

presence of water. With a constant surface, the rate of the reaction is proportional to both the concentration of ethylene and concentration of bromine. No evidence of any deviation from a bimolecular reaction was found. The specific reaction rate during the first 12 seconds of the reaction is apparently greater than the subsequent rate, but the abnormality does not involve more than 1% of the ethylene. It is thought that this small initial reaction owes its higher velocity to wall catalysis, and is not to be taken as evidence of a highly reactive form of ethylene present in small amount.

BERKELEY, CALIFORNIA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

THE UTILIZATION OF PARA-DICHLOROBENZENE FOR SYNTHESIS IN THE DIPHENIC ACID SERIES

BY EDWARD B. HUNN¹

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In the course of an investigation in the Sheffield Chemical Laboratory dealing with certain organic substances which might be expected to exert a pharmacological action similar to that of the alkaloid, morphine, it became necessary to develop a method for synthesizing disubstituted derivatives of diphenic acid with halogen substituents in the 5 and 5' or the 6 and 6' positions. These positions in the diphenic acid nucleus correspond to the 3,6 and 4,5 positions in the phenanthrene molecule, which configuration according to our present knowledge is a part of the morphine molecule.

For the synthesis of substituted diphenic acids one has recourse to three general methods, (1) the oxidation of known phenanthrene or phenanthraquinone derivatives, (2) direct substitution in the diphenic acid molecule, and (3) synthesis by bringing together 2 molecules of a substituted benzoic acid. The number of known symmetrically substituted diphenic acids is small. Schmidt² has prepared the following by the oxidation of the corresponding phenanthraquinone derivatives; 4,4'-dibromo-, 6,6'-diamino-, 6-amino-, 6'-hydroxy-, 6,6'-dinitro-, 4,4'-diamino-, and 4,4'-dihydroxy-diphenic acids. Direct nitration or halogenation leads chiefly to substitution in the 4 and 4' positions. By the third procedure Ullmann³ has prepared 4,4'-dinitro-diphenic acid from 2-iodo-3-nitrobenzoic acid, and Mayer⁴ has made 6,6'-dimethyl-diphenic acid from 2-iodo-3-methylbenzoic acid ester.

¹ This paper is constructed from a dissertation presented by Edward B. Hunn in June, 1921, to the Faculty of the Graduate School of Yale University in candidacy for the degree of Doctor of Philosophy. (T. B. Johnson.)

² Schmidt, *Ber.*, **36**, 3726 (1903); **37**, 3567 (1904); **38**, 3769 (1905).

³ Ullmann, *ibid.*, **34**, 2174 (1901).

⁴ Mayer, *ibid.*, **44**, 2298 (1911).

Reasoning that the third method of approach would be the most practical for obtaining satisfactory yields of a symmetrically substituted diphenic acid of known constitution, attention was naturally first turned toward selecting a starting point which would enable us to utilize a chemical that was both cheap and readily convertible by a few reactions into one of the desired compounds. *p*-Dichlorobenzene was chosen for this purpose. Since the war many uses have been suggested for this by-product as, for example, the manufacture of sulfur black,⁵ picric acid,⁶ and phenol.⁷ Advantage has also been taken of its antiseptic action for the preparation of disinfectants.⁸ Utilization in the chemical industry has centered around the replacement of one or both of its chlorine atoms by other groupings, usually with the aid of the catalyst, copper powder. By this means *p*-chlorophenol,⁹ *p*-aminophenol,¹⁰ *p*-phenylene-diamine,¹¹ and amino-anthraquinone derivative¹² have been prepared. The mononitro¹³ and monosulfonic acid¹⁴ derivatives of *p*-dichlorobenzene have also been widely used in synthetical reactions leading to the formation of amino, phenolic and methoxy compounds, because of the pronounced labilizing action of the negative acidic groupings upon the chlorine atom in the *ortho* position to these.

The synthesis which I have brought to a successful conclusion is represented in its various stages by the structural formulas given in Scheme 1 of the chart below. The starting point was *p*-dichlorobenzene (I) which was converted into its active nitro compound (II) by nitration. As is well known, one of the chlorine atoms is thus rendered very susceptible to chemical change. From this step on, the intermediate reactions were carefully developed with production of a good yield of the desired diphenic acid (VII). I was unable to accomplish successfully a synthesis of the diphenic acid by operating according to Scheme 2.

⁵ "Census of Dyes and Coal-Tar Chemicals," U. S. Tariff Commission, 1917, pp. 12, 27, 28; 1918, p. 34.

⁶ Marshall, "Explosives," P. Blakiston's Son and Co., 1917, vol. 1, p. 278.

⁷ Aylsworth, U. S. pat. 1,213,412, 1917. Meyer and Bergious, *Ber.*, **47**, 3165 (1914).

⁸ Curschmann, *Deut. med. Wochschr.*, **41**, 891 (1915). Küster and Günzler, *Hyg. Rundschau*, **25**, 465 (1915). Nocht and Halberkaun, *Münch. med. Wochschr.*, **62**, 626 (1916). Duckett, *U. S. Dept. Agr. Bull.*, **167** (1915). Cook, *ibid.*, **245** (1915); *J. Agr. Research*, **9**, 371 (1917). Sollmann, *J. Pharmacol.*, **12**, 129 (1917); **14**, 253 (1919). Konsantz, *Am. J. Pharm.*, **90**, 340 (1918); *J. Am. Pharm. Assoc.*, **7**, 341 (1918).

⁹ Ger. pat. 281,175, 1913.

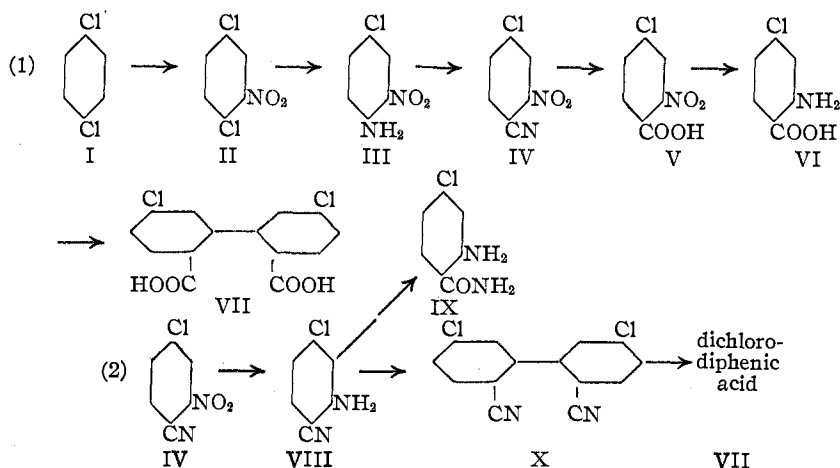
¹⁰ Ger. pat. 205,415, 1907.

¹¹ Ger. pat. 202,170, 1907; 204,848, 1908. Quick, *THIS JOURNAL*, **42**, 1033 (1920).

¹² Ger. pats. 215,294, 1905; 263,424, 1911; 175,069, 1905.

¹³ Ullmann and Sane, *Ber.*, **44**, 3730 (1911). Ullmann, *Ann.*, **332**, 93 (1904).

¹⁴ Ger. pats. 202,564, 202,565, 202,566, 204,972, 1904; 284,533, 1912; 132,423, 1901.



Experimental Part

2-Nitro-4-chloro-aniline (III).—*p*-Dichlorobenzene was nitrated according to the directions given by Crowell and Raiford.¹⁵ The resulting mononitro compound was readily converted into 2-nitro-4-chloro-aniline by the action of aqueous ammonia at 180°, without the aid of catalysts; yield, 94%. Its properties and melting point were identical with those described in the literature.

2-Nitro-4-chlorobenzonitrile (IV).—This substance has been prepared and studied by Claus and Kurz,¹⁶ who obtained it by the application of Sandmeyer's reaction to 2-nitro-4-chloro-aniline. The yield was not recorded.

Upon investigation of this reaction it was found that the nitrile could be prepared in good yield by operating under proper experimental conditions. Because of its weakly basic character 2-nitro-4-chloro-aniline dissolves only in strong acids. Experiments using hydrochloric acid as a diazotizing medium showed that the reaction was not complete even after the mixture had stood for 3 hours with an excess of nitrous acid. After several preliminary experiments the following procedure was finally adopted as the most satisfactory. The clear solution of 1 part of the amine dissolved in 1.6 parts of conc. sulfuric acid was poured with vigorous stirring into 10 parts of cold water. By this procedure the amine was precipitated in very finely divided form, which allowed of ready and complete diazotization using the calculated quantity of a 10% sodium nitrite solution. The perfectly clear diazo solution was then added in the usual manner to a cuprous cyanide solution prepared from 25 g. of crystallized cupric sulfate in 75 cc. of water and 20 g. of sodium cyanide (98%) in 50 cc. of water for each 10 g. of amine used. The crude nitrile separated in clusters of small, dark brown needles, which were filtered from the liquid and purified as described below; yield of crude product 96–99%; m. p., 92°.

For purification distillation with steam was found to be more satisfactory than either vacuum distillation or crystallization from dil. ethyl alcohol. By this means, with the flask kept at 180–190° in an oil-bath, a nearly colorless product, melting at 97°, was obtained; yield of purified product 70–80% of the weight of crude nitrile.

2-Nitro-4-chlorobenzoic Acid (V).—Claus and Kurz¹⁶ obtained this acid by the hydrolysis of 2-nitro-4-chlorobenzonitrile, and recorded its physical properties and those

¹⁵ Crowell and Raiford, *THIS JOURNAL*, **42**, 145 (1920).

¹⁶ Claus and Kurz, *J. prakt. Chem.*, [2] **37**, 197 (1888).

of its common salts. It was also prepared, about the same time, by Varnholdt¹⁷ by the oxidation of 2-nitro-4-chlorotoluene.

Two parts of purified 2-nitro-4-chlorobenzonitrile were digested for 15 minutes over a free flame with 3.5 parts by weight of conc. sulfuric acid and 1.5 parts of water. After the mixture had cooled, 10 parts of cold water were added and the gray crystals of 2-nitro-4-chlorobenzoic acid were separated by filtration. This product melted at 139° (uncorr.), the temperature given for it by Claus and Kurz,¹⁶ and required no further purification; yield 93-95%.

Attempts were also made, following a procedure recently outlined by Rosemund and Struck,¹⁸ to prepare this acid directly by heating 2,5-dichloro-nitrobenzene (II) with sodium cyanide in the presence of cuprous cyanide and a solvent. These investigators succeeded in replacing halogen by the carboxyl group in many benzene halogen derivatives. Their directions, as well as modified procedures, have in this instance led to no success. With 30% ethyl alcohol as a solvent a large amount of ammonia was formed, resulting from the hydrolysis of the sodium cyanide,¹⁹ which caused the formation of considerable 2-nitro-4-chloro-aniline (III). Rosemund and Struck made no mention of having observed a secondary reaction of this character in their experiments. When 95% ethyl alcohol was used as a solvent no ammonia was formed, but the product was a dark gum from which none of the desired acid could be isolated.

2-Amino-4-chlorobenzamide (4-Chloro-anthranilo-amide) (IX).—In attempting to reduce 2-nitro-4-chlorobenzonitrile (IV) to 2-amino-4-chlorobenzonitrile (VIII) by employing iron and acetic acid in the proportions specified in a German patent,²⁰ which describes the reduction of *o*-nitrobenzonitrile to anthranilonitrile, there was formed a mass of light brown crystals melting at 160°. From a mixture of benzene and ligroin this material crystallized in colorless, oblong plates which melted sharply at 181.5° (corr.). It was identified as 4-chloro-anthranilo-amide (IX).

Analyses. Calc. for C₇H₇ON₂Cl: N, 16.47. Found: 16.43, 16.50.

This substance was readily dissolved by conc. hydrochloric and sulfuric acids, and was insoluble in cold sodium hydroxide solution. When boiled with 50% sulfuric acid it was converted by hydrolysis to 4-chloro-anthranilic acid (VI), which crystallized in the form of colorless needles melting at 240° (corr.). When warmed with nitrous acid this amide gave 4-chlorosalicylic acid, which was identified by its melting point, 207° (corr.), when crystallized from dil. ethyl alcohol.

Further attempts to reduce 2-nitro-4-chlorobenzonitrile resulted only in the formation of the amide.

2-Amino-4-chlorobenzoic Acid (4-Chloro-anthranilic Acid) (VI).—This acid has been described by Cohen²¹ who prepared it by the oxidation of the acetyl derivative of 2-amino-4-chlorotoluene. In addition he prepared its various metallic salts and several azo dyestuffs formed from its diazotized derivative.

For the reduction of 2-nitro-4-chlorobenzoic acid the following method was adopted. Twenty g. of the nitro acid was dissolved in 250 cc. of 10% aqueous ammonia. To this was added a solution of 180 g. of crystallized ferrous sulfate in 600 cc. of water. The dark brown, pasty mixture was then heated on the steam-bath for 2 hours, the color turning to black. It was found necessary at this point to add 150 to 200 cc. of 25% sodium hydroxide solution in order to liberate the chloro-anthranilic acid from its

¹⁷ Varnholdt, *J. prakt. Chem.*, **36**, 30 (1879).

¹⁸ Rosemund and Struck, *Ber.*, **52**, 1749 (1919).

¹⁹ *J. Ind. Eng. Chem.*, **12**, 331 (1920).

²⁰ Ger. pat. 212,207, 1907.

²¹ Cohen, *Monatsh.*, **22**, 485 (1901).

insoluble iron salt. After the black iron oxide was removed, the filtrate was made weakly acid with hydrochloric acid. Pure, colorless 4-chloro-anthranilic acid separated in finely divided flakes; yield, 16 g., or 95%; m. p., 239° (corr.). From dil. ethyl alcohol it was obtained in slender, colorless needles; m. p., 240° (corr.).

Benzoyl Derivative of 4-Chloro-anthranilic Acid, $C_6H_5ClCOOHNHCOCH_2C_6H_5$.—Two g. of 4-chloro-anthranilic acid was heated with 3 g. of benzoyl chloride and 10 cc. of 10% sodium hydroxide solution on the steam-bath. The mixture was then acidified and filtered. The resulting straw-colored crystals, after successive recrystallizations from dil. ethyl alcohol and from benzene, gave colorless needles which melted sharply, without decomposition, at 223.5° (corr.); yield, 0.6 g. Analysis for nitrogen showed it to be the benzoyl derivative of 4-chloro-anthranilic acid.

Analysis. Calc. for $C_{14}H_{10}O_2NCl$: N, 5.09. Found: 5.19.

Methyl Ester of 4-Chloro-anthranilic Acid, $C_6H_5ClNH_2COOCH_3$.—Two hundred cc. of absolute methyl alcohol was saturated with 4-chloro-anthranilic acid at room temperature; 9.5 g. of the acid dissolved. This solution, cooled in an ice-bath, was then saturated with dry hydrogen chloride. The hydrochloride of the ester separated in the form of colorless needles. These were filtered, dried, and decomposed with 10% sodium hydroxide solution. The resulting ester was filtered off from the alkali and purified by distillation with steam. The melting point of the purified ester was 68.5°.

Analyses. Calc. for $C_8H_8O_2NCl$: N, 7.56. Found: 7.48, 7.62.

5,5-Dichloro-diphenic Acid (VII).—Following the directions of Ullmann and Forgan²² for the synthesis of diphenyl combinations from aniline derivatives, cuprous chloride dissolved in conc. hydrochloric acid was added to a diazotized solution of 4-chloro-anthranilic acid. A white precipitate formed immediately. When crystallized from either benzene or dil. ethyl alcohol this substance melted at 162° (corr.). It was identified as 2,4-dichloro-benzoic acid, which has been prepared by the oxidation of 2,4-dichloro-toluene.²³ None of the desired dichloro-diphenic acid was formed by this procedure.

Our next attempt was guided by the work of Vorländer and Meyer²⁴ who succeeded in converting anthranilic acid into diphenic acid by treating its diazotized solution with ammoniacal cuprous oxide; 1.71 g. of 4-chloro-anthranilic acid was diazotized with 10% sodium nitrite in dil. sulfuric acid solution. This diazotized solution was added gradually with stirring to a solution of ammoniacal cuprous oxide at 20°, which was prepared from 5 g. of cupric sulfate pentahydrate, ammonia and sulfur dioxide as described by Vorländer and Meyer. There was violent evolution of nitrogen. The solution was then acidified strongly with hydrochloric acid and a rapid stream of air bubbled through it in order to remove the dissolved sulfur dioxide and to oxidize the copper salt in solution. The white solid product which separated was washed with cold water and dried; yield, 0.8 g.; m. p., 270–280° (uncorr.). After repeated recrystallizations from benzene, and from dil. ethyl alcohol, it was finally obtained in the form of characteristic straw-colored plates; m. p., 297° (uncorr.). It was identified as 5,5'-dichloro-diphenic acid.

Analyses. Calc. for $C_{14}H_8O_4Cl_2$: Cl, 22.81. Found: 22.70, 23.00. Mol. weight. Calc: 311. Found: (abs. ethyl alcohol) 322 (acetone) 328.

This acid is insoluble in water and only slightly soluble in hot benzene or ether. It dissolves readily in boiling ethyl alcohol or acetone. It is purified best by crystallization from 50% ethyl alcohol.

²² Ullmann and Forgan, *Ber.*, **34**, 3802 (1901).

²³ *J. Chem. Soc.*, **79**, 1129 (1901).

²⁴ Vorländer and Meyer, *Ann.*, **320**, 122 (1902).

The results of several experiments to ascertain the most favorable conditions governing the synthesis of this acid are shown in Table I.

TABLE I
SYNTHESIS OF DICHLORO-DIPHENIC ACID

Expt.	4-chloro-anthr. acid G.	Diazo-soln.	Reducing agent for Cu soln.	Crude products G.	M. p. uncorr. ° C.	Yield %
1	1.71	H ₂ SO ₄	SO ₂	0.8	270-280	61
2	1.71			1.22	255-265	77
3	1.71			1.0	255-270	65
4	5.13			3.5	270-280	75
5	5.13			3.45	294	74
6	1.71			0.6	260-270	38
7	5.13	HCl	FeSO ₄	3.1	295	67
8	1.71			1.2	255-270	77
9	5.13			3.9	290	84
10	20.0			13.0	293	71
11	20.0			10.6	...	58
12	20.0			12.0	...	66
13	20.0	SO ₂	SO ₂	12.6	294	69

It is seen from these data that hydrochloric acid has considerable advantage over sulfuric acid as a diazotizing medium, in that the acid obtained is practically pure. In the experiments using sulfuric acid also, the evolution of nitrogen produced a very tough, troublesome froth in such amount that it ran over the top of the reaction vessel, carrying with it a part of the liquid. A froth of the same type was formed in Expt. 8, in which ferrous sulfate was used as a reducing agent for the ammoniacal copper solution. No such difficulty was experienced when hydrochloric acid was used as the diazotizing medium. The crystallized cupric sulfate used was equal to thrice the weight of the chloro-anthranilic acid, except in Expt. 6, in which $\frac{1}{4}$ of the usual amount was taken. This deficiency of copper in solution is reflected in the decreased yield of product. The quantities of materials taken for the best yield were: 4-chloro-anthranilic acid, 5.13 g.; hydrochloric acid (d., 1.19), 11 cc.; water, 20 cc.; sodium nitrite (5% aqueous soln.), 2.5 g.

Anhydride of 5,5'-Dichloro-diphenic Acid.—A mixture of 6.2 g. of the purified acid with 15 g. of acetic anhydride was refluxed over an oil-bath heated to 170° for 15 minutes. As the solution cooled, 3.2 g. of pale yellow needles separated, which when dried melted at 204° (corr.). From a duplicate experiment, by evaporating the mother liquor, 5.6 g. of this substance was recovered; yield, 95%. By recrystallizing the substance from a benzene-ligroin mixture the melting point was raised to 206° (corr.).

Analyses. Calc. for C₁₄H₈O₂Cl₂: Cl, 24.22. Found: 23.92, 24.40.

This anhydride dissolved readily in hot benzene, alcohol, and ether, though not in ligroin. It crystallized in nearly colorless needles from a mixture of benzene and ligroin. It was insoluble in cold sodium hydroxide solution but slowly dissolved when boiled with this reagent. Upon acidifying the resulting solution, 5,5'-dichloro-diphenic acid was precipitated, which when washed and dried melted at 297.5° (uncorr.).

Summary

A new acid, 5,5'-dichloro-diphenic acid, has been synthesized, starting from *p*-dichlorobenzene. This is a 7-stage synthesis and the optimum working conditions for each reaction have been ascertained. Several new

organic derivatives have been obtained in the course of the synthesis and are described.

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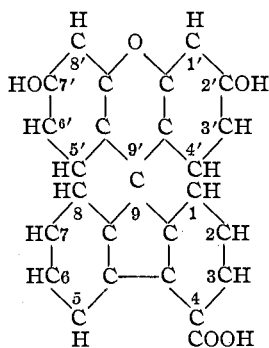
[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

THE CONDENSATION OF DIPHENIC ANHYDRIDE WITH RESORCINOL

BY FRITZ BISCHOFF AND HOMER ADKINS

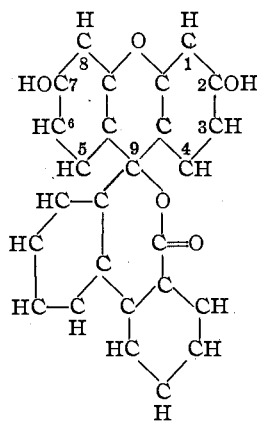
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The compounds derived from diphenic anhydride and resorcinol as fluorescein is derived from phthalic anhydride and resorcinol have never been prepared. The possibility of their formation has been questioned because of the necessity of preventing the opening of a 7-membered ring. Graebe¹ attempted to condense diphenic anhydride with phenol and resorcinol but later discovered that he had used 9,10-diphenic-ketone-4-carboxylic acid (See Formula I).² The true condensation product of



I

2',7'-Dihydroxy-*spiro* (9-fluorene-9'-xanthenene)-4-carboxylic acid



II

9-lactone of *o*-[*o*-(2,7,9-trihydroxy-xanthenyl)-phenyl]benzoic acid

the anhydride (Formula II) has been obtained in this Laboratory, and its properties and some of its derivatives studied. The condensation of the ketone with resorcinol has also been carried out. The two condensation products are very similar in properties, but are not identical. Upon acetylation, the compound from the anhydride loses its alkali solubility because it can no longer tautomerize to the alkali-soluble form. Acetylation does not affect the alkali solubility of the compound from the ketone be-

¹ Graebe, *Ber.*, 13, 1302 (1880).

² Graebe and Aubin, *Ann.*, 247, 260 (1888).