compound (*o, m* or *p*) and not at all upon the nature or directive influence of the other substituent. This means that the effect of that group upon rate of substitution is identical for the two or three positions substituted, that is, that directive influence is distributed symmetrically around the ring.

CAMBRIDGE 39, MASSACHUSETTS

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF TEXAS]

METHYLENE-CITRIC ANHYDRIDE
THE ANILINE DERIVATIVES OF CITRIC AND ACONITIC ACIDS

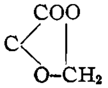
BY C. A. NAU, E. B. BROWN AND J. R. BAILEY

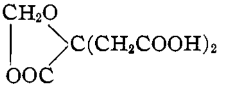
RECEIVED JUNE 20, 1925 PUBLISHED OCTOBER 6, 1925

Introduction

We find that the anhydride of methylene-citric acid reacts with aniline to form a product which hydrolyzes with the elimination of the methylene group to the unsymmetrical anil of citric acid, known as citranilic acid. This observation would seem to indicate that methylene-citric anhydride, and consequently its acid are likewise of unsymmetrical structure. In our attempt to harmonize the accepted symmetrical formula assigned to methylene-citric acid with the formation of the unsymmetrical anil of citric acid we have proved beyond question that methylene-citric acid is of symmetrical structure and have developed an explanation of the mechanism of the apparently anomalous reaction of its anhydride with aniline. Furthermore, a method of preparation of methylene-citric anhydride has been discovered which makes this interesting substance readily available by the employment of a new process of making anhydrides.

Henneberg and Tollens[1] investigated the behavior of formaldehyde toward polybasic acids of the sugar group and found that the methylene radical could be introduced for two hydroxyl hydrogens, leaving the carboxyls intact. The condensing agent employed in this reaction is aqueous hydrochloric acid. Lobry de Bruyn[2] with co-workers investigated the action of formaldehyde on certain hydroxy acids in the absence of mineral acids, obtaining an entirely different result. They assume that formaldehyde and the hydroxy acid under this condition react with the elimination of water between the molecule CH_2O and the complex HO—C—COOH so as to produce methylene derivatives containing the group I; for example, formaldehyde with citric acid gives a methylene-citric acid to which Structure II is assigned.


I


II

---

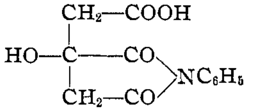
[1] Henneberg and Tollens, *Ann.*, **292**, 31 (1896).

[2] Van Ekenstein and Lobry de Bruyn, *Rec. trav. chim.*, **19**, 178 (1900); **20**, 331 (1900).

The method of Lobry de Bruyn where 40% formaldehyde is employed gives a yield of approximately 10% of that calculated.[3] Patented processes for the preparation of methylene-citric acid, in which instead of 40% formaldehyde, paraformaldehyde[4] or better still chloromethyl alcohol[5] is employed, give yields of 50 and 80%, respectively.

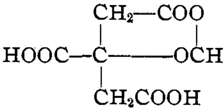
Gastaldi[6] recommends the preparation of methylene-citric acid from crystallized citric acid and paraformaldehyde in sealed tubes of 90cc. capacity at a temperature of 145°.

In the work described in this paper it is shown that methylene-citric anhydride gives with aniline a product which hydrolyzes smoothly to the long-known citranilic acid discovered by Pebal.[7] The Pebal compound undoubtedly has Structure III. This would seem to establish for methylene-citric acid the unsymmetrical formula IV, and give its anhydride a structure analogous to that assigned to acetyl-citric anhydride.[8]



III

$$\begin{array}{l} CH_2{-}COOH \\ HO{-}C{-}CO \\ CH_2{-}CO \end{array} > NC_6H_5$$

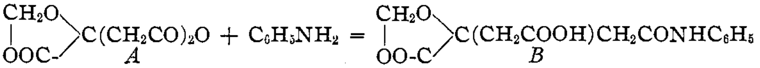


IV

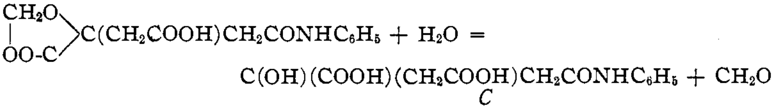
$$\begin{array}{l} \quad\; CH_2{-}COO \\ HOOC{-}C{-}OCH_2 \\ \quad\; CH_2COOH \end{array}$$

However, this view is not tenable because we find that dimethyl methylene-citrate hydrolyzes to *sym.*-dimethyl citrate,[9] the structure of which is definitely established. Furthermore, *sym.*-dimethyl citrate gives with paraformaldehyde a product identical with that obtained in the esterification of methylene-citric acid with methanol and sulfuric acid.

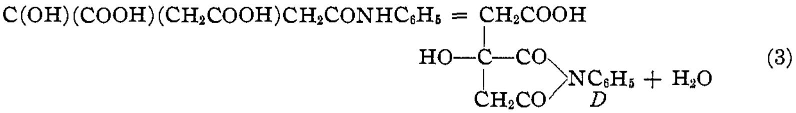
The mechanism of the reactions involved in the conversion of methylene-citric anhydride to citranilic acid apparently conforms to the following series of equations.



$$\begin{array}{l} CH_2O \\ OOC \end{array} > \underset{A}{C(CH_2CO)_2O} + C_6H_5NH_2 = \begin{array}{l} CH_2O \\ OO{-}C \end{array} > \underset{B}{C(CH_2COOH)CH_2CONHC_6H_5} \quad (1)$$



$$\begin{array}{l} CH_2O \\ OO{-}C \end{array} > C(CH_2COOH)CH_2CONHC_6H_5 + H_2O = \underset{C}{C(OH)(COOH)(CH_2COOH)CH_2CONHC_6H_5} + CH_2O \quad (2)$$



$$C(OH)(COOH)(CH_2COOH)CH_2CONHC_6H_5 = \underset{D}{\begin{array}{l} CH_2COOH \\ HO{-}C{-}CO \\ CH_2CO \end{array} > NC_6H_5} + H_2O \quad (3)$$

---

[3] (a) Ger. pat. 185,800 (1907). (b) Friedländer, "Fortschritte der Teerfarben Fabrikation," **8**, 955 (1907).

[4] Ger. pat. 129,255 (1902). Ref. 3 b, **6**, 1222 (1902).

[5] Ger. pat. 150,949 (1904). Ref. 3 b, **7**, 620 (1904).

[6] Gastaldi, *Bull. chim. pharm.*, **61**, 353 (1922).

[7] Pebal, *Ann.*, **82**, 92 (1852).

[8] Sell and Easterfield, *J. Chem. Soc.*, **61**, 1003 (1892).

[9] Schroeter and Schmitz, *Ber.*, **35**, 2085 (1902). Ref. 8, p. 1010.

The primary reaction product *B* may be isolated but since in the preparation of citranilic acid *D* from methylene-citric anhydride (*A*) hydrochloric acid is used, it is to be expected that Product *C* will quickly change to Product *D*. This view finds confirmation in that a mono-ethyl ester of Product *C* obtained in the course of our work dehydrates readily in an acid medium to ethyl citranilate.

Although acetyl-citric anhydride when heated with ammonium hydroxide gives citrazinic acid,[10] our attempts to prepare citrazinic acid by the action of ammonium hydroxide on methylene-citric anhydride were unsuccessful. The absence of the formation of citrazinic acid in this reaction, coupled with the behavior of the anhydride toward aniline, indicates a steric hindrance to the formation of pyridine derivatives.

The only mention of methylene-citric anhydride is found in patent literature[11] in a very short notice as follows: "The anhydride of methylene-citric acid is formed by the action of phosgene upon the acid in the presence of pyridine." Furthermore, we have observed that some anhydride is always formed as a by-product in the preparation of methylene-citryl chloride.[12] A method of preparation of the anhydride given in the experimental part of this work consists in bringing into reaction phosphorus pentachloride and methylene-citric acid in molecular proportions, but a better yield is obtained by the action of phosphorus oxychloride on methylene-citric acid in chloroform solution with dimethylaniline as a salifier, a method which, as far as our observation goes, has not been used previously in the preparation of anhydrides.

Processes similar to the last one of preparing anhydrides are the use of inorganic salts of the corresponding acid with phosphorus pentachloride,[13] phosgene[14] or chlorosulfonic acid.[15] These methods do not involve the use of solvents, whereas in the new process methylene-citric anhydride is made in chloroform solution. Experiments are planned to determine to what extent this method is available for the preparation of other anhydrides, and the results of this investigation will be communicated in a subsequent paper.

Contrary to the claim in patent literature[12] that methylene-citric anhydride reacts with alcohols to form the corresponding dialkyl esters, we find that the reaction proceeds normally here, in that mono-alkyl esters result. Furthermore, a statement in the same patent specifications that

---

[10] Ref. 8, p. 1008.

[11] Ger. pat. 212,554 (1909). Ref. 3 b, **9,** 899 (1909).

[12] Ger. pat. 186,659; 3 b, **8,** 958 (1907).

[13] Ger. pat. 163,103 (1905), 171,787 (1906). Ref. 3 b, **8,** 67, 68 (1907).

[14] Ger. pat. 29,669 (1884). Ref. 3 b, **1,** 574 (1902). Hentschel, *Ber.*, **17,** 1285 (1884).

[15] Ger. pat. 63,593 (1892), 161,882 (1905). Ref. 3 b, **3,** 8 (1890–1894); **8,** 66 (1905–1907).

diethyl methylene-citrate "on treatment with alkalies is completely split up" is misleading, because in the case of the dimethyl ester it is possible so to control the reaction as to obtain dimethyl citrate. It is probable that, with the detail of hydrolysis of the methylene group in mono- and dialkyl esters of methylene-citric acid developed, an excellent method of preparing unsymmetrical mono-alkyl and symmetrical dialkyl esters of citric acid would result, whereas the preparation of these esters directly from citric acid often requires involved methods of purification.[16]

Any doubt as to the analogy in structure of the anils of citric and aconitic acids is cleared up by our study of the action of phosphorus pentachloride on citranilic acid and its ethyl ester; in these reactions there result an acid and ester, respectively, which give analytical data showing a molecule of water eliminated from the citric acid derivatives.

Bertram,[17] starting with aconitic anhydride, prepared the methyl and ethyl esters of aconitylanil. Our supposed aconitylanil is readily esterified with both methanol and ethyl alcohol, giving products melting at 149° and 123°, respectively, whereas Bertram reports 143° and 112°. We prepared these esters according to the directions of Bertram and found them to be identical with our products, so that the melting points given by Bertram should be revised.

Pebal[18] investigated the action of phosphorus pentachloride on citranilic acid without reporting the melting point of the product obtained. Evidently the Pebal compound was not pure because he "could not obtain it colorless." Furthermore, his product "dissolves in dilute ammonium hydroxide very readily with a purple color." We obtained the aconitylanil colorless, and in this form it imparts to ammonium hydroxide an evanescent, yellowish-red color.

Skinner and Ruhemann[19] prepared from aconitylanil-anilide by the action of alkalies a product melting at 250°, whereas our product melts at 189°. They state: "This acid is doubtless identical with the acid prepared by Pebal by the action of phosphorus pentachloride on citranilcarboxylic acid." However, the evanescent color reactions that aconitylanil and its esters give with alkalies make it highly improbable that any of these substances could be formed in an alkaline medium.

Experimental Part

Methylene-citric Anhydride.—The methylene-citric acid used in the preparation of the anhydride was made from crystallized citric acid and paraformaldehyde in accordance with patent specifications referred to in the introduction.

[16] Compare Wolfrum and Pinnow, *J. prakt. Chem.*, [2] **97**, 23 (1918).

[17] Bertram, *Ber.*, **38**, 1615 (1905).

[18] Pebal, *Ann.*, **98**, 83 (1856).

[19] Skinner and Ruhemann, *J. Chem. Soc.*, **55**, 238 (1889).

1. When 100 g. of methylene-citric acid and 112 g. of phosphorus pentachloride are intimately mixed, reaction proceeds slowly at first with the evolution of hydrogen chloride, until after a short time liquefaction ensues, and with a rise of temperature the gas evolution becomes more vigorous. At the end of an hour the reaction mixture is heated on a boiling water-bath and, when there is no further escape of hydrogen chloride, the phosphorus oxychloride is distilled in a vacuum. The dark colored residue is now dissolved in ethyl acetate and the solution filtered. About 60 g. of the anhydride separates as the solution is cooled; yield, approximately 66%.

2. When 124 cc. of dimethylaniline is added to 100 g. of methylene-citric acid suspended in 200 cc. of chloroform, partial solution takes place. Upon the addition of 44.4 cc. of phosphorus oxychloride the heat of reaction soon brings the chloroform to its boiling point with complete solution of the reacting substances. At the end of the vigorous reaction the anhydride is made to crystallize by chilling for one-half hour. The crude product, after being filtered off, is washed with chloroform and then recrystallized from ethyl acetate; yield, about 70%.

Methylene-citric anhydride is readily soluble in ethyl acetate from which it separates in long, slender prisms with end faces, melting at 153° to a yellow liquid and decomposing at 190° with gas evolution. Formaldehyde is one of the decomposition products. The anhydride does not distil undecomposed even in a vacuum. It is difficultly soluble in chloroform and benzene, readily hydrolyzes to methylene-citric acid, and reacts with ethyl alcohol forming mono-ethyl methylene-citrate. Heated with phosphorus pentachloride at 120°, the anhydride undergoes no change. Like succinic anhydride[20] this anhydride condenses with resorcinol to form a fluorescein and the latter can be brominated to an eosin. Owing to the fact that these products have not been obtained pure, they are not described in this paper.[21]

Anal. Calcd. for $C_7H_6O_6$: C, 45.16; H, 3.22. Found: C, 45.29; H, 3.15.

Mono-anilide of Methylene-citric Acid.—To 20 g. of methylene-citric anhydride suspended in 60 cc. of ethyl acetate, 9.5 cc. of aniline is slowly added during stirring. The heat of reaction is sufficient to hold in solution the anilide which later separates as the filtered solution is cooled. For purification it is dissolved in cold alcohol and precipitated by the addition of water, in characteristic, long, slender prisms; m. p., 148°, with decomposition. It is readily soluble in alcohol and ethyl acetate and very difficultly soluble in the other common organic solvents. It dissolves readily in hot water but, due to hydrolysis of the methylene group, the solution has a distinct odor of formaldehyde.

Anal. Calcd. for $C_{13}H_{13}O_6N$: C, 55.91; H, 4.66; N, 5.02. Found: C, 56.05, H, 4.66; N, 5.26.

The Aniline Salt of the Mono-anilide of Methylene-citric Acid.—To 1 g. of methylene-citric anhydride, suspended in 3 cc. of ethyl acetate, is added slowly during stirring at ice-bath temperature 1.5 cc. of aniline. Solution of the reacting materials takes place readily, followed by precipitation of the aniline salt. After one-half hour this is filtered off and washed with ether. The salt melts at 90.5° to give a yellow liquid and decomposes with evolution of gas at about 115°. It is readily soluble in water, alcohol or ethyl acetate and practically insoluble in ether, benzene or petroleum ether. Heated in solution, it splits off formaldehyde.

Anal. Calcd. for $C_{19}H_{20}O_6N_2$: C, 61.29; H, 5.37; N, 7.53. Found: C, 61.09, 61.31; H, 5.32, 5.53; N, 7.36.

Citranilic Acid.—The crude mono-anilide of citric acid described above is dissolved

---

[20] Nencki and Sieber, *J. prakt. Chem.*, [2] **23**, 153 (1881).

[21] This work was carried out by E. W. Rugeley.

in the least amount of boiling, dil. hydrochloric acid (1:3) and the solution allowed to stand for 24 hours. At the end of this time the separated citranilic acid is filtered off and recrystallized from dil. hydrochloric acid and then from alcohol or ethyl acetate in prisms with dome-shaped end faces; m. p., 189°. It is difficultly soluble in ether and benzene.

Anal. Calcd. for $C_{12}H_{11}O_5N$: C, 57.83; H, 4.42; N, 5.62. Found: C, 58.05; H, 4.43; N, 5.65.

Preparation of Citranilic Acid from Mono-aniline Citrate.—In this method of preparation the directions of Pebal may be changed to advantage as follows: 96 g. of crystallized citric acid is dissolved in 350 cc. of 95% alcohol with the addition of 46.5 g. of aniline and, after the mixture has stood for one-half hour, the alcohol is distilled in a vacuum. As a rule a crystalline product is obtained, but sometimes there results a reddish-brown oil that may be brought to crystallization by stirring with petroleum ether. The mono-aniline citrate, thus obtained in a yield of 120 g., is next heated at 150° as long as steam issues from the mixture, which operation requires about two hours. The melt is then dissolved in the least possible amount of boiling, dil. hydrochloric acid. From the filtered solution an oil separates which when stirred is transformed into a granular, crystalline solid. After 24 hours this is filtered off and recrystallized from water with the addition of Filtchar. Citranilic acid made in this way differs from the same preparation from methylene-citric anhydride in that it does not possess as good crystallizing properties, due probably to a small amount of admixed impurities. However, the analytical data on the product agree closely with the percentage composition, whereas citranilic acid made according to the directions of Pebal invariably gave unsatisfactory analyses.

Anal. Calcd. for $C_{12}H_{11}O_5N$: C, 57.83; H, 4.42; N, 5.62. Found: C, 58.12; H, 4.37; N, 5.85.

Aniline Citranilate.—Citranilic acid forms a well-crystallizing aniline salt which may be prepared as follows. On agitation of 10 g. of citranilic acid dissolved in 20 cc. of water with 4.5 cc. of aniline, solution takes place with a slight heating effect, and soon the salt begins to separate. After filtration the excess of aniline is removed with ether, and for further purification the product is recrystallized from water with the addition of Filtchar. The aniline salt separates from water in slender prisms; m. p., 139°.

Pebal, who made this salt by a slightly different procedure, did not give its melting point. We made use of it and the following derivatives to prove the identity of citranilic acid prepared from the action of aniline on methylene-citric anhydride with citranilic acid from the dehydration of aniline citrate.

Anal. Calcd. for $C_{18}H_{18}O_6N_2$: C, 63.16; H, 5.26; N, 8.19. Found: C, 63.13; H, 5.38; N, 8.29.

Anilanilide of Citric Acid. The 1,2-Phenylimide-3-phenylamide of 2-Hydroxypropane-1,2,3-tricarboxylic Acid.—The aniline salt of citranilic acid when heated for 30 minutes at 150° is converted by the elimination of water to the corresponding anilanilide. For purification the melt is treated with sufficient alcohol to make it crystalline. The substance, dissolved in alcohol, is then decolorized with Filtchar, and to the filtered solution sufficient water is added at boiling temperature to produce cloudiness. As the mixture is cooled the anilanilide separates in rosets of microscopic prisms. This product proved to be identical with the anilanilide prepared according to the method of Pebal by heating the dianiline salt of citric acid at 150°. The same anilanilide was also obtained by Bertram among the reaction products of aniline on acetyl-citric anhydride.[22]

Anal. Calcd. for $C_{18}H_{16}O_4N_2$: C, 66.66; H, 4.93; N, 8.64. Found: C, 66.97; H, 5.22; N, 8.87.

---

[22] Ref. 17, p. 1624.

Action of Phenylhydrazine on Citranilic Acid.—To 15 g. of citranilic acid in 30 cc. of water is added during constant stirring 13 g. of phenylhydrazine. Gradual solution takes place with a considerable rise in temperature, and the reaction is brought to an end by boiling. As the mixture is cooled and stirred the new substance separates. It is filtered off, washed with ether to remove the excess of phenylhydrazine and then recrystallized successively from alcohol and ethyl acetate in fine, microscopic prisms; m. p., 132°, with decomposition. The compound readily becomes colored, due probably to atmospheric oxidation. It is insoluble in ether, benzene or petroleum ether. The following analytical data indicate that the product is the phenylhydrazine salt of the phenylhydrazide-anilide of citric acid.

Anal. Calcd. for $C_{24}H_{27}O_5N_5.H_2O$: C, 59.63; H, 6.00; N, 14.49. Found: C, 60.28, 59.88; H, 5.75, 5.97; N, 14.77, 14.45.

The Action of Hydrochloric Acid on the Phenylhydrazine Compound.—When the phenylhydrazine compound is heated with 2 molecular equivalents of *N* hydrochloric acid, partial solution takes place. After the solution is decanted from an insoluble viscous by-product, there separate on cooling, at first an oil and later a nearly white crystalline product. This is insoluble in ether, benzene and ethyl acetate and soluble in alcohol and water. From water it crystallizes in short needles melting at 118°. It titrates as monobasic with phenolphthalein as an indicator in conformity with the analytical data, which show the product to be one of the two phenylhydrazide anilides of citric acid that are theoretically possible.

Anal. Calcd. for $C_{18}H_{19}O_5N_3.H_2O$: C, 57.60; H, 5.60; N, 11.2. Found: C, 57.66; H, 5.63; N, 11.11.

Dimethyl Methylene-citrate.—A mixture of 10 g. of methylene-citric acid, 40 cc. of methanol and 25 g. of sulfuric acid is heated for several hours under a reflux condenser. The solution, diluted to thrice the original volume, is then boiled with a small amount of calcium carbonate to remove sulfuric acid together with any unchanged methylene-citric acid, and the ester extracted with ether. It is sparingly soluble in petroleum ether, readily soluble in the other common organic solvents, and from water separates as an oil which as it cools solidifies in the form of prismatic plates; m. p., 69.5°.

Anal. Calcd. for $C_9H_{12}O_7$: C, 46.55; H, 5.17. Found: C, 46.82; H, 5.09.

Conversion of *sym.*-Dimethyl Citrate to Dimethyl Methylene-citrate.—A mixture of 10 g. of *sym.*-dimethyl citrate and 1.5 g. of paraformaldehyde is heated for two hours in a sealed tube at 160°. After 12 hours an equal volume of water is added, the solution boiled with a small amount of calcium carbonate to salify any unchanged dimethyl citrate, and the dimethyl-methylene citrate is extracted with ether. A comparison of this preparation with the product obtained in esterifying methylene-citric acid with methanol, as described above, established the identity of the two products.

Anal. Calcd. for $C_9H_{12}O_7$: C, 46.55; H, 5.17. Found: C, 46.36; H, 5.06.

Conversion of Dimethyl-methylene Citrate to *sym.*-Dimethyl Citrate.—Dimethyl methylene-citrate is dissolved in the cold in *N* sodium hydroxide solution, the ester and alkali being taken in molecular proportions. The solution is then heated to incipient boiling, allowed to cool and made acid to congo red with hydrochloric acid. *sym.*-Dimethyl citrate, which is difficultly soluble in water, separates in a yield of about 25%. It was identified by comparison with the same product obtained on esterifying citric acid according to the method of Schroeter and Schmitz referred to in the introduction. Results of an analysis of our preparation agreed with the observation of the German investigators that the ester separates from water with one molecule of water of crystallization.

Anal. Calcd. for $C_8H_{12}O_7.H_2O$: C, 40.33; H, 5.88. Found: C, 40.53; H, 5.78.

Mono-ethyl Methylene-citrate.—Five g. of methylene-citric anhydride is boiled with 150 cc. of ethyl alcohol until solution is effected. As soon as the anhydride shows no tendency to separate when the solution is cooled, an equal volume of water is added and the ester extracted with ether. It can be purified by precipitation from an ether solution with petroleum ether, or it may be recrystallized from water in microscopic prisms; m. p., 109°. It is readily soluble in the common organic solvents, petroleum ether excepted.

Anal. Calcd. for $C_9H_{12}O_7$: C, 46.55; H, 5.17. Found: C, 46.64; H, 5.13.

Action of Alcoholic Ammonium Hydroxide on Citranilic Acid.—A mixture of 2 g. of citranilic acid and 20 cc. of strong alcoholic ammonium hydroxide is heated for two hours in a sealed tube in a boiling water-bath, the solution is evaporated to dryness and the residue dissolved in a little water. The ether extract of this solution after removal of the solvent gives a viscous residue that crystallizes when stirred with alcohol. The new product is readily soluble in water and can be recrystallized from either alcohol or ethyl acetate. From the latter solvent it separates in elongated prisms that begin to soften at 90°; m. p., 100–104°, with evolution of gas. When it is boiled in potassium hydroxide solution, ammonia and aniline are split off. The analysis of the substance dried in a vacuum over sulfuric acid gave results indicating the presence of an amide-anilide of citric acid with a molecule of alcohol of crystallization, and the presence of alcohol was confirmed by distilling this and applying the iodiform test. The relative positions of the NH_2 and C_6H_5NH groups in this substance are in doubt.

Anal. Calcd. for $C_{12}H_{14}O_5N_2.C_2H_6O$: C, 53.85; H, 6.41; N, 8.97. Found: C, 53.74; H, 6.51; N, 9.19.

Methyl Citranilate.—Five g. of pure citranilic acid is dissolved in a mixture of 25 cc. of methanol and 2.5 cc. of concd. sulfuric acid. After 48 hours the solution is poured onto 25 g. of crushed ice, the sulfuric acid is neutralized with calcium carbonate, and the ester extracted with ether. A viscous residue, which remains upon removal of the ether, is made to crystallize by being stirred with benzene and then is recrystallized from this solvent. A more satisfactory method of preparation is to dissolve 5 g. of citranilic acid in the least possible amount of hot alcohol and then add 10 drops of concd. aqueous hydrochloric acid. After 12 hours the solution is chilled and the ester made to crystallize by vigorous stirring. It separates from benzene in prisms with dome-shaped end faces; m. p., 89°.

Anal. Calcd. for $C_{13}H_{13}O_5N$: C, 59.32; H, 4.94; N, 5.32. Found: C, 59.42; H, 4.78; N, 5.29.

Ethyl Citranilate.—A convenient method of preparation is to use ethyl alcohol and aqueous hydrochloric acid under the same conditions that were given above for the preparation of the methyl ester. The ethyl ester is more or less readily soluble in the common organic solvents, petroleum ether excepted, difficultly soluble in water, and can be purified by recrystallization from benzene or alcohol in thin, broad, microscopic plates; m. p., 122°.

Anal. Calcd. for $C_{14}H_{15}O_5N$: C, 60.65; H, 5.42; N, 5.06. Found: C, 60.67; H, 5.52; N, 5.22.

Action of Ammonium Hydroxide on Ethyl Citranilate.—When ethyl citranilate in concd. ammonium hydroxide in the proportion of 1 g. to 10 cc. is vigorously shaken, partial solution is effected, whereupon an amido-anilido ester of citric acid begins to separate. Then after a short time this dissolves in great part with subsequent separation of a diamido-citranilide. When the mixture is now heated for 30 minutes in a sealed tube in a boiling water-bath, saponification of one amido group with the formation of a mono-amido-anilide of citric acid takes place; this product remains in solution as an ammonium salt. To obtain these three reaction products free from admixtures, a special procedure, as outlined below, for the preparation of each substance is recommended. These reactions proceed similarly to those involved in the action of ammonium hydroxide on trimethyl citrate.[23] Probably other products are formed in the action of ammonium hydroxide on ethyl citranilate, but their isolation was not attempted. To the derivatives of citric acid described above are tentatively assigned the following structural formulas: $CH_2COOC_2H_5C(OH)(CONH_2)CH_2CONHC_6H_5$ (V); $CH_2CONH_2C(OH)$-$(CONH_2)CH_2CONHC_6H_5$ (VI); $CH_2CONH_2C(OH)(COOH)CH_2CONHC_6H_5$ (VII).

Preparation of Product V.—To 2 g. of ethyl citranilate dissolved in 5 cc. of absolute alcohol, 1.2 cc. of 28% ammonium hydroxide is added; after a short time, crystallization sets in. The product is purified by recrystallization from alcohol and is then obtained in fine needles, and from water in thin, prismatic plates; m. p., 183°, with violent evolution of gas.

Anal. Calcd. for $C_{14}H_{18}O_5N_2$: C, 57.14; H, 6.12; N, 9.52. Found: C, 57.39; H, 6.02; N, 9.34.

Preparation of Product VI.—To 2 g. of ethyl citranilate in 5 cc. of absolute alcohol is added an equal volume of strong alcoholic ammonium hydroxide and the mixture allowed to react in a sealed tube for one-half hour in a boiling water-bath. As the mixture is cooled, the diamido-anilide separates in spheroidal aggregates and can be purified by recrystallization from alcohol, occurring in long, slender prisms; m. p., 185°. Product V is more difficultly soluble in alcohol than is ethyl citranilate, only sparingly soluble in the other common organic solvents and very difficultly soluble in water. Product VI is less soluble in organic solvents and more soluble in water than is Product V.

Anal. Calcd. for $C_{12}H_{15}O_4N_3$: C, 54.34; H, 5.66; N, 15.85. Found: C, 54.24; H, 5.58; N, 15.94.

Preparation of Product III.—In order to obtain a colorless substance, it is not advisable to start with ethyl citranilate in this preparation but to employ Product V or VI. A mixture of 2 g. of either intermediate and 10 cc. of concd. ammonium hydroxide is heated for one-half hour in a boiling water-bath, the solution is evaporated to dryness and the residue treated with a little dil. hydrochloric acid. On addition of alcohol the new substance crystallizes and can be purified by recrystallization from water and alcohol in microscopic plates; m. p., 171°.

Anal. Calcd. for $C_{12}H_{14}O_5N_2$: C, 54.14; H, 5.26; N, 10.53. Found: C, 54.40; H, 4.87, 5.42; N, 10.61.

Neutral Potassium Ethyl-citranilide.—When 1 g. of potassium hydroxide in 1 cc. of water is added to 5 g. of ethyl citranilate in 10 cc. of absolute alcohol, the solution turns red, and after a short time a potassium salt, probably $C_6H_5NHCOCH_2C(OH)$-$(COOK)CH_2COOC_2H_5$,[24] begins to separate. After 12 hours the solid is filtered off and recrystallized from 95% alcohol in lustrous, rectangular plates which begin to soften at 70°; m. p., 121°.

Anal. Calcd. for $C_{14}H_{16}O_6NK$: N, 4.20; K, 11.71. Found: N, 4.34; K, 11.33.

Acid Potassium Ethyl-citranilide.—On addition of glacial acetic acid to a concentrated aqueous solution of the above neutral potassium salt, an acid salt of the formula $C_{14}H_{16}O_6NK.C_{14}H_{17}O_6N$ separates. This is more difficultly soluble in water than the neutral salt and can be recrystallized from water or alcohol in slender prisms with dome-shaped end faces; m. p., 153°.

Anal. Calcd. for $C_{28}H_{33}O_{12}N_2K$: C, 53.50; H, 5.24; N, 4.46; K, 6.21. Found: C, 53.29; H, 5.19; N, 4.64; K, 6.30.

---

[23] Behrmann and Hofmann, *Ber.*, **17**, 2681 (1884).

[24] Compare Ref. 17, p. 1617.

Ethyl-citranilide.—On addition of the calculated amount of *N* hydrochloric acid to the neutral potassium salt described above, an oil results which when stirred becomes crystalline. This, on recrystallization from water, again separates as an oil. Recrystallized from benzene it melts at 108° and when heated to 150° splits out a molecule of water to form ethyl citranilate. In the presence of mineral acids the anilido ester is also readily converted to the anil ester. Attempts to isolate a second anilido ester, which might be expected in the action of potassium hydroxide on ethyl citranilate, were unsuccessful. The anilido ester on slow recrystallization from water is obtained in the form of prismatic plates.

Anal. Calcd. for $C_{14}H_{17}O_6N$: C, 56.95; H, 5.76; N, 4.75. Found: C, 56.68; H, 5.55; N, 4.59.

Anil of Aconitic Acid.—Ten g. of citranilic acid and 16.6 g. of phosphorus pentachloride are intimately mixed. After the vigorous reaction which ensues with liquefaction of the mixture subsides, a temperature of 95° is maintained for an hour, the phosphorus oxychloride formed is then distilled under reduced pressure and the resulting cake washed with ice water. The aconitylanil, extracted with boiling water from accompanying tarry matter and decolorized with Filtchar, separates in a yield of 2 g. of clusters of colorless, fine needles; m. p., 189°. For further purification alcohol may be employed. It is readily soluble in ethyl acetate and difficultly soluble in benzene or ether. It imparts to aqueous potassium hydroxide an evanescent, yellow color which fades in a few minutes, the solution becoming colorless.

Anal. Calcd. for $C_{12}H_9O_4N$: C, 62.34; H, 3.89; N, 6.06. Found: C, 62.48; H, 4.19; N, 5.99.

Methyl Ester of Aconitylanil.—Aconityl anil, dissolved in eight times its weight of methanolic hydrochloric acid, is quickly converted to the ester, which separates in prismatic plates. After recrystallization from ethyl alcohol it melts at 149°.

Anal. Calcd. for $C_{13}H_{11}O_4N$: C, 63.67; H, 4.49; N, 5.71. Found: C, 63.55; H, 4.44; N, 5.59.

Ethyl Ester of Aconitylanil.—This ester can be prepared similarly to the preceding methyl ester or as follows: phosphorus pentachloride and ethyl citranilate are mixed in molecular proportions; after 12 hours water is added to remove the phosphorus oxychloride, and the resulting gummy mass made to crystallize by being stirred with a small amount of ether. The mixture is chilled, filtered and the treatment with ether repeated. On recrystallization of the residue from alcohol the ester is obtained in microscopic plates; m. p., 123°.

Anal. Calcd. for $C_{14}H_{13}O_4N$: C, 64.86; H, 5.02; N, 5.41. Found: C, 64.59; H, 5.24; N, 5.35.

The esters of aconitylanil described above were prepared by Bertram. Since he reports the methyl ester as melting at 143° and the ethyl ester at 112°, whereas we find the esters to melt at 149° and 123°, respectively, it was deemed advisable to repeat his work. In his experiments Bertram converts aconitic anhydride to the aniline salt of the mono-anilide of aconitic acid and this to esters of aconityl anil by saturating alcoholic solutions with hydrogen chloride.

In numerous attempts to prepare aconitic anhydride according to the directions of Anschütz and Bertram[25] a smear was invariably obtained. However, it was found that when this is dissolved in the least possible amount of benzene, and petroleum ether is added, two layers of solution result, the lower of which contains the anhydride which when chilled quickly solidifies. After one recrystallization from benzene the anhydride gives the correct melting point of 76°.

---

[25] Anschütz and Bertram, *Ber.*, **37**, 3968 (1904).

In our hands Bertram's procedure for the preparation of esters of aconityl anil[26] did not lead to the isolation of the products sought. However, when, after esterification is complete, the alcohol is distilled in a vacuum at a low temperature, and the residue washed first with a little ether and then with water, recrystallization of the residue from benzene gives a pure product. A comparison of the methyl and ethyl esters made in this way with our products established their identity.

Summary

1. A new method of making anhydrides is given in connection with the preparation of methylene-citric anhydride.
2. The symmetrical structure of methylene-citric anhydride is established.
3. The formation of the unsymmetrical anil of citric acid from *sym.*-methylene-citric anhydride is cleared up.
4. Contrary to patent literature it is found that methylene-citric anhydride reacts with alcohols to form mono- and not dialkyl esters of methylene-citric acid.
5. A method of preparation of symmetrical dialkyl and unsymmetrical mono-alkyl esters of citric acid, using methylene-citric anhydride, is suggested.
6. The preparation of the anil of aconitic acid from the anil of citric acid is described and an analogy in structure definitely established.
7. A modification of the method of making aconitic anhydride is given.

AUSTIN, TEXAS

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CINCINNATI]

SOME NEW HYDROXY-URETHANS AND CHROMO-ISOMERIC SILVER SALTS OF THEIR ACYL DERIVATIVES. III[1]

BY RALPH E. OESPER AND WALTER BROKER

RECEIVED JUNE 20, 1925 PUBLISHED OCTOBER 6, 1925

The previous papers of this series[2] have contained studies of the reversibly transformable yellow silver salts of the benzoylated carbo-alkyloxy-hydroxamic acids, with the view of determining whether they corresponded to the isomeric forms I and II.

$$\underset{\text{I}}{\mathrm{RO.CO.N(Ag)OCOC_6H_5}} \rightleftharpoons \underset{\text{II}}{\mathrm{RO.C(OAg){:}N.OCOC_6H_5}}$$

The alkyl derivatives formed by interaction of alkyl iodides with either the white or yellow silver salts gave betasubstituted hydroxylamines

---

[26] Ref. 17, p. 1617.

[1] This communication is an abstract of part of a thesis submitted by Walter Broker in partial fulfilment of the requirements for the degree of Master of Arts at the University of Cincinnati.

[2] (a) Jones and Oesper, THIS JOURNAL, **36**, 2208 (1914); (b) **36**, 726 (1914). (c) Oesper and Cook, *ibid.*, **47**, 422 (1925).