

tion were introduced into the apparatus and runs were made until equilibrium had been established between liquid and vapor phases. This required three to four hours for each run. Temperatures were measured with a thermometer (0–110°) with 0.1° divisions, which was checked frequently for accuracy, the precision = 0.03°. Pressure correction to one atmosphere and stem corrections were made for all readings. The equilibrium residue and distillate were analyzed through refractive index. Data are given in Table II, and Fig. 2 shows the boiling point–composition diagram for the system.

TABLE II

BOILING POINT–COMPOSITION DATA FOR THE DIOXANE–ETHANOL SYSTEM AT ONE ATMOSPHERE

B. p., °C.	% dioxane	
	Liquid	Vapor
78.32		Ethanol
78.22	1.5	2.2
78.19	5.0	5.3
78.13 (min.)	9.3	9.3
78.17	13.0	11.7
78.23	16.8	14.8
78.35	22.0	18.3
78.36	32.0	24.7
79.10	42.0	30.5
79.87	54.0	37.3
80.15	56.5	38.7
80.18	58.5	39.7
80.93	64.7	43.3

81.32	66.7	45.1
81.40	68.5	45.5
82.33	73.0	48.4
84.42	79.9	56.5
85.43	84.8	60.3
87.17	86.4	64.9
89.08	90.2	70.5
92.02	93.3	78.0
93.00	94.0	80.0
94.89	96.3	85.0
97.99	98.7	92.5
99.05	98.8	94.8
101.07		Dioxane

A minimum boiling point of 78.13° was observed for the composition 9.3% dioxane.

Summary

1. Density, refractive index and viscosity data for the dioxane–ethanol system have been presented. The viscosity curve apparently passes through a minimum in the vicinity of 50% dioxane.

2. Boiling points and the boiling point–composition diagram for the dioxane–ethanol system have been determined. A minimum boiling temperature of 78.13° was observed at 9.3% dioxane.

NEWARK, DELAWARE

RECEIVED JULY 8, 1939

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

The Synthesis of 1,4-Dimethyl-6,7-dihydroxyphenanthrene from *para*-Xylylacetic Acid and 6-Nitroveratraldehyde by the Pschorr Reaction

BY JACK TARKINGTON CASSADAY¹ AND MARSTON TAYLOR BOGERT

Eddy² has reported that phenanthrene derivatives carrying a hydroxyl group on carbon no. 3 (no. 6 in our formula) are likely to possess analgesic properties in higher degree than when this group is in other positions on the phenanthrene nucleus.

Small, Eddy, Mosettig and Himmelsbach³ state that: "No generalizations can be made as to the influence on pharmacological action of the entrance of another substituent in a given monosubstituted phenanthrene. The changes in pharmacological action are very likely dependent to some extent upon changes in chemical or physical properties, among others, differences in acidity or basicity, and in solubility. There was a de-

cid increase in effectiveness from 3-hydroxyphenanthrene to 3,4-dihydroxyphenanthrene, but at the same time also, from 3-hydroxyphenanthrene to 3-hydroxy-4-aminophenanthrene."

So far as our examination of the literature has gone, the hydroxyphenanthrenes reported to date are all insoluble in water, and but few of them are appreciably soluble in cold olive oil.

We have therefore synthesized the 1,4-dimethyl-6,7-dihydroxyphenanthrene (V), in order that its physical, chemical, and pharmacological properties can be studied. It is a white crystalline solid, m. p. 164–164.5° (corr.), appreciably soluble in water, and dissolving in cold olive oil.

In a previous communication⁴ from these Laboratories, we reported some unsuccessful attempts to obtain this compound by the hydrolysis of the 1,4-dimethyl-6,7-methylenedioxyphenan-

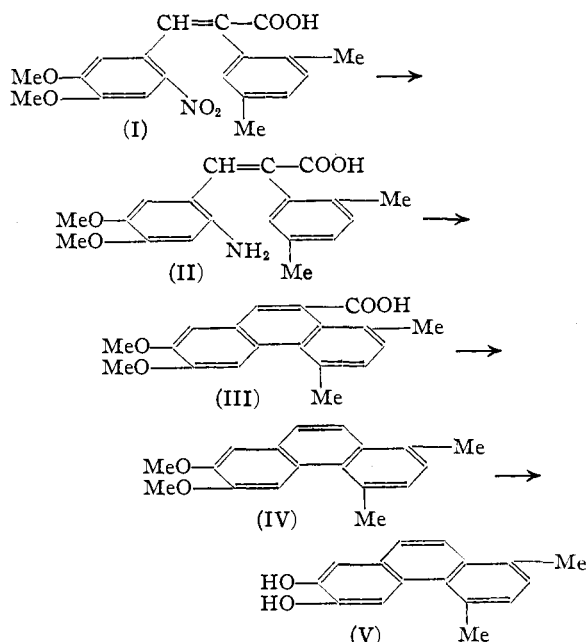
(1) Ferguson Fellow, Columbia University, 1938–1939.

(2) Eddy, *J. Pharmacol.*, **48**, 183 (1933); **51**, 75 (1934).(3) Small, Eddy, Mosettig and Himmelsbach, "Studies on Drug Addiction," *U. S. Pub. Health Repts., Suppl. No. 138*, 143 pp., 1938, p. 71.(4) Akin and Bogert, *THIS JOURNAL*, **59**, 1564 (1937).

threne. Whereas the methylenedioxy group resisted our efforts at hydrolysis, the corresponding dimethoxy compound has been found to be more tractable, and yielded the desired dihydroxy derivative when digested with a mixture of glacial acetic and hydrobromic (48%) acids.

The synthesis followed the classical Pschorr lines, with a few modifications α -(*p*-xylyl)-6-nitrodimethylcaffeic acid (I), from *p*-xylylacetic acid and 6-nitroveratraldehyde, was reduced to the corresponding amine (II) by ferrous sulfate and ammonium hydroxide. Cyclization was accomplished, in dioxane solution containing some sulfuric acid, by the action of isoamyl nitrite, with the subsequent addition of copper powder and sodium hypophosphite. By refluxing the acid (III) with quinaldine and basic copper carbonate, it was decarboxylated, and the dimethoxy compound (IV) then hydrolyzed to the dihydroxy derivative (V). It was found possible also to accomplish a simultaneous decarboxylation and hydrolysis of the dimethoxy acid (III) to the dihydroxy hydrocarbon (V), but the yield of the latter was not very good.

Acknowledgments.—We are happy to have this opportunity of expressing our thanks to the Ella Sachs Plotz Foundation and to the National Academy of Sciences for financial assistance in the purchase of the necessary chemicals and apparatus to carry out this investigation, as well as to Mr. Saul Gottlieb for the analytical work.



Experimental

6-Nitroveratraldehyde was prepared as described by Marr and Bogert,⁵ with certain modifications which increased the yield and reduced the time required.

To 300 cc. of concentrated nitric acid (sp. gr., 1.42), there was added in small portions 30 g. of finely pulverized veratraldehyde in thirty minutes, with vigorous mechanical stirring, maintaining the temperature of the mixture at 15–20°. After stirring for an additional half hour at 25–30°, the mixture was poured into about 9 liters of ice water, the precipitate collected, washed with an additional 9 liters of ice water, pressed dry on the filter, and immediately crystallized from ethyl alcohol without further drying; yield 87%, m. p. 132–133° (corr.) (lit.,⁴ 133.5–134.5°, corr.). The nitrations and crystallizations can be conducted in artificial light without any appreciable reduction in yield.

α -(*p*-Xylyl)-6-nitrodimethylcaffeic Acid (I).—A solution of *p*-xylylacetic acid (156 g.), prepared according to the procedure of Akin, Stamatoff and Bogert,⁶ and 6-nitroveratraldehyde (166.5 g.), in freshly distilled acetic anhydride (1110 cc.), was heated to 105–110° and stirred for eight hours under a reflux condenser carrying a calcium chloride guard tube. Excess of acetic anhydride was hydrolyzed by the addition of hot water, keeping the temperature of the mixture below 120°. It was then poured into a mixture (7 liters) of water, crushed ice, and a little hydrochloric acid. The tarry material which separated became crystalline on standing. It was removed, boiled with water (3–4 liters), to eliminate unchanged initial materials, and crystallized from dilute acetic acid. It separated as a pale tan solid, m. p. 221–224° (corr.), sufficiently pure for use in the next step; yield 61%. After three more crystallizations from the same solvent, it appeared as pale greenish crystals, m. p. 226–227° (corr.); yield 50–55%.

Anal. Calcd. for $C_{19}H_{19}O_6N$: C, 63.9; H, 5.3; N, 3.9. Found: C, 63.8; H, 5.7; N, 4.2.

α -(*p*-Xylyl)-6-aminodimethylcaffeic Acid (II).—A solution of 80 g. of the nitro acid (I) in dilute ammonium hydroxide solution was added, in the course of three to four minutes, to a boiling solution of 440 g. of ferrous sulfate heptahydrate and 100 cc. of ammonium hydroxide solution in 1275 cc. of water. During this addition and for the next half hour, 780 cc. of concentrated ammonium hydroxide solution was slowly run into the boiling mixture, followed by 200 cc. more of the ammonium hydroxide solution for the succeeding forty-five minutes. To prevent foaming, five drops of octyl alcohol was added. When the mixture had cooled, the upper portion was siphoned off through a filter, and the black residues extracted thrice with dilute ammonium hydroxide solution, filtered through Norite, and the combined filtrates poured into a slight excess of dilute acetic acid containing ice. The precipitated amino acid was collected, redissolved in ammonium hydroxide solution and reprecipitated, the mixture heated to boiling, cooled, and the amino acid filtered out; yield 76%, m. p. 185–186° (corr.). Recrystallized twice from benzene, it formed pale yellow crystals, m. p. 191–192° (corr.); yield, 65% or better.

(5) Marr and Bogert, *THIS JOURNAL*, **57**, 1329 (1935).

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

Anal. Calcd. for $C_{19}H_{21}O_4N$: C, 69.7; H, 6.4. Found: C, 69.6; H, 6.5.

1,4-Dimethyl-6,7-dimethoxyphenanthrene-10-carboxylic Acid (III).—In our experience with the Pschorr reaction, we have found that, in the cyclization of the *o*-aminocinnamic acids, hydroxy acids are formed often instead of the phenanthrene sought. By carrying out the diazotization in dioxane as the solvent, and using sodium hypophosphite as recommended by Ruggli and Staub,⁷ in the second step of the reaction, it has been possible to effect the cyclization without this complication. In this particular series (II), a large excess of dioxane was found requisite to prevent the separation of solid oxonium compounds formed from the sulfuric acid and the dioxane. In other series, this trouble has not been encountered.

To a solution of 44 g. of the amino acid in 850 cc. of dioxane, there was added 10 cc. of concentrated sulfuric acid, followed by 25.2 cc. of isoamyl nitrite when the solution had cooled to room temperature. The nitrite used was washed with dilute sodium bicarbonate solution, followed by a saturated sodium chloride solution, and dried over sodium sulfate. The diazo solution solidified, after about thirty minutes of stirring at 25–30°. To a solution of 139 g. of sodium hypophosphite in 139 cc. of water, there was added some freshly prepared Gattermann copper powder. The mixture was heated to incipient ebullition, cooled to 50°, and the mush of diazo compound added during thirty minutes, while the temperature was kept at 40–50°. After all of the diazo compound had been added, the mixture was heated to 80° for a short time and then poured into six liters of water containing sufficient ammonium hydroxide to assure solution of the acid. The filtered solution was run into 15 liters of very dilute hydrochloric acid containing ice, the precipitated acid removed, and dried, first in the air and then at 105°; yield of crude acid, sufficiently pure for the next step, 83%. By recrystallization from methanol, or from dilute acetic acid, and decolorization with Norite, the acid was obtained in colorless crystals, m. p. 215.5–216.5° (corr.).

Anal. Calcd. for $C_{19}H_{19}O_4$: C, 73.5; H, 5.8. Found: C, 73.2; H, 6.1.

1,4-Dimethyl-6,7-dimethoxyphenanthrene (IV).—A mixture of 1 g. of the crude acid (III), 3 cc. of freshly distilled quinaldine, and 0.2 g. of basic copper carbonate, was refluxed for forty-five minutes, then cooled, extracted with ether, the ether solution washed first with dilute hydrochloric acid, to remove quinaldine, and then with dilute potassium hydroxide solution, to free it from unchanged acid. Glacial acetic acid was added, the ether distilled off, and the residual solution diluted with water. The gummy precipitate which separated, when crystallized from alcohol, yielded 45% of the pure dimethoxy hydrocarbon (IV). Recrystallized from alcohol, in the presence of Norite, it formed glistening white platelets, m. p. 175–176° (corr.).

(7) Ruggli and Staub, *Helv. Chim. Acta*, **20**, 37 (1937).

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.2; H, 6.8. Found: C, 80.9; H, 7.0.

1,4-Dimethyl-6,7-dihydroxyphenanthrene (V).—A mixture of 1.6 g. of the dimethoxy derivative (IV), 49 cc. of glacial acetic acid, and 49 cc. of hydrobromic acid (48%), was refluxed for two hours in an all-glass apparatus, and the cold green solution poured into 300–350 cc. of water. After the mixture had stood for fifteen to twenty minutes, the precipitate was collected and crystallized thrice from water, filtering the hot solutions through cotton and filter paper at first, to remove tarry contaminants. It also could be recrystallized from hot alcohol solution by the gradual addition of water. The pure compound formed white crystals, m. p. 164–164.5° (corr.); yield 35%. With ferric chloride solution, it gave an intense green, like catechol, which was changed to a pink or reddish color by the addition of sodium hydroxide or ammonium hydroxide solutions.

Anal. Calcd. for $C_{18}H_{14}O_2$: C, 80.7; H, 5.9. Found: C, 80.8; H, 6.0.

The same compound (mixed m. p., etc.) was secured in one operation from the dimethoxy acid (III), when 0.93 g. of it was refluxed for two hours in a mixture of 31 cc. of glacial acetic acid and 31 cc. of hydrobromic acid (48%), and the crude product purified as above, but the yield was only 10–15% in the different runs.

In 100 cc. of water, the solubility of the pure compound at various temperatures ($\pm 2^\circ$) was as follows: 100°, 0.038 g.; 37°, 0.007 g.; 0°, 0.003 g. The pH of the saturated aqueous solution was 6.4 (± 0.2). In alcohol, glycol, or acetone, it was easily soluble, and dissolved also in cold olive oil.

Diacyl Derivative.—From the dihydroxy derivative (V), acetic anhydride and fused sodium acetate, after repeated crystallization from dilute acetic acid, formed white crystals, m. p. 133–133.5° (corr.).

Anal. Calcd. for $C_{20}H_{18}O_4$: C, 74.5; H, 5.6. Found: C, 74.8; H, 5.9.

Summary

1. 1,4-Dimethyl-6,7-dihydroxyphenanthrene has been synthesized by the Pschorr reaction and found to be slightly soluble in water, and to dissolve also in cold olive oil.

2. In the application of the Pschorr reaction, dioxane has been found preferable to alcohol as a solvent for the diazotization.

3. 1,4-Dimethyl-6,7-dimethoxyphenanthrene-10-carboxylic acid can be hydrolyzed and decarboxylated simultaneously by refluxing with a mixture of glacial acetic and hydrobromic (48%) acids, but the yields are not very good.