[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF SASKATCHEWAN]

A Possible Route to the Location of the Nitrogen Atom in Morphine. II. The Synthesis of 3,4-Dimethoxy-9-methylphenanthrene

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Both 3,4-dimethoxy-9-methylphenanthrene and 3,4,9-trimethoxyphenanthrene are required as reference compounds in the proposed scheme (part I of this series) for the location of the hydroxyl of hydroxycodeine and the nitrogen of morphine. The most direct route to the synthesis of these phenanthrenes appears to be from 3,4-dimethoxy-9-phenanthroic acid.[3,4,5] The following reaction sequence, $R{-}CO_2H \rightarrow R{-}CHO \rightarrow R{-}CH_3$, led to the desired 3,4-dimethoxy-9-methylphenanthrene. The Rosenmund method for the preparation of the aldehyde failed due to decomposition in the preparation of the acid chloride, however, the method for the preparation of the analogous 2,3,4,6-tetramethoxyphenanthraldehyde[6] proved very satisfactory. The benzenesulfonyl derivative of the hydrazide of 3,4-dimethoxy-9-phenanthroic acid was prepared[6] and this in turn converted to the aldehyde by the method of McFadyen and Stevens[6,7] and characterized as its oxime. The direct oxidation of the aldehyde to the acid failed but dehydration of the oxime and alkaline hydrolysis of the resulting nitrile did give 3,4-dimethoxy-9-phenanthroic acid. Although the Clemmensen reduction of the aldehyde afforded a small amount of the desired 9-methyl derivative, the reduction of the hydrazone by potassium hydroxide[6] proved to be superior from the point of view of yield and purity of the product. The 3,4-dimethoxy-9-methylphenanthrene was characterized as its picrate and trinitrobenzene derivative.

In view of the reported failure of Knorr and Hörlein[8] to obtain 3,4-dimethoxy-9-hydroxyphenanthrene from the diazotization of 3,4-dimethoxy-9-aminophenanthrene, our attention was directed to the Bucherer reaction as a method for obtaining this phenol. The intermediate sodium bisulfite addition product has been isolated but difficulty has been experienced in the decomposition of this addition product to 3,4-dimethoxy-9-phenanthrol.

Experimental Part

Methyl 3,4-Dimethoxyphenanthrene-9-carboxylate.—3,4-Dimethoxy-9-phenanthroic acid (20.4 g.), prepared according to the method of Pschorr and Sumuleanu[5] (see Table I), was esterified with an ethereal solution of diazomethane (22 cc. of nitrosomethylurethan). After removal of the ether the solid ester distilled at 225–228° (2.5 mm.); yield 21.0 g. (98.2%). The ester crystallized from ether in colorless flat plates, m. p. 93–93.5°.[9]

Hydrazide of 3,4-Dimethoxyphenanthrene-9-carboxylic Acid.—A solution of 21.0 g. of the methyl ester in 21.0 g. of absolute ethanol was refluxed with 21.0 g. of hydrazine hydrate for four hours. The solid hydrazide (20.0 g., 95.3%) was collected, washed with ethanol and dried at 110°. The colorless feathery crystals melted at 205.5° with previous softening. A small sample crystallized from alcohol in rosets of feathery crystals that melted at 207–207.5°.

The benzenesulfonyl derivative of the hydrazide was prepared by treating a solution of 10.0 g. of the hydrazide in 125 cc. of pyridine cooled to 0° with 6.0 g. of benzenesulfonyl chloride and allowed to stand in the icebox overnight. The reaction mixture was poured into ice-cold dilute hydrochloric acid and the resulting yellow solid collected and well washed with dilute hydrochloric acid and then with water. The crude product, when dried at 110°, weighed 14.7 g. and melted at 238° with decomposition. Recrystallization from ethanol gave 13.3 g. of flaky crystals, which when dried at 110° melted at 251° with decomposition setting in at 246°. An additional 0.7 g. of the crystalline material was recovered from the mother liquors. It melted at the same point, thus raising the yield to 14.0 g. (95.3%).

Anal.[11] Calcd. for $C_{23}H_{20}O_5N_2S$: N, 6.92. Found: N, 6.69, 6.52.

3,4-Dimethoxy-9-phenanthraldehyde.—To 5.0 g. of the benzenesulfonyl derivative of the hydrazide of 3,4-dimethoxyphenanthrene-9-carboxylic acid, dissolved in 75 cc. of ethylene glycol and heated to 160°, was added 3.6 g. of anhydrous sodium carbonate. The reaction was stopped in 80 seconds by the addition of 100 cc. of warm water. On cooling, the solution was extracted with ether and the ethereal extract dried over anhydrous sodium sulfate. Removal of the solvent and distillation of the yellow solid gave 2.4 g. (79%) of a solid distillate which crystallized from ethanol in slender yellowish needles, m. p. 96–97°.

Anal. Calcd. for $C_{17}H_{14}O_3$: C, 76.67; H, 5.30. Found: C, 76.56, 76.72; H, 5.53, 5.53.

The oxime was prepared in 81% yield from 2.0 g. of the aldehyde. It crystallized from methanol–water mixture in colorless, woolly crystals, m. p. 114–115°.

Anal. Calcd. for $C_{17}H_{15}O_3N$: N, 4.98. Found: N, 5.05, 4.95.

The semicarbazone crystallized from ethanol in small needles and melted at 196–197°.

3,4-Dimethoxy-9-cyanophenanthrene.—A mixture of 1.7 g. of the oxime and 4.0 cc. of acetic anhydride was cautiously heated. When the initial reaction had subsided, the solution was refluxed gently for twenty minutes and then water was cautiously added. When cold, a solid product, weighing 1.45 g., was recovered which melted over a wide range. The solid was taken up in ether and washed successively with 10% sodium hydroxide solution and water, then dried. After removal of the

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[3] Pschorr and Sumuleanu, *Ber.*, **32**, 3405 (1899).

[4] Pschorr, *ibid.*, **39**, 3106 (1906).

[5] Pschorr and Sumuleanu, *ibid.*, **33**, 1810 (1900).

[6] Buchanan, Cook and Loudon, *J. Chem. Soc.*, 325 (1944).

[7] McFadyen and Stevens, *ibid.*, 584 (1936).

[8] Knorr and Hörlein, *Ber.*, **40**, 2041 (1907).

[9] All melting points were taken in an apparatus designed by E. B. Hershberg[10] and are corrected unless otherwise stated.

[10] Hershberg, *Ind. Eng. Chem., Anal. Ed.*, **8**, 312 (1936).

[11] All compounds were analyzed in the analytical laboratory of Dr. Léo Marion at the National Research Council, Ottawa, Canada.

TABLE I

INTERMEDIATES IN THE SYNTHESIS OF 3,4-DIMETHOXY-9-PHENANTHROIC ACID

Compound	Crystal form	B. p., °C. M. p., °C.	Yield, %	Ref.
Vanillin acetate	Long crystals ($C_2H_5OH-H_2O$)	81	95	3
2-Nitrovanillin acetate	Needles ($C_2H_5OH-H_2O$)	85–87	75	3
2-Nitrovanillin	Large crystals (H_2O)	137	90	3
2-Nitroveratric aldehyde	Prisms ($C_2H_5OH-H_2O$)	205 (13 mm.) 55–56	70	4
α-Phenyl-2-nitro-3,4-dimethoxycinnamic acid	Yellow needles ($C_2H_5OH-H_2O$)	225	65	5
α-Phenyl-2-amino-3,4-dimethoxycinnamic acid	Dense prisms ($C_2H_5OH-H_2O$)	179	70	5
3,4-Dimethoxy-9-phenanthroic acid	Needles ($C_2H_5OH-H_2O$)	227–228	79	5

ether and crystallization several times from dilute acetic acid, 1.0 g. of the nitrile was obtained as yellow needles which melted at 111–112°.

Anal. Calcd. for $C_{17}H_{13}O_2N$: N, 5.32. Found: N, 5.19, 5.38.

The nitrile was hydrolyzed to the acid by refluxing for thirty hours with 20% sodium hydroxide solution and the unchanged nitrile removed by ether extraction. The alkaline solution was diluted with water, acidified and the crude acid collected. By crystallization from ethanol fine needles of the acid were obtained which melted alone or on admixture with an authentic sample of the acid at 225–227° (uncor.). The amide crystallized from alcohol in silvery needles and melted at 236° (uncor.).

3,4-Dimethoxy-9-methylphenanthrene.—A solution of 1.7 g. of the aldehyde in 10 cc. of ethanol was heated under reflux with 5 cc. of hydrazine hydrate for two hours when the solvent was removed (vacuum). To the residual yellow solid, heated to 125° in an oil-bath, was added 3.2 g. of powdered potassium hydroxide. The reaction mixture was cooled in twenty minutes, water added, and the aqueous solution extracted with ether. After drying, the ether was removed and the residual oil distilled under high vacuum yielding 1.2 g. (75%) of a yellowish oil.

The 3,4-dimethoxy-9-methylphenanthrene was purified by conversion to the picrate and crystallization from an almost saturated ethanolic solution of picric acid. The picrate crystallized in reddish-brown needles and melted at 129–130°.

Anal. Calcd. for $C_{23}H_{19}O_9N_3$: N, 8.73. Found: N, 8.61, 8.62.

The trinitrobenzene derivative crystallized in scarlet needles from ethanol; m. p. 151.8–152.8°.

Anal. Calcd. for $C_{23}H_{19}O_8N_3$: N, 9.03. Found: N, 9.03, 8.99.

Decomposition of the picrate by dilute ammonium hydroxide and extraction of the substitute phenanthrene in ether gave an oil which was crystallized from methanol–water mixture. The colorless plates of 3,4-dimethoxy-9-methylphenanthrene melted at 59–60°.

Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.90; H, 6.39. Found: C, 80.26; H, 6.66.

The Clemmensen reduction of the above aldehyde afforded a 10% yield of 3,4-dimethoxy-9-methylphenanthrene which melted alone or on admixture with the above sample at 55°.

3,4-Dimethoxy-9-aminophenanthrene.[8]—The acid azide of 3,4-dimethoxy-9-phenanthroic acid was prepared by adding a slight excess of an aqueous sodium nitrite solution to a cold (ice–water-bath) solution of 10.0 g. of the hydrazide in 125 cc. of acetic acid. The acid azide separated as a yellow powder which was collected on a Büchner funnel and air-dried. Without further purification it was converted to the urethan by refluxing in 175 cc. of absolute ethanol for six hours. The solution turned pink in the course of one hour and the colorless product began to separate. On standing overnight, rosets of colorless crystals were formed. These crystals when air-dried weighed 6.7 g.; m. p. 145–146°. An additional 0.8 g. of the urethan was recovered from the alcoholic mother liquors; total yield 7.5 g. (68%).

The hydrochloride of 3,4-dimethoxy-9-aminophenanthrene was obtained by refluxing 7.5 g. of the urethan with 150 cc. of absolute ethanol and 15 g. of potassium hydroxide for two hours. The hot solution was poured into 375 cc. of boiling 20% hydrochloric acid, when a colorless curdy precipitate settled out, which weighed 5.9 g. (88.5%). The amine was an oil.

The Bucherer Reaction on 3,4-Dimethoxy-9-aminophenanthrene.—The free amine from 5.0 g. of 3,4-dimethoxy-9-aminophenanthrene hydrochloride and 20.0 g. of sodium bisulfite in 40 cc. of water were heated in a sealed tube at 150–160° for fifty hours. The addition product was isolated as a brown solid which when purified from benzene melted at 218–219°. It gave a positive test for sulfur.

Anal. Calcd. for $C_{16}H_{16}O_5SNNa$: N, 3.92. Found: N, 4.21, 4.24.

Ammonia was evolved when the addition product was boiled in dilute aqueous sodium hydroxide. When cold, the alkaline solution was filtered to remove small amounts of suspended material and the filtrate acidified when a small amount of a solid settled out and sulfur dioxide was evolved. The solution was boiled for a short time to drive off all of the sulfur dioxide. The solid material gave a green coloration with ferric chloride solution but was only slightly soluble in sodium hydroxide solution.

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Summary

The synthesis of 3,4-dimethoxy-9-methylphenanthrene (required for the location of the newly generated hydroxyl in hydroxycodeine) has been achieved and the product characterized as its picrate and trinitrobenzene derivative. Attempts to prepare 3,4,9-trimethoxyphenanthrene by the Bucherer reaction on 3,4-dimethoxy-9-aminophenanthrene have not, as yet, been successful. A crystalline addition product from the reaction of sodium bisulfite with this amine has been isolated. Alkaline decomposition of the addition product afforded a small amount of a solid which has not, as yet, been completely characterized as 3,4-dimethoxy-9-phenanthrol.

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