

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

The Application of the Pschorr Reaction to α -(*para*-Xylylene)-2,5-di-(6'-amino-dimethylcaffeic Acid). The Synthesis of 9,10-Dimethyl-2',3',6',7'-tetramethoxy-1,2,5,6-dibenzanthracene

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Akin and Bogert² were unsuccessful in their attempts to hydrolyze the methylenedioxy groups of 9,10-dimethyl-2',3',6',7'-di-(methylenedioxy)-1,2,5,6-dibenzanthracene to the corresponding tetrahydroxy compound.

We have therefore carried out the synthesis of the analogous tetramethoxy derivative (VI), and endeavored to hydrolyze its methoxy groups but, although evidence was secured of its probable presence, we were unable to isolate the tetrahydroxy derivative (VII) in purity.

We were led to undertake this synthesis because it has been shown in a recent paper³ that, while the methylenedioxy groups of 1,4-dimethyl-6,7-methylenedioxyphenanthrene could not be hydrolyzed by any of the methods employed,² the analogous 6,7-dimethoxy derivative gave a 35% yield of the pure dihydroxy compound when refluxed with a mixture of glacial acetic and hydrobromic acids. Since this 6,7-dihydroxy derivative possessed appreciable solubility in water, it was hoped that the solubilities of the analogous tetrahydroxydibenzanthracene (VII) would also prove favorable for pharmacological testing. 9,10-Dimethyl-1,2,5,6-dibenzanthracene² is cancerigenic. It is therefore a matter of some importance to discover what activity, if any, its tetramethoxy and tetrahydroxy derivatives possess.

In applying the Pschorr reaction to the amino-caffeic acid (II), the amino groups were replaced by hydroxyls (III) when sodium nitrite, sulfuric acid and copper powder were used. Similar results have been reported by Cook,⁴ and by Mayer and English.⁵

Dropping sulfuric acid (23%) into a solution of the amino acid, potassium hydroxide, and sodium nitrite,⁶ or using isoamyl nitrite and 10% alcoholic hydrogen chloride,⁷ failed to accomplish the desired cyclization. Mixtures of unidentifi-

able products resulted in all cases. Only when dioxane was employed as the solvent, with isoamyl nitrite, sodium hypophosphite, and copper powder, was the cyclization achieved satisfactorily. Pyridine could not be substituted for the dioxane. The dihydroxy acid (III) was decarboxylated by dry distillation at 2-3 mm. pressure, and the tetramethoxy acid (V) by digestion in quinaldine with basic copper carbonate.

The hydrolysis of the tetramethoxy derivative (VI), and of its dicarboxylic acid (V), was sought by various methods, but none proved satisfactory. The most promising seemed to be the use of hydrobromic and hydriodic acids. No pure tetrahydroxy derivative was isolated, although some alcoholic extracts of the products gave green color reactions with ferric chloride, and a tetraacetate was obtained, but not in sufficient amount to saponify successfully.

Great difficulty was experienced in securing satisfactory analytical figures for several of these polycyclic compounds, especially the nitro derivatives, but whether this was due to inadequate purification, or to combustion troubles, was not clear. Similar difficulties have been reported by Gulland and Virden,⁸ Kondo and Ochiai,⁹ Cook,^{4,10} Akin and Bogert,² Hewett,¹¹ and others.

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Experimental

α -(*p*-Xylylene)-2,5-di-(6'-nitro-dimethylcaffeic Acid) (I).—By digestion of a mixture of 59 g. of potassium *p*-xylylene-2,5-*bis*-acetate² and 86.4 g. of 6-nitroveratraldehyde³ in 400 g. of acetic anhydride, and pouring the mixture into an excess of very dilute hydrochloric acid, a crystalline mass was secured, which was washed with acetone or methanol, to remove unaltered initial materials and tar.

(1) Ferguson Fellow at Columbia University, 1938-1939.

(2) Akin and Bogert, *THIS JOURNAL*, **59**, 1564 (1937).

(3) Cassaday and Bogert, *ibid.*, **61**, 2461 (1939).

(4) Cook, *J. Chem. Soc.*, 1472 (1932).

(5) Mayer and English, *Ann.*, **417**, 65 (1918).

(6) Stamatoff and Bogert, *Rec. trav. chim.*, **52**, 584 (1933).

(7) Akin, Stamatoff and Bogert, *THIS JOURNAL*, **59**, 1268 (1937).

(8) Gulland and Virden, *J. Chem. Soc.*, 931 (1928).

(9) Kondo and Ochiai, *Ann.*, **470**, 224 (1929).

(10) Cook, *J. Chem. Soc.*, 1597 (1933).

(11) Hewett, *ibid.*, 193 (1938).

Two washings with 300-cc. portions of acetone left the crude product as a pale tan solid, which decomposed between 295 and 310°, and was practically insoluble in methanol, ethanol, ether, dioxane, chloroform, acetic acid, acetone, benzene, or other solvents tried. The yield was 85%. Boiling the product for five hours with methanol and sulfuric acid had little esterifying effect, and most of the initial nitro acid was recovered unchanged. The compound therefore was dissolved repeatedly in alkali, precipitated by dilute hydrochloric acid, then washed thrice with hot acetone and dried. Pale yellow crystals were thus obtained, which darkened and decomposed above 300°.

Anal. Calcd. for $C_{30}H_{26}O_{12}N_2$: C, 59.2; H, 4.6. Found: C, 58.5; H, 4.8.

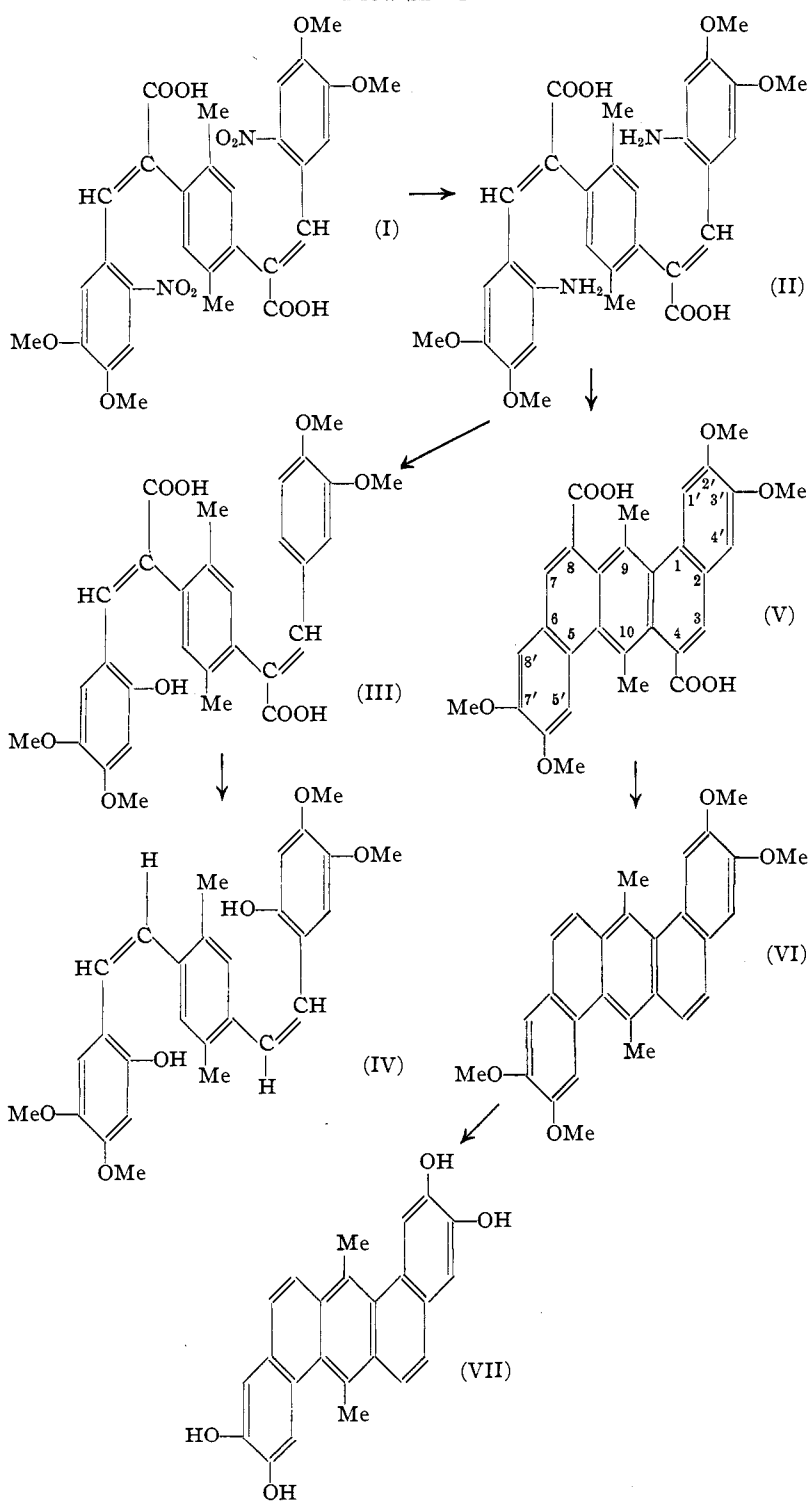
α - (*p* - Xylylene) - 2,5 - di - (6' - amino-dimethylcafeic Acid) (II).—A hot solution of 30 g. of the crude nitro acid (I) in 85 cc. of ammonium hydroxide and 340 cc. of water was added to a boiling solution of 173 g. of ferrous sulfate heptahydrate in 30 cc. of ammonium hydroxide and 715 cc. of water. During the next hour, 300 cc. of ammonium hydroxide was added. The solution was then precipitated by acetic acid, the mixture heated to boiling, cooled and filtered. The yield of crude amino acid so obtained varied from 50 to 60%. As in the case of the antecedent nitro acid (I), no suitable solvent could be found by which to purify the crude acid. Purification through the hydrochloride or acetyl derivative was also unsatisfactory. It was treated, therefore, as the crude nitro acid, *viz.*, by repeated solution in alkali and precipitation with acetic acid, followed by washing with alcohol and drying. The pale yellow crystals thus secured decomposed above 300°.

Anal. Calcd. for $C_{30}H_{32}O_8N_2$: C, 65.7; H, 5.8. Found: C, 65.4, 65.2; H, 6.2, 5.9.

Diazotized and coupled with "H" acid, the amino acid gave a deep purple solution.

α - (*p* - Xylylene) - 2,5 - di - (6' - hydroxy - dimethylcafeic Acid) (III).—To an aqueous solution containing 1.42 g. of sodium nitrite and 2.5 g. of potassium carbonate, there was added 6.8 g. of the amino acid (II), and the resulting solution was run slowly into 100 cc. of ice-cold sul-

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furic acid (5 *N*), some drops of octyl alcohol being used to check foaming. After stirring for a few minutes, copper powder was added and the stirring continued for four hours, keeping the temperature at 0-5°. The mixture was transferred to a glass-stoppered bottle and shaken for fifteen

hours at laboratory temperature. The solid was removed, dissolved in sodium carbonate solution, and reprecipitated with dilute hydrochloric acid; yield, 6.2 g. This material was dried, extracted in a Soxhlet with 150 cc. of methanol for eight hours, the extract concentrated to 25 cc., and the solute precipitated by gradual addition of water; yield, 66%. After two recrystallizations from dilute methanol, a pale brown solid was obtained, which decomposed at 245-255°.

Anal. Calcd. for $C_{30}H_{30}O_{10}$: C, 65.5; H, 5.5. Found: C, 65.4; H, 5.6.

The compound contained no nitrogen, and gave no coupling reaction with "H" acid. The hydroxyl groups could not be methylated with methyl sulfate. Cook⁴ has reported a similar failure to esterify the phenolic hydroxyls of an analogous compound by use of this same methylating agent.

2,5 - Di - (2' - hydroxy - 4',5' - dimethoxystyryl) - *p*-xylene (IV).—The dihydroxy acid (III) was distilled at 3 mm. pressure from a flask immersed in a metal bath the temperature of which was above 360°. The first receiver was surrounded by ice water, and this was followed by two traps in acetone—"Dry-ice" baths. A pale yellow sublimate collected in these traps, which were removed from the cooling baths and allowed to warm up to laboratory temperature before admitting air to restore the atmospheric pressure. The sublimate could then be shaken out of the traps without the use of any solvent. It decomposed between 55 and 60°, and became gummy in the presence of moisture. Three runs were made, the result being the same in all three.

Anal. Calcd. for $C_{28}H_{30}O_8$: C, 72.7; H, 6.5. Found: C, 73.1; H, 6.8.

9,10 - Dimethyl - 2',3',6',7' - tetramethoxy - 1,2,5,6-dibenzanthracene-4,8-dicarboxylic Acid (V).—To a solution of 20 g. of the amino acid (II) in 335 cc. of dioxane, there was added 11.1 cc. of sulfuric acid followed by 22 cc. of carefully purified isoamyl nitrite. After two hours of stirring at room temperature, the diazo solution was stirred into a solution of 138 g. of sodium hypophosphite in 138 cc. of water and containing some copper powder, keeping the temperature at 45-55°. After all the diazo solution had been run in, the temperature of the mixture was raised to 80°. The yield of crude product was 90%. This was washed with boiling acetic acid (8 cc. per g.). There remained a 59% yield of pale tan dicarboxylic acid (V), which decomposed at about 296° ($\pm 4^\circ$), and was pure enough for conversion into the tetramethoxydibenzanthracene (VI). Crystallized thrice from acetic acid, it formed white crystals, which decomposed at 315-317° (corr.). A second lot was crystallized six times from acetic acid and dried at 110° for eight hours. In the following analyses, the first figures were obtained with the first lot, the second ones with the second lot.

Anal. Calcd. for $C_{30}H_{26}O_8$: C, 70.0; H, 5.1. Found: C, 69.5, 69.6; H, 5.9, 6.1.

When the compound was boiled with methanol and sulfuric acid for five hours, it was recovered unchanged.

9,10 - Dimethyl - 2',3',6',7' - tetramethoxy - 1,2,5,6-dibenzanthracene (VI).—A mixture of 11 g. of the crude dicarboxylic acid (V), 2.2 g. of basic copper carbonate, and 66 cc. of freshly distilled quinaldine, was refluxed for six

hours at 250°, cooled, and extracted with 700 cc. of ether. The ether extract was washed twice with dilute hydrochloric acid, once with dilute potassium hydroxide, and finally with water. Ethanol was added and the ether distilled off. The solid which separated, when crystallized from alcohol, formed pale yellow crystals, insoluble in alkali; yield 25-30%. Its solutions exhibited a pale blue fluorescence. After two more crystallizations from alcohol, the crystals melted at 137-138° (corr.).

Anal. Calcd. for $C_{28}H_{26}O_4$: C, 78.9; H, 6.1; mol. wt., 426. Found: C, 78.1, 78.5; H, 6.9, 7.3; mol. wt. (Rast, average), 441.

Dry distillation of the dicarboxy acid (V) with copper powder alone failed to yield any appreciable quantity of the decarboxylated compound (VI).

Attempts to Obtain the 9,10-Dimethyl-2',3',6',7'-tetrahydroxy-1,2,5,6-dibenzanthracene (VII).—Many experiments were carried out with both the tetramethoxydibenzanthracene (VI) and its dicarboxylic acid (V), to hydrolyze their methoxyl groups, but they were uniformly unsuccessful and no analytically pure tetrahydroxy derivative (VII) could be isolated from the black tars which were formed in most cases. Hydrochloric, hydrobromic, and hydriodic acids were the attacking reagents, as well as potassium hydroxide, and the evidence for the presence of the tetrahydroxy derivative seemed strongest when hydriodic acid was used upon either (V) or (VI). Alcohol extracts of some of these tarry products, especially those obtained with hydriodic acid, gave green color reactions, like catechol, with ferric chloride. Two typical experiments follow.

A mixture of 1 g. of (V) or (VI) with 15 cc. of hydrobromic acid (48%) and 30 cc. of glacial acetic acid was refluxed for one to two hours. Poured into water, the black liquid gave a gray flocculent precipitate, which was removed, washed and dried, giving 0.8 g. of a black powder.

A mixture of 2 g. of (V) or (VI) with 10 cc. of hydriodic acid (sp. gr., 1.7) and 20 cc. of acetic acid was refluxed for three hours and the solution poured into water. The precipitate which separated was exceedingly difficult to filter and was therefore washed with water by decantation and siphoning, until the washings were no longer colored and the solid was pale gray. By centrifugation, a gray jelly was obtained, which dried to a dark gray powder, which always gave a characteristic green ferric chloride test in alcoholic solution.

Tetraacetate.—The black powder (0.8 g.), obtained above by the action of hydrobromic acid upon (V) or (VI), was refluxed for two hours with acetic anhydride (5 cc.) and fused sodium acetate, and the crude product crystallized thrice from a mixture of ethanol and ethyl acetate. A pale tan powder resulted, which decomposed at 300-350° without melting, and could not be distilled under reduced pressure.

A similar compound was obtained by the action of acetic anhydride upon the dark gray product of the action of hydriodic acid upon (V) or (VI). Attempts to saponify this to the tetrahydroxy compound proved fruitless with the minute amount of material at our command.

In the following analyses, the first figures are for the hydrobromic acid product, the second for the hydriodic acid product.

Anal. Calcd. for $C_{32}H_{26}O_8$: C, 71.4; H, 4.8. Found: C, 71.2, 71.1; H, 5.7, 5.8.

Summary

1. 9,10-Dimethyl-2',3',6',7'-tetramethoxy-1,2,5,6-dibenzanthracene, and its 4,8-dicarboxylic acid, have been prepared by the Pschorr reaction from *p*-xylylene-*bis*-(acetic acid) and 6-nitroveratraldehyde.

2. In the diazotization of the intermediate aminodimethylcaffeic acid, cyclization results only

when dioxane is used as the solvent. In aqueous solutions, the amino groups are replaced by hydroxyls.

3. Attempts to prepare the corresponding tetrahydroxydibenzanthracenes by hydrolysis of the methoxyl groups proved unsatisfactory.

4. The dibenzanthracene and its dicarboxylic acid were synthesized for testing as possible carcinogens.

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The Nitration of Diphenyliodonium Nitrate

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The nitration of diphenyliodonium nitrate has been the subject of considerable research.³ It is an interesting problem, from the standpoint of the influence of groups present in the benzene ring, on the course of further substitutions. According to Vorländer, Robinson, Ingold and others,⁴ the most strongly meta-directing groups are the positive poles directly attached to the benzene ring. For example, phenyltrimethylammonium nitrate is nitrated exclusively in the meta position.⁵ In this case the orienting group is $-\text{N}(\text{CH}_3)_3^+$. Again, a group may be meta-directing because the group as a whole carries a permanent dipole as in NO_2 . On the other hand, ortho-para orientation is associated with those radicals which lose electrons to the ring as in the case of the methyl group, or which carry unshared pairs of electrons so that conjugation with the double bonds of the ring is possible as in NH_2 .⁶

The nitration of a compound such as diphenyliodonium nitrate might be expected to be similar to the nitration of phenyltrimethylammonium nitrate, since the orienting group is $-\text{IC}_6\text{H}_5^+$.

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(3) (a) Vorländer and Büchner, *Ber.*, **58**, 1893 (1925); (b) Chalenger and Rothstein, *J. Chem. Soc.*, 1258 (1934).

(4) (a) Vorländer, *Ber.*, **52**, 262 (1919); (b) Allan, Oxford, Robinson and Smith, *J. Chem. Soc.*, 401 (1926); (c) Goss, Ingold and Wilson, *ibid.*, 2440 (1926); (d) Flürscheim and Holmes, *ibid.*, 1562 (1926); (e) Ingold, *Ann. Repts. Chem. Soc.*, **23**, 130 (1926).

(5) Vorländer and Siebert, *Ber.*, **52**, 283 (1919).

(6) For discussions on the directive influence of substituent groups, see also Gilman, "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1938, pp. 140 and 1881; Lucas, "Organic Chemistry," American Book Co., New York, N. Y., 1935, p. 360; Waters and Lowry, "Physical Aspects of Organic Chemistry," D. Van Nostrand Co., New York, N. Y., 1936, p. 439; Watson, "Modern Theories of Organic Chemistry," Oxford University Press, London, 1937, p. 57.

Vorländer^{3a} in his work showed that meta-nitration did take place. By repeated crystallization of the reaction product he isolated pure di-*m*-nitrophenyliodonium nitrate. This gave *m*-iodo-nitrobenzene and *m*-nitrophenol (free from *o*-derivative) with sodium hydroxide. Any *p*- or *o*-compound may thus have been separated. On reading Vorländer's experimental work, the reader might draw the conclusion that nitration occurs almost exclusively in the meta position. Regarding the nitration, Vorländer has this to say: "*p*-Nitro-phenol ist vielleicht in spuren, *o*-Nitro-phenol überhaupt nicht vorhanden, *o*-Nitro-phenol war nicht einmal durch seinen Geruch nachzuweisen." The experimental work which Vorländer reports gives no indication of ortho-para nitration.

However, the iodine atom in $-\text{I}(\text{C}_6\text{H}_5)_2^+$ has unshared electrons and is at the same time the positive end of a dipole. On the basis of unshared electrons one might expect the formation of some ortho and para derivatives along with the meta compound. Meta-directing groups usually do not contain unshared electrons in the shell of the atom which is directly joined to ring carbon.⁷

There is also another difference between phenyltrimethylammonium nitrate and diphenyliodonium nitrate to be considered. Since the positive electricity resides at the nucleus of the charged atom, the amount of damping action arising through the passage of the effect, through the

(7) Vorländer, *Ber.*, **58B**, 1893 (1925), has shown that $-\text{IO}_2$ in which the iodine atom has unshared electrons is meta-directing. Recently, Masson, Race and Pounder, *J. Chem. Soc.*, 1669 (1935), have nitrated iodoxybenzene and have obtained about 99.5% meta-nitration.