[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

THE PREPARATION OF DERIVATIVES OF DIPHENIC ACID POSSESSING THE PROPERTIES OF LOCAL ANESTHETICS

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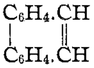
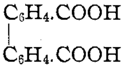
RECEIVED OCTOBER 27, 1924 PUBLISHED MAY 5, 1925

One of the many compounds produced commercially from coal tar which has not received attention from the standpoint of its possible use as a source of local anesthetic combinations is the hydrocarbon phenanthrene I. The fact alone that the nucleus of this hydrocarbon functions in the molecular construction of the vegetable alkaloid morphine $C_{17}H_{19}O_3N$ and its derivatives codeine $C_{18}H_{21}O_3N$ and thebaine $C_{19}H_{21}O_3N$, creates an especial interest in the possibility of utilizing some of its derivatives therapeutically as local anesthetics, because whatever role the phenanthrene nucleus may play in the physiological action of morphine, it seems quite probable that it would exercise a similar function or a specific and characteristic pharmacological action, in some of its synthetic derivatives. In fact, when phenanthrene was found to be formed as one of the major decomposition products of morphine we find Krause[2] predicting in 1883, that although it is a valueless product, it may yet be found to be of practical use in the preparation of alkaloidal principles.



$$\begin{array}{l} C_6H_4.CH \\ |\qquad \| \\ C_6H_4.CH \end{array}$$

I



$$\begin{array}{l} C_6H_4.COOH \\ | \\ C_6H_4.COOH \end{array}$$

II

An important derivative of phenanthrene I which can be prepared in quantity from this hydrocarbon is diphenic acid II. This acid has, so far as the writers are aware, never been utilized as a means of entering synthetically the field of local anesthetics. The incorporation of the diphenyl group into such combination also gives added interest to them because of the fundamental similarity of the chemistry of benzoic and diphenic acids; and the wide application successfully of derivatives of the former acid as local anesthetics. This paper, therefore, may be considered as a preliminary report of the development of this field of research in the phenanthrene series.[3]

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[1] Constructed from part of a dissertation presented by R. Chester Roberts to the Faculty of the Graduate School of Yale University, June, 1921, in candidacy for the degree of Doctor of Philosophy.

[2] Krause, *Chem.-Ztg.*, **371**, 387 (1883).

[3] It has been shown in the work of Lewis on bacterial disinfectants [*J. Exp. Med.*, **25**, 441 (1917)] that in dyes produced from benzidine, which contain the diphenyl configuration, there resides some specific property directed against *tubercle bacilli*. See paper by A. Elizabeth Hill on "Diphenyl-diarsonic Acid," [THIS JOURNAL, **46**, 1855 (1924)]; and also paper on "Diarsono-diphenyl and Derivatives," by Bauer and Adams, [*ibid.*, **46**, 1925 (1924)].

For the development of our research we have utilized a commercial grade of phenanthrene (80%), and prepared our diphenic acid by oxidation of this hydrocarbon according to the method described by Anschütz and Schultz,[4] and applied with modifications by Fittig and Schmitz,[5] Graebe and Aubin,[6] and also Oyster and Adkins.[7] In addition to the material prepared by this laboratory method, we have also utilized in our work a very fine grade of diphenic acid prepared by catalytic oxidation of phenanthrene.[8] The first attack made on the development of our problem was to prepare the neutral diethylamino-ethyl alcohol ester of diphenic acid. This ester of the novocaine type is easily prepared by the interaction of the acid chloride of diphenic acid and the diethylamine alcohol, forming smoothly the hydrochloride of the new ester. To our surprise, the free ester was obtained as an oil, which did not crystallize, and furthermore could not be distilled in a vacuum without decomposition. The physical properties of this compound and other derivatives of diphenic acid prepared by us suggest to the writers, that in these cases where such low-melting points are exhibited, we are probably dealing with constructions containing superimposed diphenyl rings as expressed by the Kaufler[9] formula. Evidence has already been produced that diphenic acid can function in its reactions in a tautomeric manner, due probably to a superimposed structure. This is illustrated in the formation from diphenic acid, by dehydration, of the normal anhydride[10] together with diphenylene-ketone-carboxylic acid.[11] Our ester may, therefore, be a mixture of the *cis* and *trans* modifications. It is now found that the hydrochloride of this ester is characterized by its pronounced local anesthetic action without exhibiting toxic effects. The discovery of its pharmacological action has stimulated a renewed interest in combinations of this type and attention will be directed to the synthesis and study of nucleus-substituted amino derivatives of this interesting ester. On account of its structural relationship to novocaine the diethylamino-ethyl alcohol ester of 4,7-diaminodiphenic acid and isomeric compounds are worthy of immediate attention. Structurally, the latter ester is a double novocaine molecule, and it will be of special interest to determine whether such a construction favors increased local anesthetic action of the novocaine type. The investigation of amino-derivatives of diphenic acid is now in progress in this Laboratory.

The anilide of diphenic acid has also been prepared and converted into

[4] Anschütz and Schultz, *Ber.*, **10**, 323 (1877); *Ann.*, **196**, 50 (1879).

[5] Fittig and Schmitz, *Ann.*, **193**, 116 (1878).

[6] Graebe and Aubin, *Ann.*, **247**, 263 (1888).

[7] Oyster and Adkins, THIS JOURNAL, **43**, 263 (1921).

[8] This was furnished to us gratuitously by the Barrett Co. of New York City.

[9] Kaufler, *Ann.*, **351**, 156 (1907); *Ber.*, **46**, 3250 (1907).

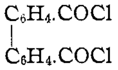
[10] Anschütz, *Ber.*, **10**, 326 (1877); **10**, 1884 (1877). Ref. 6.

[11] Graebe and Mensching, *Ber.*, **13**, 1302 (1880).

its imide chloride derivative. It seemed very probable that the introduction of an anil grouping into these diphenyl combinations would tend to stimulate local anesthetic action. So far as the writers are aware, practically no attention has been paid to the application of the imido-ester combinations as local anesthetics. The synthesis which we now describe has led to results which will encourage us to investigate the therapeutic value of other combinations of the imido-ester type. The imide chloride prepared from the anilide of diphenic acid, has been combined with ethyl alcohol and diethylamino-ethyl alcohol giving the corresponding imido esters, respectively. The ethyl ester proved to be a weakly basic or almost neutral compound, while the ethanol derivative forms a normal hydrochloride that is readily soluble in water.

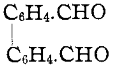
We now find that this new ethanol imido-ester exhibits a much greater local anesthetic action than the corresponding ethyl ester of diphenic acid. A comparison of the two compounds structurally brings up the interesting question of the physiological effect produced by substituting certain groups in similar combinations. Here we are dealing with the substitution of an anil or phenyl-imido grouping, $:NC_6H_5$, for an oxygen atom in the normal ester. In view of the fact that an amino group is not functioning in the *para* position with respect to carboxyl as in novocaine, perhaps the nitrogen of the anil group is exerting the same physiological influence here as the *p*-amino group in novocaine. A preliminary report of the pharmacological action of these derivatives of diphenic acid is given in the experimental part of this paper.

In the course of our work an attempt was made to convert our imide chloride into the aldehyde corresponding to diphenic acid IV by application of the method of reduction described by Sonn and Müller.[12] Thus far, the only product isolated as a result of this procedure is the anilide of diphenic acid. The method apparently is not one of very general application. Graebe and Aubin[6] have investigated the behavior of the acid chloride of diphenic acid III on reduction with zinc and hydrochloric acid, but instead of obtaining the aldehyde IV they made the interesting observation that the chloride reverted to a true phenanthrene derivative VI. From a synthetic point of view this reversion to a phenanthrene compound is a fact of considerable interest. Graebe and Aubin[6] interpret the mechanism of the formation of IX as follows.



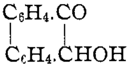
$$\begin{array}{l} C_6H_4.COCl \\ | \\ C_6H_4.COCl \end{array}$$

III



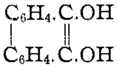
$$\begin{array}{l} C_6H_4.CHO \\ | \\ C_6H_4.CHO \end{array}$$

IV



$$\begin{array}{l} C_6H_4.CO \\ |\quad\ | \\ C_6H_4.CHOH \end{array}$$

V



$$\begin{array}{l} C_6H_4.C.OH \\ |\quad\ \| \\ C_6H_4.C.OH \end{array}$$

VI

In the light of this interpretation it will be very interesting to apply the benzoin reaction to the aldehyde of diphenyl IV. The study of phenanthrene derivatives will be continued.

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[12] Sonn and Müller, *Ber.*, **52**, 1927 (1919).

Experimental Part

The Preparation of Diphenic Acid from Phenanthrene.[13]—For the oxidation of phenanthrene Fittig and Ostermayer[13] used chromic acid in glacial acetic acid solution, and potassium dichromate in concd. sulfuric acid. The latter reagents have been most widely used by later investigators. In this work, the sodium salt has been substituted with success, giving as large yields of the pure diphenic acid as are produced by oxidation with potassium dichromate. As is well known, an intermediate oxidation product, phenanthrene-quinone, is always formed in the process of conversion to diphenic acid. Graebe and Aubin,[6] and also Oyster and Adkins[7] not only isolated it but purified it by crystallization before proceeding with the final step in the oxidation process. We found this unnecessary when the crude phenanthrene-quinone is washed free from chromium compounds and allowed to stand in concd. sulfuric acid for several hours before the oxidation is continued.[14] For the complete oxidation of 100 g. of commercial 80% phenanthrene we used 1000 g. of sodium dichromate and obtained a yield of diphenic acid corresponding to 51%. The material was purified by crystallization from hot water or glacial acetic acid and melted at 228°.

THE ANHYDRIDE OF DIPHENIC ACID.—Of the several methods recommended for preparing this anhydride that developed by Graebe and Aubin[15] using acetic anhydride as the dehydration agent, was chosen for our work, as it gives excellent yields of the pure anhydride. Graebe and Aubin used one part of diphenic acid to 1.5 parts of acetic anhydride. Oyster and Adkins[7] used a double amount of anhydride to increase the yield. We have used both methods, but were unable to increase the yield of anhydride formed by increasing the quantity of acetic anhydride. Our best results were obtained as follows. Fifty g. of diphenic acid and 75 g. of acetic anhydride were mixed in a flask and heated under a reflux condenser at 120° for one hour. The acid gradually dissolved and before the heating was stopped crystals of the anhydride began to form. As the mixture cooled it solidified completely to a mass of fine needles. The anhydride was purified by crystallization from glacial acetic acid and melted at 217°; yield, 45 g., or 97.2%.

Diphenic Acid Chloride.—Diphenic acid acts abnormally in the preparation of its acid chloride, as the latter is not obtained smoothly and in a pure condition by action of phosphorus pentachloride directly on the acid. By use of the anhydride, however, the reaction proceeds smoothly with formation of the chloride.[6] This method was used in our work and from 75 g. of the diphenic anhydride was obtained 70 g. of chloride, or a yield of 71.4%. The compound was purified by crystallization from benzene; m. p., 93–94°.

Diethylamino-ethyl Diphenate.—Twenty-five g. of diethylamino-ethyl alcohol was added slowly to a benzene solution containing 29.7 g. of diphenic acid chloride. A reaction took place immediately with the formation of the hydrochloride as an oil. After heating had been continued for one hour to complete the reaction and then cooling the mixture, the benzene was separated from the insoluble layer of oil and the latter dissolved in cold water. On the addition of aqueous ammonia the free ester separated as an oil. All attempts to purify this compound by distillation in a vacuum were unsuccessful. It is a viscous liquid with a pleasant odor; n^{21}, 1.528. It dissolves at once in dil. hydrochloric acid, ether and alcohol, and showed no sign of solidifying when cooled to 0°. The hydrochloride was prepared by passing dry hydrogen chloride through an ether solution of the ester, when it separated immediately as a thick oil that did not

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[13] Fittig and Ostermayer, *Ann.*, **166**, 361 (1873).

[14] Also recommended by Oyster and Adkins, Ref. 7.

[15] Ref. 6, p. 257.

solidify at room temperature. It showed no sign of crystallizing when allowed to stand in a vacuum desiccator over concd. sulfuric acid for several days. The yield of ester was 35 g., or 74.6%.

Anal. Calcd. for $C_{26}H_{36}O_4N_2$: N, 6.36. Found: 6.5, 6.58.

Anilide of Diphenic Acid.—This was obtained by the action of aniline on the acid chloride of diphenic acid in ether or benzene. It is purified by recrystallization from alcohol or glacial acetic acid and crystallizes in the form of octahedra; m. p., 229–230°; yield, 41 g., or 97.2%.

Anal. Calcd. for $C_{26}H_{20}O_2N_2$: N, 7.14. Found: 7.2, 7.1.

Diphenanilide Imide Chloride.—This chloride is easily prepared by action of 53 g. of phosphorus pentachloride on 50 g. of diphenanilide at 130–140°. After removal of the phosphorus oxychloride formed in the reaction the above-mentioned imide chloride is obtained as a colorless solid. It is soluble in ligroin and benzene and crystallizes from both solvents in the form of prisms; m. p., 116–117°; yield, 42 g., or 76.9%.

Anal. Calcd. for $C_{26}H_{18}N_2Cl_2$: N, 6.52; Cl, 16.55. Found: N, 6.48, 6.47; Cl, 16.66, 16.70.

Ethyl Imido-ester of Diphenanilide.—For the preparation of this ester from the imide chloride described above it is necessary to use absolute alcohol. The reaction takes place at ordinary temperatures and is completed by heating at 70° for a short time. The ester was obtained as a colorless solid crystallizing from the reaction medium in the form of prisms which melted at 216–217°. It is quite remarkable that the hydrochloride of this imido ester is not formed in this reaction.

Anal. Calcd. for $C_{30}H_{28}O_2N_2$: N, 6.25. Found: 6.3, 6.5.

Diethylamino-ethyl Imido-ester of Diphenanilide.—Diphenanilide imide chloride reacts with diethylamino-ethyl alcohol in a manner perfectly analogous to that of its corresponding acid chloride giving this new imido ester. It is prepared as follows. Five g. of the imide chloride are dissolved in dry benzene and 2.7 g. of the diethylamino-ethyl alcohol added slowly to the solution. The hydrochloride of the imido ester is formed at once, and the reaction is complete in about 15 minutes. The crystals of salt are separated by filtration, washed with anhydrous benzene and dried in a vacuum for analysis. The salt is very soluble in water and insoluble in benzene and ether.

Anal. Calcd. for $C_{38}H_{48}O_2N_2Cl_2$: N, 8.44; Cl, 11.18. Found: N, 8.6, 8.5; Cl, 11.09, 11.2.

The free imido ester separates as an oil, when the hydrochloride is decomposed by alkali.

Tetraphenyl Diphenamidine.—Diphenanilide imide chloride interacts normally with amines to form amidine compounds. The reaction takes place easily in benzene or ether solution. When aniline is used the above-mentioned base is obtained as a crystalline compound mixed with aniline hydrochloride. After treatment with water to dissolve the aniline salt, the amidine is obtained as a solid crystallizing in the form of needles and melting at 217–218°. The compound is insoluble in water, ligroin, ether, chloroform and benzene. It is easily purified for analysis by crystallization from 95% alcohol. The yield of purified amidine was about 77%.

Anal. Calcd. for $C_{38}H_{30}N_4$: N, 10.33. Found (Kjeldahl): 10.47, 10.31.

The Behavior of Diphenanilide Imide Chloride towards Stannic Chloride.—Sonn and Müller[12] have recently shown that aldehydes can be prepared by reduction of imide chlorides to their corresponding anils, followed by hydrolysis to the corresponding aldehyde. They applied this method with success in the aromatic series, but did not meet with success when working with aliphatic compounds. We have now applied this reaction to diphenanilide imide chloride with the idea of preparing the aldehyde corresponding to diphenic acid, but in no experiment have we met with success. The stannic chloride solution was prepared as recommended in anhydrous ether,[12] and to this solution was added the imide chloride also dissolved in anhydrous ether. This chloride reacted at once with formation of a yellow, oily product, which separated from the ether as a semi-solid. This was separated and then treated with cold water, when it underwent a slow change giving a solid substance which was identified as diphenanilide. It seems probable that the stannic chloride merely forms an addition product in this case, which is broken down by hydrolysis giving the corresponding anilide.

Results of Preliminary Pharmacological Tests.[16]—Tests were made to determine (1) toxicity, and (2) local anesthetic action. Twenty-two cc. of an aqueous solution prepared by dissolving 250 mg. of diethylaminoethyl diphenate in water containing the calculated quantity of hydrochloric acid to form the neutral hydrochloride was injected into the jugular vein of a dog weighing 10 kilograms. This application produced no toxic effects on the animal immediately after the injection or after several hours had elapsed.

The local anesthetic properties were determined by the application of the intracutaneous method of testing introduced by Hoffmann and Kochmann.[17] Three wheals were made by hypodermic injection of the hydrochloride across the volar surface of the upper part of the forearm for each concentration. The ester in the form of its hydrochloride was prepared in a strength of 0.05% water solution and injections were made on two subjects, one of whom was one of the writers (R. C. R.). During the injection and for less than a minute after the injection, the drug was very painful, but this pain disappeared entirely within one minute. Good local anesthesia was produced in both subjects, lasting from five to ten minutes. Only a slight inflammation could be noticed around the wheals and this disappeared in a short time. No toxic effects were produced in either subject by the injection of the hydrochloride.

The corresponding imido ester hydrochloride was also tested for its local anesthetic action by the method of Hoffmann and Kochmann.[17] Two dilutions were used in this case and each dilution was tested on two subjects. The first solution of a strength of 0.05% gave a marked increase in the length of time of anesthesia over that of the simple ester of the same strength. Good local anesthesia was obtained with both subjects for 25 to 30 minutes on all three wheals. A slight inflammation was observed for a short time after the injection but otherwise there were no pronounced toxic effects. The hydrochloride solution was diluted to a strength of 0.025% and its effect compared with that of the original solution. No pain was produced after injection with this dilution and good local anes-

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[16] Facilities for performing these tests were kindly offered by the Pharmacology Department of the Yale Medical School.

[17] Hoffmann and Kochmann, *Deutsch. Med. Woch.*, [No. 48] **38**, 2264 (1912); *Beitr. Klin. Chir.*, **91**, 489 (1914).

thesia was obtained with both subjects, lasting for 15 to 20 minutes. These results indicate the pronounced and characteristic pharmacological properties of these two compounds and show that the imido-ester grouping possesses much greater local anesthetic action than the plain diethylamino-ethyl ester of diphenic acid.

Summary

1. Diphenylchloride and the imide chloride of diphenanilide both react smoothly with diethylamino-ethyl alcohol, $(C_2H_5)_2NCH_2CH_2OH$, to form the corresponding ester and imido ester, respectively.
2. Both of these compounds have been tested pharmacologically and the preliminary tests have been very satisfactory, revealing the characteristic property of producing local anesthesia in both cases.
3. An attempt to reduce the imide chloride of diphenanilide to the corresponding aldehyde by reduction with stannic chloride in ether solution was unsuccessful.
4. The study of diphenic acid derivatives will be continued.

NEW HAVEN, CONNECTICUT

[CONTRIBUTION FROM KENT CHEMICAL LABORATORY, UNIVERSITY OF CHICAGO]

CATALYTIC TRANSMUTATION OF MALEIC ACID INTO FUMARIC ACID[1]

BY ETHEL M. TERRY AND LILLIAN EICHELBERGER[2]

RECEIVED NOVEMBER 3, 1924 PUBLISHED MAY 5, 1925

One of the curious enigmas of the chemistry of maleic acid is that this acid can undergo transmutation to fumaric acid under the influence of a catalyst such as bromine without adding the catalyst at the double bond, and yet in order to have undergone such a transmutation, the double bond of maleic acid must have passed through an active phase during which the double bond should add bromine very easily. The present paper reports measurements of the rate of transmutation of maleic acid in water solution under the influence of certain catalysts, and gives a theory of the process of transmutation deduced from these measurements. It will be shown that the mechanism suggested by the theory accounts for the above-mentioned phenomena. The catalysts employed in the experimental work reported are hydrobromic acid, hydrochloric acid and potassium thiocyanate, respectively.

Measurement of Rates of Reaction.—The measurements of rates of transmutation were carried out as follows. Samples of a given solution

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[1] Presented by title at the April Meeting (1924) of the American Chemical Society.

[2] The experimental work of this paper was carried out by Lillian Eichelberger in fulfilment of part of the requirement for the degree of Doctor of Philosophy at the University of Chicago, 1921.