change from plates to needles was never observed.

3-*p*-Ethoxyphenyl-thiohydantoic Acid, $C_2H_5OC_6H_4NHCSNHCH_2COOH$.—This acid was obtained from the alcoholic filtrate remaining after removal of the undissolved potassium salt described above. When this filtrate was diluted with water and acidified with hydrochloric acid, the free acid separated in the form of needles melting at 128° with decomposition. Attempts to purify the acid by recrystallization always led to partial conversion into the thiohydantoin.

Anal. Calcd. for $C_{11}H_{14}O_3N_2S$: N, 11.03. Found: 11.5.

3-*p*-Ethoxyphenyl-hydantoin, $C_2H_5OC_6H_4.N.CO.NH.CH_2.CO$.—This hydantoin is easily prepared by digesting the corresponding thiohydantoin in aqueous solution containing an equivalent weight of chloro-acetic acid. On cooling the acid solution, when the reaction is complete, the hydantoin separates in the form of needles; m. p., 203°; yield, 70%. This compound is soluble in hot water and boiling alcohol, but insoluble in benzene and ether.

Anal. Calcd. for $C_{11}H_{12}O_3N_2$: N, 12.73. Found: 12.61, 12.80.

Attempts to convert this compound into the corresponding phenol derivative by heating at 100° with hydrobromic acid in glacial acetic acid were unsuccessful. Two experiments were conducted in which we heated it first for six hours with a 50% excess of hydrobromic acid, and then for the same period of time with a large excess of a 25% solution of the acid, but in both cases we recovered quantitatively the original hydantoin.

3-*p*-Nitrophenyl-thiohydantoin, $NO_2C_6H_4.N.CS.NH.CH_2.CO$.—This was prepared from *p*-nitrophenyl-isothiocyanate and ethyl amino-acetate in a manner similar to that in the case of the corresponding methoxy derivative described above. The hydantoin was obtained in the form of yellow needles which were purified by recrystallization from 95% alcohol. It has no sharp melting point and decomposes when heated at 170–172°; yield, about 50%. This hydantoin is soluble in hot alcohol, acetone, glacial acetic acid and insoluble in water, ether and benzene.

Anal. Calcd. for $C_9H_7O_3N_3S$: N, 17.72. Found: 17.86, 17.90.

***p*-Methoxyphenyl-glycine,** $CH_3OC_6H_4NHCH_2COOH$.—This compound was prepared according to the method described by Vater.[16] To a solution of 24.6 g. of *p*-anisidine and 18.8 g. of monochloro-acetic acid prepared, by warming, in 500 cc. of water was added 8 g. of sodium hydroxide and the mixture boiled for one-half hour, filtered hot and finally allowed to cool. The glycine derivative separated in the form of colorless needles melting at 146° to a clear oil. Vater has described this compound as being an amorphous substance which decomposes at 200° without melting. Our yield of acid was 33 g., or 92%.

Anal. Calcd. for $C_9H_{11}O_3N$: N, 7.74. Found: 7.77, 7.55.

[16] Vater, *J. prakt. Chem.*, [2] **29**, 294 (1884).

p-Methoxyphenyl-urea, $CH_3OC_6H_4NHCONH_2$.—This compound is formed smoothly by interaction in aqueous solution of potassium cyanate with the hydrochloride of anisidine. It was purified by crystallization from hot water and separated, on cooling, as plates; m. p., 168°; yield, quantitative.

Anal. Calcd. for $C_8H_{10}O_2N_2$: N, 16.88. Found: 16.88, 16.80.

This urea does not react with chloro-acetic acid or chloro-acetyl chloride when warmed with these reagents at 100°.

1-p-Methoxyphenyl-hydantoin, $\overline{NH.CO.N(C_6H_4OCH_3).CH_2.CO}$.—This hydantoin was prepared by dissolving 15 g. of p-methoxyphenyl-glycine and the required amount of sodium hydroxide in water and boiling the solution for about 10 minutes after further addition of 10 g. of potassium cyanate. The resulting solution was then acidified with hydrochloric acid and finally heated to boiling for two hours. On cooling, 6 g. of the hydantoin separated in the form of colorless prisms. The compound melted at 196° and agreed in all its properties with the hydantoin already described by Frerichs and Breustedt.[17] In a second experiment 9 g. of p-methoxyphenyl-glycine, 6 g. of ammonium chloride and 5 g. of potassium cyanate were mixed with about 50 cc. of water and the reaction mixture was warmed for two hours, when a clear solution was obtained. This was then acidified with hydrochloric acid, boiled for about 15 minutes and finally cooled, when 5 g. of the hydantoin separated. The yield by this method was about 50%, or a slight improvement over the result obtained by using potassium cyanate alone.

1-p-Hydroxyphenyl-hydantoin, II.—This hydantoin is obtained by heating its corresponding methyl ether in glacial acetic acid with an excess of hydrobromic acid at 100°. The hydantoin separated from the acetic acid in the form of prisms; yield, about 90%. The hydantoin does not melt when heated to 280° but undergoes slight decomposition. It is insoluble in hot water, warm alcohol, glacial acetic acid, benzene, toluene, chloroform and ether. It dissolves at once in alkaline solutions and gives a strong color reaction with Millon's reagent. Due to the fact that no satisfactory method of purification could be devised, the crude reaction product was used for analysis and low analytical results were obtained.

Anal. Calcd. for $C_9H_8O_3N_2$: N, 14.58. Found: 13.4, 13.5, 13.55.

α-Amino-p-methoxyphenyl-acetic Acid, $CH_3OC_6H_4CH(NH_2)COOH$.—The method used for the preparation of this acid was essentially that applied by Adams and Marvel[18] for the preparation of the corresponding phenylamino acid. One hundred and fifty g. of sodium cyanide and 160 g. of ammonium chloride were stirred vigorously with 500 cc. of water until complete solution resulted; 136 g. of anisic aldehyde dissolved in 400 cc. of 95% alcohol was then added slowly and the stirring continued for three hours. Dilution with 1 liter of water led to the partial precipitation of the nitrile of the above-mentioned acid as an oil. The remainder of the nitrile was obtained by extraction of the solution with benzene. The benzene solution of amino nitrile was shaken repeatedly with 1:1 hydrochloric acid when the hydrochloride of the basic nitrile separated in the form of needles. On digesting this salt with acid, hydrolysis took place with formation of the amino acid. This was separated in the form of its hydrochloride which decomposed when heated at 204°. This salt is soluble in hot water and alcohol; yield, 48 g.

Anal. Calcd. for $C_9H_{12}O_3NCl$: N, 6.45. Found: 6.60.

After the hydrochloride of the amino acid had been removed the filtrate was treated with ammonium hydroxide to neutralize the hydrochloric acid and cooled, when we

[17] Frerichs and Breustedt, *J. prakt. Chem.*, [2] **66**, 231 (1902).

[18] Adams, "Organic Chemical Reagents," vol. IV, *Univ. Illinois Bull.*, **20.**

obtained 9.5 g. more of the amino acid. This material agreed in all its properties with the acid previously described by Tiemann and Köhler.[19]

The benzene solution recovered from the hydrochloric acid extraction was dried and the excess of benzene distilled, when we recovered 48 g. of anisic aldehyde. Allowing for this recovery, the yield of amino acid was about 28%.

1-Acetyl-5-*p*-methoxyphenyl-2-thiohydantoin.—To a solution of 9.5 g. of the acid just described in a mixture of 5 cc. of glacial acetic acid and 45 cc. of acetic anhydride was added 4 g. of powdered ammonium thiocyanate, and the mixture was heated on the water-bath for 15 minutes and then allowed to stand. The hydantoin separated in the form of yellow prisms. The compound is soluble in hot alcohol and cold glacial acetic acid, and insoluble in water; m. p., 165°.

Anal. Calcd. for $C_{12}H_{12}O_3N_2S$: N, 10.60. Found: 10.65, 10.38.

After working up all filtrates we finally obtained 11 g. of this hydantoin, corresponding to a yield of 70%.

5-*p*-Methoxyphenyl-2-thiohydantoin, $\overline{\text{NH.CS.NH.CH}(C_6H_4OCH_3)\text{CO}}$.—This compound was easily obtained in quantitative yield by digesting the acetyl compound described above with dil. hydrochloric acid. It crystallized from hot 95% alcohol in needles which turned red when heated at 130° and then melted with decomposition at 200–210°. It is difficultly soluble in both water and alcohol.

Anal. Calcd. for $C_{10}H_{10}O_3N_2S$: N, 12.60. Found: 12.45, 12.80.

5-*p*-Methoxyphenyl-hydantoin, $\overline{\text{NH.CO.NH.CH}(C_6H_4OCH_3)\text{CO}}$.—This hydantoin was easily obtained by digesting the sulfur compound described above with chloro-acetic acid in aqueous solution; it was purified by crystallization from hot water; m. p., 188°. This compound has been described previously by Clarke and Francis.[20] It was also prepared directly from the hydrochloride of α-amino-*p*-methoxyphenyl-acetic acid by the action of potassium cyanate. A solution of 19 g. of the hydrochloride in boiling water with an excess of potassium cyanate was acidified with hydrochloric acid and heated for 30 minutes. On cooling, the hydantoin separated in the form of prisms melting at 188°; yield, 14 g.

5-*p*-Hydroxyphenyl-hydantoin, III.—This is easily prepared by heating its methyl ether described above with hydrobromic acid in glacial acetic acid at 100°. Working with a 14-g. unit we obtained a complete reaction in three hours; m. p., 262°; yield, 70%. It is insoluble in all common solvents except glacial acetic acid, in which it is very sparingly soluble. It gives a strong color reaction with Millon's reagent.

Anal. Calcd. for $C_9H_8O_3N_2$: N, 14.58. Found: 14.25, 14.55.

1,3-Di(*p*-methoxyphenyl)-2-thiohydantoin, $CH_3O.C_6H_4\overline{\text{N.CS.N}(C_6H_4OCH_3)\text{CH}_2\text{CO}}$.—A mixture of 9.6 g. of α-amino-*p*-methoxyphenyl-acetic acid and 9.6 g. of *p*-methoxyphenyl-isothiocyanate was melted by heating in an oil-bath at 140–160° for two hours. The resulting product was digested with water for one hour, and the unaltered isothiocyanate then removed by steam distillation. We obtained 18 g. of the hydantoin which was practically insoluble in water. In three successive experiments we obtained yields of 95%, 80% and 90%, respectively. The substance is sparingly soluble in alcohol, benzene, toluene, acetone and glacial acetic acid; it is insoluble in alkaline solutions. When purified by crystallization from 95% alcohol it separated in the form of needles; m. p., 185°.

[19] Tiemann and Köhler, *Ber.*, **14**, 1979 (1881).

[20] Clarke and Francis, *J. Chem. Soc.*, **99**, 319 (1911).

Anal. Calcd. for $C_{17}H_{16}O_3N_2S$: N, 8.54. Found: 8.63, 8.88.

1,3-Di(*p*-methoxyphenyl)-hydantoin, $CH_3OC_6H_4N.CO.N(C_6H_4OCH_3)CH_2CO$.—A mixture of 18 g. of 1,3-di(*p*-methoxyphenyl)-2-thiohydantoin and 100 g. of monochloro-acetic acid was boiled in aqueous solution for 20 hours. The desulfurization was slow and the hydantoin dissolved very slowly leaving behind a small amount of oil which solidified as the mixture cooled. After the acid solution had been filtered and cooled, two types of crystals deposited. The majority were colorless prisms, and grouped around these characteristically in the form of round pincushions were masses of colorless needles. When the crude reaction product was recrystallized from hot water the same crystalline habit was revealed. This product was free from sulfur. By treating the hydantoin with glacial acetic acid the needle-like crystals were altered or dissolved, leaving behind the prismatic crystals; m. p., 157°; yield, 12 g., or 70%. The compound is soluble in hot water, hot alcohol, hot acetic acid and cold acetone. It does not dissolve in alkaline solutions.

Anal. Calcd. for $C_{17}H_{16}O_4N_2$: N, 8.95. Found: 8.79, 9.0.

1,3-Di(*p*-hydroxyphenyl)-hydantoin, IV.—This compound is formed by heating the hydantoin just described with an excess of hydrobromic acid in glacial acetic acid for two hours. After the evaporation of the excess of acid and cooling, the hydantoin was obtained in a crystalline condition; yield, 60%. It crystallizes from acetic acid in the form of plates; m. p., 242°. It dissolves in alkaline solutions and gives a strong color reaction when treated with Millon's reagent.

Anal. Calcd. for $C_{15}H_{12}O_4N_2$: N, 9.87. Found: N, 9.83, 9.86.

5,5-Di(*p*-methoxyphenyl)-hydantoin, $NH.CO.NH.C(C_6H_4OCH_3)_2.CO$.—This hydantoin was prepared according to the method previously described by Biltz.[21]

5,5-Di(*p*-hydroxyphenyl)-hydantoin, VII.—This hydantoin is easily obtained by heating the corresponding methoxy compound with hydrobromic acid in glacial acetic acid at 100° for three hours. When the hot acid solution was allowed to cool, the substance separated in the form of needles. It was purified by dissolving in alcohol and pouring the solution into toluene in which it is practically insoluble. In this manner colorless needles were obtained which did not show evidence of melting below 280°. The compound gives a strong reaction with Millon's reagent.

Anal. Calcd. for $C_{15}H_{12}O_4N_2$: N, 9.87. Found: 9.86, 9.70.

3,5-Di(*p*-methoxyphenyl)-2-thiohydantoin, $CH_3OC_6H_4N.CS.NH.CH(C_6H_4OCH_3).CO$.—Our method of preparing this compound was as follows. A solution of 5 g. of anisyl-isothiocyanate, 1.2 g. of sodium hydroxide and 6.6 g. of α-amino-*p*-methoxyphenyl-acetic acid in 80% alcohol was boiled for ten minutes. It was then acidified with hydrochloric acid and allowed to stand for about two hours on a hot-plate. The hydantoin separated as a mass of colorless plates which dissolved in hot alcohol; m. p., 193°; yield, 95%. This compound is soluble in acetone and alcohol, and insoluble in ether, benzene and toluene. It dissolves in alkali.

Anal. Calcd. for $C_{17}H_{16}O_3N_2S$: N, 8.54. Found: 8.40, 8.8.

3,5-Di(*p*-methoxyphenyl)-hydantoin, $CH_3OC_6H_4N.CO.NH.CH(C_6H_4OCH_3).CO$.—This was prepared by desulfurization of the hydantoin described above with chloro-acetic acid. It was purified by crystallization from hot water and separated in the form of needles; m. p., 170°; yield, 45%. This compound is sparingly soluble in hot water,

[21] Biltz, *Ber.*, **42**, 1800 (1909).

alcohol and glacial acetic acid, and insoluble in benzene. It dissolves in alkaline solutions.

Anal. Calcd. for $C_{17}H_{16}O_4N_2$: N, 8.97. Found: 9.00, 9.1

3,5-Di(*p*-hydroxyphenyl)hydantoin, V.—This compound was obtained in an impure condition by heating the corresponding dimethyl ether with hydrobromic acid in glacial acetic acid solution. After completion of the reaction the excess of acetic acid was evaporated and the residue then diluted with water, when an oil separated which solidified on cooling. This showed a strong color reaction with Millon's reagent but was non-crystalline, and gave no sharp melting point; yield, 75%. The compound dissolved easily in alcohol, glacial acetic acid, acetone and dil. alkali solutions, but was insoluble in water and benzene. It was dried for several weeks in a desiccator over sulfuric acid, and the nitrogen determined by the Kjeldahl method.

Anal. Calcd. for $C_{15}H_{12}O_4N_2$: N, 9.87. Found: 8.21, 8.23.

Summary

1. The desirability of synthesizing phenol derivatives of hydantoin and investigating their antiseptic properties is emphasized.

2. Six of the seven theoretically possible mono- and diphenol derivatives (*para* compounds) of hydantoin have been described.

3. All of these compounds have been synthesized by application of methods already described in the chemical literature.

4. No phenol derivatives of hydantoin have hitherto been described.

5. The antiseptic properties of these various compounds will be reported in a later publication.

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[CONTRIBUTION FROM THE JESSE METCALF CHEMICAL LABORATORY OF BROWN UNIVERSITY]

THE REACTION BETWEEN BENZAL-ANILINE AND CARBON DISULFIDE AT HIGH TEMPERATURE AND PRESSURE

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The purpose of this investigation was to study the reaction between benzal-aniline, $C_6H_5CH{=}NC_6H_5$, and carbon disulfide; first, with the idea of finding a new method for entering the mustard oil series, and second, with the intention of throwing some light upon the action of carbon-disulfide upon the $>CH{=}N-$ linkage. The reaction expected is as follows: $C_6H_5CH{=}NC_6H_5 + SCS \longrightarrow C_6H_5CHS + C_6H_5NCS$. Preliminary experiments showed that the benzal-aniline, while it is extremely soluble in carbon disulfide, crystallizes from it unchanged. Also, mixtures heated in sealed tubes at 100° showed no evidences of interaction. Experiments were then carried out in sealed tubes at higher temperatures, but these proved unsatisfactory on account of the very considerable pressures developed, and the resulting frequent explosion of the tubes. It