

The behavior of polynuclear hydrocarbons in the lead tetraacetate oxidation, aldehyde reaction, and diazo coupling test shows that the most powerfully carcinogenic hydrocarbons of the series possess special susceptibility to substitutions,

and certain indications are discernible of a relationship between this specific type of chemical reactivity and carcinogenic activity.

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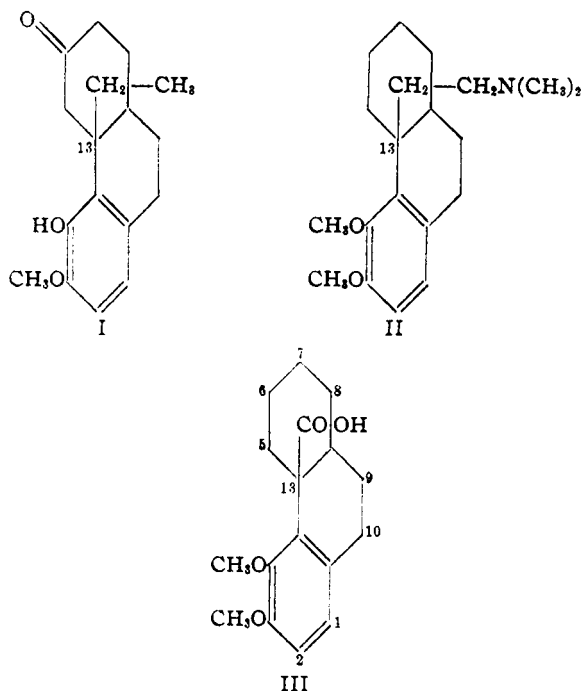
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

The Synthesis of Phenanthrene and Hydrophenanthrene Derivatives. VIII. Substances Related to Degradation Products of Morphine

BY LOUIS F. FIESER AND H. L. HOLMES

In a previous paper¹ we described a diene synthesis by which it is possible to obtain hydrophenanthrene derivatives having a carboxyl group at a quaternary carbon atom corresponding to the 13-position of the morphine alkaloids. According to the Gulland-Robinson formula for morphine, these alkaloids contain an ethanamine chain joined at the hydrocarbon end to the 13-position of the hydrophenanthrene skeleton, but the exact position of attachment is the one remaining point of uncertainty concerning the structures. The new synthesis provides a possible method of obtaining compounds of known structure which, if the Gulland-Robinson formula is correct, may be obtainable from the alkaloids by degradation, and in the present work we have investigated the possibility of synthesizing suitable compounds.

Degradative work on the alkaloids has not as yet provided many substances which seem within reach by the diene synthesis. A ketoethyloctahydromorphenol methyl ether of the probable structure I (Gulland-Robinson formulation) was obtained by Wieland and Kotake² and by Cahn³ by various degradations, but Cahn encountered difficulties on attempting to reduce the carbonyl group and to methylate the compound. Speyer and Koulen⁴ obtained as the methiodide a substance described as dihydrodesoxytetrahydro- α -methylmorphimethine and probably having the structure II, but an attempted Hofmann degradation to the corresponding vinyl compound apparently proceeded anomalously with demethylation at the 4-position and ring formation between the liberated hydroxyl and vinyl groups.⁵ Our first



objective was the synthesis of the acid III, which may be obtainable from these or other degradation products, and we also made some study of possible methods of lengthening the carbon side chain.

The synthesis of 3,4-dimethoxy-5,6,7,8,9,10,13,14-octahydrophenanthrene-13-carboxylic acid (III) was accomplished by application of the scheme of synthesis previously described. γ -(3,4-Dimethoxyphenyl)-butyric acid (IV) was prepared from veratrole by condensation with succinic anhydride and reduction, by the procedures already reported.^{6,7} This acid undergoes cyclization very readily at the position para to one of the methoxyl groups,^{8,9} and since it was

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

(2) Wieland and Kotake, *Ann.*, **444**, 69 (1925).

(3) Cahn, *J. Chem. Soc.*, 702 (1930).

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

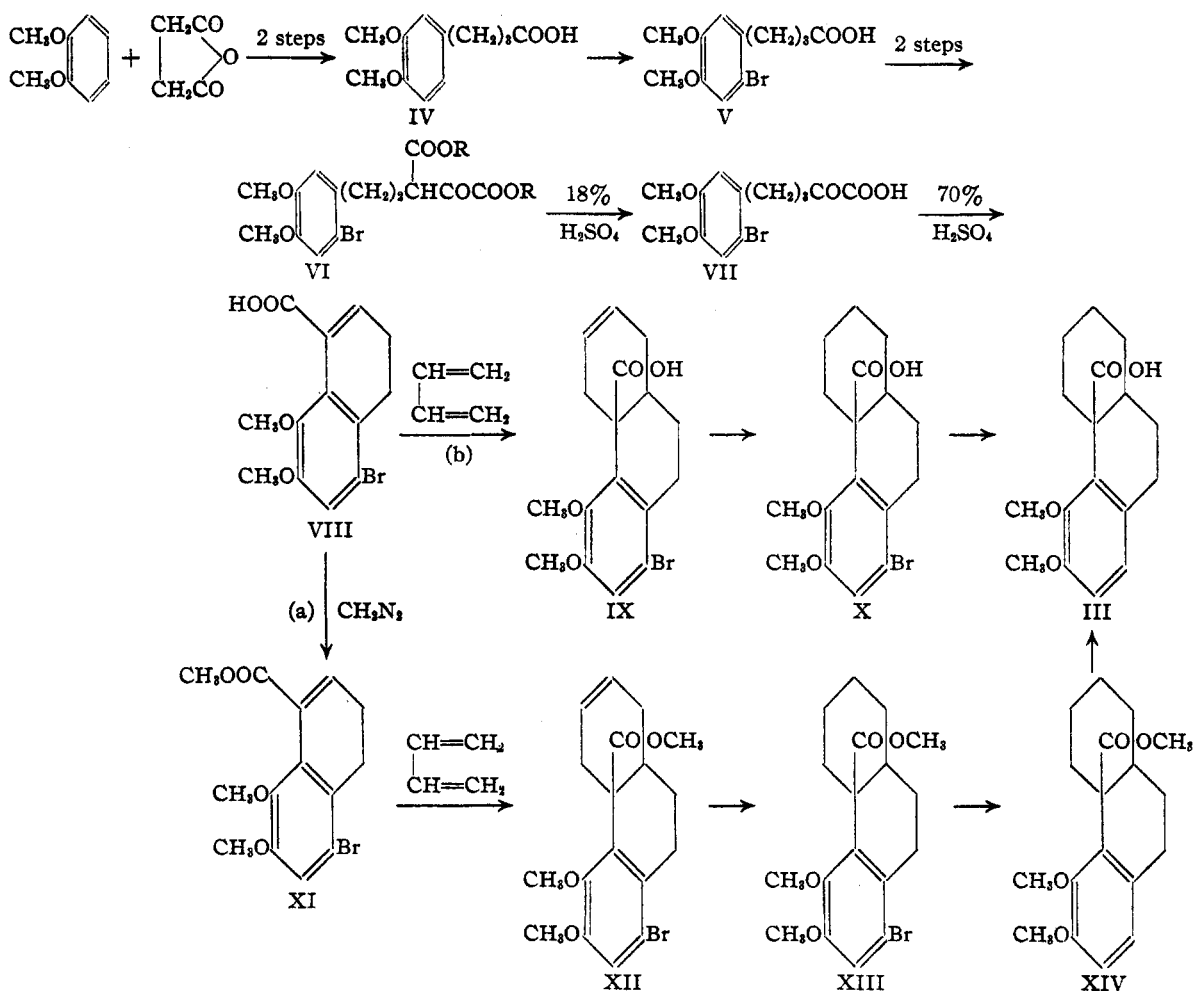
(5) Cahn, *J. Chem. Soc.*, 2582 (1928).

(6) Fieser and Hershberg, *THIS JOURNAL*, **58**, 2314 (1936).

(7) Martin, *ibid.*, **58**, 1438 (1936).

(8) Haworth, *J. Chem. Soc.*, 1485 (1932).

(9) Haworth, Mavin and Sheldrick, *ibid.*, 1423 (1934).



of palladium catalyst on barium sulfate with sodium acetate as acceptor for the hydrogen bromide. Saponification of the ester group was then accomplished with sodium ethylate at 180°, giving the desired acid III.

On repeating the whole synthesis with larger amounts, we investigated the possibility of using the free dihydronaphthoic acid VIII in the diene reaction in place of the ester, for an expensive reagent is required for the esterification and the subsequent saponification of the hindered ester group must be conducted in a sealed tube. The free acid can indeed be used, and after some exploration conditions were found permitting a better conversion than obtained with the ester. When heated with about two moles of butadiene in the presence of some benzene at 185–190° for one hundred hours, the acid was converted into the addition product IX in 18% yield, and over 50% of the starting material was recovered in a satisfactory condition. At higher temperatures there was some decarboxylation. The addition evidently proceeded in the same steric manner as before, for esterification of the addition product IX gave an ester identical with the product of the addition of butadiene to the bicyclic ester. Saturation of the double bond of IX and removal of the bromine with hydrogen and palladium catalyst gave the dimethoxyoctahydrophenanthrene-carboxylic acid III, identical with that obtained by the alternate method. The shorter route (b) clearly constitutes the better plan of synthesis, and the end-product can be obtained by this method in reasonable quantity if with a rather generous expenditure of time. The accumulation of a quantity of the diene addition product is a tedious process and the removal of bromine is slow and requires large amounts of catalyst.

It remains to be seen if an acid of the structure III can be obtained by the degradation of morphine, codeine, or thebaine, and if this can be done the stereochemical problem will require consideration. The acid has two asymmetric carbon atoms, but the addition apparently gives only one of the two possible *dl*-mixtures. The material obtained in several preparations by both methods (a) and (b) seemed entirely homogeneous, as did the various intermediates. Alder and Stein¹¹ have noted that at least in low temperature reactions dienes add to activated double bonds exclusively in the *cis* position but that at elevated

temperatures *cis*-addition may be followed by rearrangement to the *trans*-configuration. Models (Stuart) of the two diastereomers of III do not indicate any great difference in the strain, and consequently in the energy content, of the two forms, and a rearrangement from the *cis*-configuration therefore seems improbable. The configuration of the alkaloid ring system at this part of the molecule is not known. A few preliminary attempts were made to effect a resolution, but without success. The trials were confined largely to the unsaturated bromo acid IX, using brucine and strychnine as the resolving agents. Should this become a crucial point in the correlation of synthetic and natural products, a solution of the problem might still be possible in case the resolution of the synthetic acid is found to present really serious difficulty. Sinomenine belongs to a stereochemical series opposite to that of the alkaloids of the morphine group and has been degraded to the optical antipode of dihydrothebainone, and a mixture of the acids from the dual degradation of thebaine and sinomenine should yield the synthetic acid or its diastereomer.

Another possibility would be to utilize the dimethoxyoctahydrophenanthrene-13-carboxylic acid III as the starting point for the synthesis of the degradation product II of Speyer and Koulen,⁴ but difficulties are to be anticipated in attempting to convert the carboxyl group into an ethanamine chain because of the hindered nature of the functional group and the opportunity for rearrangement associated with the quaternary location. In the present work we have merely explored, with simpler compounds of the series, some of the possible starting points for a lengthening of the side chain. The experiments were made with the addition products of Δ^1 -dihydro- α -naphthoic ester and its 6-methoxy derivative with butadiene and 2,3-dimethylbutadiene, and the following observations concerning ethyl 6,7-dimethyl-5,8,9,10,13,14-hexahydrophenanthrene-13-carboxylate (XV) are typical of the rest. The unsaturated hexahydro ester, m. p. 50°, gave a liquid octahydro compound (XVI) on hydrogenation, and on reduction with sodium and isoamyl alcohol it gave in good yield a crystalline carbinol, XVII (m. p. 74°). On hydrogenation this was converted into the corresponding octahydro carbinol, XVIII (m. p. 69°), which was obtained in a more easily purified condition by the Bouveault reduction of the saturated ester XVI. In these reductions

(11) Alder and Stein, *Angew. Chem.*, **60**, 510 (1937).

with sodium and isoamyl alcohol a small amount of the ester invariably was saponified to the corresponding acid, but the yield of carbinol was good (about 70%), and nearly all of the substances were obtained in a crystalline condition. It is of interest that while ethyl abietate can be reduced to abietinol with sodium and ethyl alcohol,¹² the hydrophenanthrene-13-carboxylic esters are not attacked when ethyl alcohol is used.

The use of mineral acids was avoided in seeking to transform the carbinols into the corresponding halides, and it was found that the hexahydro carbinol XVII can be converted by the action of phosphorus pentachloride on the liquid acetate into the chloride, XIX. Attempts to convert the chloride into the nitrile, however, were unsuccessful. A Rosenmund reduction of the chloride of one of the 13-carboxylic acids was also tried without success. Selenium dehydrogenation of either the unsaturated chloride (XIX) or the unsaturated carbinol (XVII) seemed to involve some form of rearrangement, for in each case there was obtained in good yield a nicely crystalline product, m. p. 149°, having the composition of a trimethylphenanthrene (C₁₇H₁₆). The normal dehydrogenation product, 2,3-dimethylphenanthrene (XXI), was obtained by hydrogenating the unsaturated chloride to the point of replacement of most of the halogen and treating the oily hydrocarbon with selenium. This observation indicates that there probably is no rearrangement of the skeletal structure in the formation of chloride.

Experimental Part¹³

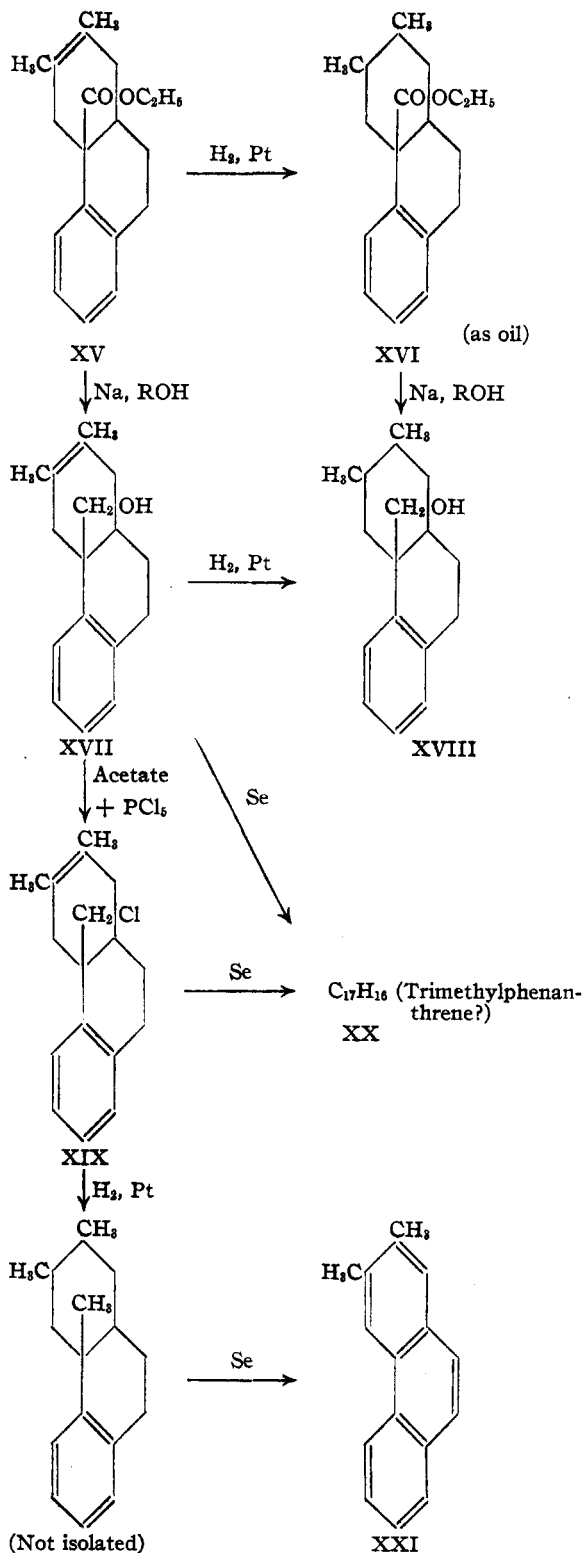
Synthesis of 3,4-Dimethoxy-5,6,7,8,9,10,13,14-octahydrophenanthrene-13-carboxylic Acid (III)

γ -(2-Bromo-4,5-dimethoxyphenyl)-butyric Acid (V).—A solution of 387 g. of γ -(3,4-dimethoxyphenyl)-butyric acid¹⁷ (b. p. 210° at 6 mm.) in 2400 cc. of glacial acetic acid was stirred mechanically in a cooling bath and treated with 122 cc. of bromine, added by drops while controlling the temperature to 4°. The bromination product soon began to separate as a pale yellow precipitate. The addition required twenty hours, and after stirring for two hours longer the crystalline bromo acid which had separated was collected and washed well with water. The product was colorless and weighed 469 g. (83%); m. p. 130–134.5°. A purified sample melted at 137.8–138.8° (Haworth,⁸ 135–136°, uncorr.).

The ethyl ester, prepared by Fischer esterification, was suitable for use after distillation; b. p. 220–222° (17 mm.); yield from 50 g. of acid, 49.6 g. (91%). The ester crystallizes from ether in elongated, stout prisms, m. p. 49.5–50.5°.

(12) Ruzicka and Meyer, *Helv. Chim. Acta*, **5**, 581 (1922).

(13) All melting points are corrected.



For proof of structure a sample of the ester was refluxed with aqueous alkali and excess permanganate. The acidic product recovered from the filtrate was crystallized from alcohol, giving colorless needles, m. p. 184–185°.

There was no depression on admixture with a sample of 2-bromo-4,5-dimethoxybenzoic acid prepared according to Heap, Jones, and Robinson,¹⁰ m. p. 185–186° (compare 185°¹⁴).

Ethyl α -Oxalyl- γ -(2-bromo-4,5-dimethoxyphenyl)-butyrate (VI).—Forty grams of ethyl γ -(2-bromo-3,4-dimethoxyphenyl)-butyrate was condensed with 20 g. of ethyl oxalate in the usual manner, using sodium ethylate (2.78 g. of sodium). On decomposing the sodium derivative in ice-cold dilute sulfuric acid the condensation product crystallized in long, feathery needles; total yield, 52 g. (96%), m. p. 69–70°. Recrystallized from ether-petroleum ether, it melted at 74.7–75.3°.

Anal. Calcd. for $C_{18}H_{20}O_7Br$: C, 50.31; H, 5.37. Found: C, 50.11; H, 5.38.

α -Keto- δ -(2-bromo-3,4-dimethoxyphenyl)-valeric Acid (VII).—The oxalyl ester VI (42 g.) was refluxed with 18% sulfuric acid (500 cc.) for twenty hours, and on cooling the mixture the keto acid solidified in round nodules. The material was dissolved in sodium carbonate solution and, after clarification, precipitated. The solid weighed 29.1 g. (90%), m. p. 85–87°. Crystallized for analysis from dilute acetic acid the substance formed silky needles, m. p. 93–94°.

Anal. Calcd. for $C_{13}H_{15}O_6Br$: C, 47.15; H, 4.57; Br, 24.13. Found: C, 47.49; H, 4.96; Br, 24.09.

The ethyl ester boils at 225–227° (9 mm.). Both the acid and the ethyl ester give a brownish-black coloration with ferric chloride solution. The enol acetate¹⁵ was obtained by refluxing 2 g. of the keto acid with 5 cc. of glacial acetic acid, 5 cc. of acetic anhydride, and 0.1 g. of zinc chloride for one hour, cautiously adding water, and allowing the solution to cool. The reaction product separated in a nearly pure condition (1.9 g.), m. p. 147–149°; on recrystallization from dilute acetic acid it formed slender needles, m. p. 148.4–149°. Saponification of the acetate gave the keto acid, m. p. 93–94°.

Anal. Calcd. for $C_{11}H_{13}O_6Br$: C, 48.27; H, 4.59; neut. equiv., 373. Found: C, 48.42; H, 4.83; neut. equiv., 369.

5-Bromo-7,8-dimethoxy- Δ^1 -dihydro-1-naphthoic Acid (VIII).—A total of 375 g. of the keto acid VII was cyclized in 65-g. batches, each batch being stirred vigorously with a mixture of 235 cc. of concentrated sulfuric acid and 135 cc. of water at 80° for one-half hour. The keto acid soon melted to a brown gum and the cyclization product then began to separate in a crystalline condition. The mixture was cooled, poured onto ice and water, and on vigorous stirring the product solidified completely in the form of pale buff-colored granules. After thorough washing, the acid was purified through the sodium salt, which crystallizes as flat white plates from a solution containing excess sodium carbonate (40 g. in 750 cc. of water for each 65-g. batch). An aqueous solution of the purified salt (25 g.) on acidification at 60° gave 17 g. (average) of acid, m. p. 168–171°. One crystallization from dilute alcohol raised the melting point to 171.5–172.5°, and the total yield of this material

was 196 g. (55%). Further purification gave colorless plates, m. p. 172–173°.

Anal. Calcd. for $C_{13}H_{11}O_4Br$: C, 49.86; H, 4.19; Br, 25.52; neut. equiv., 313. Found: C, 49.92; H, 4.31; Br, 25.31; neut. equiv., 316.

The methyl ester (XI), prepared with diazomethane, distilled at 174–175° (2 mm.) and was obtained as a viscous oil in 97% yield. It slowly solidified on standing, and when purified by crystallization from hexane formed blades, m. p. 76–77°.

5-Bromo-7,8-dimethoxy-1,2,3,4-tetrahydro-1-naphthoic acid was obtained by hydrogenation of VIII in alcohol in the presence of Adams catalyst. It crystallized from dilute alcohol as long, flat needles, m. p. 147–148°.

Anal. Calcd. for $C_{13}H_{15}O_4Br$: C, 49.54; H, 4.84. Found: C, 49.48; H, 4.99.

7,8-Dimethoxy-1,2,3,4-tetrahydro-1-naphthoic Acid.—Hydrogenation of the above compound (0.9 g.) in absolute alcohol (40 cc.) was accomplished in the presence of palladium oxide catalyst (35 mg.) in about three hours. The recovered product (0.6 g.) was bromine free and crystallized from benzene-hexane as elongated prisms, m. p. 119.5–120°.

Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.08; H, 6.82. Found: C, 66.36; H, 6.66.

Methyl 1-Bromo-3,4-dimethoxy-6,7-dimethyl-5,8,9,10,13,14-hexahydrophenanthrene-13-carboxylate.—The ester XI (14 g.) was heated with 2,3-dimethylbutadiene (5 g.) at 175–185° for thirty-one hours and the mixture on distillation gave a fraction boiling at 190–205° (2 mm.) and giving 9.6 g. (54%) of crystals from dilute alcohol. Further crystallization from alcohol gave plates, m. p. 154–155°. Some starting material was recovered from the fore-run.

Anal. Calcd. for $C_{20}H_{28}O_4Br$: C, 58.69; H, 6.16; Br, 19.52. Found: C, 58.91; H, 6.14; Br, 19.32.

This substance proved to be very resistant to hydrogenation under various conditions.

Methyl 1-Bromo-3,4-dimethoxy-5,8,9,10,13,14-hexahydrophenanthrene-13-carboxylate (XII).—In the most successful experiments 20 g. of the unsaturated ester XI was heated in a thick-walled Pyrex tube with 15 g. of butadiene at 220–230° for seven days. After several fractional distillations 9.2 g. of starting material was recovered and the bulk of the addition product was collected in an 8.6-g. fraction boiling at 185–196° (3 mm.). On crystallization of this from petroleum ether it gave in the first crop 3.2 g. more starting material, and the next crystallize consisted of crude addition product (2.4 g.) m. p. 89–100°. Two further crystallizations raised the melting point to 101–103°, and the average yield, not allowing for recovery of considerable starting material, was 8–9%. The mother liquors contained about 3.4 g. of oil which failed to crystallize. The fully purified ester formed elongated prisms, m. p. 105–106°.

Anal. Calcd. for $C_{18}H_{20}O_4Br$: C, 56.70; H, 5.55; Br, 20.96. Found: C, 56.47; H, 5.67; Br, 21.02.

Methyl 1-Bromo-3,4-dimethoxy-5,6,7,8,9,10,13,14-octahydrophenanthrene-13-carboxylate (XIII).—The addition product XII (2.75 g.) in glacial acetic acid (50 cc.) with Adams catalyst (50 mg.) absorbed one mole of hydrogen in

(14) Henry and Sharp, *J. Chem. Soc.*, 2286 (1930).

(15) The analogous enol acetate obtained by this method from α -keto- δ -phenylvaleric acid melted at 98.8–99.1° (Calcd.: C, 68.85; H, 6.03. Found: C, 68.68; H, 6.13); that from α -keto- δ -(4-methoxyphenyl)-valeric acid melted at 89–90° (Calcd.: C, 63.63; H, 6.10. Found: C, 64.03; H, 6.26).

fifteen minutes. The purified product crystallized from ether as fine needles, m. p. 112.5–113.5°.

Anal. Calcd. for $C_{18}H_{20}O_4Br$: C, 56.41; H, 6.06; Br, 20.85. Found: C, 56.45; H, 6.28; Br, 20.61.

Methyl 3,4-Dimethoxy-5,6,7,8,9,10,13,14-octahydrophenanthrene-13-carboxylate (XIV).—For removal of the bromine, 0.65 g. of XIII in 35 cc. of glacial acetic acid was shaken with hydrogen in the presence of 0.1 g. of fused sodium acetate and 2 g. of palladinized barium sulfate.¹⁶ One mole of gas was absorbed in about seventeen hours. After concentration of the filtered solution in vacuum and dilution with water the product separated as a crystalline powder (0.49 g.), m. p. 135–142°. Four recrystallizations from dilute acetic acid raised the m. p. to 141.5–142.5° (previous softening), and crystallization from petroleum ether then gave glistening cubes, m. p. 142.8–143.2°. The substance gave no test for bromine.

Anal. Calcd. for $C_{18}H_{20}O_4$: C, 71.03; H, 7.94. Found: C, 70.85; H, 7.65.

In another experiment the unsaturated bromo ester XII (0.85 g.) was hydrogenated in acetic acid using the palladium catalyst (2 g.). Absorption of gas was rapid at first and then slower, and on working up the product after four hours there was obtained 0.65 g. (94%) of the saturated bromine-free ester, m. p. 142.5–143°.

3,4 - Dimethoxy - 5,6,7,8,9,10,13,14 - octahydrophenanthrene-13-carboxylic Acid (III). Method (a).—The ester XIV (0.2 g.) was heated in a sealed tube with a solution from 0.9 g. of sodium and 15 cc. of absolute alcohol at 175–180° for eighteen hours. The solidified product was taken up in water and the solution was shaken with dimethyl sulfate until neutral, cooled to 0°, and acidified. The acid which separated was taken into ether, extracted from the ether with sodium bicarbonate solution, and obtained on acidification as a cream colored solid; yield, 75 mg. (39%). Evaporation of the ethereal solution gave 0.1 g. of unchanged ester, m. p. 140–141°. The acid crystallized from dilute alcohol in the form of flat needles, m. p. 202.4–203.4°. It is readily soluble in dilute solutions of sodium bicarbonate and ammonia.

Anal. Calcd. for $C_{17}H_{22}O_4$: C, 70.33; H, 7.64; neut. equiv., 290. Found: C, 70.11; H, 7.39; neut. equiv., 286.

1 - Bromo - 3,4 - dimethoxy - 5,8,9,10,13,14 - hexahydrophenanthrene-13-carboxylic Acid (IX).—The best conditions found for effecting the reaction consisted in heating a mixture of 20 g. of 5-bromo-7,8-dimethoxy- Δ^1 -dihydro-1-naphthoic acid, 8 g. of butadiene, and 15 cc. of dry benzene in a sealed tube at 185–190° for one hundred hours. The cooled mixture was diluted with 75 cc. of benzene and refluxed for two hours with a solution of 15 g. of sodium carbonate in 200 cc. of water. The pale yellow aqueous layer was separated from the benzene and polymer, decolorized with Norite, and acidified carefully. The precipitated acid was collected, dried, and crystallized from alcohol to separate the reaction product from the more soluble starting material. The crude addition product collected amounted to 4.3 g. (18%), m. p. 248–252°, dec. One recrystallization brought the m. p. to 256–258°, dec., and the purest sample formed small plates, m. p. 260–261°

dec. Dilution of the mother liquors gave 11.1 g. of starting material, m. p. 163–164°.

Anal. Calcd. for $C_{17}H_{18}O_4Br$: C, 55.60; H, 5.21; neut. equiv., 367. Found: C, 55.65; H, 5.55; neut. equiv., 364.

Esterification with diazomethane gave a product which when crystallized from ether–petroleum ether melted at 105–106° and gave no depression when mixed with the ester XII prepared by method (a).

1 - Bromo - 3,4 - dimethoxy - 5,6,7,8,9,10,13,14 - octahydrophenanthrene-13-carboxylic Acid (X).—The unsaturated acid IX (1 g.) in glacial acetic acid (65 cc.) with Adams catalyst (30 mg.) absorbed one mole of hydrogen in twenty minutes, and the product, recrystallized from alcohol, formed glistening plates, m. p. 233–234°; yield, 0.7 g. (70%).

Anal. Calcd. for $C_{17}H_{20}O_4Br$: C, 55.28; H, 5.73. Found: C, 54.65; H, 5.93.

Esterification with diazomethane and crystallization from ether gave an ester melting at 112.5–113.5° and identical with the sample of XIII described above.

3,4 - Dimethoxy - 5,6,7,8,9,10,13,14 - octahydrophenanthrene-13-carboxylic Acid (III). Method (b).—The saturated bromo acid X (0.35 g.) in glacial acetic acid (25 cc.) with palladinized barium sulfate (1 g.) and fused sodium acetate (0.1 g.) in two trials absorbed somewhat less than the theoretical amount of hydrogen in twelve to eighteen hours, when the reaction stopped. Three crystallizations from aqueous alcohol gave 0.2 g. (57%) of bromine-free acid melting constantly at 202–203°. This did not depress the melting point of the sample described above, and the ester formed cubes, m. p. 142.5–143.5°, identical with the other sample of XIV.

Concerning Other Diene Addition Products

In preparing a larger quantity of ethyl hexahydrophenanthrene-13-carboxylate¹ 90 g. of the unsaturated ester was heated with 30 g. of butadiene at 170–180° for thirty-six hours, giving 26.2 g. (23%) of purified product, b. p. 197–198° (14 mm.), 214–215° (31 mm.). The corresponding acid on hydrogenation in glacial acetic acid solution gave octahydrophenanthrene-13-carboxylic acid in 85% yield as small needles from dilute alcohol, m. p. 144–145°.

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 78.22; H, 7.88; neut. equiv., 230. Found: C, 78.59; H, 8.20; neut. equiv., 233.

Ethyl octahydrophenanthrene-13-carboxylate, prepared by hydrogenation of the hexahydride, was obtained as a viscous liquid, b. p. 180–181° (16 mm.).

The yield of ethyl 6,7-dimethylhexahydrophenanthrene-13-carboxylate¹ was increased considerably by heating 50 g. of the unsaturated ester with 30 g. of the diene at 170–180° for thirty-six hours; yield, 52.5 g. (74%); b. p. 197–198° (14 mm.). Similarly, ethyl 3-methoxyhexahydrophenanthrene-13-carboxylate,¹ b. p. 212–215° (17 mm.), was obtained in 31% yield from 30 g. of ester and 15 g. of butadiene at 150–160° for sixty-three hours. 3-Methoxyhexahydrophenanthrene-13-carboxylic acid¹ (1 g.) on dehydrogenation with selenium (2 g.) at 300–320° for twenty-four hours gave 3-methoxyphenanthrene, m. p. 58.5–59.5°; picrate, m. p. 123–124°.

3-Methoxyoctahydrophenanthrene-13-carboxylic acid, prepared from the hexahydride¹ with Adams catalyst in

(16) Schmidt, *Ber.*, **52**, 409 (1919).

TABLE I
 CARBINOLS FROM THE HYDROPHENANTHRENE-13-CARBOXYLIC ESTERS

Substituents	Yield, %	Crystal form	M. p., °C.	B. p., °C.	Analyses, %			
					Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Derivatives of 13-Hydroxymethyl-5,8,9,10,13,14-hexahydrophenanthrene								
6,7-Dimethyl	72	Needles	73-74	Acetate: 176-177 (5 mm.)	84.21	84.41	9.15	9.45
3-Methoxy	43	Prisms	122.4-122.8		77.87	77.86	8.26	8.30
3-Methoxy-6,7-dimethyl	77	Small prisms	66-67		79.35	79.31	8.89	8.72
Derivatives of 13-Hydroxymethyl-5,6,7,8,9,10,13,14-octahydrophenanthrene								
None	77	Fine needles	48.8-49.5	Acetate: 136-138 (3 mm.)	83.28	83.55	9.32	9.47
6,7-Dimethyl	73	Small needles	68-69	203-205 (15 mm.)	83.56	83.57	9.90	10.23
3-Methoxy-6,7-dimethyl	70	Micro crystals	76.7-77.9	Acetate: 210-212 (15 mm.)	78.76	79.15	9.55	9.80

acetic acid, formed thin plates from dilute acetic acid, m. p. 174.5-175.5°.

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 73.82; H, 7.75; neut. equiv., 260. Found: C, 74.05; H, 7.90; neut. equiv., 260.

Ethyl 3-methoxy-6,7-dimethylhexahydrophenanthrene-13-carboxylate, prepared from 15 g. of unsaturated ester and 10.6 g. of 2,3-dimethylbutadiene at 120-160° for forty-eight hours and isolated in the usual way, was obtained as a viscous oil, b. p. 197-199° (5 mm.); yield, 17.3 g. (85%). The ester slowly crystallized and when purified from petroleum ether formed crusts of microcrystals, m. p. 67-68°.

Anal. Calcd. for $C_{20}H_{22}O_2$: C, 76.40; H, 8.34. Found: C, 76.74; H, 8.52.

Saponification of the above ester with sodium ethylate at 170° for seventeen hours gave in 72% yield **3-methoxy-6,7-dimethylhexahydrophenanthrene-13-carboxylic acid**, which forms glistening, slender needles from dilute alcohol and melts at 164-165°.

Anal. Calcd. for $C_{18}H_{20}O_3$: C, 75.49; H, 7.74; neut. equiv., 286. Found: C, 75.90; H, 7.83; neut. equiv., 290.

The chloride of this acid was a liquid, b. p. 215° (15 mm.). Dehydrogenation of the acid (1 g.) with selenium as above gave **3-methoxy-6,7-dimethylphenanthrene**, which crystallized in plates, m. p. 119-120° (0.1 g.), from dilute alcohol. The picrate formed reddish-orange needles from alcohol; m. p. 160-162°.

Anal. Calcd. for $C_{17}H_{18}O$: C, 86.41; H, 6.83. Found: C, 86.22; H, 6.71.

Hydrogenation of the unsaturated acid gave **3-methoxy-6,7-dimethyloctahydrophenanthrene-13-carboxylic acid** as long blades, m. p. 204-206°, from dilute alcohol.

Anal. Calcd. for $C_{18}H_{22}O_3$: C, 74.97; H, 8.39; neut. equiv., 288. Found: C, 75.05; H, 8.65; neut. equiv., 288.

Carbinols from the Hydrophenanthrene-13-carboxylic Esters

The following procedure for the preparation of 13-hydroxymethyl-5,6,7,8,9,10,13,14-octahydrophenanthrene illustrates the general method of conducting the Bouveault reduction of the esters. A solution of 11 g. of ethyl octahydrophenanthrene-13-carboxylate in 250 cc. of isoamyl alcohol was stirred mechanically and kept at 90-95° in a water-bath and 9 g. of sodium was added in small pieces.

After the sodium had all reacted the solution was cooled, treated with 8-9 cc. of water added by drops, and stirred for one-half hour at 90-95°. The solvent was then removed by steam distillation, the brown oil extracted with ether, and the washed solution was dried, clarified with Norite, and evaporated. The residual oil was dissolved in petroleum ether (20-40°), and seed was obtained by cooling a portion for several hours in a carbon dioxide bath. The carbinol then crystallized from the main solution on seeding at room temperature, and it was obtained in rosetts of fine, feathery needles (colorless). The alkaline layer from the reduction gave an oily product on acidification (1.2 g.), and on purification from dilute alcohol this formed needles, m. p. 144-145°, identical with the sample of octahydrophenanthrene-13-carboxylic acid described above.

The other reductions were conducted in the same manner and the yields, properties, and analyses of the carbinols are recorded in the table. The neutral reaction products usually were not distilled; crystals were obtained by cooling a petroleum ether solution with solid carbon dioxide. The same solvent was used for recrystallization. The presence of the hydroxyl group was shown in representative cases by Zerewitinoff determination (0.88 mole gas) and by the preparation of the acetates, using hydrogen chloride-free acetyl chloride (80% yield). The 6,7-dimethyloctahydro derivative was prepared both by the Bouveault reduction and by hydrogenating the hexahydride in acetic acid in the presence of Adams catalyst; the reaction product in the latter case was not as easily purified as before, but a satisfactory sample was obtained (m. p. 68-69°) giving no depression with the other material. The acidic by-product of the Bouveault reduction, **6,7-dimethyloctahydrophenanthrene-13-carboxylic acid**, has not been described before. It formed long needles from alcohol and crystallized from benzene-hexane in flat prisms, m. p. 189-191°, with some previous softening.

Anal. Calcd. for $C_{17}H_{20}O_3$: C, 79.03; H, 8.58; neut. equiv., 258. Found: C, 79.19; H, 8.95; neut. equiv., 256.

5,6-Dimethyl-13-chloromethylhexahydrophenanthrene (XIX).—The carbinol XVII (4 g.) was converted into the acetate by heating for two hours with one equivalent of purified acetyl chloride and the mixture was poured onto ice and extracted with ether. After washing with bicarbonate solution and water, the solvent was removed and

the acetate distilled, b. p. 176–177° (5 mm.); yield, 4.1 g. The viscous oil, which showed no sign of crystallizing, was allowed to stand in dry benzene (10 cc.) with phosphorus pentachloride (12 g.) for two hours, the solution turning brownish-yellow. After refluxing for one-half hour, the mixture was decomposed with ice and water and the product extracted with ether, washed with bicarbonate, dried, and distilled. After several distillations of the yellow oil a fraction was obtained boiling at 196–198° (3 mm.); yield, 2.5 g. (65%).

Anal. Calcd. for $C_{17}H_{11}Cl$: C, 78.30; H, 8.13; Cl, 13.59. Found: C, 77.87; H, 7.76; Cl, 13.19.

In an attempt to prepare the nitrile, 13 g. of the chloride was heated with 2 g. of potassium cyanide in 30 cc. of alcohol at 160–180° for twenty-four hours; repeated distillation gave a fraction boiling at 210–220° (2 mm.) and containing nitrogen (1.8 g.) but this did not solidify and gave only a small amount of oily acidic material on alkaline hydrolysis.

The unsaturated chloride (1.3 g.) absorbed hydrogen fairly rapidly in glacial acetic acid solution in the presence of Adams catalyst, and considerable hydrogen chloride was found to have been produced. The oily reaction product appeared to be a mixture; on dehydrogenation with selenium it gave a solid (0.5 g.), m. p. 59–63°, giving a picrate, m. p. 145–146°. The hydrocarbon recovered from the picrate and crystallized from alcohol formed fluorescent plates, m. p. 77.5–78°. Mixed with 2,3-dimethylphenanthrene and its picrate, the samples showed no depression.

Dehydrogenation of the unsaturated chloride or carbinol

with selenium gave a much less soluble hydrocarbon which after purification by crystallization from alcohol and from hexane formed small scales, m. p. 148–149°. The substance gives a red coloration in alcohol or benzene with picric acid, but no picrate could be isolated. The yield from the carbinol was 66% and from the chloride 35%.

Anal. Calcd. for $C_{17}H_{16}$: C, 92.69; H, 7.32. Found: C, 92.66; H, 7.31.

Summary

As a step toward a proof of the location of the ethanamine chain in the morphine alkaloids, 3,4-dimethoxy-5,6,7,8,9,10,13,14-octahydrophenanthrene-13-carboxylic acid has been synthesized for comparison with a possible degradation product of the alkaloids. The synthesis involves a diene addition to a brominated Δ^1 -dihydro- α -naphthoic acid or ester obtained synthetically, the bromine being required to control the direction of cyclization and being removed in the end stages of the synthesis.

In a preliminary study of a possible lengthening of the carbon chain at C_{13} , a number of esters of substituted hexa- and octahydrophenanthrene-13-carboxylic acids have been reduced to the corresponding carbinols.

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Meso Aldehydes of Anthracene and 1,2-Benzanthracene

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Substitution reactions of polynuclear aromatic hydrocarbons have gained special interest with the observation that the most actively carcinogenic compounds of the hydrocarbon series show a high degree of susceptibility to diazo coupling² and to oxidation with lead tetraacetate.^{3,4} Another substitution which it seemed of interest to investigate is the reaction with methylformanilide, which Vollmann, Becker, Corell and Streeck⁵ recently applied with success for the conversion of pyrene into pyrene-3-aldehyde.

$$ArH + C_6H_5N(CH_3)CHO \xrightarrow{POCl_3} ArCHO + C_6H_5NHCH_3$$

Previous applications of the reaction were concerned chiefly with ortho-para substitutions of phenol ethers and amines, but the above ob-

servation shows that a sufficiently reactive hydrocarbon is capable of entering into the condensation. According to a brief report in the patent literature,⁶ anthracene also reacts with methylformanilide. The present investigation of other applications of the reaction was undertaken with the idea that information might be obtained on the relative reactivities of carcinogenic hydrocarbons and in the hope of obtaining derivatives of carcinogens having the reactive aldehydic group.

By modifying slightly the procedure of Vollmann, *et al.*,⁵ it was found possible to obtain the known 9-anthraldehyde in 92% yield after heating the reaction mixture for two hours on the steam-bath. 1,2-Benzanthracene reacts less readily, for under the same conditions about half of the hydrocarbon was recovered unchanged and

(1) Research Fellow of the National Cancer Institute.

(2) Fieser and Campbell, *This Journal*, **60**, 1142 (1938).

(3) Fieser and Hershberg, *ibid.*, **60**, 1893 (1938).

(4) Fieser and Hershberg, *ibid.*, **60**, 2542 (1938).

(5) Vollmann, Becker, Corell and Streeck, *Ann.*, **531**, 1 (1937).

(6) I. G. Farbenindustrie A.-G., English Patent 811,208 (1928).