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Summary

1. Naphthalic anhydride or 4-bromonaphthalic anhydride cannot be used in place of phthalic anhydride in the Friedel and Crafts reaction.

2. Acenaphthene may be used in the Rubidge and Qua reaction for the preparation of phthalides from phthalic anhydride and aromatic hydrocarbons.

3. Many new derivatives of acenaphthene have been described.

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RESEARCHES ON HYDANTOINS. XLII. A METHOD OF SYNTHESIZING 1,5-DIARYL-HYDANTOINS: 1,5-DI(PARA-HYDROXYPHENYL)-HYDANTOIN¹

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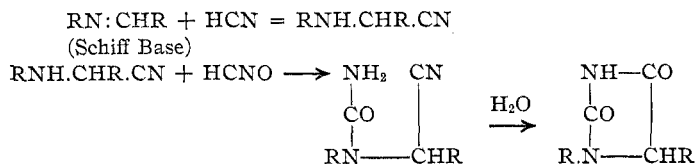
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In a previous paper³ on hydantoins, a description has been given of three of the four possible di-(*p*-phenol) derivatives of hydantoin the 1,3-diphenol, the 3,5-diphenol and the 5,5-diphenol. The synthesis and properties of the fourth representative of this series, the 1,5-diphenol, $\text{NHCON}(\text{C}_6\text{H}_4\text{OH}).\text{CH}(\text{C}_6\text{H}_4\text{OH}).\text{CO}$, are now described in this paper. I

shall also report here the results of preliminary bacteriological tests carried out to determine the comparative antiseptic properties of several of these new phenolic derivatives.

The method of synthesis which was undertaken and applied successfully for the preparation of the diphenol-hydantoin is expressed by the formulas below.



The Schiff base which served as the starting point of the synthesis was *p*-anisal-anisidine I. This is easily prepared by condensation of *p*-anisic aldehyde with *p*-anisidine or by the action of the latter amine on the cyano-

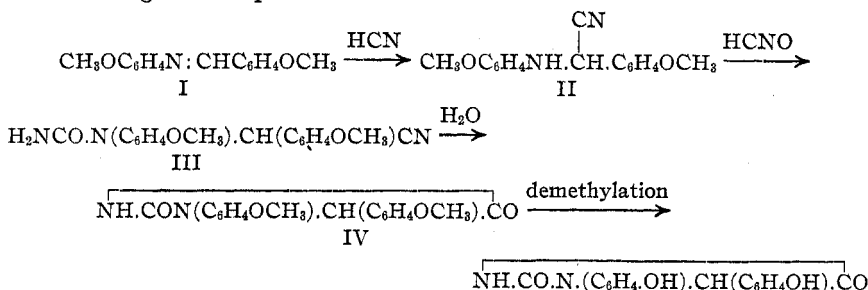
¹ A contribution to the research on antiseptics conducted in coöperation with the National Research Council Sub-committee on "Internal Antisepsis."—T. B. Johnson, Chairman.

² Holder of the du Pont Fellowship in Chemistry, 1923-1924.

³ Coghill and Johnson, *THIS JOURNAL*, **47**, 184 (1925).

hydrin of anisic aldehyde. Quite in accord with observations made by several workers who have investigated the behavior of hydrocyanic acid towards unsaturated compounds of this type,⁴ the base I adds hydrocyanic acid almost quantitatively at ordinary temperature with the formation of the saturated amino acid nitrile II. Attempts to convert this compound into the corresponding acid or acid amide by hydrolysis under different experimental conditions were unsuccessful. The nitrile easily undergoes dissociation with loss of hydrocyanic acid, being transformed into the original Schiff base. In fact, this reaction is reversible and the dissociation takes place even on warming an alcoholic solution of the nitrile.

The nitrile II is easily transformed into its corresponding urea derivative III by interaction with cyanic acid in glacial acetic acid solution; a method of operating which was applied with success by Bailey⁵ in his work on iminodiacetonitrile. This urea is extremely stable but undergoes hydrolysis easily by digestion with hydrochloric acid giving quantitatively the hydantoin IV. Demethylation of the latter compound is easily brought about by heating it with hydrobromic acid in glacial acetic acid at 100°, when the desired diphenolic derivative of hydantoin is formed. These changes are represented as follows.



A complete description of these operations and the properties of the various compounds involved in the synthesis of the diphenol is given in the experimental part of this paper. These researches are being continued in the Sterling Laboratory.

Experimental Part

The Cyanohydrin of *p*-Anisic-aldehyde, $\text{CH}_3\text{OC}_6\text{H}_4\text{CH}(\text{OH})\text{CN}$.—This compound, which was used as the starting point in this research, was synthesized according to the method described by McCombie and Parry.⁶

⁴ Cech, *Ber.*, **11**, 246 (1878). Plöchl, *Ber.*, **14**, 1139 (1881). Tiemann and Piest, *Ber.*, **15**, 2028 (1882). Von Miller and Plöchl, *Ber.*, **25**, 2020 (1892); *Ann.*, **283**, 11 (1894); **290**, 1 (1896); **303**, 75 (1898). Delepine, *Bull. soc. chim.*, [3] **29**, 1200 (1903).

⁵ Bailey and Snyder, *THIS JOURNAL*, **37**, 935 (1915). Bailey and Lochte, *ibid.*, **39**, 2443 (1917).

⁶ McCombie and Parry, *J. Chem. Soc.*, **95**, 584 (1909).

Action of *p*-Anisidine on this Cyanohydrin.—A solution of 3.6 g. of the hydroxynitrile and 3.3 g. of *p*-anisidine in alcohol was heated on a boiling water-bath for two hours. As the liquid cooled, a thick magma of crystalline material was obtained which was recognized as a mixture of two compounds. Separation into two distinct fractions was easily accomplished by crystallization from boiling 95% alcohol.

(a) ***p*-Anisal-anisidine, I.**—This was easily separated from the reaction product obtained as described above, in the form of diamond-shaped prisms. They melted sharply at 146° to an oil. The constitution of the compound was established by the fact that the same product (Schiff base) was obtained by direct condensation of anisic aldehyde with *p*-anisidine. A mixture of compounds prepared by the two different methods melted at 146°.

Anal. Calcd. for $C_{15}H_{15}O_2N$: N, 5.80. Found: 6.13, 6.0.

(b) (***p*-Methoxyphenylamino)-methoxyphenyl-acetonitrile, II.**—This new compound, when separated from the Schiff base described above, crystallized in the form of slender needles melting at 90° to a clear oil. It was purified by crystallization from 95% alcohol. Repeated recrystallizations from this solvent always led to partial decomposition of the nitrile with formation of the Schiff base. This probably accounts for the low percentage of nitrogen found by analysis.

Anal. Calcd. for $C_{16}H_{16}O_2N_2$: N, 10.45. Found: 9.90, 9.93.

The Schiff base and corresponding nitrile were obtained in the reaction described above in yields of about equal proportions (50%). When this reaction was conducted in benzene the Schiff base was the only product and the yield was quantitative.

This substituted amino nitrile was also synthesized according to the method described by Tiemann and Piest,⁴ namely, by adding hydrocyanic acid to the Schiff base.

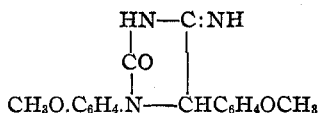
The Schiff base was first formed in alcoholic solution by warming anisic aldehyde with the required amount of *p*-anisidine. Five g. of powdered sodium cyanide was then added to the hot solution followed by 10 cc. of concd. hydrochloric acid, slowly, through a dropping funnel, the tip of which extended below the surface of the alcohol. After final addition of the acid the solution was filtered and cooled immediately when the nitrile or hydrocyanic acid addition product separated in the form of small, yellow needles melting constantly at 90°. By using a large excess of hydrogen cyanide it was possible to reduce the dissociation of the nitrile and avoid practically all formation of the Schiff base. In fact, we were able to obtain consistently almost quantitative yields of the nitrile by this method.

Behavior of the Nitrile on Hydrolysis.—Attempts to hydrolyze the nitrile to its corresponding acid were unsuccessful on account of the easy dissociation of the compound with loss of hydrocyanic acid. Heating with hydrochloric and sulfuric acids led to complete destruction of the compound. I also investigated the behavior of the nitrile towards hydrogen peroxide.⁷ To 125 cc. of 3% hydrogen peroxide solution made alkaline with sodium hydroxide was added 2 g. of the aminonitrile. The mixture was stirred vigorously for an hour at room temperature and then heated to 60° and the stirring continued for another half hour. The odor of isonitrile became apparent toward the end of the stirring period. The resulting crystalline product was identified as the Schiff base melting at 146°. This experiment was repeated, keeping the reaction temperature at 40° instead of 60°, when we again obtained the Schiff base and in a quantitative yield.

Action of Cyanic Acid on the Aminonitrile.—THE FORMATION OF THE CORRESPONDING UREA DERIVATIVE, III. To a solution of 9 g. of the aminonitrile in glacial acetic acid was added 7 g. of pulverized potassium cyanate while the mixture was slowly stirred.

⁷ McMaster and Langreck, *THIS JOURNAL*, 39, 103 (1917).

The product was allowed to stand for ten hours at ordinary temperature and then poured into a large volume of water, whereupon a crystalline material separated immediately. This was identified as the urea derivative; yield, 9 g., or 87%. It was purified by recrystallization from 95% alcohol and separated in light yellow prisms; m. p., 131°. The urea is insoluble in alkaline solutions, thus proving that it is not an isomeric substance having the following constitution.



Anal. Calcd. for $\text{C}_{17}\text{H}_{17}\text{O}_5\text{N}_3$: N, 13.50. Found: 13.38, 13.54.

1,5-Di-(*p*-methoxyphenyl)-hydantoin, IV.—Nine g. of the urea-nitrile described above was digested with 100 cc. of 1:4 hydrochloric acid for one-half hour. It dissolved immediately on warming and when the solution was cooled the hydantoin separated in a crystalline condition. The yield was quantitative (9 g.). This compound crystallized from 95% alcohol in the form of prisms; m. p., 190°. This hydantoin dissolves at once in dil. alkali.

Anal. Calcd. for $\text{C}_{17}\text{H}_{19}\text{O}_5\text{N}_2$: N, 8.97. Found: 8.89, 8.93.

1,5-Di-(*p*-hydroxyphenyl)-hydantoin.—This hydantoin was formed by heating the compound described above, in glacial acetic acid solution with hydrobromic acid. This change was easily brought about by heating for three hours at 100°. After removal of the excess of acetic acid by evaporation, the reaction product was purified by dissolving it in alcohol and pouring this solution into benzene. The hydantoin then separated in the form of needles which were sparingly soluble in water, alcohol, glacial acetic acid and alkaline solutions, and insoluble in benzene and toluene. The hydantoin gives a strong color reaction with Millon's reagent; yield of purified hydantoin, 50%. For analysis the hydantoin was purified by crystallization from boiling water; m. p., 160°.

Anal. Calcd. for $\text{C}_{16}\text{H}_{12}\text{O}_5\text{N}_2$: N, 9.87. Found: 9.80, 9.88.

Preliminary Bacteriological Examination of Phenol Hydantoins

In order to determine whether or not the seven *p*-hydroxyphenol derivatives of hydantoin described in this and in our previous publication⁸ are characterized by any specific antiseptic action, tests were made for antiseptic power according to a simplified form of the method devised by Anderson and McClintic⁸ of the United States Public Health and Marine Hospital Service. No attempt was made to determine the actual phenol coefficients of any of the combinations, but only a preliminary series of comparative experiments was conducted to ascertain their relative antiseptic merits. The purpose of these tests was to obtain a clue or suggestion to direct us in new lines of research in this field of compounds.

A 24-hour broth culture of the Hopkins-Cole strain of *Bacillus typhosus* was used and just prior to using the suspension of bacteria it was filtered through absorbent cotton in a sterile funnel into a sterile tube. This excluded clumps of bacteria from the experiments. One-half g. of the hydantoin to be tested was weighed into an Erlenmeyer flask and 50 cc.

⁸ Anderson and McClintic, *J. Infectious Diseases*, 8, 1 (1911).

of distilled water added. None of the seven compounds under examination dissolved at ordinary temperatures. Those which did not dissolve in hot water and remain in solution were treated with just enough standard sodium hydroxide solution to dissolve them in the form of their sodium salts. Two-cc. samples of each hydantoin solution were then tubed and plugged with cotton. To be certain that these solutions were aseptic, they were then autoclaved for 15 minutes at one atmosphere pressure.

The method of testing was as follows. Four tubes of hydantoin solution and one tube of sterile distilled water were placed in the rack, and to each was added, at 30-second intervals, 0.1 cc. of the culture of *Bacillus typhosus*. Two and one-half minutes after the bacteria had been added to the first tube, one loopful of the solution was withdrawn and planted in plain broth. Thirty seconds later a loopful from the second tube was removed and planted. This operation was continued through the five tubes, so that we had removed a sample from each tube at the end of two and a half minutes. By starting again with the first tube and repeating, it was thus possible to secure a sample of the bacteria which had been exposed for 5 minutes to the action of the phenol-hydantoin solution. In like manner samples were removed at intervals of 10, 15, 20, 25, 45 and 60 minutes. The broth tubes were then all placed in an incubator and maintained at 37° for 48 hours.

The phenol-hydantoin solutions submitted to these tests were the following: (a) 1-, 3- and 5-*p*-hydroxyphenyl-hydantoin; (b) 1-, 3-, 3,5-, 5,5- and 1,5-di(*p*-hydroxyphenyl)-hydantoin.

Of these 7 phenol-hydantoin solutions, none exhibited an antiseptic activity at all comparable with that of phenol itself. Most of the combinations were too insoluble in water to be of any value as antiseptic principles. We are dealing in this series with specific combinations in which the phenol group is joined directly to the hydantoin ring. In the light of the results obtained showing the low bactericidal activity, it will be of especial interest to study other hydantoin solutions in which the phenolic residue is joined to the hydantoin ring by aliphatic chains such as $-\text{CH}_2-$ and $-\text{CH}_2.\text{CH}_2-$, etc.⁹

Summary

1. In this paper is described a new method of preparing 1,5-diaryl-hydantoin.
2. This new method of synthesis has been applied with success for the preparation of 1,5-di(*p*-hydroxyphenyl)-hydantoin.
3. Several *p*-phenol-hydantoin solutions have been submitted to bacteriological tests in order to ascertain their comparative antiseptic strengths. In no

⁹ I desire to express my appreciation of the coöperation of Professor L. F. Rettger of the Department of Bacteriology, who gave me facilities for carrying out the bacteriological tests of antiseptic properties.

case examined was a value found comparable with the antiseptic strength of phenol.

NEW HAVEN, CONNECTICUT

[CONTRIBUTION FROM THE COLOR LABORATORY, BUREAU OF CHEMISTRY, JOINTLY WITH
SOIL FERTILITY INVESTIGATIONS, BUREAU OF PLANT INDUSTRY, UNITED STATES
DEPARTMENT OF AGRICULTURE, No. 100]

THE SPECTROPHOTOMETRIC DETERMINATION OF HYDROGEN-ION CONCENTRATIONS AND OF THE APPARENT DISSOCIATION CONSTANTS OF INDICATORS. II. THYMOL BLUE¹

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In the Sørensen (*P_H*) range between 4.5 and 6.0, thymol blue (thymol-sulfonephthalein) exists in what will be termed its "mid-form," in which it is yellow, with an absorption band in the violet portion of the spectrum. As the alkalinity of the solution is increased over the *P_H* range 6.0 to 12.0, the indicator is progressively and completely transformed into its alkaline form in which it is violet-blue, with an absorption band in the yellow and

TABLE I
THYMOL BLUE: ALKALINE RANGE

<i>P_H</i> Corr.	Temp. °C.	Indicator per liter of solution Mg.	<i>E</i> at 460 μ	<i>E</i> at 595 μ	<i>R</i> ₂	<i>R</i> ₁	<i>K</i>
5.2	24	40	0.70	...	∞	0.00	..
7.25	24.5	80	1.38	0.07	19.7	.017	(9.01)
7.73	23.5	80	1.35	.23	5.87	.056	(8.96)
7.94	24	80	1.30	.37	3.51	.090	(8.94)
8.31	26.5	40	0.59	.42	1.40	.204	(8.90)
8.50	24.5	40	.56	.57	.98	.279	8.92
8.71	23.5	40	.50	.79	.63	.388	8.91
8.91	22	40	.42	1.03	.40	.507	8.90
9.09	24.5	40	.36	1.25	.29	.610	8.89
9.13	25.5	32	.28	1.035	.27	.631	8.90
9.31	25	32	.25	1.165	.215	.710	8.92
9.53	23.5	32	.205	1.325	.155	.808	8.91
9.75	23.5	32	.18	1.425	.126	.869	8.92
9.98	23	32	.155	1.51	.10	.922	(8.93)
10.74	24	32	.125	1.595	.08	.972	(9.00)
11.37	24.5	32	.125	1.625	.077	.991	(9.37)
0.05 <i>M</i> NaOH	24	32	.12	1.64	.075	1.00	..

¹ Presented before the Dye Section of the American Chemical Society at its Washington meeting, April 21-26, 1924.

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