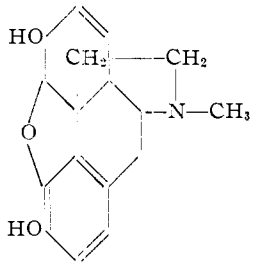
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF SASKATCHEWAN]

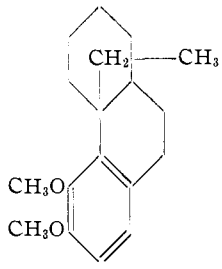
The Synthesis of Possible Degradation Products of Morphine and Metathebainone. III[1]

BY H. L. HOLMES[2] AND K. M. MANN[3]

Elucidation of the hydrophenanthrene structure of morphine, I[4] and the related alkaloids, codeine and thebaine, has depended largely on their degradation to substituted phenanthrenes. The structures of most of these phenanthrenes have been established from analytical data and confirmed by synthesis following the general method of Pschorr.[5,6] However, evidence necessary to definitely assign the ethanamine chain to position C_9–C_{13} is still lacking. The two attempts[7,8,9] to degrade these alkaloids to 3,4-dimethoxy-13-ethyloctahydrophenanthrene (II) (the *cis* form of this product has recently been synthesized[10]) failed due to the anomalous reactions encountered in intermediate stages of the degradations. Although the above degradations failed, the 9,10-dihydro derivative of one of the intermediates (III) might be used as a starting material for an alternate solution to this problem. The oxidation of the vinyl group to a carboxyl, followed by reductive cleavage of the oxide bridge and methylation of the resulting phenol should lead to IVa.



I



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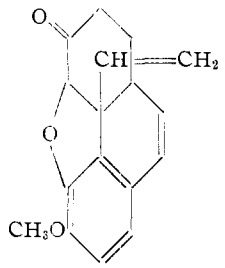
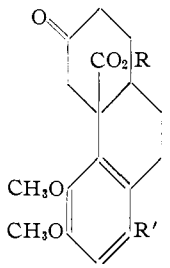
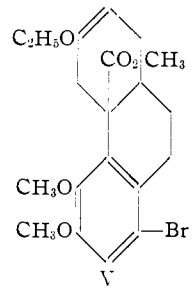


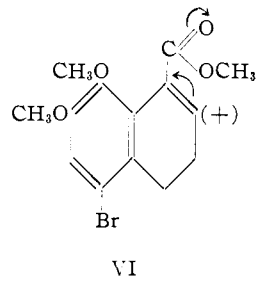
III



IVa, R = R′ = H
IVb, R = CH_3, R′ = Br



V



VI

A possible route to the synthesis of IVa would appear to lie in the synthesis of V from 2-ethoxybutadiene-1,3 and methyl 5-bromo-7,8-dimethoxy-3,4-dihydro-1-naphthoate followed by acid hydrolysis[11] of the enol ethyl ether and elimination of the halogen. Furthermore, the product of bromination of the C_4-phenol of IVb at C_5 would possess all the necessary groups for formation of the hydrophenanthrylene oxide system.[12]

An adduct (no isomeric product was observed) has been isolated in 13.8% yield from the reaction of methyl 5-bromo-7,8-dimethoxy-3,4-dihydro-1-naphthoate with 2-ethoxybutadiene-1,3, while the acid hydrolysis of the enol ether of this adduct afforded a ketonic ester in almost quantitative yield. The bromination of this ketone proceeded without difficulty. It is to be emphasized that while this keto-ester might have a similar structure to that of the degradation product yet the steric arrangement at C_{13} and C_{14} might place these products in different stereochemical series. The sterically uniform *cis*-addition products from most Diels–Alder reactions would suggest that the C_{13}-carbomethoxy group and the C_{14}-hydrogen atom of this adduct are *cis*.

The unsymmetrical nature of the addends in this Diels–Alder reaction requires that V and its isomer with the ethoxyl group at C_7 be considered for this adduct. If the Diels–Alder reaction is initiated[13] by a coupling of the more anionoid end of the diene system with the cationoid carbon of the dienophile, then the C_7-ethoxy-adduct is to be expected rather than V.[14]

An insight into the orientation of the addends during this reaction has been gained from the addition of this diene to methyl 3,4-dihydro-1-naphthoate, for acid hydrolysis of the adduct,

(1) Parts I and II of this series appear in *Can. J. Research*, **22B**, 56, 109 (1944).

(2) Associate Professor of Chemistry.

(3) Merck Fellow, 1944–1946. This paper is based on a thesis submitted by K. M. Mann to the College of Graduate Studies in partial fulfilment of the requirements for the degree of Master of Science, April, 1946.

(4) Gulland and Robinson, *Mem. Proc. Manchester Lit. & Phil. Soc.*, **69**, 79 (1925).

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

(6) Pschorr, Seydel and Stöhrer, *ibid.*, **35**, 4400 (1902).

(7) Speyer and Koulen, *Ann.*, **438**, 34 (1924).

(8) Cahn, *J. Chem. Soc.*, 2562 (1926).

(9) Cahn, *ibid.*, 702 (1930).

(10) Ghosh and Robinson, *ibid.*, 506 (1944).

(11) Fiesselmann, *Ber.*, **75**, 881 (1942).

(12) Schöpf, *et al.*, *Ann.*, **483**, 157 (1930); **492**, 213 (1932).

(13) Hudson and Robinson, *J. Chem. Soc.*, 715 (1941).

(14) It is considered here that a carbomethoxy group of methyl 5-bromo-7,8-dimethoxy-3,4-dihydro-1-naphthoate (VI) would exert a stronger directive influence in the orientation of the addends in this addition than would the more remote alkoxy groups.

treatment with methylmagnesium iodide, dehydration and dehydrogenation led to 2-methylphenanthrene. The addition of 2-ethoxybutadiene to methyl 5-bromo-7,8-dimethoxy-3,4-dihydro-1-naphthoate, in an analogous way, would lead to methyl 1-bromo-3,4-dimethoxy-7-ethoxyhexahydrophenanthrene-13-carboxylate. Similarly, methyl 1-bromo-3,4-dimethoxy-6-ethoxyhexahydrophenanthrene-14-carboxylate would be expected from methyl 5-bromo-7,8-dimethoxy-3,4-dihydro-2-naphthoate (the ketone of this enol ether is a possible degradation product of metathebainone). Attempts to prepare 5-bromo-7,8-dimethoxy-3,4-dihydro-2-naphthoic acid by the method described in the first paper of this series[1] failed for the bromine atom was eliminated during the condensation of the formic ester with ethyl γ-[2-bromo-4,5-dimethoxyphenyl]-butyrate. However, it is possible that by replacement of the bromine by the less reactive chlorine atom[15] that this halogen might withstand the conditions of this reaction.

Experimental Part[16]

The Synthesis of 2-Ethoxybutadiene-1,3.—The 2-ethoxybutadiene was prepared by the addition of ethyl hypobromite to butadiene followed by elimination of hydrogen bromide.[17]

Benzenesulfondibromamide.—The hypobromous acid required for the bromination of benzenesulfonamide was prepared as follows. Eighty grams (25.1 cc.) of bromine was added dropwise to a cold (0°) suspension of 53.0 g. of yellow mercuric oxide in 1 liter of water. The resulting mercuric bromide was collected in a sintered glass funnel and the cold filtrate used directly in the bromination of the sulfonamide.

To the cold, well-stirred aqueous solution of hypobromous acid was added a solution of 20.0 g. of benzenesulfonamide in 200 cc. of hot water. The reaction mixture was stirred for one hour and the solid dibromoamide collected on a Büchner funnel and well washed with cold water. The yellow benzenesulfondibromamide weighed 39.3 g. (98%) and melted at 110–111°.

Traces of water, which materially reduce the yield in the next step, were removed from the dibromamide by drying a chloroform solution of the product over sodium sulfate.

4-Bromo-3-ethoxybutene-1.—One hundred and five grams of dry benzenesulfondibromamide was added in small portions to a stirred and cooled (−15°) solution of 51.0 g. (75 cc.) of butadiene in 300 cc. of absolute ethanol. The reaction mixture was stirred for one hour after the last addition of the sulfondibromamide. The 4-bromo-3-ethoxybutene-1 was removed from the reaction mixture by steam distillation. The heavy oil was extracted in ether, washed with water and dried over calcium chloride. The 4-bromo-3-ethoxybutene-1 boiled at 154–157° (724 mm.) (n^{20}D 1.4561) and weighed 75.9 g. (63%). Petrov reports the following figures: yield, 69%; b. p. 153–154.2°; n^{20}D 1.4595.

2-Ethoxybutadiene-1,3.—Forty grams of 4-bromo-3-ethoxybutene-1 was added dropwise with shaking to a flask containing 83 cc. of 30% ethanolic potassium hydroxide and surmounted by an efficient Tamworth condenser. Heat was evolved, the reaction mixture became yellow and grew more viscous. On completion of the addition the pasty mass was refluxed for twenty minutes, a small amount of water added, and the ethoxybutadiene removed by steam distillation. The heavy oil was salted out with sodium chloride, separated, dried over calcium chloride and distilled; b. p. 95° (712 mm.); yield 23.1 g. (86.6%); n^{25}D 1.4372. Petrov reports n^{20}D 1.4420. The diene can be stored for months at 5° if stabilized with hydroquinone.

5-Bromo-7,8-dimethoxy-3,4-dihydro-1-naphthoic Acid.[18]—**β-Veratroylpropionic acid** (m. p. 153–157°) was prepared from veratrole and succinic anhydride in 84% yield. The Clemmensen reduction of this crude product afforded a 69–74% yield of **γ-veratrylbutyric acid**, b. p. 180–184° (2.5 mm.). The distillate solidified in the receiver. Bromination of γ-veratrylbutyric acid by the method of Haworth and Mavin[19] gave an 83% yield of **γ-[2-bromo-4,5-dimethoxyphenyl]-butyric acid** melting at 131–135°. This acid was sufficiently pure for conversion to the ethyl ester, which was recovered in 91% yield; b. p. 220–222° (17 mm.). The ester crystallized from ether in long stout prisms, m. p. 50°.

α-Keto-δ-[2-bromo-4,5-dimethoxyphenyl]-valeric acid, was prepared by condensing 100.0 g. of ethyl γ-[2-bromo-4,5-dimethoxyphenyl]-butyrate in ethereal solution with 50.0 g. of redistilled ethyl oxalate in the presence of sodium ethylate (6.94 g. of sodium and 25.6 cc. of absolute ethanol) under the usual conditions.[18] The unchanged starting material (11.9 g.) was separated by pouring into ice and water and separating the ether layer. The glyoxylic ester was recovered by acidifying the aqueous solution of the sodio-salt with ice cold 2 *N* sulfuric acid and extraction with ether. Removal of the solvent left 114 g. of an oily ester which was decarboxylated by boiling with 18% sulfuric acid for twenty hours; 86.5 g. The α-keto-δ-[2-bromo-4,5-dimethoxyphenyl]-valeric acid may be purified by decolorization of the sodium salt with Norit and crystallization of the acid from dilute acetic acid, m. p. 93–94°.

The **5-bromo-7,8-dimethoxy-3,4-dihydro-1-naphthoic acid** was prepared by stirring 40.0 g. of the impure keto-acid with dilute sulfuric acid (145 cc. of concentrated sulfuric acid and 83 cc. of water) at 80°. The acid was purified by crystallization of its sodium salt.[18] The yield of the acid, melting at 165°, was 36.0 g. The acid, after crystallization from dilute ethanol, melted at 170–171°.

The acid (24.0 g.) was converted to its methyl ester with an ethereal solution of diazomethane. Removal of the ether and distillation of the residual oil gave a pale yellow distillate, 22.0 g., b. p. 185–187° (2 mm.), which crystallized readily.

Methyl 1-Bromo-3,4-dimethoxy-7-ethoxy-5,8,9,10,13,-14-hexahydrophenanthrene-13-carboxylate.—A solution of 3.4 g. of 2-ethoxybutadiene and 0.1 g. of hydroquinone in 10 cc. of dry toluene was heated in a sealed tube with 10.0 g. of methyl 5-bromo-7,8-dimethoxy-3,4-dihydro-1-naphthoate for ninety-six hours at 210–212°. The toluene and low boiling polymer were removed under 15 mm. pressure and the fraction boiling at 195–230° (3 mm.) was collected. This fraction was separated into two fractions, A, boiling up to 195° (3 mm.) and B, boiling at 195–230° (3 mm.). Fraction A proved to be starting material while B was a mixture of starting ester and the adduct. Fraction B was dissolved in excess of ether and upon spontaneous evaporation of the solvent a solid (1.8 g.) separated, m. p. 160–164°. Recrystallization from ethanol afforded beautiful, small, clear crystals melting at 167–169°.

Anal.[20] Calcd. for $C_{20}H_{25}O_5Br$: C, 56.47; H, 5.92. Found: C, 56.55, 56.58; H, 5.79, 5.89.

The enol ethyl ether was hydrolyzed by dissolving 0.5 g. of the adduct in 50 cc. of methanol and allowing it to stand with 2 cc. of 6 *N* sulfuric acid and 3 cc. of water. In one and one-half hours the reaction mixture was diluted with water and extracted with ether. Removal of the solvent left a solid residue, which, when crystallized from

(15) Speyer and Rosenfeld, *Ber.*, **58**, 1110 (1925).

(16) All melting points are corrected.

(17) Petrov, *J. Gen. Chem. U. S. S. R.*, **8**, 208 (1938).

(18) Fieser and Holmes, THIS JOURNAL, **60**, 2548 (1938).

(19) Haworth and Mavin, *J. Chem. Soc.*, 1485 (1932).

(20) All compounds were analyzed in the laboratory of Dr. L. Marion, Division of Chemistry, National Research Council, Ottawa, Canada.

aqueous methanol, gave fine, white needles melting at 159.8–161.0°.

This ketone readily reacted with a solution of bromine in carbon tetrachloride with the evolution of hydrogen bromide.

The addition of a weakly acidic aqueous ethanolic solution of 2,4-dinitrophenylhydrazine to an alcoholic solution of the adduct, on standing, yielded a flocculent yellow precipitate; m. p. 169–190°. Recrystallization from benzene–petroleum ether mixture gave fine yellowish-orange crystals melting at 183.5–185.5°.

Anal. Calcd. for $C_{24}H_{25}N_4O_8Br$: N, 9.70. Found: N, 9.53, 9.60.

The oxime was prepared from the keto-ester and after three crystallizations from ethanol the woolly mass of crystals melted at 154–159°.

Anal. Calcd. for $C_{18}H_{22}NO_5Br$: N, 3.40. Found: N, 3.18, 3.20.

Reduction of Methyl 1-Bromo-3,4-dimethoxy-7-ethoxy-5,8,9,10,13,14-hexahydrophenanthrene-13-carboxylate.—A solution of 0.500 g. of the adduct in absolute ethanol was hydrogenated over Adams catalyst (0.100 g.). Hydrogen slightly in excess of the theoretical amount (102%, 24.4° and 713 mm.) was rapidly absorbed. Upon removal of the catalyst and solvent 0.1 g. of a solid separated in fine crystals, m. p. 120–127°. The remainder of the material crystallized only very slowly and appeared to be different. Purification of the solid reduction product from aqueous ethanol afforded small spear-shaped crystals which melted at 116–119°.

5-Bromo-7,8-dimethoxy-3,4-dihydro-2-naphthoic Acid.—Attempts have been made to apply the method described in a previous paper[1] to the synthesis of this unsaturated acid without success. Various conditions were used for the condensation of ethyl or isoamyl formate with ethyl γ-[2-bromo-4,5-dimethoxyphenyl]-butyrate but the bromine atom was eliminated in every case for the cyclized product was 6,7-dimethoxy-3,4-dihydro-2-naphthoic acid, m. p. 186–188°, which was characterized by dehydrogenation to 6,7-dimethoxy-2-naphthoic acid.

6,7-Dimethoxy-3,4-dihydro-2-naphthoic acid, for comparison, was prepared by the condensation of 47.85 g. of ethyl γ-veratrylbutyrate with 28.2 g. of isoamyl formate using sodium ethylate (4.7 g. of sodium) as a catalyst. Cyclization of the 32.5 g. of the oily formylation product in 99.6 cc. of phosphoric acid (sp. g. 1.75) and 21 cc. of sulfuric acid (sp. g. 1.832) resulted in a 45% over-all yield of 6,7-dimethoxy-3,4-dihydro-2-naphthoic acid. The acid was recrystallized first from ethyl alcohol then from chloroform; m. p. 187–188.5°.

Anal. Calcd. for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02; neut. equiv., 234.2. Found: C, 66.35; H, 5.95; neut. equiv., 229.

A mixture of the ethyl and isoamyl esters of γ-veratrylbutyric acid (14.3 g.) was recovered; b. p. 205–225° (22 mm.).

6,7-Dimethoxy-2-naphthoic acid results from heating 2.0 g. of 6,7-dimethoxy-3,4-dihydro-2-naphthoic acid in a von Braun flask with 0.3 g. of sulfur at 250° for thirty minutes. After distillation (2 mm.) the solid distillate was crystallized from ethanol; m. p. 246.5–247.0°.

Anal. Calcd. for $C_{13}H_{12}O_4$: neut. equiv., 232.2. Found: neut. equiv., 231.

The sodium salt of 6,7-dimethoxy-2-naphthoic acid crystallized from bicarbonate solution in long feathery needles. The amide melts at 180.5–181.5°.

Anal. Calcd. for $C_{13}H_{13}O_3N$: N, 5.92. Found: N, 5.80, 5.82.

Esterification of this acid by the Fischer method gave a 71.2% yield of the ethyl ester, boiling at 183.5–185.0° (2.5 mm.). The solid distillate, after crystallization from petroleum ether, melted at 66.5–67.0°. The methyl ester, prepared with an ethereal solution of diazomethane, crystallized from methanol in long feathery needles and melted at 106.5–107.5°.

Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.31; H, 5.69. Found: C, 68.13; H, 5.96.

6,7-Dimethoxy-1,2,3,4-tetrahydro-2-naphthoic acid was obtained in 83% yield from reduction of 1.001 g. of the dihydro-acid in 75 cc. of glacial acetic acid (0.100 g. of Adams catalyst). The hydrogenated acid was recovered in the usual manner and crystallized from dilute acetic acid; m. p. 136.5–137.5°.

Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.06; H, 6.83. Found: C, 66.24; H, 6.86.

The sodium salt of the acid crystallized in long feathery needles from bicarbonate solution. The amide melts at 176.5–177.0° with previous softening and darkening.

3,4-Dihydro-1-naphthoic Acid.[21]—Ethyl γ-phenylbutyrate (50.0 g.) was condensed with 57.0 g. of ethyl oxalate in the presence of sodium ethylate (from 6.1 g. of sodium) at −10°. The resulting glyoxylic ester was isolated in the usual way and decarboxylated by boiling for eighteen hours with 350 cc. of 15% sulfuric acid. The resulting α-keto-δ-phenylvaleric acid was extracted in ether, dried over anhydrous sodium sulfate, and esterified by the Fischer method. The pale yellow ethyl ester (27.5 g.) boiled at 145–150° (4 mm.).

Twenty-five grams of ethyl α-keto-δ-phenylvalerate was cyclized by stirring it vigorously in 150 cc. of 65% sulfuric acid at 100° for two hours. The somewhat darkened mixture was cooled, poured onto ice, and extracted with ether. Following the removal of the solvent, the ester was saponified with 10% sodium hydroxide solution. Cautious acidification of the alkaline solution yielded a light yellow solid (13.1 g.) which melted at 110–112°. The **3,4-dihydro-2-naphthoic acid** crystallized from benzene in clear rhombohedral crystals; m. p. 119–120°.

The acid (36.1 g.) was treated with an ethereal solution of diazomethane and the methyl ester was isolated in 87% yield; b. p. 135–137° (4 mm.).

Methyl 7-Ethoxy-5,8,9,10,13,14-hexahydrophenanthrene-13-carboxylate.—Twenty grams of methyl 3,4-dihydro-1-naphthoate and 0.2 g. of hydroquinone in 20 cc. of dry toluene were heated with 12.0 g. of 2-ethoxybutadiene in a sealed tube at 178–180° for fifty hours. After removal of the solvent and the low boiling polymer at 15 mm. pressure, the reaction mixture was distilled and the fraction (24.1 g.) boiling at 130–200° (4 mm.) was collected. Redistillation gave a fraction A (8.5 g.) boiling up to 160° (2 mm.), which proved to be starting material, and a second fraction B (15.0 g.) boiling up to 195° (2 mm.). Fraction B, dissolved in ether, slowly deposited a white solid (6.2 g., m. p. 81–84°) on spontaneous evaporation of the solvent. The adduct crystallized from dilute ethanol in fine needles; m. p. 90–91°.

Anal. Calcd. for $C_{18}H_{22}O_3$: C, 75.50; H, 7.74. Found: C, 75.71, 75.39; H, 7.83, 7.51.

Methyl 7-Keto-5,6,7,8,9,10,13,14-octahydrophenanthrene-13-carboxylate.—A solution of 6.3 g. of the adduct in 100 cc. of methanol was stirred at room temperature with 10 cc. of 6 *N* sulfuric acid and 5 cc. of water for one hour. The methanolic solution was copiously diluted with water and extracted with ether. The solvent was spontaneously evaporated and the solid keto-ester (m. p. 95–97°) (5.7 g.) precipitated from the concentrated ethereal solution by the cautious addition of petroleum ether. Recrystallization from aqueous methanol raised the melting point to 100.0–101.0°.

Anal. Calcd. for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02. Found: C, 74.27, 74.29; H, 7.08, 7.10.

A carbon tetrachloride solution of the keto-ester readily decolorized bromine with the evolution of hydrogen bromide. The 2,4-dinitrophenylhydrazone, prepared by the method previously described, crystallized in yellowish-orange crystals from benzene–petroleum ether and melted at 187.5–190.0°.

Anal. Calcd. for $C_{22}H_{22}O_6N_4$: N, 12.75. Found: N, 12.68, 12.83.

(21) Fieser and Holmes, THIS JOURNAL, **58**, 2319 (1936).

The **piperonylidene derivative** of the keto-acid was prepared by heating 0.2 g. of the keto-ester and 0.30 g. of freshly distilled piperonal in 10 cc. of ethanol with a solution of 0.5 g. of potassium hydroxide in 2 cc. of water. In fifteen minutes the bright yellow solution was cooled, diluted with water and acidified with hydrochloric acid. The brown, solid piperonylidene derivative of the keto-acid was collected and repeatedly recrystallized from aqueous ethanol. The product which proved difficult to purify was a canary-yellow and melted at 149° with previous softening and decomposition. It dissolved in concentrated sulfuric acid to give a blue solution which soon turned a deep purple. Analysis would indicate that it contained a molecule of ethyl alcohol of crystallization.

Anal. Calcd. for $C_{25}H_{26}O_5$: C, 71.06; H, 6.21. Found: C, 71.27; H, 5.85.

2-Methylphenanthrene.—A solution of methylmagnesium iodide (from 1.28 g. of methyl iodide) in 30 cc. of ether was added dropwise, with stirring, to a solution of 2.1 g. of the above keto-ester in 100 cc. of dry ether. After the Grignard reagent had been added the reaction mixture was refluxed for half an hour and allowed to stand overnight. The reaction product was decomposed with cold 10% sulfuric acid and the ether layer separated, washed with water and dried over anhydrous sodium sulfate. The residual oil, after removal of the solvent was dehydrated by distillation; b. p. 170–180° (4 mm.); yield, 1.5 g.

The dehydration product (1.5 g.) was dehydrogenated with 2.0 g. of selenium at 320–330° for twenty hours. The dehydrogenation product was recovered in dry ether, the solvent removed and the product distilled in a small von Braun flask. The distillate (0.7 g.) soon solidified and for purification was converted to the picrate; m. p. 116–117°. Several crystallizations from alcohol raised the melting point to 118–119°. This product when mixed with picric acid melted at 95–100°.

The pale orange crystals were decomposed with ammonia and the hydrocarbon extracted with ether, washed with water and dried over sodium sulfate. Upon removal of the solvent and crystallization from aqueous methanol the 2-methylphenanthrene was obtained in glistening plates; m. p. 53–54°. 2- and 3-methylphenanthrene[22] melt, respectively, at 55–56° and 62–63°; their picrates at 118–119° and 137–138°.

Summary

In attempts to prove the location of the ethanamine chain in the morphine alkaloids, efforts were made to prepare methyl 1-bromo-3,4-dimethoxy-6-keto-5,6,7,8,9,10,13,14-octahydrophenanthrene-13-carboxylate for comparison with possible degradation products of the alkaloids.

The addition of 2-ethoxybutadiene to methyl 5-bromo-7,8-dimethoxy-3,4-dihydro-1-naphthoate gave a 13.8% yield of one, of two possible adducts, which by hydrolysis of the enol ethyl ether was converted to the corresponding ketone. Subsequent work has indicated this to be methyl 1-bromo-3,4-dimethoxy-7-keto-octahydrophenanthrene-13-carboxylate. The analogous ketone fromme thyl 3,4-dihydro-1-naphthoate provided evidence for this conclusion. The tertiary alcohol, resulting from the action of methylmagnesium iodide, when dehydrated and dehydrogenated gave 2-methylphenanthrene.

(22) Haworth, *J. Chem. Soc.*, 1125 (1932).

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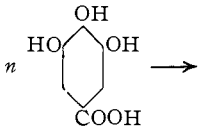
[CONTRIBUTION FROM THE EASTERN AND NORTHERN REGIONAL RESEARCH LABORATORIES[1]]

Direct Esterification of Gallic Acid with Higher Alcohols

BY WALDO C. AULT,[2] JAMES K. WEIL,[2] GEORGE C. NUTTING[2] AND J. C. COWAN[2a]

The esters of gallic acid with alcohols containing more than six carbon atoms have not been prepared by the usual direct esterification process. Recently, however, Morris and Riemenschneider[3] prepared esters of all the alcohols containing an even number of carbon atoms from 6 to 18, inclusive, by an indirect method that involved protection of the hydroxyl groups of gallic acid by benzylation and treatment of the resulting tribenzyl ether with thionyl chloride to form the corresponding galloyl chloride, which was then esterified with the appropriate alcohol. The resulting ester was debenzylated by hydrogenation.

Recent indications of the potential value of the higher fatty alcohol esters of gallic acid as antioxidants[4] made a more direct synthesis of these compounds desirable. This need led to speculation as to why the higher fatty alcohol esters of gallic acid should be so difficult or impossible to prepare by techniques that give excellent yields of the short-chain alcohol esters. Although gallic acid is soluble in the lower alcohols and almost insoluble in the higher ones, in view of the excess proportions of the latter which were tried, it does not seem probable that solubility is the determining factor. One of the most interesting theories presumes that the carboxyl group of the gallic acid is coördinated in such a manner that the higher alcohols cannot readily react with it. For example, a chelate ring may be formed from two molecules of gallic acid as



(1) Laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

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(3) Morris and Riemenschneider, THIS JOURNAL, **68**, 500 (1946).

(4) "Antioxidant Properties of the Fatty Alcohol Esters of Gallic Acid," by Morris, Kraekel, Myers and Riemenschneider. Paper presented at the fall Meeting of American Oil Chemists' Society, 1946.