g. (79%) of XV as hygroscopic, light tan crystals, m.p. 133° dec.

D. Dichloride Salt of XV (XVa).—A solution of 600 g. of XV in 12 liters of distilled water was passed through a column of Amberlite anion exchange resin, IRA 401 (regenerated with aqueous sodium chloride), and the column was washed with fresh water. The eluate was concentrated *in vacuo* and the residue was crystallized from ethanol–acetone to yield 425 g. (86%) of the dichloride salt, XVa, m.p. 195° dec.

Two alternative routes to XVa have been found quite satisfactory: 1. A solution of 4-(1-methyl-3-indolylethyl)-pyridine and 3-chloropropyltrimethylammonium bromide[22] in dimethylformamide was heated at 120–125° (oil-bath temperature) for 24 hr. and the crude mixed halide product passed through a column of Amberlite IRA 401. 2. A dimethylformamide solution of the pyridine base and 3-chloropropyltrimethylammonium chloride[23] was heated at 120° (oil-bath) for 24 hours, thus directly affording a 55% yield of XVa.

Condensation of II with Aldehydes. A. Benzaldehyde. The Preparation of IV.—To a solution of 6.3 g. (0.018 mole) of II and 3.8 g. (0.036 mole) of freshly distilled benzaldehyde in 50 ml. of methanol was added 1 ml. of piperidine. After 4 hr. reflux on the steam-bath, the deep purple solution was cooled, diluted with ether and the purple precipitate was recrystallized from ethanol to provide 4.3 g. (54% yield) of IV, melting with decomposition and gas evolution at 150°.

B. 1-Naphthaldehyde. The Preparation of VII.—Refluxing a solution of 4.4 g. (0.028 mole) of 1-naphthaldehyde and 10 g. (0.028 mole) of II in 50 ml. of ethanol containing 1 ml. of piperidine for 3 hr., diluting with ether and crystallizing the resultant purple, oily precipitate from ethanol–ether yielded 9.6 g. (69%) of VII, m.p. 178° dec.

C. 3-Indolecarboxaldehyde. The Preparation of XIII.—In similar fashion, 3-indolecarboxaldehyde[24] was condensed with II to yield, after recrystallization from methanol–ethyl acetate, 56% of bright orange crystals of XIII, melting with decomposition and gas evolution at 275°.

Acknowledgments.—The authors wish to thank Mrs. Dorothy Schlieper for assistance with some of the synthetic work and Mr. Dean F. Cortright for the ionic halogen and basic nitrogen determinations.

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[22] This salt was prepared from trimethylene chlorobromide and trimethylamine, m.p. 204–206°.

[23] Prepared from 3-chloropropyltrimethylammonium bromide by passage over the anion exchange resin, m.p. 202° dec.

[24] Prepared as described by F. T. Tyson and J. T. Shaw, THIS JOURNAL, **74**, 2273 (1952), from indole and dimethylformamide with phosphorus oxychloride.

DECATUR, ILLINOIS

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Quinone Imides. XLIV. The Orientation of Groups in Addition Reactions to Substituted p-Quinonedibenzimides

BY ROGER ADAMS AND HARRY J. NEUMILLER, JR.[1]

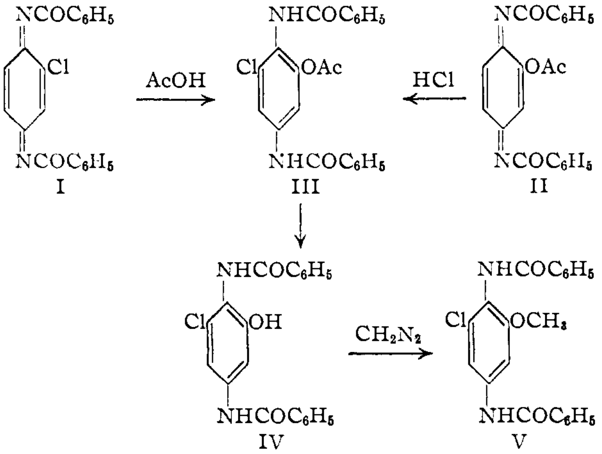
RECEIVED FEBRUARY 1, 1957

The acetoxychloro-*p*-phenylenedibenzamide isomer, which results both from the addition of acetic acid to 2-chloro-*p*-quinonedibenzimide and from the addition of hydrogen chloride to 2-acetoxy-*p*-quinonedibenzimide, has been identified as 2-acetoxy-6-chloro-*p*-phenylenedibenzamide. The oxidation of 2-methoxy-*p*-phenylenedibenzamide with lead tetraacetate affords 2-methoxy-*p*-quinonedibenzimide which adds hydrogen chloride to give a mixture of 2-chloro-5-methoxy- and 2-chloro-6-methoxy-*p*-phenylenedibenzamides, both identified by unequivocal syntheses.

In a recent paper[2] the orientation of groups in the adducts of 2-substituted *p*-quinonedibenzenesulfonimides and 2-substituted *p*-quinonedibenzimides was summarized. 2-Chloro-*p*-quinonedibenzenesulfonimide adds hydrogen chloride to afford a mixture of 2,3- and 2,5-dichloro-*p*-phenylenedibenzenesulfonamides. The addition of hydrogen chloride and a number of other reagents to 2-methoxy-*p*-quinonedibenzenesulfonimide results in substituted *p*-phenylenedibenzenesulfonamides having exclusively the 2,5-orientation.

In contrast to the foregoing, the addition of hydrogen chloride to 2-chloro-*p*-quinonedibenzimide (I) affords 2,6-dichloro-*p*-phenylenedibenzamide; the addition to 2-methyl-*p*-quinonedibenzimide yields exclusively 6-chloro-2-methyl-*p*-phenylenedibenzamide. The 2-phenylmercapto analog gives 3-chloro-2-phenylmercapto-*p*-phenylenedibenzamide and the 2-benzenesulfonyl derivative gives a mixture of 2-benzenesulfonyl-3-chloro- and 2-benzenesulfonyl-6-chloro-*p*-phenylenedibenzamides.

Previous investigators demonstrated that both the addition of acetic acid to 2-chloro-*p*-quinonedibenzimide (I) and the addition of hydrogen chloride to 2-acetoxy-*p*-quinonedibenzimide (II) yielded the same acetoxy-chloro-*p*-phenylenedibenzamide isomer as the sole product of each reaction.[3] The product has now been identified as 2-acetoxy-6-chloro-*p*-phenylenedibenzamide (III).



I III II IV V

For the purpose of its identification, III was hydrolyzed with dilute aqueous sodium hydroxide to

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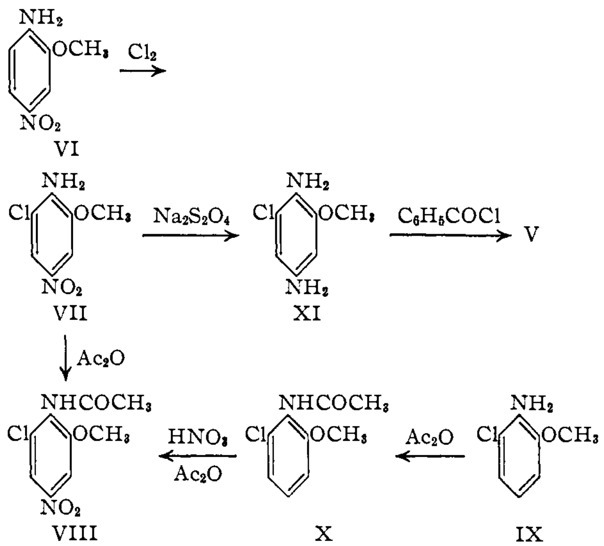
[1] An abstract of a thesis submitted by Harry J. Neumiller, Jr., to the Graduate College of the University of Illinois, 1956, in partial fulfillment of the requirements for the Degree of Doctor of Philosophy; Minnesota Mining and Manufacturing Fellow, 1952–1954; University of Illinois Fellow, 1953 and 1954–1955.

[2] R. Adams and M. D. Nair, THIS JOURNAL, **78**, 5927, 5932 (1956).

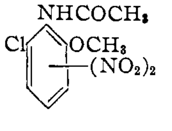
[3] R. Adams and D. S. Acker, *ibid.*, **74**, 3657 (1952).

2-chloro-6-hydroxy-*p*-phenylenedibenzamide (IV), and this was methylated with diazomethane to give 2-chloro-6-methoxy-*p*-phenylenedibenzamide (V). The unequivocal synthesis of V was then accomplished through the following steps. 2-Amino-5-nitroanisole (VI) was chlorinated to 2-amino-3-chloro-5-nitroanisole (VII). The position of the chlorine atom in this compound was established by its acetylation to afford 2-chloro-6-methoxy-4-nitroacetanilide (VIII); the same compound resulted from a sequence involving acetylation of 2-amino-3-chloroanisole (IX) to 2-chloro-6-methoxyacetanilide (X) followed by nitration to VIII. Compound VIII is the only possible common product of these two reaction sequences. By reduction with sodium hydrosulfite, VII was converted to 2-chloro-6-methoxy-*p*-phenylenediamine (XI), which was then benzoylated to the desired 2-chloro-6-methoxy-*p*-phenylenedibenzamide (V). Through comparison of infrared spectra and melting points, the compound prepared in this manner was shown to be identical with the sample of V obtained from 2-chloro-*p*-quinonedibenzimide (I).

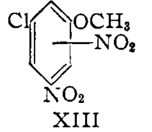


An initial attempt was made to prepare V through 2′-chloro-6′-methoxy-4′-nitrobenzanilide, the benzoyl derivative of VII. Benzoylation of VII was difficult and was achieved only by a long period of refluxing with benzoyl chloride in pyridine and subsequent separation of the benzoyl derivative from unreacted amine by chromatography.

While studying the conditions under which X could best be mononitrated to VIII, it was found that 2-chloro-6-methoxyacetanilide (X) was dinitrated (XII) by means of a mixture of cold concentrated sulfuric and nitric acids. When 2-chloro-6-methoxy-4-nitroacetanilide (VIII), prepared from 2-amino-3-chloro-5-nitroanisole, was nitrated in a similar fashion a different dinitro compound XIII resulted. This suggests that VIII is not an intermediate in the formation of the dinitro derivative of X.

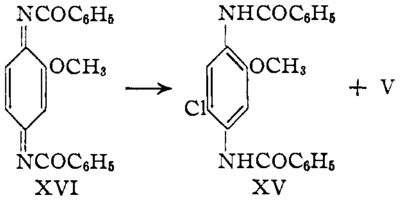


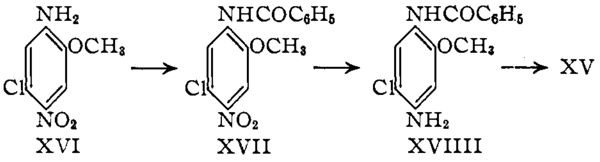
XII



XIII

2-Methoxy-*p*-quinonedibenzimide (XIV) could not be isolated in a crystalline state, but treatment of the solution in which it was prepared with hydrogen chloride resulted in a mixture of chloromethoxy-*p*-phenylenedibenzamide isomers. The mixture was cleanly separated by chromatography on a column of aluminum oxide into 2-chloro-5-methoxy-*p*-phenylenedibenzamide (XV) and 2-chloro-6-methoxy-*p*-phenylenedibenzamide (V). The unequivocal synthesis of the latter of these two isomers already has been described. The former was synthesized through the following sequence: 2-Amino-4-chloro-5-nitroanisole (XVI) was benzoylated to 5′-chloro-2′-methoxy-4′-nitrobenzanilide (XVII), reduced to 4′-amino-5′-chloro-2′-methoxybenzanilide (XVIII) and benzoylated to XV.





Acknowledgment.—The authors are indebted to Mr. Joseph Nemeth, Mrs. Lucy Chang, Mrs. Esther Fett and to Mr. R. Maria Benassi for the microanalyses, and to Mr. James Brader, Mrs. Louise Griffing and Miss Helen Miklas for the determination and interpretation of the infrared spectra.

Experimental

All melting points are corrected. The infrared spectra were run in Nujol mulls, using a Perkin-Elmer model 21 double beam spectrophotometer.

2-Acetoxy-6-chloro-*p*-phenylenedibenzamide.—A solution of 0.52 g. of 2-chloro-*p*-benzoquinonedibenzimide[4] in 10 ml. of glacial acetic acid was prepared by gentle warming. The red solution was allowed to stand at room temperature for 14 hours. The addition of 20 ml. of petroleum ether (b.p. 80–110°) did not cause the precipitation of the product, as previously reported,[3] and most of the petroleum ether was retained as an upper layer. As much as possible of the petroleum ether was therefore removed *in vacuo*, and 25 ml. of water was added, causing the precipitation of the very crude product. After one recrystallization from benzene (Darco) it weighed 0.24 g. (39%). Two more recrystallizations from benzene (Darco) afforded small white lustrous crystals, m.p. 179.5–181° dec. (lit.[3] m.p. 181–182°).

2-Chloro-6-hydroxy-*p*-phenylenedibenzamide.—A suspension of 0.08 g. of 2-acetoxy-6-chloro-*p*-phenylenedibenzamide in 25 ml. of 5% aqueous sodium hydroxide was allowed to stand at room temperature for 7.5 hours. The solid went slowly into solution during the course of this period. The mixture was filtered, and the filtrate was made acidic to congo red with concentrated hydrochloric acid, causing the precipitation of the very crude product. After one recrystallization from an ethyl acetate–petroleum ether (b.p. 80–110°) solvent pair, it weighed 0.03 g. (43%). Further recrystallization from the same solvent pair (Darco) gave white needles, m.p. 240–243° (lit.[3] m.p. 246–246.5°).

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[4] R. Adams and J. L. Anderson, THIS JOURNAL, **72**, 5154 (1950).

2-Amino-3-chloro-5-nitroanisole.—Into a stirred suspension of 8.40 g. of 2-amino-5-nitroanisole in 200 ml. of concentrated hydrochloric acid and 100 ml. of glacial acetic acid, maintained at a temperature of 5–15°, was passed a stream of chlorine gas (dried by passage through concentrated sulfuric acid) at a moderate rate until the increase in the weight of the mixture was 5.8 g. (45 minutes). The mixture was filtered through a sintered-glass funnel and the precipitate was stirred with 200 ml. of 10% aqueous sodium bisulfite for *ca.* 20 minutes. The product was then collected by suction filtration, washed with water, and recrystallized once from 95% ethanol, after which it weighed 3.76 g. Concentration of the ethanolic mother liquors afforded an additional 1.42 g. of the product, and thus the total crude yield was 5.18 g. (51%). Attempts to obtain an additional quantity of the product from the chlorination liquors were unsuccessful. Seven recrystallizations from carbon tetrachloride gave small flat orange-yellow prisms, m.p. 122–124°.

Anal. Calcd. for $C_7H_7ClN_2O_3$: C, 41.49; H, 3.48; N, 13.83. Found: C, 41.66; H, 3.28; N, 13.86.

The steps through the first recrystallization should be carried out without delay, since unrecrystallized product darkened rapidly upon standing, and could subsequently be purified only with great loss. In runs in which concentrated hydrochloric acid was used as the solvent for chlorination a very impure grade of product was obtained. The use of dimethylformamide resulted in the formation of an uncrystallizable tarry product. When glacial acetic acid, or a hydrochloric acid–glacial acetic mixture containing a relatively large proportion of the latter substance, was used as the solvent the chlorination was incomplete, and the product was badly contaminated with starting material.

2-Chloro-6-methoxyacetanilide.—To a solution of 1.58 g. of 2-amino-3-chloroanisole[5] in 10 ml. of glacial acetic acid and 3 ml. of water was added 1.23 g. of acetic anhydride all in one portion. The solution was boiled for 10 minutes and, with continued boiling, water was added slowly until the cloud point was attained after another 40 minutes. The solution was cooled under the tap and the oil which began to form was scratched with a glass rod to initiate crystallization. After the resulting mixture had cooled to room temperature, filtration gave 1.64 g. of crystalline product, m.p. 145–146.5° with sintering at 144°. By concentration of the filtrate and further addition of water an additional 0.06 g. of the product was obtained and thus the total yield was 1.70 g. (85%). Three recrystallizations from water followed by two recrystallizations from a benzene–petroleum ether solvent pair afforded small lustrous white prisms, m.p. 145.5–147°, with sintering at 144.5°.

Anal. Calcd. for $C_9H_{10}ClNO_2$: C, 54.15; H, 5.05; N, 7.02. Found: C, 54.19; H, 5.09; N, 6.70.

This compound was reported by Meldola and Eyre[6] as melting at 147–148°, with softening between 115 and 125°, and by Hodgson and Kershaw[5] as melting at 123°. Furthermore, the latter investigators reported that 2-chloro-N,N-diacetyl-6-methoxyaniline melted at 145.5°. The infrared spectrum of the compound prepared by the method described above showed N–H stretching absorption at 3195 cm.$^{-1}$, and a single amide C═O band at 1664 cm.$^{-1}$. These data, together with the composition of the compound, leave no doubt that it is the desired monoacetyl derivative of 2-chloro-6-methoxyaniline. In one attempt to monoacetylate 2-chloro-6-methoxyaniline, the amine was heated with acetic anhydride on the steam-bath for 1.5 hours, in accordance with the procedure described by Hodgson and Kershaw[5] for the preparation of the monoacetyl derivative. After the subsequent addition of water to decompose the acetic anhydride, the precipitate, m.p. *ca.* 100–123°, was repeatedly recrystallized from petroleum ether (b.p. 80–110°), water, and petroleum ether again, giving small white plates, m.p. 123–125°, in very low yield. This material was apparently the diacetyl derivative of the amine, since a mixture of it and the previously described monoacetyl derivative melted at 107–111°. Thus, the melting points as reported by Hodgson and Kershaw[5] for the monoacetyl derivative and the diacetyl derivative should be reversed. The compound reported by Meldola and Eyre[6] was undoubtedly the monoacetyl derivative.

2-Chloro-6-methoxy-4-nitroacetanilide. Method A.—A suspension of 0.33 g. of 2-chloro-6-methoxyacetanilide in 3.0 ml. of acetic anhydride was cooled to −10° by the direct addition of Dry Ice. While maintaining the temperature below 0°, a cooled solution of 0.12 g. of fuming nitric acid (sp. gr. 1.5) in 1.0 ml. of acetic anhydride was added, with constant agitation, over a period of 5 minutes. Agitation was continued for a period of 20 minutes during which the temperature was permitted to rise rapidly to 10° and was then held at 10–15°. All of the suspended solid went into solution during the period in which the temperature was rising. The solution was poured into 10 ml. of water and the resulting mixture was shaken until all of the acetic anhydride had decomposed. After allowing the mixture to stand overnight, 0.09 g. (22%) of the crystalline product was obtained by filtration. Dilution of the filtrate with water and subsequent concentration did not afford more product. The product was recrystallized three times from an ethanol–water solvent pair (Darco), giving white needles, m.p. 223.5–225°.

Anal. Calcd. for $C_9H_9ClN_2O_4$: C, 44.19; H, 3.71; N, 11.45. Found: C, 44.17; H, 3.45; N, 11.47.

Method B.—To a boiling solution of 1.01 g. of 2-amino-3-chloro-5-nitroanisole in 75 ml. of dry benzene was added a solution of 0.61 g. of acetic anhydride in 5 ml. of dry benzene, followed by several mg. of benzenesulfonic acid. The solution was allowed to continue to boil and evaporate until the volume had been reduced to *ca.* 20 ml. Petroleum ether (b.p. 80–110°) was then added until the cloud point was reached. Allowing the solution to cool to room temperature caused the crystallization of 1.02 g. (84%) of the product, contaminated with unreacted 2-amino-3-chloro-5-nitroanisole. After one recrystallization from an ethanol–water solvent pair (Darco), the product was reasonably pure (m.p. 221–224°) and weighed 0.77 g. (63%). Several additional recrystallizations from this same solvent pair gave white needles, m.p. 224–226°.

Anal. Calcd. for $C_9H_9ClN_2O_4$: C, 44.19; H, 3.71; N, 11.45. Found: C, 44.12; H, 3.54; N, 11.66.

Concentrated sulfuric acid served equally well in place of benzenesulfonic acid as a catalyst for the acetylation of 2-amino-3-chloro-5-nitroanisole. With no catalyst acetylation did not occur.

The melting point of a mixture of samples of 2-chloro-6-methoxy-4-nitroacetanilide prepared by the two different methods was not depressed. The infrared spectra of the two products were identical.

2-Chloro-6-methoxy-*p*-phenylenediamine.—To a boiling solution of 1.01 g. of 2-amino-3-chloro-5-nitroanisole in a mixture of 100 ml. of 95% ethanol and 100 ml. of water was added 2.65 g. of sodium hydrosulfite, in small portions over a period of 3 minutes. The solution was heated under reflux for one-half hour, and then concentrated to the cloud point on the hot-plate. Subsequent storage in the refrigerator at 0–5° for 3 hours caused the crystallization of 0.53 g. (62%) of the diamine. One recrystallization from a benzene–petroleum ether (b.p. 80–110°) solvent pair gave medium brown needles, m.p. 97–99.5° dec. The product deteriorated upon standing, and it was used in the following experiment without further characterization.

2-Chloro-6-methoxy-*p*-phenylenedibenzamide. Method A.—A solution of 0.28 g. of 2-chloro-6-methoxy-*p*-phenylenediamine and 0.56 g. of benzoyl chloride in 20 ml. of pyridine was heated under reflux for 2 hours. After cooling to room temperature it was poured into 200 ml. of 10% hydrochloric acid containing 75 g. of ice, causing the precipitation of 0.45 g. (74%) of light gray solid. Four recrystallizations from benzene (Darco) gave the pure compound; white needles, m.p. 224–225.5°.

Anal. Calcd. for $C_{21}H_{17}ClN_2O_3$: C, 66.23; H, 4.50; N, 7.36. Found: C, 66.15; H, 4.43; N, 7.36.

Method B.—The method used for the preparation of the ethereal solution of diazomethane in the following experiment was the one described in reference 7.

To a mixture of 30 ml. of ether and 9 ml. of 40% aqueous potassium hydroxide, cooled to *ca.* 5° in an ice-bath, was added 3.00 g. of α-nitroso-α-methylurea[8] in small portions

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(5) H. H. Hodgson and A. Kershaw, *J. Chem. Soc.*, 191 (1928).

(6) R. Meldola and J. V. Eyre, *ibid.*, **81**, 988 (1902).

(7) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., **1943**, p. 165.

(8) Reference 7, p. 462.

over a period of 3 minutes. The ether layer was decanted from the mixture and slowly added, with constant swirling, to a suspension of 0.15 g. of 2-chloro-6-hydroxy-*p*-phenylenedibenzamide in 15 ml. of methanol, cooled to *ca.* 5° in an ice-bath. Slight effervesence occurred, and the diamide went into solution. The solution was allowed to stand in the ice-bath for one-half hour, and 25 ml. of glacial acetic acid was then added to destroy excess diazomethane. The solvents were removed by means of a current of dry air, and the resulting residue was dissolved in 50 ml. of hot acetone. The hot solution was treated with Darco and filtered, and 0.07 g. (45%) of crystalline product was precipitated from the filtrate by the addition of water. Four recrystallizations from benzene gave white needles, m.p. 224–225.5°.

Anal. Calcd. for $C_{21}H_{17}ClN_2O_3$: C, 66.23; H, 4.50; N, 7.36. Found: C, 66.35; H, 4.78; N, 7.46.

The melting point of a mixture of samples of 2-chloro-6-methoxy-*p*-phenylenedibenzamide prepared by the two different methods was not depressed. The infrared spectra of the two products were identical.

2-Chloro-x,y-dinitro-6-methoxyacetanilide.—A solution of 0.28 g. of 2-chloro-6-methoxyacetanilide in 1.00 ml. of concentrated sulfuric acid was prepared by the slow addition of the solid to the acid. The solution was agitated and maintained at a temperature of 12–18°, and a solution of 0.18 g. of concentrated nitric acid (sp. gr. 1.42) in 0.25 ml. of concentrated sulfuric acid was added over a period of 5 minutes. The mixture was agitated at 12–15° for an additional 30 minutes, and was then allowed to stand at room temperature for 40 minutes. The mixture was poured onto 10 g. of ice, causing the precipitation of a yellow solid which was washed with water, 60 ml. of 5% aqueous sodium carbonate, and then with water again. It weighed 0.24 g. and melted at *ca.* 150–190° dec. Repeated fractional crystallization of this material from 95% ethanol gave 0.07 g. (24%, based on the amount of nitric acid employed) of white needles, m.p. 215.5–216.5° with simultaneous bubbling. For analysis, the compound was sublimed at 1.5–1.8 mm. pressure, which did not alter the melting point.

Anal. Calcd. for $C_9H_8ClN_3O_6$: C, 37.33; H, 2.78; N, 14.51. Found: C, 37.51; H, 3.07; N, 14.31.

The infrared spectrum showed N-H stretching absorption at 3190 cm.$^{-1}$, an amide C=O band at 1683 cm.$^{-1}$, and $-NO_2$ bands at 1537 cm.$^{-1}$ and 1350 cm.$^{-1}$.

2-Chloro-4,z-dinitro-6-methoxyacetanilide.—A solution of 0.49 g. of 2-chloro-6-methoxy-4-nitroacetanilide in 1.50 ml. of concentrated sulfuric acid was prepared by adding the solid to the acid over a period of 4 minutes. The solution was agitated and maintained at a temperature of 10–13°, and a solution of 0.23 g. of concentrated nitric acid (sp. gr. 1.42) in 0.30 ml. of concentrated sulfuric acid was added over a period of 4 minutes. The mixture was agitated at 10–16° for an additional 25 minutes, and was then allowed to stand at room temperature for 55 minutes. The mixture was poured onto 10 g. of ice, causing the precipitation of the product. Sufficient water was added to bring the volume to 25 ml., and the precipitate was collected by filtration and washed with water. After one recrystallization from an ethanol–water solvent pair it weighed 0.27 g. (47%). Five more recrystallizations from this same solvent pair (Darco) afforded white needles. The substance behaved in a peculiar fashion in the melting point determination: A sample inserted into the melting-point bath at room temperature melted at 221–223°, with slight decomposition, after previously softening at 213.5°, while a sample inserted at 217° immediately melted completely, with frothing and moderate decomposition. It is possible that the compound was contaminated to some extent with an isomer.

Anal. Calcd. for $C_9H_8ClN_3O_6$: C, 37.33; H, 2.78; N, 14.51. Found: C, 37.43; H, 2.83; N, 14.29.

The infrared spectrum had an amide C=O band at 1674 cm.$^{-1}$. The N-H stretching region contained two bands of only medium intensity, one at 3140 cm.$^{-1}$ and the other at 3060 cm.$^{-1}$.

A mixture of the 2-chloro-4,z-dinitro-6-methoxyacetanilide and the 2-chloro-x,y-dinitro-6-methoxyacetanilide described in the immediately preceding experiments melted at 180–195°.

2′-Chloro-6′-methoxy-4′-nitrobenzanilide.—A solution of 1.01 g. of 2-amino-3-chloro-5-nitroanisole and 0.84 g. of benzoyl chloride in 20 ml. of pyridine was heated under reflux for 21 hours. The bright red solution was allowed to cool to room temperature and then poured into 200 ml. of 10% hydrochloric acid containing 75 g. of ice, causing the precipitation of an orange-brown gum. After having been washed with water, the gum was dissolved in 150 ml. of carbon tetrachloride, and the solution was passed through a 1.7 × 32.8 cm. column of aluminum oxide (Merck, Reagent Grade). The column was eluted with *ca.* 275 ml. of chloroform. The eluate was collected in 25-ml. fractions, and each fraction was evaporated to dryness. Fractions 1–6 contained nothing, fraction 7 contained 0.05 g. of impure 2-amino-3-chloro-5-nitroanisole, fraction 8 contained 0.16 g. of the same substance, fairly pure, fraction 9 contained 0.07 g. of a mixture of 2-amino-3-chloro-5-nitroanisole and the product, and fractions 10–16 contained 0.68 g. of the product desired. Further elution afforded only colored amorphous material. The yield of the product, based on fractions 10–16, and corrected for reusable starting material recovered (fraction 8), was 53%. Several recrystallizations from carbon tetrachloride gave small white needles, m.p. 176.5–178°.

Anal. Calcd. for $C_{14}H_{11}ClN_2O_4$: C, 54.82; H, 3.62; N, 9.14. Found: C, 54.95; H, 3.47; N, 9.42.

A complete separation of the product from the unreacted starting material was obtained by using a mixture of equal parts by volume of carbon tetrachloride and chloroform as an initial elutant in the chromatogram. The process was considerably slower than the one described above, and the given procedure is more convenient from a preparative standpoint.

Reaction of 2-Methoxy-*p*-quinonedibenzimide with Hydrogen Chloride: 2-Chloro-5-methoxy-*p*-phenylenedibenzamide (Method A) and 2-Chloro-6-methoxy-*p*-phenylenedibenzamide (Method C).—A suspension of 0.87 g. of 2-methoxy-*p*-phenylenedibenzamide[9] and 1.14 g. of lead tetraacetate in 50 ml. of dry, thiophene-free benzene was stirred and heated under gentle reflux for 50 minutes. The mixture was allowed to cool to room temperature and filtered to remove the insoluble material, and 100 ml. of petroleum ether (b.p. 80–110°) was added to the orange-yellow filtrate.[10] Hydrogen chloride gas was passed into the solution at a moderate rate for 10 minutes, causing rapid bleaching of the color to light greenish-yellow and the concomitant formation of a precipitate. The solvents were removed *in vacuo* and the resulting residue was dissolved in a mixture of 300 ml. of carbon tetrachloride and 150 ml. of chloroform. This solution was passed through a 1.7 × 35.5 cm. column of aluminum oxide (Merck, Reagent Grade). The eluate was collected in 50-ml. fractions. The first 8.5 fractions resulted from the addition of the original solution; during the collection of the succeeding 16.5 fractions, 2:1 by volume carbon tetrachloride and chloroform was used as the elutant; and during the collection of the remaining fractions, chloroform was used as the elutant. The rate of elution ranged from 4.5 ml. per minute to 6.3 ml. per minute. The fractions were evaporated to dryness, and the following results were observed: Fractions 1–9 contained nothing, fractions 10–13 contained 2-chloro-5-methoxy-*p*-phenylenedibenzamide, fractions 14–19 contained unidentified traces of residues which melted over large ranges, fraction 20 contained nothing, fraction 21 contained a trace of residue which melted over a large range, fractions 22–27 contained 2-chloro-6-methoxy-*p*-phenylenedibenzamide, and fractions 28 and 29 contained only faint traces of residue.

The residues from fractions 10–13 were combined and recrystallized once from benzene (Darco), giving 0.22 g. (23%) of small lustrous white prisms, m.p. 225.5–226.5°. Two more recrystallizations from benzene did not alter the melting point.

Anal. Calcd. for $C_{21}H_{17}ClN_2O_3$: C, 66.23; H, 4.50; N, 7.36. Found: C, 66.46; H, 4.51; N, 7.11.

The melting point of a mixture of this product and the authentic 2-chloro-5-methoxy-*p*-phenylenedibenzamide, to be described, was not depressed. The infrared spectra of the two samples were identical.

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[9] R. Adams and D. S. Acker, THIS JOURNAL, **74**, 5872 (1952).

[10] If the mixture was now cooled in a Dry Ice–methanol-bath, a yellow crystalline solid separated which became a brownish-orange viscous oil upon warming to room temperature after removing the solvent. The diimide turned darker on standing and was not obtained in a pure crystalline form.

The residues from fractions 22–27 were combined and recrystallized once from benzene (Darco), affording 0.22 g. (23%) of crystalline product, m.p. 225–226°, with slight sintering at 223°. Two more recrystallizations from benzene gave white needles of 2-chloro-6-methoxy-*p*-phenylenedibenzamide, m.p. 225–226.5°.

Anal. Calcd. for $C_{21}H_{17}ClN_2O_3$: C, 66.23; H, 4.50; N, 7.36. Found: C, 66.24; H, 4.51; N, 7.23.

The melting point of a mixture of this product and the previously described authentic 2-chloro-6-methoxy-*p*-phenylenedibenzamide was not depressed. The infrared spectra of the two samples were identical.

The total yield of chloro-methoxy-*p*-phenylenedibenzamide isomers from the addition of hydrogen chloride to 2-methoxy-*p*-quinonedibenzimide was thus 0.44 g. (46%), based on the quantity of 2-methoxy-*p*-phenylenedibenzamide employed.

Although the two isomers melted at essentially the same point, the melting point of a mixture was depressed. The infrared spectra of the compound were different. The 2,5-isomer was more soluble in benzene than the 2,6-isomer.

5′-Chloro-2′-methoxy-4′-nitrobenzanilide.—To a solution of 0.72 g. of 2-amino-4-chloro-5-nitroanisole[11] in 10 ml. of pyridine was added 1.00 g. of benzoyl chloride. The reaction mixture was allowed to stand for 12 minutes and then boiled for 2 minutes, cooled to room temperature, and poured into 100 ml. of 10% hydrochloric acid containing 50 g. of ice. An oil precipitated which rapidly solidified. The solid was collected by filtration, washed with water, and recrystallized once from carbon tetrachloride, after which it weighed 0.79 g. (73%). A subsequent recrystallization from an acetic acid–water solvent pair (Darco) gave pinkish-yellow needles, m.p. 138–143° (lit.[12] m.p. 142°). Further recrystallization improved the melting point only very slowly.

4′-Amino-5′-chloro-2′-methoxybenzanilide.—To a boiling solution of 0.58 g. of 5′-chloro-2′-methoxy-4′-nitrobenzanilide in 35 ml. of ethanol, water was added until the cloud point was attained. To the still boiling solution was slowly added 1.01 g. of sodium hydrosulfite, followed by water until the cloud point was again attained. The solution was cooled, caused the crystallization of 0.28 g. of the product, m.p. 151.5–153°, which was collected by filtration. By dilution of the filtrate with water, followed by heating and recooling, an additional 0.02 g. of crystals was obtained, thus bringing the total yield to 0.30 g. (58%). The product was recrystallized once from an ethanol–water solvent pair, giving lustrous creamish needles, m.p. 152–154° (lit.[12] m.p. 152.5°).

2-Chloro-5-methoxy-*p*-phenylenedibenzamide. Method B.—To a solution of 0.11 g. of 4′-amino-5′-chloro-2′-methoxybenzanilide in 1.0 ml. of pyridine, cooled in an ice-bath, was added a solution of 0.07 g. of benzoyl chloride in 1.0 ml. of pyridine. The solution was allowed to stand at room temperature for 10 minutes, then boiled for 2 minutes, and finally cooled and allowed to stand at room temperature for another 5 minutes. The solution was poured into 20 ml. of 10% hydrochloric acid containing 5 g. of ice, causing the precipitation of 0.14 g. (93%) of the product, which was collected by filtration and washed with water. Two recrystallizations from benzene gave small lustrous white prisms, m.p. 225.5–226.5°.

Anal. Calcd. for $C_{21}H_{17}ClN_2O_3$: C, 66.23; H, 4.50; N, 7.36. Found: C, 66.24; H, 4.58; N, 7.31.

URBANA, ILLINOIS

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[11] Aktien-Gesellschaft für Anilin-Fabrikation, German Patent 137,956 (December 1, 1902); *Chem. Zentr.*, **74**, I, 112 (1903); T. E. Young, Thesis Doctor of Philosophy, University of Illinois, 1952.

[12] N. Kizhner and V. Krasnova, *Anilinokrasochnaya Prom.*, **3**, 179 (1933); *Chem. Zentr.*, **105**, I, 2354 (1934); *C. A.*, **27**, 5319 (1933).

[CONTRIBUTION FROM THE THOMPSON CHEMICAL LABORATORY, WILLIAMS COLLEGE, AND THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

The Synthesis and Antibiotic Activity of Analogs of Citrinin and Dihydrocitrinin

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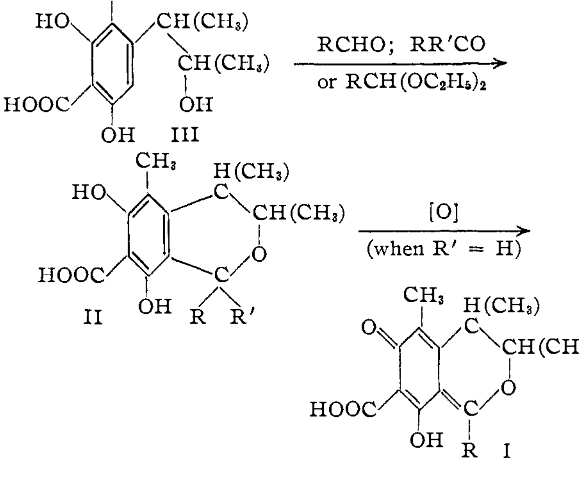
A method has been developed for the preparation of 1-substituted dihydrocitrinin derivatives (II) by the cyclization of the carboxylic acid derivative of Compound A (III) with acetals, aldehydes and ketones, and the conversion of the dihydro derivatives to the corresponding 1-substituted citrinin derivatives (I) by oxidation. Assay of the antibiotic activity of the compounds prepared indicated that the 1-methyl-, 1-ethyl- and 1-phenylcitrinin derivatives possess considerably less activity than the parent compound. The 1-methyl-, 1-ethyl-, 1-phenyl- and 1,1-dimethyldihydrocitrinin derivatives are inactive as is dihydrocitrinin, while the 1-benzyl derivative shows moderate activity.

In a previous article[2] we reported a partial synthesis of citrinin[3] (I, R = H) involving the cyclization of the carboxylic acid derivative of Raistrick's Compound A[4] (III) with methylal to give dihydrocitrinin[5] (II, R = H; R′ = H) and the oxidation of the latter with bromine to citrinin. The purpose of the present work was to extend this synthesis to the preparation of dihydrocitrinin and citrinin derivatives bearing alkyl and aryl substituents at the 1-position and to determine the effect of such structural variation on their antibiotic activity.

It has been found that aldehydes, acetals and ketones will condense with the carboxylic acid derivative of Compound A in a fashion analogous to that of methylal. The reactants used and the products obtained are summarized in Table I.



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[1] Thompson Chemical Laboratory, Williams College, Williamstown, Mass.

[2] H. H. Warren, G. Dougherty and E. S. Wallis, THIS JOURNAL, **71**, 3422 (1949).

[3] 4,6-Dihydro-8-hydroxy-3,4,5-trimethyl-6-oxo-3H-2-benzopyran-7-carboxylic acid.

[4] 4-(2-Hydroxy-1-methylpropyl)-3-methyl-γ-resorcylic acid.

[5] 6,8-Dihydroxy-3,4,5-trimethyl-7-isochromancarboxylic acid.