This was dissolved in 5 ml. of dry ethyl ether and then treated with 10 ml. of petroleum ether. After filtration to remove flocculent material, the filtrate was concentrated by gentle warming to a volume of *ca.* 2 ml. The concentrate was cooled in an ice-bath and the sides of the flask were scratched. Tiny white crystals separated, which melted at 89–90°.

Anal. Calcd. for $C_{18}H_{23}NO_3$: C, 71.75; H, 7.69. Found: C, 71.82; H, 7.60.

Dihydroerythramine Hydrobromide Monohydrate.—A quantity of 99 mg. of pure dihydroerythramine hydriodide yielded 64 mg. of gummy base by the usual procedure. It was dissolved in 1 ml. of absolute ethanol, treated with 0.3 ml. of 40% hydrobromic acid, and a little dry ether was added. After filtration of flocculent precipitate, the solution was allowed to stand overnight at 10°. The hydrobromide (34 mg. yield) melted constantly at 240° after recrystallization from ethanol. For analysis, the salt was dried at 25° *in vacuo*.

Anal. Calcd. for $C_{18}H_{23}NO_3 \cdot HBr \cdot H_2O$: C, 54.00; H, 6.54. Found: C, 54.26; H, 6.04.

Drying of 5 mg. of this monohydrate at 140° and 2 mm. for two hours caused a decrease in weight of only 0.04 mg. (0.8%). The anhydrous hydrobromide could not be obtained. Longer drying periods initiated thermal decomposition.

Dihydroerythramine Methiodide Hemihydrate.—A quantity of 52 mg. of dihydroerythramine base was dissolved in 1 ml. of methanol and 1 ml. of redistilled methyl iodide. Ethyl ether was added to the point of turbidity. Crystals of the methiodide separated after refrigeration overnight; m. p. 160–161°. The substance was dried at 78° and 2 mm. for two hours before analysis.

Anal. Calcd. for $C_{18}H_{23}NO_3 \cdot CH_3I \cdot {}^1/_2H_2O$: C, 50.45; H, 6.01. Found: C, 50.61; H, 6.13.

This substance could not be dehydrated at 140° *in vacuo* without decomposition.

Acknowledgment.—We wish to express our appreciation to Mr. B. A. Krukoff for his advice on botanical matters and to Mr. Douglass Hayman and Mr. Wilhelm Reiss for their coöperation in performing the microanalyses.

Summary

Erythramine, which has the empirical composition $C_{18}H_{21}NO_3$, contains one methoxy group and one methylenedioxy group. The nitrogen atom is tertiary and in all probability is common to two nuclei of the molecule. The unsaturation consists of one benzenoid nucleus and one ethylenic double bond. The molecule appears to contain four six-membered nuclei exclusive of the methylenedioxy bridge.

Erythramine methiodide was about one-fifth as active and dihydroerythramine was about one-thirtieth as active as the natural erythramine for curare-like action in frogs.

RAHWAY, N. J. RECEIVED JULY 28, 1939

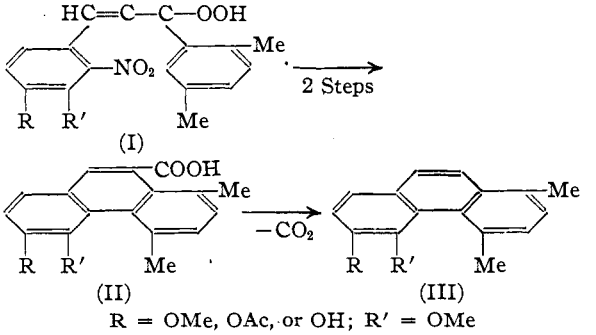
[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

The Synthesis of Some New 1,4-Dimethylphenanthrenes Structurally Related to Morphol

BY JACK TARKINGTON CASSADAY[1] AND MARSTON TAYLOR BOGERT

In a recent communication,[2] we described the preparation of 1,4-dimethyl-6,7-dihydroxyphenanthrene from *p*-xylylacetic acid and 6-nitroveratraldehyde by the Pschorr reaction. The work recorded in the present paper consists of the extension of that investigation by substituting 2-nitroveratraldehyde and 2-nitroacetovanillin for the 6-nitroveratraldehyde, resulting in the production of the 5,6-dimethoxy and 5-methoxy-6-hydroxy derivatives of 1,4-dimethylphenanthrene, and their 10-carboxylic acids.

In the case of the 1,4-dimethyl-5,6-dimethoxyphenanthrene, or 1,4-dimethyl-5-methoxy-6-hydroxyphenanthrene, the methoxyl groups could not be hydrolyzed by the process which proved



R = OMe, OAc, or OH; R′ = OMe

effective with the 6,7-dimethoxy isomer,[2] or by any of the other methods used. This is in agreement with the experience of other investigators. Pschorr and Sumuleanu[3] found it impossible to demethylate 3,4-dimethoxyphenanthrene. Mo-

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

(2) Cassaday and Bogert, THIS JOURNAL, **61**, 2461 (1939).

(3) Pschorr and Sumuleanu, *Ber.*, **33**, 1810 (1900).

settig and Burger[4] were unsuccessful in their attempts to demethylate either a 3-methoxyacetylphenanthrene or the corresponding carboxylic acid.

The 5-methoxy-6-hydroxy derivative was prepared primarily because it carried its hydroxyl group in the position which Eddy's investigations[5] have shown to be most favorable for the development of analgesic properties. Unfortunately, however, it was not appreciably soluble in water.

Both of the above compounds (III) are closely related structurally to morphol (3,4-dihydroxyphenanthrene), and to methylmorphol (3-methoxy-4-hydroxyphenanthrene), a degradation product of the alkaloid codeine.

It may be recalled that morphol has a stronger analgesic action than 3-hydroxyphenanthrene.

Acknowledgments.—We are indebted to the Ella Sachs Plotz Foundation and to the National Academy of Sciences for financial assistance in the purchase of the chemicals and apparatus required for this investigation. Our thanks are due also to Mr. Saul Gottlieb, of these Laboratories, who carried out the necessary microanalyses.

Experimental

2-Nitroveratraldehyde was prepared by the method of Slotta and Lauersen,[6] but the introduction of nitrogen during the methylation of the acetovanillin was found unnecessary, and a simple 3-necked flask was employed instead of their more elaborate apparatus. The process of Pschorr and Sumuleanu[7] proved much less satisfactory, because of the formation of a mixture of isomers in the nitration of the acetovanillin.[8]

α-(*p*-Xylyl)-2-nitro-dimethylcaffeic Acid (I).—A mixture of 32.4 g. of potassium *p*-xylylacetate, 33.5 g. of 2-nitroveratraldehyde, and 285 g. of freshly distilled acetic anhydride, in a 3-necked flask equipped with a mechanical stirrer and mercury seal, a reflux condenser carrying a calcium chloride guard tube, and a thermometer, was stirred for eight hours at 105–110°. Excess of acetic anhydride was hydrolyzed by the addition of hot water, maintaining the temperature of the mixture below 120°. It was then poured into very dilute hydrochloric acid containing cracked ice. After standing for a few minutes, the supernatant solution was decanted from the tarry precipitate and fresh water added, under which the tar became crystalline more quickly. One crystallization from dilute acetic acid gave a 67% yield of the product sought, sufficiently pure for reduction to the amino acid. Five additional crystallizations from the same solvent resulted in white crystals, m. p. 205.5–206.5° (corr.).

Anal. Calcd. for $C_{19}H_{19}O_8N$: C, 63.9; H, 5.3; N, 3.9. Found: C, 64.3; H, 5.6; N, 4.0.

α-(*p*-Xylyl)-2-nitro-3-methoxy-4-acetoxycinnamic Acid (I).—Application of the above process to a mixture of 35 g. of potassium *p*-xylylacetate, 33 g. of 2-nitroacetovanillin prepared as described by Slotta and Lauersen,[6] and 250 g. of acetic anhydride, gave a 50% yield of pale tan acid, m. p. 202.5–203.5° (corr.), pure enough for reduction to the amino acid. After two recrystallizations from glacial acetic acid, in one of which Norite was used, the acid was obtained in crystals of a pale greenish tint, m. p. 211–214° (corr.).

Anal. Calcd. for $C_{20}H_{19}O_7N$: C, 62.3; H, 4.9; N, 3.6. Found: C, 62.3; H, 5.1; N, 3.7.

α-(*p*-Xylyl)-2-amino-dimethylcaffeic acid was prepared by reduction of the nitro acid with ferrous sulfate and ammonium hydroxide essentially as described for the 6-amino isomer in our previous paper[2]; yield, 61–67% of a light gray crude acid, m. p. 110–113° (corr.). No appreciable amount of acetic acid could be left in the amino acid, or it turned black on drying. Attempts to purify further this gray crude failed, and an analytically pure amino acid was not secured.

Hydrochloride.—This was prepared easily by dissolving the amino acid in dilute alcohol containing a little hydrochloric acid, recrystallizing the product from the same solvent, and drying the crystals in an evacuated desiccator. When left in an oven at 110°, the compound decomposed partially.

Anal. Calcd. for $C_{19}H_{21}O_4N \cdot HCl$: C, 62.7; H, 6.1. Found: C, 62.4; H, 6.2.

α-(*p*-Xylyl)-2-amino-3-methoxy-*p*-coumaric acid was prepared similarly from the nitromethoxyacetoxy acid. There was obtained an 80% yield of the crude acid, as a pale yellow solid, m. p. 198.5–200° (corr.), pure enough for cyclization. Six recrystallizations from 95% alcohol gave lemon colored needles, m. p. 203–204° (corr.).

Anal. Calcd. for $C_{18}H_{19}O_4N$: C, 69.0; H, 6.1. Found: C, 68.8; H, 6.2.

It will be observed that in this reduction the acetyl group of the initial nitro acid was hydrolyzed off. Pschorr[9] had a similar experience in the reduction of the α-phenyl-2-nitro-3-methoxy-4-acetoxycinnamic acid.

1,4-Dimethyl-5,6-dimethoxyphenanthrene-10-carboxylic Acid (II).—This was secured from the corresponding aminodimethylcaffeic acid by following the directions for the preparation of the 6,7-dimethoxy isomer,[2] except that potassium hydroxide was found preferable to ammonium hydroxide for solution of the 10-carboxylic acid prior to its precipitation by dilute hydrochloric acid. The yield of crude acid, pure enough for decarboxylation, was 50%. By redissolving in dilute potassium hydroxide, reprecipitating in dilute hydrochloric acid containing ice, recrystallizing twice from dilute alcohol, decolorizing with Norite, and three recrystallizations from 95% ethanol, it was obtained in white crystals, m. p. 180.5–181.5° (corr.).

Anal. Calcd. for $C_{19}H_{18}O_4$: C, 73.5; H, 5.8. Found: C, 73.7; H, 6.0.

(4) Mosettig and Burger, THIS JOURNAL, **55**, 2981 (1933).
(5) Eddy, *J. Pharmacol.*, **48**, 183 (1933); **51**, 75 (1934).
(6) Slotta and Lauersen, *J. prakt. Chem.*, [2] **139**, 220 (1934).
(7) Pschorr and Sumuleanu, *Ber.*, **32**, 3405 (1899).
(8) Raiford and Stoesser, THIS JOURNAL, **50**, 2556 (1928).
(9) Pschorr, *Ber.*, **33**, 1822 (1900).

Attempts to hydrolyze the methoxyl groups of this compound by the action of hydrobromic or hydriodic acid proved futile. Only black tars resulted, which gave no color reactions with ferric chloride. Nor could any pure acetyl derivatives be secured from them.

1,4 - Dimethyl - 5 - methoxy - 6 - hydroxyphenanthrene-10-carboxylic Acid (II).—Following the same procedure, 17.5 g. of the crude α-(*p*-xylyl)-2-amino-3-methoxy-*p*-coumaric acid gave a 47% yield of the crude phenanthrenecarboxylic acid, sufficiently pure for decarboxylation. No satisfactory solvent was found for further purification of this crude acid. Recourse was had therefore to acetylation.

Acetate.—A mixture of 1.765 g. of the crude acid, 0.882 g. of fused sodium acetate, and 15 cc. of acetic anhydride, was refluxed for two hours, the excess of acetic anhydride then hydrolyzed by the addition of hot water, and the mixture poured into 100 cc. of water and ice. The gummy solid which separated was removed, dissolved in acetic acid, and the solution placed in a refrigerator. After 2–3 hours, crystals separated, which were recrystallized thrice, once using Norite. White blades were thus obtained, m. p. 170.5–171.5° (corr.).

Anal. Calcd. for $C_{20}H_{18}O_5$: C, 71.0; H, 5.3. Found: C, 71.2; H, 5.4.

From 120 g. of 2-nitroacetovanillin and 80 g. of potassium phenylacetate, Pschorr[9] obtained only 3 g. of 5-methoxy-6-hydroxyphenanthrene-10-carboxylic acid.

1,4-Dimethyl-5,6-dimethoxyphenanthrene (III).—When a mixture of 5 g. of the 10-carboxylic acid with 1 g. of dry copper powder was distilled at a pressure of 25 mm., a thick red oil was obtained, which was easily crystallized from 95% ethanol; yield, 47%; m. p. 71.5–72.5° (corr.). After four recrystallizations from the same solvent, the product formed white crystals, m. p. 73.5–74° (corr.), insoluble in alkali.

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

The carboxylic acid could not be decarboxylated by refluxing with quinaldine and basic copper carbonate.

This compound is a homolog of dimethylmorphol. Attempts to hydrolyze the methoxy groups by hydrochloric, hydrobromic, or hydriodic acid, resulted in tars, which gave an intense green-red fluorescence in most organic solvents tried. Neither an acetate nor a picrate could be isolated in crystalline form. One sample of the dimethoxy compound was heated in a sealed tube for sixteen hours at 200° with alcoholic potassium hydroxide, following the technique of Campbell, Dodds and Lawson,[10] but the product gave no ferric chloride color reaction, and no pure compound could be isolated.

1,4-Dimethyl-5-methoxy-6-hydroxyphenanthrene (III) was prepared by distilling a mixture of 7 g. of the 10-carboxylic acid (II) with 1.4 g. of dry copper powder at 25 mm. pressure and crystallizing the resultant viscous yellow oil from alcohol; yield 42%; m. p. 133–134° (corr.). After two recrystallizations from alcohol, the compound appeared as white crystals, m. p. 136.5–137° (corr.).

Anal. Calcd. for $C_{17}H_{16}O_2$: C, 81.0; H, 6.4; MeO, 12.3. Found: C, 81.2; H, 6.6; MeO, 11.0.

These crystals were soluble in cold olive oil, acetone or alkali, as well as in warm glycol.

In another run, 8 g. of the crude carboxy acid yielded 2.9 g. of the crystalline 1,4-dimethyl-5-methoxy-6-hydroxyphenanthrene.

In Pschorr's experiments[9] on the decarboxylation of 2 g. of 5-methoxy-6-hydroxyphenanthrene-10-carboxylic acid, he obtained only an oil, from which he prepared 0.3 g. of the 5-methoxy-6-acetoxyphenanthrene.

Efforts to hydrolyze the methoxyl group of the above (III) with either hydrobromic or hydriodic acid gave much the same results as with the 1,4-dimethyl-5,6-dimethoxyphenanthrene, and proved equally futile.

Summary

1. 1,4 - Dimethyl - 5,6 - dimethoxyphenanthrene and 1,4-dimethyl-5-methoxy-6-hydroxyphenanthrene have been synthesized from *p*-xylylacetic acid and 2-nitroveratraldehyde or 2-nitroacetovanillin. It is planned to investigate their analgesic properties.

2. The successful cyclization of 2-amino-3-methoxy-*p*-coumaric acid by the Pschorr reaction was accomplished without blocking the free hydroxyl group.

3. The methoxyl groups in 1,4-dimethyl-5,6-dimethoxyphenanthrene, or 1,4-dimethyl-5-methoxy-6-hydroxyphenanthrene, could not be hydrolyzed by any of the methods tried.

NEW YORK, N. Y. RECEIVED AUGUST 23, 1939

(10) Campbell, Dodds and Lawson, *Nature*, **141**, 78 (1938).